PARTIALLY FLUORINATED CROWN ETHER DERIVATIVES: SYNTHESIS, PHASE TRANSFER CATALYSIS AND RECYCLING STUDIES.

Thesis submitted for the degree of

Doctor of Philosophy

At the University of Leicester

by

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Statement of Originality

The experimental work in this thesis has been carried out by the author in the department of chemistry at the University of Leicester between September 2003 and November 2006. The work has not been submitted, and is not presently being submitted, for any other degree at this or any other university.

Signed..... Date..03-08-2007.....

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Abstract.

A series of *N,N'*-dialkyl-4,13-diaza-18-crown-6 derivatives containing C_8H_{17} [**2.6**], $(CH_2)_3C_8F_{17}$ [**2.36**], $(CH_2)_3C_{10}F_{21}$ [**2.37**], and $(CH_2)_2C_8F_{17}$ [**2.19**] sidearms were synthesized in good yields by *N*-alkylation of 4,13-diaza-18-crown-6 [**2.7**]. The light fluorous macrocycles gave similar, if not better, catalytic activity compared to the non-fluorinated phase-transfer catalyst [**2.6**] under solid-liquid conditions in conventional organic solvents in both an aliphatic and an aromatic nucleophilic substitution. *N,N'*-Bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-undecyl)-4,13-diaza-18-crown-6 [**2.36**] was recycled six times in the iodide displacement reaction of 1-bromooctane and four times in the fluoride displacement reaction of 2,4-dinitrochlorobenzene using fluorous solid-phase extraction without any loss in activity.

Different functionalized dibenzo-18-crown-6 derivatives possessing C_7H_{15} [**4.17**], $(CH_2)_2C_6F_{13}$ [**4.26**], $(CH_2)_2C_8F_{17}$ [**4.27**], $NHC_{17}F_{15}$ [**4.31a-b**], and $NHCH_2C_6F_{13}$ [**4.35a-b**] sidearms were synthesized following different approaches. Acylation of dibenzo-18-crown-6 [**4.5**] with heptanoic acid gave bis(heptanoyl)dibenzo-18-crown-6 which was reduced to obtain bis(heptyl)dibenzo-18-crown-6 [4.17]. Bis-perfluoroalkylated dibenzo-crown ethers, [**4.26**] and [**4.37**], were synthesized *via* Heck coupling reaction followed by hydrogenation. The aminoalkylated and partially fluorinated aminoalkylated dibenzo-18-crown-6 ethers, [**4.31a-b**] and [**4.35a-b**], were obtained by reacting the corresponding *cis*- or *trans*-(aminobenzo)-18-crown-6 isomer with heptanoyl chloride or 1*H*,1*H*-perfluoroheptanoyl chloride respectively, followed by reduction of the resulting amide. The catalytic testing on an aliphatic nucleophilic substitution under solid-liquid conditions demonstrated that by adding perfluoroalkyl sidearms to a dibenzo-18-crown-6 type structure, [**4.26**] and [**4.27**], the phase transfer catalytic activity was improved significantly in comparison to the poor performance of alkylamino [**4.31a**] and perfluoroalkylamino derivatives [**4.35a**]. In contrast, it was found that the catalytic activities of bis-alkylated and aminoalkylated dibenzo-18-crown-6 derivatives were very similar in an aromatic nucleophilic substitution. *Bis*(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6 [**4.26**] was recycled four times in the iodide displacement reaction of 1-bromooctane using supported fluorous phase catalysis and four times in the fluoride displacement reaction of 2,4-dinitrochlorobenzene using fluorous solid-phase extraction without any loss in activity.

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In Spanish... quiero agradecer a mi familia, especialmente a mis padres, who do not speak English, y a mi hermano y futura hermana por todo su apoyo y cariño durante todos estos años. También a los "Químicos Mediocres" porque NO&DO.

Finally, to Alex and Tara. The first because she has been the source of strength, love and support all through this work, and the second, because the (un)timely distractions "*blowing raspberries*" and changing nappies. To them I dedicate this thesis.

Contents

Appendix

Abbreviations

ABC	Aqueous biphasic catalysis
BTF	Benzotrifluoride
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
EI	Electron impact
ES	Electrospray
FAB	Fast atom bombardment
FBC	Fluorous biphasic catalysis
FRPSG	Fluorous reverse phase silica gel
FSPE	Fluorous solid phase extraction
GC	Gas chromatography
Hz	Hertz
ICP-OES	Inductively coupled plasma optical emission spectroscopy

IL	Ionic liquid
IR	Infrared
J	Coupling constant
m	Multiplet
mp	Melting point
NMR	Nuclear magnetic resonance
Ph	Phenyl fragment
PP3	Perfluoro-1,3-dimethylcyclohexane
ppm	Parts per million
Rf	Perfluoroalkyl group
RT	Room temperature
s	Singlet
SAPC	Supported aqueous phase catalysis
$scCO_2$	Supercritical carbon dioxide
SCF	Supercritical fluid
SOPC	Supported organic phase catalysis
t	Triplet
TBAB	Tetrabutylammonium bromide
Tf	Triflate
THF	Tetrahydrofuran
wt	Weight

CHAPTER ONE

Introduction

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1.1 Introduction.

1.1.1. Homogeneous and heterogeneous catalysis.

In 1836, Berzelius defined a catalyst as a compound that increases the rate of a chemical reaction, but which is not itself consumed by the reaction. When Berzelius first suggested the idea that some reactions should be classified together as "catalysed", the emphasis was placed almost entirely upon the nature and amount of the products rather than upon the rate of their formation. It appeared that the rate of reaction was increased in the presence of a catalyst, which could be recovered from the reaction and reused.

Today, it is still useful to classify some reactions as catalysed, and to speak in terms of "catalyst for a reaction". A catalyst does not increase the yield of a reaction but it increases the rate of approach to an equilibrium position that is thermodynamically controlled, which otherwise would be difficult to reach in the absence of catalyst. Generally, the catalyst provides an alternative and faster reaction route, which can usually be explained in terms of normal chemical reactions between catalyst and substrate to give intermediates. These eventually yield the products and regenerate the catalyst.

Catalysed reactions are divided into two main categories:

1. The first group, *homogeneous catalysis*, includes reactions that proceed in simple homogeneous steps involving molecules, ions or free radicals as intermediates in the same phase.
2. The second, *heterogeneous catalysis,* refers to reactions proceeding at an interfacial layer between two discrete phases.

Homogeneous catalysis has become a very important process covering large areas of research.[1] The hydrogenation of olefins using Wilkinson's Catalyst, $[RhCl(PPh_3)_3]$, is a typical example that illustrates the performance of a transition metal catalyst in a homogeneous system.[2] The triphenylphosphine ligands give solubility in organic solvents to the catalytic complex and help to stabilise the metal during the reaction. The substrate can be added as either a liquid or a gas along with hydrogen, both of which are taken up into solution to give the catalyst and reactants in a single phase. One catalytic cycle gives the hydrogenation product and regenerates the active catalyst.

Heterogeneous catalysis involves the use of a catalyst in a different phase from the reactants. Typical examples involve a solid catalyst with the reactants as either liquids or gases. Generally, the reaction takes place on the surface of the catalyst, where one or more of the reactants are adsorbed. In order for the reaction to occur one or more of the reactants must diffuse to the catalyst surface and adsorb onto it. After reaction, the products must desorb from the surface and diffuse away from the solid surface. This transport of reactants and products from one phase to another plays a dominant role in limiting the reaction rate. Therefore, to obtain a better yield maximising the catalytic activity, the catalyst must have a large active surface. In addition, the catalyst needs to adsorb the reactant molecules strongly enough for them to react, but not so strongly that the product molecules cannot be released from the surface. Heterogeneous catalysts are normally thermostable and due to this can often be used in more extreme conditions. The isolation of the product from the catalyst is easily achieved by separating the phases, which is another important advantage of these catalysts.

A simple example of heterogeneous catalysis is the reduction of ethene with hydrogen using a platinum catalyst. Ethene gas and hydrogen gas are absorbed onto the surface of the platinum catalyst. The ethene molecule is hydrogenated to yield ethane, which is then desorbed from the platinum surface and released back into the gas phase.

However, a disadvantage of heterogeneous catalysis is its lack of specificity and tuneability. In contrast, homogeneous catalysts can be tuned to catalyse a reaction specifically. Although homogeneous catalysis has a large number of benefits, it suffers generally from an inability to isolate catalysts from products. Normally, it is expensive and difficult to prepare ligands for use as catalysts and this makes it critically important to develop procedures to separate and reuse the catalyst. This problem has severely restricted the application of homogeneous catalysts in industry, even though much higher selectivities and specificities are generally possible.

It is clear that homogeneous catalysis would be widely used in industrial processes if the problem of catalyst separation could be solved. Various techniques that allow homogeneous systems to be used by separating and recycling the catalyst have been developed. These techniques for the "*heterogenisation*" of homogeneous catalysts include non-conventional and tuneable solvents, such as supercritical fluids,[3] and ionic liquids,[4] post-reaction catalyst recovery,[5] biphase systems[6] and

supported systems.[5] The last two will be examined in detail over the following sections.

1.1.2. Separation and Purification.

The development of the safest, least expensive and most environmentally-friendly synthetic routes possible is recognized as an essential aim for the progress of organic chemistry. Despite the advancements in synthetic chemistry over the last few decades, separation and purification of the reaction mixture remains an important factor to be developed further.[7]

The purification techniques used to "*work-up*" reaction mixtures have been improved,[8] but have not changed much over the past 50 years. The development of new synthetic techniques such as parallel synthesis demands simple separation and purification methods, not only for the product but also for the catalyst. Therefore, the design of a new synthetic reaction must take this into account. The use of volatile or water-soluble reagents, acid-base extractions,[9] solid-phase synthesis[10] and, more recently, fluorous synthesis[11] are some of the most successful approaches.

1.2 Catalysis and Product Recovery.

1.2.1. Biphase Catalysis.

The application of biphase systems to homogeneous catalysis can lead to simple separation of products from catalysts. Although it is possible to design biphase systems with a wide range of binary solvent combinations, the two systems outlined below have been studied in most detail.

1.2.1.1. *Aqueous Biphase System.*

In the aqueous biphase system, the aqueous phase, containing the water-soluble catalyst, is immiscible with the organic phase, which contains both reactants and reaction products. The reaction takes place in the interphase region and not in the bulk aqueous phase.[12] Product isolation involves simple decantation of the organic phase, leaving the aqueous catalyst-containing solution intact for further catalytic cycles. This technique, therefore, combines the advantages of homogeneous catalysis with the ease of separation inherent in heterogeneous systems, thereby "heterogenising" a homogeneous system.[13] An important aspect of aqueous biphase

catalysis is the ability to tune organometallic catalyst complexes. To solubilise a catalyst in the aqueous phase and hence, reduce its affinity for non-polar organic solvents, the catalysts are modified with polar substituents such as SO_3H or CO_2H.[14]

Some properties and advantages of using water as a liquid support in aqueous biphase catalysis are listed below:

- Easy to separate from non-polar solvents or products.
- Inflammable.
- Odourless and colourless, making contamination easily recognizable.
- Density of 1 g/cm^3 provides a sufficient difference from most organic substances.
- Very high dielectric constant.
- High thermal conductivity, high specific heat capacity and high evaporation enthalpy.
- Low refractive index.
- High solubility of many gases, especially CO_2.
- Formation of hydrates and solvates.

An important industrial application of the aqueous biphase system is the continuous biphase hydroformylation of lower olefins, which was developed in the early 1980's by Ruhrchemie AG and Rhône-Poulenc. This method corresponds to approximately 10% of the world production of C3-C4 aldehydes (see ***Scheme 1.1***).[15] The reaction takes place when an inflow containing the olefins and a gas mixture containing hydrogen and carbon monoxide are fed into a reactor in the presence of the hydroformylation catalyst. This process, which is mainly described in patents and therefore little known, is based on the ability to anchor the homogeneous catalyst in the aqueous phase by appropriate modification of the ligands with sulfonate groups.[16] The catalyst formed after pre-activation is readily soluble in water.

Some characteristics of this process are:

- High selectivity, producing virtually exclusively aldehydes, which are up to 98% linear.
- Simplicity in terms of apparatus and process operation.
- Very simple recycling of the homogeneous catalyst by immobilization in the "mobile support" water, and extremely low leaching of the catalyst into the organic phase (< 0.1 ppm).

- Low purity demands on the reactants.
- Excellent process potential from safety and environmental points of view.
- Lower production costs and excellent yields.

$$RCH{=}CH_2 + CO + H_2 \xrightarrow[TPPTS]{in\ H_2O} \underset{normal\ aldehydes}{RCH_2CH_2CHO} + \underset{isoaldehydes}{RCH(CHO)CH_3}$$

Scheme 1.1. Ruhrchemie/Rhône-Poulenc's oxo process. The active catalyst of Ruhrchemie/Rhône-Poulenc's hydroformylation process uses trisulfonated triphenylphosphine (**TPPTS** = $[HRh(CO)\{P(3\text{-}C_6H_4SO_3Na)_3\}_3]$) as ligand.

Aqueous biphase catalysis has been also utilized in a number of other industrial processes[17] such as hydrodimerization of butadiene and water (a telomerization variant) to yield 1-octanol, catalysed hydrogenations for fine chemicals[18] and the Rhône-Poulenc catalytic C-C coupling processes for small-scale production of various vitamin precursors. Moreover, TPPTS modified catalysts have been proposed for homogeneously catalysed biphasic carbonylations.[19]

Finally, it is important to mention the Suzuki coupling of aryl halides and arylboronic acids. In earlier laboratory methods, starting from expensive brominated or iodinated aromatics, only homogeneous palladium catalysts had been modified with triply meta-sulfonated triphenylphosphine (TPPTS) or the monosulfonated TPP (TPPMS) could be used; the chlorine derivatives required much more basic phosphines for the modification. Nowadays, cheaper chlorinated aromatics and catalysts based on Pd/TPPTS can be used in an aqueous procedure on a commercial scale.[20]

However, despite the number of advantages outlined above, the aqueous biphase system has some disadvantages associated with the aqueous process itself. For example, the rate of reaction depends on the solubility of the substrate in the aqueous phase. Therefore, when the substrates are water-immiscible, the reaction can only occur at the limited interface between the solvents and this can significantly reduce the reaction rate. Another important drawback of the use of any biphase system containing an aqueous phase is that moisture-sensitive reagents, catalysts or products cannot be used or produced. This reduces the applications of these systems in synthetic processes.[21]

The technique of aqueous biphase catalysis has had such an impact on the chemistry of biphase reactions that different solutions have been proposed. Fluorous systems may have advantages in the "homogeneous" reaction and the "heterogeneous" separation owing to the thermoreversibility of its phase behaviour.

1.2.1.2. *Fluorous Biphase Systems.*

In 1994 Horváth and Rábai introduced the concept of the "*fluorous biphase system*" (FBS) in order to facilitate the separation of a homogeneous catalyst from products.[22] The term "fluorous" is an analogue to the term aqueous and describes a system where the aqueous phase has been replaced with a non-polar perfluorocarbon solvent, to form a "*fluorous phase*". The FBS is based on the limited and temperature controlled miscibility of organic and perfluorocarbon solvents (PFC). It consists of a fluorous phase containing a preferentially fluorous-soluble reagent or catalyst and an organic phase, which may be any organic compound or solvent with very limited solubility in the fluorous phase. Reagents and catalysts can be made fluorous soluble by attaching perfluoroalkyl groups, nicknamed "fluorous ponytails", of appropriate size and number.

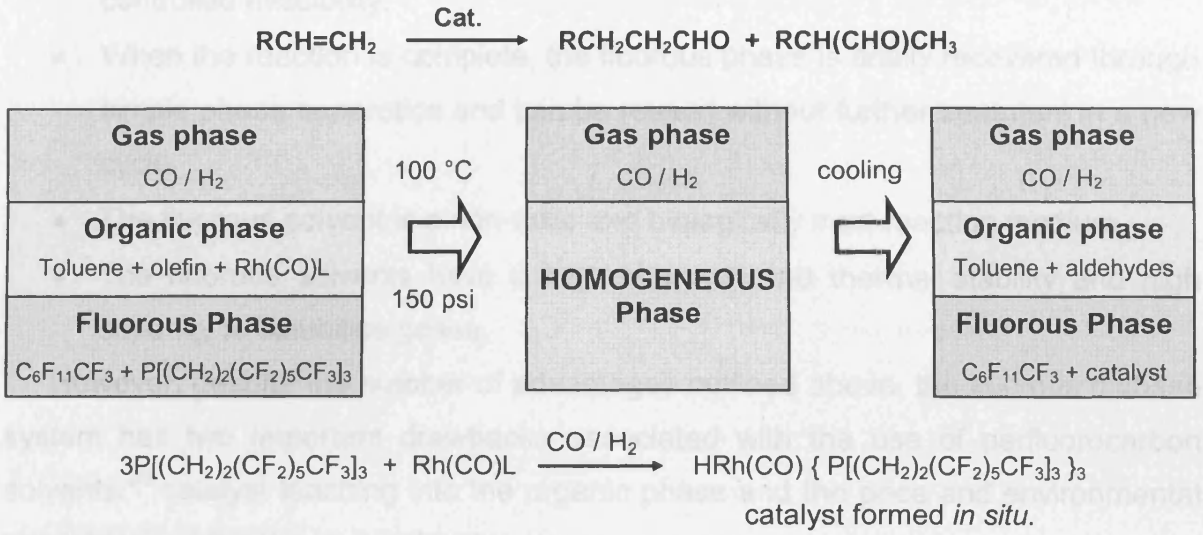
$$[\text{-}(CH_2)_m(CF_2)_n\text{-}CF_3] \quad \text{or} \quad [\text{-}R_{mfn}]$$

Equation 1.1.

Equation 1.1 illustrates the general formula of a fluorous ponytail. The non-fluorinated $(CH_2)_m$ spacer segments constitute a tuning element that can insulate the active centre of the catalyst from the highly electron-withdrawing effect of the perfluoroalkyl groups. In order to insulate the active centre of the catalyst completely from this electronic effect, Gladysz and co-workers suggested that the value of **m** has to be equal or higher than 3.[23] In addition, to make compounds preferentially soluble in the fluorous phase, the fluorine content of the molecule must be more than 60%.[24]

At low temperatures, many systems that consist of an organic and a fluorous solvent are not miscible and give two phases. However, heating a fluorous biphasic system causes them to form a homogeneous solution and the catalytic process can then take place more rapidly. Cooling down the reaction mixture leads to the reformation of the two separate phases. Afterwards, easy product isolation and recovery of the perfluoro-tagged metal catalyst can be achieved by simple phase

separation. Therefore, the advantages of both homogeneous and heterogeneous catalysis are combined within the FBC method.



Scheme 1.2. Hydroformylation of Olefins in the Fluorous Biphase System.

Scheme 1.2 exemplifies the hydroformylation of olefins under FBC conditions. In this case, the rhodium catalyst is generated *in situ*, keeping the percentage of fluorine high enough to immobilize it in the fluorous phase, where both CO/H_2 and small amounts of olefin are dissolved. The aldehydes formed during the reaction are expelled from the fluorous phase, due to their higher polarity. On completion of the reaction, the fluorinated phase is easily recovered by phase separation and can be reused again in a new catalytic cycle. During this process, the catalyst loss was insignificant (4.2% Rh loss after 9 consecutive runs).[25]

In the last ten years the fluorous biphase concept developed rapidly and a wide variety of catalytic reactions involving perfluoroalkyl derivatised ligands were investigated. Although most of the work concentrated on phosphorus (III) ligands,[26] many different ligand systems such as β-diketonates,[27] cyclopentadienides,[28] porphyrins,[29] bipyridines,[30] and tetraazacyclotetradecanes[31] have been functionalised with fluorous ponytails. Consequently, the fluorous biphase system has been widely used for hydroformylations,[32] hydroborations,[33] hydrogenations,[34] oxidations,[35] epoxidations,[36] and C–C bond formation.[37]

Several advantages of the fluorous biphase systems are outlined below:

- It is possible to carry out the reaction under homogeneous conditions by choosing a fluorous solvent/organic solvent couple that shows a thermally controlled miscibility.
- When the reaction is complete, the fluorous phase is easily recovered through simple phase separation and can be reused without further treatment in a new cycle.
- The fluorous solvent is a non-toxic and biologically inert reaction medium.
- The fluorous solvents have a high chemical and thermal stability and high capacity to solubilise gases.

However, despite the number of advantages outlined above, the fluorous biphase system has two important drawbacks associated with the use of perfluorocarbon solvents:[38] catalyst leaching into the organic phase and the price and environmental persistence of the fluorous solvents.

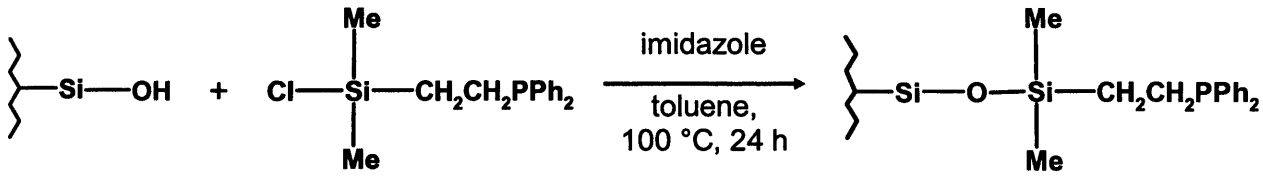
1.2.2. Solid–Phase Synthesis.

The ability to recycle in homogeneous catalytic systems can be improved by attaching the homogeneous catalysts to an insoluble support *via* covalent bonding. This attachment can help to stabilise the catalyst due to the controlled stereochemical conformation offered by the solid support. In this case, when the reaction is complete, the catalyst can be easily separated from the products by filtering out the solid support.

There are principally two types of support extensively used:

Organic Support. Polystyrene and styrene-divinylbenzene copolymer beads are the most utilised organic supports. These organic resins can be tuned to contain functional groups that can bind to metal centres, suiting perfectly the system in which they are going to be used.[39] Organic polymer-supported catalysis has been applied to numerous reactions, but this technique still does not have any remarkable industrial application. [40] Although numerous studies show that similar selectivities are obtained using polymer supported systems and their analogous homogeneous systems, the rates of reaction are generally lower if a solid support is used. This is probably due to the poor diffusion rates of reactants into the polymer support. In addition, the high degree of bonding between the support and the catalyst can make it difficult for the catalyst to assume the required conformation during the catalytic cycle.[41]

Inorganic Support. This kind of solid support is more stable than the organic resins having a very rigid structure and well-defined pore network. Silica is the most commonly used support and can be functionalised relatively easily.[42] ***Scheme 1.3*** illustrates an example of the synthesis of an inorganic support based on silica. Surface silanol groups will react with chlorosilanes or alkoxysilanes to give a stable Si–O–Si linker.



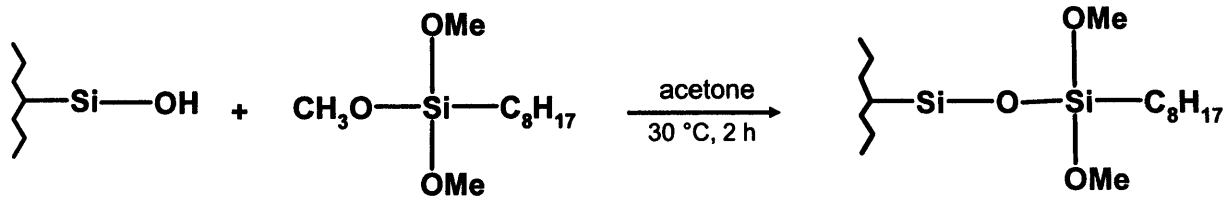
Scheme 1.3. Synthesis of Silica Solid Support.

The surface-bound coordinating ligands can be used to bind catalytically active metal centres or, in the case of metal carbonyls and alkoxides, the surface OH groups can be used as binding sites. Sometimes, the reactive silanol groups can make the surface of the support unstable. To make the surface more inert, these groups can be neutralised by reacting with a hydrocarbon chlorosilane.[43] Spacer groups, inserted to distance the coordinating ligands from the surface of the support, can have an important effect on reaction rates, and can contribute to increased catalytic activity.[44] Usually, inorganic supports lead to higher rates than those observed for organic supports. However, the activities are still lower than the analogous homogeneous systems. This is a consequence of anchoring a catalytically active metal centre to the support, inhibiting catalyst mobility and molecular rearrangements. Although certain supported systems show improved activity they are rare and the use of these supports is unlikely to be commercially widespread.

1.2.3. Supported Organic Phase Catalysis (SOPC).

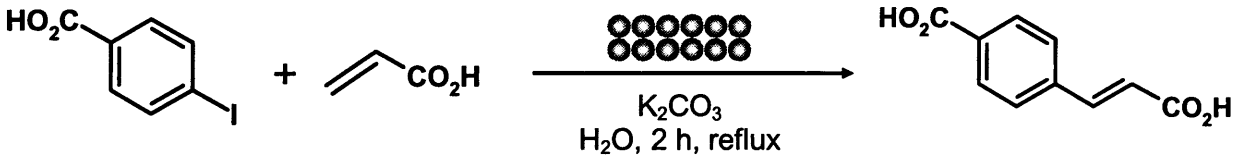
Coupling the reactive hydroxyl groups to hydrophobic silanes can modify the normal hydrophilicity of the silica surface. This resulting silica support is known as "*Reverse Phase Silica*", and shows a large affinity for organic solvents (***Scheme 1.4***). The reverse phase silica can be used in a technique known as Supported Organic Phase Catalysis.[45] This procedure is a heterogeneous process in which a thin layer of a non-polar organic solvent is supported on the surface of the silica. An

unmodified, aqueous-insoluble catalyst can then be supported in the solvent while polar reactants/products reside in a bulk polar phase.



Scheme 1.4. Synthesis of Reverse Phase Silica.

The activity of the supported catalyst is increased with respect to solid supported systems due to a larger surface area between the bulk solvent and the supported thin layer of non-polar organic solvent. The mobility of the catalyst in the supported phase is also high, which leads to rates approaching those observed in homogeneous systems.



Scheme 1.5. SOPC.

Scheme 1.5 illustrates the use of reverse phase silica in a Heck coupling of iodobenzoic acid and acrylic acid.[46] The derivatised silica beads are converted into active catalyst by treatment with palladium acetate and triphenylphosphine in cyclohexane. After removal of solvent, this solid supported catalyst is a free flowing powder that is stable in air and easy to handle. The product was obtained in good yield (90%) with less than 0.2% leaching of the catalyst into the aqueous phase. The reverse phase beads can be easily filtered and reused in several cycles without any apparent loss of activity.

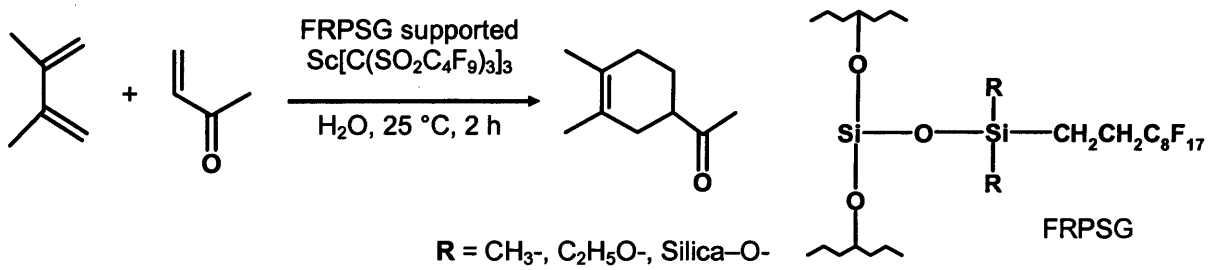
Despite the improved activity and other advantages over the simple biphase techniques, supported organic phase catalysis, like the aqueous/organic biphase, is

incompatible with water-sensitive reaction components. This drawback reduces the industrial applications of SOPC systems.

1.2.4. Supported Fluorous Phase Catalysis (SFPC).

This new technique, which allows the use of water sensitive components, utilises highly reactive fluorous chlorosilanes to modify the silica surface. Usually, in SFPC, a fluorous-soluble catalyst and a layer of fluorous solvent are supported on the fluorous modified support. The silica modified in this way is called Fluorous Reverse Phase Silica Gel (FRPSG).[47]

The general use of FRPSG is limited, although several applications in aqueous and organic media with high activity of the catalyst have been carried out successfully (***Scheme 1.6***).[48] In the particular case of aqueous media, these studies showed that the Diels-Alder reaction illustrated in ***Scheme 1.6*** was accelerated when the catalyst was immobilized on FRPSG in comparison with the same reaction using reverse phase silica, normal silica and no support material. The immobilization of the catalyst allows its recycling by simple filtration.



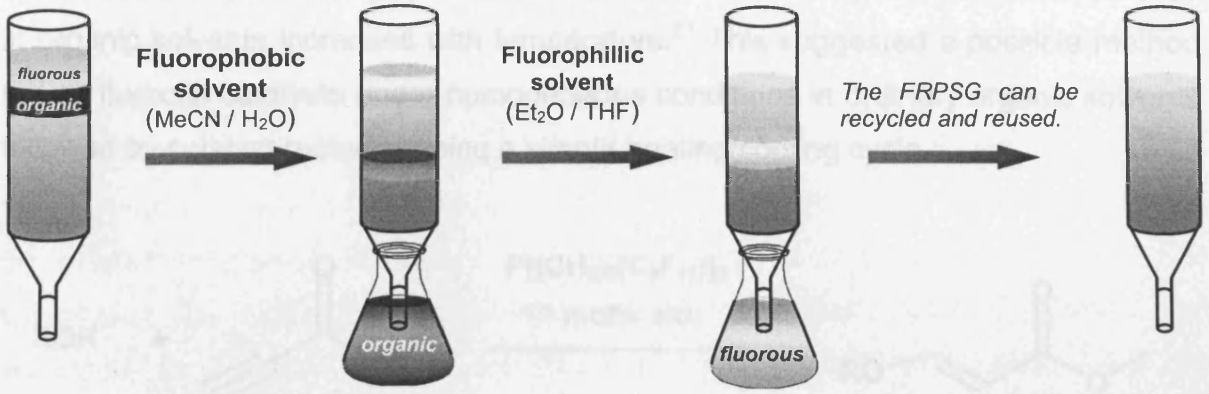
Scheme 1.6. Diels-Alder reaction using FRPSG supported catalyst.

These advantages suggest that FRPSG-supported catalysts should be a remarkably useful tool for the progress of environmentally benign green processes. Further studies should be made to develop this field.

1.2.5. Fluorous Solid Phase Extraction (FSPE).

The separation of fluorous derivatised compounds, especially catalysts, from organic compounds has become increasingly important during recent years.[49] The separation methods outlined above have been enlarged recently by the new and

more efficient procedures, *Fluorous Solid Phase Extraction* and *Fluorous Chromatography*.[50]



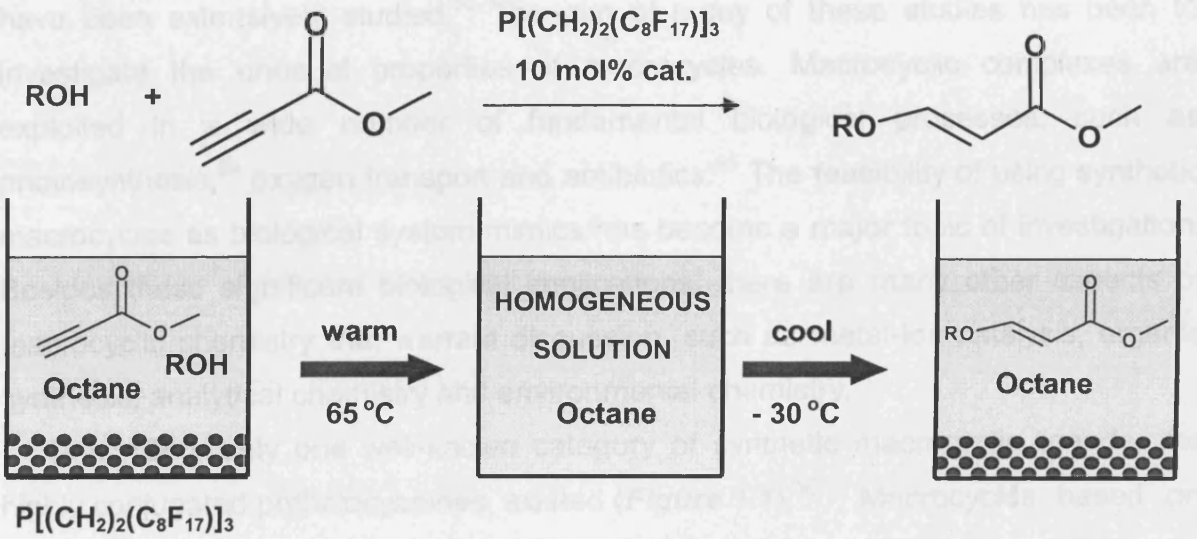
Scheme 1.7. Fluorous Solid Phase Extraction.

As illustrated in ***Scheme 1.7***, in FSPE, a mixture of organic and fluorous compounds is loaded onto the FRPSG packed column. The column is then eluted with a "*fluorophobic*" solvent. Polar solvents such as methanol or acetonitrile are the most commonly used fluorophobic solvents. During this first elution, the organic compound is easily washed through the column, while the fluorous compound is retained due to its interaction with the FRPSG. A second elution with a "*fluorophilic*" solvent, often Et_2O or THF, washes the fluorous fraction from the column.

In FSPE the separation of components is based on their different fluorine content and their polarity. In comparison with fluorous biphase systems (*Section 1.2.1.2*), the FSPE allows the use of much smaller and lighter fluorous-tags. To solubilize the reaction compounds in the fluorous phase in a FBS, the percentage of fluorine has to be greater than 60%. Using FSPE it is not necessary to make the catalyst or reaction products soluble in fluorous solvents, therefore the catalyst can be tuned with less fluorine content within the fluorous-tags (*fluorous ponytails*). The addition of a small number of fluorous-tags only slightly affects the solubility of the catalyst in common organic solvents, requiring little or no modification to the solvent system employed in the reaction. Hence, using this method of separation no fluorous solvent is necessary, avoiding the problems of catalyst leaching into organic phase and environmental persistence. Fluorous solid phase extraction is a well-established technique in fluorous synthesis and separation but its applications in catalysis are, as yet, very limited.

1.2.6. Thermomorphic Catalysis.

Thermomorphic catalysis utilises the temperature-dependent solubility of heavy fluorinated catalysts. Gladysz demonstrated that the solubility of fluorous compounds in organic solvents increases with temperature.[51] This suggested a possible method to use fluorous catalysts under homogeneous conditions in ordinary organic solvents followed by catalyst recovery using a simple heating/cooling cycle.



Scheme 1.8. Addition of alcohols to methyl propiolate catalysed by a thermomorphic fluorous phosphine.

Scheme 1.8 shows the addition of alcohols to methyl propiolate catalysed by an easily prepared fluorous phosphine, which exhibits thermomorphic properties. At room temperature, this mixture forms a two-phase heterogeneous system. However, when the mixture is warmed, the system becomes homogeneous and the catalytic reaction can take place. When the reaction is finished, cooling to –30 °C precipitates the catalyst. The recovery of the catalyst involves a simple liquid/solid phase separation. Using this procedure, the catalyst was recycled four times without deterioration in yield. In addition, the catalyst leaching was less than 0.33% per cycle.

1.3 Crown Ethers.

1.3.1. Introduction.

Macrocyclic ligands are polydentate ligands containing donor atoms incorporated in, or less commonly attached to, a cyclic backbone. By definition macrocyclic ligands contain at least three donor atoms, and the macrocycle itself should consist of a minimum of nine atoms.[52] A large number of both synthetic and natural macrocycles have been extensively studied.[53] The aim of many of these studies has been to investigate the unusual properties of macrocycles. Macrocyclic complexes are exploited in a wide number of fundamental biological processes, such as photosynthesis,[54] oxygen transport and antibiotics.[55] The feasibility of using synthetic macrocycles as biological system mimics has become a major topic of investigation. Besides these significant biological implications, there are many other aspects of macrocyclic chemistry that warrant discussion, such as metal-ion catalysis, organic synthesis, analytical chemistry and environmental chemistry.

Until 1960, only one well-known category of synthetic macrocyclic ligands, the highly conjugated phthalocyanines, existed (***Figure 1.1***).[56] Macrocycles based on the phthalocyanines are important commercial colouring agents, and are widely used as pigments and dyes. Aside from their intense colours, their transition metal complexes also exhibit marked resistance to degradation, high thermal stability and inertness to acids and alkalis.

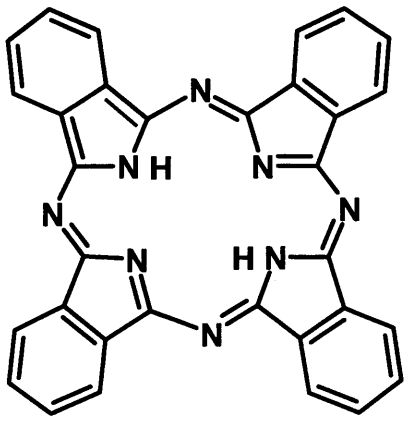


Figure 1.1. Phthalocyanine.

In 1967 Charles Pedersen extended these ideas and synthesised a macrocycle containing only hydrogen, carbon and oxygen. The crystal structure of this so-called

"crown ether" showed that each oxygen atom was bound to two carbons atoms, and arranged in a ring, hence the term "*crown*". The original crown ether discovered by Pedersen was dibenzo-18-crown-6 which is shown in ***Figure 1.2***.[57]

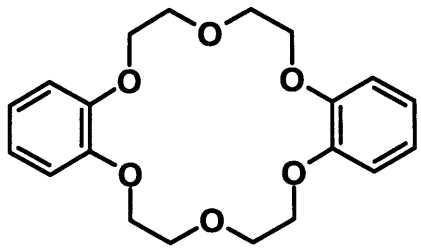


Figure 1.2. Dibenzo-18-crown-6.

Pedersen synthesised numerous crown ethers in order to understand the limitations of ring sizes, heteroatom content and other features. He also investigated the different species that could be bound or complexed by these novel macrocycles and demonstrated that crown ethers interact strongly with metal ions. It was found that, in addition to the alkaline earth metal cations, alkylammonium ions and several other species could be complexed by these electron rich crown ethers due to the existence of donor atoms capable of acting as Lewis bases.

1.3.2. Types of Crown Ethers.

Crown ethers are usually considered as macrocyclic polyethers. Due to the complicated systematic nomenclature of these complexes, Pedersen developed a new shorthand method. This semi-systematic nomenclature uses the general notation "x-crown-y", where x denotes the number of atoms forming the ring, and y denotes the number of heteroatoms (***Figure 1.3***). Mixed ethers, comprising of oxygen, nitrogen and sulphur are also known. Replacement of oxygen by other heteroatoms has been extensively studied, and has led to azacrown ethers, thiacrown ethers and other derivatives.[58] Some examples are shown in ***Figure 1.3***, as well as examples of cryptands that form an important class of three-dimensional cation binders. Three-dimensional macrocycles have now been extended to form the basis of other ligand classes, such as spherands, cavitands and lariat ethers.

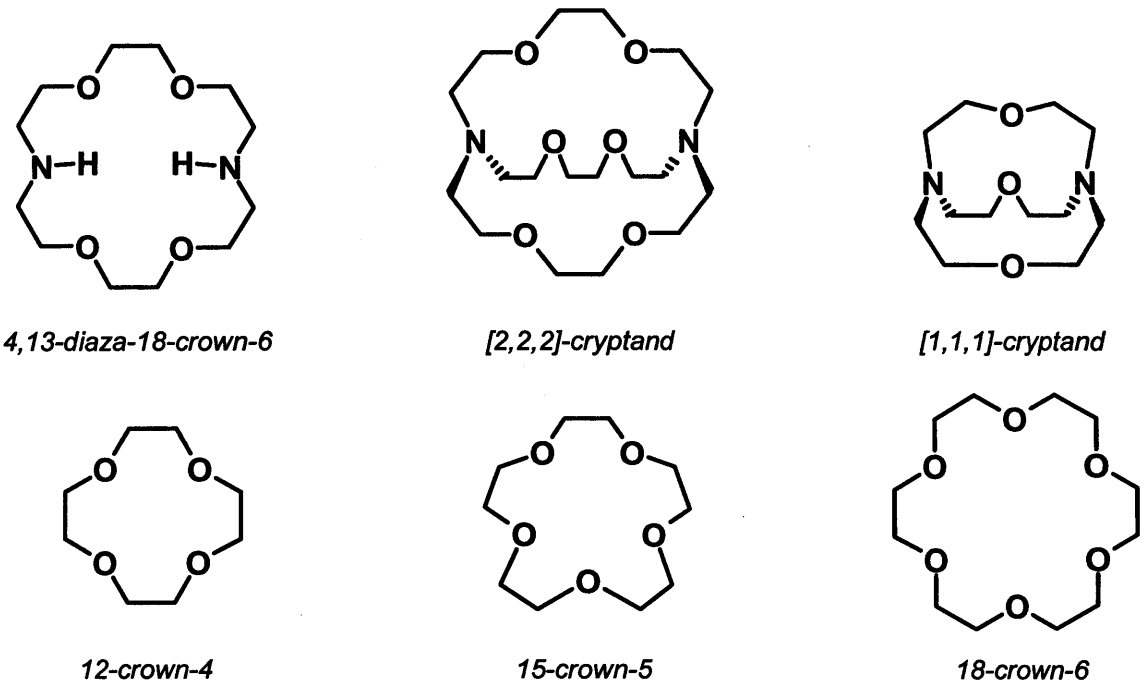
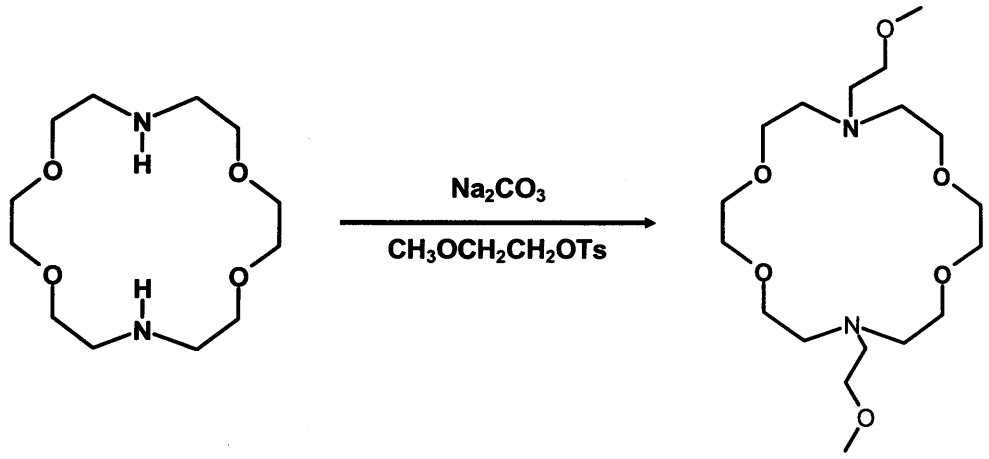


Figure 1.3. Crown Ethers and Cryptands.

Lariat ethers are structures where the macrocycle and the sidearm attached to it can co-operate to bind a cation. This term is commonly applied to any structure having a sidearm, whether it is involved in binding or not. They are readily available by alkylation of azacrown ethers (***Scheme 1.9***). Using the Latin term "*bracchium*" (arm), macrocycles with two arms are called **bib**racchial **l**ariat **e**thers or **BiBLEs**. Similarly, macrocycles with three arms called are **trib**racchial **l**ariat **e**thers or **TriBLEs.**



Scheme 1.9. Synthesis of lariat ethers.

1.3.3. Complexation Activity.

Arguably, the most important property of crown ethers is their ability to form stable complexes with alkali metal ions.[59] Several macrocycles also exhibit complexing ability for a range of other inorganic and organic cations, as well as for a variety of neutral molecules. The types of complexes formed by crown ethers, which contain species incorporated in the macrocyclic cavity, are generally known as *inclusion complexes*. Most inclusion complexes are usually stoichiometric complexes of metallic or organic cations in which the positively charged species interacts with the macrocycle by dipole-dipole or hydrogen bonding interactions.[59,60]

1.3.3.1 *Variables that affect the Complexation Properties of Crown Ethers.*

The most common explanation for the metal cation selectivities of crown ethers in solution is that crown ethers bind metals best when they have similar dimensions to the size of the crown cavity. Therefore, the selectivity of crown ethers has often been described in terms of the size-fit concept. However, different effects that are sometimes equally as important must be taken into consideration.

i) *Solvent Environment.* Among several factors influencing the formation of crown ether complexes in solution, the stability and selectivity depend strongly on the solvating ability of the solvent, not only with respect to the cation, but also to the ligand and the resulting complex.[61] Therefore, the ability of solvent molecules to compete with the donor atoms of the crown ether for the coordination sites of the central cation plays a fundamental role.[62] In solution, during the complexation step, the crown ether must be able to replace the solvent molecules as completely as possible in the first solvation shell of the cation, or *vice versa* if decomplexation is required. This solvation/desolvation process has a significant influence on the stability of the resulting complex in solution.

For example, in aprotic solvents with high solvating abilities, such as DMF or DMSO (with donor numbers of 26.6 and 29.8 respectively), the solvation of the metal cation and probably of the ligand is high and, thus, the stability of the complexes is low. However, the addition of a solvent with relatively low ability to solvate a metal cation, such as MeCN (DN=14.1), increases the stability of the complexes.[63]

In the cases of 18-crown-6 (18C6) and its derivative dibenzo-18-crown-6 (DB18C6), different studies have demonstrated that their selectivity varies considerably with the solvent.[64] For example, in MeCN and propylene carbonate

(PC), the selectivity of DB18C6 for the cation varies in the order: $Na^+ \approx K^+ >> Rb^+ > Cs^+$. In H_2O, MeOH, DMF and DMSO, the selectivity sequence of DB18C6 for the alkali metal ions apparently observes the size-fit model, $Na^+ < K^+ > Rb^+ > Cs^+$. However, the selectivity of DB18C6 with respect to complexation of alkali ions in THF is $Na^+ >> K^+ > Rb^+ > Cs^+ > Li^+$.[65] The solvation power of DB18C6 decreases in the order, MeCN ≈ DMF ≈ $MeNO_2$ > PC >> MeOH >> H_2O, whereas its solubility follows the inverse pattern.

For the potassium cation and its DB18C6 complex, the solvation power decreases as follows:

K^+ ⇒ DMF ≈ DMSO >> H_2O >> MeCN ≈ PC ≈ MeOH >> $MeNO_2$.

$K(DB18C6)^+$ ⇒ DMF ≈ DMSO >> MeCN >> $MeNO_2$ = PC >> MeOH >> H_2O.

The alkali metal ion complexes of DB18C6 are generally more stable in $MeNO_2$ (DN = 2.7) than in other solvents (DMF, DMSO or MeCN). This is mainly attributed to the greater solvation of the alkali metal ion in these solvents than in $MeNO_2$ and its desolvation upon complexation. The $MeNO_2$ molecules compete weakly with DB18C6 during the complexation process, and do not solvate the first coordination sphere of the metal cation entirely due to their weak coordinating properties. This leads to highly stable DB18C6 complexes in $MeNO_2$. The lower complex stability in H_2O or MeOH can be explained by the hydrogen bonding between the solvent and the oxygen atoms of the free DB18C6, reducing their ability for complexation. It can be concluded that the variation of selectivity with the solvent and the stability of the complexes is completely governed by the corresponding variation in solvation of the free alkali metal ions and the crown ether.

ii) *Electronic Substituent Effects.* The main factors influencing the formation of cation-crown ether complexes are the relative sizes of the cavity crown and cation, and the degree of cation solvation. However, several studies with substituted DB18C6 in solution have demonstrated that electronic effects also play an important role in the complexation process.[66] For instance, it has been found that the presence within the crown ether of substituents with electron-withdrawing properties led to the formation of weaker complexes.[67] Therefore, the basicity of the four oxygen atoms in the macrocyclic ring of DB18C6 can be affected by the introduction of electron-withdrawing or electron-donating substituents onto its aromatic rings.

Where the ring frame remains the same, the stabilities of the complexes vary in the order DC18C6>18C6>DB18C6, independent of the solvent used. The presence of two cyclohexyl groups in DC18C6 can inductively enhance the electron density of the ligand ring, increasing the basicity of the oxygen atoms, while the flexibility of the macrocycle remains more or less the same as 18C6. Therefore, it is not surprising to observe the highest stability for the DC18C6 complex among these crowns. On the other hand, the addition of two benzo- groups to 18C6 decreases the stability of the resulting complexes. This behaviour could be due to the combination of the electron-withdrawing effect of benzo groups, which reduces the electron-donating ability of the oxygen atoms of the ring and also reduces the flexibility of the ligand, preventing DB18C6 wrapping itself around the cation.

The strongly electrophilic NO_2 group exemplifies such influence. For instance, comparison of the respective equilibrium constants for complexation of Na^+ ions in DMF at 25 °C reveals that the dinitro-DB18C6 derivative binds Na^+ five times less effectively than the unsubstituted DB18C6. On the other hand, the complexing properties of DB18C6 and of its diamino- derivate are almost identical in DMF. In this case, the enthalpy of complexation is unaffected by this strongly electron-donating substituent. Such anomalous behaviour may, perhaps, be attributed to conformational changes in the macrocyclic ring due to hydrogen-bonding interactions involving the two amino groups.[68]

In addition, for substituted DB18C6, the electronic effects are more significant for the K^+ complexes than for the Na^+. In the K^+ complexes, the metal interacts with all the oxygen donor atoms of DB18C6. Thus, in the case of electron-withdrawing substituents, if electron density is withdrawn from any of the oxygen atoms, the complex will be weakened. In the Na^+ complexes, the smaller metal ion does not simultaneously interact with all the crown oxygen atoms, so if binding to some of the oxygen atoms is weakened by electron-withdrawing substituents the metal can simply shift coordination to a different oxygen atom that is not affected, maintaining strong binding.

The above issues strongly emphasize the combination of factors that affect the stability and selectivity of the crown ether complexes. While the relative sizes of the cation and of the macrocyclic ring play an important role, this is certainly neither exclusive nor always the most important factor in determining the stabilities of the resulting complexes. The relative donor abilities of the oxygen atoms of the

macrocyclic ring as well as the degree of flexibility of the macrocyclic molecule are also of considerable importance. Moreover, the importance of solvent properties is significant. In non-aqueous solutions, not only the solvent–cation, but also the solvent–ligand and solvent–complex interactions are important factors in the complexation reactions.

1.3.3.2 *Picrate Extraction Technique.*

The evaluation of cation binding strengths and dynamics are essential to the understanding of macrocyclic properties. The complexation process has been studied extensively. Numerous approaches have been employed to carry out these studies, but the two most widely applied are the *extraction technique* and the determination of the *stability constants*.

The extraction technique is based on the insolubility of crown ethers in water, and on the insolubility of metal salts in organic solvents. For instance, equal volumes of organic solvent and water may be mixed, but readily form a biphase. Due to its hydrophobic exterior, when the crown ether is added to this system, it partitions into the organic phase. On the other hand, when a salt, such as a picrate, is added to the same system, the picrate dissolves in the aqueous phase.

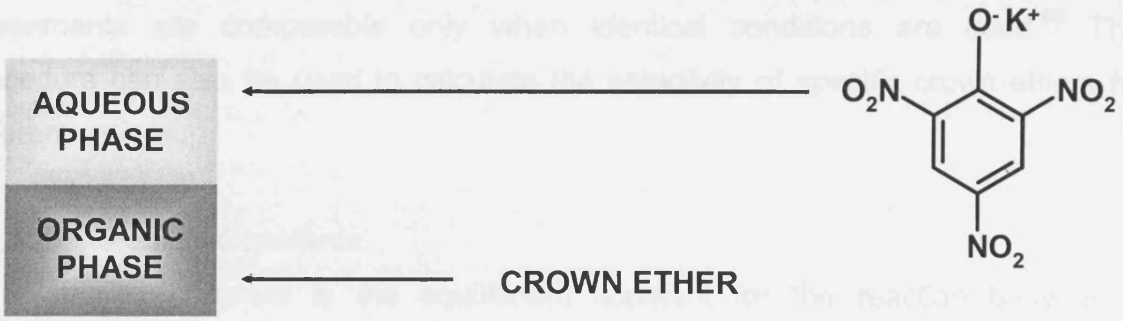


Figure 1.4. Extraction Technique.

Figure 1.4 shows a classic extraction experiment. In a mixture of chloroform and water, the potassium picrate dissolves only in the aqueous phase turning it bright yellow. In the absence of crown ether, even after stirring, the organic phase remains colourless because the picrate does not partition into it. When crown ether is added to the mixture it dissolves in the organic phase, and can then complex the potassium cation at the interface. Since the potassium ion cannot be extracted into the organic phase in the absence of the anion, the picrate also partitions into the organic phase,

becoming yellow. If all the potassium picrate is extracted into the organic phase, the aqueous phase turns colourless.

