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**Solid Phase and Solution NMR Studies of
Stereochemistry and Complexation Effects in
Monomeric, Polymeric, and Model Crown Ethers**

By

A.Moghimi, MSc

**A thesis submitted to the
Faculty of Graduate Studies and Research
in partial fulfilment of the requirements for the degree of**

Doctor of Philosophy

Carleton University

Ottawa, Ont.

1994

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Abstract

A copolymer of vinyl-benzo-24-crown-8 ether and styrene has been prepared, containing the monomeric ratio of 2:7 respectively. This copolymer has been employed for the attempted extraction of Ra^{+2} from water, with an efficiency of ca. 10%.

For 4-carboxybenzo-24-crown-8 ether, **8**, the synthesis of two selectively deuterated-d4 derivatives was carried out. Segmental motion in the macroscopic portion of these solid molecules has been probed via ^{13}C and ^2H Nuclear Magnetic Resonance Spectroscopy (NMR). A phase change in these solids has been detected by ^2H NMR and further probed via Differential Scanning Calorimetry (DSC).

The solution complexation of **8** with Ba^{+2} , K^{+} and Na^{+} cations has been studied via ^{13}C NMR spin-lattice relaxation times (T_1). The influence of metal ion complexation on solid phase macroscopic motion in **8** has also been examined.

Selectively deuterated benzo-9-crown-3-d4 ether (B9C3-d4), its 4-nitro derivative, the related cyclohexyl-9-crown-3 (CH9C3-d4), and dibenzo-18-crown-6-d8 (DB18C6-d8) have been prepared in order to facilitate the analysis of their solid state and solution NMR spectra. Deuterium isotope effects on ^{13}C chemical shifts operating through one to four bonds have been measured and their origins probed. Some interesting stereochemical dependent results for B9C3, DB18C6 and CH9C3 are found.

An acyclic model crown ether, 1,5-dicyclohexyloxy-3-oxapentane, has been prepared. Conformational interchange in this molecule has been studied via low temperature ^1H and ^{13}C NMR methods, and a single cyclohexane ring inversion has been found as dominant process.

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Chapter 1

General Introduction

1.1 : Crown Ethers

The discovery that cations form stable complexes with macrocyclic polyethers of the type $(-\text{CH}_2-\text{CH}_2-\text{O}-)_n$ (Fig. 1) by Pedersen¹ was, in fact, a starting point for "*Host-Guest*" chemistry. The special shorthand nomenclature "*Crown*" was given to this class of compounds by him.

Fig. 1 : Complexation of dibenzo-18-Crown-6 (DB18C6) with K^+ ion.

A crown ether as a host, can surround the guest in such a way that the crown forms a solvation shell and allows the guest to be soluble in organic solvents or transferable from one medium to another. The interest in these macrocycles was

stimulated when it was found that preferential cation complexation resulted when the relative sizes of the cation and the ligand cavity were matched.² While the complexation of transition-metal cations is a commonplace phenomenon, practically no alkali-metal ion complexes were known before the advent of the crown compounds.

Three kinds of complexes of crown ethers have been reported. Although alkali and alkaline-metal cations are involved in most of these complexes, transition-metal,^{3,4} and lanthanide^{5,6} cations may be involved. In order to make more stable complexes with transition-metal cations, the donor oxygen atoms of crown ethers are normally replaced by the soft Lewis acids such as S, or N atoms.^{7,8} In general, the stabilities of the crown ether complexes depend not only on the size of the donor in the crown cavity but also on anion, and the solvent.⁹

The pioneers of crown-cation complexes, Pedersen and Cram, also described first the examples of the complexes between neutral molecules and crown ethers. In 1971, Pedersen¹⁰ observed the formation of the solid complexes with thiourea and in 1974 Cram et.al. reported the formation of crystalline complex between 18-Crown-6 (18C6) and acetonitrile. Voegtle¹¹ has had a major contribution in the preparation of the variety of complexes of benzo-annulated crown ethers and neutral small molecules possessing N-H or O-H functionalities.

The third group of complexes with very relatively limited examples are so called "*electrides*" and "*alkalides*".^{12,13} The first single-crystal electride was reported by Dye et. al.¹⁴ in 1982. Alkalides, on the other hand, are the same salts as electrides with an anion metal (M^-) instead of electron. $Cs^+(15C5)2.e^-$, and $Cs^+(18C6)2.e^-$ are two examples of electrides while $Cs^+(18C6)2 Na^-$ is an example of alkalides. These unit complexes in

crown ether chemistry are especially interesting because of their optical, magnetic, and electrical behaviour. The presence of potassium anions and complexed potassium cations in a potassium solution in THF containing 18C6 have been confirmed by ^{39}K NMR spectroscopy.^{15,16} Interestingly, the complexation of cations by two different crown ethers to form a mixed sandwich complexes has also been reported.¹²

About 50 crown ethers with 9 to 60-membered oligoether rings and variety of complexes were synthesised by Pedersen. This was followed by the synthesis of a great number of macrocyclic compounds having more than one cyclic ring or possessing donor atoms other than oxygen atom.^{17,18} This led to the development of new families of compounds with the same complexing properties as crown ethers such as Cryptands,¹⁹ and Calixarines.²⁰ Fig. 2 shows some typical examples.

The ability of crown ethers to transport of biologically significant cations across membranes and their ability to differentiate in their complexation properties between related biologically important cations makes them potentially important. To achieve the goal, crown ethers are normally bonded to a biologically important fragment like carbohydrates.²¹

If the binding ability of crown ethers is changed in response to some appropriate input, they could function as efficient ion-transfer carriers. So far four general switching modes have been identified in this regard : "Photoresponse Switching"^{22,23,24} which changes bonding ability in response to the light irradiation, "Redox Switching"²⁵ which changes the bonding ability in response to the level of redox potentials, PH Switching, and finally Thermal Switching.²⁶

Fig. 2 : Some typical Crown Ethers(a : Ref. 1; b: Ref. 26, p. 22; c : Ref. 27; and 28).

Fig. 3 : Some typical examples of polymeric crown ethers.

Polymeric Crown Ethers

For several applications it is necessary to anchor the crown ether ligand to an insoluble support like silica gel or a network polymer (Fig. 3).²⁹ The binding characteristics of the macrocycle could change significantly when it becomes incorporated into a polymer backbone or anchored as pendant moiety to a macrocycle chain. The difference in binding between these materials and the monomeric analogues arises from the possibility of cooperative binding between proximate crown ether cavities for the formation of stable macromolecule-cation complexes. The resulting polymeric crown ethers can be used for the purposes of both solid-liquid or liquid-liquid extraction of cations or neutral molecules selectively; as has been reported for separation of enantiomers.³⁰ The polymeric crown ethers have the advantage that they can be used, readily removed from the reaction mixture, and used again.³¹

Some typical examples of polymeric crown ethers are shown in Fig. 3. Polymer "a" is the first linear condensation polymer containing a crown ether structure in the backbone.³² Polymer "b" is a photoresponsive azobenzene-bridged polymer²². Polymer "c" is an amorphous polymer bearing pendent crown ethers.^{33,34} Radical copolymerization with styrene as comonomer resulted in copolymer "d", the reactivity ratio being close to unity.³⁵ Example "e" is a copolymer where the crown ether is bonded to another pre-prepared copolymer. Silica gel bonded crown ether " f " is the one Cram et.al. used for the separation of an enantiomeric mixture of methyl phenylalaninate.³⁰

1.2 : Introduction to Solid State ^{13}C and ^2H NMR

From a fundamental point of view it is important to understand that solution NMR

NMR techniques do not easily carry over to the solid state. Since the basic requirement for observation of a nuclear magnetic resonance signal is based on the energy absorption by nuclei, one must consider the general Hamiltonian governing the energy levels of a nucleus. A general Hamiltonian for a nucleus with a spin quantum number I , once it is placed in a magnetic field B_0 , can be written as:³⁶

$$H = H_z + H_{CS} + H_D + H_{sc} + H_Q \quad (1)$$

where H_z is the Zeeman interaction, H_D is the nuclear dipolar interaction, H_{CS} is the chemical shielding interaction, H_{sc} is the scalar or spin-spin coupling, and H_Q is the quadrupolar interaction. Since H_Q only exists for nuclei with spins greater than $I=1/2$, it will be explained separately in solid phase ^2H NMR section.

The Zeeman Hamiltonian is given by:³⁷

$$H_z = - \gamma \hbar B_0 I_z \quad (2)$$

In all the cases of interest, here, the Zeeman interactions which lift the degeneracy of the $2I+1$ nuclear spin energy levels will be taken to be much larger than the other interactions. The gyromagnetic ratio (γ) and eigenstates of energy levels ($2I+1$) will be introduced next.

From quantum mechanics, for any nucleus with spin I there is an associated quantized angular momentum (P) as:

$$P = \hbar [I (I+1)]^{\frac{1}{2}} \quad (3)$$

Angular momentum P is a vector whose direction is described by another quantum number, m , where :

$$m = I, (I-1), (I-2), \dots -I \quad (4)$$

In a classical terms, the nucleus can be thought of as a spinning particle. Any spinning charged particle generates a magnetic moment, μ , which is proportional to its angular momentum :

$$\vec{\mu} = \gamma \vec{P} \quad (5)$$

where γ (the gyromagnetic ratio) is constant for each nucleus. Once a nucleus with spin $I > 0$ is placed in a magnetic field, B_z , the magnetic moment interacts with B_z and the resulting energy is given by:

$$E = - \vec{\mu} \cdot \vec{B}_z \quad (6)$$

If the reference axis is designated the Z axis and corresponds to the direction of the external applied magnetic field, then :

$$\Delta E = h\nu = \gamma h B_z \quad (7)$$

$$P_z = \hbar m \quad (8)$$

$$E = - \mu_z B_z = - \gamma \hbar m B_z \quad (9)$$

Thus for a spin $1/2$ nucleus such as ^{13}C or ^1H there are two possible energy levels shown in Fig. 4.

Fig. 4 : Energy levels for a nucleus $I=1/2$ in a magnetic field B_0 .

The related frequency for the above absorption would be :

$$\nu = \frac{\gamma}{2\pi} B_0 \quad (10)$$

where ν is referred to as "Larmor frequency" which is unique for each nucleus since magnetogyric ratios for different nuclei are distinct. For readily available magnets, the resonance frequency, ν , (in Hz) is in the radio frequency region of the electromagnetic spectrum.