In a typical experiment, one equivalent of crown ether and one equivalent of potassium picrate are partitioned between equal volumes of chloroform and water. This mixture is then introduced into a stoppered flask and stirred to establish phase equilibrium. The equilibrated mixture is then allowed to stand to allow complete phase separation. The absorbance of the picrate in the aqueous phase is measured using UV-visible Spectroscopy and the concentration of the picrate is determined from its absorbance peak in the UV-visible spectrum at approximately 356 nm. The percentage of potassium extracted (*Extraction constant*) is calculated by:

$$\% \text{ Extraction (\%Ext.)} = [100 \times (A_0 - A_1)] / A_0$$

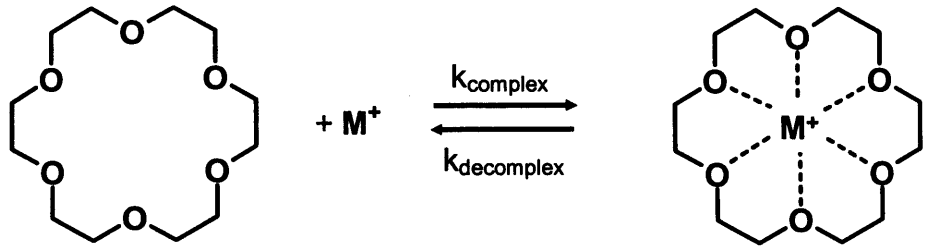
Equation 1.2.

where A_1 is the absorbance of a mixture sample with crown ether in the organic phase and A_0 is the absorbance of an equal mixture sample without crown ether in the organic phase.

The identity of the two solvents chosen, the solvent volumes, temperature and other variables affect the extraction constants. Consequently, the results of different experiments are comparable only when identical conditions are used.[69] This procedure can also be used to calculate the selectivity of specific crown ethers for different cations.

1.3.3.3 *Stability Constants.*

A stability constant is the equilibrium constant for the reaction between a macrocycle and a cation (***Scheme 1.10***). The stability or binding constants are expressed as log K_S, where K_S is the position of this equilibrium. It is the ratio of the rates for the forward (k_f or $k_{complex}$) and reverse (k_r or $k_{decomplex}$) reactions. Therefore, $K_S = k_{complex} / k_{decomplex}$. Calorimetry methods, nuclear magnetic resonance spectroscopy and the use of ion selective electrodes are the most important and most useful methods to determine stability constants.[70]



Scheme 1.10. Cation complexation equilibrium for 18-crown-6 and a metal cation (M^+).

Stability constants differ from extraction constants in that both ligand and salt are present in the same medium simultaneously. Chloride is commonly used as the anion, and methanol is the most common solvent used to carry out these studies, although the solvent selected depends on the solubility of the ligand, the technique used and the value of the binding constant in this solvent.

1.3.3.4 *Generation of Free Crown Ethers from Their Metal Complexes.*

The release of a macrocycle from its coordinated metal ion is a common process in macrocyclic ligand synthesis. This can be achieved by a variety of methods. For instance, the addition of excess acid leads to demetallation of complexes of azacrown ethers; the acid protonates the amine, releasing the metal ion and generating the macrocycle as its *N*-protonated form.

Demetallation may be induced by addition of a strongly competing ligand to a solution of the macrocyclic complex. For example, when sulphide or hydroxide ions are used as the scavenging ligands, the metal can be removed as an insoluble precipitate salt leaving the metal-free macrocycle in solution. Sometimes, the template ion is only weakly coordinated and the demetallation can be induced just by dissolution of the complex in a coordinating solvent or even water, in which the free macrocycle has reduced solubility.[71]

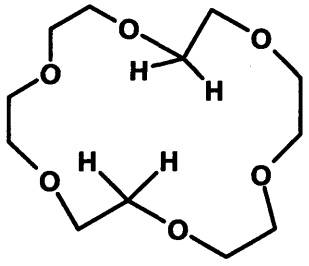
Redox reactions (usually a reduction) can also be useful. This is often the case when the metal ion oxidation state is kinetically inert [Co(III) or Cr(III)]. In these cases, reduction of the metal ion to a lower oxidation state leads to its spontaneous dissociation from the macrocycle.

1.3.4 Structural Aspects of Crown Ethers and their Complexes.

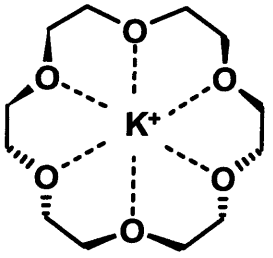
1.3.4.1 *Structure of Uncomplexed Crown Ethers.*

In general, it can be assumed that uncomplexed macrocycles cannot adopt a symmetrical conformation, with all the donors atoms turned inward, because it is energetically unfavourable. Instead, the macrocycles adopt conformations in which the space is filled by methylene groups or hydrogen atoms. Some relevant 18-membered crown ethers are discussed below.

- *18-membered macrocycles.* ***Figure 1.5*** shows schematically the crystal structure of 18-crown-6 (***1***). When a cation occupies the cavity, the methylene groups in the central space rotate outward, creating the cavity (***2***).[72]



uncomplexed 18-crown-6 (***1***)

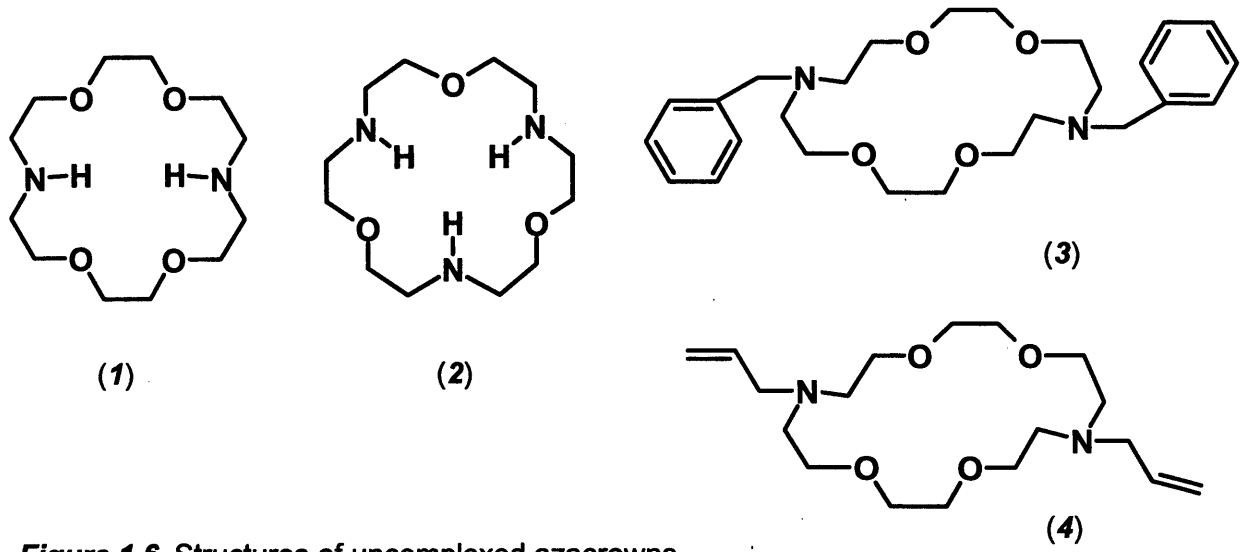


complexed 18-crown-6 (***2***)

Figure 1.5. Crystal Structure of 18-crown-6.

This rotation of the methylene groups inward in order to stabilize the structure is characteristic of uncomplexed crown ethers, and has also been observed for dibenzo-18-crown-6 and dicyclohexane-18-crown-6.[73]

- *18-membered aza macrocycles.* In these types of macrocycles the N-H bonds are orientated inwards, filling the cavity, and therefore no inward rotation of the methylene group is required to stabilise the structure. Diaza-18-crown-6 (**1**) and triaza-18-crown-6 (**2**) adopt the D_{3d} conformation in the free state (see ***Figure 1.6***). The scheme also shows the schematic structures of *N,N´*-dibenzyl-4,13-diaza-18-crown-6 (**3**) and *N,N´-bis*(allyl)-4,13-diaza-18-crown-6 (**4**).[74]



(*1*) (*2*) (*3*) (*4*)

Figure 1.6. Structures of uncomplexed azacrowns.

1.3.4.2 *Structure of Complexed Crown Ethers.*

Crown ethers can not only form complexes with cations that fit their cavity sizes (for example, 18-crown-6 complexed with potassium or sodium) or cations that are larger than their cavities (for example, 15-crown-5 ether type structure complexed with cesium cation) via "*sandwich*" type structures,[75] in which the cation lies between the two crown ligands, but also with cations smaller than their cavities. They do so either by constricting their cavities or, in a few cases, complexing more than one cation. Another important concept to consider is that in flexible systems such as crown ethers, cations have little preference for one cavity side over another. Furthermore, some studies have shown that due to this flexibility, the cation sometimes is not necessarily complexed within the macroring, and the counterion may not be in the solvation sphere at all if the crown itself provides sufficient donor groups.[74]

Figure 1.7 shows the general structure of Na^+ and K^+ complexes of diaza crown ethers with donor sidearms.[76] These sidearms can stabilise the cation from the same side (*syn*) or from the opposite side (*anti*). If the sidearm is $-CH_2CH_2OH$, the observed structure is always *syn,* regardless of the cation. If the cation is Na^+ and the sidearm is $-CH_2CH_2OCH_3$, the conformation is also *syn*. On the other hand, with the same sidearm, if the cation is the bigger K^+ the conformation is *anti*. This is because the sidearms of K^+ complexes are too sterically crowded when they are on the same side.[77]

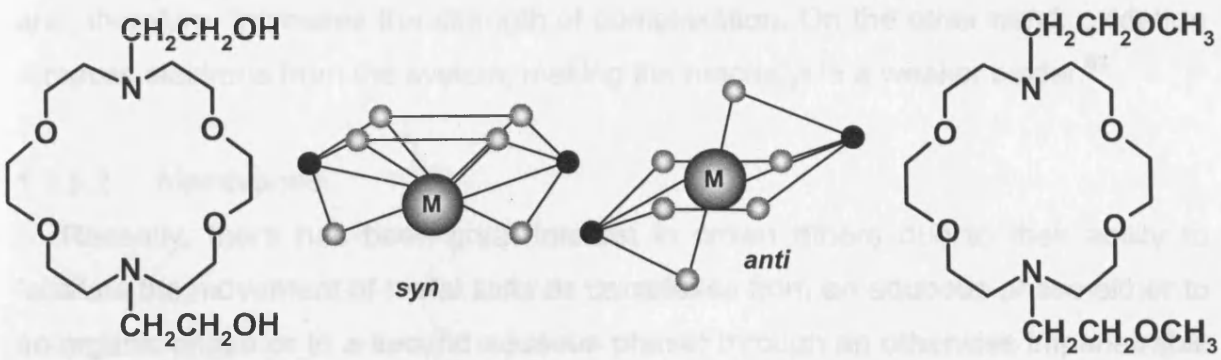


Figure 1.7. Structure of Complexed diaza-BiBLEs.

1.3.5 Applications of Crown Ethers.

Since Pedersen discovered crown ethers nearly forty years ago, the number of their applications has vastly increased. Some of the many uses are briefly discussed below.

1.3.5.1 *Sensors and Switching.*

The ability of crown ethers to complex a wide range of species is their most significant application, but by no means the only one. Based on their remarkable complexation capability, the use of crown ethers as detectors of cations and other species has been developed. This approach consists of altering the complexation macrocycle properties by a switching mechanism. The principal switching techniques are:

- *pH-Switching*. The charge state of the compound is altered by modification of the pH. An important characteristic of this switching technique is that complexation may alter the properties of the donor system.[78]
- *Photochemical Control*. This approach involves the use of a "receptor" in the macrocycle to absorb the light and undergo a structural modification as a result.[43]
- *Thermal Switching*. Uses a variation of the temperature to displace the equilibrium of complexation. [79]
- *Redox Switching*. This technique is based on the principle that a compound existing in one form can be converted, by an electron transfer process, into another form. This change involves an alteration in the binding strength by changing the electron density. For example, the reduction of a system makes it more electron-rich

and, therefore, increases the strength of complexation. On the other hand, oxidation removes electrons from the system, making the macrocycle a weaker binder.[80]

1.3.5.2 *Membranes.*

Recently, there has been great interest in crown ethers due to their ability to facilitate the movement of metal salts as complexes from an aqueous phase either to an organic phase or to a second aqueous phase, through an otherwise impenetrable organic phase called a "membrane".[81] Most of the investigations in this field try to mimic the participation of crown ethers in natural processes.[82] Indeed, many studies involving crown ethers and related ligands have been performed that mimic the ion-transport behaviour of the natural antibiotic carriers across natural membranes.[83]

There are three conditions that affect the transport of cations across membranes.

- Strong binding at the source phase.
- Cation strongly bound within the membrane.
- Weak binding at the receiving phase.

A schematic diagram of the membrane system is presented in ***Figure 1.8***.

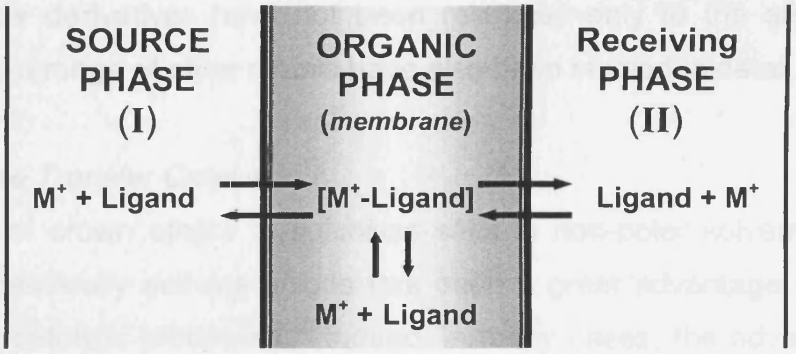


Figure 1.8. Membrane System.

A typical system is of the type water-phase (I) / organic-phase (*dichloromethane or another organic solvent*) / water-phase (II). The metal ion is added to water-phase (I) and the crown ether to the organic phase (the liquid "membrane"). The crown acts as a carrier for the metal ion from water-phase (I) across the liquid "membrane" phase into water-phase (II). Because the metal ion has to be taken from the water-phase (I) / organic-phase interface and released at the organic phase / water-phase (II) interface, the best carrier for this type of ion transport is a crown ether that only forms a moderately stable complex.[84] During the transition through the hydrophobic

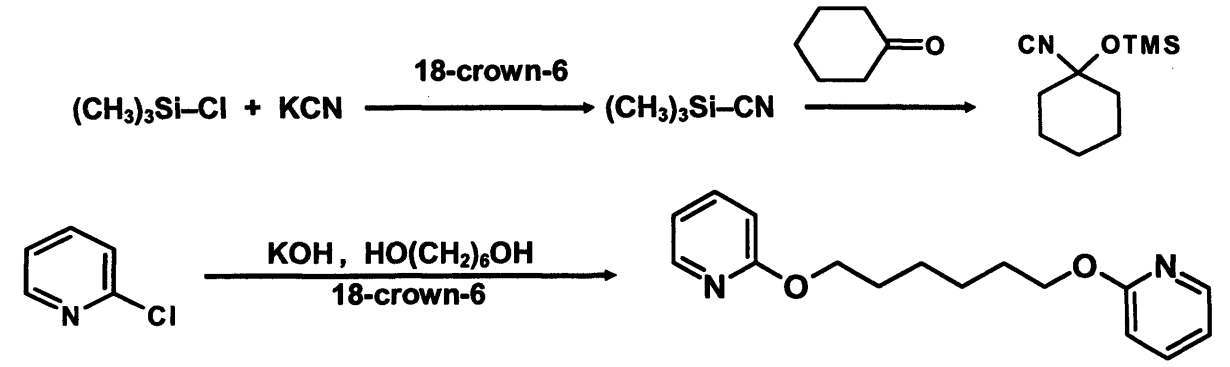
liquid "membrane", a counter-ion must accompany the complexed cation in order to maintain electrical neutrality. Therefore, the nature of the anion has a large effect on the cation transport between phases.[85] Others factors that influence the rate of metal-ion transport across artificial membranes are the complexation strength, concentration of the metal ion in the source phase and lipophilicity of the crown ether.[86] To improve the transport across membranes it is necessary to alternate between strong and weak binding. This switch between binding strengths is based on the switching techniques described previously.

Lamb and co-workers have shown that cation transport selectivities for single cation transport membranes, coincides with the stability constant (log K_S) selectivities for the cation-macrocycle complexation reaction.[87] The log K_S values are related to, among others factors, the match in size of the cation and the macrocycle cavity. Therefore, in single cation transport experiments, the cations that fit best into the cavity of the crown ether are usually transported faster. The exception to this general rule occurs when the stability constant of the cation is so high that release of the cation from the membrane to the receiving phase is inhibited.[88]

It should be noted that selective membrane transport experiments involving crown ethers and their derivatives have not been restricted only to the alkali metals or alkaline earths; a range of other metals have also been studied in detail.[89]

1.3.5.3 *Phase Transfer Catalysts.*

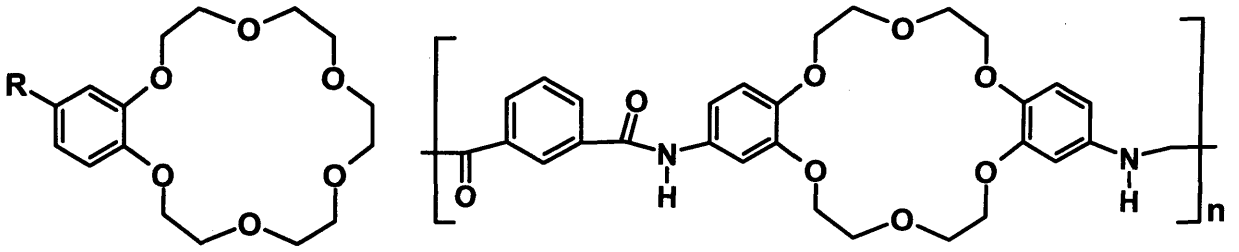
The ability of crown ethers to solubilize salts in non-polar solvents, deactivate cations and specifically activate anions has been a great advantage in developing phase transfer catalytic processes.[90] Indeed, in many cases, the advance of phase transfer techniques has been parallel to the development of crown ether chemistry. A few examples of crown ethers as phase transfer catalysts are illustrated in ***Scheme 1.11***.[91] There are many other applications of crown ethers, which will not be discussed here, including analytical chemistry,[92] synthesis of chiral macrocycles,[93] synthesis of enzymes,[94] synthesis of receptor and sensor molecules[95] and biomimetic science.[96] However, crown ethers are still relatively expensive to be used widely in the chemical industry. Since the main aim of the work presented in this thesis was to synthesised novel, recyclable crown ethers for phase transfer catalysis, a review on phase transfer catalysis is presented below (Section 1.4).



Scheme 1.11. Crown Ethers as Phase Transfer Catalysts.

1.3.5.4 *Polymer-supported Crown Ethers.*

Polymer-supported crown ethers are effective catalysts for phase transfer reactions.[97] They are easily separated and reused and find a wide range of applications,[98] making them potentially applicable to many industrial chemical processes. A large number of polymer-supported crown ethers have been prepared and studied.[99] Various examples are illustrated in ***Figure 1.9.***



R = $(\text{-CH-CH}_2\text{-})_n$ or $(\text{-CH}_2\text{-CH-})_n\text{COO}$

Figure 1.9. Polymer-supported crown ethers.

An important drawback of polymer-supported crown ethers is that their activity is often substantially lower than the analogous soluble phase transfer catalyst, because diffusional processes limit reaction rates. In order to solve this difficulty and improve the catalytic activity of polystyrene-supported crown ethers, a donor spacer group can be introduced between the catalyst centre and the polymer support. These products have shown high catalytic activity due to the cooperative action of the crown ether and the adjacent donor groups of the sidearm.[100]

1.4 Phase Transfer Catalysis.

1.4.1. Introduction.

Organic synthesis is the principal way to produce chemical products for widespread daily applications. Transformations of starting materials into desired final products normally require a number of chemical operations in which additional reagents, catalysts and solvents are involved. Therefore, during synthesis waste materials are normally obtained because these transformations are generally neither quantitative nor selective processes. It is important for the chemical industry to develop and use new synthetic methodologies that solve, or at least minimize, this problem.

Phase transfer catalysis (PTC) can improve process efficiency, safety and reduce environmental impact.[101] PTC is applicable to a wide variety of reactions in which inorganic and organic anions react with organic substrates. This methodology, developed in the 1970's, is based on a heterogeneous two-phase system in which the organic reactants and catalyst are located in the organic phase, whereas the reacting anions are in the non-organic second phase (*solid or aqueous*).

In PTC, the catalyst, also called the phase transfer agent, is a shuttling agent that transfers the anion from the non-organic phase (aqueous or solid) into the organic phase. The anion can then react with the organic reactant already situated in the organic phase. The reacting anions are continuously transferred into the organic phase as lipophilic ion pairs with lipophilic cations supplied by the catalyst.[102] Since both phases are mutually immiscible, the reaction does not take place unless the catalyst is present. At the end of the reaction, an anionic leaving group is usually generated in the organic phase. This anionic group is conveniently transferred into the non-organic phase by the catalyst.

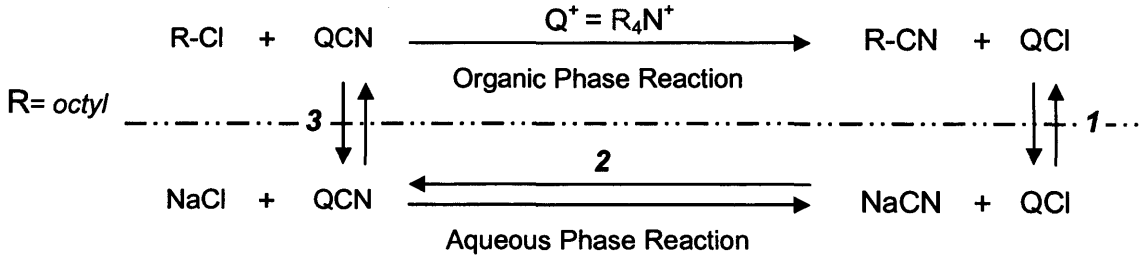
This technology is involved in the commercial manufacture of millions of pounds worth of chemicals per year, such as monomers, polymers, agricultural chemicals, pharmaceuticals, additives, flavourings, fragrances, dyes, explosives, surfactants, petrochemicals and rubber. PTC is involved in more than 600 industrial applications, and more than 1700 patents and 8000 publications on PTC have been published.[103] The application of PTC, instead of traditional technologies for industrial processes for organic synthesis not only provides important advantages to these processes, but can also benefit the environment.

Most publications and patents in relation to PTC refer to reactions involving transfer of anions from an aqueous or solid phase into an organic phase, simply because this is the requirement of the most practical PTC organic reactions. However, this concept is also applicable to the transfer of whole molecules, cations, free radicals, or other species.

Phase transfer catalytic reactions often provide higher yields, lower reaction temperature, and shorter reaction times than non-PTC reactions. This is due to several reasons that are generally related to the higher selectivity (minimizing side reactions). Higher selectivity results from allowing the phase transfer catalyst to regulate the reaction between the reactants located in a "common phase" (after phase transferring) in a controlled solvation environment and in a controlled concentration of the reactant being transferred.[104, 105] Due to the efficiency of transfer and reaction of anions in PTC systems, it is often possible to reduce the excess of reactant used and the amount of non-desired material produced, minimizing the environmental impact of the reaction.

Phase transfer catalysis offers many advantages as a process technology, though it also has some drawbacks. The most important limitation of PTC technology relates to the catalyst. The need to separate the catalyst from the desired product, treatment or recycle of the recovered catalyst, catalyst decomposition and its cost and toxicity, are the most important handicaps of PTC.[106]

1.4.2. Mechanism of Phase Transfer Catalysis.



Scheme 1.12. Schematic representation of phase transfer-catalysed cyanide displacement in 1-chlorooctane.

Scheme 1.12 exemplifies the liquid-liquid PTC mechanism, which is also called the "extraction mechanism".[107] Since 1-chlorooctane forms a separate phase from the aqueous sodium cyanide, the only location where the reagents can interact is at

the interfacial region. Therefore, in order to transfer the cyanide ion (nucleophile) into the organic phase, the associated cation must be more organophilic than sodium ion. Without a catalyst, heating of this two-phase mixture under reflux and stirring for one or two days gives no apparent reaction. However, if 1 wt% of an appropriate quaternary ammonium or phosphonium salt substituted with organophilic alkyl and/or aryl groups (Q^+ = *phase transfer catalyst*) is added, then the displacement reaction occurs rapidly, producing 1-cyanooctane in nearly 100% conversion in 2-3 h. The quaternary ammonium cation (Q^+) transfers the cyanide (CN^-) anion (nucleophile) into the organic phase, activates the transferred cyanide for reaction with 1-chlorooctane (RCl), and allows displacement to occur rapidly, producing 1-cyanooctane (R-CN) and QCl, then transfers the displaced chloride anion back to the aqueous phase to start a new catalytic cycle.[108]

Considering the PTC mechanism outlined in ***Scheme 1.12***, two general steps can be identified in this catalytic cycle.

Transfer step. The sequence of reactions that cause cyanide to be transferred into the organic phase, called the transfer step, is represented by three equilibria that (***1***) transfer quaternary ammonium chloride from the organic to the aqueous phase, (***2***) exchange chloride for cyanide anion in the aqueous phase, and (***3***) transfer quaternary ammonium cyanide from the aqueous to organic phase. It is important to remember that the transfer rate of interest is the net rate of delivery of cyanide to the organic phase. It is not simply the rate of the physical process of taking the cyanide across from the aqueous to the organic phase.

Organic phase reaction. The reaction or sequence of reactions in the organic phase, starting with the transferred anion that results in the formation of the product is called the intrinsic reaction or more commonly, the organic phase reaction. In ***Scheme 1.12***, this step consists only of the displacement reaction between the quaternary ammonium cyanide (QCN) and 1-chlorooctane (R-Cl) to produce 1-cyanooctane (R-CN). In other reactions, the intrinsic organic phase reaction may consist of more than one chemical reaction. A good PTC process is based on high rates for both steps. The kinetics of both steps is also closely interrelated to the nature of catalyst.

The other major type of PTC is solid-liquid phase transfer catalysis. This represents a heterogeneous PTC reaction processes involving a liquid organic phase and a solid salt phase. In general, crown ethers, as well as quaternary ammonium

salts, have been found to be very efficient catalysts for solid-liquid PTC processes. It should be emphasized that there are a variety of mechanistic schemes found in the literature,[109] however these are variations on the extraction mechanism outlined in ***Scheme 1.12***. Nevertheless, the fundamental principles governing them are consistent with ***Scheme 1.12***. The first step involves the transport of the reactant anion from the solid phase to the organic phase by a phase transfer cation. This could be an organophilic quaternary cation or an organophilic cation derived from the complexation of a metal cation with a multidentate ligand, such as crown ether or cryptand. The second step is the reaction of the transferred anion with the reactant in the organic phase. Finally, the third step involves the transport of the product anion by the phase transfer cation to the solid phase and the transport of another reactant anion into the organic phase.

It has been demonstrated that a small quantity of water added is often necessary in order to facilitate the so called solid-liquid PTC.[109] For instance, in the reaction of benzyl halide with solid potassium cyanide in toluene using 18-crown-6 as PT catalyst, it was found that adding a very small quantity of water to the system the reaction rate was significantly improved. By adding water, the crown was translocated from the toluene phase onto the surface of the suspended salt. It was postulated that the initial water added to the salt-toluene system coats the surface of the salt particles to form a third phase consisting of water, "dissolved" salt, and toluene. It is this third phase, called "the omega phase", which extracts the crown ether from the toluene phase.[109]

1.4.3. Phase Transfer Catalysis Variables.

Phase transfer catalysis reactions can be influenced by a number of variables, the most important of which are outlined below.

- *Catalyst structure.* The selection of the appropriate catalyst is the most important step in the design of a phase transfer process. This must have two particular chemical features: it must be an efficient transfer agent, and it must make the transferred species available in a highly reactive form.[110]
- *Agitation.* This factor can simplify the transfer between phases, increasing the interfacial area between the organic and the aqueous phases. This makes the transfer of the reactants faster.[109]

- *Inorganic reagent.* The type of anion transferred from the non-organic phase (aqueous or solid) into the organic phase and its concentration in this phase are important factors to consider. For example, in the case of macrocyclic polyethers,[111] which can transfer inorganic compounds as solids, it is better to add no water or just the minimum amount required because the presence of too much water can affect their complexation capabilities.[112]
- *Organic solvent.* The PTC reactions can be carried out without organic solvent.[113] This advantageous characteristic can contribute to improved product purity and yield, and also avoid the use of environmentally hazardous solvents.[114] On the other hand, sometimes the presence of a solvent is important. For example, a polar solvent could be necessary to obtain an appropriate rate of anion transfer to the organic phase.[115] Occasionally, the participation of solvent in the reaction is necessary because the organic reagent is an unreactive solid under the reaction conditions.
- *Temperature.* Increasing the temperature can accelerate markedly the PTC organic reactions, especially in PTC reactions with slow organic phase rates. Heating with microwave radiation can also accelerate the reaction. This radiation can transfer energy specifically to water. In these cases, there is an increase in the anion reactivity due to the dissociation of water from these anions facilitated by the microwave radiation.[116]
- *Cocatalysts.* Sometimes the participation of a cocatalyst is necessary to increase the ratio of the transfer step or the ratio of the organic phase reaction. This can also minimise or even avoid the presence of side reactions.

There are many other significant factors that affect the mass transfer and distribution of the PT catalyst anion-cation pair between the organic and aqueous phases, including:

- The combination of the charge-volume ratio, the polarizability and the anion structure,[117]
- The hydrophilic-organophilic balance of the associated cation,[118]
- The polarity of the organic phase,[119]
- The hydration of the anion,[109]
- Ion pair-free ion equilibrium,[120]

1.4.4. Phase Transfer Catalysts.

As the pharmaceutical industry strives to increase efficiency, improve process safety, and reduce environmental impact, phase transfer catalysis has become recognized as a useful tool for achieving these goals.

Soluble PTC Catalysts

Organic –Soluble catalysts

- Onium Salts, N, P, As, S.
- Crown Ethers, cryptands.
- Soluble polymers.
  - Polyethylene glycols and derivates.
  - Other polymers containing dipolar aprotic groups.

Aqueous –Soluble catalysts

- "Inverse PTC" Catalysts.
- Cyclodextrins.

Insoluble Catalysts

- Resin-bound.
- Inorganic Solid-bound.
- Third-Liquid Phase.

Figure 1.10. General outline of types of PT catalysts.[109]

The diagram in ***Figure 1.10*** presents a general outline of several categories of PTC catalysts.[121] Several types of compounds have been shown to have at least some activity as soluble phase-transfer catalysts. Most practical work has centred on the types listed and this includes compounds that are readily available commercially, usually at low cost.

The unique ability of quaternary ammonium and phosphonium salts to dissolve in both aqueous and organic liquids have made these compounds the catalyst of choice for the majority of PTC applications, from displacement reactions to transition metal co-catalysis. For instance, for PTC processes involving relatively soft anionic reagents, such as cyanide or acetate, the most effective quaternary salts are those that contain organophilic alkyl or aryl substituents, which substantially separate the cationic centre (the positively charged nitrogen) from the anionic centre of the nucleophilic reagent. In contrast, for PTC processes involving hard anions, such as hydroxide ion promoted C- and N-alkylation reactions, quaternary salts which have

organophilic character but which have at least one alkyl substituent and allows the anion (hydroxide ion) to approach close to the centre of positive charge are usually the most effective. During the past years a wide range of this type of PT catalysts has been developed, becoming commercially available from many different sources.

Sometimes it is desirable for a catalyst to have a special property. For example, a high-temperature (> 150 °C) stable catalyst, like crown ethers, is useful for displacement reactions on activated aromatic compounds under solid-liquid conditions. Chiral compounds can also be synthesised from optically inactive starting materials using chiral phase transfer catalysts.[122]

1.4.5. Separation and Recovery of Phase Transfer Catalysts.

The most frequent technical difficulty found during a PTC process is the need to separate the desired product from the phase transfer catalyst. Quaternary ammonium salts, which are widely used in the pharmaceutical industry, are easily separated by aqueous phase extraction or by extracting with diluted sodium hydroxide solution, but are normally disposed of as aqueous waste. Polyethylene glycols can also be easily extracted into water, but there are environmental concerns about the waste disposal of such large amounts of phase transfer catalysts on a commercial scale every year.

In order to make the catalyst more suitable for industrial use, the catalyst should be recyclable. The most commonly used methods for separation and recovery of soluble phase transfer catalysts on an industrial scale are extraction and distillation, although sorption on ion exchange resins[123] or silica gel[124] are also frequently utilised. When the product has a relatively low boiling point it can be distilled away from the phase transfer catalyst, as, for example, in the industrial manufacturing of Neoprene by DuPont Dow. However, the separation by distillation has several disadvantages. For example, quaternary ammonium salts decompose at high temperature (> 100 °C), moreover, although the distilled catalyst may be reused, sometimes the number of byproducts and other residual materials make the recycling very difficult and not cost efficient. In addition with the possible instability of the catalyst at high temperature or under acidic/basic conditions, these separation steps usually require extra process unit, and therefore, increase the manufacturing costs.

This problem can be avoided by using insoluble catalysts, which can be easily separated by filtration, centrifugation or phase separation. The term insoluble catalyst

includes both solid (where the PTC function is bound to an insoluble polymeric resin or an inorganic solid)[125] and liquid catalyst (where the PTC catalyst is predominately located in a third-liquid phase).[126] All common phase transfer catalysts such as quaternary ammonium and phosphonium groups, cryptands or polyethylene glycol (PEG) can be bound to a resin to form the equivalent supported PT catalyst. Certainly, quaternary ammonium salts adsorbed on organophilic clays are the most used and the least expensive resin-bound phase transfer catalysts. In addition, the advantages of insoluble catalysts and the efficiency of the crown ethers as solid-liquid phase-transfer catalysts has been combined using resin-bound crown ethers as phase transfer catalysts (Section 1.3.5.3). Furthermore, these insoluble catalysts, together with resin-bound PEGs, have been recycled repeatedly in laboratory reactions with only slight loss of activity.[109] However, the most promising recyclable system is the so call third-liquid phase, where the catalyst is neither in the organic or the aqueous phase, but in a third layer that can be easily separated and reused. For example, quaternarium ammonium salts can form three-phases systems when used with non-polar organic solvents and concentrate aqueous solution of inorganic salts. Additionally, third-liquid systems can achieve higher reaction rates than insoluble or even soluble catalysts. However, these systems are not yet industrially used because it is very difficult to find the right conditions to obtain a third-liquid system where the catalyst does not leach in to the organic or aqueous phases.

Despite the evident advantages of insoluble PT catalysts, they still have limitations such as decreasing the rate of the organic reaction and, overall, the cost. Besides, solid insoluble PT catalysts generally require high physical and chemical stability necessary to be reused for long cycles as well as longer reaction times.[127] These problems restrict the industrial uses of insoluble phase transfer catalysts.

1.4.6. Conclusions.

Phase transfer catalysis has delivered exceptional results in cost-effective and environmentally acceptable commercial manufacturing processes for a wide range of products and industries. It represents an important advance in heterogeneous and homogeneous reaction processes. Phase transfer catalysis delivers high productivity, enhances environmental control and improves safety and product quality. PTC increases industrial operability in hundreds of commercial manufacturing processes for organic chemicals in several reaction categories. However, in certain cases, the

difficult separation of the catalyst from the organic product can reduce the effectiveness of this technique. Therefore, it is necessary to develop new catalysts that can be easily recycled and reused.

1.5 Outline of Research.

Phase transfer catalysis has demonstrated to be a powerful tool for the chemical industry, because it increases the rate of reaction, product selectivity, and yield while lowering the energy requirements. The main disadvantage, however, is that the phase transfer catalyst is not normally recovered and is disposed of as waste. This problem has been overcome by the use of insoluble phase-transfer catalysts that are bound to either an insoluble resin or an insoluble inorganic support. Although insoluble phase transfer (PT) catalysts offer easy separation from the organic product and the potential to recycle, the reactions are much slower compared to using the analogous conventional soluble PT catalysts. In addition, the cost of the resin-bound PT catalyst is usually prohibitively expensive, and solid insoluble PTC catalysts are not normally robust enough to survive repeated long-term use in industrial-scale reactors.

Fluorous separation techniques have advanced significantly over the past decade and reagents/catalysts containing long perfluoroalkyl groups can now be recovered, recycled, and reused without the need to use expensive and environmentally persistent fluorous solvents. Although fluorous solid phase extraction was originally designed for high throughput organic synthesis, recent work has demonstrated that it can also be used to recycle conventional homogeneous catalysts. With the use of the "light fluorous" approach, reactions with "lightly" fluorinated catalysts can be carried out homogeneously in conventional organic solvents and potentially recovered by fluorous solid phase extraction.

The work presented in this thesis describes the synthesis and applications of a range of "light fluorous" 4,13-diaza-18-crown-6 and dibenzo-18-crown-6 derivatives. **Chapter 2** focuses on the synthesis of partially fluorinated diaza-crown ethers, as well as preliminary separation and recovery studies. **Chapter 3** focuses on the phase transfer catalytic applications of the partially fluorinated diaza-crown ethers. Their catalytic activities are evaluated in the iodide displacement reaction of 1-bromooctane and in the fluoride displacement reaction of 2,4-dinitrochlorobenzene.

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In addition, this chapter discusses the recovery and reuse of "light fluorous" 4,13-diaza-18-crown-6 derivatives using FSPE and SPE.

Chapter 4 describes the synthesis of a series of partially fluorinated dibenzo-crown ethers using different approaches. Their potential recyclability is also investigated. **Chapter 5** discusses the phase transfer catalytic applications of "light" fluorinated dibenzo-crown ethers. Their catalytic activities are examined in the iodide displacement reaction of 1-bromooctane and in the fluoride displacement reaction of 2,4-dinitrochlorobenzene and compared with the ones obtained by partially fluorinated diaza-crown ethers (**Chapter 3**). In addition, this chapter examines the recovery and reuse of partially fluorinated dibenzo-18-crown-6 derivatives using FSPE, SPE, SFPC and thermomorphic catalysis.

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CHAPTER TWO

Synthesis of Partially Fluorinated 4,13-Diaza-18-crown-6 Ethers

University *of*
Leicester

2.1 Introduction.

2.1.1 Diaza-crown Ethers.

The recognition of the biological role of sodium, potassium, magnesium and calcium cations has been one of the main factors that has caused the development of crown ether chemistry during recent years. Another important factor is the discovery of natural macrocyclic antibiotics, which are capable of forming complexes and transporting alkali metal cations.[1] Diaza-crown ethers represent a significant variety of these macrocyclic compounds because their complexing properties are similar to those of several biological systems.[2] In addition, diaza-crown derivatives and cryptands formed from diaza-crown ethers can be attached to synthetic polymers[3] or silica gel.[4]

These types of crown ethers are important intermediates in the synthesis of cryptands and other *N*-substituted ligands.[5] Diaza-18-crown-6 ethers with two *N*-substituents have proven to be an interesting group of compounds both in terms of their cation binding strengths and selectivities. Gokel and co-workers showed that when sidearms are attached to a nitrogen atom rather than carbon, the crown ether is relatively more flexible and exhibits more dynamic complexing properties. Furthermore, if the sidearms attached to the nitrogen atoms contain donor groups, these contribute more to the cation binding than in the case of *carbon-pivot* crown ethers. These structures exhibit a three-dimensional binding due to the cooperation of sidearms in the complexation of the cation and, at the same time, retain flexibility and binding dynamics (***Figure 2.1***).[6]

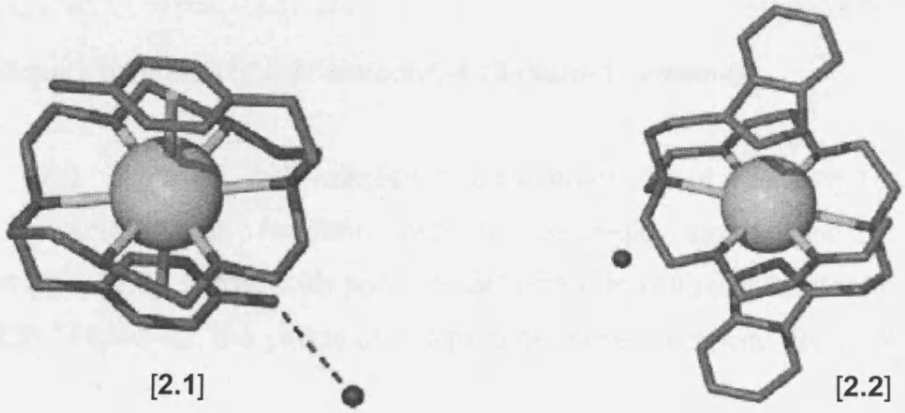
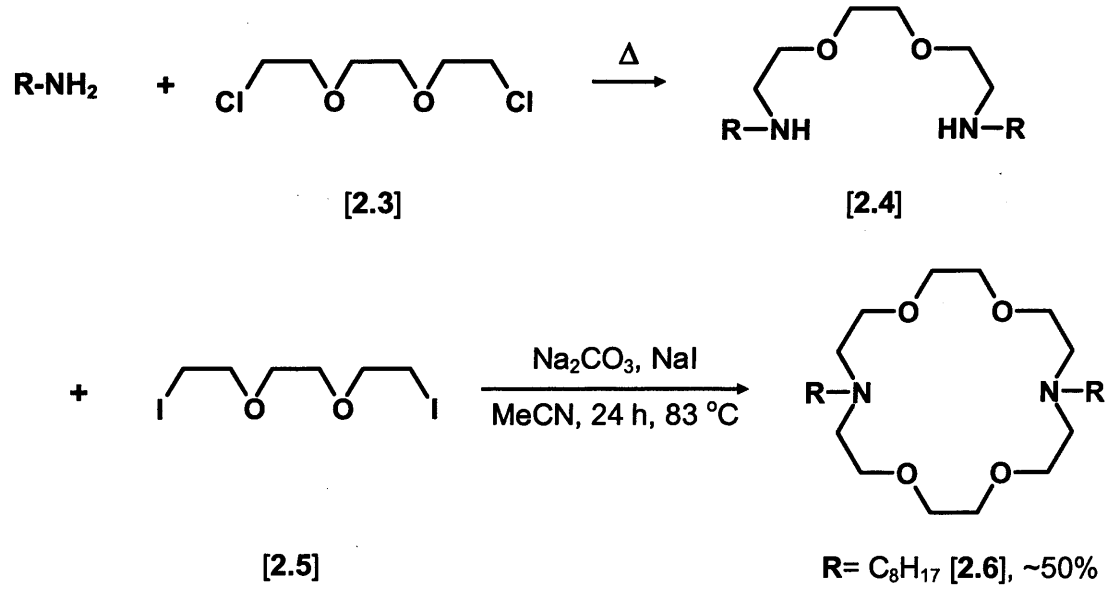


Figure 2.1. Potassium (KI) complexes of *N,N'*-bis(2-(4-hydroxyphenyl)ethyl)-4,13-diaza-18-crown-6 (left) and *N,N'*-bis(2-(3-indolylethyl))-4,13-diaza-18-crown-6 (right) with cation-π interactions with the sidearms.

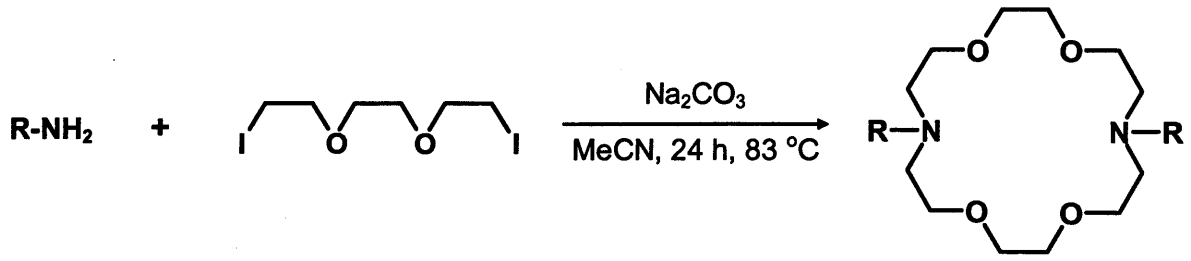
Besides alkali metals and alkaline earth metals, diaza-18-crown-6 ethers offer a unique possibility to create a specific ligand for heavy metal cations, such as copper (I) or silver (I), with the aid of cavity size and the presence of heteroatoms in the ring.[7]

Recently, *N,N'*-bis(alkyl)-4,13-diaza-18-crown-6 ethers have been prepared using different methods. For instance, Gokel and co-workers developed a two step procedure by alkylation of primary amines followed by cyclization with 1,2-bis(2-iodoethoxy)ethane in the presence of sodium carbonate and sodium iodide in refluxing acetonitrile (***Scheme 2.1***).[8] In the initial stages of the reaction, the sodium cation (NaI) acts as a template helping in the cyclization reaction, which involves the formation of two new C-N bonds and an 18-membered ring. Using this method, the sidearms are incorporated prior to cyclization.



Scheme 2.1. Gokel's synthesis of *N,N'*-bis(octyl)-4,13-diaza-18-crown-6.

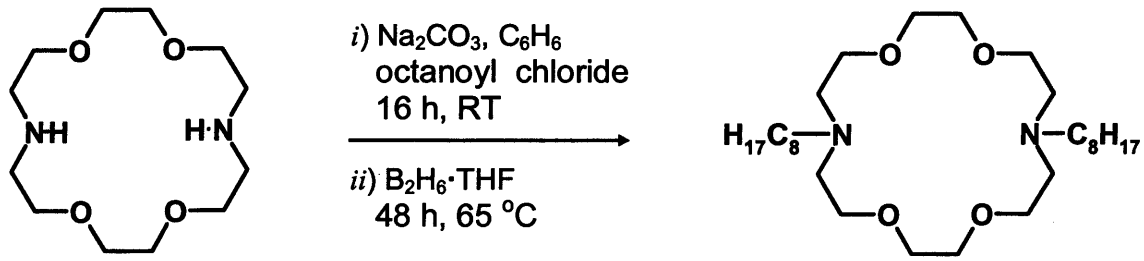
Gokel also reported *N,N'*-alkylated derivatives of 4,13-diaza-18-crown-6 prepared in a single step reaction with an aliphatic amine and 1,2-bis-(2-iodoethoxy)ethane, [**2.5**], stirred with sodium carbonate in refluxing acetonitrile for 24 h (***Scheme 2.2***).[9] However, the yields of this method were moderate (20-30%).



[2.5] 20 – 30%

Scheme 2.2. Gokel's general synthesis of *N,N'*-disubstituted 4,13-diaza-18-crown-6.

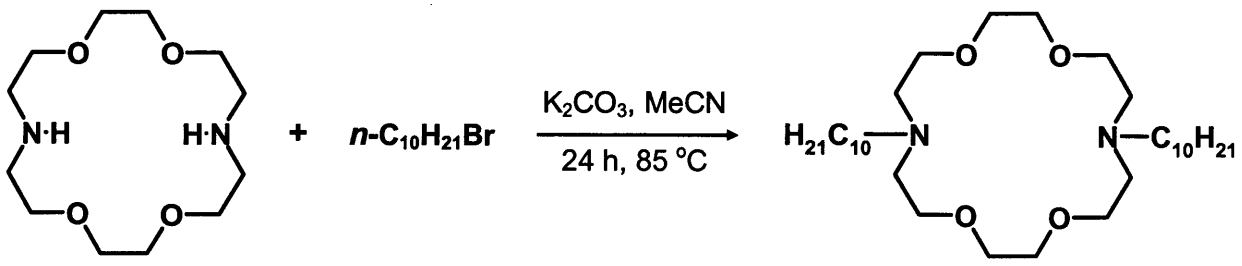
In a different approach, Gokel synthesised bis(octyl)-4,13-diaza-18-crown-6 by reacting 4,13-diaza-18-crown-6 with octanoyl chloride to form the amide, which was then reduced with diborane to give the bis(alkyl)-derivative.[8]



[2.7] [2.6]

Scheme 2.3. Gokel's synthesis of *N,N'*-dioctyl-4,13-diaza-18-crown-6.

Bartsch *et al.* suggested a different approach where 4,13-diaza-18-crown-6 [**2.7**] was *N,N'*-alkylated by reacting with 1-bromodecane and potassium carbonate in refluxing acetonitrile to give *N,N'*-bis(decyl)-4,13-diaza-18-crown-6 in high yield (***Scheme 2.4***).[10]

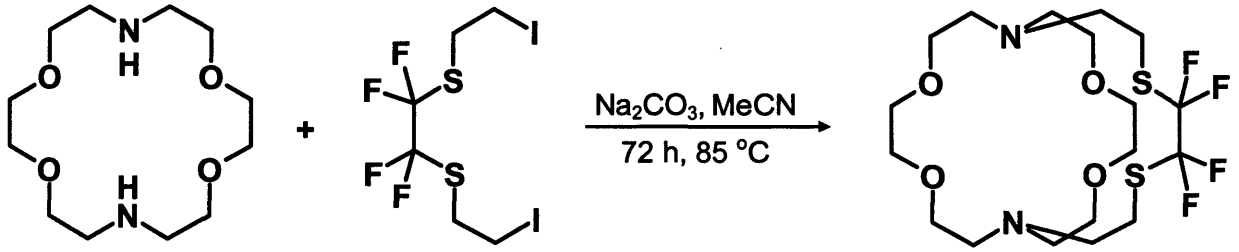


[2.7] [2.8] [2.9], 92%

Scheme 2.4. Bartsch's synthesis of *N,N'*-bis(decyl)-4,13-diaza-18-crown-6 [**2.9**].

2.1.2 Fluorinated Diaza-crown Ethers.

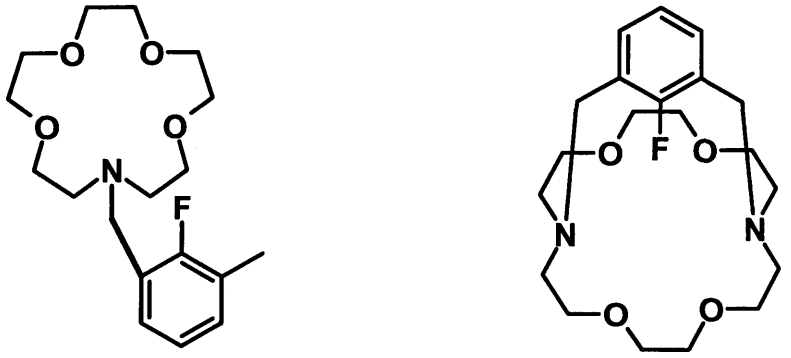
Using 4,13-diaza-18-crown-6 **[2.7]** as starting material, Plenio *et al.* synthesised the first partially fluorinated diaza-crown derivative, a cryptand, by reaction with 1,8-diiodo-3,6-dithia-4,4,5,5-tetrafluorooctane in refluxing acetonitrile. Cryptand **[2.11]** was capable of forming stable complexes with alkaline metal ions (***Scheme 2.5***).[11] The four oxygen atoms in the cavity centre mainly coordinated to the metal ions, although when binding to a sodium cation, the weak participation of sulphur and nitrogen to the coordination was also demonstrated.



[2.7] **[2.10]** **[2.11]**

Scheme 2.5. Synthesis of the first fluorinated cryptand capable of forming stable complexes with metal cations.

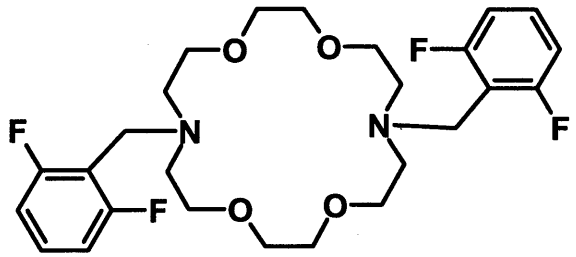
More recently, Plenio and Diodone demonstrated that, in certain fluorinated cryptands and aza-crown ethers, the C-F group could be an efficient donor unit, increasing the stability of the metal complexes in solution relative to that of the analogous non-fluorinated complexes.[12] This approach resulted in complexes in which alkaline earth metal ions interact closely with covalently bonded fluorine (***Figure 2.2***).



[2.12] **[2.13]**

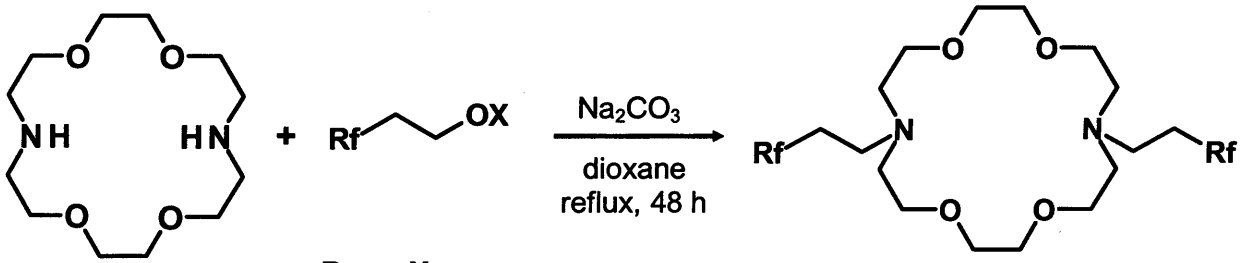
Figure 2.2. Fluoro aza-crown ether and fluoro cryptand with fluorine as a σ-donor for group I and II metal ions.

A very limited number of aza- or diaza-crown ethers with fluorinated sidearms have been reported so far. For instance, Chi *et al.* synthesised a series of diaza-18-crown-6 ethers with partially fluorinated benzyl sidearms (***Figure 2.3***)[13] and they found that the fluorinated diaza-crown **[2.14]** formed more stable complexes with metal cations than the non-fluorinated analogue. Chi explained this in terms of the electron-donating interaction of the aromatic rings (cation-π) and/or fluorine atoms with the metal cations.



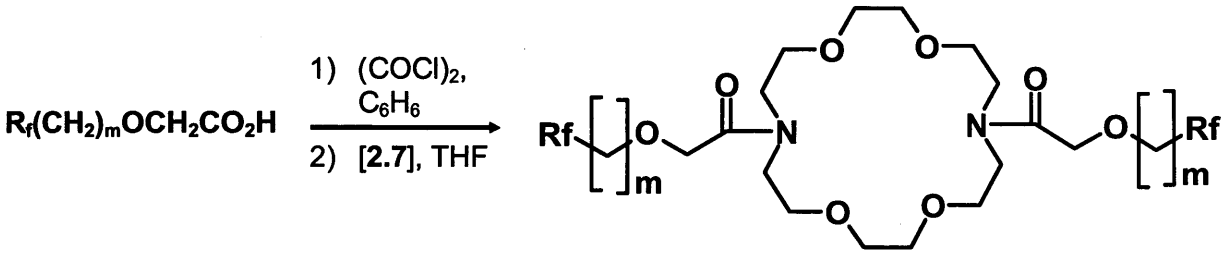
[2.14]

Figure 2.3. *N,N'*-Bis(2',6'-difluorobenzyl)-4,13-diaza-18-crown-6.



R_f	X	
C_6F_{13}	Ts	[2.15]
C_8F_{17}	Ts	[2.16]
C_8F_{17}	Ms	[2.17]

R_f		Yield (%)
C_6F_{13}	[2.18]	14
C_8F_{17}	[2.19]	16 (Ts)



Rf	m	
C_7F_{15}	1	[2.20]
C_8F_{17}	2	[2.21]
$C_{10}F_{21}$	2	[2.22]

Rf	m		Yield (%)
C_7F_{15}	1	[2.23]	95
C_8F_{17}	2	[2.24]	83
$C_{10}F_{21}$	2	[2.25]	78

Scheme 2.6. Bartsch's synthesis of macrocyclic polyethers with partially fluorinated sidearms.

Bartsch and co-workers reported the preparation of a series of aza and diaza macrocyclic ligands containing partially fluorinated sidearms,[10] by a variety of synthetic strategies. ***Scheme 2.6*** outlines two generic routes. All of the macrocycles were evaluated for their metal cation complexation behaviour. Bartsch recognised the potential applications of these partially fluorinated diaza-crown ethers in metal ion separations involving a fluorous phase or supercritical carbon dioxide. However, to date, no examples exploiting these concepts have been reported. Furthermore, the use of these perfluorinated or partially fluorinated diaza-crown ethers as phase transfer catalysts has not yet been investigated.

2.2 Synthesis of Non-Fluorinated and Partially Fluorinated Diaza-18-crown-6 Ethers.

The most common approach for recycling phase transfer catalysts is to attach them to an organic or inorganic support to form insoluble phase transfer catalysts. However, the simplicity of the separation protocol often sacrifices catalyst activity due to the heterogeneous nature of the supported phase transfer catalyst. Hence, the objective of the research discussed in this chapter was to develop a new class of fluorinated catalysts, based on diaza-crown ethers, which could be employed in phase transfer catalysis and recovered and reused efficiently using fluorous phase technology. 4,13-Diaza-18-crown-6, **[2.7]**, was selected as starting material owing to its versatile applicability, and its potential for facile *N,N'*-functionalisation. In addition, these phase transfer catalysts are chemically and thermally more stable than the traditional ammonium and phosphonium salts, which is essential for developing a robust and reusable phase transfer catalyst. Furthermore, they should possess good solubility in non-polar and partially fluorinated solvents or supercritical carbon dioxide, yet provide strong metal ion coordinating abilities.

The partially fluorinated sidearms, $-(CH_2)_3C_8F_{17}$ and $-(CH_2)_3C_{10}F_{21}$, were chosen to be attached because three methylene spacer groups were considered *a priori* to be an adequate insulator to avoid the electron withdrawing effect of the fluorine atoms.[14] The analogue diaza-crown ether **[2.19]**, with two methylene spacer groups, was also synthesised in order to investigate the electron withdrawing effect on the complexation capabilities of the partially fluorinated diaza-crown ethers.

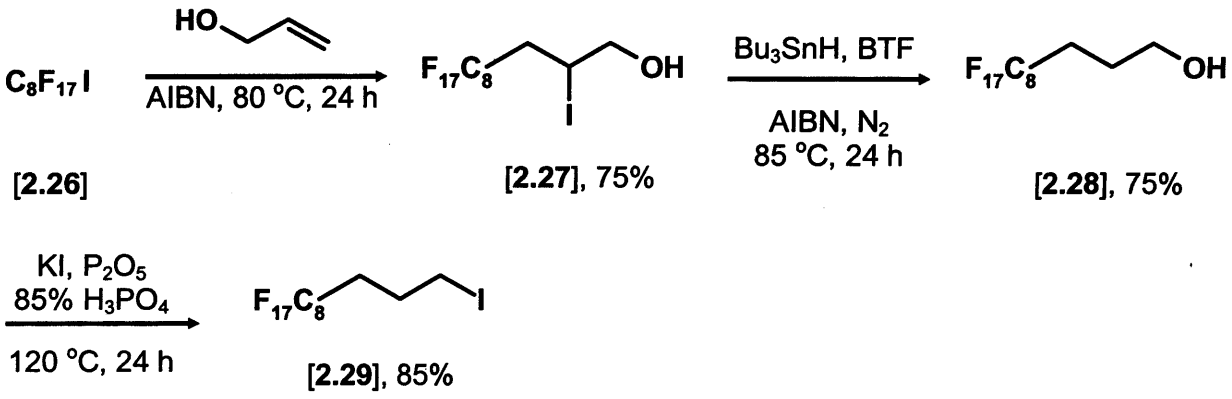
Furthermore, in contrast with heavily fluorinated catalysts, that can be recovered by fluorous liquid-liquid extraction or fluorous biphase catalysis but, due to the high

fluorine content, cannot be expected to behave as "ordinary" organic molecules, these relatively light fluorous-tagged diaza-crown ether catalysts should not have their chemical properties significantly affected.[15] In addition, partially fluorinated diaza-crown ethers should be recovered by fluorous solid-phase extraction.

2.2.1. Synthesis of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl and 1*H*,1*H*,2*H*,2*H*,3*H*, 3*H*-perfluoro-*n*-tridecyl iodide.

Previously to the synthesis of partially fluorinated diaza-crown ethers, the ponytails 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide and 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-tridecyl iodide were prepared.

The synthesis of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide was developed from the protocol that was originally reported by Fish and co-workers for the preparation of a partially fluorinated triazacyclonanone.[16] The original three steps procedure is outlined in ***Scheme 2.7***.



[2.26] [2.27], 75% [2.28], 75% [2.29], 85%

Scheme 2.7. Synthesis of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide.

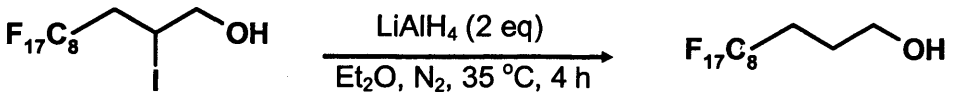
After numerous experiments the overall reaction was improved and scaled up. For instance, in the radical reaction of perfluorooctyl iodide with allyl alcohol initiated by azobisisobutyronitrile (AIBN), the yield and purity of 1*H*,1*H*,2*H*,3*H*,3*H*-perfluoro-2-iodo-*n*-undecanol, compound [**2.27**], was optimised after testing different additions and concentrations of AIBN. ***Table 2.1*** summarizes the progress of the experiments. Procedure **1** is the original reaction protocol developed by Fish and co-workers. In procedure **2**, the yield of the reaction was improved by adding 6 aliquots of AIBN, one every 2 hours. The highest yield was achieved using the third procedure, in which the reaction time was extended for an extra 9 h and a lower amount of radical

initiator was added only once at the beginning of the reaction. Procedure **4** is the successful scale-up of procedure **3**.

Procedure	$C_8F_{17}I$ (mmol)	Allyl Alcohol (mmol)	AIBN (mmol)	Reaction Time (h)	Yield (%)
1	12.5	14.4	4.0	14	71.2
2	12.5	14.4	3.0	12	86.2
3	12.5	14.4	1.2	21	96.6
4	25.0	28.8	2.4	20	94.7

Table 2.1. *Summary of the synthesis of* 1*H*,1*H*,2*H*,3*H*,3*H*-perfluoro-2-iodo-*n*-undecanol, **[2.27]**.

In the second step, the reduction of the iodinated compound to yield the alcohol 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecanol, **[2.28]**, was carried out with two different reducing agents, lithium aluminium hydride and tributyltin hydride. It was found that the reduction of iodide with lithium aluminium hydride was a better approach to obtain compound **[2.28]** than using tributyltin hydride (***Scheme 2.8***), since it avoids the formation of tributyltin iodide that contaminated the product. In addition, the reaction time was reduced from 24 h with tributyltin hydride to only 4 h with lithium aluminium hydride. Although the reaction yield was lower, the higher purity and the shorter reaction time of the reduction with lithium aluminium hydride made this procedure more suitable.



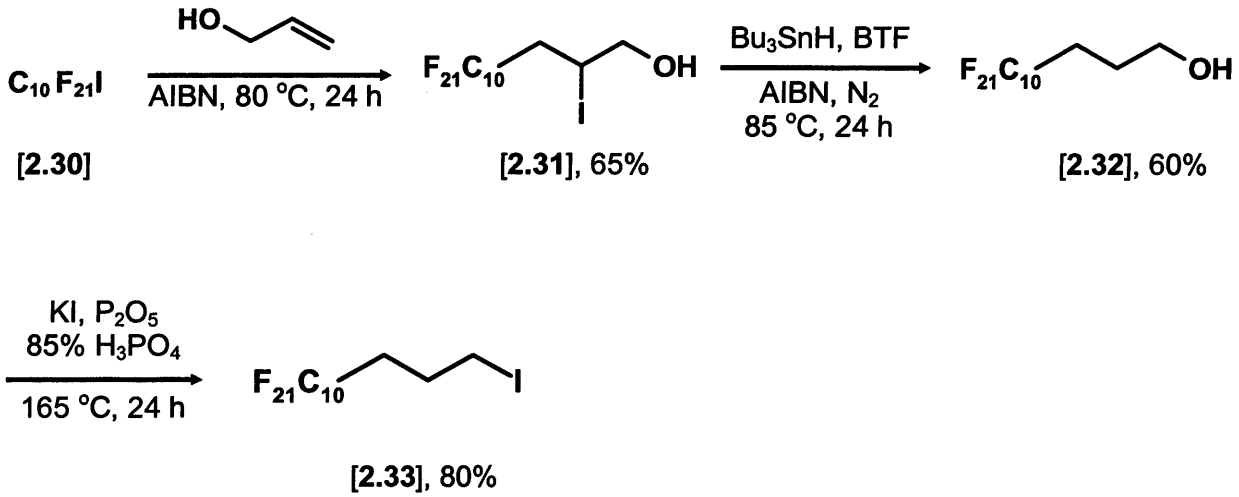
[2.27] **[2.28]**, 75%

Scheme 2.8. Synthesis of the partially fluorinated alcohol 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecanol, **[2.28]**.

The fluorinated intermediate 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide, compound **[2.29]**, was synthesised by refluxing potassium iodide in acidic media with

1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecanol for 24 h, following the procedure developed by Fish *et al.* with no further modifications. The pure product was easily purified by recrystallization from methanol and was isolated in good yields.

Initially, the procedure outlined in ***Scheme 2.7*** was used for the synthesis of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-tridecyl iodide. However, due to the low solubility of each of the compounds containing the perfluorotridecyl group in organic solvents, modifications were needed to optimise the procedures to attach this new fluorinated sidearm. This solubility behaviour, which has been observed many times before in fluorous chemistry, is due to the high fluorine content that makes each of the compounds highly organophobic.[17] After several experiments, the yields and purities of the products in every step of the reaction were improved. ***Scheme 2.9*** summarises the final four step procedure that was used to prepare this partially fluorinated alkyl iodide.



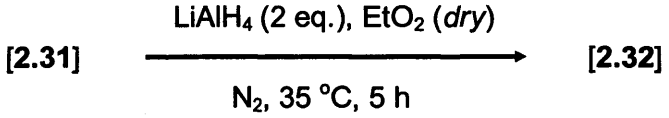
[2.30] **[2.31]**, 65% **[2.32]**, 60%

[2.33], 80%

Scheme 2.9. Synthesis of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-tridecyl iodide, **[2.33]**.

The radical addition of perfluorodecyl iodide to allyl alcohol proceeds well under the same conditions that were originally optimised for the perfluorooctyl derivative. At the end of the reaction the excess allyl alcohol was removed by evaporation and the product was easily purified by recrystallization from hexane. Initially, the synthesis of compound **[2.32]** was investigated using two different approaches. It was found that the reduction of compound **[2.31]** with lithium aluminium hydride (***Scheme 2.10***) was not an acceptable approach because the reaction did not go to completion and undesirable by-products were obtained due to the low solubility of compound **[2.31]** in

diethyl ether. The reduction was then carried out using tributyltin hydride in dry benzotrifluoride and azobisisobutyronitrile as the radical initiator (***Scheme 2.9***). Compound [**2.32**] was obtained pure after column chromatography on silica gel (petroleum ether/diethyl ether = 1/1) giving the desired product in an acceptable yield (60%).



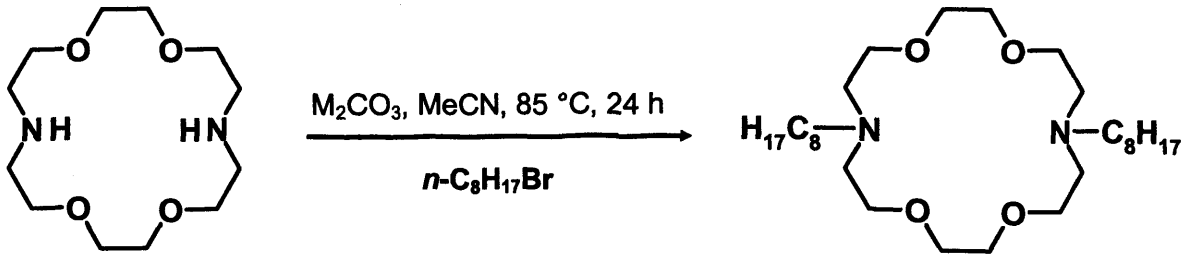
Scheme 2.10. Synthesis of *1H,1H,2H,2H,3H,3H*-perfluoro-*n*-tridecan-1-ol [**2.32**].

The iodination of the perfluoroalkyl alcohol [**2.32**] was initially carried out following the procedure outlined in ***Scheme 2.7***. However, it was found that by increasing the temperature to 165 °C a much better yield was obtained. *1H,1H,2H,2H,3H,3H*-perfluoro-*n*-tridecyl iodide was obtained in a 80% yield and no further purification was necessary.

2.2.2. Synthesis of *N,N'*-bis(alkyl)-4,13-diaza-18-crown-6.

The *N,N'*-bis(alkyl) derivative was synthesised in order to provide a model compound for comparison between fluorinated and non-fluorinated diaza-crown ethers in the metal ion complexation and phase transfer catalysis studies. The protocol developed by Bartsch and co-workers, ***Scheme 2.4***, was preferred for the synthesis of *N,N'*-bis(octyl)-4,13-diaza-18-crown-6, [**2.6**], due to the simplicity of the single step procedure, the commercial availability of all the reactants and the high yield obtained.

Based on the metal ion-macroring size compatibility concept, high complexation with potassium metal cation was anticipated for 4,13-diaza-18-crown-6 and its *N,N'*-derivatives. Hence, in order to investigate how the complexation process affects the synthesis, the reaction was not only carried out using potassium carbonate but also using cesium carbonate (***Scheme 2.11***). The cesium cation is bigger than the cavity of the macrocycle and therefore, the amount of coordination was expected to be much lower.

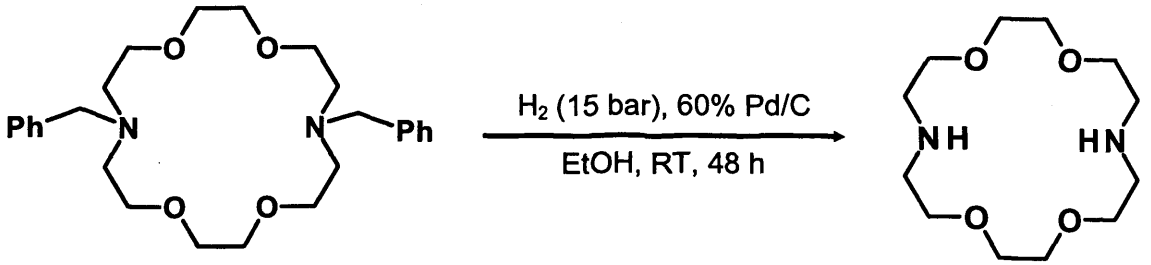


[2.7] [2.34] [2.6], M = K (78%)
M = Cs (52%)

Scheme 2.11. Synthesis of *N,N'*-bis(octyl)-4,13-diaza-18-crown-6 [**2.6**].

Fast atom bombardment (FAB) mass spectroscopy analysis demonstrated that compound [**2.6**] was isolated without complexation independent of the metal cation used. When potassium carbonate was used as base, the alkylated diaza-crown was probably uncomplexed by washing with water during the work-up procedure. Although, the solubility of potassium carbonate in acetonitrile is low, the solubility of cesium carbonate in the same solvent is even lower. This could explain the low yield of the reaction when this cation was used. In both cases, it was necessary to purify the crude product by Kugelröhr distillation to obtain pure alkylated diaza-crown [**2.6**].

4,13-Diaza-18-crown-6 ether, [**2.7**], is the essential starting material for the synthesis of the fluorinated and non-fluorinated diaza-crown derivatives, but its high price and limited commercial availability could have caused serious problems by reducing the number and scale of the experiments. Hence, it was decided to synthesise this reagent *via* deprotection of the less expensive, commercially available *N,N'*-dibenzyl-4,13-diaza-18-crown-6, [**2.35**], in order to facilitate the investigations. ***Scheme 2.12*** shows the hydrogenation, which was optimised to obtain an excellent 90% yield.[18]

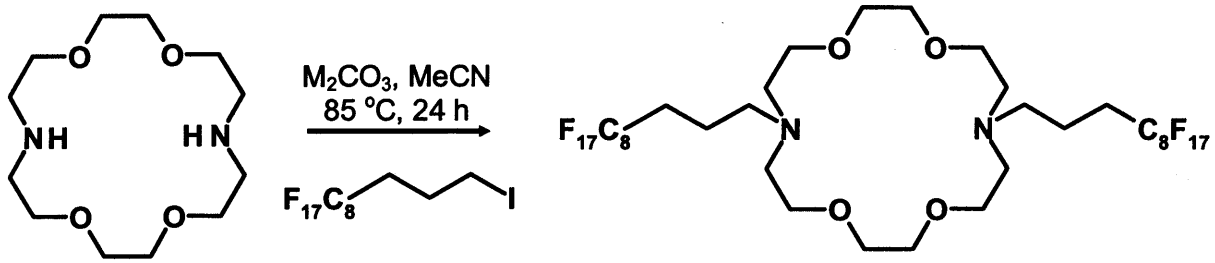


[2.35] [2.7], 90%

Scheme 2.12. Synthesis of 4,13-diaza-18-crown-6 by deprotection of *N,N'*-dibenzyl-4,13-diaza-18-crown-6.

2.2.3. Synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**].

The synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, partially fluorinated diaza-crown [**2.36**], is outlined in ***Scheme 2.13***. The protocol is based on the synthesis of [**2.6**] (***Scheme 2.11***) using carbonate as base in refluxing acetonitrile. With this procedure, partially fluorinated diaza-crown [**2.36**] was obtained in an excellent yield (81%) after recrystallization from methanol.



[**2.7**] [**2.29**] [**2.36**], M = K (81%)
M = Cs (48%)

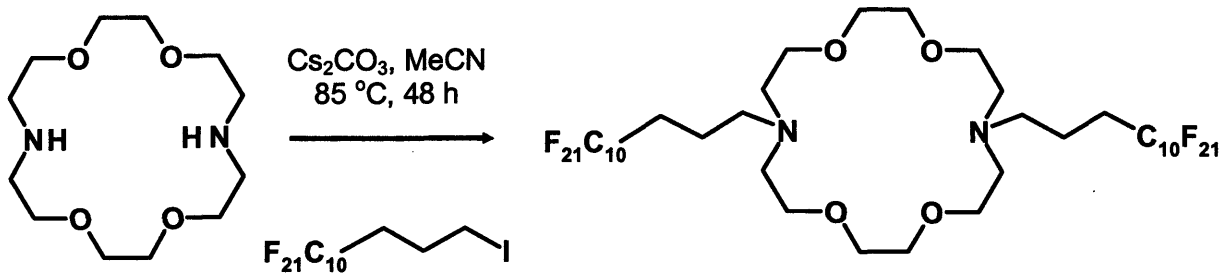
Scheme 2.13. Synthesis of compound *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**].

The influence of the cation was also investigated by using potassium and cesium carbonates. As in the synthesis of the analogous non-fluorinated diaza-crown ether *N,N'*-bis(octyl)-4,13-diaza-18-crown-6, [**2.6**], a better yield was obtained using potassium carbonate as the base. In both cases, FAB mass spectroscopy showed that the product was isolated without coordination to the metal cation.

2.2.4. Synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6 [**2.37**].

Scheme 2.14 summarizes the synthesis of partially fluorinated diaza-crown ether [**2.37**], which was carried out following the procedure developed for the synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**]. Diaza-crown ether [**2.37**] was obtained pure directly after the work-up in an acceptable yield (53%). The yield was increased to 62% after 48 h. Cesium carbonate was used as the base and, surprisingly, mass spectroscopy (FAB) analysis showed that, for the first time, compound [**2.37**] was isolated as a complex

of cesium metal cation. However, elemental analysis proved that diaza-crown ether [**2.37**] was obtained pure.

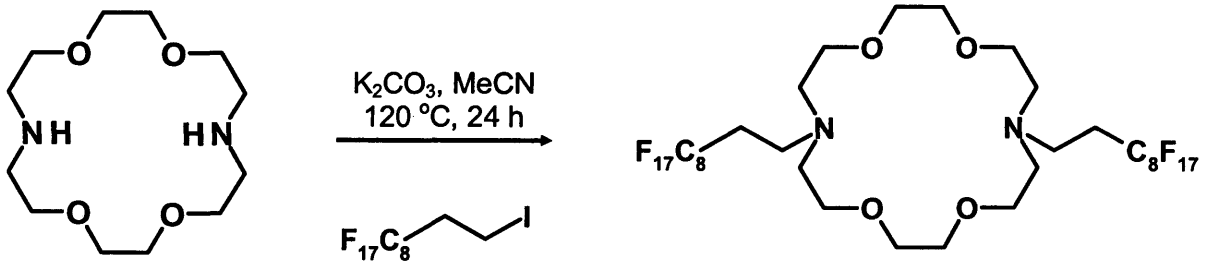


[**2.7**] [**2.33**] [**2.37**], 62%

Scheme 2.14. Synthesis of *N,N'-bis*(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6 [**2.37**].

2.2.5 Synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, [**2.19**].

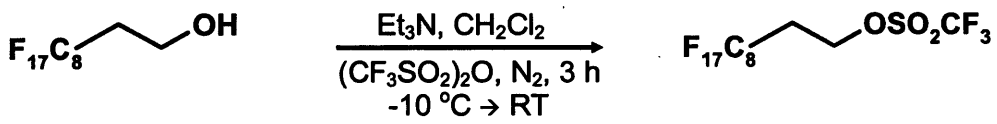
The synthesis of partially fluorinated diaza-crown ether [**2.19**] was carried out following two different methods. The first procedure (***Scheme 2.15***) was based on the synthesis developed for the partially fluorinated diaza-crown ethers [**2.36**] and [**2.37**]. When 4,13-diaza-18-crown-6, [**2.7**], was reacted with the commercially available 1*H*,1*H*,2*H*,2*H*-perfluorodecyl iodide, [**2.38**], only a 9% yield of the partially fluorinated macrocycle [**2.19**] was obtained. This may be due to the elimination of HI prevailing rather than alkylation.[16] The iodide is not insulated from the electron withdrawing effect of the perfluoroalkyl group, thus making it an extremely poor leaving group for the nucleophilic substitution reaction.



[**2.7**] [**2.38**] [**2.19**], 9%

Scheme 2.15. Synthesis of compound [**2.19**].

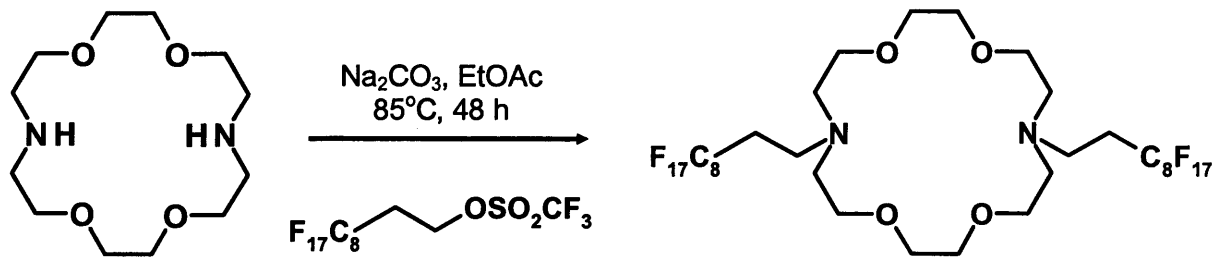
Scheme 2.17 outlines a different approach developed for the synthesis of macrocycle [**2.19**]. Here, 1*H*,1*H*,2*H*,2*H*-perfluorodecyl trifluoromethanesulfonate, [**2.40**], was used instead of 1*H*,1*H*,2*H*,2*H*-perfluorodecyl iodide, [**2.38**], since the triflate is much better leaving group than iodine. The triflate derivative, [**2.40**], was synthesised in a high yield from the commercially available alcohol using triflic anhydride and triethylamine as the base (***Scheme 2.16***). Compound [**2.40**] was purified by extraction with perfluoro-1,3-dimethylcyclohexane, PP3.



[**2.39**] [**2.40**], 89%

Scheme 2.16. Synthesis of compound [**2.40**].

N,N'-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, [**2.19**], was prepared previously by Bartsch and co-workers in low yield (16 %) by *N,N'*-alkylation with 1*H*,1*H*,2*H*,2*H*-perfluorodecyl tosylate by refluxing with 4,13-diaza-18-crown-6 and sodium carbonate for 48 h in dioxane (***Scheme 2.5***). Following the procedure outlined in ***Scheme 2.17***, the yield was improved considerably (42 %) by using 1*H*,1*H*,2*H*,2*H*-perfluorodecyl triflate in ethyl acetate for 48 h. After 72 h the yield was increased to 53%. Although the elemental analysis demonstrated the purity of the product isolated, ICP analysis showed that diaza-crown ether [**2.19**] was isolated as a mixture of sodium (0.16 mol of Na^+ per 1 mol of compound [**2.19**]) and potassium (0.38 mol of K^+ per 1 mol of compound [**2.19**]) cation complexes.



[**2.7**] [**2.40**] [**2.19**], 42%

Scheme 2.17. Synthesis of partially fluorinated diaza-crown ether [**2.16**].

2.3 Separation and Recovery Studies.

The main disadvantage of crown ethers is that, like the majority of phase transfer catalysts, they are not normally recovered and, hence, they are disposed of as waste. The use of fluorous separation techniques[16,19] is an approach that has advanced significantly over the last decade and now, catalysts containing perfluoroalkyl groups can be recovered, recycled and reused.[20]

The separation and recovery of the non-fluorinated and partially fluorinated diaza-crown ethers from organic products was studied in order to recover and reuse the phase transfer catalysts. The solubility was investigated in order to establish the compatibility of the synthesised diaza-crown ethers with their recovery using the light fluorous approach.[15] Preliminary fluorous solid phase extraction experiments using fluorous reverse phase silica gel were carried out to determine the appropriate solvent systems. Additionally, the separation by solid phase extraction on normal silica gel was also investigated.

2.3.1 Partition Coefficients and Solubility.

Partition coefficients provide valuable data on the distribution of a solute between two immiscible phases. The determination of partition coefficients gives a direct measure of the fluorophilicity or fluorous affinity of the catalyst, which will be very important in order to chose the right solvent system for the fluorous solid phase extraction. These are normally expressed as ratios, normalised to 100, indicating the percentage of fluorinated catalyst that partitions into each phase.

No fluorinated crown ether partition coefficients have been reported until now. However, Gladysz and co-workers have investigated a wide range of phosphines containing fluorinated ponytails and determined their partition coefficients experimentally.[21] These experiments demonstrated that the partition into the fluorous phase increases with the length of the fluorinated sidearms. On the other hand, as the hydrocarbon spacer group increases, the partitioning of the fluorinated catalyst into the fluorous phase decreases. In general, to endow a fluorinated catalyst with fluorous phase solubility, it has been suggested that the fluorine content of the molecule must be at least 60%, although this might not be enough if the substrate contains polar functional groups.[22]

The partition coefficient of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, compound [**2.36**], between fluorous and organic solvents was

determined using a gravimetric method. A known amount of the catalyst was accurately weighed and placed in a sample vial containing an organic solvent (2 cm^3) and a perfluorocarbon solvent (2 cm^3). The phases were then stirred for 30 minutes and left to stand for an additional 30 minutes. A sample (1 cm^3) of each solvent was removed, placed in a pre-weighed flask and concentrated down to dryness. Then, to ensure complete dryness, the sample was placed under high vacuum for 1 h. All the experiments were carried out between 18-20 °C.

Diaza-crown ether **[2.36]**, containing 54.6% of fluorine by molecular weight, is soluble in conventional organic solvents such as dichloromethane (DCM), diethyl ether, ethyl acetate, toluene, benzotrifluoride and trifluoroethanol. Surprisingly, this fluorinated diaza-crown ether is only soluble in hot perfluorohexane and is insoluble in perfluoro-1,3-dimethylcyclohexane (PP3). Therefore, although macrocycle **[2.36]** has a relatively high fluorine content, it partitions preferentially into the organic phase of a toluene:PP3 biphase (64:36) or a DCM:PP3 biphase system (70:30). When the more polar fluorinated solvent, nonafluorobutyl methyl ether (MNFB),[23] was used, the fluorinated diaza-crown ether **[2.36]** partitioned only into the fluorous phase. This illustrates that, as well as fluorine content of the solvent, its polarity must also be taken into account; consider the scale of polarity where water is value 10, the polarity of PP3 is lower than 0, while MNFB is higher than 5 (DCM = 3.1; toluene = 2.4 and perfluorohexane < 0). Therefore, the fluorine content of MNFB and its increased polarity compared to traditional perfluorocarbon solvents favour the partition of macrocycle **[2.36]** into the fluorous phase. The high polarity of MNFB also makes it miscible with methanol (MeOH), and consequently, a mixture of MeOH/H_2O (4:1) was used as the 'organic' phase.

Interestingly, the solubility profile of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, **[2.19]**, with 56.0% of fluorine by molecular weight, is very similar to diaza-crown ether **[2.36]**. It also partitions preferentially into the organic phase of a toluene:PP3 biphase system (59:41), but by increasing the polarity of the organic phase, it becomes preferentially soluble in the fluorous phase of an acetonitrile:PP3 biphase system (0.5:99.5) at room temperature. Fluorinated macrocycle **[2.37]**, that contains the $C_{10}F_{21}$ group and 57.7% of fluorine, is only soluble in diethyl ether, benzotrifluoride and trifluoroethanol.

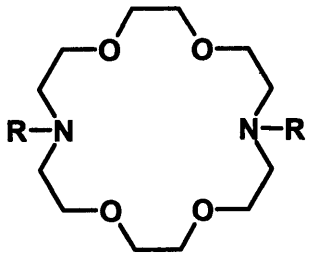
2.3.2 Fluorous Solid Phase Extraction (FSPE).

The main aim of the separation and recovery studies was to develop an efficient protocol for the separation and recovery of the partially fluorinated diaza-crown ethers using solid-phase extraction on fluorous reverse phase silica gel.

Preliminary FSPE experiments were carried out using the partially fluorinated diaza-crown ethers **[2.36]**, **[2.37]** and **[2.19]**, as well as the alkyl derivate **[2.6]**. A known amount of each diaza-crown ether (50 mg) was dissolved in the minimum volume of dichloromethane and loaded onto a FRPSG packed column (0.5 cm x 3.0 cm approx.). The column was then eluted with a "fluorophobic" solvent. Dichloromethane, toluene and acetonitrile were selected as fluorophobic solvents. During the elution, the solvent eluted was collected (30-35 mL) and analysed by thin-layer chromatography every 5 mL. In all cases, no macrocycle was eluted from the column by the fluorophobic solvents. The FRPSG packed column was then eluted with "fluorophilic" solvents. Diethyl ether, benzotrifluoride, trifluoroethanol and ethyl acetate were all tested as fluorophilic solvents. All of the diaza-crown ethers are soluble in these solvents. The solvent eluted was collected (30-35 mL) and analysed by thin-layer chromatography every 5 mL. When the chromatographic analysis was positive, the solvent was removed under reduced pressure in order to calculate the amount of catalyst recovered. After the elution, the catalysts were analysed by ^{1}H and ^{19}F NMR demonstrating their stability during the FSPE experiments.

Table 2.2 shows the percentage of catalyst recovered, the volume of solvent used and the amount of FRPSG loaded into the column respectively. The complete elution of the macrocycles from the packed column depends not only on the amount of fluorine in the macrocycle, but also on their polarity. Initially, it was thought that the alkylated diaza-crown ether **[2.6]** would be eluted easily from the short column of FRPSG since it does not contain any fluorine atoms, but unfortunately it was not possible to recover any of this macrocycle.

Compound **[2.6]** does not have any fluorine content resulting in a more polar compound in comparison with partially fluorinated diaza-crown ethers. Because of this, it may interact strongly with the hydroxy groups remaining on the FRPSG. In direct contrast, the partially fluorinated macrocycles are less polar than the alkyl derivate, being more easily eluted from the column. Using benzotrifluoride as a fluorophilic solvent, only compound **[2.19]** was eluted. However, it was possible to recover only 37%.



catalyst	R
[2.6]	C_8H_{17}
[2.36]	$C_8F_{17}(CH_2)_3$
[2.37]	$C_{10}F_{21}(CH_2)_3$
[2.19]	$C_8F_{17}(CH_2)_2$

FSPE	Et_2O			BTF			TFE			EtOAc		
	%	ml	g	%	ml	g	%	ml	g	%	ml	g
[2.6]	0	35	0.97	0	35	0.76	0	35	0.64	0	35	0.76
[2.36]	94	35	0.97	0	35	0.76	99	30	0.64	99	30	0.76
[2.37]	47	35	0.65	0	35	0.76	89	35	0.76	16	30	0.79
[2.19]	99	30	0.82	37	35	0.76	99	20	0.60	65	30	0.76

Table 2.2. Fluorous solid phase extraction results.

The results demonstrated that the partially fluorinated diaza-crown ethers **[2.36]**, **[2.37]** and **[2.19]** can be eluted from the FRPSG packed column and recovered quantitatively when the appropriate solvent system is used. However, although macrocycles **[2.36]** and **[2.19]** were easily recovered from the column, it was more difficult to eluted compound **[2.37]**, that contains the perfluorodecyl group, and only trifluoroethanol gave a good recovery of this macrocycle. Hence, these catalysts should be suitable for recovery and recycling in phase transfer catalysis using the FSPE technique.

2.3.3 Solid Phase Extraction (SPE).

The recovery of the partially fluorinated diaza-crown ethers was also investigated using SPE. The separation using the solid phase extraction methodology is primarily based on the polarity of the species eluted. The advantage of this technique is the relatively low cost of silica gel in comparison with FRPSG. In an analogous experiment, the same procedure developed for the FSPE was repeated using normal silica gel instead of FRPSG. The diaza-crown ethers investigated were loaded onto the silica packed column dissolved in the minimum amount of dichloromethane. Thin-layer chromatography was used to monitor the elution of the diaza-crown ether. No

catalyst was eluted from the column using dichloromethane, toluene or acetonitrile as solvents.

Table 2.3 summarizes the recovery of the derivatised diaza-crown ethers using diethyl ether, benzotrifluoride, trifluoroethanol and ethyl acetate as solvents. ***Table 2.3*** shows the percentage of catalyst recovered, the volume of solvent used and the amount of silica gel loaded into the column respectively.

SPE	Et_2O			BTF			TFE			EtOAc		
	%	ml	g	%	ml	g	%	ml	g	%	ml	g
[2.6]	0	35	0.52	0	35	0.75	0	35	0.53	0	35	0.52
[2.36]	99	35	0.52	0	35	0.75	60	55	0.53	99	35	0.52
[2.37]	86	40	0.61	0	35	0.75	47	55	0.54	93	50	0.61
[2.19]	94	35	0.54	0	35	0.75	55	35	0.60	90	30	0.52

Table 2.3. Solid phase extraction results.

No matter what solvent was used, it was not possible to elute the alkylated diaza-crown ether [**2.6**] from the column, possibly due to the strong interaction of the non-fluorinated macrocycle with the hydroxy groups of the polar silica gel. 4,13-Diaza-18-crown-6, [**2.7**], was also investigated. Like its alkylated derivative it was not possible to elute it from the column. Compounds [**2.36**] and [**2.19**] were recovered quantitatively by eluting the column with diethyl ether or ethyl acetate. Diaza-crown ether [**2.37**] was also recovered in a high percentage using ethyl acetate, but the amount of solvent used was much higher in comparison with the volume of ethyl acetate used to recover compound [**2.36**]. This may be due to the lower solubility in conventional organic solvents. In contrast to the fluorous solid phase extraction, trifluoroethanol was not efficient at recovering the partially fluorinated macrocycles from conventional silica gel. Overall, these results confirmed the potential of this extraction technique for recovering the partially fluorinated diaza-crown ethers under investigation.

2.4 Conclusions.

A small series of non-fluorinated and partially fluorinated diaza-crown ethers were synthesised in good yields by *N,N'*-alkylation of 4,13-diaza-18-crown-6 using different procedures. In the case of the synthesis of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, **[2.19]**, the procedure was improved considerably over previous investigations by using 1*H*,1*H*,2*H*,2*H*-perfluorodecyl triflate in ethyl acetate for 48 h.

The low solubility of *N,N'-bis(*1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6, **[2.37]**, in conventional organic solvents, implies that it may have a lower catalytic activity in phase transfer catalysis in these solvents. Preliminary separation studies have indicated that solid phase extraction and fluorous solid phase extraction are suitable techniques for recovering the partially fluorinated diaza-crown ethers quantitatively by eluting with the appropriate fluorophilic solvent. However, it was not possible to recover the non-fluorinated diaza-crown ether **[2.6]** using these techniques.

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CHAPTER THREE

Partially Fluorinated Diaza-18-crown-6 Ethers. PTC Applications.

University *of* Leicester

3.1 Introduction.

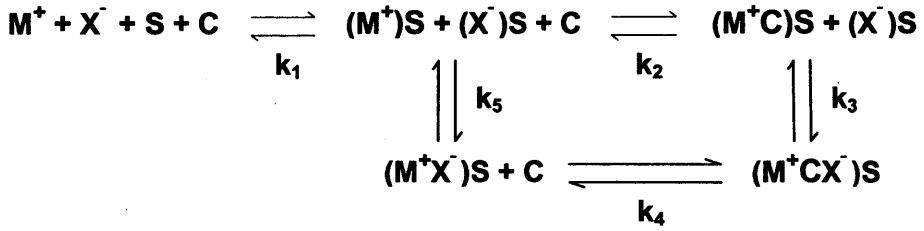
The aim of this chapter was to establish if the partially fluorinated diaza-crown ethers could still coordinate to a potassium metal cation, and therefore, could be used as phase transfer catalysts. Two different model reactions, an aliphatic nucleophilic substitution and an aromatic nucleophilic substitution, were investigated to evaluate their catalytic activity. In addition, this chapter also discusses the studies that were carried out in order to separate and recover the catalysts after each reaction.

3.2 Study of the Metal Ion Complexation of Partially Fluorinated and Non-Fluorinated Diaza-18-crown-6 Ethers.

3.2.1 Introduction.

The evaluation of cation binding strengths and dynamics is especially important for understanding the properties of crown ethers and, in the particular case of macrocycles with partially fluorinated sidearms, how the fluorinated groups affect their binding abilities. The ability of crown ethers to form stable complexes with metal ions is essential for their applications not only as phase transfer catalysts, but also in ion-selective electrodes,[1] membrane separation processes and chelation therapy.[2]

The crown ether complexation process depends on several factors associated with the specific properties of the ligand, reacting ions and solvent. Considering the possible equilibria that can originate from these factors, the cation-macrocycle complexation process must be seen as part of the Born-Haber cycle outlined in ***Scheme 3.1***,[3] where $\mathbf{M^+}$ is the cation; $\mathbf{X^-}$ is the anion; **S** is the solvent; $\mathbf{(M^+)S}$ is the solvated cation; $\mathbf{(X^-)S}$ is the solvated anion; **C** is the crown ether; $\mathbf{(M^+C)S}$ is the solvated metal crown complex; $\mathbf{(M^+X^-)S}$ is the solvated ion pair, and $\mathbf{(M^+CX^-)S}$ is the solvated ion pair between the complexed cation and anion. Each of the five equilibria depends specifically on the interactive forces that take place in solution between the components and is, therefore, correlated with the characteristic properties (size, charge, dipole moment, polarizability, etc.) of the species involved. Hence, the equilibria associated with k_1, k_3, k_4, and k_5 have a crucial influence on that associated with the proper ion macrocycle complexation (k_2).[4]



Scheme 3.1. Metal cation-crown ether complexation process.

Many different factors contribute to the extraction efficiency of diaza-crown ethers with two sidearms. For instance, steric factors and 3D structure are important in determining the overall binding properties, which also depend on:[5]

- Sidearm/s containing donor groups;
- Steric accessibility of the donor group to the macroring bound cation;
- Number of 3D geometries that the complex can adopt, which is related to steric accessibility to the coordination centre.

	R_f	X	Picrate Extracted (%)	
			Na^+	K^+
[3.1]	C_7F_{15}	none	2.4	29.5
[2.19]	C_8F_{17}	CH_2	6.1	46.8
[3.2]	C_7F_{15}	CH_2OCH_2	15.2	69.9
[3.3]	C_8F_{17}	$CH_2CH_2OCH_2$	22.1	73.3
[3.4]	$C_{10}F_{21}$	$CH_2CH_2OCH_2$	22.6	72.1
[3.5]	C_6F_5	none	10.4	58.9
[3.6]	none	C_9H_{19}	31.9	69.8
[2.35]	none	C_6H_5	10.4	45.7

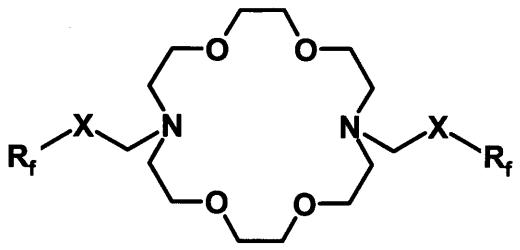


Table 3.1. Alkali metal picrate extractions results obtained by Bartsch and co-workers.[6]

Bartsch and co-workers have already described the metal ion complexation properties of several non-fluorinated and partially fluorinated diaza-crown ethers using the picrate extraction technique.[6] The following alkali metal picrate extraction

order was found: $K^+ > Rb^+ > Na^+ > Cs^+ > Li^+$. ***Table 3.1*** illustrates the results of the sodium and potassium picrate extractions from aqueous solutions into chloroform.

In summary, Bartsch demonstrated that macrocycles with longer spacer groups between the macroring and perfluoroalkyl group exhibited greater extraction efficiencies than those with shorter spacer units.

3.2.2 Potassium Picrate Extraction Studies.

Since previous work had already established that partially fluorinated diaza-crown derivatives exhibited greater selectivity for potassium metal ions,[5] the extraction of potassium picrate from an aqueous solution into both dichloromethane and benzotrifluoride was investigated for *N,N'*-bis(octyl)-4,13-diaza-18-crown-6, compound **[2.6]**, 4,13-diaza-18-crown-6, **[2.7]**, *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, **[2.19]**, *N,N'*-dibenzyl-4,13-diaza-18-crown-6, **[2.35]**, *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, **[2.36]**, and *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6, **[2.37]**. In the procedure followed, equal volumes (10 mL) of the appropriate solution of the crown ether (10^{-4} M) and an aqueous solution of the potassium picrate (10^{-4} M) were introduced into a stoppered flask (25 mL) and shaken for 30 min at 20 ± 1 °C, in order to establish the equilibrium between the two phases. The equilibrated mixture was then allowed to stand for 2 h at the same temperature in order to allow complete phase separation. The absorbance of the picrate in the aqueous phase was measured using a UV-visible Spectrophotometer at 356 ± 0.5 nm. The percentage of potassium extracted into the organic phase was calculated by (***Equation 3.1***):

$$\% \text{ Extraction (\% Ext.)} = [100 \cdot (A_0 - A_1)] / A_0 \qquad \textit{Equation 3.1.}$$

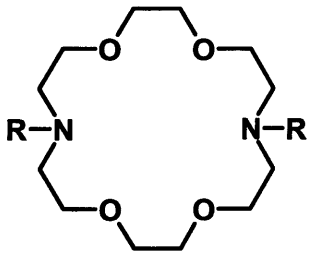
A_0 = Absorbance of a sample mixture without crown ether in the organic phase.

A_1 = Absorbance of a sample mixture with crown ether in the organic phase.

Three independent extractions were performed for each crown ether and the results are averaged in ***Figure 3.1***. The standard deviation of the average extraction values obtained from the three determinations was 2% or less. In all cases, no detectable amount of picrate was extracted into the organic phase in the absence of the crown ethers.

The six diaza-crown ethers studied in this experiment have the same cavity-size relationship and therefore, the results obtained only illustrate the effect of the perfluoroalkyl group (R_f) on the coordination centre of the diaza macrocycle. Compound **[2.35]** is commercially available and was purchased for the experiment, whilst macrocycles **[2.7]**, **[2.6]**, **[2.19]**, **[2.36]**, and **[2.37]** were synthesised by the procedures described in **Chapter 2**. The results for extracting potassium picrate into dichloromethane and benzotrifluoride (BTF) are summarized in ***Figure 3.1***.

The low extracting-ability of 4,13-diaza-18-crown-6 **[2.7]** was expected because the molecular conformation of this macrocycle, with both N–H bonds orientated inwards, makes it more difficult for the potassium atom to occupy the cavity.[7] *N,N'*-dibenzyl-4,13-diaza-18-crown-6, **[2.35]**, extracts the potassium picrate considerably better than **[2.7]** but significantly worse than the alkylated diaza-crown **[2.6]**. Compound **[2.35]** does not have any N–H bonds turned inward and, therefore, the cavity is unobstructed. However, compound **[2.6]** is a superior coordinator than compound **[2.35]**, as the benzyl side chains can interact with each other by π-π interactions and block one side of the cavity.



	R	K^+ Picrate Extracted (%)	
		DCM	BTF
[2.7]	H	0.9	0.2
[2.35]	$PhCH_2$	29.1	35.5
[2.6]	C_8H_{17}	47.7	52.9
[2.36]	$C_8F_{17}(CH_2)_3$	32.8	21.8
[2.37]	$C_{10}F_{21}(CH_2)_3$	26.2	17.4
[2.19]	$C_8F_{17}(CH_2)_2$	10.9	3.0

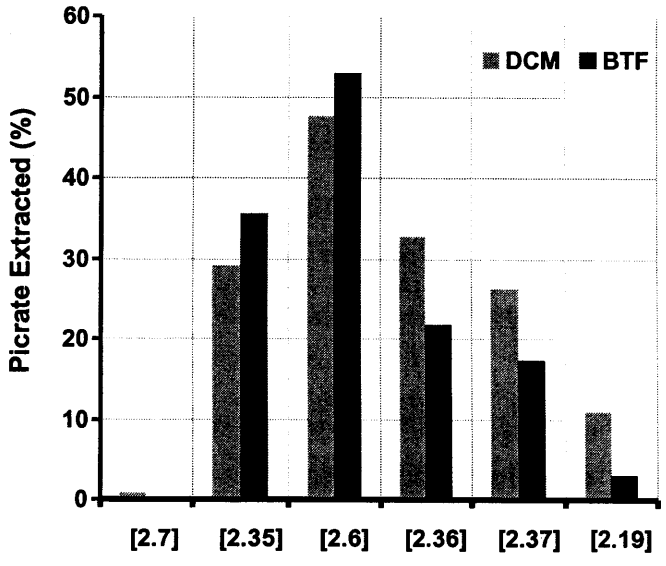


Figure 3.1. Potassium picrate extractions.

Comparing compounds **[2.36]** and **[2.6]** it is possible to appreciate the influence of the fluorine atoms on the coordination capability of the macrocycle. *N,N'*-Bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6 and *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6, **[2.36]** and **[2.37]** respectively, have three methylene groups between the perfluoroalkyl group and the coordination centre. These spacer groups were expected to insulate the coordination centre from the electron withdrawing effect of the perfluoroalkyl group (C_8F_{17} and $C_{10}F_{21}$ respectively). However, the results show a decrease in the amount of potassium extracted compared to the octyl derivative **[2.6]** demonstrating that the spacer group does not completely insulate the donor atoms from the electron withdrawing effect. The small differences in the extracting ability between compounds **[2.36]** and **[2.37]** is due to their different fluorine content, presumably caused by the low solubility of **[2.37]** in organic solvents.

The percentage of potassium extracted by fluorinated diaza-crown ether **[2.19]**, is much lower than the amount extracted by compounds **[2.36]** or **[2.37]**. Hence, two spacer groups do not insulate the donor atoms of the diaza-crown ether from the electron withdrawing effect of the perfluoroalkyl groups. Similarly, a three methylene spacer group has been shown to be more effective than a two methylene spacer group in insulating the phosphorus donor atom from the electron withdrawing effect of fluorinated ponytails in trialkylphosphines.[8]

Overall, whatever solvent is used (benzotrifluoride or dichloromethane), the coordination is relatively weak when the diaza-crown ether does not contain a sidearm group. Alternatively, when alkyl or perfluoroalkyl groups are attached, the coordination to potassium metal cation is improved and makes the diaza-crown ether more acceptable in terms of suitability as a phase transfer catalyst. Furthermore, the fluorinated sidearms of **[2.36]** and **[2.37]** make them appropriate for recovery processes involving fluorous solid phase extraction. The results also show the importance of insulating the coordination centre of the diaza-crown ether from the electron withdrawing effect of the fluorinated sidearms.

It is important to recognise that the complexation of alkali metal cations with macrocycles is not a simple process, depending on several factors related to the specific properties of the ligand, reacting ions and solvent. The purpose of this study was merely to investigate how the fluorinated and non-fluorinated sidearms affected the complexation ability of the diaza-crown ethers in order to evaluate their potential

as phase transfer catalysts. For this reason, the system was over simplified and most of the interactions (solvation, ion pairing, etc.) were *a priori* not considered. In order to have a better understanding of the role of these interactive forces on the metal cation-fluorinated diaza-crown ethers complexation process, alternative methods, such as conductimetry studies,[4] potentiometry with ion-selective electrodes[9] or capillary zone electrophoresis,[10] that will take into account all of these different factors, should be considered.