The two energy levels, $m_s = +1/2$ and $-1/2$, are not equally populated. At thermal equilibrium, the ratio of the populations is given by the Boltzmann equation:³⁸

$$\frac{N_b}{N_a} = \exp \left(\frac{-\Delta E}{KT} \right) \quad (11)$$

where N_a and N_b are the populations of lower and higher states respectively, K is Boltzmann's constant and T is the temperature. According to the equation (10) the population difference is dependent both on the field and the nuclear species under observation. Although the population difference is remarkably small, of the order of 1 in 10^5 for ^1H at 200 MHz, it is enough to establish a net macroscopic magnetization.

In a macroscopic sample, in the absence of an applied field, nuclei are randomly oriented. Once a strong B_0 is applied, they are oriented aligned with B_0 or against it. The net magnetization as a product of the B_0 , the energy difference between levels, and the number of nuclei per unit volume N is achieved by:³⁹

$$M_z = \frac{N \cdot \gamma^2 \cdot \hbar^2 \cdot B_0}{4KT} \quad (12)$$

1.2.1 : The Chemical Shielding Interaction

The frequency of an NMR transition depends not only on the Zeeman interaction but also on the electronic environment around the nucleus. The mobile electrons surrounding the nucleus generate their own magnetic fields which shield or deshield the nucleus from B_0 . For this reason the NMR spectrum is useful to chemists because all nuclei in the sample don't resonate at precisely the same Larmor frequency. Since the electronic orbitals surrounding a nucleus are not normally spherically symmetric but are usually anisotropic, the chemical shielding interaction must therefore be a tensorial property. The degree of shielding around a nucleus will depend on the orientation of the

molecules with respect to the magnetic field. The chemical shielding Hamiltonian can be represented as follows :

$$H_{CS} = \sum \gamma \hbar J_z \sigma_i \cdot B. \quad (13)$$

where σ is called the chemical shielding tensor which is a 3x3 matrix describing the three dimensional electronic environment around the nucleus. So, considering the Zeeman and the Chemical Shielding Interactions, the signal position can be expressed in terms of the direction of the tensor components with respect to the magnetic field B_0 :

$$\nu = \frac{\gamma}{2\pi} B_0 [1 - (\sigma_{xx} \cos^2 \theta_{xx} + \sigma_{yy} \cos^2 \theta_{yy} + \sigma_{zz} \cos^2 \theta_{zz})] \quad (14)$$

where σ_{ii} are the principal components of the shielding tensors and θ_{ii} are the angles between these components and the magnetic field vector. If one examines the ^{13}C spectrum of a single crystal one finds that in the absence of the dipolar coupling the chemical shift of a single resonance for each nucleus depends on the orientation of the crystal with respect to the applied magnetic field.

Usually one measures the NMR spectrum of polycrystalline or amorphous samples with a variety of crystal orientations, and therefore a variety of θ_{ii} are present with respect to the magnetic field. In such cases the so called powder spectrum is a superposition of all possible crystal orientations. This would result in a range of contributions to each different nuclear shift and thus the broad appearance of spectral resonances.

In the liquid and solution states the molecular orientations vary rapidly and all orientations with respect to B_0 are sampled over time, leading to an isotropic average for σ . This isotropic average is a scalar quantity and it is the origin of the chemical shift values in solution. This isotropic chemical shift is expressed as :

$$\sigma_{iso} = \frac{1}{3} (\sigma_{xx} + \sigma_{yy} + \sigma_{zz}) \quad (15)$$

and therefore the chemical shift observed in solution is given by :

$$\nu = \frac{\gamma}{2\pi} B_0 (1 - \sigma_{iso}) \quad (16)$$

In order to observe a solution-like ^{13}C NMR spectrum for a solid material, a number of difficulties must be removed. The solution to the shift anisotropy is the technique known as Magic Angle Spinning, MAS, as shown in Fig. 5:⁴⁰

Fig. 5 : Effect of magic angle spinning on binding vectors time-averaging.

By rotating the sample about the magic angle, the time averaged value of all

binding vectors becomes 54.7° .

If the expression for the orientationally dependent chemical shift is expanded to allow explicit time dependence due to sample rotation at angular frequency W_r about an axis at an angle β to the magnetic field and at angle χ_{ii} ($i = 1, 2, 3$) to the principal components of σ then the direction Cosines θ_{ii} become time dependent and can be expressed in terms of other angles in the system.

$$\cos\theta_{ii} = \cos\beta\cos\chi_{ii} + \sin\beta\sin\chi_{ii}\cos(\omega_r t + \phi_{ii}) \quad (17)$$

where ϕ_{ii} are the azimuth angles of the principal components of σ at time $t=0$. So the equation (14) can be rewritten as :

$$\nu = \frac{\gamma}{2\pi} B_0 \left[1 - \left(\frac{3}{2} \sigma_{zz} \sin^2\beta + \frac{1}{2} (3\cos^2\beta - 1) \sum_{ii} \sigma_{ii} \cos^2\chi_{ii} \right) \right] \quad (18)$$

If β is chosen such that the term $(3\cos^2\beta - 1) = 0$ (i.e. $\beta = 54.7^\circ$) then the anisotropic term vanishes leaving an isotropic chemical shift term :

$$\nu = \frac{\gamma}{2\pi} B_0 \left(1 - \frac{3}{2} \sigma_{zz} \sin^2\beta \right) = \frac{\gamma}{2\pi} B_0 (1 - \sigma_{iso}) \quad (19)$$

which is similar to the equation (16) obtained for solution.

The presence of molecular motion in the solid phase may affect the lineshape resulting from chemical shielding anisotropy in some cases depending on the rate and the sort of the motion. Considering the fact that Magic Angle Spinning is a coherent averaging process and since molecular motion in the solid phase causes random averaging, the later averaging may interfere with the prior one and therefore produce anomalous spectral broadening for specific motional rates. The maximum broadening

occurs for spinning rates such that the motional correlation time $\tau_c \sim 1/\omega_r$.

1.2.2 : The Nuclear Dipolar Interaction

The magnetic field at a nucleus is also affected by the local fields due to the magnetic dipole moments of the neighbouring nuclei. For typical interatomic distances it is of the order of few millitesla (mT) for homonuclear ^1H - ^1H dipolar interaction producing a separation of the order of tens of KHz. This interaction is decreased for ^{13}C - ^1H dipolar interaction to the order of 0.2 mT which is significant when compared to the coupling constants or even chemical shifts which are in the range of μT .

In classical physics the energy of interaction through space between two unlike magnets having magnetic moments μ_1 and μ_2 is:⁴¹

$$U = \frac{\mu_0}{4\pi} \left[\frac{\mu_1 \cdot \mu_2}{r_{12}^3} - \frac{3(\mu_1 \cdot r_{12})(\mu_2 \cdot r_{12})}{r_{12}^5} \right] \quad (20)$$

where r_{12} is the internuclear vector between the interacting spins and μ_0 is the permeability constant ($4\pi \cdot 10^{-7} \text{ kg.m.S}^{-2}.\text{A}^{-2}$) which is used to maintain S.I. units. The following Dipolar Hamiltonian⁴² can be written based on the equation (20) with the use of $\mu_i = \gamma \hbar I_i / 2\pi$

$$H_D = \left(\frac{\hbar}{2\pi} \right) \left[\left(\frac{\mu_0}{4\pi} \right) \left(\frac{\gamma_1 \gamma_2}{|r_{12}|^3} \right) \right] [I_1 I_2 - \frac{3(I_1 r_{12})(I_2 r_{12})}{|r_{12}|^2}] \quad (21)$$

where the collective term in the first bracket is referred to as *dipolar coupling constant* and is often given the symbol "R". When the cross product is expanded and the coordinate system is converted to *polar* coordinates with the Z direction being parallel to the magnetic field, the Hamiltonian becomes :

$$H_D = \left(\frac{h}{2\pi}\right) (R) (A + B + C + D + E + F) \quad (22)$$

where the terms A, B, ... can be expressed as a function of either $(3\cos^2\theta-1)$ or $e^{i\theta}$ where θ is the angle between internuclear vector and the magnetic field.

In general, the dipolar Hamiltonian can be split into the Homo and Hetero HD terms. However, for the dilute nuclei (i.e. ^{13}C), the Homo term can be neglected and therefore the dipolar Hamiltonian for ^{13}C - ^1H bond is expressed as :

$$H_D = \hbar R (3\cos^2\theta - 1)(-I_{1z} I_{2z}) \quad (23)$$

where 1 and 2 in I_{1z} terms denote C and H nuclei. When the dipolar interaction is considered as a perturbation on the Zeeman interaction then three new energy levels are generated with corresponding transition frequencies :

$$\nu = \frac{\gamma B_0}{2\pi} \pm \frac{3R}{8\pi} (3\cos^2\theta - 1) \quad (24)$$

and therefore one would expect to see a doublet for a rigid ^{13}C - ^1H .

In the solid state many spin pairs (^{13}C , ^1H) with different r_{12} and θ relationships exist, therefore a broad resonance lines result. In solution, rapid tumbling averages all such contributions to zero and the result is that dipolar interactions do not affect the transitions.

In order to remove the dipolar interactions a high power r.f. field at the resonance

frequency of the protons must be applied to cancel the I_{zz} term in equation (23) and make the dipolar Hamiltonian zero. To do so, the strength of the decoupler needs to be at least of the order of the dipolar coupling to be effective. This is usually >50 KHz which requires ~100 Watts of power and is applied for long periods of time ~ 10-100 msec per Free Induction Decay (FID). This dipolar decoupling is described theoretically as a "coherent averaging" process. As explained for coherent averaging CSA, this may interfere with the random averaging in some solids and produces anomalous spectral broadening for specific motional rates.⁴³ The maximum broadening occurs when $\tau_c \sim B_1/\gamma$ where B_1 is the power of the decoupler.

The removal of dipolar coupling between ^{13}C and quadrupolar nuclei such as N and ^2H relies only on the MAS which is often not enough to fully remove these interactions. Mixing between the quadrupolar and Zeeman Hamiltonian gives rise to new angular terms in the dipolar Hamiltonian which are not removed by MAS. Consequently the resulting ^{13}C resonances in such cases are either broad or asymmetrically split.