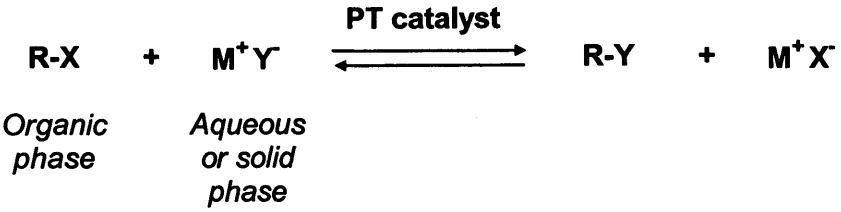
3.3 Phase Transfer Catalysis. Aliphatic Nucleophilic Substitution.

3.3.1 Introduction.

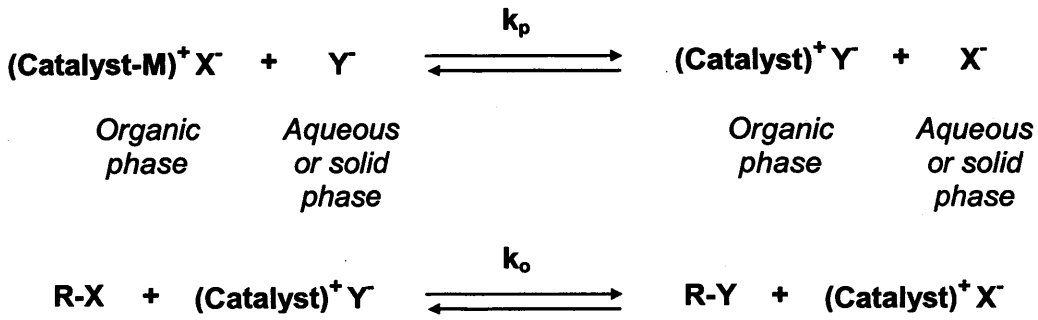
Phase transfer catalysis has been applied to a large variety of displacement reactions involving alkyl halides or aryl halides containing strong electron-withdrawing *ortho*- or *para*-substituents.[11] This technique uses a variety of reaction conditions, organic substrates and, moreover, a wide range of phase transfer catalysts. For instance, bulky quaternary ammonium or phosphonium salts[12] and polyethylene glycols (PEG)[13] are good phase transfer catalysts for nucleophilic substitution reactions, although crown ethers and cryptands have been shown to be more effective under solid-liquid conditions.[14]

In general, when crown ethers are used as phase transfer catalysts, it is known that the active catalyst is not the neutral ligand that is added to the reaction mixture but the ligand-cation complex, which is formed *in situ*. Its' concentration in the organic phase is a function of at least two factors: the partition of the ligand and ligand-cation complexes between the organic and aqueous phase (liquid-liquid) or dry salt phases (solid-liquid) and the stability of the ligand-cation complex in each phase. It has also been affirmed that the more lipophilic ligands are superior catalysts in liquid-liquid phase transfer reactions.[15]

Phase transfer catalysed nucleophilic substitution reactions are represented by the equilibrium outlined in ***Scheme 3.2***. However, the rate of product (R-Y) formation is determined by two subequilibria, one involving anion transfer and the other involving the organic reaction (***Scheme 3.3***).

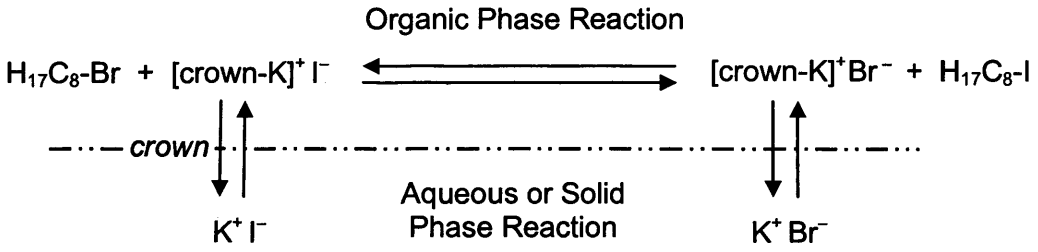


Scheme 3.2. Phase transfer catalysed nucleophilic substitution reaction.



Scheme 3.3. Equilibria involved in a phase transfer catalysed nucleophilic substitution reaction.

There are many important factors that can affect phase transfer catalysed nucleophilic substitution reactions. For instance, the structure of the **R** group ($PhCH_2$ > allyl > primary alkyl > secondary alkyl), the activity of the leaving group (X^-: $MeSO_3^-$ > Br^- > Cl^-), the nucleophilicity of the displacing group (Y^-: RS^- > SCN^-, I^- > CN^- > Cl^- > F^-, OH^-), the relative ease of transfer of X^- and Y^- to the organic phase, the catalyst structure and concentration, the reaction temperature, the enthalpy of solvation of all the species involved in the reaction, and agitation are important aspects to be considered.



Scheme 3.4. Conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$ catalysed by Crown Ethers.

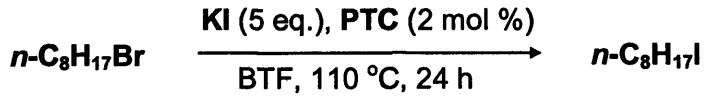
Iodide displacement reactions (***Scheme 3.4***) with various alkyl chlorides, bromides or methanesulfonates have been used as model reactions in phase transfer catalysis due to the ease of transfer of iodide into the organic phase by phase transfer catalysts, its strong nucleophilicity and very low hydration. The main problem associated with iodide displacement reactions is the fact that salts containing the iodide anion are often insoluble in organic solvents. However, this difficulty can be easily solved by the use of the appropriate phase transfer catalyst. Crown ethers,[16] PEG[17] and quaternary ammonium or phosphonium salts, are catalysts usually employed for iodide displacement reactions.[18] Polymer-supported macrocyclic polyethers and cryptands[19] have also been shown to have excellent catalytic activity for iodide displacement on alkyl chlorides, bromides or methanesulfonates.

Crown ethers have been shown to be more effective catalysts for iodide displacement reactions than quaternary ammonium salts, due to the inefficiency of the latter in transporting the nucleophilic iodide anion from the solid to the organic phase.[20] In the case of liquid-liquid conditions, the reactions were found to take place only in the organic phase, not in the aqueous phase or at the interface. In addition, the reaction of the nucleophile with the substrate was determined to be rate limiting. Landini *et al.* showed that it is not necessary for the phase transfer catalyst to be transported back and forward across the interface, only the anions need to make the crossing.[21] For different types of phase transfer catalysts almost all the differences in effectiveness result from the differences in the partition of the catalyst between the two phases. The greater the proportion of the catalyst that is in the organic phase, the higher the rate of reaction.[22] In the case of solid-liquid iodide displacement reactions, Starks and co-workers established that these phase transfer reactions obey pseudo-first-order kinetics and that the observed rates of reaction are proportional to the amount of catalyst used.

3.3.2 Conversion of 1-bromooctane into 1-iodooctane.

Having established that the fluorinated 4,13-diaza-18-crown-6 ethers retain their potassium ion complexing abilities, these novel diaza-crown ethers were evaluated as phase transfer catalysts in a classical iodide displacement reaction; the conversion of 1-bromooctane into 1-iodooctane (***Scheme 3.5***). Partially fluorinated crown ethers have never been used as phase transfer catalysts before. The efficiency of these new phase transfer catalysts were examined under both liquid-

liquid conditions, involving a heterogeneous reaction process between two liquid phases (benzotrifluoride/water biphase), and solid-liquid conditions, which involves the reaction of the solid ionic reagent, KI, with the reactant, 1-bromooctane, in benzotrifluoride.



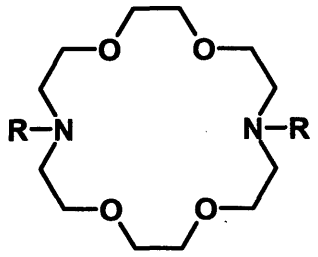
Scheme 3.5. Conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$.

The iodide displacement reactions were carried out by stirring a mixture of 1-bromooctane and an excess of potassium iodide in benzotrifluoride at 110 °C in the presence of catalytic amounts (2 mol %) of the different diaza-crown ethers. In the case of liquid-liquid conditions, the potassium iodide was added as an aqueous solution. After cooling to room temperature, the organic phase was filtered through silica gel using benzotrifluoride as eluent. A sample of the solution was collected and analysed by gas chromatography to determine the percent conversion to product using biphenyl as the internal standard. The results are summarized in ***Figure 3.2***.

Two independent reactions were performed for each combination of reactants and diaza-crown ether. The results are averaged and the standard deviation of the average conversions obtained from the two determinations was 4% or less in the case of liquid-liquid conditions, and 0.7% or less when solid-liquid conditions were used. All the macrocycles are soluble in benzotrifluoride at room temperature and, in the absence of phase transfer catalysts under both liquid-liquid and solid-liquid conditions, the conversion to product was negligible.

Figure 3.2 demonstrates clearly that all of the derivatised 4,13-diaza-18-crown-6 ethers performed better under solid-liquid conditions. Under liquid-liquid conditions, however, there was a dramatic decrease in the activity of the fluorinated diaza-crown ethers **[2.36]**, **[2.37]** and **[2.19]** in comparison to the octyl derivative **[2.6]**. This may be due to the hydrophobic effect of the perfluoroalkyl groups that make these macrocycles interact inadequately with the aqueous phase, causing the rate of anion transfer to slow and essentially resulting in a transfer-limited process with restricted rates of anion transfer across the interface. A similar effect was also observed with the dramatic reduction in the picrate extraction efficiency of the same fluorinated macrocycles compared to the octyl derivative **[2.6]** in benzotrifluoride (***Figure 3.1***).

This effect was more pronounced in benzotrifluoride and was probably because benzotrifluoride has a much lower solubility in water (S_w = 0.0031 mol/l) compared to dichloromethane (S_w = 0.23 mol/l).[23] In addition, the results demonstrate the importance of the enthalpy of solvation of the potassium cation in water in the crown ether complexation process among other factors such as solubility, reaction temperature, dipole moment, etc.[24]



	R	CONVERSION (%)	
		L-L	S-L
No PTC	---	0.2	0.4
[2.7]	H	66.0	97.0
[2.35]	$PhCH_2$	24.6	96.5
[2.6]	C_8H_{17}	88.1	97.0
[2.36]	$C_8F_{17}(CH_2)_3$	22.7	96.8
[2.37]	$C_{10}F_{21}(CH_2)_3$	20.6	93.5
[2.19]	$C_8F_{17}(CH_2)_2$	16.6	82.6

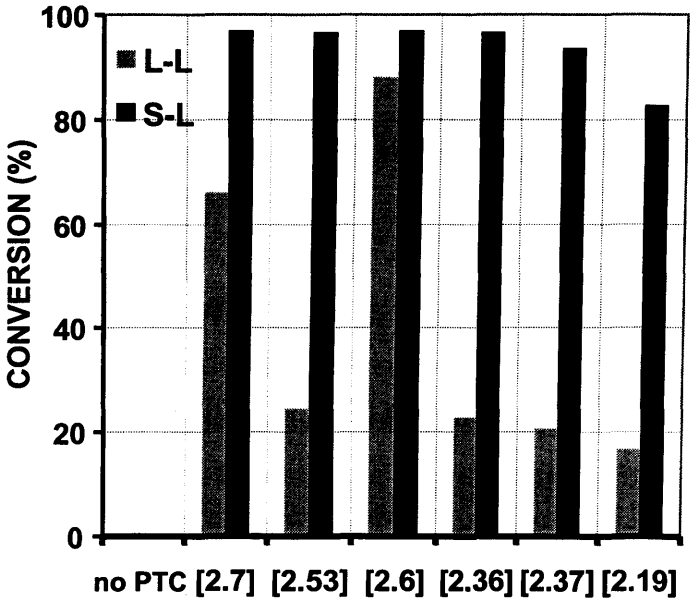


Figure 3.2. Phase transfer catalytic activity of diaza-crown ethers in the conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$ in benzotrifluoride under liquid-liquid and solid-liquid conditions.

In order to establish a more detailed comparison between the catalytic activities of the derivatised 4,13-diaza-18-crown-6 ethers, they were compared under solid-liquid conditions by monitoring the aliphatic nucleophilic substitution in benzotrifluoride by gas chromatography every hour over a 10 h period (***Figure 3.3***). The fluorinated macrocycles, **[2.36]** and **[2.37]**, with three methylene spacer groups exhibited higher activities than macrocycle **[2.19]**, which contained a shorter spacer group. However, the non-fluorinated macrocycles, **[2.6]** and **[2.7]**, were the most active phase transfer

catalysts. A longer spacer unit would be required to completely insulate the nitrogen donor atoms from the electron-withdrawing effects of the fluorinated sidearms of diaza-crown ethers **[2.36]** and **[2.37]**.

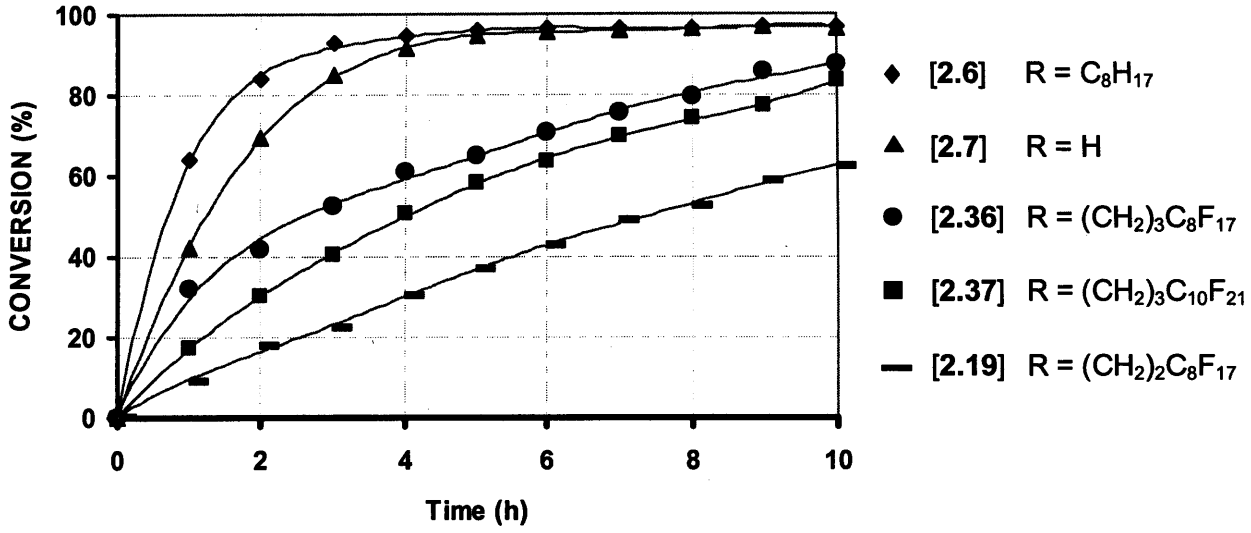


Figure 3.3. Phase transfer catalytic activity of diaza-crown ethers in the conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$ in benzotrifluoride under solid-liquid conditions.

Finally, the effect of changing the solvent to toluene was also investigated for both the alkyl diaza-crown ether **[2.6]** and the partially fluorinated diaza-crown ether **[2.36]**. ***Figure 3.4*** illustrates the time-dependent catalytic activity of these macrocyclic derivatives in toluene and benzotrifluoride. The results show the importance not only of the dielectric constant of the solvent (BTF >> toluene) but also its fluorophilicity. When the partially fluorinated macrocycle **[2.36]** was used, the reaction carried out in benzotrifluoride gave higher conversions than the reaction carried out in toluene. In this particular reaction, the decrease in the catalytic activity of macrocycle **[2.36]** compared to the bis(octyl) derivative **[2.6]** should be seen not only as a result of the electron-withdrawing effect of the fluorine atoms on its coordination centre, but also as a result of modifying the properties of this macrocycle, such as polarity and solubility, due to the fluoroponytails, that have an important effect on the reaction equilibria constants (***Scheme 3.3***).

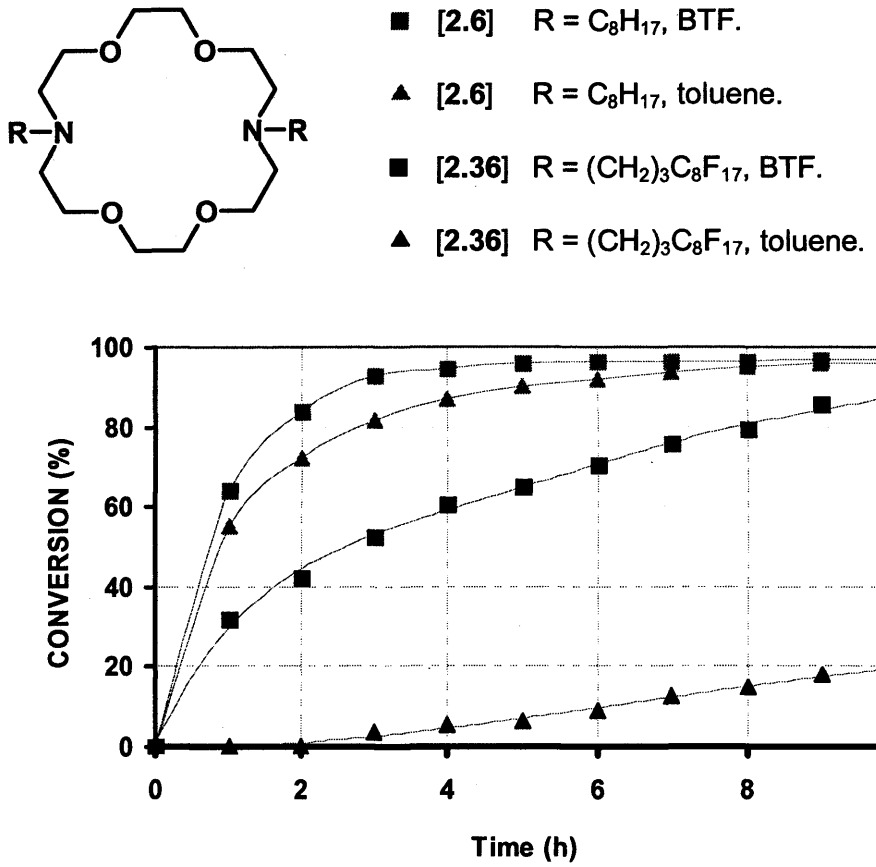


Figure 3.4. Phase transfer catalytic activity of diaza-crown ethers **[2.6]** and **[2.36]** in the conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$ in benzotrifluoride and toluene under solid-liquid conditions.

3.3.3 Separation and Recovery.

3.3.3.1 *Fluorous Solid Phase Extraction* (FSPE).

The separation and recovery of the most active fluorinated phase transfer catalyst **[2.36]** was investigated in the iodide displacement reaction in benzotrifluoride under solid-liquid conditions (***Scheme 3.5***) using fluorous solid-phase extraction. After 12 hours the organic phase was filtered and washed with water to eliminate the excess of potassium salts. After drying over magnesium sulphate, the clear organic phase was passed through a short column of fluorous reverse phase silica gel (~ 4 g). The column was then eluted with benzotrifluoride to obtain the clean organic products. No leaching of the catalyst was detected by ^1H and ^{19}F NMR spectroscopy. Partially fluorinated phase transfer catalyst **[2.36]** was then recovered (90-96%) by eluting with trifluoroethanol. In this way, macrocycle **[2.36]** was reused in the aliphatic

nucleophilic substitution six times (***Table 3.2***), with the slight drop in conversion caused by the mechanical losses of **[2.36]** after each recycle.

RUN	CATALYST USED (g)	CATALYST RECOVERED (g)	CONVERSION (%)
1	0.257	0.248	88.0
2	0.248	0.239	86.8
3	0.239	0.225	86.6
4	0.225	0.202	86.0
5	0.202	0.191	85.8
6	0.191	0.179	85.6

Table 3.2. Recycling results of macrocycle **[2.36]** with aqueous wash.

Diaza-crown ether **[2.36]** could also be recovered almost quantitatively (83-99 %) without the aqueous wash. However, the conversions for the subsequent aliphatic nucleophilic substitutions were not consistent after the fourth run (***Table 3.3***).

RUN	CATALYST RECOVERED (%)	CONVERSION (%)
1	99.4	89.5
2	98.6	87.4
3	98.0	87.1
4	89.3	90.2
5	84.1	66.3
6	83.3	93.0

Table 3.3. *Recycling results of macrocycle* **[2.36]** *without the aqueous wash.*

The aqueous wash of the organic phase before loading the reaction mixture onto the FRPSG column was demonstrated to be essential for the recovery process since

it removed the potassium metal cation coordinated with in the macrocycle. The coordinated potassium cation may interact with the hydroxy groups that are present in the FRPSG and this interaction could make the elution of the catalyst much more difficult. Hence, a series of experiments were carried out to investigate the best approach for removing the cation from the coordination centre of the macrocycle. Analysis by inductively coupled plasma (ICP) spectrometry showed that, after the synthesis, the presence of potassium metal cation in diaza-crown ethers **[2.6]** and **[2.36]** was extremely low (***Table 3.4***). To evaluate the complexation process with potassium iodide, the catalyst was stirred in refluxing dichloromethane for 1 h with 5 equivalents of potassium iodide. The solution was then filtered and the solvent was removed under reduced pressure. The diaza-crown ether was analysed by ICP spectrometry. The results in ***Table 3.4*** demonstrated that the amount of potassium metal cation coordinated with in the catalyst increased significantly after the complexing process, especially in the case of the partially fluorinated diaza-crown ether **[2.36]**. It was found that the best procedure for decomplexing the diaza-crown ethers was to wash the organic phase with water. Using this procedure, the amount of potassium coordinated to the catalyst was minimized (***Table 3.4***).

DIAZA-CROWN	After Synthesis	After Stirring with KI (5 eq)	After KI (5 eq) & aqueous wash
[2.6]	0.7	51.5	2.9
[2.36]	1.0	73.8	1.0

Table 3.4. Mol % of potassium detected by ICP analysis.

3.3.3.2 *Solid Phase Extraction.*

Macrocycle **[2.36]** was also recovered and reused using conventional silica gel (***Figure 3.5***), although the large volume of ethyl acetate (250 mL) that was required to recover the catalyst quantitatively (92-98%) in each cycle makes this method unpractical. Interestingly, the octyl derivative **[2.6]** could not be recovered from the column when solid phase extraction was attempted using conventional silica gel.

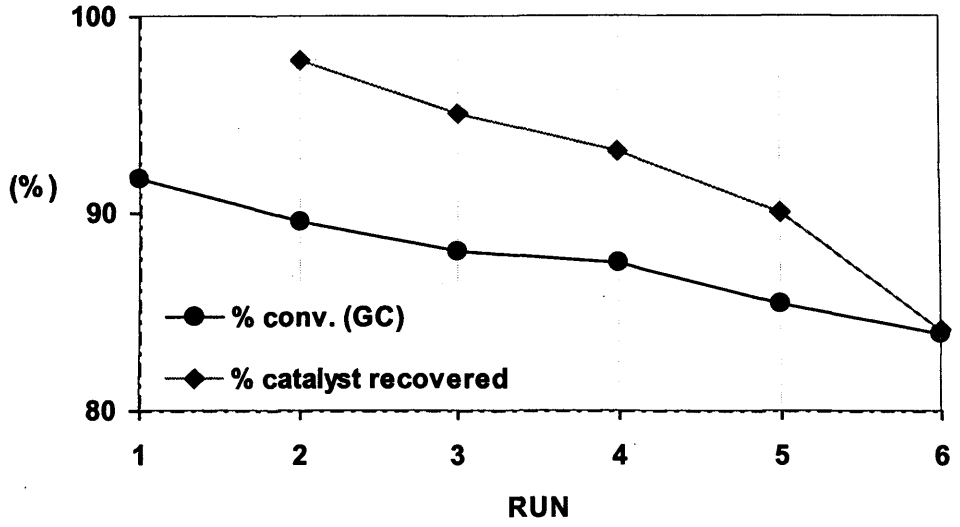


Figure 3.5. Separation and recovery of fluorinated diaza-crown ether **[2.36]** by SPE.

3.4 Phase Transfer Catalysis. Aromatic Nucleophilic Substitution.

3.4.1. Introduction.

Iodide displacement reactions provide straightforward model reactions because of the relative ease of iodide transfer into organic phases combined with its strong nucleophilicity and neglible hydration. However, in order to evaluate the catalytic activities of the new fluorinated phase transfer catalysts, they were tested in a fluoride displacement, also known as the Halex reaction. This is a more demanding nucleophilic substitution because the transfer of fluoride into organic solvents is difficult and, in addition, fluoride, particularly when hydrated, is not a good nucleophile.

Halex (halogen exchange) reactions are widely used for the synthesis of fluoroaromatics where a chlorinated or brominated aromatic compound undergoes substitution of the halogen atom for fluorine.[25] Introduction of fluorine into an organic molecule is a process of great importance because many pharmaceuticals, agrochemicals and other important chemical compounds contain fluorinated substituents.[26] This important, widely used reaction requires harsh conditions due to the insolubility of potassium fluoride (KF), the common source of fluoride anions, in the majority of solvents.

The use of dipolar aprotic solvents, like dimethylformamide (DMF), dimethylsulphoxide (DMSO), dimethylimidazolidinone (DMI), sulpholane, acetone or acetonitrile,[27] has led to significant increases in the rates of these aromatic

nucleophilic substitution reactions. In addition, most of these solvents have high boiling points and hence, the reaction can also be promoted thermally. Furthermore, the nucleophilicity of the fluoride ion is sufficiently high only in aprotic solvents, where the solubility of the metal fluoride is relatively low. The high charge density of the fluoride anion, and hence, its high energy of solvation in aprotic solvents makes halex reactions in liquid–liquid conditions an inefficient procedure.[28] Therefore, these reactions are heterogeneous solid-liquid systems, although it has been postulated that traces of water (0.2 - 0.3% w/w) may be essential to promote an effective transfer of the fluoride anion from the solid alkali metal fluoride surface into the organic phase.[29]

The alkali metal fluorides are the normal source of fluorine for the halex reaction. Their activity increases with the size of the metal cation: CsF > RbF > KF > NaF > LiF.[30] Unfortunately, the most active reagents, rubidium and cesium fluoride, are the most expensive whilst the cheapest reagents, sodium and lithium fluoride, are inactive in halex reactions. Consequently, potassium fluoride is normally chosen as the convenient, commercially available choice for halex reactions. In order to facilitate the transfer of fluoride into the organic phase, different physical modifications have been made to solid KF. For instance, it can be freeze dried,[31] dispersed on calcium fluoride[32] or spray dried.[33] Since the latter form of KF has a higher surface area, it is a much better source of fluoride.[33]

The use of phase transfer catalysts, such as quaternary ammonium and phosphonium salts, poly(ethylene glycol) or crown ethers, can also increase the amount of fluoride transferred into the organic solvent. Additionally, these catalysts enable the reaction to proceed under milder conditions. Crown ethers have been demonstrated to be very efficient halex catalysts, increasing the activity of alkali metal fluorides in aromatic nucleophilic substitution reactions.[28] Liotta *et al.* showed that fluoride ion, solubilised by 18-crown-6 from the potassium salt in acetonitrile or benzene, is sufficiently nucleophilic to give displacement reactions at sp^2 hybridised carbon. This is due to an increased solubility of alkali metal fluorides, and therefore, an increase in the concentration of the fluoride anion. In addition, the nucleophilicity of the fluorine ion is also improved as a consequence of the complexation of the alkali metal cation with the crown ether.

However, despite these improvements, occasionally the high energy of the crystalline network of KF and the low lipophilicity of fluoride anions, make the ion exchange equilibrium proceeding on the surface of solid KF unfavourable (***Scheme***

3.6), decreasing the concentration of fluoride in the organic phase.[34] Additionally, the high basicity of fluoride anions often results in a Hoffmann decomposition of the most common inexpensive phase transfer catalysts, the tetraalkylammonium salts.[35] This problem can be solved by using catalysts, such as crown ethers that react rapidly with potassium fluoride forming a reversible anionic complex of higher lipophilicity than "naked" fluoride anions and transferring these into the organic phase, where the reaction with the organic substrate takes place.

$$KF_{solid} + Q^+X^-_{org} \rightleftharpoons Q^+F^-_{org} + KX_{solid}$$

Scheme 3.6. Fluoride displacement equilibrium.

3.4.2. Fluorination of 2,4-dinitrochlorobenzene.

3.4.2.1. *Introduction.*

Due to the mesomeric effect of the *ortho*- and *para*-nitro groups in the plane of the aromatic ring, 2,4-dinitrochlorobenzene (2,4-DNCB) is relativity activated to aromatic nucleophilic substitution, and therefore, mild conditions can be used to carry out this type reaction. The product of the fluorination, 2,4-dinitrofluorobenzene (2,4-DNFB), also known as Sanger's reagent, is used as a reagent for labelling terminal amino acid groups in protein chains.[36] In addition, it is used as an intermediate for the synthesis of pesticides and pharmaceuticals such as flurbiprofen, which is a non-steroidal anti-inflammatory agent produced by Pfizer.

Yakobson *et al.* demonstrated that even a small amount of crown ether could markedly promote the synthesis of 2,4-DNFB from 2,4-DNCB in acetonitrile. It was established that, in the case of 2,4-DNCB, the yield linearly depends on the concentration of crown ether only at the initial stage of the reaction.[30] He also demonstrated that the catalytic activity of the crown ethers is practically independent of the nature of the substrate, but it strongly depends on the nature of the alkaline metal fluoride.

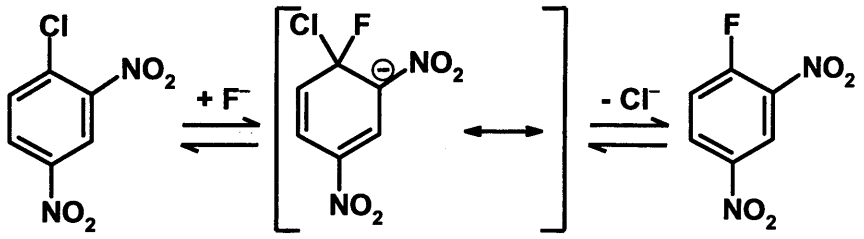
Using a real-time electrochemical detection methodology based on the use of square wave voltammetry Compton and co-workers demonstrated that, under solid-liquid conditions, the fluorination of 2,4-DNCB exhibits a mixed homogeneous and heterogeneous kinetic behaviour. Initially, it was observed that the homogeneous reaction, where the fluoride anion in solution is consumed, dominates the reaction

kinetics according to the second-order rate constant k_{hom} (***Equation 3.2***). As time progresses, ***Equation 3.3*** describes the decreasing amount of fluoride anion, consumed by the homogeneous reaction, and the production of fluoride anion by dissolution of KF;

$$\frac{d\,[DNCB]}{dt} = -\,k_{hom}\cdot[DNCB]\cdot[F^-] \qquad \textit{Equation 3.2}$$

$$\frac{d\,[F^-]}{dt} = -\,k_{hom}\cdot[DNCB]\cdot[F^-] + K_L\cdot([F^-]_{sat} - [F^-]) \qquad \textit{Equation 3.3}$$

where $[F^-]_{sat}$ is the saturation concentration of F^- and K_L is the effective mass transport coefficient, which increases linearly with the mass of KF added to the system. Compton observed that 2,4-DNCB disappears rapidly over the first few minutes of the reaction, although the formation of 2,4-DNFB is much slower over a longer period. Therefore, it is a combined fast homogeneous and slow heterogeneous kinetics, where the reaction rate is *dissolution-rate-limited* after a long time.[37] ***Scheme 3.7*** illustrates the mechanism proposed for this reaction based on the voltammetry and UV-visible spectroscopy experiments.



2,4-DNCB **2,4-DNFB**

Scheme 3.7. Proposed mechanism for the synthesis of 2,4-DNFB.[37]

It is commonly accepted that nucleophilic aromatic substitution reactions involving activated substrates and good leaving groups proceed by a two-step mechanism; the first step is the covalent addition of a nucleophile to a substituted ring carbon atom of the aromatic substrate, leading to an anionic σ-complex known as the Meisenheimer complex (***Figure 3.6***).[38]

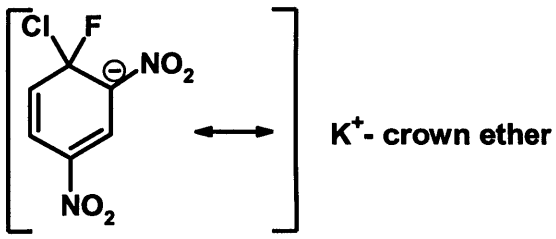


Figure 3.6. *Meisenheimer Complex.*

It is well established that ion-pairing plays an important role in the stabilisation of Meisenheimer complexes and that a poor interaction between the dinitrobenzene anion and the crown ether complexed potassium cation could make the Meisenheimer complex unstable towards decomposition (to product or to starting material).[39] Therefore, it is important that the fluorinated crown ether "helps" to stabilize the Meisenheimer complex *via* strong cation coordination.

3.4.2.2. *Fluorination of 2,4-dinitrochlorobenzene. Results and Discussion.*

A small series of common, commercially available phase transfer catalysts, such as dibenzo-18-crown-6 (DB18C6), tetraphenylphosphonium bromide (Ph_4PBr), 4,13-diaza-18-crown-6, [**2.7**], and 18-crown-6 were first used to optimise the reaction conditions for the fluorination of 2,4-dinitrochlorobenzene in acetonitrile using spray-dried potassium fluoride, previously activated by heating at 170 °C for 8 h. Initially, the reaction was carried out in refluxing acetonitrile using 5 mol % of catalyst and 1 equivalent of KF. In these conditions, with dibenzo-18-crown-6 as phase transfer catalyst, the conversion, analysed by gas chromatography, was only 19.5% after 12 h. When the amount of KF was increased to 1.5 equivalents, the results obtained did not show any significant improvement (***Table 3.5***). Surprisingly, after increasing the amount of KF to 3 equivalents, the conversion after 12 h was only improved significantly when DB18C6 was used as the catalyst (***Table 3.6***).

	CONVERSION (%)
18-crown-6	64.6
dibenzo-18-crown-6	25.1
4,13-diaza-18-crown-6	12.5
tetraphenylphosphonium bromide	31.3

Table 3.5. Fluorination of 2,4-dinitrochlorobenzene in acetonitrile using 5 mol % of catalyst and 1.5 eq. of KF for 12 h under solid-liquid conditions.

	CONVERSION (%)	
	12 h	24 h
18-crown-6	60.0	71.1
dibenzo-18-crown-6	47.0	56.3
4,13-diaza-18-crown-6	14.2	18.5
tetraphenylphosphonium bromide	39.5	41.2

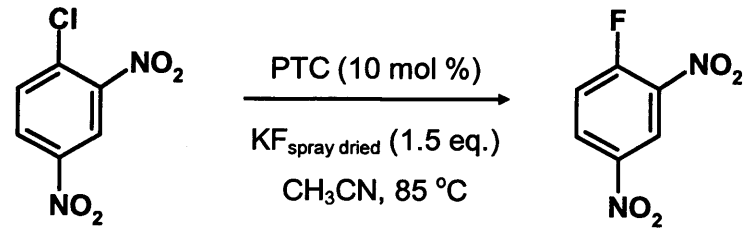
Table 3.6. Fluorination of 2,4-dinitrochlorobenzene in acetonitrile using 5 mol % of catalyst and 3 eq. of KF for 12 h and 24 h under solid-liquid conditions.

By increasing the amount of phase transfer catalyst to 10 mol %, and using 1.5 equivalents of potassium fluoride, the conversions were improved dramatically after 12 h and 24 h of reaction (**Table 3.7**).

	CONVERSION (%)	
	12 h	24 h
18-crown-6	89.5	90.5
dibenzo-18-crown-6	81.0	76.7
4,13-diaza-18-crown-6	44.9	49.9
tetraphenylphosphonium bromide	61.7	81.3

Table 3.7. Fluorination of 2,4-dinitrochlorobenzene in acetonitrile using 10 mol % of catalyst and 1.5 eq. of KF for 12 h and 24 h under solid-liquid conditions.

The catalytic activities of the derivatised diaza-crown ethers **[2.6]**, **[2.36]**, **[2.37]** and **[2.19]** were therefore investigated in the fluorination of 2,4-DNCB under solid-liquid conditions using 1.5 equivalents of spray-dried potassium fluoride in refluxing acetonitrile with 10 mol % of the phase transfer catalyst (***Scheme 3.8***). Two conventional phase transfer catalysts, tetraphenyphosphonium bromide (TPPB) and dibenzo-18-crown-6 (DB18C6), were also used for direct comparison. Two independent reactions were carried out for each catalyst, one for 12 h and the other for 24 h. A sample of the solution was collected after the reaction time, and analysed by gas chromatography to determine the percent conversion to product using biphenyl as the internal standard. The results are illustrated in ***Figure 3.7***.



2,4-DNCB **2,4-DNFB**

Scheme 3.8. Fluorination of 2,4-DNCB.

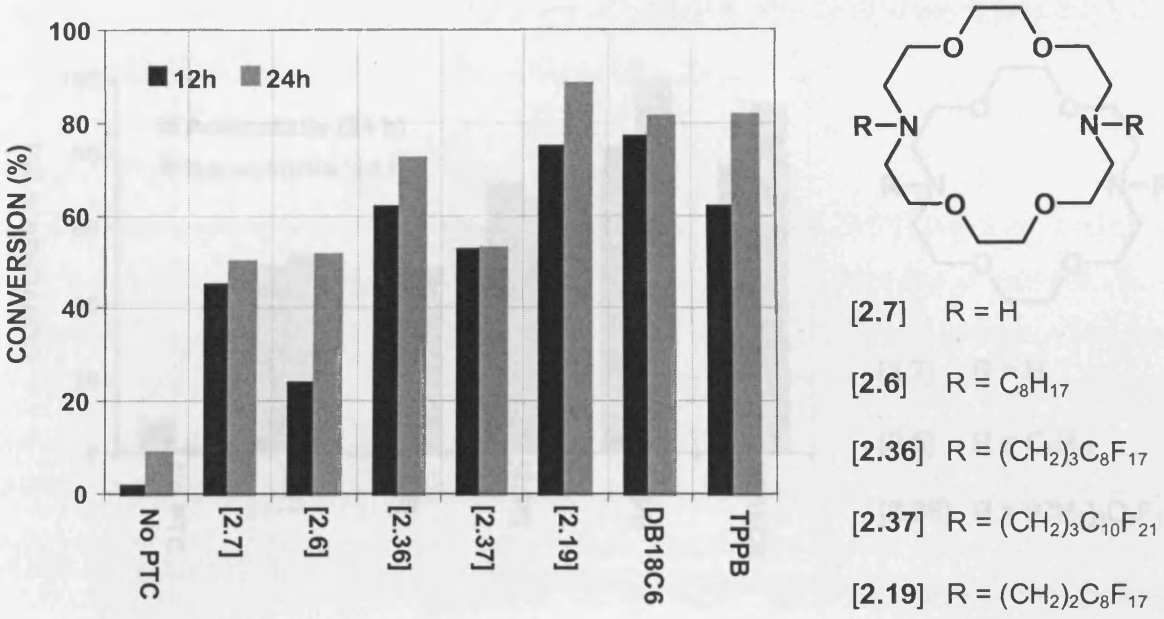


Figure 3.7. Phase transfer catalytic activity of diaza-crown ethers in the fluorination of 2,4-dinitrochlorobenzene in acetonitrile under solid-liquid conditions.

There was only 9 % conversion to 2,4-dinitrofluorobenzene in 24 h in the absence of a phase transfer catalyst due to the low solubility of fluoride in acetonitrile. In contrast to the iodide displacements, the reactivity of the diaza-crown ethers was completely reversed. The fluorinated macrocycle [**2.19**] with the smallest spacer group (two methylene units) was more reactive than macrocycle [**2.36**], which contained three methylene spacer groups, and they were both more reactive than the alkyl derivative [**2.6**] and 4,13-diaza-18-crown-6, [**2.7**]. The lower reactivity of macrocycle [**2.37**], compared to macrocycle [**2.36**], was expected due to its' lower solubility in acetonitrile because of the longer perfluorodecyl groups. Surprisingly, *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6 [**2.19**] proved to be an extremely effective phase transfer catalyst for the halex reaction with comparable reactivity to the conventional phase transfer catalysts, tetraphenylphosphonium bromide (TPPB) and dibenzo-18-crown-6 (DB18C6).

In order to improve the catalytic activity of diaza-crown ethers [**2.6**], [**2.7**] and [**2.36**], these phase transfer catalysts were investigated in the same reaction using benzonitrile as the dipolar aprotic solvent (***Figure 3.8***). The boiling point of this solvent is significantly higher (190.7 °C), allowing a higher reaction temperature. However, during the synthesis of 2,4-DNFB the temperature was fixed at 120 °C due to the potential risk of explosion of the dinitroaromatic compounds.

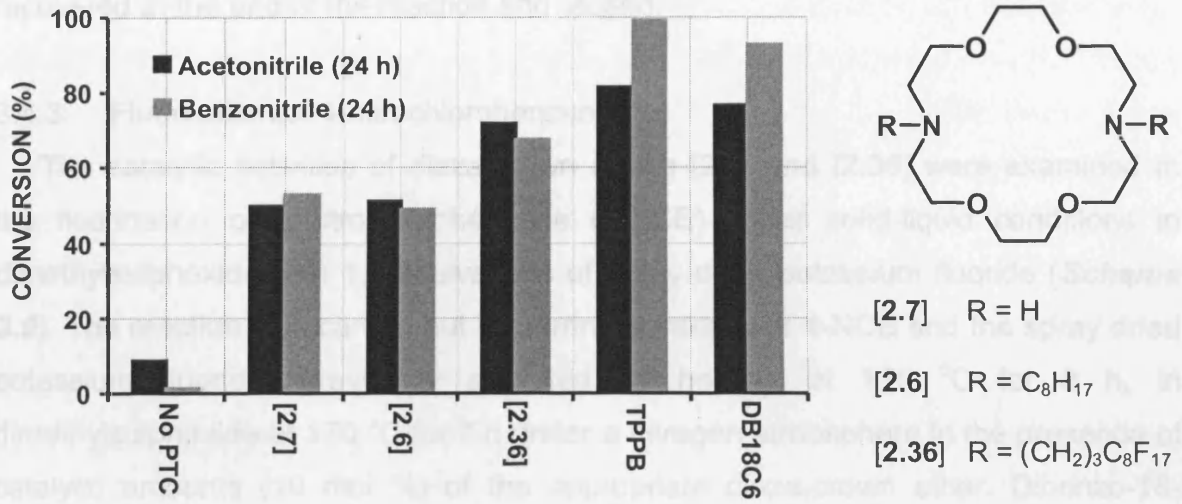


Figure 3.8. Phase transfer catalytic activity of different diaza-crown ethers in the fluorination of 2,4-dinitrochlorobenzene in acetonitrile and benzonitrile under solid-liquid conditions after 24 h.

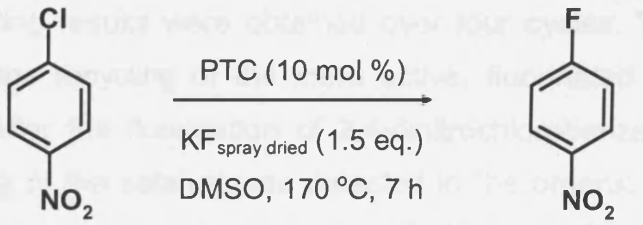
Without phase transfer catalyst in the organic phase there was practically no conversion into product (< 2%). The catalytic activities after 24 h were similar to the results obtained using acetonitrile, evidencing the same general trend. These results showed that, although temperature is a crucial factor in order to promote phase transfer catalysed reactions, in this particular case, an increase of 35 °C did not have a great impact on the catalytic activity of the diaza-crown ethers.

The fluorination reaction of 2,4-dinitrochlorobenzene was also carried out in dimethylformamide at different temperatures and reaction times in the absence of a phase transfer catalyst. The results showed that after 12 h at 85 °C, the reaction was complete (97.0%). Furthermore, when the reaction temperature was increased to 120 °C, the conversion was 81.4% in only 2 h. These results show why DMF is normally used in fluorination reactions. Although the reaction time can be reduced significantly by using DMF and there is no need for phase transfer catalysts, this solvent presents two problems, namely difficult work-up and very high toxicity. Due to these difficulties, the procedure developed for the fluorination of 2,4-dinitrochlorobenzene using acetonitrile as a less toxic, aprotic solvent seems preferable because it allows the reaction to take place under milder conditions, using efficient phase transfer catalysts that can be recycled using fluorous techniques. In addition, the recyclability of the

catalyst implicates that this could be used in higher percentage since it is going to be recovered at the end of the reaction and reused.

3.4.3. Fluorination of 4-nitrochlorobenzene.

The catalytic activities of diaza-crown ethers [**2.7**] and [**2.36**] were examined in the fluorination of 4-nitrochlorobenzene (4-NCB) under solid-liquid conditions in dimethylsulphoxide with 1.5 equivalents of spray dried potassium fluoride (***Scheme 3.9***). The reaction was carried out by stirring a mixture of 4-NCB and the spray dried potassium fluoride, previously activated by heating at 170 °C for 8 h, in dimethylsulphoxide at 170 °C for 7 h under a nitrogen atmosphere in the presence of catalytic amounts (10 mol %) of the appropriate diaza-crown ether. Dibenzo-18-crown-6 (DB18C6) and 18-crown-6 (18C6) were also investigated for direct comparison. A sample of the solution was collected at the end of the reaction and analysed by gas chromatography to determine the percent conversion to product using biphenyl as an internal standard. The results are summarised in ***Figure 3.9***.



4-NCB **4-NFB**

Scheme 3.9. Fluorination reaction of 4-NCB.

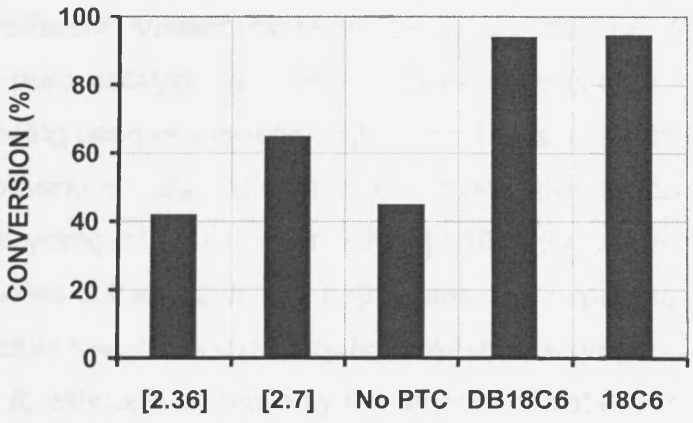


Figure 3.9. Fluorination of 4-NCB in DMSO.

Since 4-nitrochlorobenzene is less activated towards nucleophilic substitution, the conversion was much lower than in the fluorination of 2,4-dinitrochlorobenzene even although more drastic reaction conditions were used. Surprisingly, the fluorinated diaza-crown ether **[2.36]** does not catalyze the fluorination of 4-NCB under these reaction conditions. Different reaction conditions and solvent systems, such as acetonitrile or PEG, were studied in order to improve the catalytic activity of the diaza-crown ether, however, no satisfactory results were achieved.

3.4.4 Separation and Recovery. Results and Discussion.

Using a similar protocol to that developed for the iodide displacement reaction, the perfluoroalkylated diaza-crown ether **[2.36]** was recycled efficiently after the fluorination of 2,4-dinitrochlorobenzene by fluorous solid-phase extraction (***Table 3.8***). After an aqueous work up, the crude reaction mixture was loaded onto a short column of FRP silica gel. The clean organic products were eluted first from the column using dichloromethane. By a simple solvent switch to trifluoroethanol, and then ethyl acetate, the fluorinated catalyst was recovered quantitatively (94-97 %) and excellent recycling results were obtained over four cycles. The same protocol was also used for the recycling of the more active, fluorinated diaza-crown ether **[2.19]** (***Table 3.9***) after the fluorination of 2,4-dinitrochlorobenzene. Unfortunately, although no leaching of the catalyst was detected in the organic phase after FSPE experiment, only a low recovery of macrocycle **[2.19]** (74-86 %) from the column of fluorous reverse phase silica gel resulted in a drop in conversion on recycling the catalyst in runs 2 and 3. These results are in contrast with the preliminary recycling results discussed in **Chapter 2**. Based on the preliminary studies partially fluorinated diaza-crown ether **[2.19]** should be easily recovered by fluorous solid-phase extraction using different solvent systems. However, the previous results were obtained with the pure catalyst and not with potassium coordinated to the diaza-crown ether after being used in a reaction, although it was found that, after synthesis, the presence of potassium metal cation in diaza-crown ether **[2.19]** was high (38 mol % by ICP). The recycling of diaza-crown ether **[2.19]** was carried with and without aqueous wash (***Tables 3.9 and 3.10***). In both cases, the experiments were repeated twice with reproducible results. Without aqueous wash, the drop in activity appears to be faster than with it, although surprisingly the amount of catalyst recovered after the third run was higher without aqueous wash. ICP spectroscopy demonstrated that the

amount of potassium coordinated after the aqueous wash was still very high, 90 mol %.

RUN	CATALYST USED (g)	CATALYST RECOVERED (g)	CONVERSION (%)
1	0.119	0.112	70.8
2	0.112	0.108	69.4
3	0.108	0.105	68.7
4	0.105	0.099	67.9

Table 3.8. Recycling results of diaza-crown ether **[2.36]**.

RUN	CATALYST USED (g)	CATALYST RECOVERED (g)	CONVERSION (%)
1	0.116	0.100	89.9
2	0.100	0.084	82.6
3	0.084	0.062	68.8

Table 3.9. Recycling results of diaza-crown ether **[2.19]** using an aqueous wash.

RUN	CATALYST USED (g)	CATALYST RECOVERED (g)	CONVERSION (%)
1	0.115	0.098	86.0
2	0.098	0.094	65.4
3	0.094	0.089	63.9

Table 3.10. Recycling results of diaza-crown ether **[2.19]** without an aqueous wash.

3.5 Conclusions.

N,N'-Bis(octyl)-4,13-diaza-18-crown-6 **[2.6]**, *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6 **[2.36]**, *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6 **[2.37]** and *N,N'*-bis-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6 **[2.19]** were successfully used for the first time as phase transfer catalysts under solid-liquid conditions in aliphatic and aromatic nucleophilic substitution reactions with iodide and fluoride respectively. The fluorinated macrocycles **[2.36]** and **[2.19]** gave similar, if not better, phase transfer catalytic activity compared to the non-fluorinated catalyst 4,13-diaza-18-crown-6, **[2.7]**, and the alkylated diaza-crown ether **[2.6]**. Although macrocycle **[2.19]** gave higher catalytic activity in the difficult aromatic chloride-to-fluoride exchange, only poor recycling results were obtained by fluorous solid-phase extraction. Fluorinated diaza-crown ether **[2.36]**, on the other hand, was recycled six times using fluorous solid-phase extraction in the conversion of 1-bromooctane into 1-iodooctane and four times in the conversion of 2,4-dinitrochlorobenzene into 2,4-dinitrofluorobenzene without any loss in activity. Further work should be focussed on further applications of this stable, recyclable phase transfer catalyst.

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CHAPTER FOUR

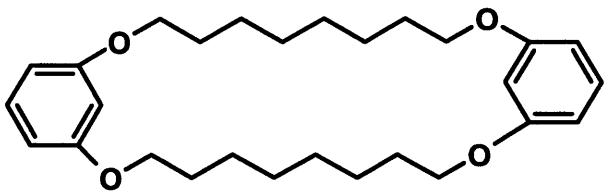
Synthesis of Partially Fluorinated Dibenzo-18-crown-6 Ethers

University *of* Leicester

4.1 Introduction to Dibenzo-18-Crown-6 Ethers.

4.1.1 Introduction.

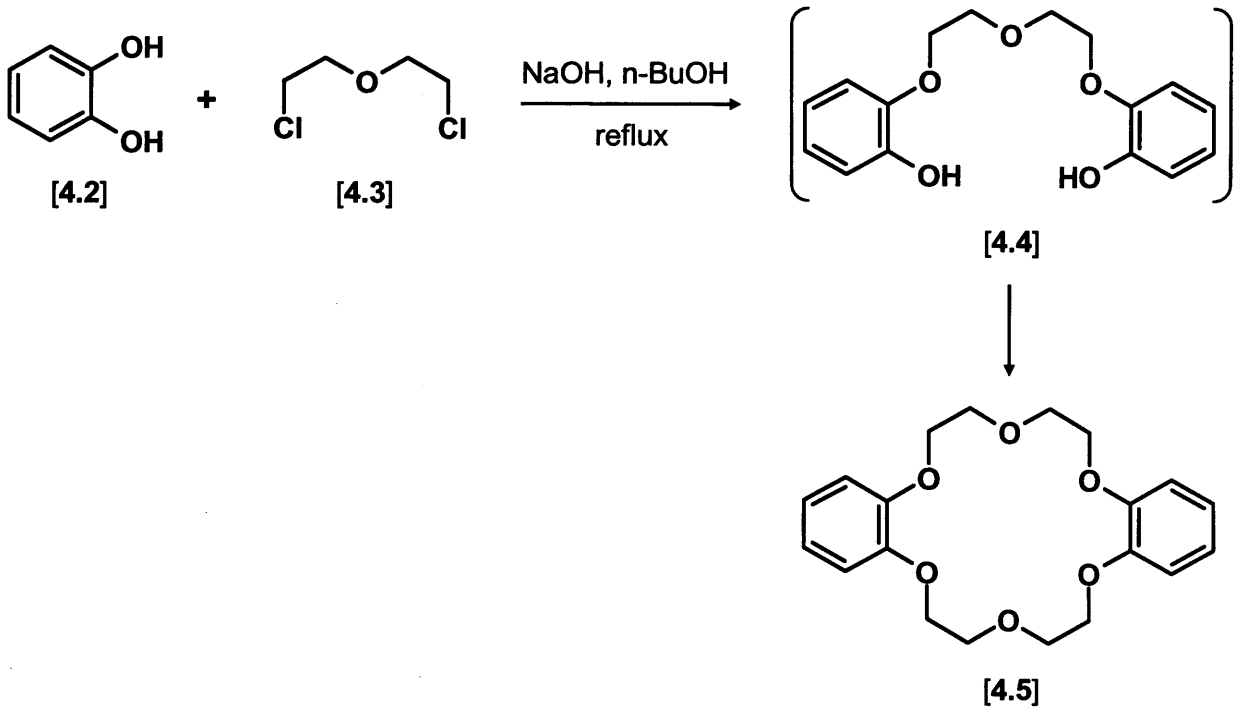
In the 1950's, pioneering work by Lüttringhaus in the field of macrocyclic chemistry led to the synthesis of a large macrocycle containing two aromatic rings by reacting 1,3-dihydroxybenzene with long-chain dithiol derivatives (***Figure 4.1***).[1] Dibenzo macrocycle compound [**4.1**] lacked sufficient donor groups to exhibit any significant cation binding properties, however, this first work opened the door to different studies targeting the synthesis of such compounds.



[4.1]

Figure 4.1. Macrocycle of Lüttringhaus.

It was not until 1967, that Pedersen reported the synthesis of the first crown ether, dibenzo-18-crown-6, a macrocyclic compound containing six donor groups that proved to be unusually effective for cation complexation (***Scheme 4.1***).[2]

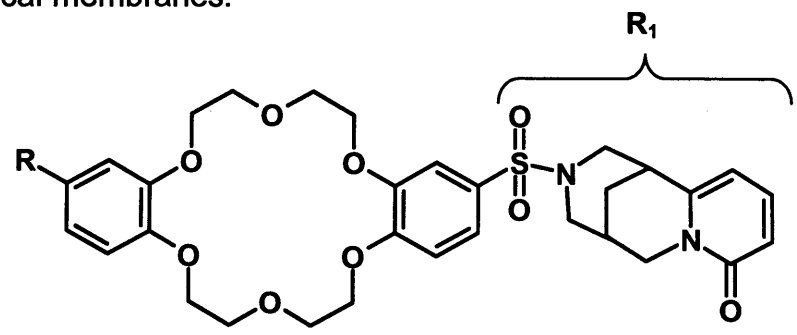


[4.2] [4.3] [4.4] [4.5]

Scheme 4.1. Synthesis of dibenzo-18-crown-6.

In the presence of sodium hydroxide, 1,2-dihydroxybenzene **[4.2]** forms a nucleophilic species, which will react with 2,2'-dichlorodiethyl ether **[4.3]** in a quadruple Williamson reaction to yield dibenzo-18-crown-6. Pedersen immediately recognised the remarkable property of crown ethers, and dibenzo-crown ether in particular, to complex other species. This ability to form stable complexes with different cations and anions initiated new areas of chemical research.

The aromatic rings of dibenzo-18-crown-6 are relatively reactive toward electrophilic aromatic substitutions. Thus, different modifications have been made to the dibenzo-crown ether structure in order to investigate the influence of ligand configuration on their metal cation complexing properties. These modifications have ranged from adding alkyl or haloalkyl chains[3] to different functional groups such as ketones,[4] alcohols,[4] amines,[5] amides,[6] thiolenes[7] and sulfamides.[8] It is important to observe that, unlike 18-crown-6 or dicyclohexyl-18-crown-6, while dibenzo-18-crown-6 has rarely been used as a catalyst because of its lower solubility and relatively lower binding constants for alkali cations, alkylated dibenzo-18-crown-6 compounds have shown their potential to perform more efficiently as phase transfer catalysts due to their higher solubilities in common organic solvents and better complexing abilities.[9] However, although their coordination properties have been investigated in depth, the applications of dibenzo-crown ether derivatives are still very limited. An interesting application of dibenzo-crown ethers is the preparation of sulfonic acids with potential medical applications derived from dibenzo-18-crown-6 containing the quinolizidine alkaloid cytisine (***Figure 4.2***),[8] which is used medically as a respiratory stimulant. The resulting sulfamides include the physiologically active alkaloid, the pharmacological sulfamide, and the dibenzo-crown ether, which has the ability to form stable complexes and transfer calcium, sodium, and other vital metal cations through biological membranes.



R = CH_3CO [4.6a], *sec*-C_4H_9 [4.6b], R_1 [4.6c]

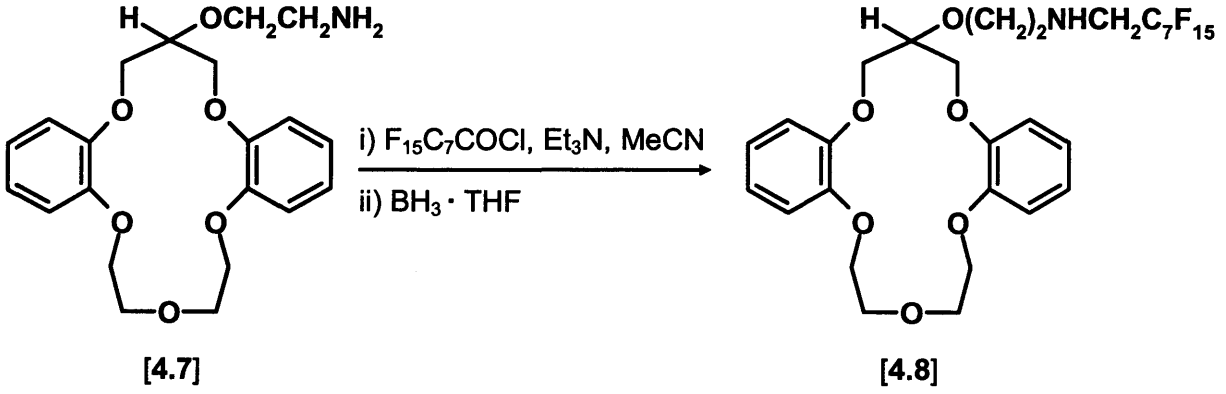
Figure 4.2. Cytisine dibenzo-crown derivative.

4.1.2 Fluorinated Dibenzo-18-crown-6 Ethers.

Recently, the discovery that macrocyclic ligands with fluorine atoms in their cavities or attached fluorinated sidearms have potential applications in metal ion separations involving a fluorous phase,[10] has attracted an increasing attention to these macrocyclic compounds. In addition, it has been found that macrocycles with a fluorine label on the macrocyclic framework have potential applications as ^{19}F NMR imaging agents.[11]

Although the synthesis of fluorine-containing crown ethers is still rarely reported due to limited of starting materials containing fluorine atoms, a number of fluorinated and perfluorinated crown ethers have been synthesised in recent years.[12] In general, the complexing abilities of these fluorinated macrocycles and, therefore, their catalytic activities, are greatly affected by the electron-withdrawing effect of the fluorine atoms.

Amongst the different fluorinated crown ethers that have been synthesised, the number of fluorinated benzo or dibenzo-crown ether derivatives is still very limited. For instance, Bartsch and co-workers reported the synthesis of macrocyclic amines with a partially fluorinated side arm based on a *sym*-dibenzo-16-crown-5 scaffold (***Scheme 4.2***).[13] Dibenzo-crown ether derivative [**4.8**] was prepared by the reaction of commercially available perfluorooctanoyl chloride with amine [**4.7**][14] and triethylamine in acetonitrile, followed by reduction with the borane-tetrahydrofuran complex in tetrahydrofuran. The analogous 1,2-dicyclohexane substituted crown ether was synthesised using the same procedure.



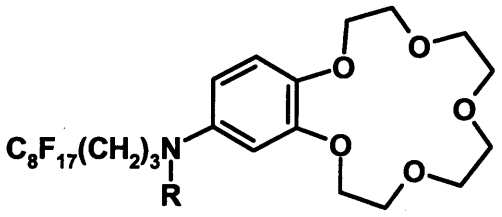
[4.7] [4.8]

Scheme 4.2. Synthesis of *N*-(1*H*,1*H*-perfluorooctyl) *sym*-(2-aminoethyl)dibenzo-16-crown-5.

Bartsch determined that the alkali metal picrate complexation ability increases when dialkyl ether oxygens replace alkyl aryl ether oxygens. Therefore, the primary structural difference between 1,2-dicyclohexanyl and 1,2-dibenzo substituted

crown ethers decreases of oxygen basicity of the latter crown ether, probably due to the mesomeric effect of the aromatic rings over the four oxygen atoms that makes them weaker electron-donors. Furthermore, its molecular conformation probably also contributes to the lower extraction value due to π–π interactions of the two benzene rings that could block one side of the cavity. Another contributing factor could be that dicyclohexanyl derivative gives sp^3-hybridised ethers whilst dibenzo gives sp^2-hybridised ethers. It was also observed that these bis(crown ethers) can form intramolecular sandwich complexes in which adjacent crown ether units cooperate in metal ion binding.[13]

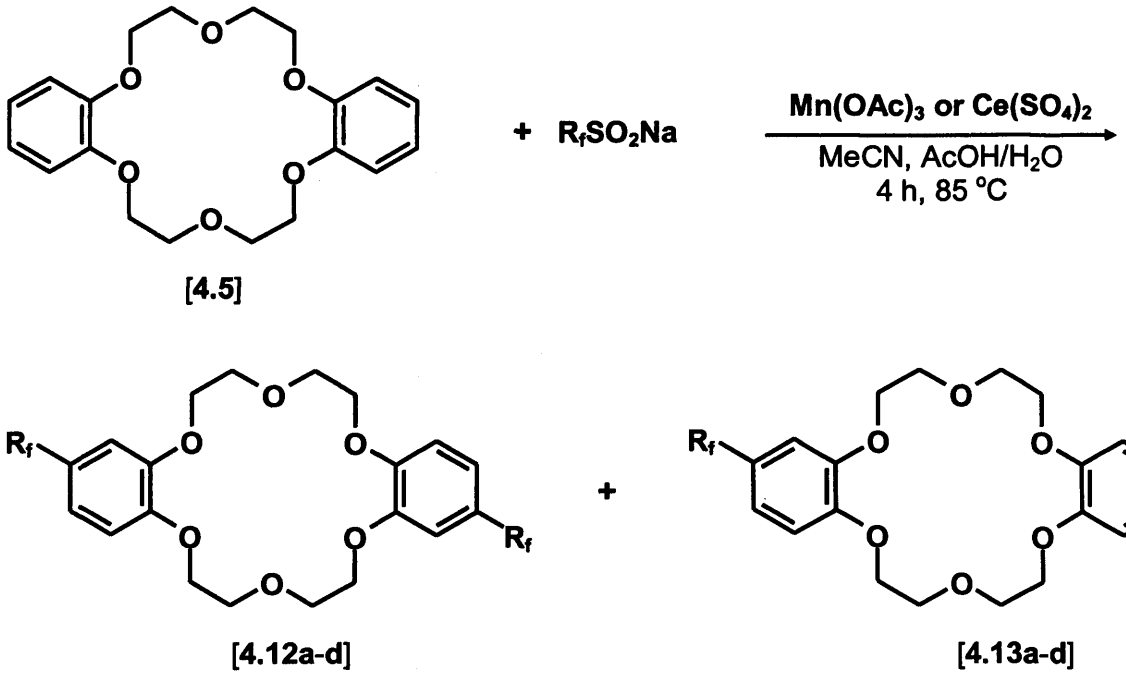
Using Bartsch's approach,[13] Shinkai and co-workers synthesised a series of fluorinated benzo-15-crown-5 ethers with the structure shown in ***Figure 4.3***. These fluorinated aminobenzo-crown ethers were used successfully as thermally controlled ion-carriers through a polycarbonate/liquid crystal membrane, also known as an immobilized liquid membrane.[15]



R = H [**4.9**], $Me(CH_2)_2CO$ [**4.10**], $Me(CH_2)_{10}CO$ [**4.11**].

Figure 4.3. Synthesis of fluorinated aminobenzo-crown ethers [**4.9**], [**4.10**] and [**4.11**].

More recently, a facile synthesis of perfluoroalkyl dibenzo-crown ethers has been reported by direct perfluoroalkylation with sodium perfluoroalkanesulfinates in the presence of an oxidant.[16] Cerium sulphate or manganese acetate and dibenzo-18-crown-6 [**4.5**] were reacted with sodium perfluoroalkanesulfinates (R_fSO_2Na) in aqueous acetonitrile-acetic acid mixture at 85 °C, giving the corresponding perfluoroalkylated products as a mixture of two isomers, [**4.12a-d**] and [**4.13a-d**], which were separated by column chromatography over silica gel (***Scheme 4.3***).



$R_f = F(CF_2)_6$, $F(CF_2)_8$, $Cl(CF_2)_6$ or $Cl(CF_2)_8$

Scheme 4.3. Perfluoroalkylation of dibenzo-crown ethers with sodium perfluoroalkanesulfinates.

The reaction of sodium perfluoroalkanesulfinate with the oxidant results in the formation of a perfluoroalkyl radical.[17] Thus, a free radical-cation mechanism was proposed. The radical intermediate generated from the reaction of the perfluoroalkyl radical and the dibenzo-crown ether was further oxidized to form the corresponding cation, which lost a proton to give the products.

Preliminary metal ion extraction studies showed that their complexing ability decreased with the introduction of the perfluoroalkyl groups. However, the perfluoroalkylated crown ethers possessed good solubilities in most organic solvents as well as perfluorocarbon solvents such as Freon 113 (1,1,2-trichloro-1,2,2-trifluoroethane) and hexafluorobenzene.

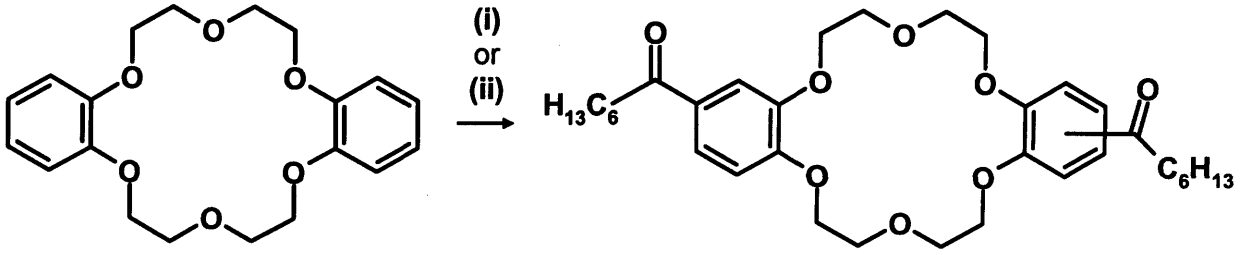
4.2 Synthesis of Partially Fluorinated Dibenzo-18-crown-6 Ethers. Results and Discussion.

Dibenzo-18-crown-6 was chosen as starting material for the second generation of crown ether derivatives because this catalyst has superior phase transfer activity in comparison with the diaza-18-crown-6 derivatives studied previously. In addition, it

was expected to be relatively easy to functionalise the aromatic rings. Initially, it was decided to look at two different types of derivatised dibenzo-18-crown 6 ethers; fluorinated and non-fluorinated amino derivatives, and alkyl and perfluoroalkyl derivatives. In both classes of fluorinated derivatives, spacer groups were incorporated to minimize the electron-withdrawing effect of the fluorine atoms.

4.2.1 Synthesis of bis(heptyl)dibenzo-18-crown-6.

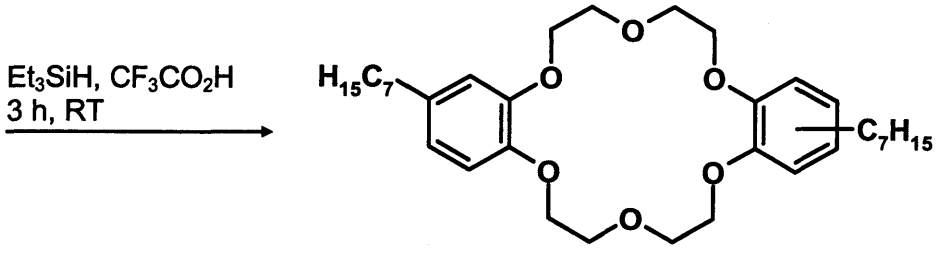
It was decided to synthesise alkylated and perfluoroalkylated dibenzo-crown ether derivatives to investigate the binding properties of the dibenzo-crown ethers bearing sidearms without donor atoms. Bis(heptyl)dibenzo-18-crown-6 [**4.17**] was synthesised (***Scheme 4.4***) in order to have a direct comparison between the catalytic activities and chemical properties of the non-fluorinated and fluorinated dibenzo-crown ether derivatives.



[**4.5**] [**4.16**] (84%); **i.**

(i) $C_6H_{13}CO_2H$ [**4.14**], PPA, 1 h, 90 °C.

(ii) $C_6H_{13}COCl$ [**4.15**], $AlCl_3$, $CHCl_3$, 4 h, 50 °C.



[**4.17**] (40%)

Scheme 4.4. Synthesis of bis(heptyl)dibenzo-18-crown-6.

Scheme 4.4 illustrates the two routes that were investigated for the synthesis of bis(heptanoyl)dibenzo-18-crown-6, [**4.17**]. The first approach (**i**) consists in the

acylation of dibenzo-18-crown-6 [**4.5**] with heptanoic acid [**4.14**] using polyphosphoric acid as both solvent and catalyst to afford bis(acylated)dibenzo-18-crown-6 [**4.16**] in high yield (84%). Diacylation of dibenzo-18-crown-6 lead to both the *cis*- and *trans*-isomers, which were not separated. This is a better method than the more commonly used acylation of dibenzo crown ethers with carboxylic acids and Eaton's reagent (phosphorus pentoxide in methanesulfonic acid).[18]

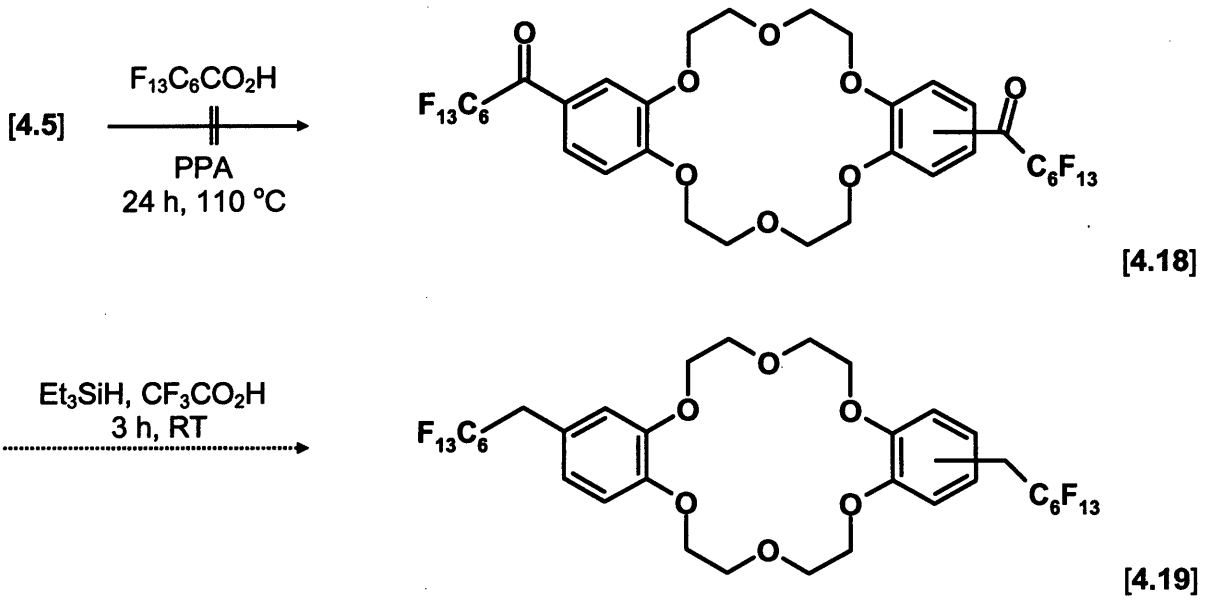
Route (**ii**) is a Friedel-Crafts acylation with heptanoyl chloride in chloroform, using aluminium trichloride as the Lewis acid catalyst.[19,20] This procedure was repeated a number of times with different reaction parameters, but compound [**4.16**] was always isolated in a low yield. This is because the acylation of benzo crown ether derivatives in the presence of aluminium trichloride results in the formation of undesired side products, including strong stable complexes. The Lewis acid catalyst and/or the reactive electrophilic intermediate may become complexed and consequently, deactivated by the crown ether.[21] Therefore, the approach utilizing polyphosphoric acid as catalyst was found to be the most suitable acylation procedure.

A number of different methods have been reported in the literature for the selective reduction of aryl ketone groups in acylated benzo crown ethers to methylene.[22] However, the reduction of the carbonyl groups of compound [**4.16**] by triethylsilane in trifluoroacetic acid (***Scheme 4.4***) at room temperature was preferred due to the selective reaction giving only the desired product in an expected high yield. Alkylated dibenzo-crown ether [**4.17**] was obtained in an acceptable yield (40%). This dibenzo-crown ether derivative is soluble in conventional solvents such as chloroform, dichloromethane, tetrahydrofuran, ethyl acetate and diethyl ether.

4.2.2 Synthesis of bis(perfluoroalkyl)dibenzo-18-crown-6.

Scheme 4.5 illustrates the proposed method for the synthesis of bis(perfluoroalkyl) dibenzo-18-crown-6, which is based on the procedure that was described above for the preparation of bis(heptyl)dibenzo-18-crown-6 [**4.17**]. Although the reaction conditions in the first step were more severe than in the synthesis of the non-fluorous analogue, no reaction took place. This must be due to the strong electron-withdrawing effect of the perfluoroalkyl groups of the heptanoic acid that inhibits the formation of the active electrophilic species, $F_{13}C_6C{\equiv}O^+$, and, hence, the reaction cannot take place. *2H,2H*-Perfluorooctan-1-oic acid [**4.20**] was also utilized for the synthesise of the corresponding perfluoroacyl dibenzo-crown ether derivative. However, no reaction occurred. This demonstrates that the

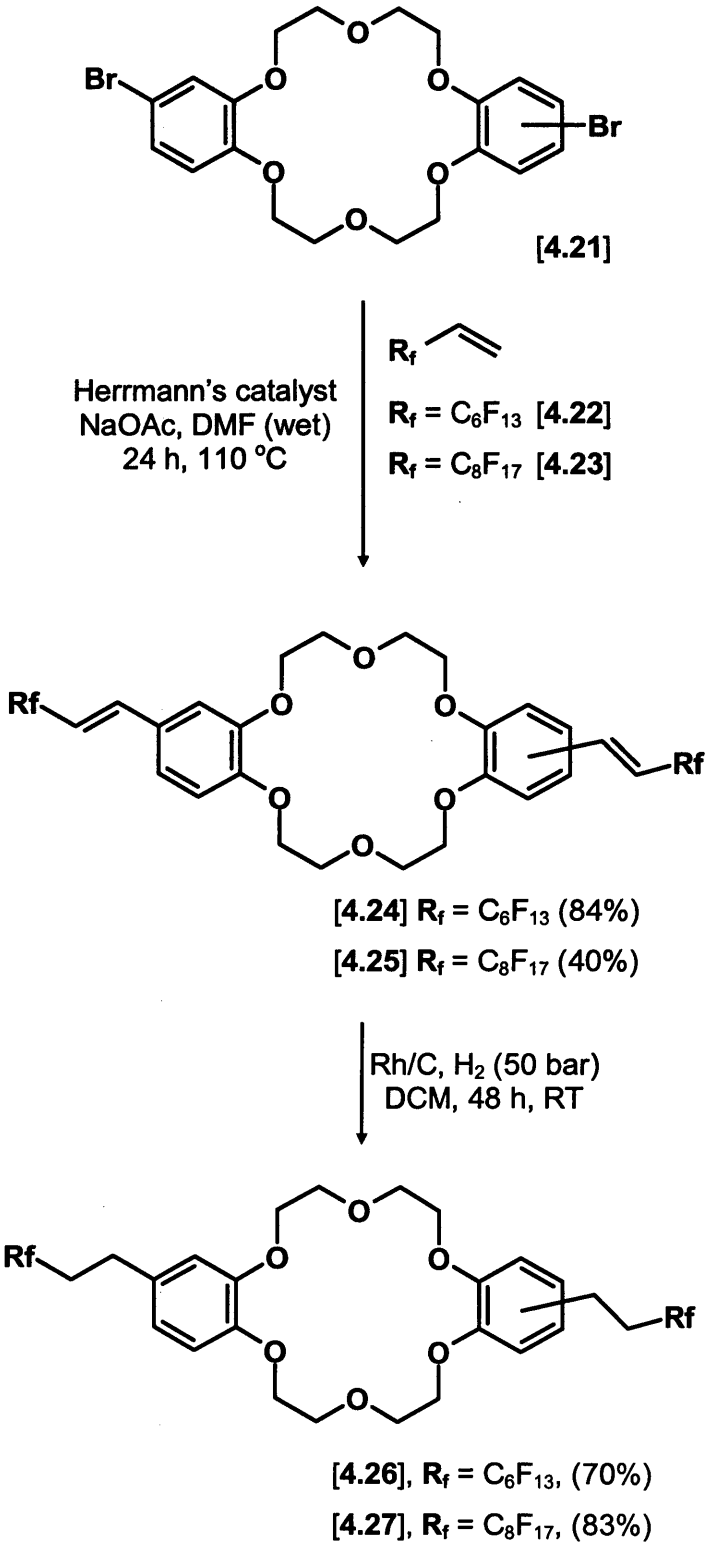
methylene group did not isolate the reactive centre of compound [**4.20**], and the electrophile was not formed.



Scheme 4.14. Attempted synthesis of bis(1*H*,1*H*-perfluoroheptyl)dibenzo-18-crown-6 [**4.31**].

A completely different approach was eventually developed for the synthesis of two novel perfluoroalkylated dibenzo-crown ethers (***Scheme 4.6***). Fluoroponytails of different lengths, R_f = C_6F_{13} and C_8F_{17}, were attached to dibenzo-18-crown-6 with the aim of investigating how the different fluorine content affects their catalytic activities, chemical properties and recyclability.

The first step in ***Scheme 4.6*** shows the Heck coupling reaction for the synthesis of perfluoroalkenyl dibenzo-crown ethers [**4.26**] and [**4.27**].[23] Inexpensive, commercially available dibromo-dibenzo-18-crown-6 [**4.21**] was reacted with the perfluoroalkenes, [**4.22**] or [**4.23**], using Herrmann's palladium catalyst instead of conventional palladium acetate, because it is more efficient for this particular reaction.[24] The method proved to be successful, resulting in an isolated yield of approximately 84% for bis(1*H*,2*H*-perfluoro-1-octenyl)dibenzo-18-crown-6 [**4.24**] and 40% for the heavier fluorinated and less soluble dibenzo-crown ether [**4.25**]. Both products were mixture of *cis*- and *trans*-isomers. The perfluoroalkylated dibenzo-crown ethers [**4.26**] and [**4.27**] were obtained in good yields (***Scheme 4.6***) after high-pressure hydrogenation of the corresponding perfluoroalkene derivatives using rhodium as the catalyst. Partially fluorinated dibenzo-crown ethers [**4.26**] and [**4.27**] are soluble in common organic solvents.

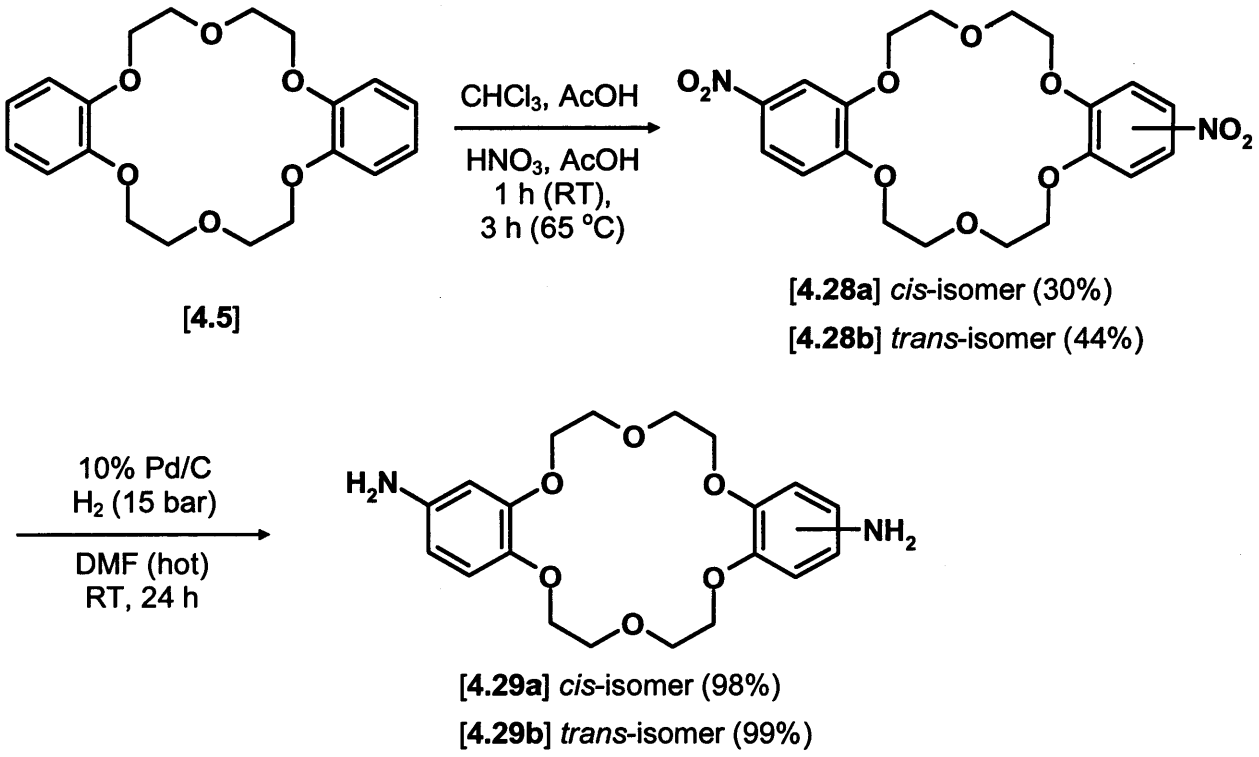


Scheme 4.6. Synthesis of bis(perfluoroalkyl)dibenzo-18-crown-6 ethers [**4.26**] and [**4.27**].

4.2.3 Synthesis of Diamino Derivatives of Dibenzo-18-crown-6 Ethers.

Di(aminobenzo)-18-crown-6 was identified as an important starting material in order to synthesise a new family of perfluoroalkylated dibenzo-18-crown-6 derivatives by facile *N*-functionalisation. In addition, it has been suggested that a donor atom within the attached sidearm may also contribute to the coordination effort of the crown ether,[25] and furthermore, in the case of perfluoroalkylated sidearms, it should provide the coordination centre of the crown ether with more effective insulation from the electron-withdrawing effect of the fluorine atoms.

Cis- and *trans*-di(aminobenzo)-18-crown-6 were both synthesised in good yields following the literature procedure developed by Smith (***Scheme 4.7***).[26] Inexpensive and commercially available dibenzo-18-crown-6 was nitrated in the first step to give a mixture of *cis*- and *trans*-isomers, **[4.28a]** and **[4.29b]** respectively, which were readily separated by fractional crystallization.



[4.5]

[4.28a] *cis*-isomer (30%)
[4.28b] *trans*-isomer (44%)

[4.29a] *cis*-isomer (98%)
[4.29b] *trans*-isomer (99%)

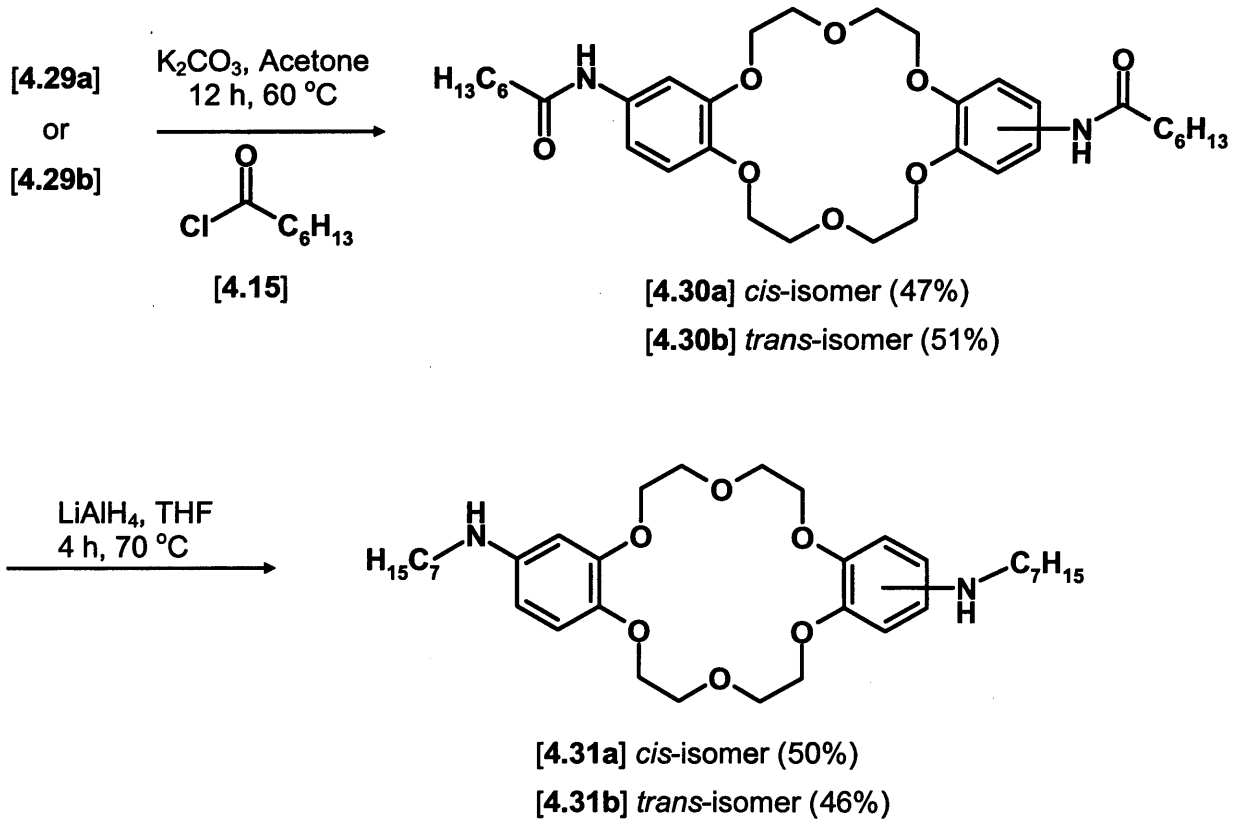
Scheme 4.7. Synthesis of *cis*- and *trans*-di(aminobenzo)-18-crown-6.

Initially, the *trans*-isomer **[4.28b]** was reduced by catalytic hydrogenation to give the amine derivative **[4.29b]** in excellent yield. The *cis*-isomer can also be utilised for the preparation of **[4.29a]**. Unfortunately, both isomers are not soluble in conventional organic solvents at room temperature and are only soluble in trifluoroethanol,

dimethylformamide and dimethylsulphoxide, and in acetone, acetonitrile, ethanol and tetrahydrofuran at high temperatures.

4.2.4 Synthesis of Dialkylamino Derivatives of Dibenzo-18-crown-6 Ethers.

In order to develop an appropriate procedure for the synthesis of fluorinated dialkylamino dibenzo-crown ethers, as well as, to compare the chemical properties and catalytic activities of the novel fluorinated phase transfer catalysts with their non-fluorinated analogues, it was decided to synthesise the dialkylamino dibenzo-crown ethers, **[4.31a]** and **[4.31b]**. The amide derivatives, **[4.30a]** and **[4.30b]**, were first synthesised in high purity and acceptable yield by reacting the corresponding di(aminobenzo)-18-crown-6 isomer with heptanoyl chloride **[4.15]** in the presence of potassium carbonate (***Scheme 4.8***).[27]

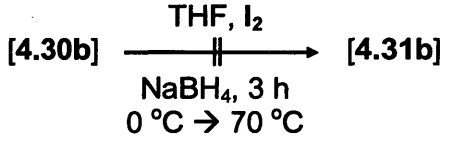


Scheme 4.5. Synthesis of *cis*- and *trans*-di(alkylaminobenzo)-18-crown-6.

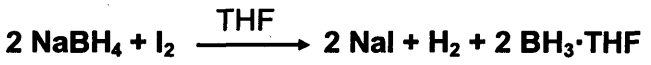
A different protocol was also studied in order to improve the yield of the reaction. *Trans*-di(amidobenzo)-18-crown-6 **[4.30b]** was also prepared using dimethylformamide instead of acetone as solvent and the temperature was increased to 100 °C. Using this approach the amide derivative was obtained in high purity,

although the yield was much lower (20%). Solubility tests showed that these amide derivatives have a very limited solubility in most common organic solvents, being only soluble in highly polar organic solvents such as dimethyl sulfoxide and dimethyl formamide.

A procedure developed by Periasamy for the reduction of the secondary amides was selected initially for the synthesis of *trans*-di(heptylaminobenzo)-18-crown-6 **[4.18b]** (***Scheme 4.9***).[28] This method uses the sodium borohydride/iodine system, which generates the reducing-agent diborane (2 BH_3) *in situ*, in dry tetrahydrofuran (***Scheme 4.10***). In the first attempt, hydrochloric acid was added carefully in order to destroy the excess of hydride, followed by the addition of sodium hydroxide to neutralise the solution. After extracting the aqueous phase with dichloromethane, the combined organic phases were washed and dried. No traces of the expected product were detected by NMR spectroscopy or mass spectrometry.



Scheme 4.9. Synthesis of *trans*-di(heptylaminobenzo)-18-crown-6.



Scheme 4.10. Reaction of $NaBH_4$ with I_2 to form $2BH_3$·THF.

In order to improve the reaction, the reaction time was increased to 24 h and a different work-up procedure was carried out. Instead of hydrochloric acid, cold water was used to destroy the excess of hydride. Tetrahydrofuran was eliminated under reduced pressure and the resulting solid was dissolved in a hydrochloric acid-water-methanol mixture and refluxed for 8 h at 75 °C. After cooling to room temperature, the solvent was removed, and the residue neutralised with an alkaline solution, which was extracted with dichloromethane. The organic phase was then washed and dried. However, although the desired product was obtained, the yield of the reaction was poor (25%).

In a different approach, lithium aluminium hydride was used as the reducing agent (***Scheme 4.8***) and the amine derivative **[4.31b]** was obtained in high purity and

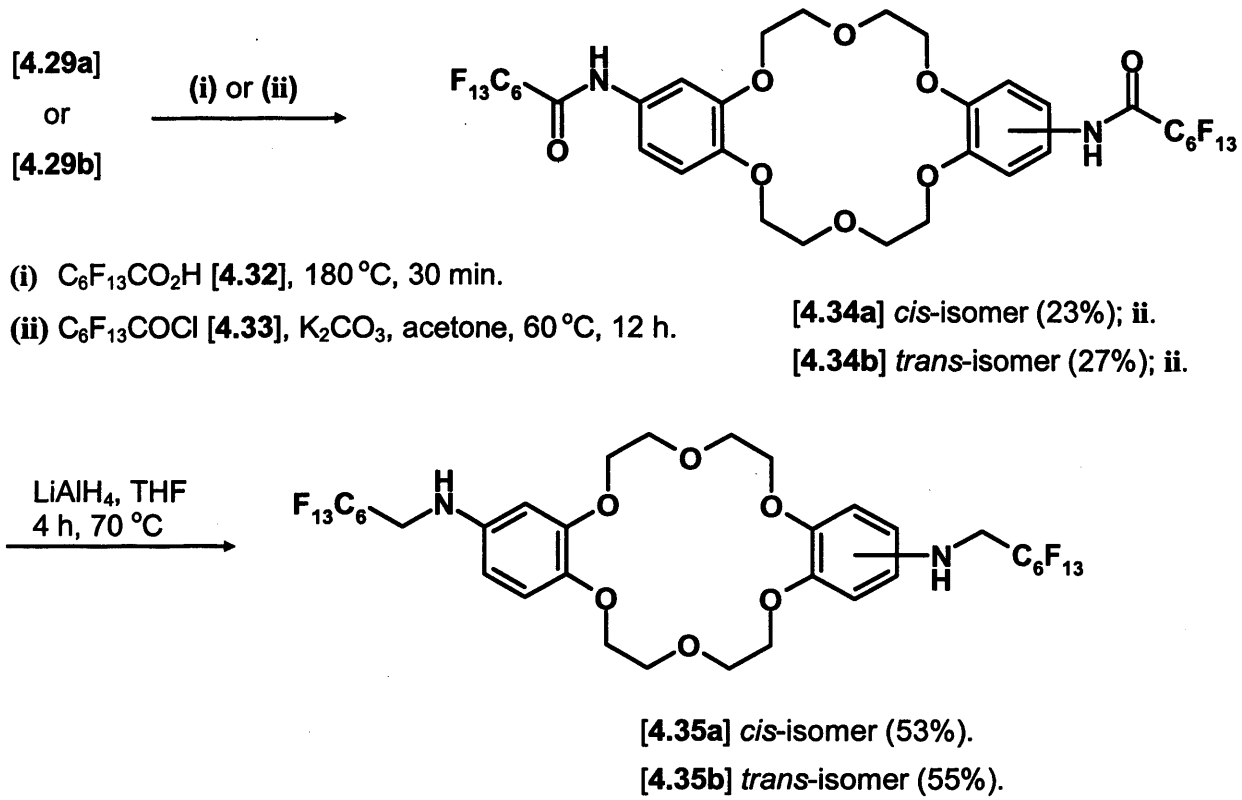
reasonable yield (46%). The same protocol was used for the reduction of the *cis*-isomer [**4.30a**] to give [**4.31a**]. The main advantage of the dialkylamino derivatives over the amide derivatives [**4.30a-b**], is their solubility in conventional organic solvents such as acetonitrile, dichloromethane, benzotrifluoride, ethyl acetate, and tetrahydrofuran, as well as in ether and ethanol at high temperatures.

4.2.5 Synthesis of Diperfluoroalkylamino Derivatives of Dibenzo-18-crown-6 Ethers.

The fluorinated diaminobenzo-crown ethers, [**4.35a**] and [**4.35b**], were synthesised in order to investigate how fluorinated-amino sidearms containing a donor atom within the perfluoroalkyl chain, affect the coordination capabilities of dibenzo-18-crown-6 type structures. The cooperation of a donor atom in the fluoroponytail to the binding capacity of crown ethers has been studied in recent years. For instance, Bartsch observed that partially fluorinated diaza-crown ethers extract metal picrates more efficiently when they have donor atoms in the fluoroponytail.[18] However, this influence has never been investigated for dibenzo-crown ether derivatives.

The partially fluorinated sidearm $-NHCH_2C_6F_{13}$ was chosen because this spacer group was considered to be an adequate insulator in order to avoid the electron-withdrawing effect of the fluorine atoms on the coordination centre of the macrocycle. Furthermore, the total percentage of fluorine in the final molecule is approximately 45%, which should facilitate the separation and recycling of these dibenzo crown ethers using fluorous solid phase extraction.[29]

Scheme 4.11 outlines the synthetic route followed to obtain the fluorinated diaminobenzo-crown ethers [**4.35a**] and [**4.35b**]. The first step is the preparation of two novel amidobenzo-crown ethers, which were synthesised by two different approaches. In the first approach, (**i**), the amide precursors, [**4.34a**] and [**4.34b**], were prepared by heating a mixture of the corresponding amines, [**4.29a**] or [**4.29b**], with perfluoroheptanoic acid without any catalyst or solvent.



Scheme 4.11. Synthesis of *cis*- and *trans*-di(perfluoroheptylaminobenzo)-18-crown-6.

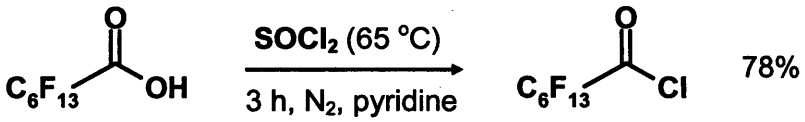
The basic principle of this reaction is that the reaction equilibrium shown in ***Scheme 4.12*** must be shifted in the direction of the product by constant elimination of the water formed in the reaction.

$$R_1NH_2 + R_2COOH \underset{}{\overset{\Delta}{\rightleftharpoons}} R_1NHCOR_2 + H_2O$$

Scheme 4.12. Synthesis of amides by pyrolysis of amine-carboxylic acid mixtures.

The optimal conditions for the pyrolysis of amine-carboxylic acid mixture are approximately 160-190 °C for 10-30 min, since longer heating can cause formation of undesired tar.[30] Therefore, both components must have melting points below 200 °C. Since the melting point of both di(aminobenzo)-18-crown-6 ethers is lower than 185 °C and the boiling point of perfluoroheptanoic acid is 175 °C (at 742 mm), the pyrolysis reaction was carried out at 180 °C for 30 min. Unfortunately, although it was possible to isolate the fluorinated amide derivative [**4.34**], the yield was very poor (15%).

In the second approach, (ii), perfluoroheptanoyl chloride was reacted with compound [**4.29a**] in the presence of potassium carbonate to give dibenzo-crown ether [**4.34a**] in 23% yield. Perfluoroheptanoyl chloride [**4.33**] was easily prepared in good yield (80%) by refluxing the inexpensive and commercially available perfluoroheptanoic acid [**4.32**] in thionylchloride in the presence of pyridine (***Scheme 4.13***).[31]



[4.32] [4.33]

Scheme 4.13. Synthesis of perfluoroheptanoyl chloride.

Both isomers of di(perfluoroheptylamidobenzo)-18-crown-6 were reduced to the corresponding secondary amine using lithium aluminium hydride (***Scheme 4.11***). The partially fluorinated amine derivatives, [**4.35a**] and [**4.35b**], were obtained in high purity and acceptable yields (53%-55%). In addition, solubility tests demonstrated that the fluorinated diaminobenzo derivatives are more soluble in common organic solvents than the amido derivatives.

4.3 Separation and Recovery Studies.

The isolation of the non-fluorinated and partially fluorinated dibenzo-crown ethers from the organic products was investigated in order to recover and reuse these phase transfer catalysts. Two different methods were studied: 1) recovery by fluorous solid phase extraction using fluorous reverse phase silica gel; 2) recovery by solid phase extraction.

The partition coefficients between a fluorous and an organic phase were not investigated due to the insolubility of the dibenzo-crown derivatives in perfluorocarbon solvents. Therefore, liquid-liquid extraction was not investigated as a potential recovery method.

4.3.1 Fluorous Solid Phase Extraction (FSPE).

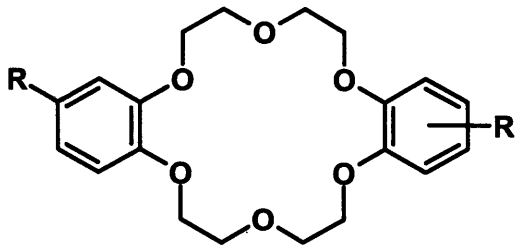
Preliminary FSPE experiments were carried out using only the partially fluorinated dibenzo-crown ethers [**4.26**] and [**4.27**], as well as the alkyl derivate [**4.17**]. By the

time that these experiments were carried out, the synthesis of compounds **[4.31a-b]** and **[4.35a-b]** was still under investigation. Therefore, separation and recovery studies with these amino diaza-crown ethers derivatives were not investigated. Nevertheless, their abilities as phase transfer catalysts as well as their recovery will be discussed in detail in **Chapter 5**.

A known amount of each dibenzo-crown ether studied was dissolved in the minimum volume of dichloromethane and loaded onto a FRPSG packed column. The column was then eluted with "fluorophobic" solvents, such as dichloromethane, toluene and acetonitrile, in order to recover and separate a hypothetical organic phase from the phase transfer catalyst. During the elution, the solvent was collected and analysed by thin-layer chromatography. No macrocycle was eluted from the column using toluene or dichloromethane, however, all the catalysts were recovered quantitatively when the column was eluted with acetonitrile (30 mL) (***Table 4.1***). This was an unexpected result since acetonitrile was successfully used as a fluorophobic solvent with the partially fluorinated diaza-crown ethers. Then, the FRPSG packed column was eluted with "fluorophilic" solvents with the purpose of recovering the fluorinated catalysts. Diethyl ether, benzotrifluoride, trifluoroethanol and ethyl acetate were used as fluorophilic solvents. All the dibenzo-crown ethers are soluble in these solvents. During the elution, the solvent was collected and analysed by thin-layer chromatography every 5 mL. When the chromatographic analysis was positive, the solvent was removed under reduced pressure in order to calculate the amount of catalyst recovered. No catalyst was eluted using benzotrifluoride as solvent. After the elution the catalysts were analysed by NMR spectroscopy, proving that they were not affected by the solid experiments in FRPSG.

Table 4.1 shows the percentage of catalyst recovered and the volume of solvent used respectively. Not only the polarity of the dibenzo-crown ethers, but also the amount of fluorine in the macrocycle must be taken into account in order to explain the results obtained. For instance, non-fluorinated dibenzo-crown ether **[4.17]** does not have any fluorine-fluorine interactions with the FRPSG and, therefore, can be eluted more easily from the column independent of the solvent used. The partially fluorinated alkyl dibenzo-crown ethers **[4.26]** and **[4.27]** were not eluted as easily from the column, especially using ethyl acetate as an eluant. Eluting with ethyl acetate there is only a small difference between the more fluorinated dibenzo-crown ether **[4.27]**, which should interact more strongly with the FRPSG via fluorine-fluorine interactions and, hence, will be retained better, and the less fluorinated dibenzo-

crown [**4.26**] ether. In fact, dibenzo-crown ethers [**4.26**] and [**4.27**] were eluted from the column using ethyl acetate. Using trifluoroethanol, TFE, all the catalysts were eluted using 10 to 15 mL of solvent. However, only 5 mL of solvent were needed when the column was eluted with the much less polar diethyl ether.



	R
[4.17]	C_7H_{15}
[4.26]	$C_6F_{13}(CH_2)_2$
[4.27]	$C_8F_{17}(CH_2)_2$

FSPE	Et_2O		MeCN		TFE		EtOAc	
	%	ml	%	ml	%	ml	%	ml
4.17	98.4	5	98.1	30	95.1	10	98.3	10
4.26	94.4	5	94.3	30	96.7	15	43.1	60
4.27	96.0	5	96.3	30	94.4	10	37.7	60

Table 4.1. *Fluorous Solid Phase Extraction results.*

Under the experimental conditions, the results demonstrated that the non-fluorinated and partially fluorinated dibenzo-crown catalysts were eluted from the FRPSG packed column and recovered quantitatively using the appropriate solvent systems, demonstrating their suitability for recycling using the FSPE technique.

4.3.2 Solid Phase Extraction (SPE).

The recovery of the above dibenzo-crown ethers and dibenzo-18-crown-6, compound [**4.5**], was investigated using the SPE methodology. Using this technique there is not fluorine-fluorine interactions and the separation is primarily based on the polarity of the species eluted. The procedure developed for the FSPE experiment was followed using normal silica gel instead FRPSG. The catalysts investigated were loaded onto the silica gel packed column dissolved in the minimum amount of dichloromethane, which was used as a fluorophobic solvent. Toluene and acetonitrile were also investigated as fluorophobic solvents. The elution of the catalysts was monitored using thin-layer chromatography. No catalyst was recovered using

dichloromethane or toluene as solvents. However, like in the case of the FSPE methodology, although a high volume of solvent was required, all the catalysts except dibenzo-18-crown-6, [**4.5**], were eluted from the column using acetonitrile.