1.2.3 : Cross-Polarization

The problem of low sensitivity of ^{13}C in solution is easily removed by a rapid pulse/acquisition sequence, but the long T_1 's in solids do not allow one to choose a fast repetition sequence. Therefore even with the improvement in resolution achieved by MAS and under the high decoupling power, a pulsed NMR experiment in a solid system is potentially time consuming. This problem can be solved via polarization transfer between highly polarizable abundant spins such as protons, and dilute observed ^{13}C spins. This process is termed "Cross-Polarization"⁴⁴ and results in "proton enhanced" ^{13}C signals. The pulse sequence for Cross-Polarization experiment is shown in Fig. 6 :⁴⁵

Fig. 6 : Pulse sequence for cross polarization experiment.

The experiment starts by giving the abundant spins a 90°_x pulse (2.5 $\mu\text{sec.}$) along the x' axis of the rotation frame. The phase of the r.f. is then shifted by 90° . This locks the magnetization along the y' axis. At the same time the pulses shown for ^{13}C channel are applied to the ^{13}C . The amplitude of the applied pulse is adjusted so that the following condition holds (known as the Hartmann-Hahn matching condition):⁴⁶

$$\gamma_s H_{1s} = \gamma_r H_{1r} \quad (25)$$

where γ_s and γ_r are gyromagnetic ratios of abundant and rare nuclei (^1H and ^{13}C). During the contact time (T_c)(0.5-10 msec.) the very small amount of magnetization lost by the

abundant spins makes a great deal of difference to the rare spins. The delay between successive sequences is now governed by the usually much shorter relaxation times of the abundant spins. There is then an overall gain in signal/noise ratio achieved over the simple $\pi/2$ -acquire sequence both from the cross polarization (maximum gain is γ_s/γ_r), and the shorter delay times allowed by more efficient relaxation of the abundant spins. The combination of cross-polarization and MAS when used under the dipolar decoupling condition is called CPMAS.

1.2.4 : Dipolar Dephased Experiment

A degree of editing may be introduced into the acquisition of CPMAS spectra of organic compounds by the Dipolar Dephasing technique. This technique is identical to the standard CPMAS experiment except that a delay just prior to ^{13}C data acquisition is inserted where the power decoupling is switched off for a period of $\sim 40\text{-}100$ μsec . During this short period, the ^{13}C - ^1H dipole interactions are active and line broadening occurs. Then the decoupler is switched on for the dipolar decoupling purpose during the collection of data. For ^{13}C atoms with strong dipolar interactions with ^1H such as static methines (CH) and methylenes (CH_2), the magnetization dies away during the dephasing time and therefore the spectrum will be free of these ^{13}C resonances. So the resulting spectrum contains only quaternary carbons as well as mobile protonated carbons.

1.2.5 : Solid Phase ^2H NMR

The ^2H nucleus with spin $I=1$ is considered, here, to introduce the Quadrupolar Interactions. Broad-line ^2H NMR spectra in the solid state samples are generally

dominated by the quadrupole coupling tensor which arises from the interaction of the nuclear quadrupole with the electric field gradient (efg) tensor. The quadrupole coupling tensor acts as the major perturbation on the Zeeman interaction. Considering this fact, if the quadrupolar nucleus ^2H is placed in a strong magnetic field the total Hamiltonian can be approximated as :³⁶

$$H_{\text{total}} = H_Z + H_Q \quad (26)$$

and H_Q is given by :

$$H_Q = \frac{e^2 q Q}{4I(2I-1)} [3I_z^2 - I^2 + \frac{\eta}{2}(I_+^2 + I_-^2)] \quad (27)$$

where eQ is the quadrupole moment; eq and η are the largest component and asymmetric parameters of the diagonalized electric field gradient tensor, respectively; I_+ and I_- are the raising and lowering operators. The electric field gradient tensor with its three principal components V_{xx} , V_{yy} , and V_{zz} is defined in a coordinate system attached to the molecule so that :

$$\eta = \frac{|V_{yy} - V_{xx}|}{|V_{zz}|} \quad (28)$$

If the quadrupolar interaction is treated as a perturbation on the Zeeman interaction (i.e. high field case) then three energy levels are generated as shown in Fig. 7.

Fig. 7 : The Zeeman nuclear energy levels of $I=1$ nucleus with and without the influence of quadrupole interaction

Therefore for a single rigid C-D bond with a specific orientation (θ) of the quadrupole coupling tensor with respect to the magnetic field, two allowed transitions which give rise to a doublet of lines which are symmetric about the Zeeman frequency are created (Figures 8 and 8a) such that :

$$V = -\gamma\hbar B_z \pm \frac{3}{8} \left(\frac{e^2 q Q}{h} \right) (3\cos^2\theta - 1) \quad (29)$$

with the frequency separation of :

where $e^2 q Q/h$ is known as quadrupole coupling constant (qcc) (Fig. 8).

$$\Delta V = \frac{3}{4} \left(\frac{e^2 q Q}{h} \right) (3\cos^2\theta - 1) \quad (30)$$

Fig. 8 : Orientation dependent line splittings for C-D bond in a single crystal (a); and axially symmetric powder pattern (b).

The powder line shape then results from the summation of such line pairs for a distribution over all orientations (Fig. 8b). They show either two or three pairs of characteristic features (edges, shoulders, and peaks) separated by frequencies :

$$\Delta V_z = \frac{3}{2} \chi = V_Q \quad (31)$$

$$\Delta V_y = \frac{3}{4} \chi (1 + \eta) \quad (32)$$

$$\Delta V_x = \frac{3}{4} \chi (1 - \eta) \quad (33)$$

where χ is qcc and V_Q is known as quadrupole frequency in the so-called axial case where $\eta=0$, and $\Delta_{xx}=\Delta_{yy}=\Delta_{zz}/2$. In solution, the quadrupole interactions are averaged to zero and this leads to a singlet peak if no other interactions are present.

The main use of ^2H NMR has been to study dynamics in the solid state. Since the qcc's depend on the electric field gradients at the nucleus, the molecular motions with a characteristic rate and amplitude average the gradients and hence the observable qcc's. This results in the changes of ^2H line shape. Motions start to affect the line shape when the rate becomes similar to the line width ($1/\pi T_2$) of the individual powder lineshape components, with a maximum effect when the rate is similar to the quadrupole splitting.

Results and Discussion

Specific Introduction :

At the outset, the synthesis of a polymer with pendant 24-Crown-8 ether was planned in order to investigate cooperative cation binding by adjacent crown units in the polymer chain. A potential application of such a polymer to the removal of Ra^{+2} from water was envisaged.

Additionally, solid state conformational motion has recently been detected in these laboratories for 18-crown-6 complexes using ^{13}C and ^2H NMR. A logical extension to the synthesis of suitably deuterated 24-crown-8 systems was planned in order to probe the motional features of these larger macrocycles in both the solid and solution.

The next section of work to be described in this thesis evolved from the requirement for specifically deuterated benzo-9-crown-3, 4-nitrobenzo-9-crown-3, cis-cyclohexyl-9-crown-3, and dibenzo-18-crown-6 ethers, to aid in the NMR spectral assignments of unlabelled counterparts. Since X-ray crystallographic data were available for such molecules, an opportunity to investigate the stereochemical dependence of ^2H isotope shifts on ^{13}C chemical shifts emerged.

Finally, the possibility of observing double cyclohexane ring inversion in a model crown ether has been examined since no information on conformational equilibria in such systems had been available previously.

Chapter 2

Benzo-24-Crown-8

"Polymer, Complexation, Conformational Analysis, and Molecular Motion in the Solid Phase"

2.1 : Synthesis and Characterization of Copolymer 4

In order to synthesize the polystyrene copolymer 4 bearing pendant B24C8 ether, 4-vinylbenzo-24C8 ether monomer 3 is required.

Fig. 9 : The chemical structure of Monomer 3 and Copolymer 4.

The monomer 3 was synthesized in four steps (see fig. 10). In order to optimize the reaction conditions of the cyclization step, three factors " The base", "The concentration", and "The template effect"⁴⁷ were examined. The results are summarized in Tab. 1.

Fig. 10 : Synthetic scheme for 1, 2, monomer 3 and copolymer 4 .

* 1,2-dimethoxyethane (DME), azobis(isobutyronitrile) (AIBN).

The mild base K_2CO_3 , and dilute condition using acetonitrile as solvent were found to be the best.

Tab. 1 : Yields of the cyclization step at different conditions.

<i>X</i>	<i>Base</i>	<i>Solvent</i>	<i>Refluxing time(h)</i>	<i>Yield %</i>
Cl	NaOH	BuOH	33	17
Cl	t-BuONa	t-BuOH	72	30
Cl	K_2CO_3	CH_3CN	120	50
OTS	K_2CO_3	CH_3CN	100	51
OTS	t-BuONa	THF	144	49

All the cyclization reactions were carried out under the dilution condition 0.03 M and the yields were calculated based on the pure product obtained after purification by flash chromatography.

The Wittig reaction was carried out with ethylene glycol dimethyl ether as solvent using sodium hydride to obtain monomer 3 in 66% yield.

The following approach, at the early stage of the work, was designed as an alternative route to the first step of Fig. 10 to obtain heptaethylene glycol :

Fig. 11 : The failed synthetic approach in heptaethylene glycol preparation.

The molecular ion peak at $m/z = 326$ in the MS spectrum suggested the formation of the desired product (heptaethylene glycol) but a quartet and a doublet ^1H NMR signals at 4.85 and 1.35 ppm respectively and also two ^{13}C peaks at 19.31, and 99.65 ppm should not exist if the product was heptaethylene glycol. In fact, an acetal had been formed. So, the synthetic approach previously used by Krespan⁴⁸ was followed.

As can be seen from Fig. 10 the radical homopolymerization of 3 ether failed although the homopolymerization of a few similar vinyl compounds with smaller crown rings, 15 and 18 member rings, had been reported by Smid.^{49,50} Anionic homopolymerization at -70°C using $n\text{-BuLi}^{51}$ as a base was also tried but no polymer was formed. Therefore copolymerization of monomer 3 with styrene was carried out at two different molar ratios $n/n'=1$ and 7 (Fig. 12) in identical conditions as for homopolymerization.

Fig. 12 : General copolymerization scheme of vinyl compound 3 with styrene.

No copolymerization occurred for the ratio $n/n'=1$, while a copolymer with average molecular weight of 16,000, as determined by GPC, was obtained once the ratio $n/n'=7$ was used. The value $m/m'=7/2$ in the resulting copolymer was determined by integration from the ^1H NMR spectrum.

Also, the polymerization of monomer 5 shown below was performed using exactly the same conditions.

Fig. 13 : Polymerization of monomer 5.

The above monomer was chosen to see how the two bulky groups at the end of the two open ether chains could affect polymerization. The result is summarized in Tab.2.