Diethyl ether, benzotrifluoride, trifluoroethanol and ethyl acetate were investigated as fluorophilic solvents in order to recover the catalysts from the silica gel packed column. ***Table 4.2*** summarizes the results of the solid phase extraction experiments. The table shows the percentage of catalyst recovered and the volume of solvent used.

SPE	Et_2O		MeCN		TFE		EtOAc	
	%	ml	%	ml	%	ml	%	ml
4.5	90.4	40	54.0	60	94.5	10	94.8	10
4.17	96.4	35	94.5	30	98.3	30	96.7	30
4.26	96.2	10	96.4	40	96.9	5	95.8	10
4.27	98.0	10	92.2	45	96.3	5	95.8	10

Table 4.2. *Solid Phase Extraction results.*

Benzotrifluoride performs yet again as a fluorophobic solvent and, not surprisingly, no catalyst was recovered using this partially fluorinated solvent. All the catalysts were eluted from the column almost quantitatively under these conditions using the appropriate volume of the fluorophilic solvents. However, a comparatively large volume of acetonitrile was needed to recover the catalysts. Indeed, 60 mL of acetonitrile were needed to elute only 54.0 % of dibenzo-crown ether [**4.5**]. In general, partially fluorinated dibenzo-crown ethers [**4.26**] and [**4.27**] were recovered more easily using lower volumes of solvent than the analogous non-fluorinated dibenzo-crown ether [**4.17**] and non-derivatised dibenzo-18-crown-6, [**4.5**].

These results confirmed the potential to recycle the partially fluorinated dibenzo-crown ethers using this extraction technique.

4.4 Partially Fluorinated Dibenzo-crown Ethers. Conclusions.

A small series of novel partially fluorinated and non-fluorinated alkyl and amino alkyl dibenzo-crown ethers were synthesised in good yields using different approaches.

The recovery of the catalysts was investigated using different separation techniques. The results obtained demonstrated that, under the experimental conditions, the partially fluorinated dibenzo-crown ethers could be eluted from the FRPSG packed column and recovered quantitatively when the appropriate solvent system was used. Analogously, the catalysts were recovered by SPE using silica gel. Hence, these catalysts should be suitable for recycling studies using both separation techniques. However, it is important to observe that these extraction experiments were carried out in the absence of any reactants or, more importantly, any ionic species, which will interact with the dibenzo-crown ether. Therefore, these preliminary recycling results may not provide sufficient and reliable information about the recovery of the catalysts under the actual reaction conditions. Nevertheless, the separation studies did give useful information on the solvent systems that could be used.

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CHAPTER FIVE

Partially Fluorinated Dibenzo-18-crown-6 Ethers. PTC Applications

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Leicester

5.1 Study of the Metal Cation Complexing Abilities of Partially Fluorinated Dibenzo-Crown Ethers.

5.1.1 Introduction.

In solution the prototypical-substituted crown ether, dibenzo-18-crown-6 (DB18C6), has complexation properties similar to 18-crown-6. Its' aromatic substituents make it less soluble in aqueous solution, but on the other hand, increase its' solubility in nonpolar solvents in comparison to 18-crown-6. Dicyclohexano-18-crown-6, with the same basic structure but not aromatic substituents, has higher affinities for alkali cations than 18-crown-6 because of its higher polarizability. This is due to the cyclohexyl groups that inductively enhance the electron density of the ligand ring, increasing the basicity of the oxygen atoms, while the flexibility of the macrocycle remains more or less the same as 18-crown-6. DB18C6 is an interesting macrocycle because its polarizability is comparable to that of dicyclohexano-18-crown-6, although its structure is more rigid due to the aromatic substituents, which could prevent the ligand wrapping itself around the cation.[1]

Complexes of DB18C6 with diverse alkali metal and alkaline earth metal cations have been investigated extensively.[2] Recently, experimental and computational studies have shown that lithium and sodium dibenzo-18-crown-6 complexes are highly twisted structures. In these very similar twisted conformers, the metal ion is located approximately at the centre of the ligand cavity, allowing maximum interaction between the small, charge dense metal centre and the electronegative donor groups of the ligand. On the other hand, with the bigger potassium, rubidium, and caesium metal cations, DB18C6 forms complexes that have boat-shaped structures, where the metal ion lies above the plane of the oxygen donor atoms.[3] The distance of the metal centre above the donor plane increases with the cation radius. In addition, the ligand becomes flatter when the cation size increases.

Different dibenzo-18-crown-6 complexes containing transition metals, such as cobalt (II), nickel (II), copper (II), zinc (II), cadmium (II), lead (II),[4] thallium (I),[5] or even lanthanides, such as praseodymium (II) are also known.[6] Silver perchlorate dibenzo-18-crown-6 complex is a significant example, because in this case, the binding does not take place only at the crown ether oxygen centres but also by cation-π interactions with the benzene rings. This complex adopts a symmetric boat conformation with two benzene rings facing each other, where the silver cation has eight coordinated centres, involving coordination with seven oxygen atoms in which

six of them come from dibenzo-18-crown-6, one from the perchlorate anion, and one from the η^2-benzene ring of the other dibenzo-18-crown-6. It is also possible to detect a π–π interaction of two parallel benzene rings in the plane of the dinuclear unit.[7] Similar cation-π interaction has also been observed in the potassium dibenzo-18-crown-6 complex, $[K(DB18C6)]_2[Pt(SCN)_4]$.[8]

There are many variables than can affect the complexation properties of crown ethers. In the particular case of dibenzo-18-crown-6 ethers, besides the relative sizes of the cation and the dibenzo-crown ether cavity or the ion pair formation process, other factors, such as the solvent environment, play an important role in the complexation process. Different studies have demonstrated that its' selectivity varies considerably with the solvent.[9] For example, in acetonitrile (MeCN) and propylene carbonate (PC), the selectivity of DB18C6 for the cation varies in the order: $Na^+ \approx K^+ >> Rb^+ > Cs^+$. In water ($H_2O$), methanol (MeOH), dimethylformamide (DMF) and dimethylsulphoxide (DMSO), the selectivity sequence of this macrocycle for the alkali metal ions apparently observes the size-fit model, $Na^+ < K^+ > Rb^+ > Cs^+$. However, its selectivity with respect to complexation of alkali ions in tetrahydrofuran (THF) is $Na^+ >> K^+ > Rb^+ > Cs^+ > Li^+$.[10]

This variation of selectivity with the solvent, as well as the stability of the dibenzo-18-crown-6 complexes, depends strongly on the solvating ability of the solvent not only with respect to the cation, but also to the ligand and the resulting complex.[11] The solvation power of dibenzo-18-crown-6 decreases in the order: MeCN ≈ DMF ≈ nitromethane ($MeNO_2$) > PC >> MeOH >> H_2O. For instance, the solvation power of a given solvent for the potassium metal cation and its DB18C6 complex, decrease as follows:

$\mathbf{K^+}$ $\Rightarrow$ DMF ≈ DMSO >> H_2O >> MeCN ≈ PC ≈ MeOH >> $MeNO_2$.

$\mathbf{K(DB18C6)^+}$ $\Rightarrow$ DMF ≈ DMSO >> MeCN >> $MeNO_2$ = PC >> MeOH >> H_2O.

The alkali metal ion complexes of DB18C6 are generally more stable in $MeNO_2$ than in other common organic solvents. This is mainly attributed to the greater solvation of the alkali metal ion in these solvents than in $MeNO_2$ and its desolvation upon complexation. The $MeNO_2$ molecules compete poorly with DB18C6 during the complexation process, not solvating entirely the first coordination sphere of the metal cation due to their weak coordinating properties. The lower complex stability in H_2O or MeOH, in addition to its low solubility, can be explained by the hydrogen bonding

to the oxygen atoms of the free DB18C6, reducing their ability to coordinate.[12] In general, the interaction of the DB18C6-alkali metal ion complex with the solvent is mostly characterized by that of free DB18C6 because of the effective desolvation and shielding of the metal ion upon complexation.

Until now the complexation properties of substituted dibenzo crown ethers have not attracted the same interest and, with some exceptions,[12,13] not much is known about the complexes of dibenzo-crown ether derivatives.

5.1.2 Potassium Picrate Extraction Studies.

The ability of the new alkylated and perfluoroalkylated dibenzo-18-crown-6 derivatives, **[4.17]**, **[4.26]**, **[4.31a]** and **[4.35a]**, to coordinate to potassium was investigated initially by carrying out potassium picrate extraction studies between dichloromethane and water. Dichloromethane was chosen as the organic solvent because of its' nonpolar nature. In addition, its' lack of Lewis base properties (DN = 0.0 Kcal/mol) make it an appropriate solvent for studying inorganic and organometallic complexes because the effect of the solvent on the reactivity is minimized.[14]

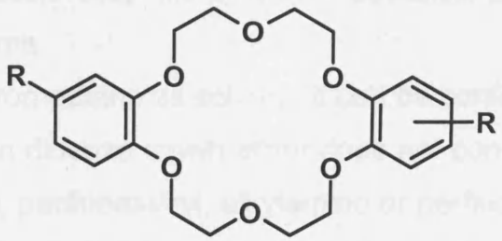
The same procedure that was described for the study of the partially fluorinated diaza crown ethers was followed for these experiments.[15] Equal volumes (25 mL) of a dichloromethane (DCM) solution of the respective crown ether (10^{-4} M) and an aqueous solution of potassium picrate (10^{-4} M) were introduced into a stoppered flask (50 mL) and stirred vigorously for 30 min at 21 ± 1 °C, in order to establish equilibrium between the two phases. The equilibrated mixture was allowed to stand for 2 h at the same temperature to allow complete phase separation. The absorbance of the picrate in the aqueous phase at 356 ± 0.7 nm was then measured using UV-visible spectrophotometry and the percentage of potassium extracted was calculated.

Two independent extractions were performed for each combination of potassium picrate and dibenzo-crown ether. The results shown are an average and the standard deviations of the average extraction values obtained from the two determinations were 2.3 % or less. In all cases, without crown ether in the organic phase, there was no transfer of picrate from the aqueous phase to the organic phase.

The results are summarized in ***Figure 5.1***. The five macrocycles studied in this experiment have the same cavity-size relationship and the steric effect of different cations was avoided by using only potassium. Therefore, the results obtained only illustrate the effect of the different substituents on the coordination centre of the

macrocycle. Compound [**4.5**] is commercially available and was purchased for the experiment, whereas macrocycles [**4.17**], [**4.26**], [**4.31a**] and [**4.35a**] were synthesised in our laboratory. No potassium picrate experiments were carried out with the trans-amino derivatives since the results were expected to be the same.

Figure 5.1 demonstrates that, independent of the type of sidearm attached, the percentage of potassium picrate extracted into the organic phase by the dibenzo-crown ether derivatives is very similar. It is important to observe that, like the diaza crown ether derivatives, only a low percentage of potassium picrate was extracted into the organic phase. This could be due to the structure of the dibenzo-crown ether derivatives, in which four oxygen atoms are directly bonded to aromatic rings. Due to the mesomeric effect of the aromatic rings, these oxygen atoms are weak electron-donors, and therefore, the complexation process is not entirely favourable. In addition, prior to any extraction of the potassium metal picrate from water into the dichloromethane phase, it is necessary for the dibenzo-crown ether to complex the potassium cation replacing most, or all, of the solvated water.



DIBENZO-CROWN	R	Picrate Extracted (%)
		DCM
[4.5]	H	1.4
[4.17]	C_7H_{15}	25.6
[4.26]	$C_6F_{13}(CH_2)_2$	26.4
[4.31a]	$C_7H_{15}NH$	24.4
[4.35a]	$C_6F_{13}CH_2NH$	25.3

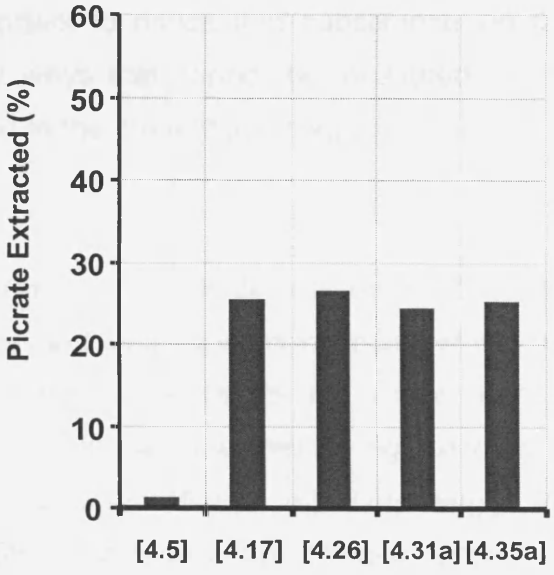


Figure 5.1. Potassium Picrate Extraction Results.

It may be expected that dibenzo-crown ethers **[4.31a]** and **[4.35a]** with polar amino groups, particularly compound **[4.31a]** without any electron-withdrawing fluorine atoms, would be significantly more solvated by water molecules, and such solvation could affect their relative solubility in the aqueous phase and hence, their extraction efficiency. However, such an effect was not reflected in the results illustrated in ***Figure 5.1***.

The amount of potassium picrate extracted into the organic phase by the fluorinated and non-fluorinated dibenzo-18-crown-6 derivatives is significantly higher than the original dibenzo-18-crown-6. The sidearms directly attached to the dibenzo-crown ether structure decrease the polarity of these crown ethers, making them more soluble in the organic phase. The hydrophobicity and low solubility of dibenzo-18-crown-6 in dichloromethane at room temperature will also influence its' poor extractability. In addition, the molecular conformation of DB18C6 may also contribute to the low extraction value due to π–π interactions of two of the benzene units on the ring that could block one side of the cavity.[16] In the case of the dibenzo-crown ether derivatives, this interaction may be avoided because of the steric hinderance generated by the sidearms.

Overall, using dichloromethane as solvent, it can be confirmed that coordination is exceptionally weak when dibenzo crown ether does not contain any sidearm groups. Alternatively, when alkyl, perfluoroalkyl, alkylamino or perfluoroalkylamino groups are attached, the coordination is improved, making them more suitable as catalysts in liquid-liquid conditions. However, it is important to notice that substituents on the crown ether structure are acting in several ways that cannot be measured by the simple picrate extraction technique employed in the present investigation.

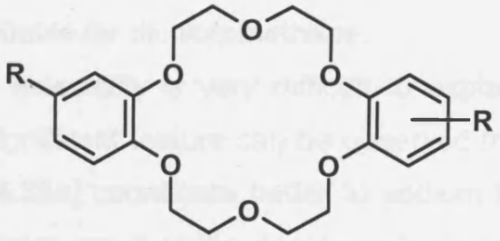
5.1.3 Sodium Picrate Extraction Studies.

Immediately after synthesising the dibenzo-18-crown-6 derivatives **[4.17]**, **[4.26]** **[4.31a]** and **[4.35a]**, the amount of sodium and potassium complexed within the macrocycle was determined by ICP-MS analysis. The results are summarized in ***Table 5.1*** and show that although no potassium was detected, a high amount of sodium was complexed within each macrocycle (24-45 mol %). Surprisingly, the perfluorinated derivatives, **[4.26]** and **[4.35a]**, contained the highest amount of sodium.

DIBENZO-CROWN	R	Mol % *of* Na^+ *in the crown*	Mol % *of* K^+ *in the crown*
[4.17]	C_7H_{15}	24	0
[4.26]	$C_6F_{13}(CH_2)_2$	45	0
[4.31a]	$C_7H_{15}NH$	27	0
[4.35a]	$C_6F_{13}CH_2NH$	44	0

Table 5.1. ICP-MS Results.

Therefore, in order to investigate this complexing behaviour, it was decided to carry out sodium picrate extraction experiments in a dichloromethane-water biphase. The same procedure that is described above was followed. Two independent extractions were performed for each combination of sodium picrate and dibenzo-crown ether. The results are averaged and the standard deviations were 3.3% or less. In all cases, without crown ether in the organic phase, there was no transfer of picrate from the aqueous phase to the organic phase.



DIBENZO-CROWN	R	Picrate Extracted (%)	
		K^+Pic^-	Na^+Pic^-
[4.5]	H	1.4	8.8
[4.17]	C_7H_{15}	25.6	9.1
[4.26]	$C_6F_{13}(CH_2)_2$	26.4	22.9
[4.31a]	$C_7H_{15}NH$	24.4	23.4
[4.35a]	$C_6F_{13}CH_2NH$	25.3	31.3

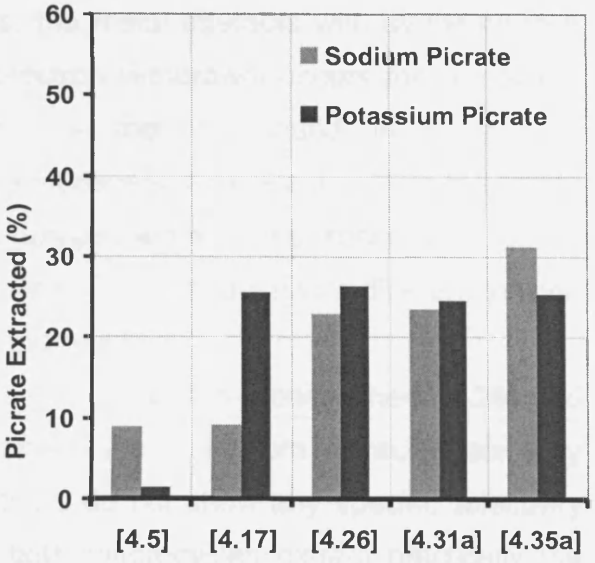


Figure 5.2. Picrate Extraction Results.

Unexpectedly, the figure shows that the amount of sodium picrate extracted by dibenzo-18-crown-6, **[4.5]**, was not improved by attaching alkylated sidearms, compound **[4.17]**. However, the sodium picrate extraction capability of compound **[4.5]** was considerably improved by attaching partially fluorinated sidearms. The results obtained by the alkyl amino dibenzo-crown ether derivative **[4.31a]** were very similar in comparison with partially fluorinated dibenzo-crown ether **[4.26]**. Surprisingly, the nitrogen group in the alkyl sidearm seems to have the same contribution to the sodium cation complexation process as the perfluoroalkyl group. The best sodium picrate extraction was achieved by partially fluorinated amino dibenzo-crown ether derivative **[4.35a]**. The combined effects of the donor atom in the sidearm and perfluoroalkyl group may contribute to the better sodium cation extractability.

Figure 5.2 also compares the results obtained in both potassium and picrate experiments. Normally, in relatively non-polar organic solvents, such as tetrahydrofuran, the selectivity of dibenzo-18-crown-6 for sodium metal cation is higher than for potassium cation. With more polar organic solvents, such as dimethylformamide or dimethylsulphoxide, the selectivity seems to follow the size-fit model, $Na^+ < K^+ > Rb^+ > Cs^+$.[10] However, such data for dibenzo-18-crown-6 or its derivatives is not yet available for dichloromethane.

Although the Na^+/K^+ selectivity is very difficult to explain based on only these picrate experiments, a significant feature can be observed from the results obtained. Macrocycles **[4.5]** and **[4.35a]** coordinate better to sodium than to potassium metal cation. This may be a direct result of the decrease in basicity of the oxygen crown system. In the potassium metal complexes, the metal interacts with all the oxygen donor atoms of the dibenzo-crown, so if electron withdrawal occurs for any of the oxygen atoms the complex is weakened. On the other hand, in the sodium complexes, the smaller metal ion does not simultaneously interact with all the ligand oxygen atoms, so if binding to some of the oxygen atoms is weakened by electron-withdrawing substituents the metal can simply shift coordination to a different oxygen atom that is not affected, maintaining a stronger binding.

However, this behaviour was not observed for dibenzo-crown ethers **[4.26]** and **[4.31a]**. In this case, the percentages of potassium or sodium extracted are very similar, and hence, these dibenzo-crown ethers do not show any specific selectivity for any of the metal cations. In addition, both macrocycles extract practically the same amount of metal cation. Therefore, the different sidearms help to increase their

complexation capabilities in comparison with unsubstituted compound **[4.5]**, but do not affect their selectivity. Surprisingly, although compound **[4.26]** has two electron-withdrawing groups attached, and dibenzo-crown **[4.31a]** has two amino electron-donor groups attached, the effect of these different substituents seems to be the same.

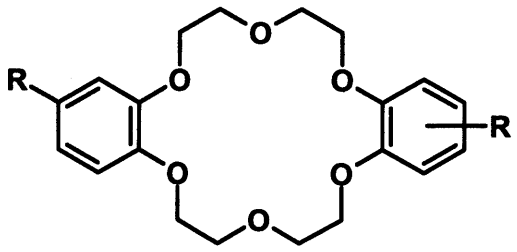
The results show that attaching alkyl groups to compound **[4.5]** to form the alkylated dibenzo-crown **[4.17]** does not have any effect in the percentage of sodium picrate extracted into the organic phase. However, when alkyl or perfluoroalkyl groups are attached to the dibenzo-crown **[4.5]** structure, its potassium metal cation complexation capabilities increase significantly. With the bigger potassium metal cation, alkylated macrocycle **[4.17]** extracts much better than dibenzo-crown **[4.5]**. This increase in the potassium cation complexing capabilities of compound **[4.17]** is probably due to an increase of its solubility in dichloromethane when alkyl groups are attached.

The above results corroborate the complexity of the crown ether complexing process, strongly emphasizing the number of factors that affect the stability and selectivity of the dibenzo-crown ether complexes. The different substituents attached to the dibenzo-crown ether structure modified their complexing capabilities in many different ways. However, the results positively confirm the potential of the substituted dibenzo-crown ethers to act as phase transfer catalysts.

5.2 Phase Transfer Catalysis. Aliphatic Nucleophilic Substitution.

5.2.1 Introduction.

To date, there have been no reports on the catalytic reactivity of fluorinated dibenzo-crown ether derivatives in phase transfer catalysed nucleophilic substitutions. However, Bradshaw and co-workers studied the performance of a series of functionalised dibenzo-crown ethers shown in ***Figure 5.3***, in the reaction of potassium iodide with allyl bromide in chlorobenzene.[17]



R = CH_3	R = $CH_3(CH_2)_5CO$
R = CH_3CO	R = $CH_3(CH_2)_6$
R = $CH_3CH(OH)$	R = $CH_3(CH_2)_9$
R = $(CH_3)_3C$	R = $CH_3(CH_2)_{12}CO$
R = $CH_3(CH_2)_4$	R = $CH_3(CH)_{12}CH(OH)$
R = $(CH_3)_2CHCH_2CH(OH)$	R = $CH_3(CH_2)_{13}$

Figure 5.3. Bis(substituted)dibenzo-18-crown-6 ethers studied by Bradshaw.[17]

Some interesting conclusions were drawn from this investigation. Like aliphatic nucleophilic substitution reactions catalyzed by onium salts, the rate of the reaction obeyed pseudo-first order kinetics, and was directly proportional to the amount of crown ether-metal complex in the organic phase. In addition, it was observed that the catalyst efficiency was affected by the stability of the crown ether-potassium complex and the lipophilicity of the dibenzo-crown ether derivative. The activities were also related to the electronic effects of the substituents, with some secondary effects attributable to the steric effects. The stability constants and reaction rates of dibenzo-crown ethers with electron-withdrawing carbonyl groups were lower, and vice versa with alkylated ligands. Interestingly, as the length of the alkyl group increases, the catalytic activity of the bis(*n*-alkylbenzo)-18-crown-6 compounds decreased. Longer substituents could interfere with the approach of the substrate molecule to the reacting anion that is loosely associated with the crown-ether metal complex.

However, Bradshaw concluded that, considering the price, dibenzo-crown ethers, no matter how modified, do not appear to be the catalysts of choice for phase transfer catalysis. Maybe this is true for the above reaction, but this investigation intends to challenge this generalisation by making the functionalised DB18C6 ethers recyclable.

5.2.2 Conversion of 1-bromooctane into 1-iodooctane.

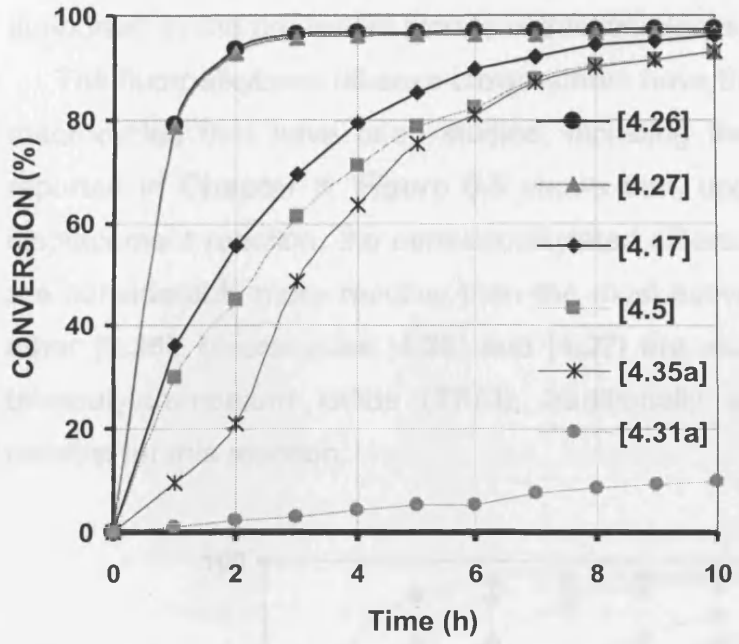
The metal picrate extraction experiments demonstrated that the fluorinated and non-fluorinated dibenzo-crown ether derivatives retain their complexing abilities. Hence, it was decided to evaluate their phase transfer catalytic activity in the classical iodide displacement substitution that was studied with the diaza-crown ethers (Section 3.3.2); the conversion of 1-bromooctane into 1-iodooctane (***Scheme 5.1***).

$$n\text{-}C_8H_{17}Br \xrightarrow[\text{BTF, 110 °C, t (h)}]{\text{KI (5 eq.), PTC (2 mol \%)}} n\text{-}C_8H_{17}I$$

Scheme 5.1. Conversion of n-C_8H_{17}Br into n-C_8H_{17}I.

There are no examples of dibenzo-crown ether derivatives being used as phase transfer catalysts in the conversion of *n*-octyl bromide into *n*-octyl iodide. However, some studies using dibenzo-18-crown-6, **[4.5]**, as catalyst have been carried out. For instance, Montanari demonstrated that compound **[4.5]** is at least as useful as ammonium or phosphonium salts in this phase transfer catalyzed reaction.[18] It was noticed that, when the aliphatic character of the dibenzo-18-crown-6 is increased, for example, using dicyclohexyl-18-crown-6, the reaction rate increased significantly.

The efficiencies of the new dibenzo-crown ether catalysts were examined under solid-liquid conditions. This procedure involves stirring the solid ionic reagent, potassium iodide, with the reactant, *n*-octyl bromide, in refluxing benzotrifluoride in the presence of catalytic amounts (2 mol %) of the different functionalised dibenzo-crown ethers. After filtering the organic phase through silica gel, a sample of the solution was collected and analysed by gas chromatography to determine the percent conversion to product using biphenyl as the internal standard. All of the dibenzo-crown ethers are soluble in benzotrifluoride at room temperature. In the absence of catalyst in the organic phase, no conversion to product was detected. The monitoring reaction was carried out only once for each dibenzo-crown derivative. ***Figure 5.4*** illustrates the time-dependent catalytic activity of the dibenzo macrocyclic derivatives in benzotrifluoride.



DIBENZO-CROWN	R
[4.26]	$C_6F_{13}(CH_2)_2$
[4.27]	$C_8F_{17}(CH_2)_2$
[4.17]	C_7H_{15}
[4.5]	H
[4.35a]	$C_6F_{13}CH_2NH$
[4.31a]	$C_7H_{15}NH$

Figure 5.4. Phase transfer catalytic activity of dibenzo-crown ethers in the conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$ in benzotrifluoride under solid-liquid conditions.

Figure 5.4 demonstrates clearly that by adding perfluoroalkyl sidearms to a dibenzo-18-crown-6 type structure, [**4.26**] and [**4.27**], the phase transfer catalytic activity is increased significantly. However, when alkyl sidearms, [**4.17**], are attached to the dibenzo-18-crown-6 structure, the catalytic activity only increases moderately. The results show that compounds [**4.26**] and [**4.27**] have essentially the same catalytic activity and so, an increase in the amount of fluorine does not affect the catalytic activity of the fluoroalkylated dibenzo-crown ethers in benzotrifluoride. The two-spacer methylene groups appear to isolate adequately the coordination centre of these dibenzo-crown ethers from the electron-withdrawing effect of the fluorine atoms in the sidearms. Surprisingly, the *cis*-alkylamino crown ether [**4.31a**] showed extremely poor catalytic activity under the same reaction conditions, whilst the *cis*-perfluoroalkylamino derivatised crown ether [**4.35a**] had a very similar rate profile to dibenzo-18-crown-6 after 5 h. Presumably, the polarity and solubility of [**4.31a**] had an important effect on the reaction equilibria constants in benzotrifluoride. This catalyst may be more efficient in an alternative non-fluorinated organic solvent. Another possible explanation is that the stability of the diaminobenzo-crown ether-potassium complex is higher because of the amino donor groups and this makes the

uncomplex-complex process much more difficult, although this explanation is not supported by the potassium picrate extraction results.

The fluoroalkylated dibenzo-crown ethers have the best catalytic activity of all the macrocycles that have been studied, including the diaza-crown ether derivatives reported in **Chapter 3**. ***Figure 5.5*** shows that, under the conditions of this iodide displacement reaction, the perfluoroalkylated dibenzo-crown ethers [**4.26**] and [**4.27**] are considerably more reactive than the most active perfluoroalkylated diaza-crown ether [**2.36**]. Macrocycles [**4.26**] and [**4.27**] are also significantly more active than tetrabutylammonium iodide (TBAI), traditionally employed as a phase transfer catalyst for this reaction.

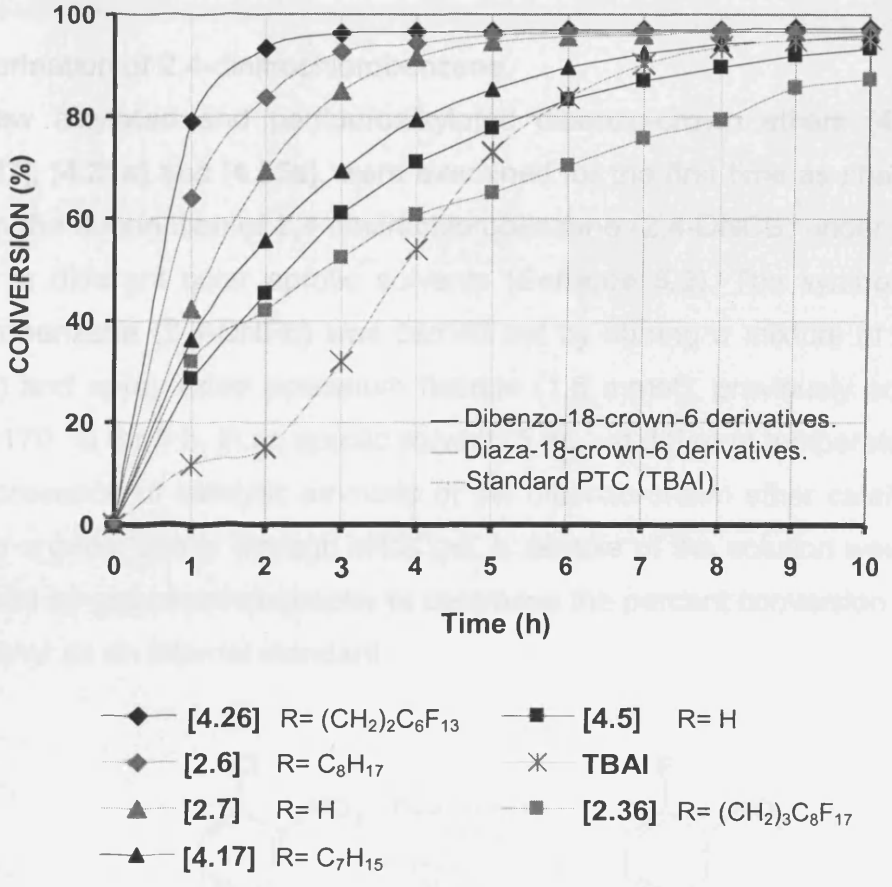


Figure 5.5. Comparison between the catalytic activity of diaza-crown and dibenzo-crown ether derivatives in the conversion of *n*-$C_8H_{17}Br$ into *n*-$C_8H_{17}I$ under solid-liquid conditions.

Surprisingly, in the case of non-fluorinated derivatives, dialkylaza-crown ether [**2.6**] is more reactive than the dialkylbenzo-crown derivative [**4.17**] and the same is true for the unsubstituted crown ethers, [**2.7**] and [**4.5**]. There are many variables that

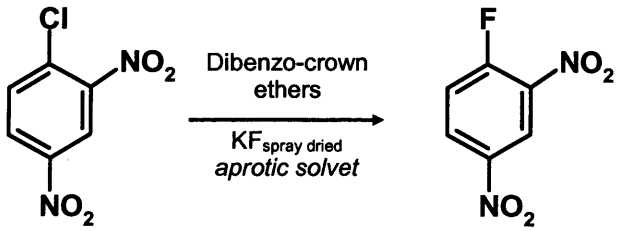
could explain this fact, however, the obvious and more important must be the different structure.

5.3 Phase Transfer Catalysis. Aromatic Nucleophilic Substitution.

To date, no study of phase transfer catalyzed aromatic nucleophilic substitution reactions has investigated the catalytic activity of fluorinated dibenzo-crown ether derivatives. Due to the importance of these reactions, it is of great interest to find a catalyst that is not only capable of performing adequately under solid-liquid conditions, but that can also be easily recovered. Fluorinated dibenzo-crown ethers were investigated for this purpose.

5.3.1 Fluorination of 2,4-dinitrochlorobenzene.

The new alkylated and perfluoroalkylated dibenzo-crown ethers **[4.5]**, **[4.17]**, **[4.26]**, **[4.27]**, **[4.31a]** and **[4.35a]**, were examined for the first time as phase transfer catalysts in the fluorination of 2,4-dinitrochlorobenzene (2,4-DNCB) under solid-liquid conditions in different polar aprotic solvents (***Scheme 5.2***). The synthesis of 2,4-dinitrofluorobenzene (2,4-DNFB) was carried out by stirring a mixture of 2,4-DNCB (1.0 mmol) and spray dried potassium fluoride (1.5 mmol), previously activated by heating at 170 °C for 8 h, in an aprotic solvent (5 mL) at different temperatures under N_2 in the presence of catalytic amounts of the dibenzo-crown ether catalysts. After filtering the organic phase through silica gel, a sample of the solution was collected and analysed by gas chromatography to determine the percent conversion to product using biphenyl as an internal standard.



2,4-DNCB **2,4-DFCB**

Scheme 5.2. Fluorination reaction of 2,4-dinitrochlorobenzene.

Initially, the reaction was carried out with only 5 mol % of standard phase transfer catalysts tetraphenylphosphonium bromide (TPPB) and dibenzo-18-crown-6, [**4.5**], in order to determine the optimum conditions. Acetonitrile was selected as the reaction media. ***Figure 5.6*** compares the conversion using 1.5 and 3 equivalents of potassium fluoride after 12 h. The increment was very low using the phosphonium salt, however, the conversion was significantly improved (21.9%) in the case of dibenzo-crown ether [**4.5**]. The higher amount of potassium cation available may make the complexation-cation transfer into the organic phase process easier for the dibenzo-crown ether.

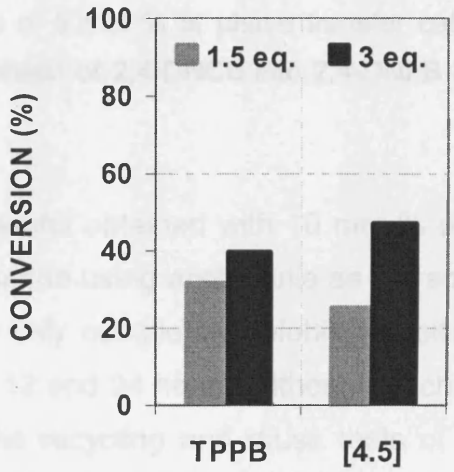


Figure 5.6. Catalytic activities phase transfer catalysts (5 mol %) TPPB and dibenzo-crown ether [**4.5**], in the conversion of 2,4-DNCB into 2,4-DNFB in acetonitrile with 1.5 eq. and 3 eq. of KF after 12 h.

Figure 5.7 shows the results obtained after 24 h using 3 eq. of potassium fluoride. The conversion in 24 h does not differ significantly from the results found after 12 h of reaction.

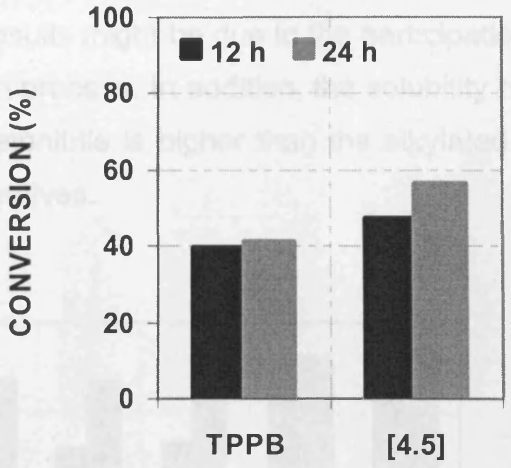
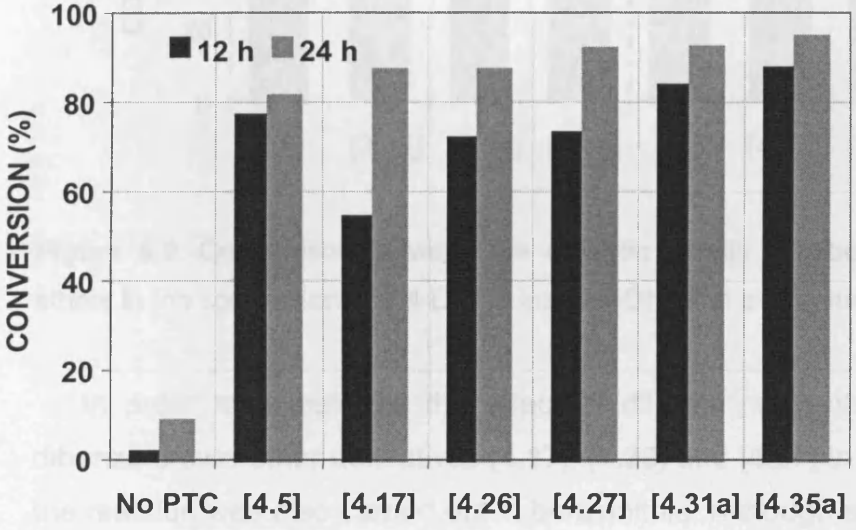


Figure 5.7. Catalytic activities of 5 mol % of phase transfer catalysts TPPB and dibenzo-crown ether [**4.5**] in the conversion of 2,4-DNCB into 2,4-DNFB in acetonitrile with 3 eq. of KF after 12 h and 24 h.

Figure 5.8 shows the results obtained with 10 mol % of phase transfer catalyst and 1.5 eq. of potassium fluoride using acetonitrile as the solvent. The functionalised dibenzo-crown ethers were only completely soluble in boiling acetonitrile and each reaction was carried out for 12 and 24 hours. Although each reaction was carried out once, successive runs in the recycling and reuse tests of the catalysts after 24 h demonstrated the consistency of the results. For instance, for catalyst [**4.26**] the average conversion from the six experiments was 86.5 % and the standard deviation of the average was less than 2 %.

Without a phase transfer catalyst the conversion to product was less than 10% after 24 h. Surprisingly, in contrast with their reduced catalytic activity in the iodide displacement reaction, the *cis*-alkylated amino [**4.31a**] and *cis*-perfluoroalkylated amino [**4.35a**] dibenzo-crown ethers are the best catalysts for the synthesis of 2,4-DNFB, with both macrocycles giving practically the same conversion after 24 h. ***Figure 5.8*** demonstrates that attaching sidearms, fluorinated or not, to the parental dibenzo-crown structure of dibenzo-18-crown-6, compound [**4.5**], only increases the catalytic activity moderately for the fluorination of 2,4-DNCB after 24 h. The sidearms may help to reduce the high solvation of the non-substituted compound [**4.5**] in acetonitrile, and therefore, makes the complexation process slightly more favourable for dibenzo-crown ether derivatives. After 12 h the fluorinated and non-fluorinated amino dibenzo-crown ether derivatives [**4.31a**] and [**4.35a**] gave higher conversion than dibenzo-18-crown-6 [**4.5**], which had similar reactivity to the perfluoroalkylated

derivatives, [**4.26**] and [**4.27**], and was more catalytically activate than the alkylated derivative [**4.17**]. These results might be due to the participation of the nitrogen donor atoms in the complexation process. In addition, the solubility of the amino derivatives [**4.31a**] and [**4.35a**] in acetonitrile is higher than the alkylated and perfluoroalkylated dibenzo-crown ether derivatives.



	R
[4.5]	H
[4.17]	C_7H_{15}
[4.26]	$C_6F_{13}(CH_2)_2$
[4.27]	$C_8F_{17}(CH_2)_2$
[4.31a]	$C_7H_{15}NH$
[4.35a]	$C_6F_{13}CH_2NH$

Figure 5.8. Phase transfer catalytic activity of dibenzo-crown ethers in the conversion of 2,4-DNCB into 2,4-DNFB in acetonitrile under solid-liquid conditions.

Figure 5.9 compares the results obtained with the dibenzo-crown ether derivatives with the results from the diaza-crown ether derivatives (**Chapter 3**, Section 3.4.2.2). With the exception of compound [**2.19**], in general, the dibenzo-crown derivatives perform more efficiently than the diaza-crown ethers. Compounds [**2.19**] and [**4.26**] have practically the same catalytic activity, although they are based on completely different structures. The dibenzo structure was expected to produce a better catalyst due to the fact that oxygen is a stronger electron donor than nitrogen, and hence, can complex more strongly to potassium cation, transferring more fluoride anions into the organic phase. For example, the conversion to 2,4-DNFB using dibenzo-18-crown-6 is 81.0% after 24 h, however, using diaza-18-crown-6 the conversion is only 49.9%. The overall improvement of the catalytic activity due to the electronic effects of the perfluoroalkylated sidearms is more evident in the diaza-crown derivatives, especially in compound [**2.19**], than in the dibenzo-18-crown-6 derivatives.

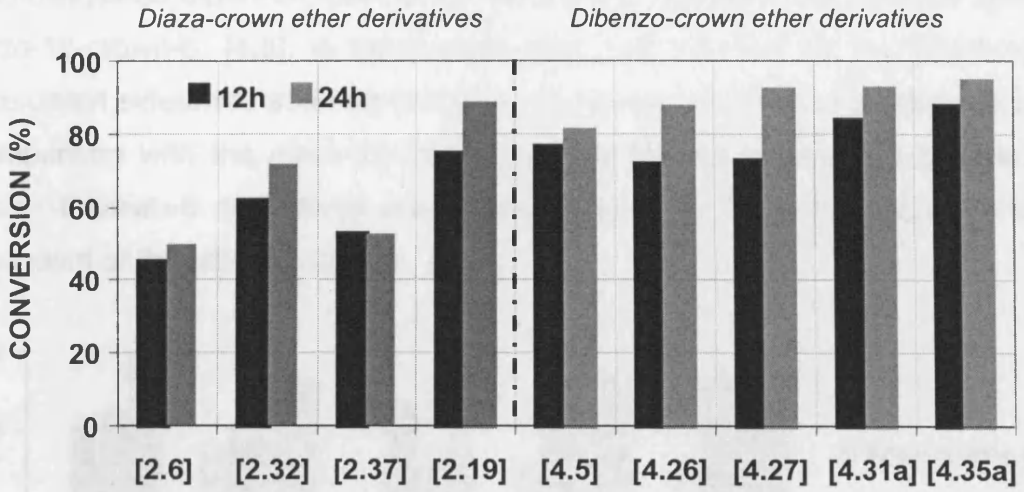


Figure 5.9. Comparison between the catalytic activity of dibenzo-crown and diaza-crown ethers in the conversion of 2,4-DNCB into 2,4-DNFB in acetonitrile.

In order to investigate the effect of different solvents on the reactivity of the dibenzo-crown ether derivatives [**4.17**], [**4.26**] and [**4.27**] in the fluoride displacement, the reaction was also carried out in benzonitrile. Although similar to acetonitrile, it has a much higher boiling point, which should potentially improve the reaction rate. Two independent experiments were performed for each combination of reactant and macrocycle. The results shown are an average. The standard deviation of the average conversion obtained from the two experiments was less than 2.3%. All the macrocycles are soluble in benzonitrile at 120 °C and in all cases, without a phase transfer catalyst in the organic phase there was practically no conversion into product (< 2%). The standard phase transfer catalyst, tetraphenylphosphonium bromide (TPPB), was also investigated in order to compare its activity with the dibenzo-crown ether derivatives.

Figure 5.10 illustrates the results obtained after 12 h and 24 h respectively. With the exception of alkylated compound [**4.17**], the catalytic activity of the dibenzo-crown ether derivatives increases slightly in benzonitrile. When the reaction time is extended from 12 h to 24 h there is only a small improvement in the conversion, although the increment is more significant in acetonitrile than in benzonitrile. The perfluoroalkylated dibenzo-crown ethers [**4.26**] and [**4.27**] have practically the same catalytic activity as TPPB, which is normally used to catalyze this type of fluoride displacement. In addition, independent of the solvent used, the figure shows that an increase in the percentage of fluorine in the sidearm does not affect the activity of the

perfluoroalkylated dibenzo-crown ether derivatives. However, the catalytic activity of dibenzo-18-crown-6, [**4.5**], in benzonitrile does not improve by the attachment of perfluoroalkyl sidearms, and surprisingly, it decreases when alkyl groups are added. In comparison with the diaza-18-crown-6 ethers studied in previous chapters, the dibenzo-18-crown-6 derivatives are better catalysts under the reaction conditions independent of the solvent used.

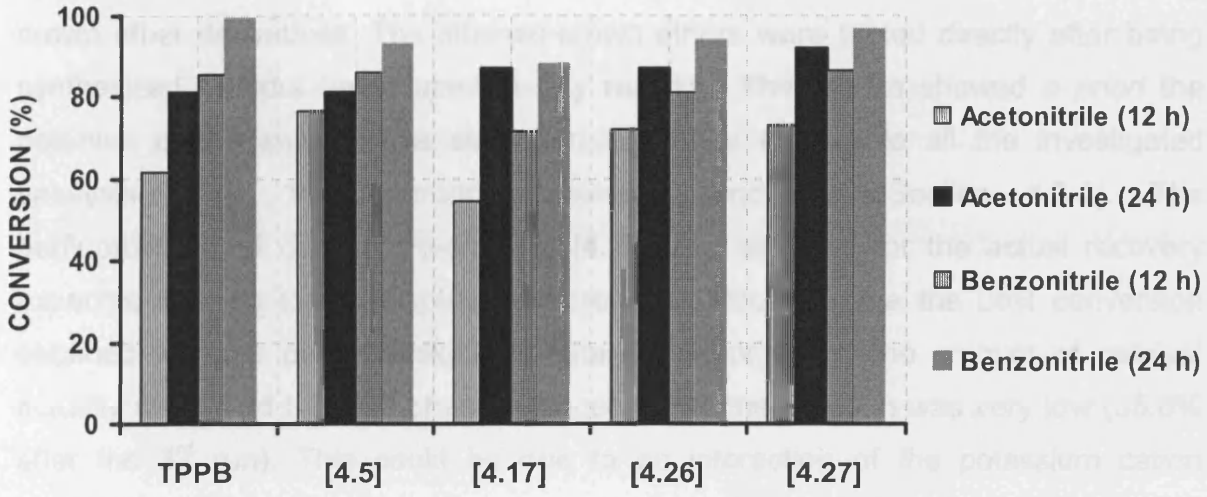


Figure 5.10. Comparison between the catalytic activities of dibenzo-crown ethers and TPPB in the conversion of 2,4-DNCB into 2,4-DNFB in acetonitrile and benzonitrile after 12 h and 24 h.

Higher temperature means higher energy costs and considering the small increment in the conversion, it could be argued that using benzonitrile as reaction media is not really an improvement. Different solvents, such as acetone and tetrahydrofuran, were also tested but no conversion was obtained. Using highly toxic dimethylformamide the reaction was complete (97.2%) after 12 h at 85 °C without catalyst. However, the use of acetonitrile together with dibenzo-crown derivatives, especially fluorinated, as phase transfer catalysts was considered an improvement because this solvent is less toxic and fluorinated dibenzo-crowns are potentially recyclable.

In order to improve the results further, the promotion of the reaction by microwave (50 W) was investigated. The reaction mixture was stirred at 85 °C for 30 min in acetonitrile with 1.5 eq. of KF and dibenzo-18-crown-6 [**4.5**] (5 mol %). Unexpectedly, only 1.3% conversion was obtained using this method.

5.4 Separation and Recovery Results.

5.4.1 Iodide displacement.

5.4.1.1 *Solid Phase Extraction* (SPE).

Several solid phase extraction experiments using silica gel and different solvent systems were performed with the novel alkylated and perfluoroalkylated dibenzo-crown ether derivatives. The dibenzo-crown ethers were tested directly after being synthesised, without being used in any reaction. The results showed *a priori* the potential of the solid phase extraction technique to recycle all the investigated catalysts under the appropriate solvent conditions (Section 4.3.2). The perfluoroalkylated dibenzo-18-crown-6 **[4.26]** was selected for the actual recovery experiment in an iodide displacement reaction since it gave the best conversion obtained using a perfluoroalkylated catalyst. Surprisingly, the amount of catalyst actually recovered by solid phase extraction after the reaction was very low (35.6% after the 3rd run). This could be due to an interaction of the potassium cation complexed by the dibenzo-crown ether with the hydroxy groups present on the silica gel. In order to minimise the possible potassium cation effect, the catalyst was washed with water. ICP-MS analysis showed that, unlike the case of diaza-crown **[2.37]** where the amount of potassium complexed was reduced from 74 mol % to 1 mol % after washing with water, the percent of potassium coordinated within dibenzo-crown ether **[4.26]** was reduced from 13 mol % to only 9 mol % after washing with water.

The solid phase extraction technique was not found to be suitable for the recycling of the perfluoroalkylated dibenzo-crown catalyst **[4.26]** in the iodide displacement reaction.

5.4.1.2 *Fluorous Solid Phase Extraction* (FSPE).

Similar to the solid phase extraction technique, dibenzo-crown ether **[4.26]** was not eluted entirely from the fluorous reverse phase silica gel packed column after the aliphatic nucleophilic substitution in preliminary recycling results, although different fluorophilic solvents, such as trifluoroethanol, ethyl acetate and tetrahydrofuran, were used. Interactions between potassium cation and hydroxy groups on the fluorous reverse silica gel may explain the results obtained. Although most of the hydroxy groups are derivatised with perfluoroalkyl chains in FRPSG, there are still some

underivatised hydroxy groups remaining within the FRPSG structure. In addition, in both extraction techniques, the effects of the counter anion, which forms the neutral complex with dibenzo-crown [**4.26**] and potassium cation, should also be taken into account in order to explain the results obtained.

5.4.1.3 *Supported Fluorous Phase Catalysis* (SFPC).

Due to the problems recovering the perfluoroalkylated catalyst [**4.26**] from FRPSG in FSPE, supported fluorous phase catalysis was investigated as an alternative recycling technique in the conversion of *n*-octyl bromide into *n*-octyl iodide. The perfluoroalkylated dibenzo-18-crown-6 [**4.26**] was selected as the phase transfer catalyst due to its excellent performance under normal solid-liquid conditions. The perfluoroalkylated dibenzo-crown ether [**4.26**], 2 mol %, was immobilised on FRPSG by simply refluxing in dichloromethane for 2 h. After cooling to room temperature, the solvent was eliminated under reduced pressure, giving the FRPSG-supported dibenzo-crown ether [**4.26**] ready to be used. Initially, when the reaction was carried out in benzotrifluoride at 110 °C with the supported catalyst, the conversion was 30% after 5 h, and 94% after 24 h. However, in the second run after 24 h, the conversion was only 23 %, although almost 90 % of the catalyst was recovered from run 1. In comparison with the homogeneous reaction, which was complete after 3 h, these results show the reduced catalytic activity of the catalyst after being supported.

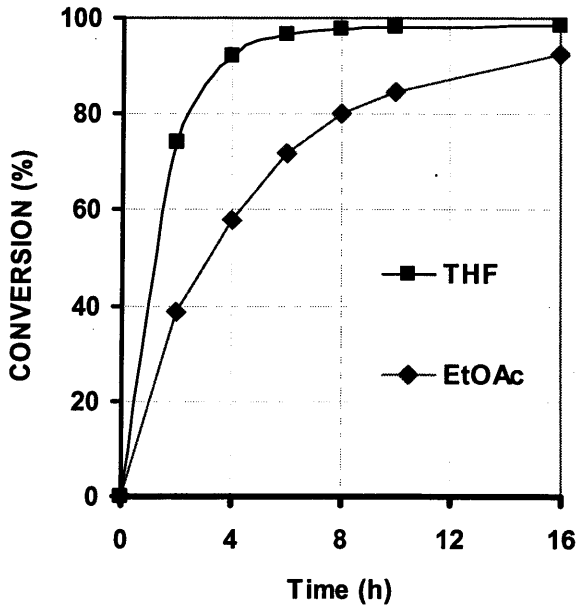


Figure 5.11. Catalytic activities of dibenzo-crown ether [**4.26**] supported on FRPSG in THF and EtOAc.