Tab. 2 : The dependence of m/m' values on n/n' ratio in the polymerization of monomer 5.

n/n'	Copolymer	m/m'
0	-	-
1	-	-
5	Copolymer 6	12/1
	Copolymer 7	2/1

Like before, no homopolymerization ($n/n' = 0$) or even copolymerization at the ratio of $n/n' = 1$ was detected. At the ratio of $n/n' = 5$, two copolymers 6, and 7 with different m/m' values and average molecular weights of 47,000, and 44,000 respectively were separated by fractional precipitation.

Comparison between the spectra a and b in Fig. 14 indicates that the intensity of the acetal hydrogens peak at 4.7 ppm is doubled in spectrum b while the intensity of the aromatic region is considerably decreased. These, in turn, means decreasing the m/m' value in copolymer 7.

The melting point of the copolymer 6 ($T_m = 69-65^\circ\text{C}$) is greater than that of copolymer 7 ($T_m = 50-60^\circ\text{C}$). This is relevant because : i) The average molecular weight of copolymer 6 (47,000) is more than that of copolymer 7 (44,000) and ii) The number of benzene rings in copolymer 6 repeat unit is also more than that of copolymer 7. This, in fact, gives more rigidity to copolymer 6.

According to the above observations it can be concluded that two factors might

Fig. 14 : ^1H NMR spectra of copolymers 6 (a), and 7 (b) in CDCl_3 .

influence the polymerization of **3** : "The reactivity of the monomer", and "The steric effect". It is hard to believe the reactivity of **3** is much different from vinyl-B18C6 while the later monomer undergoes homopolymerization. In fact the Vinyl groups in both should not be influenced by para and meta oxygens differently. So, the other factor, "Steric effect", as a prohibiting factor, could have a substantial role on homopolymerization of **3**. This steric effect may arise from the large size crown cavity in monomer **3**. However, to test this assumption one may try homopolymerization of the homologous monomers with intermediate ring size (i.e. 21C7).

2.2 : Complexation of copolymer with Ra^{2+}

Since this project was started on the basis of generation of Poly(vinylbenzo-24C8 ether) to remove Ra^{2+} (4 ng/l) from water and because the homopolymerization did not succeed, it was decided to test the efficiency of the resulting copolymer.

A liq. liq. extraction using CH_2Cl_2 / H_2O was applied to measure the complexation ability of 100 mg of copolymer toward 2 ng Ra^{2+} . According to the results* obtained about 10% of Ra^{2+} was extracted into the organic phase showing that this copolymer is not a good candidate for such a purpose. The low extraction ability might be due to the absence of the two proximate crown cavities for sandwich complex formation. However, due to our interest in both the solution and the solid phase NMR of crown ethers, the project at this point was turned into these fields.

2.3 : Synthesis of **8**

In order to have a solid benzo-24C8 ether at room temperature, the crown ether

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* The results are taken from Sudbury Neutrino Observatory (SNO) project group.

8 was synthesized according to the following scheme :

Fig. 15 : Synthetic scheme of COOH-B24C8, **8**.

Tollen's reagent⁵² was chosen as oxidant in order to prevent any possible ether-bond breakage during oxidation. In the approach applied, Ag_2O was used in the presence of the base NH_4OH (0.73 M) to get 56.3% yield. The crown ether **8** was easily separated from the unreacted starting aldehyde by acid-base chemistry. The melting point of product (89 °C) was significantly increased in contrast with starting **2** (liq. at RT). The chemical formula of **8** was confirmed by High Resolution Mass Spectroscopy to be $\text{C}_{21}\text{H}_{32}\text{O}_{10}$.

2.4 : Solution ^1H and ^{13}C NMR of **8**

In order to aid the analysis of solid phase ^{13}C spectra, it is often useful to carefully examine the solution counterpart.

The aromatic part of ^1H spectrum is AMX pattern for the protons 2, 3, and 5. The proton H3 is coupled, first, with H2 and then with H5 giving a doublet of doublets (dd) at 7.75 ppm. The C2, C3, and C5 resonances can be assigned through HETCOR connectivity pattern (Fig. 16).

Fig. 16 : HETCOR spectrum, part of aromatic region, of crown ether 8.

One can then assign the resonance at 124.95 ppm to C4. Tab. 3 shows the summary of the spectral analysis of the aromatic region.

Tab. 3 : ^1H and ^{13}C chemical shifts of crown ether 8 (aromatic region).

C/H	1	2	3	4	5	6
δ_{C} (ppm)	153.74	115.27	122.58	124.95	112.61	148.57
δ_{H} (ppm)	—	6.91	7.88	—	7.61	—

C1 is more deshielded than C6 because of the existence of the carboxy group at para

Fig. 17 : 400 MHz ^1H (a), and 100.6 MHz ^{13}C (b) NMR spectra of crown ring in crown ether 8.

position to C1.

In connection with the aliphatic methylene region, at least six hydrogen sets and almost all the carbon resonances were resolved (Fig. 17). In the ^1H spectrum, the integration of the four down-field multiplets and one high-field sharp peak are almost the same while that of the doublet at 3.7 ppm is twice indicating that this doublet contains 8H. The multiplet ether hydrogens in the ^1H spectrum is typical of what was observed for $\text{X-CH}_2\text{CH}_2\text{-Y}$ fragment (i.e. AA'XX' or AA'BB' pattern) when it undergoes rapid rotamer conversion.⁵³ Such a multiplicity for methylene hydrogens is very common in crown ethers containing this fragment.^{54,55}

The analysis of ^1H and ^{13}C spectra in Fig. 17 was performed using both the NOESY (Nuclear Overhauser Enhancement Spectroscopy) and the HETCOR. The key point was found to be long range connectivity between two ortho aromatic hydrogens (2, 5) and the crown cavity hydrogens, as shown below :

Fig. 18 : Expected long range nOe in crown ether 8.

Having the assignments of aromatic H2 and H5 in hand, one can proceed to assignment of H7, and H7' through NOESY (Fig. 19a). So, the most deshielded multiple

Fig. 19 : The NOESY (a), and the HETCOR (b) of the crown ether **8** by 400 MHz NMR.

methylene peak at 4.25 ppm should correspond to H7, and H7'. Such a ^1H - ^1H nOe (nuclear Overhauser effect) also has been found in a number of benzo crown ethers.⁵⁴ One then can have access to the assignment of C7 and C7' through HETCOR (Fig. 19b).

The three remaining ^1H multiple peaks were assigned as (H8, H8'), (H9, H9'), and (H10, H10') through connectivity pattern in the NOESY as shown below :

Fig. 20 : The NOESY of crown ring part of the crown ether 8 by 400 MHz NMR.

Now, one can determine Carbons 8, 8', 9 and 9' (but not carbons 10 and 10') through HETCOR (Fig.19b).

As a matter of fact, the closer the crown ring hydrogens to the benzene ring, the more deshielded they are. The assignment of ^1H methylene peaks in the case of DB18C6, DB24C8, B15C5, B18C6,^{54,56} and also some Bis(benzocrown ethers)⁵⁷ supports this statement. This behaviour is thought to originate from an aromatic ring current effect.⁵⁸⁻⁶⁰ Unfortunately, Subramanian, S. has recently made a few mistakes in the ^{13}C spectral analysis of DB24C8 and B15C5.⁵⁴

The solution ^{13}C signals of the nearest methylene carbons to the benzene ring in benzocrown ethers (C7,7' in this current case) in most of the cases are the most shielded resonances among all methylene signals. There are two contributing factors in this regard : i) The dihedral angles C7'-O-C1-C6 and C7-O-C6-C1 in B3nCn ethers, as will be discussed later on, are close to the 180° which cause shielding of C7 and C7'⁶¹ and ii) The well known γ -substituent effect⁶² caused by in-plane 2,7' and 5,7 hydrogen interactions.

None of the NMR techniques permit assignment of C10-C13 resonances. The following hypothesis was found to be effective for this purpose.

The hypothesis is : *"The chemical shift differences between each carbon pair, (C7, 7'), (C8, 8'), etc. should be reduced going from C7 to C13"*. This idea, in fact, originates from the fact that the deshielding effect, applied from carboxyl group, is transferred to the aliphatic ether chain $\text{C1}(\text{OCH}_2\text{CH}_2)_3\text{OC13}'$, but it is not spread out identically over all the carbon atoms in this aliphatic ether chain. So, $\Delta\delta_{7,7'} > \Delta\delta_{8,8'} > \Delta\delta_{9,9'}$, etc. The lone pair of *para* oxygen to COOH is in better conjugation with the benzene ring than those of the other oxygen bonded to the aromatic ring and this resonance interaction changes the $\text{C1}(\text{OCH}_2\text{CH}_2)_3\text{OC13}'$ chain conformation. As a consequence,

the torsional angles C-O-C-C and O-C-C-O change and therefore the chemical shifts of methylene carbons,⁶³⁻⁶⁵ in $C1(OCH_2CH_2)_3OC13^+$ would become different from those appropriate torsional angles in $C6(OCH_2CH_2)_3OC13$ ether branch. Such substituent influence transformations through aliphatic chains have also been reported for 4-substituted DB18C6 or DB24C8 crown ethers by Loktev.⁶⁶

The ^1H -coupled ^{13}C spectrum of 8 as well as the complete peak assignments are shown below :

Fig. 21 : The ^1H -coupled ^{13}C NMR spectra of 8 by 200 MHz NMR.

One may find the assignment of C2 and C5 not to be correct because C2 is coupled twice, first by H2 followed by H3, while C5 is coupled just with H5 and therefore the sharp high-field doublet should be corresponded to C5 not C2. If this is true, then our previous assignments (Tab. 3) will be wrong!

This comment is not true because : i) If $\delta C_2 > \delta C_5$, then the assignments of H2 and H5 in Fig. 16 should be reversed and this, in turn, means $^3J_{H_2-H_3} < ^4J_{H_5-H_3}$ which is not acceptable. ii) The main assumption on which the above comment is based is : " $^2J_{C-H}$ should be greater than $^3J_{C-H}$ ". This is incorrect. In fact, *geminal carbon-hydrogen coupling* $^2J_{CH}$ can be negative, zero, or positive depending on the system under study and the C-C-H bond angle.⁶⁷ The $^nJ_{CH}$ values have been summarized in Tab. 4.

Tab. 4 : " J_{C-H} values" (± 0.5 Hz) for aromatic carbons of **8** by 100 MHz ^{13}C NMR.