The iodide displacement reaction was then carried out in ethyl acetate (EtOAc) and tetrahydrofuran (THF) in order to evaluate the effect of a different solvent environment on the reactivity of the supported catalyst. ***Figure 5.11*** shows the conversions obtained when the reaction was monitored every 2 h over a 16 h period. The results established that the supported fluorous phase catalyst [**4.26**] is more active in tetrahydrofuran than in ethyl acetate and benzotrifluoride. Tetrahydrofuran has higher electron pair donating ability than ethyl acetate, and hence, it is more capable of coordinating strongly towards cations.[19] On the other hand, potassium metal cation is known to have certain solubility in ethers with good solvating properties, such as tetrahydrofuran. Therefore, potassium iodide may be more dissociated in tetrahydrofuran and the potassium cation could be easily complexed by the perfluoroalkylated dibenzo-crown. In addition, dibenzo-crown ether [**4.26**] might be more soluble in THF, coming off the support more easily and making the reaction homogeneous. In comparison with the traditional homogeneous solid-liquid conditions using the unsupported catalyst, the conversion is slightly slower when the catalyst is immobilized on fluorous reverse silica gel due to its heterogenisation. However, this technique may allow an easy recycling of the supported catalyst.

RUN	SUPPORTED CATALYST USED (g)	SUPPORTED CATALYST RECOVERED (g)	Conv. (%, GC)
1	0.500	0.473	95.2
2	0.473	0.445	93.3
3	0.445	0.419	90.0
4	0.419	0.392	87.5

Table 5.2. Recycling results of compound [**4.26**] used supported fluorous phase catalysis in THF.

Table 5.2 shows the recycling results for the supported dibenzo-crown ether [**4.26**] in the iodide displacement in tetrahydrofuran. The perfluoroalkylated phase transfer catalyst was recovered (94-95%) quantitatively after each cycle. After eliminating the solvent under reduced pressure, the resulting solid was washed with hexane at -18 °C, cold water and again with cold hexane. The solid was then dried

overnight at 60 °C. In this way, macrocycle [**4.26**] was reused in the aliphatic nucleophilic substitution four times, with only a small drop in conversion. No catalyst leaching into the organic phase was detected either by ^{1}H or ^{19}F NMR spectroscopy.

In order to improve the reaction conversion, it was also decided to investigate dibutyl ether as a reaction media. This highly boiling point solvent has very similar properties to tetrahydrofuran, although its electron pair donating ability is lower, being similar to ethyl acetate. However, while the temperature was increased up to 120 °C for 5 h, the conversion was lower (56.8%) in comparison with the same reaction in tetrahydrofuran at 70 °C for 6 h (95.2%). When the temperature was raised up to 130 °C for 12 h, the conversion only increased to 68.8%, although 96.6 % of the catalyst was recovered after the first run following the procedure described above. Increasing the reaction time to 24 h at 100 °C, gave only a 51.5% conversion, with 93.8% of the catalyst recovered after the second run. ***Table 5.3*** summarizes the different reaction conditions that were tested and the results obtained. In this case, it was not possible to obtain good conversions.

Temp. (°C)	**Time** (h)	**Conv. (%, GC)**
120	5	56.8
130	12	68.8
100	24	51.5

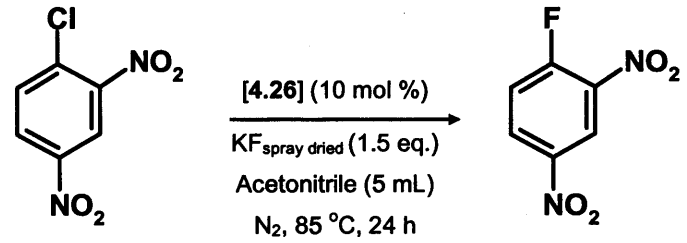
Table 5.3. Results obtained using Bu_2O as the solvent.

The above results demonstrated that, although supporting the catalyst on FRPSG produces a decrease in the reaction rate in comparison with normal solid-liquid conditions, supported perfluoroalkylated dibenzo-crown ether [**4.26**] can be easily recycled by simple filtration.

5.4.2 Fluoride displacement.

The separation and recovery of the perfluoroalkylated dibenzo-crown ether [**4.26**] was investigated in the fluoride displacement in acetonitrile (Section 5.3.1) using fluorous solid-phase extraction. After 24 hours the organic phase was filtered and washed with water to eliminate the excess of potassium salts. After drying over

magnesium sulphate, the clear organic phase was passed through a short column of fluorous reverse phase silica gel (FRPSG). The column was eluted with dichloromethane to obtain the organic products. ^{1}H and ^{19}F NMR analysis demonstrated that no catalyst leached into the organic phase. The fluorinated phase transfer catalyst was then recovered (93-95%) quantitatively by eluting with trifluoroethanol. In this way, the fluorinated dibenzo-18-crown-6 ether [**4.26**] was recovered and reused four times (***Table 5.4***), with the slight drop in conversion caused by the mechanical losses of [**4.26**] after each recycle.



2,4-DNCB **2,4-DFCB**

RUN	CATALYST USED (g)	CATALYST RECOVERED (%)	Conv. (%, GC)
1	0.106	95.1	89.5
2	0.101	94.9	86.8
3	0.095	93.2	85.3
4	0.089	93.5	83.5

Table 5.4. Recycling results of dibenzo-crown ether [**4.26**] using FSPE.

It was not possible to recycle dibenzo-crown ether [**4.26**] by solid phase extraction on conventional silica gel. Probably, even with the electron-withdrawing effect of the fluorine groups, this compound remains so polar that it is not possible to elute from the silica packed column. The same reason is attributed to the difficulty of recycling alkylated dibenzo-crown [**4.17**] using the solid phase extraction technique. However, different solid phase extraction (SPE) and fluorous solid phase extraction (FSPE) experiments without reaction, and hence, without taking into account how the chemical properties of dibenzo-crown derivatives might vary during the complexation

process, demonstrated the possible recovery of these catalysts using extraction techniques.

Preliminary FSPE and SPE experiments also showed the potential recyclability of fluorinated and non-fluorinated amino dibenzo-crown ethers [**4.31a**] and [**4.35a**]. However, when the recycling of these catalysts (10 mol %) was attempted after the reaction using the extraction techniques, the amount of amino derivatives recovered after the first run was unexpectedly low in all cases (< 20%). The recycling process of catalysts [**4.31a**] and [**4.35a**] was carried out only once following the procedure developed for compound [**4.26**] and no further attempts to recycle these amino derivatives were undertaken.

During the catalytic testing of the heaviest fluorinated compound [**4.27**], it was found that the solubility of this catalyst in acetonitrile was dependent on the temperature. Based on this observation, thermomorphic catalysis was investigated for recovering the catalyst. The reaction was performed under the same reaction conditions, but after 24 h, the reaction media was cooled down to -18 °C for 15 h. The solid was then filtered off and washed with cold acetonitrile (-18 °C) to collect the organic products. In order to recover dibenzo-crown ether [**4.27**], the remaining solid was extracted with hot tetrahydrofuran. Before reusing the catalyst, it was dried at 60 °C for 2 h under reduced pressure. The results demonstrated that this method is not suitable for the recovery of this catalyst. After the second catalytic cycle, the amount of catalyst recovered dropped to 69.7%, and the conversion to 67.9% (***Figure 5.12***).

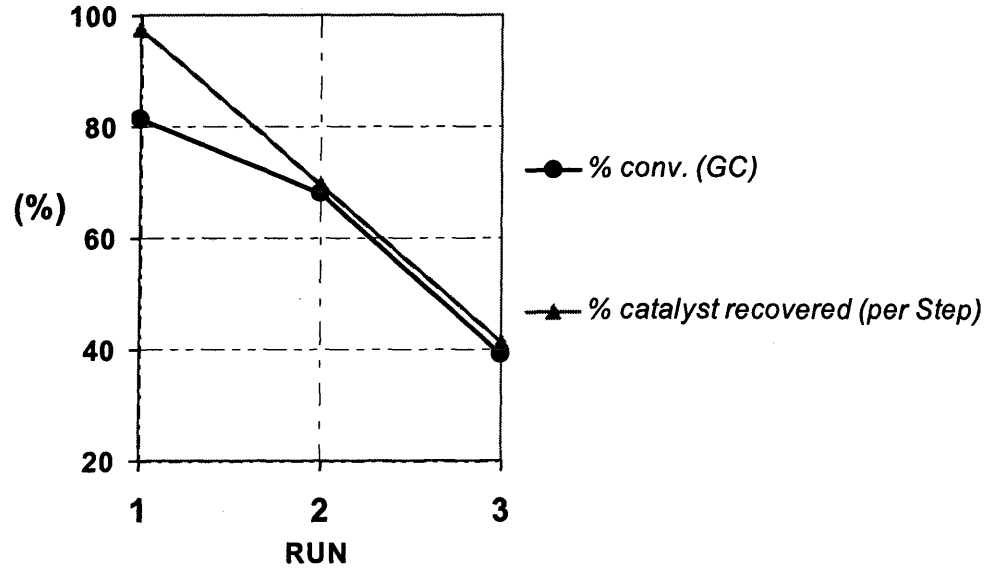


Figure 5.12. Recycling of dibenzo-crown ether [**4.27**] using thermomorphic catalysis.

The recyclability of perfluoroalkylamino dibenzo-crown ether **[4.35a]** was studied using the same technique due to the temperature-dependent solubility of the pure catalyst in acetonitrile without reaction. However, no catalyst was recovered after the reaction following the procedure described above. Unfortunately, although different procedures were investigated, such as adding water (18 %) to the reaction mixture or cooling it down to -18 °C overnight, no catalyst was recovered after the first run in any case.

5.5 Partially Fluorinated Dibenzo-Crown Ethers. Conclusions.

During this study several fluorinated alkyl and amino alkyl dibenzo-crown ethers were tested as phase transfer catalysts. Under solid-liquid phase transfer conditions, fluorinated dibenzo-crown derivatives give similar, if not better, phase transfer catalytic activity compared to the non-fluorinated analogues. In addition, perfluoroalkylated dibenzo-crown ether **[4.26]** was recycled four times using supported fluorous phase catalysis in the conversion of 1-bromooctane into 1-iodooctane and four times in the conversion of 2,4-dinitrochlorobenzene into 2,4-dinitrofluorobenzene using fluorous solid-phase extraction with only a small loss in activity. Unfortunately, it was not possible to recycle perfluoroalkylamino dibenzo-crown ether derivative **[4.35a]** using this technique. The thermomorphic catalysis technique was also investigated for compounds **[4.26]** and **[4.35a]**. However the recycling process was not as efficient as expected considering the temperature-dependent solubility properties in acetonitrile shown by these dibenzo-crown ethers before the reaction. Further work should be focussed on more applications of these stable and recyclable dibenzo-crown ether derivatives, as well as on the synthesis and applications of new fluorous analogues of conventional crown ethers, for instance, chiral crown ethers for asymmetric synthesis, that should find more applications in phase transfer catalysis.

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CHAPTER SIX

Experimental Section

University *of*
Leicester

6.1 General Procedures.

6.1.1. Nuclear Magnetic Resonance Spectroscopy.

The ^{1}H, ^{19}F and $^{13}C\{^{1}H\}$ NMR spectroscopies were carried out on Bruker AM 300 spectrometer at 300, 282 and 75 MHz respectively and were referenced to internal tetramethylsilane (^{1}H), deuterated chloroform ($^{13}C\{^{1}H\}$) and trichlorofluoromethane (^{19}F) using the high frequency positive convention. Deuterated chloroform was used as solvent unless otherwise quoted. The highly coupled ^{13}C signals of the fluorinated carbons are not listed below.

6.1.2. Mass Spectrometry.

Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos Concept 1H, double focussing, forward geometry mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix for the FAB spectra. Electrospray mass spectra were obtained on a Micromass Quatro LC.

6.1.3. Gas Chromatography.

The chromatograms were carried out on a Perkin Elmer Claurus 500 Gas Chromatograph using a Perkin Elmer-Elite Series PE-5 (30 m x 0.25 mm, Film= 0.25nm, 5% diphenyl, 95% dimethyl polysiloxane) column.

6.1.4. Elemental Analysis.

The Science Technical Support Unit of the London Metropolitan University carried out the elemental analyses.

6.1.5. Inductively Coupled Plasma Optical Emission Spectrometry.

Inductively Coupled Plasma analyses were carried out at the University of Leicester by the Analytical Services using as a spectroscopic source inductively coupled argon plasma in a Philips PV 8060 ICP-OES spectrometer.

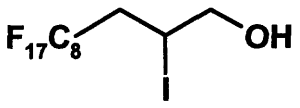
6.1.6. Starting Materials.

Compounds were generally used as supplied from Sigma-Aldrich, Apollo, Avocado, Acrōs Organics, Fluka or Fluorochem, whilst solvents were dried according to standard methods. Dichloromethane, tetrahydrofuran and diethyl ether were dried using the departmental solvent purification/drying system. All of the solvents were

stored in sealed ampoules under an atmosphere of dry nitrogen over molecular sieves.

6.2 Synthesis.

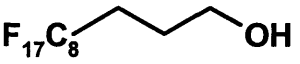
6.2.1. Preparation of 1*H*,1*H*,2*H*,3*H*,3*H*-perfluoro-2-iodo-*n*-undecanol, [**2.27**].



Perfluorooctyl iodide (13.7 g, 25.0 mmol), allyl alcohol (2 mL, 28.8 mmol) and azobisisobutyronitrile (0.40 g, 2.4 mmol) were heated at 80 °C under an inert atmosphere for 24 h. The pale yellow solid obtained was recrystallized from hexane (30 mL) to give the product (11.9 g, 87%). The preparation of 1*H*,1*H*,2*H*,3*H*,3*H*-perfluoro-2-iodo-*n*-undecanol was carried out by an adaptation of Fish's method.[1]

mp 92-94 °C (lit.,[1] 93-95 °C); δ_H ($CDCl_3$) 4.37 (1H, m, CHI), 3.75 (2H, m, CH_2OH), 2.95 (1H, m, $C_8F_{17}CH_A$), 2.68 (1H, m, $C_8F_{17}CH_B$), 1.97 (1H, br s, OH); δ_F ($CDCl_3$) -80.72 (3F, t, $^4J_{FF}$ 9.9, CF_3), -112.50 (1F, m, $^4J_{FF}$ 13.8, α-CF_A), -114.14 (1F, m, $^4J_{FF}$ 13.0, α-CF_B), -120.84 (2F, m, CF_2), -121.53 (2F, m, CF_2), -121.86 (2F, m, CF_2), -122.67 (2F, m, CF_2), -123.46 (2F, m, CF_2), -126.07 (2F, m, CF_2); δ_C ($CDCl_3$) 67.9 (CH_2), 37.5 (t, $^2J_{CF}$ 21.1, CH_2), 21.8 (CH); HRMS (EI) Calcd. for $C_{11}H_6F_{17}IO$: 603.91920, found: 603.91918.

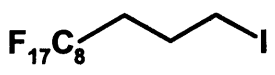
6.2.2. Preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecanol, [**2.28**].



A solution of lithium aluminium hydride (1.00 g, 26.5 mmol) in diethyl ether (13 mL) was added dropwise over 30 min. to 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-2-iodo-*n*-undecanol (8.00 g, 13.2 mmol) stirring in diethyl ether (13 mL) at 0 °C under an inert atmosphere. The reaction mixture was then warmed to 50 °C and stirred at that temperature for 4 h. After cooling to room temperature, water (10 mL) was added dropwise and then sulphuric acid (20 mL, 6 M) was added until everything dissolved. The resulting grey solution was extracted with diethyl ether (3 x 30 mL). The ether extracts were combined, washed twice with sodium thiosulfate (30 mL, 0.1 M), dried over sodium sulphate and the solvent was removed to give the desired product as a white powder (4.10 g, 51%). The preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecanol was carried out by an adaptation of Fish's method.[1]

mp 163-165 °C (lit.,[1] 166-168 °C); δ_H ($CDCl_3$) 3.75 (2H, m, CH_2OH), 3.05 (2H, m, $C_8F_{17}CH_2$), 2.87 (2H, m, CH_2), 1.97 (1H, br s, OH); δ_F ($CDCl_3$) -81.14 (3F, t, $^4J_{FF}$ 9.5, CF_3), -114.25 (2F, t, $^4J_{FF}$ 12.5, α-CF_2), -121.01 (2F, m, CF_2), -121.87 (2F, m, CF_2), -122.67 (2F, m, CF_2), -123.46 (2F, m, CF_2), -124.04 (2F, m, CF_2), -126.06 (2F, m, CF_2); δ_C ($CDCl_3$) 61.4 (CH_2), 28.6 (t, $^2J_{CF}$ 21.5, CH_2), 24.4 (CH_2); HRMS (EI) Calcd. for $C_{11}H_7F_{17}O$: 478.02255, found: 478.02246.

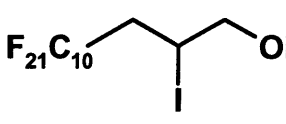
6.2.3. Preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide, [**2.29**].



Phosphorus pentoxide (4.00 g) was added to phosphoric acid (85%, 10 mL) in a 50 mL round-bottomed flask and the mixture was stirred at room temperature for 20 min. Potassium iodide (2.50 g, 14.7 mmol) was then added, followed immediately by 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecanol (1.50 g, 3.1 mmol). The mixture was heated to 120 °C for 24 h. After cooling to room temperature, water (10 mL) was added, and the resulting brown solution was extracted four times with diethyl ether (4 x 25 mL). The ether extracts were combined, washed twice with sodium thiosulfate (25 ml, 0.1 M), dried over sodium sulphate and the solvent was removed under reduced pressure to give a pale yellow solid that was recrystallized from methanol (30 mL), to give the pure product (1.10 g, 75%). The preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide was carried out by following the procedure developed by Fish *et al.*[1]

mp 36-38 °C (lit.,[1] 37-39 °C); δ_H ($CDCl_3$) 3.18 (2H, t, $^3J_{HH}$ 6.4, CH_2I), 2.14 (4H, m, $C_8F_{17}CH_2CH_2$); δ_F ($CDCl_3$) -80.89 (3F, t, $^4J_{FF}$ 9.8, CF_3), -114.25 (2F, t, $^4J_{FF}$ 12.4, α-CF_2), -121.66 (2F, m, CF_2), -121.80 (4F, m, 2 x CF_2), -122.60 (2F, m, CF_2), -123.92 (2F, m, CF_2), -126.10 (2F, m, CF_2); δ_C ($CDCl_3$) 31.9 (CH_2), 24.3 (t, $^2J_{CF}$ 22.6, CH_2), 3.7 (CH_2); HRMS (EI) Calcd. for $C_{11}H_6F_{17}I$: 587.92428, found: 587.92443.

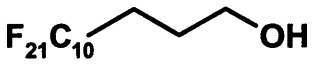
6.2.4. Preparation of 1*H*,1*H*,2*H*,3*H*,3*H*-perfluoro-2-iodo-*n*-tridecanol, [**2.31**].



Perfluorodecyl iodide (7.00 g, 26.1 mmol), allyl alcohol (3 mL, 44.1 mmol) and azobisisobutyronitrile (0.40 g, 2.4 mmol) were heated at 80 °C under an inert atmosphere for 24 h. The yellow solid obtained was recrystallized from hexane (20 mL). The resulting mixture was purified by column chromatography on silica gel (petroleum ether/diethyl ether = 3/2) affording the pure product as a white solid (6.5 g, 60%).

mp 121-123 °C; Anal. Calcd. for $C_{13}H_6F_{21}IO$: C, 22.18; H, 0.86 %. Found: C, 22.03; H, 0.76 %; δ_H ($CDCl_3$) 4.39 (1H, m, CHI), 3.78 (2H, m, CH_2OH), 2.96 (1H, m, $C_{10}F_{21}CH_A$), 2.71 (1H, m, $C_{10}F_{21}CH_B$), 1.95 (1H, br s, OH); δ_F ($CDCl_3$) -80.68 (3F, t, $^4J_{FF}$ 9.9, CF_3), -112.94 (1F, m, $^4J_{FF}$ 13.0, α-CF_A), -114.63 (1F, m, $^4J_{FF}$ 13.0, α-CF_B), -121.71 (10F, m, 5 x CF_2), -122.63 (2F, m, CF_2), -123.44 (2F, m, CF_2), -126.05 (2F, m, CF_2); δ_C ($CDCl_3$) 67.9 (CH_2), 37.5 (t, $^2J_{CF}$ 21.3, CH_2), 21.8 (CH); HRMS (EI) Calcd. for $C_{13}H_6F_{21}IO$: 703.91280; found: 703.91281.

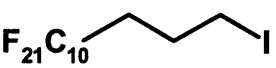
6.2.5. Preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecan-1-ol, [**2.32**].



1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-Perfluoro-2-iodo-*n*-tridecanol (4.30 g, 6.1 mmol) and azobisisobutyronitrile (45.0 mg, 0.2 mmol) were suspended in dry trifluorotoluene (40 mL). Tributyltin hydride (3.3 mL, 12.2 mmol) was then added dropwise and the reaction mixture heated to 85 °C under an inert atmosphere for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting residue was redissolved in diethyl ether and washed with water and brine. The organic layer was dried over sodium sulphate and filtered. Potassium fluoride (0.70 g, 12.2 mmol) was dispersed in the organic layer and stirred for 12 h. After filtration and removing the solvent, the resulting solid was purified by column chromatography on silica gel (petroleum ether/diethyl ether = 1/1) to give the product as a white solid (2.30 g, 65%). The preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecan-1-ol was carried out by following the procedure developed by Rábai *et al.*[2]

mp 85-87 °C (lit.,[2] 86-89 °C); Anal. Calcd. for $C_{13}H_7F_{21}O$: C, 27.09; H, 1.04 %. Found: C, 27.01; H, 1.22 %; δ_H ($CDCl_3$) 3.71 (2H, m, CH_2OH), 2.16 (2H, m, $C_{10}F_{21}CH_2$), 1.82 (2H, m, $C_{10}F_{21}CH_2CH_2$), 1.48 (1H, br s, OH); δ_F ($CDCl_3$) -80.73 (3F, t, $^4J_{FF}$ 9.5, CF_3), -114.24 (2F, t, $^4J_{FF}$ 16.1, α-CF_2), -121.70 (10F, m, 5 x CF_2), -122.65 (2F, m, CF_2), -123.45 (2F, m, CF_2), -126.06 (2F, m, CF_2); δ_C ($CDCl_3$) 61.4 (CH_2), 27.6 (t, $^2J_{CF}$ 21.5, CH_2), 23.0 (CH_2); HRMS (EI) Calcd. for $C_{13}H_7F_{21}O$: 578.01612; found: 578.01616.

6.2.6. Preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-tridecyl iodide, [**2.33**].

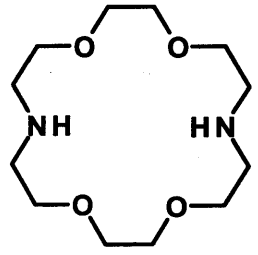


Phosphorus pentoxide (10.00 g) was added to phosphoric acid (85%, 40 mL) in a 50 mL round-bottomed flask and the mixture was stirred at room temperature for 30 min. Potassium

iodide (5.00 g, 30.0 mmol) was then added, followed immediately by 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecan-1-ol (3.50 g, 5.1 mmol). The mixture was heated to 165 °C for 24 h. After cooling to room temperature, water (10 mL) was added, and the resulting brown solution was extracted four times with diethyl ether (4 x 40 mL). The organic layer was washed twice with sodium thiosulfate (50 ml, 0.1 M), dried over sodium sulphate and the solvent was removed to give a white solid (3.40 g, 83%). The preparation of 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-tridecyl iodide was carried out by following the procedure developed by Sinou *et al.*[3]

mp 76-78 °C (lit.,[3] 80-82 °C); Anal. Calcd. for $C_{13}H_6F_{21}I$: C, 22.63; H, 0.70 %. Found: C, 22.69; H, 0.88 %; δ_H ($CDCl_3$) 3.15 (2H, t, $^3J_{HH}$ 6.3, CH_2I), 2.15 (4H, m, $C_{10}F_{21}CH_2CH_2$); δ_F ($CDCl_3$) -80.71 (3F, t, $^4J_{FF}$ 9.5, CF_3), -113.65 (2F, t, $^4J_{FF}$ 13.3, α-CF_2), -121.68 (10F, m, 5 x CF_2), -122.64 (2F, m, CF_2), -123.36 (2F, m, CF_2), -126.05 (2F, m, CF_2); δ_C ($CDCl_3$) 32.0 (CH_2), 24.3 (t, $^2J_{CF}$ 22.7, CH_2), 3.8 (CH_2); HRMS (EI) Calcd. for $C_{13}H_6F_{21}I$: 687.91800; found: 687.91790.

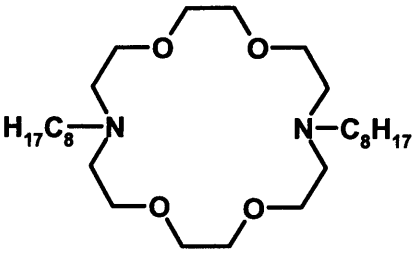
6.2.7. Preparation of 4,13-diaza-18-crown-6, [**2.7**].



N,*N*'-Dibenzyl-4,13-diaza-18-crown-6 (3.00 g, 6.8 mmol), 10% Pd/C (0.30 g) and absolute ethanol (30 mL) were stirred in a hydrogenation apparatus at 60 psi H_2 pressure and 25 °C for 24 h. The mixture was filtered and the solvent eliminated under reduced pressure to yield, after recrystallisation from hexane, a white solid (1.60 g, 90%).

mp 112-114 °C (lit.,[4] 114-115 °C); δ_H ($CDCl_3$) 3.52 (16H, m, $CH_2O(CH_2)_2OCH_2$), 2.73 (8H, t, $^3J_{HH}$ 4.9, CH_2NCH_2), 2.17 (2H, s, NH).

6.2.8. Preparation of *N*,*N*'-bis(octyl)-4,13-diaza-18-crown-6, [**2.6**].

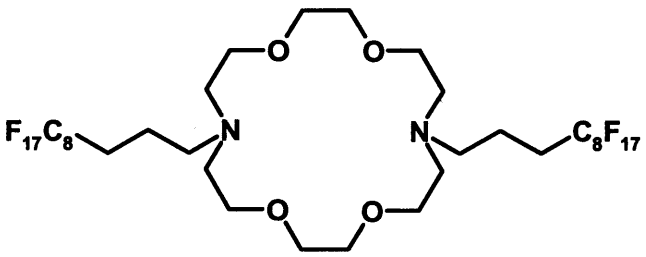


A solution of 4,13-diaza-18-crown-6 (0.20 g, 0.8 mmol), potassium carbonate (0.20 g, 1.5 mmol), and 1-bromooctane (0.30 g, 1.5 mmol) in acetonitrile (20 mL) was heated at 85 °C for 24 h. After cooling to room temperature, the solid was filtered and washed with hot acetonitrile (15 mL x 2). The filtrate and washings were combined and evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 mL). The solution was washed with water (20 mL x 2), dried over magnesium sulphate and evaporated under reduced pressure. The

resultant oil was purified by Kugelröhr distillation (0.1 mbar, 75 °C) to give the pure product as a brown oil (0.30 g, 78%).

Anal. Calcd. for $C_{28}H_{58}N_2O_4$: C, 69.07; H, 12.03; N, 5.75 %. Found: C, 69.16; H, 11.84; N, 5.64 %; δ_H ($CDCl_3$) 3.55 (16H, m, $CH_2O(CH_2)_2OCH_2$), 2.72 (8H, t, $^3J_{HH}$ 6.5, NCH_2CH_2O), 2.43 (4H, t, $^3J_{HH}$ 7.1, $NCH_2C_7H_{15}$), 1.38 (4H, m, CH_2), 1.19 (20H, s, 5 x CH_2), 0.81 (6H, t, $^3J_{HH}$ 6.5, CH_3); δ_C ($CDCl_3$) 70.8 (CH_2), 69.9 (CH_2), 55.8 (CH_2), 53.8 (CH_2), 31.8 (CH_2), 29.5 (CH_2), 29.03 (CH_2), 27.5 (CH_2), 26.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); *m/z* (FAB) 487 (MH^+, 100 %); HRMS (EI) Calcd. for $C_{28}H_{58}N_2O_4$: 486.43966, found: 486.43968.

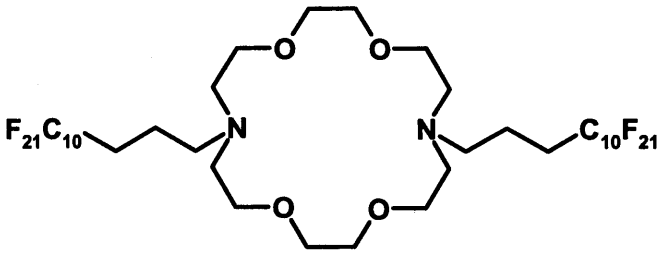
6.2.9. Preparation of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**].



A solution of 4,13-diaza-18-crown-6 (0.20 g, 0.8 mmol), caesium carbonate (0.50 g, 1.5 mmol), and 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-undecyl iodide (0.90 g, 1.5 mmol) in acetonitrile (20 mL) was heated at 85 °C for 24 h. After cooling to room temperature, the solid was filtered and washed with acetonitrile (15 mL x 2). The filtrate and washings were combined and evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 mL). The solution was washed with water (20 mL x 2), dried over magnesium sulphate and evaporated under reduced pressure to give a white solid, which was recrystallized from methanol to afford the pure product (0.44 g, 48%).

mp 66-68 °C; Anal. Calcd. for $C_{34}H_{36}F_{34}N_2O_4$: C, 34.53; H, 3.07; N, 2.37 %. Found: C, 34.61; H, 3.02; N, 2.32 %; δ_H ($CDCl_3$) 3.54 (16H, m, $CH_2O(CH_2)_2OCH_2$), 2.69 (8H, t, $^3J_{HH}$ 5.7, NCH_2CH_2O), 2.50 (4H, t, $^3J_{HH}$ 6.6, $NCH_2(CH_2)_2C_8F_{17}$), 2.06 (4H, m, $CH_2C_8F_{17}$), 1.67 (4H, quintet, $^3J_{HH}$ 7.3, $CH_2CH_2C_8F_{17}$); δ_F ($CDCl_3$) -80.74 (3F, t, $^4J_{FF}$ 9.5, CF_3), -113.91 (2F, t, $^4J_{FF}$ 15.2, α-CF_2), -121.86 (6F, m, 3 x CF_2), -122.68 (2F, m, CF_2), -123.35 (2F, m, CF_2), -126.06 (2F, m, CF_2); δ_C ($CDCl_3$) 70.8 (CH_2), 70.0 (CH_2), 54.5 (CH_2), 54.0 (CH_2), 28.6 (t, $^2J_{CF}$ 22.7, CH_2), 18.5 (CH_2); *m/z* (FAB) 1183 (M^+, 100%).

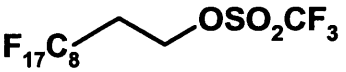
6.2.10. Preparation of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorotridecyl)-4,13-diaza-18-crown-6, [**2.37**].



A solution of 4,13-diaza-18-crown-6 (0.20 g, 0.8 mmol), cesium carbonate (0.50 g, 1.5 mmol) and 1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoro-*n*-tridecyl iodide (1.10 g, 1.6 mmol) in acetonitrile (30 mL) was heated at 85 °C for 24 h. After cooling to room temperature, the solid was filtered and washed with acetonitrile (15 mL x 2). The filtrate and washings were combined and evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 mL). The solution was washed with water (20 mL x 2), dried over magnesium sulphate and evaporated under reduced pressure to give a white solid (0.30 g, 53%).

mp 91-93 °C; Anal. Calcd. for $C_{38}H_{36}F_{42}N_2O_4$: C, 33.01; H, 3.00; N, 2.24 %; Found: C, 32.92; H, 3.00; N, 2.37 %; δ_H ($CDCl_3$) 3.54 (16H, m, $CH_2O(CH_2)_2OCH_2$), 2.68 (8H, t, $^3J_{HH}$ 6.9, NCH_2CH_2O), 2.51 (4H, t, $^3J_{HH}$ 8.0, $NCH_2(CH_2)_2C_{10}F_{21}$), 2.10 (4H, m, $CH_2C_{10}F_{21}$), 1.66 (4H, quintet, $^3J_{HH}$ 7.9, $CH_2CH_2C_{10}F_{21}$); δ_F ($CDCl_3$) -80.80 (3F, t, $^4J_{FF}$ 9.8, CF_3), -114.30 (2F, t, $^4J_{FF}$ 15.8, α-CF_2), -121.77 (10F, m, 5 x CF_2), -122.35 (2F, m, CF_2), -123.39 (2F, m, CF_2), -126.13 (2F, m, CF_2); δ_C ($CDCl_3$) 70.8 (CH_2), 69.9 (CH_2), 54.4 (CH_2), 54.0 (CH_2), 28.6 (t, $^2J_{CF}$ 22.5, CH_2), 18.7 (CH_2); *m/z* (FAB) 1383 (M^+, 100%).

6.2.11. Preparation of 1*H*,1*H*,2*H*,2*H*-perfluorodecyl trifluoromethanesulfonate, [**2.40**].

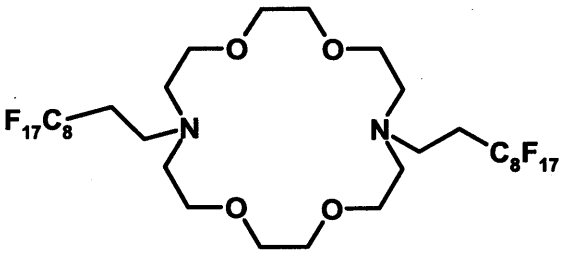


A solution of 1*H*,1*H*,2*H*,2*H*-perfluoro-1-decanol (15.0 g, 32.3 mmol), triethylamine (5.1 mL, 35.9 mmol) and dichloromethane (30 mL) was added dropwise over 1 h to trifluoromethanesulphonic anhydride (8.3 mL, 49.1 mmol) with stirring at -5 °C in dichloromethane (60 mL) under an inert atmosphere. After stirring the reaction mixture for 1 h at -5 °C, it was allowed to warm to room temperature over 30 min. and stirred for a further 30 min. at room temperature. The reaction mixture was then extracted twice with perfluoro-1,3-dimethylcyclohexane, PP3, (2 x 50 mL). The fluorous layers were combined, washed three times with water (3 x 100 mL) and dried over magnesium sulphate and calcium chloride. The solvent was removed under reduced pressure to give a white solid (17.1 g, 89%). The preparation of

1*H*,1*H*,2*H*,2*H*-perfluorodecyl trifluoromethanesulfonate was carried out by following the procedure developed by Kvíčala *et al.*[5]

mp = 44-46°C (lit.,[4] 40-42 °C); Anal. Calcd. for $C_{11}H_4F_{26}O_3S$: C, 22.16; H, 0.68 %; Found: C, 22.51; H, 0.73 %; δ_H ($CDCl_3$) 2.62 (2H, tt, $^3J_{HF}$ 17.4, $^3J_{HH}$ 6.2, $C_8F_{17}CH_2$), 4.72 (2H, t, $^3J_{HH}$ 6.3, $CH_2OSO_2CF_3$); δ_F ($CDCl_3$) -74.53 (3F, s, OSO_2CF_3), -80.74 (3F, t, $^4J_{FF}$ 9.9, CF_2CF_3), -113.43 (2F, t, $^4J_{FF}$ 14.7, α-CF_2), -122.33 (6F, m, 3 x CF_2), -123.37 (2F, m, CF_2), -123.97 (2F, m, CF_2), -126.65 (2F, m, -CF_2); δ_C ($CDCl_3$) 67.6 (CH_2), 31.3 (t, $^2J_{CF}$ 22.7, CH_2).

6.2.12. Preparation of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, **[2.19]**. Method (i).



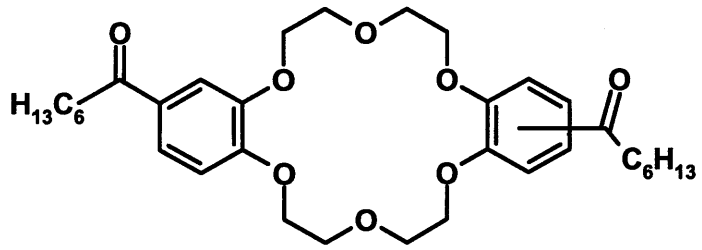
A mixture of 4,13-diaza-18-crown-6 (250 mg, 1.0 mmol), 1*H*,1*H*,2*H*,2*H*-perfluorodecyl trifluoromethanesulfonate (1.40 g, 2.4 mmol), sodium carbonate (250 mg, 2.4 mmol) and dry ethyl acetate (30 mL) was refluxed under an inert atmosphere for 48 h. After cooling to room temperature, the solvent was removed under reduced pressure, and water was added (30 mL). The aqueous mixture was extracted with dichloromethane (3 x 30 mL). The dichloromethane extracts were combined, dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with dichloromethane and then with ethyl acetate as eluants. The ethyl acetate fractions were combined and evaporated under reduced pressure to give a white solid, which was recrystallized from methanol (0.40 g, 42%). The preparation of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6 was carried out by adapting the procedure developed by Bartsch *et al.*[6]

mp 62-64°C (lit.[5] 60-62 °C); Anal. Calcd. for $C_{32}H_{32}F_{34}N_2O_4$: C, 33.29; H, 2.79; N, 2.43 %; Found: C, 33.14; H, 2.58; N, 2.29 %; δ_H ($CDCl_3$) 3.54 (16H, m, $CH_2O(CH_2)_2OCH_2$), 2.83 (4H, t, $^3J_{HH}$ 7.9, $NCH_2CH_2C_8F_{17}$), 2.73 (8H, t, $^3J_{HH}$ 5.5, NCH_2CH_2O), 2.21 (4H, m, $CH_2C_8F_{17}$); δ_F ($CDCl_3$) -80.93 (3F, t, $^4J_{FF}$ 9.9, CF_3), -114.00 (2F, t, $^4J_{FF}$ 15.6, α-CF_2), -122.02 (6F, m, 3 x CF_2), -122.81 (2F, m, CF_2), -123.51 (2F, m, CF_2), -126.21 (2F, m, CF_2); δ_C ($CDCl_3$) 70.8 (CH_2), 69.9 (CH_2), 54.0 (CH_2), 46.7 (CH_2), 29.0 (t, $^2J_{CF}$ 21.5, CH_2); *m/z* (FAB) 1155 (M^+, 100%).

Preparation of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, [**2.19**]. Method (ii).

A solution of 4,13-diaza-18-crown-6 (200 mg, 0.76 mmol), K_2CO_3 (500 mg, 1.52 mmol), and *1H,1H,2H,2H*-perfluoro-*n*-decyl iodide (900 mg, 1.57 mmol) in MeCN (20 mL) was heated at 85 °C for 24 h. After cooling to room temperature, the solid was filtered and washed with MeCN (15 mL x 2). The filtrate and washings were combined and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with water (20 mL x 2), dried over $MgSO_4$ and evaporated under reduced pressure to give a pale yellow solid (70 mg, 9%).

6.2.13. Preparation of *bis*(heptanoyl)dibenzo-18-crown-6, [**4.16**]. Method (i).



A slurry of heptanoic acid (4.2 g, 31.9 mmol) and dibenzo-18-crown-6 (5.0 g, 13.9 mmol) was added to polyphosphoric acid (25 mL, 51.3 g). The mechanically stirred (600 rpm) reaction mixture was heated for 1 h at 90 °C. Then, the hot solution was poured into a mechanically stirred ice-cold water bath (400 mL). After stirring for 4 h, the resulting pale yellow precipitate was filtered and recrystallized from EtOH (250 mL) to afford the pure product as a pale brown solid (6.8 g, 84%). The final product was isolated as a mixture of the *cis*- and *trans*- isomers. No attempt was made to separate these isomers.

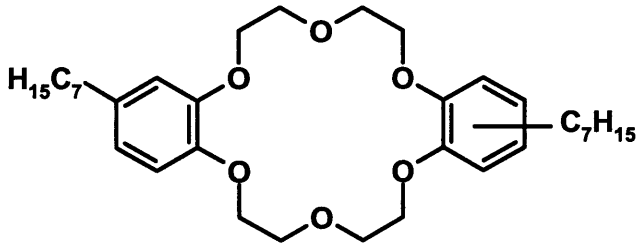
mp 118-120 °C; Anal. Calcd. for $C_{34}H_{48}O_8$: C, 69.84; H, 8.27 %; Found: C, 69.94; H, 8.38 %; δ_H ($CDCl_3$) 7.48 (2H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.41 (2H, d, $^4J_{HH}$ 2.3 Hz, ArH), 6.76 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 4.12 (8H, m, $ArOCH_2$), 3.93 (8H, m, $ArOCH_2CH_2$), 2.82 (4H, t, $^3J_{HH}$ 7.5, $COCH_2$), 1.63 (4H, quintet, $^3J_{HH}$ 7.2, $COCH_2CH_2$), 1.25 (12H, m, 3 x CH_2), 0.81 (6H, t, $^3J_{HH}$ 6.4, CH_3); δ_C ($CDCl_3$) 199.3 (CO), 152.8 (C), 148.5 (C), 130.3 (C), 122.9 (CH), 111.9 (CH), 111.3 (CH), 69.7 (CH_2), 68.5 (CH_2), 38.2 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (EI) Calcd. for $C_{34}H_{48}O_8$: 585.34260; found: 585.34274.

Preparation of *bis*(heptanoyl)dibenzo-18-crown-6, [**4.16**]. Method (ii).

Heptanoyl chloride (4.6 g, 30.9 mmol) was added dropwise to a suspension of aluminium trichloride (8.5 g, 63.75 mmol) in chloroform (50 mL). The mixture was

heated to 50 °C for 20 min. Dibenzo-18-crown-6 (5 g, 13.85 mmol) was then added at a rate such that the temperature did not exceed 50 °C. The reaction mixture was stirred at 50 °C for 4h. Then, the reaction mixture was poured into ice (200 g) and stirred for 5 min. The solution was acidified with hydrochloric acid concentrate to pH=1-2 (10 mL). The aqueous phase was separated and extracted with DCM (2 x 100 mL). The combined organic extracts were washed with 2% sodium hydroxide (3 x 100 mL), water (2 x 100 mL), dried over magnesium sulphate and the solvent eliminated under reduced pressure to afford a white solid, which was recrystallized from ethanol (100 mL).

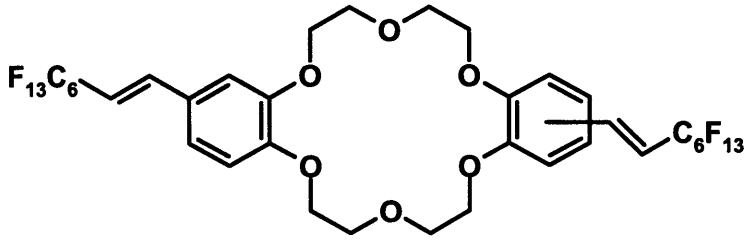
6.2.14. Preparation of *bis*(heptyl)dibenzo-18-crown-6, [**4.17**].



Triethylsilane (4.9 g, 41.8 mmol) was added to a stirring solution of *bis*(heptanoyl)dibenzo-18-crown-6 (5.0 g, 8.6 mmol) in trifluoroacetic acid (60 mL). The solution was stirred at room temperature for 3h under an inert atmosphere. Then, the reaction mixture was diluted with chloroform (75 mL). An aqueous solution of sodium hydrogencarbonate was added slowly until no further exothermicity was observed. The organic phase was separated, washed with water (2 x 75 mL) and dried over magnesium sulphate. The solvent was removed and the resulting yellow solid was recrystallized from ethanol to give the desired product as a pale brown powder (1.9 g, 40%).

mp 84-86 °C; Anal. Calcd. for $C_{34}H_{52}O_6$: C, 73.35; H, 9.41 %; Found: C, 73.43; H, 9.25 %; δ_H ($CDCl_3$) 6.70 (2H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.1 Hz, ArH), 6.62 (2H, d, $^3J_{HH}$ 8.7 Hz, ArH), 6.59 (2H, d, $^4J_{HH}$ 2.4 Hz, ArH), 4.07 (8H, m, $ArOCH_2$), 3.94 (8H, m, $ArOCH_2CH_2$), 2.44 (4H, t, $^3J_{HH}$ 7.6, $ArCH_2$), 1.48 (4H, quintet, $^3J_{HH}$ 7.0, CH_2), 1.21 (16H, m, 4 x CH_2), 0.80 (6H, t, $^3J_{HH}$ 6.7, CH_3); δ_C ($CDCl_3$) 148.6 (C), 146.8 (C), 136.2 (C), 120.8 (CH), 114.2 (CH), 113.8 (CH), 70.0 (CH_2), 69.0 (CH_2), 35.5 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS (EI) Calcd. for $C_{34}H_{52}O_6$: 556.37624; found: 556.37639.

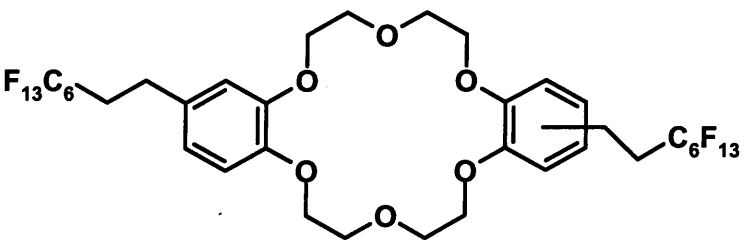
6.2.15. Preparation of *bis*(1*H*,2*H*-perfluoro-1-octenyl)dibenzo-18-crown-6, [**4.24**].



A suspension of bis (dibromobenzo)-18-crown-6 (0.5 g, 1.0 mmol), 1*H*,1*H*,2*H*-perfluoro-1-octene (1.4 g, 4.0 mmol), *trans*-di-*m*-acetatobis[2-(di-*o*-tolylphosphino) benzyl]dipalladium (II), Herrmann's catalyst, (30 mg, 30.0 x 10^{-3} mmol) and sodium acetate (250 mg, 3.0 mmol) in wet *N,N'*-dimethylformamide (2 mL of water in 30 mL of *N,N'*-dimethylformamide) was stirred under an inert atmosphere at 120 °C for 72 h. After cooling to room temperature, the solvent was eliminated under reduced pressure. The resulting solid was partitioned between dichloromethane (40 mL) and water (40 mL). The organic layer was washed with water (40 mL) and brine (40 mL), and dried over magnesium sulphate. The solvent was removed and the resulting pale yellow solid was recrystallized from ethanol to give the desired product as a white solid (0.9 g, 84%).

mp 100-102 °C; Anal. Calcd. for $C_{36}H_{26}F_{26}O_6$: C, 41.24; H, 2.50 %; Found: C, 41.16; H, 2.42 %; δ_H ($CDCl_3$) 7.02 (2H, dt, $^3J_{HH}$ 15.8, $^4J_{HF}$ 2.1, C*H*=CHCF$_2$), 6.95 (2H, dd, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 2.1 Hz, ArH), 6.89 (2H, d, $^4J_{HH}$ 1.8 Hz, ArH), 6.78 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 5.95 (2H, dt, $^3J_{HH}$ 16.1, $^3J_{HF}$ 12.3, CH=C*H*CF$_2$), 4.12 (8H, m, ArOCH$_2$), 3.96 (8H, m, ArOCH$_2$C*H*$_2$); δ_F ($CDCl_3$) -80.77 (3F, t, $^4J_{FF}$ 9.9, CF_3), -110.48 (2F, t, $^4J_{FF}$ 12.2, α-CF_2), -121.57 (2F, m, CF_2), -122.84 (2F, m, CF_2), -123.07 (2F, m, CF_2), -126.12 (2F, m, CF_2); δ_C ($CDCl_3$) 150.7 (C), 148.4 (C), 139.4 (t, $^2J_{CF}$ 22.1, CH), 126.7 (C), 122.1 (CH), 112.8 (CH), 112.3 (CH), 111.7 (CH), 69.75 (CH_2), 68.75 (CH_2); *m/z* (FAB) 1048 (M^+, 100%).

6.2.16. Preparation of *bis*(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6, [**4.26**].

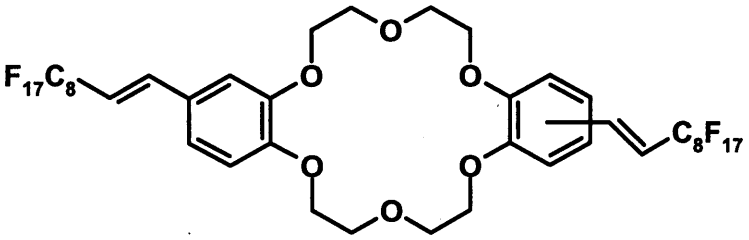


Bis(1*H*,2*H*-perfluoro-1-octenyl) dibenzo-18-crown-6 (0.5 g, 0.5 mmol), 5% rhodium in charcoal (20 mg) and dichloromethane (25 mL) were stirred in a hydrogenation

apparatus at 50 bar hydrogen pressure at room temperature for 48 h. The organic phase was filtered through celite and concentrated under reduced pressure to yield, after recrystallisation from ethanol, a white solid (0.4 g, 69%).

mp 118-120 °C; Anal. Calcd. for $C_{36}H_{30}F_{26}O_6$: C, 41.08; H, 2.87 %; Found: C, 41.13; H, 2.78 %; δ_H ($CDCl_3$) 6.74 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 6.67 (2H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 6.64 (2H, d, $^4J_{HH}$ 1.5 Hz, ArH), 4.09 (8H, m, $ArOCH_2$), 3.95 (8H, m, $ArOCH_2CH_2$), 2.76 (4H, m, $ArCH_2$), 2.26 (4H, m, CH_2CF_2); δ_F ($CDCl_3$) -80.74 (3F, t, $^4J_{FF}$ 9.5, CF_3), -114.60 (2F, t, $^4J_{FF}$ 14.6, α-CF_2), -121.85 (2F, m, CF_2), -122.80 (2F, m, CF_2), -123.47 (2F, m, CF_2), -126.08 (2F, m, CF_2); δ_C ($CDCl_3$) 148.9 (C), 147.5 (C), 132.1 (C), 120.7 (CH), 113.7 (CH), 113.7 (CH), 69.9 (CH_2), 68.9 (CH_2), 33.2 (t, $^2J_{CF}$ 25.4, CH_2), 26.0 (CH_2); *m/z* (FAB) 1052 (M^+, 100%).

6.2.17. Preparation of *bis*(1*H*,2*H*-perfluoro-1-decyl)dibenzo-18-crown-6, **[4.25]**.

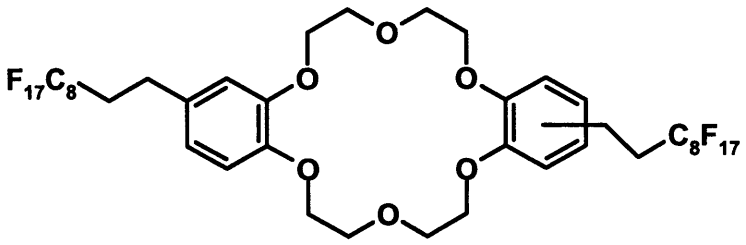


A suspension of bis(dibromobenzo)-18-crown-6 (0.5 g, 1.0 mmol), 1*H*,1*H*,2*H*-perfluoro-1-decene (1.8 g, 4.0 mmol), *trans*-di-*m*-acetatobis[2-(di-*o*-tolylphosphino) benzyl]dipalladium (II), Herrmann's catalyst, (30 mg, 30 x 10^{-3} mmol) and sodium acetate (250 g, 3.0 mmol) in wet *N,N'*-dimethylformamide (2 mL of water in 30 mL of *N,N'*-dimethylformamide) was stirred under an inert atmosphere at 120 °C for 72 h. After cooling to room temperature, the solvent was eliminated under reduced pressure. The resulting solid was partitioned between dichloromethane-ethyl acetate (20-20 mL) and water (40 mL). The organic layer was washed with water (40 mL) and brine (40 mL), and dried over magnesium sulphate. The solvent was removed and the resulting yellow solid was recrystallized from ethanol to give the desired product as a white solid (0.5 g, 40%).

mp 130-132 °C; Anal. Calcd. for $C_{40}H_{26}F_{34}O_6$: C, 38.48; H, 2.10 %; Found: C, 38.61; H, 2.01 %; δ_H ($CDCl_3$) 7.02 (2H, dt, $^3J_{HH}$ 15.8, $^4J_{HF}$ 2.1, CH=$CHCF_2$), 6.97 (2H, dd, $^3J_{HH}$ 8.2 Hz, $^4J_{HH}$ 2.1 Hz, ArH), 6.89 (2H, d, $^4J_{HH}$ 1.8 Hz, ArH), 6.74 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 5.95 (2H, dt, $^3J_{HH}$ 16.4, $^3J_{HF}$ 12.0, CH=$CHCF_2$), 4.12 (8H, m, $ArOCH_2$), 3.97 (8H, m, $ArOCH_2CH_2$); δ_F ($CDCl_3$) -80.71 (3F, t, $^4J_{FF}$ 10.0, CF_3), -110.43 (2F, t, $^4J_{FF}$ 12.6, α-CF_2), -121.31 (6F, m, 3 x CF_2), -121.84 (2F, m, CF_2), -

122.64 (2F, m, CF_2), -123.01 (2F, m, CF_2); δ_C ($CDCl_3$) 150.5 (C), 148.8 (C), 139.4 (t, $^2J_{CF}$ 25.2, CH), 126.6 (C), 122.0 (CH), 112.4 (CH), 112.0 (CH), 111.2 (CH), 69.6 (CH_2), 68.6 (CH_2); *m/z* (FAB) 1271 (MNa^+, 100%).