C_i	C_2	C_3	C_4	C_5
$^1J_{CH}$	161	165	--	161
$^3J_{CH}$	--	007	007	007

* Digital resolution is 0.5 Hz/point.

In fact, C5 is first coupled with H5 by 161 Hz and then with H3 by 7 Hz while C2 is just coupled to H2 by 161 Hz.

2.5 : ^{13}C CPMAS NMR of copolymer, **8**, and K^+ complex

The normal and Dipolar Dephased ^{13}C CPMAS spectra of copolymer are shown in Fig. 22.

Fig. 22 : Normal (a) and dipolar dephased (b) ^{13}C CPMAS NMR spectra of copolymer 4.

The four broad peaks in spectrum "a" centred at 40, 71, 146, and 128 ppm are assigned to be the resonances of benzylic carbons, methylene $-\text{OCH}_2-$, aromatic carbons 1, 2 and finally carbons 3-12 respectively. The two aromatic broad peaks in the dipolar dephased spectrum are due to the tertiary carbons, but how could the intensive peak at 71 ppm be interpreted? No resonance for carbon atoms attached to hydrogen normally are observed under the condition of dipolar dephased technique. Thus the remainder signal at 71 ppm is attributed to the partial motion in the crown cavity of copolymer 4.

To find out whether the motion is an intrinsic characteristic for 24 membered-ring, the ^{13}C CPMAS of a nonpolymeric B24C8 is required. This is shown for 8 in Fig.23. The solution ^{13}C spectrum has also been included to simplify the analysis of the CPMAS

Fig. 23 : Solution ^{13}C (50.3 MHz)(a), normal (b), and Dipolar Dephased (c) ^{13}C CPMAS NMR spectra of crown ether 8.

spectrum.

Since the pattern of the seven ^{13}C aromatic resonances in the powder spectrum is very similar to that of solution, it is safe to assign the solid phase resonances as in solution. The four low field signals in the dipolar dephased spectrum which are attributed to the four tertiary carbons, 1, 4, 6, and -COOH are in agreement with this statement. The existence of the huge peak at the region of 68-72 ppm is definitely an indication of an intrinsic molecular motion just in the crown ring.

The expanded part of the methylene region of ^{13}C CPMAS spectra have been presented in Fig. 24. The broad resonances in circle *m* are due to C7, C7', C8, and C8' while that in circle *n* to C9, C9'. A very obvious difference between *b* and *c* spectra is elimination of circled part *m* and intensity reduction of circled part *n* in dipolar dephased spectrum. This reveals that not the whole crown ring is involved in the motion and in fact, a "*partial motion*" involving part K (Fig. 24c) is the case.

Is the motion stopped upon complexation of the **8** with cations? This appears to be the case. Complexations of this crown ether with cations Ba^{2+} , K^+ , and Na^+ were successfully performed. The ^{13}C powder spectrum of K^+ complex is presented in Fig. 25.

The intensity of methylene signal has been reduced to almost zero. This confirmed the absence of the motion in the K^+ complex. The very weak peak left at the position of methylene peak is due to the presence of trace free crown ether **8** left in the K^+ complex.

There are two differences between the CPMAS spectra of free crown ether (Fig. 23) and K^+ complex (Fig. 25); the appearance of the methylene signals and the chemical shifts of aromatic rings. These are all as a result of conformational changes occurred upon complexation. Such chemical shift changes have also been reported for both host crown

Fig. 24 : The expanded part, 60-80 ppm, of the methylene region of the solution ^{13}C (100 MHz)(a), normal and Dipolar Dephased ^{13}C CPMAS NMR spectra (b, c) of the crown ether 8.

Fig. 25 : Normal ^{13}C CPMAS (a), and Dipolar Dephased (b) ^{13}C CPMAS NMR spectra of crown ether 8 / KSCN complex.

ethers⁵⁴ and guest molecule.⁶⁸⁻⁷⁰ Efforts to get single crystals of both complexed and uncomplexed 8 crown ether for X-ray study unfortunately failed.

2. 6 : Spin Lattice Relaxation Time

Spin-lattice relaxation time (T_1) measurements give useful information on molecular dynamics. For isotropic tumbling, we would expect to get the same T_1 values for all carbon atoms attached to the same number of hydrogens in a particular molecule.⁷¹ Therefore, one can compare the T_1 values of different $-CH_2-$ carbons to find out if any preferred segmental motion exists in the crown ring. The results of T_1 measurement by "Inversion-Recovery" technique for 8 are presented below :

Fig. 26 : ^{13}C spin lattice relaxation times (T_1)(± 0.01 sec.) of 8 in CDCl_3 .

Unfortunately, not all of the signals were resolved, by 50.3 MHz ^{13}C NMR. The T_1 values of C7, C7', C8, and C8' are smaller than those of the carbons which are further away

from the benzene ring.

As can be seen from Fig. 27, the T_1 values are inversely proportional to the correlation times (τ_c), in the extreme narrowing limit region, and therefore correlated to molecular motion.⁷²

Fig. 27 : The effect of correlation time on T_1 .

For a molecule undergoing dipolar relaxation, as the mobility of the C-H bond increases in solution, the correlation time decreases and this would lead to an increase in T_1 . According to the T_1 data of **8**, it can be concluded that the rigidity of the crown ring decreases as $\text{C7} \rightarrow \text{C13}$.

The T_1 measurement was carried out, once more, for both free **8** and its K^+ complex, with the same concentration of 0.25 M in DMSO-d_6 . The results are presented in Tab. 5.

Tab. 5 : ^{13}C spin lattice relaxation times (T_1) for free **8** and its K^+ complex in DMSO-d_6 .

	C7 , C7'	C8 , C8'	C10 - C13
T_1 (crown ether)	0.20 ± 0.01	0.21 ± 0.01	0.40 ± 0.01
T_1 (K^+ complex)	0.14 ± 0.01	0.14 ± 0.01	0.25 ± 0.01
ΔT_1	0.06 ± 0.02	0.06 ± 0.02	0.15 ± 0.02

The T_1 values are decreased upon complexation because of the intermolecular host-guest interactions⁶² that restrict the freedom of crown ring. This is in agreement with was found in the dipolar dephased ^{13}C CPMAS spectrum of K^+ complex in Fig. 25.

From the theoretical and experimental point of view, T_1 decreases with viscosity enhancement.⁷³ However, in the case of **8**, the results are entirely contrary! The T_1 values in CDCl_3 solvent (Fig. 26) are lower than the corresponding values in DMSO-d_6 (Tab. 5). This is because of the "*Association of the two molecules of **8** through hydrogen bonding in the less polar CDCl_3 solvent*". This dimerization increases the effective molecular weight, enhances the correlation time, and therefore decreases the T_1 values. Overall, the association effect overcomes the viscosity effect in CDCl_3 and therefore lower T_1 values are found.

One fast experimental method that can confirm this hypothesis is solution IR spectroscopy. This was performed (see APP. I for result) on the same solutions that were used for T_1 measurements. The carbonyl stretching was found to be 1692.8 cm^{-1} in DMSO-d_6 while 1685.9 cm^{-1} in CDCl_3 . This shift is assumed to result from hydrogen bonding.

In order to ensure that dipole-dipole relaxation is the dominant mechanism of the spin-lattice relaxation in **8**, decoupled ^{13}C spectra with and without nOe were obtained. The overall nOe of 2.85 (95%) was obtained indicating that dipole-dipole relaxation is the dominant mechanism of spin-lattice relaxation.

2.7 : Synthesis of deuterated crown ethers

To study the motion of **8** in more detail, deuterated crown ethers were needed. Systematically, deuterium atoms have to be placed at the susceptible location where the motion is occurring. Thus positions (13, 13') and (11, 11') were chosen as targets and two deuterated crown ethers **10**, and **14** were synthesized through the pathway shown in Figures 28, and 29.

The following four different approaches were examined to synthesize the diester **11** :

- a) direct mild oxidation of triethylene glycol by PCC (pyridinium chlorochromate) and also by PDC (pyridinium dichromate) in DMF to get diacid^{74,75} followed by esterification.
- b) Oxidation of triethylene glycol by "Swern" method using dimethyl sulfoxide-oxalyl chloride at low temperature^{76,77} to get dialdehyde followed by more oxidation and esterification.
- c) A substitution reaction using ethylene glycol and ethylbromo acetate.
- d) An insertion reaction using ethylene glycol and ethyldiazoacetate⁷⁸ in the presence of BF_3 as catalyst.

Neither of the first two attempts succeeded. Approach c gave a mixture of products, including the desired diester **11**. The best way was found to be the d approach because it is a very clean (if done properly under anhydrous conditions), one step

Fig. 28 : Synthetic route to *COOH*-B24C8 (13, 13'-d4), **10**.

Fig. 29 : Synthetic route to *COOH*-B24C8 (11, 11'-d4), **14**.

reaction that can be simply carried out over a period of half an hour.

The chemical formulas of two deuterated crown ethers **10** and **14** were confirmed by High Resolution MS and the molecular ions with m/z 448.22438 and 448.22604 respectively corresponding to $C_{21}H_{22}O_{10}D_4$ with deviation of - 0.28 and +1.39 mmv were found.

2.8 : Solution NMR spectral analysis of 10 and 14

Preparation of two deuterated crown ethers provided us a chance to double check the previous solution ^{13}C and ^1H spectral analysis of **8**. The ^{13}C spectra of two deuterated crown ethers, in accompany with that of **8**, have been presented in Fig. 30.

The four high field and the two low field peaks due to C7, C7', C8, C8', C9 and C9', have remained intact since their chemical shifts are not substantially affected by incorporation of ^2H at positions 11, 11', 13, and 13'. The comparison between the spectra *a*, and *b* indicated that the sharp peak at 70.82, due to C13 and C13', is removed and a wavy baseline around 70 ppm, due to two weak overlapped quintets arising from CD_2 , is created. The four signals 10, 10', 11, and 11' have collapsed into two more intense signals in spectrum *b*.

In the spectrum *c* the four deuterium atoms at positions 11, 11' cause the signals of C10, C10' to shift upfield more than C12 and C12'. Thus the two sharp peaks hidden under the strong resonance at 70.75 ppm are attributed to C10 and C10'.

The upfield shift ^2H isotope effects on the chemical shifts are produced by either ^2H inductive effect or negative hyperconjugation mechanism as will be discussed in more detail later.

In Fig. 31, the four downfield multiple peaks are virtually identical in all three

Fig. 30 : The expanded parts of the regions 69.0-71.5 ppm of ^{13}C spectra of nondeuterated (a), and deuterated (b, c) crown ethers by 100.6 MHz ^{13}C NMR.