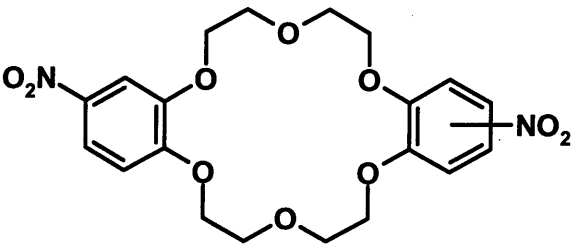
6.2.18. Preparation of *bis*(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)dibenzo-18-crown-6, [**4.27**].



Bis(1*H*,1*H*,2*H*,2*H*-perfluoro-1-decyl)dibenzo-18-crown-6 (0.5 g, 1.0 mmol), 5% rhodium in charcoal (20 mg) and dichloromethane (25 mL) were stirred in a hydrogenation apparatus at 50 bar hydrogen pressure at room temperature for 48 h. The organic phase was filtered through celite and concentrated under reduced pressure to yield, after recrystallisation from ethanol, a white solid (0.8 g, 64%).

mp 136-138 °C; Anal. Calcd. for $C_{40}H_{30}F_{34}O_6$: C, 38.36; H, 2.41 %; Found: C, 38.51; H, 2.36 %; δ_H ($CDCl_3$) 6.75 (2H, d, $^3J_{HH}$ 7.9 Hz, ArH), 6.67 (2H, dd, $^3J_{HH}$ 7.3 Hz, $^4J_{HH}$ 2.0 Hz, ArH), 6.64 (2H, d, $^4J_{HH}$ 1.8 Hz, ArH), 4.09 (8H, m, $ArOCH_2$), 3.96 (8H, m, $ArOCH_2CH_2$), 2.76 (4H, m, $ArCH_2$), 2.25 (4H, m, CH_2CF_2); δ_F ($CDCl_3$) -80.71 (3F, t, $^4J_{FF}$ 9.5, CF_3), -114.55 (2F, t, $^4J_{FF}$ 15.2, α-CF_2), -121.62 (6F, m, 3 x CF_2), -122.65 (2F, m, CF_2), -123.42 (2F, m, CF_2), -126.04 (2F, m, CF_2); δ_C ($CDCl_3$) 148.9 (C), 147.5 (C), 132.2 (C), 120.8 (CH), 114.0 (CH), 113.6 (CH), 70.0 (CH_2), 69.1 (CH_2), 33.6 (t, $^2J_{CF}$ 22.4, CH_2), 26.0 (CH_2); *m/z* (FAB) 1275 (MNa^+, 100%)

6.2.19. Preparation of *cis*- and *trans*-di(nitrobenzo)-18-crown-6, [**4.28a-b**].



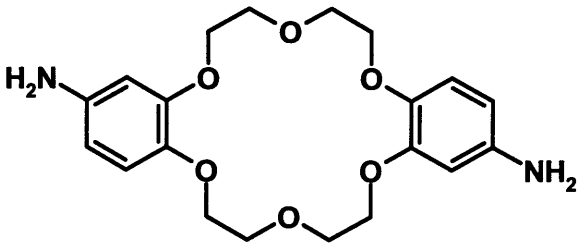
Acetic acid (100 mL) was added over 10 min. to a solution of dibenzo-18-crown-6 (5.00 g, 13.9 mmol) in chloroform (100 mL). After stirring the solution at room temperature for an additional 10 min., a solution of nitric acid (4 mL) in acetic acid (11 mL) was added dropwise over 20 min. The solution was stirred at room temperature for 1 h and then heated for 3 h at 65 °C. The solution was cooled, and the precipitate was filtered. The pale beige solid obtained was predominantly the *trans*-isomer [**4.28b**] (2.80 g, 44%).

mp_{trans} 240-242 °C (lit.,[7] 242-244 °C); δ_H (DMSO-d_6) 7.89 (2H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH), 7.72 (2H, d, $^4J_{HH}$ 2.7 Hz, ArH), 7.15 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 4.21(8H, m, $ArOCH_2$), 3.85 (8H, m, $ArOCH_2CH_2$); δ_C (DMSO-d_6) 153.7 (C), 147.6 (C), 140.5 (C), 117.6(CH), 111.2 (CH), 106.6 (CH), 68.4 (CH_2), 68.0 (CH_2); HRMS (EI) Calcd. for $C_{20}H_{22}N_2O_{10}$: 451.13527; found: 451.13536.

The *cis*-isomer **[4.28a]** precipitated from the mother solution within 48 h as a pale yellow solid. Residual acetic acid was removed by dissolving the sample in *N,N*-dimethylformamide followed by addition of water to precipitate pure *cis*-di(nitrobenzo)-18-crown-6 (1.90 g, 30%).

mp_{cis} 203-205 °C (lit.,[8] 200-201 °C); δ_H (DMSO-d_6) 7.89 (2H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH), 7.72 (2H, d, $^4J_{HH}$ 2.7 Hz, ArH), 7.15 (2H, d, $^3J_{HH}$ 9.0 Hz, ArH), 4.21(8H, m, $ArOCH_2$), 3.85 (8H, m, $ArOCH_2CH_2$); δ_C (DMSO-d_6); δ_C (DMSO-d_6) 153.8 (C), 147.7 (C), 140.6 (C), 117.6(CH), 111.3 (CH), 106.5 (CH), 68.2 (CH_2), 68.0 (CH_2).

6.2.20. Preparation of *cis*- and *trans*-di(aminobenzo)-18-crown-6, [4.29a-b].



Trans-di(nitrobenzo)-18-crown-6 (2.60 g, 6.0 mmol) was dissolved in hot *N,N*-dimethylformamide (70 mL). 10% Pd/C (0.60 g) was added and the reactor was placed in a pressurized hydrogenation apparatus. The reactor was charged with hydrogen (15 bar) and stirred for 24 h at room temperature. The mixture was filtered through silica gel and celite. The solvent was removed under reduced pressure to afford the *trans*-amino derivative **[4.29b]** as a dark orange solid (2.4 g, 99%).

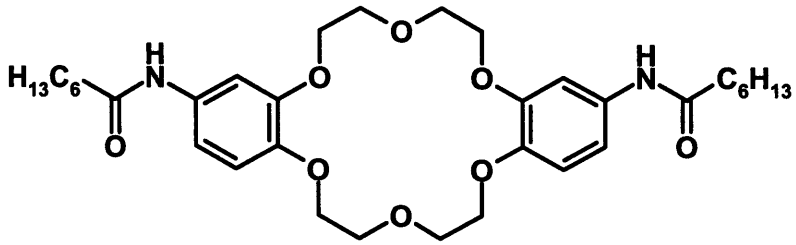
mp_{trans} 184-186 °C (lit.,[9] 180-184 °C); δ_H (DMSO-d_6) 6.63 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH), 6.25 (2H, d, $^4J_{HH}$ 2.3 Hz, ArH), 6.05 (2H, dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 4.65 (4H, brs, NH_2), 3.95 (8H, m, $ArOCH_2$), 3.74 (8H, m, $ArOCH_2CH_2$); δ_C (DMSO-d_6) 149.1 (C), 143.5 (C), 139.0 (C), 115.6 (CH), 105.3 (CH), 100.6 (CH), 69.0 (CH_2), 67.6 (CH_2); HRMS (EI) Calcd. for $C_{20}H_{26}N_2O_6$: 390.17909; found: 309.17908.

The same procedure was followed for the synthesis of the *cis*-isomer **[4.29a]** (98%).

mp_{cis} 178-180 °C (lit.,[10] 178-182 °C); δ_H (DMSO-d_6) 6.62 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH), 6.23 (2H, d, $^4J_{HH}$ 2.3 Hz, ArH), 6.05 (2H, dd, $^3J_{HH}$ 8.4 Hz, $^4J_{HH}$ 2.4 Hz, ArH), 4.65 (4H, brs, NH_2), 3.93 (8H, m, $ArOCH_2$), 3.77 (8H, m, $ArOCH_2CH_2$); δ_C (DMSO-d_6)

149.1 (C), 143.4 (C), 139.2 (C), 115.6 (CH), 105.4 (CH), 100.8 (CH), 69.2 (CH_2), 67.6 (CH_2).

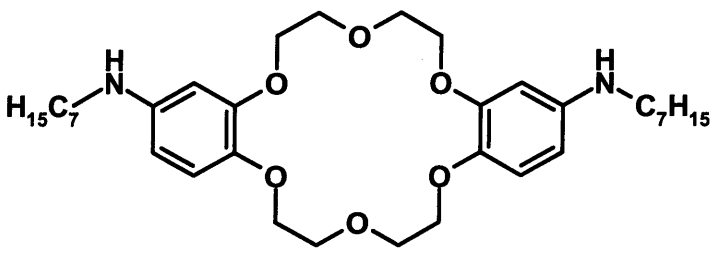
6.2.21. Preparation of *cis*-di(heptylamidobenzo)-18-crown-6, [**4.30a**].



A solution of heptanoyl chloride (0.5 g, 3.1 mmol) in acetone (10 mL) was added to a solution of *cis*-di(aminobenzo)-18-crown-6 (0.5 g, 1.3 mmol) in acetone (40 mL). The mixture was stirred for 2 h at room temperature and for a further 12 h at 60 °C. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting solid was dissolved in trifluoroethanol (40 mL), and water (40 mL) was added to the solution. The mixture was stirred for 1 h at -5 °C. The resulting precipitate was filtered and the solid was recrystallized from ethanol to afford a pale red solid (0.40 g, 47%).

mp_{cis} 192-194 °C; Anal. Calcd. for $C_{34}H_{50}N_2O_8$: C, 66.43; H, 8.20; N, 4.56 %; Found: C, 66.36; H, 8.16; N, 4.42 %; δ_H (DMSO-d_6) 11.01 (2H, br s, NHCO), 7.36 (2H, d, $^4J_{HH}$ 2.4 Hz, ArH), 7.09 (2H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.4 Hz, ArH), 6.88 (2H, d, $^3J_{HH}$ 8.9 Hz, ArH), 4.06 (8H, m, $ArOCH_2$), 3.87 (8H, m, $ArOCH_2CH_2$), 2.26 (4H, t, $^3J_{HH}$ 7.3, $NHCOCH_2$), 1.56 (4H, quintet, $^3J_{HH}$ 6.4, $COCH_2CH_2$), 1.27 (12H, s, 3 x CH_2), 0.86 (6H, t, $^3J_{HH}$ 6.7, CH_3); δ_C (DMSO-d_6) 170.79 (CO), 147.1 (C), 143.2 (C), 133.1 (C), 120.0 (CH), 111.0 (CH), 104.4 (CH), 68.9 (CH_2), 67.4 (CH_2), 36.3 (CH_2), 31.0 (CH_2), 28.3 (CH_2), 25.1 (CH_2), 22.0 (CH_2), 13.9 (CH_3); HRMS (EI) Calcd. for $C_{34}H_{50}N_2O_8$: 614.35679; found: 614.35672.

6.2.22. Preparation of *cis*-di(heptylamino)dibenzo-18-crown-6, [**4.31a**]. Method (i).



cis-Di(heptylamidobenzo)-18-crown-6 (0.5 g, 0.8 mmol) and lithium aluminium hydride (0.4 g, 10.4 mmol) were dissolved in dry tetrahydrofuran (20 mL). The suspension was heated for 4 h at 70 °C under an inert atmosphere. After cooling to room temperature, water was added carefully until no reaction occurred. The mixture was filtered and the filtrate

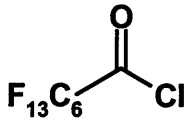
was washed with hot diethyl ether. The aqueous phase was extracted with diethyl ether (2 x 20 mL). The combined organic phases were washed with water (2 x 20 mL), and dried over magnesium sulphate. The solid was recrystallized from diethylether to afford a pale brown solid (0.25 g, 50%). The same protocol is applicable to the synthesis of the *trans*- isomer.

mp_{cis} 122-124 °C; Anal. Calcd. for $C_{34}H_{54}N_2O_6$: C, 69.59; H, 9.28; N, 4.77 %; Found: C, 69.51; H, 9.18; N, 4.68 %; δ_H ($CDCl_3$) 6.69 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH), 6.53 (2H, d, $^4J_{HH}$ 2.6 Hz, ArH), 6.07 (2H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 2.6 Hz, ArH), 4.04 (8H, m, $ArOCH_2$), 3.91 (8H, m, $ArOCH_2CH_2$), 3.28 (2H, br s, NH), 2.96 (4H, t, $^3J_{HH}$ 7.1, NCH_2), 1.52 (4H, quintet, $^3J_{HH}$ 7.2, NCH_2CH_2), 1.23 (16H, m, 4 x CH_2), 0.81 (6H, t, $^3J_{HH}$ 6.7, CH_3); δ_C ($CDCl_3$) 150.4 (C), 144.1 (C), 140.9 (C), 117.2 (CH), 104.7 (CH), 100.6 (CH), 70.3 (CH_2), 68.8 (CH_2), 44.9 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 27.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (EI) Calcd. for $C_{34}H_{55}N_2O_6$: 587.40600; found: 587.40601.

Preparation of *cis*-di(heptylamino)dibenzo-18-crown-6, [**4.31a**]. Method (ii).

cis-Di(heptylamidobenzo)-18-crown-6 (0.5 g, 0.8 mmol) and sodium borohydride (140 mg, 3.7 mmol) were dissolved in dry tetrahydrofuran (20 mL). Iodine (0.5 g, 1.5 mmol) in dry tetrahydrofuran (10 mL) was added dropwise under an inert atmosphere at 0 °C for 2.5 h. The reaction mixture was heated for 24 h at 70 °C. After cooling to room temperature, water (5 mL) was added. The solvent was eliminated under reduced pressure. The resulting mixture was dissolved in hydrochloric acid-water-methanol (3: 4.5: 15 mL) and heated at 75 °C for 8h. After cooling to room temperature, the mixture was extracted with dichloromethane (2 x 25 mL). The organic phase was washed with sodium thiosulphate (25 mL) and water (25 mL), and dried over anhydrous magnesium sulphate. The solvent was eliminated under reduced pressure and the resulting solid was recrystallized from ethanol to afford the pure product as a pale yellow solid (120 mg, 26%).

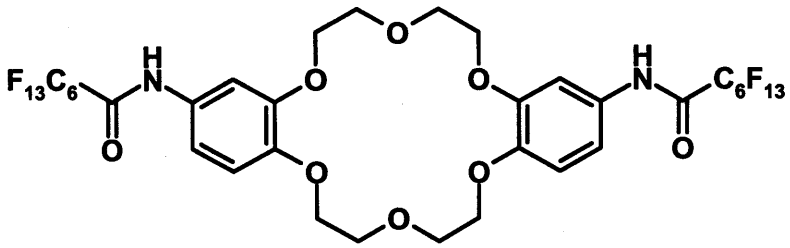
6.2.23. Preparation of tridecafluoroheptanoyl chloride, [**4.33**].



Perfluoroheptanoic acid (7.2 g, 20.0 mmol), thionylchloride (4.0 g, 20.0 mmol) and pyridine (0.1 g, 1.0 mmol) were stirred under an inert atmosphere at 65 °C for 3 h. After cooling to room temperature, the lower layer was separated and distilled. The fraction collected at 110-115 °C was the pure perfluoroheptanoyl chloride (6.0 g, 78%).

δ_F ($CDCl_3$) -80.01 (3F, t, $^4J_{FF}$ 10.0, CF_3), -113.06 (2F, t, $^4J_{FF}$ 12.8, α-CF_2), -121.31 (2F, m, CF_2), -121.51 (2F, m, CF_2), -122.89 (2F, m, CF_2), -126.28 (2F, m, CF_2); δ_C ($CDCl_3$) 161.75 (t, $^2J_{CF}$ 36.5, CO). *The characterization data is in agreement with the literature.*[11]

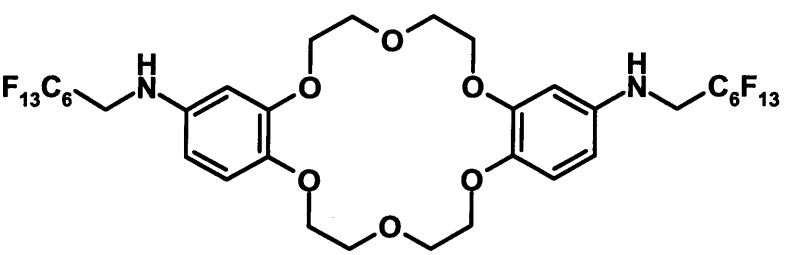
6.2.24. Preparation of *cis*-di(perfluoroheptylamidobenzo)-18-crown-6, [**4.34a**].



A mixture of perfluoro heptanoyl chloride (4.8 g, 12.6 mmol), *cis*-di(aminobenzo)-18-crown-6 (2.1 g, 5.3 mmol) and potassium carbonate (2.0 g, 14.5 mmol) in acetone (40 mL) was stirred at room temperature for 2h. The reaction mixture was then heated at 60 °C for 12 h. After cooling to room temperature, the solvent was eliminated under reduced pressure. The resulting solid was stirred in trifluoroethanol-water (75 mL : 75 mL) at room temperature for 1 h. The precipitate was filtered and recrystallized from trifluoroethanol to afford a pale brown solid (0.5 g, 23%).

mp 220-222 °C; Anal. Calcd. for $C_{34}H_{24}F_{26}N_2O_8$: C, 37.72; H, 2.23; N, 2.59 %; Found: C, 37.74; H, 2.18; N, 2.69 %; δ_H (DMSO-d_6) 11.02 (2H, br s, NHCO), 7.33 (2H, d, $^4J_{HH}$ 2.3 Hz, ArH), 7.30 (2H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 2.3 Hz, ArH), 7.01 (2H, d, $^3J_{HH}$ 8.8 Hz, ArH), 4.12 (8H, m, $ArOCH_2$), 3.90 (8H, m, $ArOCH_2CH_2$); δ_F (DMSO-d_6) -80.17 (3F, t, $^4J_{FF}$ 9.7, CF_3), -117.87 (2F, t, $^4J_{FF}$ 14.2, α-CF_2), -121.50 (2F, m, CF_2), -121.98 (2F, m, CF_2), -122.49 (2F, m, CF_2), -125.67 (2F, m, CF_2); δ_C (DMSO-d_6) 155.2 (t, $^2J_{CF}$ 22.7, CO), 148.5 (C), 146.7 (C), 130.1 (C), 114.4 (CH), 113.7 (CH), 107.9 (CH), 69.5 (CH_2), 68.8 (CH_2); *m/z* (FAB) 1083 (M^+, 100%).

6.2.25. Preparation of *cis*-di(1*H*,1*H*-perfluoroheptylaminobenzo)-18-crown-6, [**4.35a**].



A solution of lithium aluminium hydride (120 mg, 3.0 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to *cis*-di(perfluoroheptylamidoben zo)-18-crown-6 (250 mg, 0.2 mmol) stirring in dry tetrahydrofuran (10 mL) at room

temperature under an inert atmosphere. The reaction mixture was then heated to 70 °C and stirred at that temperature for 4 h. After cooling to room temperature, water (2 mL) was added dropwise and then sulphuric acid (4 mL, 6 M) was added until everything dissolved. The resulting solution was extracted with dichloromethane (3 x 30 mL). The extracts were combined, washed with sodium thiosulphate (30 mL, 0.1 M) and then with water (30 mL). The organic phase was dried over magnesium sulphate and the solvent was removed to give the desired product as a pale brown powder (130 mg, 53%).

mp_{cis} 140-142 °C; Anal. Calcd. for $C_{34}H_{28}F_{26}N_2O_6$: C, 38.72; H, 2.68; N, 2.66 %; Found: C, 38.81; H, 2.68; N, 2.70 %; δ_H ($CDCl_3$) 6.71 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH), 6.25 (2H, dd, $^3J_{HH}$ 8.8 Hz, $^4J_{HH}$ 2.1 Hz, ArH), 6.16 (2H, d, $^4J_{HH}$ 2.1 Hz, ArH), 4.05 (8H, m, $ArOCH_2$), 3.93 (8H, m, $ArOCH_2CH_2$), 3.74 (4H, t, $^3J_{HF}$ 15.9 Hz, $NHCH_2$), 2.06 (2H, br s, NH); δ_F ($CDCl_3$) -80.71 (3F, t, $^4J_{FF}$ 10.0, CF_3), -118.04 (2F, t, $^4J_{FF}$ 12.2, α-CF_2), -121.96 (2F, m, CF_2), -122.80 (2F, m, CF_2), -123.31 (2F, m, CF_2), -126.09 (2F, m, CF_2); δ_C ($CDCl_3$) 142.3 (C), 141.5 (C), 130.1 (C), 116.8 (CH), 105.3 (CH), 101.6 (CH), 70.5 (CH_2), 69.7 (CH_2), 46.0 (CH_2); *m/z* (FAB) 1054 (M^+, 100%).

6.3 General Procedure for the Picrate Extraction Studies.

6.3.1. Preparation of the metal picrates.

The potassium and sodium metal picrates were prepared by adding the appropriate carbonate salt to a saturated aqueous solution of picric acid (250 mL) at 80 °C until pH = 7. The solution was allowed to cool to room temperature. The resulting precipitate was recrystallised from water. The picrate salt was dried under reduced pressure and stored in the dark. δ_H (d_6-acetone) 8.50 (2H, s, ArH). *The characterization data is in agreement with the literature.*[12]

6.3.2. Picrate Extraction Procedure.

Equal volumes of a dichloromethane (10 mL) or benzotrifluoride solution (10 mL) of the required macrocycle (0.1 mM) and an aqueous solution of the metal picrate (0.1 mM) were introduced into a stoppered flask and stirred for 30 min at 20 ± 1 °C. The mixture was allowed to stand for 2 h at the same temperature to allow complete phase separation. The absorbance of the picrate salt in the aqueous phase was measured at 356 nm with a Shimadzu 1601 UV-visible spectrophotometer. The percentage extraction was calculated by:

Equation 6.1 $\%\ \text{Extraction} = [100 \times (A_0 - A_1)] / A_0$

where A_1 is the absorbance of the potassium picrate solution after extraction with crown ether and A_0 is the absorbance of the potassium picrate solution without crown ether in the organic phase. Three independent extractions were performed for each combination of potassium picrate and crown ether, and the results were averaged (***Table 6.1***).

Crown Ether	% Extraction	
	DCM	BTF
Diaza-18-crown-6 (D18C6), [**2.7**]	0.9	0.2
D18C6-$(C_8H_{17})_2$, [**2.6**]	47.7	52.9
D18C6-$(C_3H_6C_8F_{17})_2$, [**2.36**]	32.8	21.8
D18C6-$(C_3H_6C_{10}F_{21})_2$, [**2.37**]	26.2	17.4
D18C6-$(C_2H_4C_8F_{17})_2$, [**2.19**]	10.9	3.0
Dibenzo-18-crown-6 (DB18C6), [**4.5**]	1.4	—
DB18C6-$(C_7H_{15})_2$, [**4.17**]	25.6	—
DB18C6-$(C_2H_4C_6F_{13})_2$, [**4.26**]	26.4	—
DB18C6-$(NHC_7H_{15})_2$, [**4.31a**]	24.4	—
DB18C6-$(NHCH_2C_6F_{13})_2$, [**4.35a**]	25.3	—

Table 6.1. Potassium picrate extraction results.

Crown Ether	% Extraction	
	DCM	BTF
Dibenzo-18-crown-6 (DB18C6), [**4.5**]	8.8	—
DB18C6-$(C_7H_{15})_2$, [**4.17**]	9.1	—
DB18C6-$(C_2H_4C_6F_{13})_2$, [**4.26**]	22.9	—
DB18C6-$(C_2H_4C_8F_{17})_2$, [**4.27**]	9.5	—
DB18C6-$(NHC_7H_{15})_2$, [**4.31a**]	23.4	—
DB18C6-$(NHCH_2C_6F_{13})_2$, [**4.35a**]	31.3	—

Table 6.2. Sodium picrate extraction results.

6.4 General Procedures for Phase Transfer Catalysis.

6.4.1 Conversion of 1-bromooctane into 1-iodooctane under liquid-liquid conditions.[13]

A mixture of 1-bromooctane (200 mg, 1.0 mmol), potassium iodide (840 mg, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), benzotrifluoride (4 mL), water (2 mL) and the appropriate crown ether (0.02 mmol) was refluxed at 110 °C for 24 h. After cooling to room temperature, the organic phase was filtered through silica gel using benzotrifluoride as eluent. A sample of the collected solution was analysed by gas chromatography to determine the conversion to product using biphenyl as the internal standard (***Table 6.3***). GC conditions: 115 °C for 3 min followed by 45 °C min^{-1} ramp to 195 °C, held for 1 min. Injector: 300 °C, detector: 300 °C. Retention times: 2.13 min (1-bromooctane), 2.85 min (1-iodooctane), 4.05 min (biphenyl).

Crown Ether	**% conversion** (average)
No PTC	0.2
Diaza-18-crown-6 (D18C6), **[2.7]**	61.0
D18C6-$(C_8H_{17})_2$, **[2.6]**	90.2
D18C6-$(C_3H_6C_8F_{17})_2$, **[2.36]**	26.0
D18C6-$(C_3H_6C_{10}F_{21})_2$, **[2.37]**	23.6
D18C6-$(C_2H_4C_8F_{17})_2$, **[2.19]**	16.6

Table 6.3. Conversion of 1-bromooctane into 1-iodooctane under liquid-liquid conditions.

6.4.2 Conversion of 1-bromooctane into 1-iodooctane under solid-liquid conditions.

A mixture of 1-bromooctane (200 mg, 1.0 mmol), potassium iodide (840 mg, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), benzotrifluoride (4 mL) and the appropriate crown ether (0.02 mmol) was refluxed at 110 °C for 24 h. After cooling to room temperature, the organic phase was filtered through silica gel using benzotrifluoride as eluent. A sample of the collected solution was analysed by gas chromatography to determine the conversion to product using biphenyl as the internal standard (***Table 6.4***).

Crown Ether	% conversion (average)
No PTC	0.4
Diaza-18-crown-6 (D18C6), [**2.7**]	97.0
D18C6-$(C_8H_{17})_2$, [**2.6**]	97.0
D18C6-$(C_3H_6C_8F_{17})_2$, [**2.36**]	96.8
D18C6-$(C_3H_6C_{10}F_{21})_2$, [**2.37**]	93.5
D18C6-$(C_2H_4C_8F_{17})_2$, [**2.19**]	82.6

Table 6.4. Conversion of 1-bromooctane into 1-iodooctane under solid-liquid conditions.

The above reaction was monitored for a 10 hour period by taking samples (25 μL) every hour. The samples were diluted with benzotrifluoride (2 mL) and analysed by gas chromatography (***Table 6.5***).

Crown Ether	Conversion (%)									
	1 h	**2 h**	**3 h**	**4 h**	**5 h**	**6 h**	**7 h**	**8 h**	**9 h**	**10 h**
Diaza-18-crown-6, [**2.7**]	42.2	69.3	84.8	91.6	94.6	95.7	96.0	96.6	96.7	96.6
D18C6-$(C_8H_{17})_2$, [**2.6**]	64.0	83.8	92.8	94.5	95.9	96.3	96.6	96.6	96.7	96.7
D18C6-$(C_3H_6C_8F_{17})_2$, [**2.36**]	32.0	42.0	52.5	60.7	65.2	70.5	75.7	79.5	85.7	87.4
D18C6-$(C_3H_6C_{10}F_{21})_2$, [**2.37**]	17.3	30.1	40.5	50.6	58.0	63.7	69.6	74.1	77.5	83.7
D18C6-$(C_2H_4C_8F_{17})_2$, [**2.19**]	9.0	17.6	22.0	30.3	37.0	42.6	48.8	52.4	58.6	62.4
DB18C6-$(C_2H_4C_6F_{13})_2$, [**4.26**]	79.1	93.3	96.2	96.8	96.8	96.9	97.1	97.1	97.5	97.4
DB18C6-$(C_2H_4C_8F_{17})_2$, [**4.27**]	78.8	92.6	95.6	96.1	96.3	96.4	96.4	96.7	96.7	96.9
DB18C6-$(C_7H_{15})_2$, [**4.17**]	36.3	55.7	69.5	79.3	85.3	89.7	92.2	94.4	95.0	96.0

Table 6.5. Conversion of 1-bromooctane into 1-iodooctane under solid-liquid conditions.

6.4.3 Conversion of 1-bromooctane into 1-iodooctane by supported fluorous phase catalysis.

Bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6 (0.02 mmol) was supported on fluorous reverse phase silica gel (95% w/w) by stirring in dichloromethane at 40 °C for 2 h. After cooling to room temperature, the solvent was eliminated under reduced pressure and the supported catalyst was dried under vacuum for 2h.

A mixture of 1-bromooctane (200 mg, 1.0 mmol), potassium iodide (840 mg, 5.0 mmol), biphenyl (154 mg, 1.0 mmol), the supported fluorinated crown ether (0.02 mmol) and either tetrahydrofuran (4 mL) or ethyl acetate (4 mL) was refluxed at 70 °C for 6 h. The above reaction was monitored for a 10 hours period by taking samples (25 μL) every 2 hours. The samples were diluted with the appropriate solvent (2 mL) and analysed by gas chromatography to determine the conversion to product using biphenyl as the internal standard (***Table 6.6***).

Time	% conversion	
(h)	THF	EtOAc
2	74.1	38.8
4	92.2	57.9
6	96.7	71.7
8	97.7	79.9
10	98.2	84.5
16	98.5	92.5

Table 6.6. Conversion of 1-bromooctane into 1-iodooctane using *bis*(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6 supported on fluorous reverse phase silica gel.

6.4.4 Fluorination of 2,4-dinitrochlorobenzene.[14]

A mixture of 2,4-dinitrochlorobenzene (207 mg, 1.0 mmol), biphenyl (154 mg, 1.0 mmol), spray-dried potassium fluoride (87 mg, 1.5 mmol), which had been dried previously under oil pump vacuum at 170 °C for 8 h, acetonitrile (5 mL) and the appropriate phase transfer catalyst (0.1 mmol) was refluxed at 85 °C under an inert atmosphere. After cooling to room temperature, the organic phase was filtered

through silica gel. A sample of the collected solution was analysed by gas chromatography to determine the conversion to product using biphenyl as the internal standard (***Table 6.7***).

GC conditions: 195 °C for 2.0 min followed by 10 °C min^{-1} ramp to 220 °C, held for 0.0 min. Injector: 320 °C, detector: 340 °C. Retention times: 2.86 min (biphenyl), 2.95 min (2,4-dinitrofluorobenzene), 3.62 min (2,4-dinitrochlorobenzene).

The above reaction was carried out for 2 h, 12 h and 24 h. Samples were taken (25 μL), diluted with acetonitrile (2 mL) and analysed by gas chromatography.

Crown Ether	Conversion (%)		
	2 h	12 h	24 h
No PTC	0.3	1.6	8.5
18-crown-6	81.0	89.5	90.5
Diaza-18-crown-6 (D18C6), [**2.7**]	11.7	44.9	49.9
D18C6-$(C_2H_4C_8F_{17})_2$, [**2.19**]	39.9	74.5	88.2
D18C6-$(C_3H_6C_8F_{17})_2$, [**2.36**]	19.8	61.8	71.9
D18C6-$(C_3H_6C_{10}F_{21})_2$, [**2.37**]	16.3	52.4	52.6
D18C6-$(C_8H_{17})_2$, [**2.6**]	8.8	23.6	51.3
Dibenzo-18-crown-6 (DB18C6), [**4.5**]	39.9	81.0	77.0
DB18C6-$(NHCH_2C_6F_{13})_2$, [**4.35a**]	66.8	87.6	94.3
DB18C6-$(NHC_7H_{15})_2$, [**4.31a**]	61.5	83.6	92.3
DB18C6-$(C_2H_4C_8F_{17})_2$, [**4.27**]	41.0	72.8	91.7
DB18C6-$(C_2H_4C_6F_{13})_2$, [**4.26**]	44.0	71.9	87.1
DB18C6-$(C_7H_{15})_2$, [**4.17**]	37.8	54.3	86.9

Table 6.7. Results from the fluorination of 2,4-dinitrochlorobenzene.

6.4.5 Fluorination of 2,4-dinitrochlorobenzene under thermomorphic conditions.

A mixture of 2,4-dinitrochlorobenzene (207 mg, 1.0 mmol), biphenyl (154 mg, 1.0 mmol), spray-dried potassium fluoride (87 mg, 1.5 mmol), which had been dried previously under oil pump vacuum at 170 °C for 8 h, acetonitrile (5 mL) and the

appropriate phase transfer catalyst (0.1 mmol) was refluxed at 85 °C under an inert atmosphere. After cooling to room temperature, the organic phase was filtered. A sample of the collected solution was analysed by gas chromatography to determine the conversion to product using biphenyl as the internal standard.

6.4.6 Fluorination of 4-nitrochlorobenzene.[15]

A mixture of 4-nitrochlorobenzene (156 mg, 1.0 mmol), biphenyl (154 mg, 1.0 mmol), spray-dried potassium fluoride (87 mg, 1.5 mmol), which had been dried previously under oil pump vacuum at 170 °C for 8 h, dimethyl sulfoxide (5 mL) and the appropriate phase transfer catalyst (0.1 mmol) was refluxed at 190 °C for 7 h under an inert atmosphere. After cooling to room temperature, the organic phase was filtered through silica gel. A sample of the collected solution was analysed by gas chromatography to determine the conversion to product using biphenyl as the internal standard (***Table 6.8***).

GC conditions: 195 °C for 2.0 min followed by 10 °C min^{-1} ramp to 220 °C, held for 0.0 min. Injector: 320 °C, detector: 340 °C. Retention times: 2.20 min (4-nitrofluorobenzene), 2.48 min (4-nitrochlorobenzene), 2.86 min (biphenyl).

The above reaction was monitored for an 8 hour period by taking samples (25 μL) every 2 hours. The samples were diluted with acetonitrile (2 mL) and analysed by gas chromatography.

Crown Ether	% Conversion			
	2 h	4 h	6 h	7 h
No PTC	32.1	51.7	63.1	69.6
18-crown-6	56.3	80.1	89.4	94.5
D18C6, [**2.7**]	30.0	45.2	58.8	66.9
DB18C6 (10 mol %), [**4.5**]	57.1	81.4	91.7	94.2
DB18C6 (20 mol %), [**4.5**]	40.2	65.2	75.3	80.9

Table 6.8. Monitoring the fluorination of 4-nitrochlorobenzene.

6.5 General Procedures for Separation and Recovery.

6.5.1. Separation and recovery of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**], in the conversion of 1-bromooctane into 1-iodooctane by fluorous solid phase extraction.

After 12 h the reaction mixture was allowed to warm at room temperature. The reaction mixture was then filtered to remove the excess potassium salts and they were extracted with benzotrifluoride (5 mL). The organic phase was then washed once with water (10 mL) before drying over magnesium sulphate. The clear organic phase was passed through a short column of fluorous reverse phase silica gel (4 g, 5.3 cm^3) and the column was eluted with benzotrifluoride (40 mL) to obtain the clean organic products. The fluorinated phase transfer catalyst was then recovered (90-96 %) by eluting with trifluoroethanol (70 mL). After removing the trifluoroethanol, the phase transfer catalyst was dried *in vacuo* for 2 h at 60 °C before being reused in the next run (***Table 6.9***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.269	0.248	88.0
2	0.248	0.239	86.8
3	0.239	0.255	86.6
4	0.255	0.202	86.0
5	0.202	0.191	85.8
6	0.191	0.179	85.6

Table 6.9. Recycling results of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**], by fluorous solid phase extraction.

6.5.2. Separation and recovery of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**], in the conversion of 1-bromooctane into 1-iodooctane by solid phase extraction.

After 12 h the reaction mixture was allowed to warm at room temperature. The reaction mixture was then filtered to remove the excess potassium salts and they were extracted with benzotrifluoride (5 mL). The organic phase was then washed

once with water (10 mL) before drying over magnesium sulphate. The clear organic phase was passed through a short column of fluorous reverse phase silica gel (2.8 g, 5.3 mL, 3 cm long, 1.5 cm diameter) and the column was eluted with benzotrifluoride (40 mL) to obtain the clean organic products. The fluorinated phase transfer catalyst was then recovered (97-98 %) by eluting with diethyl ether (300 mL). After removing the diethyl ether, the phase transfer catalyst was dried *in vacuo* for 2 h at 60 °C before being reused in the next run (***Table 6.10***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.257	0.251	91.7
2	0.251	0.244	89.5
3	0.244	0.239	88.0
4	0.239	0.231	87.4

Table 6.10. Recycling results of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**], by solid phase extraction.

6.5.3. Separation and recovery of *bis*(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6, [**4.26**], in the conversion of 1-bromooctane into 1-iodooctane *via* supported fluorous phase catalysis.

After 6 h the reaction mixture was allowed to warm at room temperature. The solvent was then eliminated under reduced pressure. The resulting solid was washed with cold hexane (25 mL, -18 °C) in order to separate the clean organic products. The insoluble supported catalyst was filtered and washed with water (25 mL) to remove the excess potassium salts and washed again with cold hexane (20 mL, -18 °C). The supported fluorinated phase transfer catalyst was dried *in vacuo* overnight at 60 °C before being reused in the next run (***Table 6.11***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.500	0.473	95.2
2	0.473	0.455	93.3
3	0.455	0.419	90.0
4	0.419	0.392	87.5

Table 6.11. Recycling results of *bis*(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6, [**4.26**], supported on fluorous reverse phase silica gel.

6.5.4. Separation and recovery of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**], in the fluorination of 2,4-dinitrochlorobenzene by fluorous solid phase extraction.

After 24 h the reaction mixture was allowed to warm at room temperature. The reaction mixture was then filtered to remove the excess potassium salts and they were extracted with hot dichloromethane (5 mL). The solvent was then eliminated under reduced pressure. The resulting solid was redissolved in dichloromethane (5 mL). The organic phase was then washed once with water (5 mL). The water was extracted with dichloromethane (3 x 5 mL). The combined dichloromethane extracts were dried over magnesium sulphate. The solvent was again eliminated under reduced pressure and the resulting solid dissolved in dichloromethane (2 mL). The organic phase was passed through a short column of fluorous reverse phase silica gel (~ 3 g, 2.5 cm long, 1.5 cm diameter, 4.4 cm^3). The column was eluted with dichloromethane (20 mL) to obtain the clean organic products. The fluorinated phase transfer catalyst was then recovered (94-96 %) by eluting with trifluoroethanol (20 mL) and ethyl acetate (20 mL). The solvents were combined and removed under reduced pressure. The fluorinated crown ether was dried *in vacuo* for 2 h at 60 °C before being reused in the next run (***Table 6.12***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.119	0.113	70.8
2	0.113	0.108	69.4
3	0.108	0.105	68.7
4	0.105	0.099	67.9

Table 6.12. Recycling results of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.36**], in the fluorination of 2,4-dinitrochlorobenzene by fluorous solid phase extraction.

6.5.5. Separation and recovery of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-4,13-diaza-18-crown-6, [**2.19**], in the fluorination of 2,4-dinitrochlorobenzene by fluorous solid phase extraction.

After 24 h the reaction mixture was allowed to warm at room temperature. The reaction mixture was then filtered to remove the excess potassium salts and they were extracted with hot dichloromethane (15 mL). The solvent was then eliminated under reduced pressure. The resulting solid was redissolved in dichloromethane (5 mL). The organic phase was then washed once with water (5 mL). The water was extracted with dichloromethane (3 x 5 mL). The combined dichloromethane extracts were dried over magnesium sulphate and the solvent was eliminated under reduced pressure. The resulting residue was dissolved in dichloromethane (1 mL). The clear organic phase was passed through a short column of fluorous reverse phase silica gel (4 g, 5.3 cm^3) and the column was eluted with dichloromethane (15 mL) to obtain the clean organic products. The fluorinated phase transfer catalyst was then recovered by eluting with trifluoroethanol (50 mL) and tetrahydrofuran (50 mL). After removing the solvent mixture, the phase transfer catalyst was dried *in vacuo* for 2 h at 60 °C before being reused in the next run (***Table 6.13***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.116	0.100	89.9
2	0.100	0.084	82.6
3	0.084	0.062	68.8
4	0.062	0.023	41.2

Table 6.13. Recycling results of *N,N'*-bis(1*H*,1*H*,2*H*,2*H*-perfluoroundecyl)-4,13-diaza-18-crown-6, [**2.19**], in the fluorination of 2,4-dinitrochlorobenzene by fluorous solid phase extraction.

6.5.6. Separation and recovery of *bis(*1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dibenzo-18-crown-6, [**4.26**], in the fluorination of 2,4-dinitrochlorobenzene by fluorous solid phase extraction.

After 24 h the reaction mixture was allowed to warm at room temperature. The reaction mixture was then filtered. The filtrate was washed with hot dichloromethane (15 mL). The solvents were combined and eliminated under reduced pressure. The resulting residue was redissolved in dichloromethane (5 mL) and washed once with water (5 mL). The water phase was extracted three times with dichloromethane (5 mL). The combined dichloromethane extracts were dried over magnesium sulphate. The solvent was eliminated under reduced pressure and the resulting residue was redissolved in dichloromethane (1 mL). The organic phase was passed through a short column of fluorous reverse phase silica gel (4 g, 5.3 mL) and the column was eluted with dichloromethane (15 mL) to obtain the clean organic products. The fluorinated phase transfer catalyst (93-95%) was then recovered by eluting with trifluoroethanol (50 mL). After removing the solvent under reduced pressure, the phase transfer catalyst was dried *in vacuo* for 2 h at 60 °C before being reused in the next run (***Table 6.14***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.106	0.101	89.5
2	0.101	0.095	86.8
3	0.095	0.089	85.3
4	0.089	0.083	83.5

Table 6.14. Recycling results of *bis(1H,1H,2H,2H*-perfluorooctyl)dibenzo-18-crown-6, [**4.26**], in the fluorination of 2,4-dinitrochlorobenzene by fluorous solid phase extraction.

6.5.7. Separation and recovery of *bis(1H,1H,2H,2H*-perfluorooctyl)dibenzo-18-crown-6, [**4.26**], in the fluorination of 2,4-dinitrochlorobenzene by solid phase extraction.

After 24 h the reaction mixture was allowed to warm at room temperature. The reaction mixture was then filtered to remove the excess potassium salts and they were extracted with benzotrifluoride (5 mL). The solvents were combined and eliminated under reduced pressure. The resulting residue was redissolved in benzotrifluoride (5 mL). The organic phase was then washed once with water (5 mL) before drying over magnesium sulphate. The clear organic phase was passed through a short column of silica gel (~ 2 g, 3 cm long, 1.5 cm diameter, 5.3 cm^3) and the column was eluted with benzotrifluoride (20 mL) to obtain the clean organic products. The fluorinated phase transfer catalyst was then recovered by eluting the column with tetrahydrofuran (10 mL), ethyl acetate (10 mL) and trifluoroethanol (10 mL). The fluorinated phase transfer catalyst (67-95%) was obtained after removing the combined solvents. The catalyst was dried *in vacuo* for 2 h at 60 °C before being reused in the next run (***Table 6.15***).

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.106	0.101	85.0
2	0.101	0.094	85.3
3	0.094	0.063	60.2

Table 6.15. Recycling results of *bis(1H,1H,2H,2H*-perfluorooctyl)dibenzo-18-crown-6, **[4.26]**, in the fluorination of 2,4-dinitrochlorobenzene by solid phase extraction.

6.5.8. Separation and recovery of *bis(1H,1H,2H,2H*-perfluorodecyl)dibenzo-18-crown-6, **[4.26]**, in the fluorination of 2,4-dinitrochlorobenzene *via* thermomorphic catalysis.

After cooling to room temperature, water was added to the reaction mixture (1.5 mL) to precipitate the catalyst. The fluorinated dibenzo catalyst was filtered, washed with water (10 mL) and dried *in vacuo* overnight at 60 °C before being reused in another run (***Table 6.16***). The organic phase was separated and dried over magnesium sulphate. The solvent was eliminated under reduced pressure to afford the organic products.

Run	Catalyst Used (g)	Catalyst Recovered (g)	Conversion (%)
1	0.125	0.122	81.4
2	0.122	0.085	67.9
3	0.085	0.035	38.9

Table 6.16. Recycling results of *bis(1H,1H,2H,2H*-perfluorodecyl)dibenzo-18-crown-6, **[4.26]**, in the fluorination of 2,4-dinitrochlorobenzene by thermomorphic catalysis.

6.6 References.

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APPENDIX

University *of*
Leicester

Appendix

A 1 Lecture Courses Attended (2003 to 2004)

Title	
Retrosynthetic Analysis	Dr. P, Jenkins
Organic Strategies	Dr. P, Jenkins / Dr. S. Handa

A 2 Organic/Inorganic Seminar Programme

2003

Monday 6th October, Dr Chris Richards (Queens Mary, University of London), *Very Active Planar Chiral Catalysts for Asymmetric Synthesis*

Wednesday 8th October, Prof. Iain Campbell, FRS (University of Oxford), 2nd Tim Norwood Memorial Lecture, *NMR and Proteins*

Monday 20th October, Dr Sandie Dann (University of Loughborough), *Unusual Complex Oxides and Sulfides*

Monday 27th October, Dr Chris Hayes (University of Nottingham), *Natural and Non-natural Products: Total Synthesis and Biological Applications*

Friday 14th November, Prof. Walter Leitner (Max Planck Institute, Mülheim), Greiss Lecture (RSC)

Monday 24th November, Prof. Thomas Wirth (Cardiff University), *Scope and Potential of Chiral Electrophiles in Stereoselective Synthesis*

Monday 8th December, Prof. Peter Hore (University of Oxford), *Real-time NMR Techniques for Studying Protein Structure and Folding*

2004

Monday 12th January, Dr Liam Cox (University of Birmingham), *Exploiting Silicon Reagents in Asymmetric Reactions*

Monday 19th January, Prof. Bill Levason (University of Southampton), *Recent Developments in the Chemistry of Antimony Ligands*

Monday 9th February, Dr Michael Whitlesey (University of Bath), *Stoichiometric and Catalytic Ruthenium Carbene Systems*

Monday 1st March, Dr Iain Coldham (University of Sheffield), *Stereoselective Synthesis of Cyclic Amines using Chiral Organolithium Species and Cycloaddition Reactions*

Monday 26th April, Dr Graham Sandford (University of Durham), *PolyfunctionalHeterocycles and Macrocycles*

Monday 10th May, Dr Dominic Wright (University of Cambridge), *Torocyclic Ligands*

Monday 24th May, Dr Steve Allin (Loughborough University), *New Asymmetric Routes to Chiral Heterocycles*

Monday 7th June, Prof. Peter Scott (University of Warwick), *Catalysis with Chiral Metal Complexes*

Monday 15th October, Prof. Eric Herbst (Ohio State University), *Chemistry and Star Formation*

Monday 25th October, Prof. Alan Armstrong (Imperial College, London), *New Methods and Synthetic Applications of Asymmetric Heteroatom Transfer*

Monday 11th November, Dr Helen Aspinall (University of Liverpool), *Chiral Lanthanides Complexes for Organic Synthesis*

Monday 15th November, Dr Gareth J. Pritchard (University of Loughborough), *New Routes to Heterocyclic Systems From Vinylcyclopropanes*

2005

Monday 17th January, Dr Stuart McGregor (Heriot-Watt University, Edinburgh), *Non-innocent N-Heterocyclic Carbene and Phosphine Ligands*

Monday 7th February, Dr Mike Hill (Imperial College, London), *Molecular Catalysis with Group 2 Metals*

Monday 14th June, Dr Simon Jones (University of Sheffield), *Fiddling With Phosphorus*

Monday 10 October, Dr. Christopher Frost (University of Bath), *Exploring New Strategies in Organic Synthesis via Catalytic Conjugate Addition*

Monday 17 October, Prof Gary Attard (University of Cardiff), *Aspects of Chiral Surface Chemistry: an Electrochemical Perspective*

Wednesday 26 October, Prof. R.H. Holm (Harvard University), *Structural and Functional Analogues of Molybdenum and Tungsten Oxotransferases/Hydroxylases: What can be Learned?*

Monday 31 October, Prof. Matthew Davidson (University of Bath), *Metal and Metal-free Phenolates: Catalysts, Sensors and Surprises*

Monday 7 November, Prof. Richard Templar (Imperial College London), *How Cells Survive- from Lipids to Liquid Crystals*

Wednesday 9 November, Prof.. Peter H. Seeberger (ETH, Zurich), *Chemical Glycomics: Automated Synthesis of Carbohydrates as a Platform for Biological and Medical Research*

Monday 14 November, Dr. Richard S. Grainger (University of Birmingham), *Harnessing Reactive Intermediates for Organic Synthesis*

Tuesday 29 November, Prof. Tim Softley (University of Oxford), *From Highly Excited to Ultracold Molecules: Chemical Dynamics in the Extreme*

Monday 5 December, Prof. Tom Simpson (University of Bristol), *Chemical and Biochemical Studies on Polyketide Natural Products*

2006

Monday 30 January, Prof. Michiel Sprik (University of Cambridge), *Density Functional Based Molecular Dynamics Simulation of Redox Reactions in Solution*

Monday 20 February, Prof. Colin Creaser (Nottingham-Trent University), *Ion Mobility Spectrometry: Shaping up for the Structural and Trace Analysis*

Monday 6 March, Prof. Mikiko Sodeoka (Tohoku University, Japan), *Rosalind Franklin Lectureship 2006*

Monday 13 March, Dr. Paul Howes (Department of Physics, University of Leicester), *Nanoparticle Toxicology*

Monday 3rd April, Prof. Jonathan Williams (University of Bath), *C-C Bond Formation from Alcohols*

A 3 Conferences Attended

Organic Synthesis Symposium. University of Loughborough, October 2003
3rd Leicester Catalysis Symposium. University of Leicester, February 2004
Crystal Faraday Associates Workshop. University of Leicester, April 2004
4th Bristol Synthesis Meeting. University of Bristol, April 2004
Coordination Chemistry Discussion Group Meeting. University of Leicester, July 2004
4th RSC Fluorine Subject Group Meeting. University of Durham, September 2004

Sheffield Stereochemistry Meeting. University of Sheffield, December 2004
5th Bristol Synthesis Meeting. University of Bristol, April 2005
Fluorination Technologies. Applications and Challenges. Syngenta, April 2005
RSC Fluorine Group Postgrad Symposium, Oxford University, September 2005
Organic Synthesis Symposium. University of Loughborough, October 2005
Half-day Synthesis Symposium, University of Leicester, February 2006
Postgrad. Fluorine Subject Group Meeting. University of Manchester, Sept. 2006

A 4 Presentations

University of Manchester. 6th Annual Royal Society of Chemistry Fluorine Subject Group Postgraduate Meeting,. September 2006.
University of Leicester, Green Chemistry Section Talk, Leicester, 2006.
University of Leicester, Organic Section Talk, Leicester, 2005.
University of Leicester, Organic Section Talk, Leicester, 2004.

A 5 Publications

"Syntheses and Properties of Fluorous Quaternary Phosphonium Salts that Bear Four Ponytails; New Candidates for Phase Transfer Catalysts and Ionic Liquids". C. Emnet, K. M. Weber, J. A. Vidal, C. S. Consorti, A. M. Stuart, J. A. Gladysz, *Adv. Synth. Catal.*, 2006, **348**, 1625.

"Perfluoroalkylated 4,13-diaza-18-Crown-6 Ethers: Synthesis, Phase Transfer Catalysis and Recycling Studies". A. M. Stuart, J. A. Vidal, *J. Org. Chem.*, 2007, **72**, 3735.