Fig. 31 : The expanded parts of the regions 3.6–4.4 ppm of ^1H spectra of nondeuterated (a), and deuterated (b, c) crown ethers by 400.1 MHz ^1H NMR.

spectra. The sharp signal due to hydrogens 13, 13' is obviously removed in spectrum b. The two sharp singlets, in spectrum c, are due to hydrogens (12, 12'), and (13, 13'). These are all in agreement with our previous ^1H and ^{13}C assignments for 8.

2.9 : ^{13}C solid phase NMR of 10 and 14

The ^{13}C CPMAS of two deuterated crown ethers 10 and 14 are presented in Fig. 32. The peaks at 67.7 and 68.9 ppm in spectrum a; 67.5 and 69.0 ppm in spectrum a' have been removed in the corresponding Dipolar Dephased spectra while the intensities of the signals at 71.9 and 72.0 ppm in CPMAS spectra have been strongly reduced. These differences are similar to what was previously found for 8. Also, as noticed in the case of 8, the resonance at 71.3 remains in both Dipolar Dephased spectra b and b'. Considering the fact that the rigid methylene carbons are not expected to show up in Dipolar Dephased ^{13}C CPMAS spectra, the above observations indicate that : i) The rigid methylene carbons are not CD_2 carbons. ii) Methylene C10,10' are also involved in the motion because their corresponding signals are not completely removed in the Dipolar Dephased ^{13}C CPMAS.

More interestingly, the overall shape of the spectra b and b' are not the same. This is due to the deuterium isotope effect. Deuteration of C11 and C11' produces upfield shift for C11 and C11' resonances causing them to be hidden under the peak at 70.6 ppm in spectrum b'. Also, upon deuteration of C13,13' the chemical shifts of C13,13' move upfield and this causes a new peak at 70.3 ppm in spectrum b.

2.10 : ^2H NMR of 10 and 14

The idea of the existence of the motion in solid phase crown ethers was originally proposed by Buchanan et. al. based on accumulated evidence obtained by solid state

Fig. 32 : Methylene regions of normal CPMAS (a, a'), and Dipolar Dephased (b, b') ^{13}C CPMAS NMR spectra of crown ethers 10, and 14.

^{13}C NMR (CPMAS) of 18C6 complexes.^{43,63,79,80} This was then confirmed by solid phase ^2H NMR⁸¹ and a "*Merry-Go-Round*" motion with rates of the order of 10^5 - 10^6 Jumps/s was found at RT.

There were two goals of performing ^2H NMR of **10** and **14**. Firstly, to confirm or reject the existence of the partial motion in solid phase for B24C8 derivatives qualitatively, and secondly, to analyze such a motion quantitatively to refine a model to account for the motion. ^2H NMR spectra were performed in the range of 238-347K and 241-361K for deuterated crown ethers **10** and **14** respectively and the results are presented in Fig. 33. The higher temperatures were not examined because the melting points of **10** and **14** are 360-362K.

As can be seen from Fig. 33, the ^2H NMR line shapes in both cases are temperature dependent and this is an indication of the existence of the motion, at least in the deuterated regions, which is in agreement with our original prediction. Acceptance of the motion for methylene carbons C11, C11', C13, and C13' convinces one to accept that at least two other methylene carbons C12 and C12' are also involved in such a motion because these are located between methylene carbons where are subjected to the motion.

If one carefully analyzes the ^2H NMR spectra of two deuterated crown ethers, one can conclude the following :

- i) Both of the crown ethers **10** and **14** exhibit static lineshapes at about 240K. Although the CD_2 segments at positions 11 and 13 don't behave motionally the same, they both are participating in the same overall motion. In other words, their motions are not independent from each other and as a consequence, they both show static lineshapes at about 240K.

Fig. 33 : ^2H NMR line shape of crown ethers 10, and 14 at various temperatures.

- ii) The line shape changes in **10** and **14** are not identical. This is as a result of the fact that the motion is not symmetric in the entire crown cavity. So, the amplitude of the motion is varied from one methylene to another. Recall the fact that the motion is restricted to a part of the crown cavity.
- iii) Both ^2H NMR spectra are slightly narrower than those reported for the complexes of 18-Crown-6⁸¹ and 12-Crown-4⁸². The values for the static tensor components derived from the low temperature spectra of 18C6 and 12C4 complexes have been compared with those of crown ether **14** in Tab. 6. The temperatures at which the measurements were made are also reported.

Tab. 6 : The values for the static tensor components in three deuterated crown ethers.

Crown Ether	V _{zz}	V _{yy}	V _{xx}	Temperature(K)
18C6 Complex	246.1	131.8	114.3	198
12C4 Complex	250	132.8	117.2	175
14	240	128	112	241

- iv) The static tensor component V_{xx} appears to be the most constant, among two other parameters V_{yy} and V_{zz}, as a function of temperature enhancement. Tab. 7 shows the observed values of lineshape components at two different temperatures for crown ether **14**. This suggests that a major motion is a flip in the CD₂ plane. This has been calculated to be 19.6° from 265K static and 278K dynamic parameters.

Tab. 7 : The observed lineshape components at two temperatures for crown ether 14.

Temperature (K)	V _{zz}	V _{yy}	V _{xx}
241	240	128	112
361	134	38	95

The fact that V_{xx} changes gradually with temperature indicates further motion outside this plane but probably of lower amplitude (perhaps a twist of the group). However, this makes it difficult to separate the two motions as temperature increases since both probably have increasing amplitude and both contribute to the narrowing.

v) The next problem is the appearance of an extra set of features in the 278-347K range. These can be attributed to a second tensor whose yy component is the same as the yy of the fast tensor. This is calculated to be 30.9° from the 265K static and 293K dynamic parameters for an in-plane flip.

vi) Both ²H NMR spectra have shown great changes around 277K and as a result, sharp isotropic lines show up in both cases. This was predicted to be resulting from a phase change. This was examined by DSC (Differential Scanning Calorimetry) and was found to be the case as explained in following section.

2.11 : DSC on 14

The DSC plots of deuterated crown ether 14 has been shown in Fig. 34. In order to test the reproducibility of the plots and the experimental errors, the DSC was run twice on a sample of 14.

Fig. 34 : DSC plots of crown ether 14.

Crown ether 14, in the first run, was first cooled to $-50\text{ }^{\circ}\text{C}$ slowly followed by warming up to record the phase changes. Two phase changes at -0.6 and $86.7\text{ }^{\circ}\text{C}$ were observed of which the second one is due to the melting point. The minor phase change was accompanied by an absorption of 21.7 mJ/mg energy. The sample was cooled down to $-50\text{ }^{\circ}\text{C}$ slowly once more and the second run was performed. The phase change this time was observed at $2.3\text{ }^{\circ}\text{C}$, surprisingly, with a new absorption of 15.7 mJ/mg . So, the phase change position moves to a higher temperature by $2.9\text{ }^{\circ}\text{C}$ and the magnitude of the corresponding heat absorption increases by 27.7% . Interestingly, these relatively big changes have not been observed, to this extent, in the major phase change at about $87\text{ }^{\circ}\text{C}$. The prediction made by ^2H NMR appears to be true since the observed phase change occurs at about $0\text{ }^{\circ}\text{C}$, in agreement with results obtained by ^2H NMR.

The changes observed in the first and second runs for the minor phase change can not be simply attributed to experimental errors. Two possibilities that can be suggested to rationalize this behaviour are : i) Decomposition of the complex formed between crown ether and H_3O^+ and ii) breakage of intermolecular hydrogen bonding. The heat absorption measured ($21.7\text{ mJ/mg} = 9.8\text{ kJ/mol}$) is within the hydrogen bonding energy. So, the minor phase change observed could be due to the intermolecular hydrogen bonding between two carboxylic acid functional groups. The reason why the heat absorption has been decreased in the second run is that once the melted crown ether is cooled down, it neither has enough time nor is free like in the solution to rebuild the maximum possible hydrogen bonding. As a consequence, in the second run less energy is required to overcome such hydrogen bonding.

2.12 : Complexation of 8 with Ba²⁺, K⁺, and Na⁺

Efforts to make the complexes of 8 with seven salts, Ba(ClO₄)₂, NaSCN, KSCN, LiSCN, NaClO₄, KI, and NaI resulted in just three complexes; Ba²⁺ (mp=260-263 °C), Na⁺(140-150 °C)(from NaSCN), and K⁺(107-110 °C)(from KSCN). The melting point enhancement in all the complexes, in comparison with free 8, are assumed to be an indication of complex formation. The efforts to obtain X-ray grade single crystals were unsuccessful.

The FAB (Fast Atomic Bombardment) MS was run on complexes and the appropriate molecular ions of three complexes were observed; a peak at 483.3 (100%) for 1:1 complex (C₂₁H₃₂O₁₀K); a peak at 467.2 (100%) due to 1:1 Na⁺ complex; and a peak at 681.1 for 1:1 complex of C₂₁H₃₂O₁₄BaCl, were detected. In addition to these major m/z peaks, other minor peaks due to 2:1 complexes were also observed. These ion masses are available from Appendix I.

Interestingly, further analysis of the fragmentation pattern showed a strange peak at 577.2 in all three MS spectra (see APP. I) which was not matched with any of the possible fragmentations. This was found then to be the molecular ion of the crown ether/Cs⁺ complex because Cs⁺ was used as reference in FAB MS.

Chapter 3

²H isotope"

in

***"Solution and Solid Phase Conformational Analysis, NMR spectral Analysis of
B9C3, 4-NO₂-B9C3, DB18C6, and CH9C3"***

3.1 : Background

The ²H isotope in NMR spectroscopy is normally used to i) facilitate a direct ²H NMR experiment ii) understand the origins of nuclear shielding through isotope shifts, and iii) study the other NMR active nuclei (normally ¹H or ¹³C) in ²H labelled compounds. In its third application, the ²H isotope is mostly used to simplify the complex NMR spectra. Crown ethers B9C3, DB18C6, 4-NO₂-B9C3, and CH9C3 (17, 18, 19, 20) are examples of such complex situations whose NMR spectra, mostly ¹³C CPMAS, could not be simply analyzed. The following deuterated crown ethers were synthesized :

Fig. 35 : The chemical structures of 9- and 18-membered ring deuterated crown ethers.

Once the ^{13}C resonances are unambiguously assigned, one can rationalize their origins based on the known conformations and X-ray data which are available for both the 9-membered⁸³ and 18-membered⁸⁴ ring crown ethers.

The incorporation of ^2H at the positions 7 and 10 is useful because it : i) simplifies not only the overall ^1H spectrum but also ^1H splitting pattern of $-\text{OCH}_2\text{CH}_2\text{O}-$ (i.e. AA'XX' spin system) due to the different resonance frequencies of ^2H and the small vicinal $^2\text{H}-^1\text{H}$ coupling. ii) allows one to distinguish a $-\text{CH}_2-$ carbon from $-\text{CD}_2-$ one, in solution, because of the quintet pattern of $-\text{CD}_2-$, and in the solid , because of the both weaker and split $-\text{CD}_2-$ signal. iii) permits one to identify a $-\text{CD}_2-$ signal in a Dipolar Dephased ^{13}C CPMAS spectrum.

3.2 : Synthesis of deuterated crown ethers

The approaches applied to synthesize the title crown ethers are depicted in Fig. 36. Diglycolic acid was transformed to its diester due to the poor solubility of the diacid in ether or THF solvents which are normally used for reductions with LiAlH_4 . The first two synthetic steps, esterification and reduction, were performed with 98% and 95% yields respectively, while the cyclization step gave 33% major product 17-d4 and 1.6% minor product 18-d8 respectively. The nitration of 17-d4 was performed using the approach applied by Fiegenbaum⁸⁵ with a 55% yield. The catalytic hydrogenation using the rhodium catalyst on aluminium powder under high H_2 pressure at 40°C gave 20-d4 in 80% yield. In order to maximize the cyclization yield in the preparation of 17-d4, some efforts including variation of the solvent, base, and leaving group were made and the best conditions were found to be water as solvent and LiOH as base. The chemical formulas

Fig.36 : General synthetic scheme for deuterated crown ethers 17-d4, 18-d8, 19-d4, and 20-d4.

* Crown ethers B9C3, DB18C6, 4-NO₂-B9C3, and CH9C3 are numbered as 17, 18, 19, and 20.

of crown ethers 17, 18, 19, and 20 were confirmed by high resolution MS.

Upon hydrogenation of 17-d4, the byproduct 21 was also obtained. The chemical structure of this byproduct was confirmed by ^{13}C NMR comparison with the synthesized nondeuterated homologue (App. I).

3 . 3 : Solution NMR Spectral Analysis, and Conformational Analysis

3 . 3 . 1 : Solution NMR of 17-d4 and 18-d8

The solution ^{13}C NMR spectra of 17-d4 and 18-d8 are shown in Fig. 37. Both spectra exhibit 5 ^{13}C resonances in solution indicating rapid conformational averaging of their 9- and 18-membered rings on the NMR timescale. The solution ^{13}C spectrum of 17 is independent of temperature (apart from minor chemical shift changes) over the range of 300 to 173K. Hence, the conformational interconversion in the 9-membered ring must remain fast on the NMR timescale at all accessible temperatures.

The quintets at 73.2 and 68.2 ppm correspond to the CD_2 carbons. Apparently, crown ether 17 is the only member, among all Benzo-3n-Crown-n and Dibenzo-3n-Crown-n (B3nCn and DB3nCn) crown ethers, which shows exceptional behaviour in terms of ether carbon chemical shifts because of the strain which exists in the 9-membered ring crown cavity. In other cases, the nearest ether carbon to the benzene ring is the most shielded methylene carbon. It is noted that there is a huge difference in the local ether ring conformation about C7 vs. C10 in the solid phase (see ORTEP plot of 17, App. II) and as we will see, this influences the averaged solution chemical shift observed for C7,10 at RT. However, such an unusual chemical shift position for C7 and C10 were not found for methylene hydrogens H7A, H7B, H10A, and H10B. These

Fig. 37 : Solution ^{13}C NMR spectra of 17-d4 and 18-d8.

hydrogens are the most deshielded hydrogens due to the aromatic ring current deshielding effect.

3.3.2 : Solution NMR of 19-d4

Since there is no symmetry element in this molecule, ten ^{13}C signals were observed for **19** in solution. We, here, focus our attention to the relatively more complicated part, i.e. the methylene region. One can easily distinguish C7 and C10 peaks from C8 and C9 as well as their corresponding hydrogens using **19-d4** (Fig.38).

To explain how C7 and C8 are distinguished from their counterparts C10 and C9, some 2-dimensional (2D) NMR spectra are required. The key point was found to be the assignment of H7. This was identified through long range ^1H - ^{13}C HETCOR ($J = 5\text{ Hz}$), because C1 as the most deshielded resonance was known. Then, H10 was recognized. With H7 and H10 proton assignments in hand one can identify C7 and C10 through HETCOR of **19** as shown in Fig. 39a. Once H7 and H10 are identified, the COSY of **19** (App. I) furnishes the assignments of H8 and H9. This was followed by HETCOR of **19-d4** (Fig. 39b) to distinguish C8 signal from C9. The reason HETCOR of labelled nitro-compound was used for the last step is that protons H8 and H9 are clearly resolved in ^1H spectrum of the labelled crown ether while there is an intensive overlapping between these protons in ^1H spectrum of the unlabelled moiety (Fig. 39a).

3.3.3 : Solution NMR of 20-d4 at RT and LT

The solution ^{13}C spectrum of **20** in CDCl_3 at RT consists of 5 resonances as shown in Fig. 40.

Fig. 38 : ^{13}C (a) and ^1H (b) solution NMR spectra of labelled and unlabelled 19, crown ring regions.

Fig. 39 : ^1H ^{13}C HETCOR of labelled, and unlabelled 19, ether region.

Fig. 40 : ^{13}C solution NMR spectrum of **20** at RT.

From the known data for substituted cyclohexanes^{86,87} and from the characteristic ^{13}C signal for all cyclohexyl methine carbons bearing oxygen in *cis*- CH_3nCn crown ethers,⁸⁸ all the ^{13}C resonances, except those of C7 and C8, could be easily assigned. At 210K, 10 resonances are clearly resolved.

Fig. 41 : ^{13}C solution DEPT NMR spectrum of **20** at 210K.

As shown in the 210K DEPT spectrum, there are two positive signals due to the methine carbons and eight negative signals for the methylenes. The two unknown peaks at RT now have split to four. One should not forget that the spectral complexity in *cis*-1,2-CH₃nCn crown ethers will become even more if $n > 3$. It is for this reason that the complete ¹³C assignments in these cases have never been unambiguously reported at low temperature.^{88,89} However, for the relatively simple cases like **20**, this problem can be removed by **20-d4**.

The methine (CH) carbon signal at 82.2 ppm (Fig. 41) can be assigned with confidence to C1 the carbon bearing equatorial oxygen, by analogy with well established stereochemical trends.^{90,91} Its counterpart, the C2 carbon bearing axial oxygen is shielded by 6.5 ppm and appears at 75.70 ppm.

The temperature dependence of the ¹³C NMR of **20-d4** is shown in Fig. 42. The quintet ¹³C peak at 70.3 ppm at RT clearly indicates that C7,10 are more shielded than C8,9. This is opposite to what was observed in **17-d4**. At 210K, the two quintet signals corresponding to C7,10 are obviously distinguishable from the sharp signals of C8,9. The distinction between C7 and C10 as well as C8 and C9 could be made via a combination of 2D NMR spectra such as inverse detected ³J HETCOR, ¹J HETCOR, NOESY, and COSY at 210K (see App. I).

The chemical shift difference between C8 and C9 is 4.3 ppm, C8 being more shielded, while that of C7 and C10 is only 0.8 ppm (i.e., 71.6 vs. 70.8 ppm). Since the ¹³C NMR spectrum of **20** in both solution LT and solid phase, are very similar to each other, therefore, the 4.3 ppm difference will be addressed in the solid phase NMR discussion.

Fig. 42 : Temperature dependence of ^{13}C NMR of 20-d₄.

The assignments of the cyclohexane methylene carbons, shown in Fig. 41, were made through the splitting patterns of ^{13}C signals below the coalescence temperatures as well as 2D NMR spectra using C1 and C2 assignments as key starting points. As expected, C6 is more shielded than C3 because of the γ -gauche relation to the axial oxygen. For the same reason, C4 is more shielded than C5.

The chemical shift differences between C3 and C6 ($\Delta\delta_{\text{C3,C6}}$) in 20, DCH24C8, and DCH14C4 have been compared with the corresponding calculated values in *cis*-dimethoxy cyclohexane (*cis*-1,2-dimethoxy CH) in the following Table :

Tab. 8 : $\Delta\delta_{\text{C3,C6}}$ in some CH₃nCn and *cis*-dimethoxy cyclohexane.

	DCH24C8	DCH14C4	20	<i>cis</i> -1,2-dimethoxy CH
$\Delta\delta_{\text{C3,C6}}$	1.5	1.4	2.2	1.9

$\Delta\delta_{\text{C3,C6}}$ calculation on *cis*-1,2-dimethoxy cyclohexane was performed using the additivity consideration^{91,92} based on the α , β , and γ substituent effects provided by Schneider et.al.⁸⁷ in related *axial* and *equatorial* methoxy cyclohexanes. Clearly, both observation/calculation show C6 is shielded by about 2 ppm relative to C3 even though equatorial β deshielding effect of -OCH₃ group is 5.23 ppm.⁸⁷ This unambiguous finding for the chemical shift difference between C3 and C6 in *cis*-1,2-CH₃nCn crown ethers is a good way to distinguish C3 from C6.

3.4 : ^{13}C Solid Phase NMR Spectral Analysis, and Conformational Analysis

3.4.1. : ^{13}C Solid Phase NMR of 17-d4

The ^{13}C CPMAS spectra of labelled and unlabelled **17** along with the Dipolar Dephased ^{13}C CPMAS spectrum of **17-d4** are shown in Fig. 43. In the solid phase, the number of ^{13}C peaks for **17** has been doubled in comparison with solution ^{13}C NMR. In the solid phase, the ^{13}C NMR spectral multiplicity will reflect the asymmetric unit in the crystal if no unusual crystal packing effects or nonequivalent molecules in the unit cell are present.⁵³ For **17**, neither of these complicating phenomena are present in the crystal structure. Thus, based on the X-ray crystallographic structure,⁶¹ one would expect to see ten distinct resonances in the ^{13}C CPMAS spectra.

From Fig. 43c, both the methylene C7 and C10 can be unambiguously distinguished from C8,9. Interestingly, C8 and C9 are separated by 2.5 ppm, while C7 and C10 differ by 7.9 ppm. No experimental method is presently available to distinguish between C7 from C10 or C8 from C9.

In order to assign the ^{13}C CPMAS peaks more specifically; one has to use the X-ray data of **17**. Some of the important torsional angles of **17** are presented in Tab. 9.

Fig. 43 · Normal ^{13}C CPMAS NMR spectra of 17 (a), and 17- d_4 (b); and Dipolar Dephased ^{13}C CPMAS NMR of 17- d_4 (c).

Tab. 9 : Torsional angles for two most important torsional units containing C7 and C10 in 17.

$C7-O1-C1-C6 = 170.3^\circ$	$C10-O2-C2-C3 = 79.9^\circ$
$C7-O1-C1-C2 = 10.5^\circ$	$C10-O2-C2-C1 = 105.0^\circ$

As a result of the C7-O1-C1-C6 torsional angle, one of the O1 lone pairs occupies an orbital which is nearly perpendicular to the plane of the aromatic ring. This geometry is optimal for conjugative electron release by O1. Hence, C2, C4, and C6 are expected to be shielded relative to C1, C5, and C3 respectively. An sp^2 C1-O1-C7 bond angle of 124.4° , an sp^3 C2-O2-C10 bond angle of 115.4° , and finally the shorter C1-O1 bond length ($0.04 \text{ \AA}$) relative to average corresponding value⁹⁴ all indicate that the electron pairs on O1 are substantially delocalized into the aromatic ring.

The substantial shielding difference between C7 and C10 originates mainly from the difference between corresponding torsional angles which involve C7 and C10. It has been suggested⁹⁵⁻⁹⁷ that C-O-C-C and O-C-C-O torsional angles, play an important role on ^{13}C chemical shifts of the methylene carbons bearing oxygen in the solid phase.

The dependence of the CH3 shielding of anisole on the CH3-O-C-C dihedral angle has been recently calculated by Buchanan.⁶¹ The results are depicted in Fig. 44.

Fig. 44 : LORG calculation of angular dependence of ¹³C shielding for the methyl group of anisole.

As it is clear, for a torsional angle of 79.9°, there would be smaller total shielding than for a value of 170.3°. This is, most probably, the main reason of 7.9 ppm shielding of C7 over C10.

The results of solution and solid phase ¹³C spectral analysis in hand, one can assess the results of Localized Orbital Local Origin (LORG)^{98,99} calculations on 17^b (Tab. 10).

^bab initio shift calculations on 17, in the gas phase, was performed by Kirby at Southern Illinois University.

Tab. 10: Observed and Calculated ^{13}C chemical shifts (from TMS ± 0.1) of 17.

Ci	Solution	Solid (obs.)	LORG (calc.)	$\Delta(\text{calc.}-\text{obs.})$
C1	151.4	151.0	152.9	1.9
C2	151.4	148.7	150.0	1.3
C3	122.9	(127.2) ^a	137.9	10.7
C4	123.9	121.8	134.4	12.6
C5	123.9	(124.6) ^a	136.8	12.2
C6	122.9	119.0	126.9	7.9
C7	74.0	68.2	61.9	- 6.3
C8	72.3	(72.9) ^b	69.6	- 3.3
C9	72.3	(70.4) ^b	69.7	- 0.7
C10	74.0	76.1	70.1	- 6.0

^{a,b} Assignments may be interchanged.

Interestingly, the theoretical LORG calculations have C6 being shielded relative to its counterpart C3, C4 being shielded relative to C5, and finally C2 being shielded relative to C1. These are in agreement with previous discussion on enhanced partial negative charge built up at *para* and *ortho* carbons to O1. The calculations also predict that C8 and C9, being remote from the aromatic ring, will have a smaller shift difference relative to the large calculated 8.2 ppm shift difference between C7 and C10 with C7 the

more shielded of this pair. This is close to what experimentally has been observed. So, with more powerful computing capabilities becoming available, one can anticipate extension of studies on this nature to molecules of increasing complexity. At the present time, a collaborative project with the University of Utah is in progress involving "Slow Spinning Magic Angle Spinning NMR" experiment on powder **17**. This is a 2D experiment with the isotropic shift in one dimension and the spinning side band powder pattern in the other. This will provide the principle values of the shielding tensor for each carbon and will be helpful for the subsequent single crystal NMR experiment.

3.4.2 : ^{13}C solid phase of **19-d4**

The normal and the Dipolar Dephased ^{13}C CPMAS NMR of this crown ether are shown below :

Fig. 45 : Normal (a) and Dipolar Dephased (b) ^{13}C CPMAS NMR spectra of **19-d4** (* : spinning sidebands).

The six aromatic ^{13}C resonances in solid 17-d4 were collapsed to five in 19-d4 with low-field resonances at 157.7 and 147.5 ppm due to C1 and C2 respectively and two high-field peaks at 121.7 and 120.8 ppm due to C3,5, and 6. The C4 resonance is an asymmetric doublet, at 139.9 ppm, characteristic of a carbon bonded to the quadrupolar N atom.

The aliphatic region of ^{13}C CPMAS is similar to that of 17-d4. Methylene C7,10 resonances were found at 68.8 and 76.6 ppm while the resonances at 73.10 and 70.10 were assigned to C8 and C9 respectively.

The overall geometry of 19 is remarkably similar to that of 17. The most pronounced effect of the introduction of the 4- NO_2 group has been inducing a flattening effect in the C7-O1-C1-C2 and C7-O1-C1-C6 units (-0.9° and 179.0° respectively) so that there is essentially a planar conformation induced in the C7-O1-aryl geometry as shown below :

Fig. 46 : The resonance structure of 19.

3.4.3: ^{13}C and ^2H solid phase NMR of 18-d8

Among DB3nCn and B3nCn crown ethers, there are a few cases such as DB12C4;¹⁰⁰ DB30C10 and DB24C8;⁹³ DB15C5;⁹⁵ B15C5⁹³ and finally 17⁶¹ for which both ^{13}C CPMAS and X-ray crystal structures have been reported. The best known member of DB3nCn family is 18 whose X-ray structure was reported 24 years ago,⁶⁴ but no ^{13}C CPMAS analysis has been reported to date.

3.4.3.1 : ^{13}C Solid Phase

Some important torsional angles of 18¹⁰¹ and 17 are presented below:

Tab. 11 : Important torsional angles in 18 and 17.

Network I	$\text{C7-O1-C1-C2} = 174.1^\circ$	$\text{C10-O2-C2-C1} = 155.0^\circ$
Network II	$\text{C7-C8-O4-C9}' = 176^\circ$	$\text{C10-C9-O3-C8}' = 103.4^\circ$
Network III	$\text{O1-C7-C8-O4} = 164.3^\circ$	$\text{O2-C10-C9-O3} = 77.3^\circ$
17	$\text{C7-O1-C1-C2} = 10.5^\circ$	$\text{C10-O2-C2-C1} = 105.0^\circ$

Unlike 17-d4, there is not a big difference between the key torsional angles C7-O1-C1-C2 and C10-O2-C2-C1 in 18 (i.e. 174.1° vs 155.0°). Therefore one would expect to see considerable differences between the ^{13}C CPMAS spectra of 18-d8 and 17-d4.

Based on the X-ray data, one would expect to see 6 aromatic resonances in the ^{13}C powder spectrum if a real centre of symmetry was present and if no unusual crystal packing effects were present. However, the ^{13}C CPMAS of 18-d8 (Fig. 47) showed more resonances than expected for the aromatic carbons. These multiplicities could be due to one or both of the following facts : the absence of a real centre of symmetry, and the presence of intermolecular interactions resulting from crystal packing.

From the five sets of peaks in the CPMAS spectrum, two sets in the region 65.8-69.6 ppm are corresponding to the ether carbons, two sets 111-113 ppm and 118-121 ppm are due to the "CH" aromatic carbons, and the third set at ca. 148 ppm belongs to the tertiary aromatic carbons bearing oxygens.

A closer look at the aromatic region reveals that the high-field set (111-113 ppm) originates from the carbons *ortho* to the oxygens i.e. C3,6 while the other set (118-121 ppm) can be assigned to the remaining CH aromatic carbons i.e. C4,5. The reason why the *ortho* carbons are more shielded than *para* is presumably because of the existence of γ -steric repulsion between C7, C6 in one hand and C10, C3 in the other hand. This effect arises from the near coplanarity of C7,10 with the aromatic ring. However, the ca. 8 ppm gap between two sets of "CH" aromatic carbons may not be simply explained by steric repulsion and therefore the possibility of crystal packing effects is suggested.

The ^{13}C chemical shifts in three DB3nCn and two B3nCn crown ethers in the solid phase are collected in Tab. 12.

Fig. 47 : Normal (a), and Dipolar Dephased (b) ^{13}C CPMAS NMR spectra of 18-d_8 .

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Tab. 12 : ^{13}C chemical shifts^a and two torsional angles^b of some crown ethers in the solid phase.

	C1 C2	C5 C4	C3 C6	θ_1 θ_2	C7 C10
DB12C4	152.1 , 150.6	126.7 , 122.8	121.3 , 114.0	155.1 , 119.4 ^c	72.5 , 75.0
18-d4	148.3 , 147.4	121 - 118	113 - 111	174.1 , 155.0 ^d	66 - 70
DB24C8	149.5 , 149.5	119.7 , 119.7	119.7 , 119.7	174.6 , 172.3 ^e	68 - 74
B15C5	150.4 , 149.4	120.0 , 119.0	120.0 , 119.0	167 , 166 ^f	67 - 71
17-d4	151.4 , 149.1	125.0 , 122.3	127.7 , 119.5	10.5 , 105.0 ^d	68.5 , 76.2

^a Chemical shifts from TMS.

^b Torsional angles C7-O1-C1-C2 and C10-O2-C2-C1.

^c X-ray, Ref. 102.

^d The torsional angles are those of unlabelled 18 and 17.

^e X-ray, Ref. 103.

^f X-ray, Ref. 104.

In general, the chemical shift differences between each ipso (C1,2), ortho, and para couple are very dependent on the differences in torsional angles θ_1 and θ_2 . Upon shifting both the θ_1 and θ_2 values to 180° , the chemical shift differences move toward zero and all the aromatic carbon signals shift to higher field. The chemical shift difference between the ipso carbons C1 and C2 in 18-d8 is only 1 ppm while the corresponding value in 17 is 2.3 ppm. Due to the solid state conformation, the O1 lone pairs in 18 are in better conjugation with the aromatic ring than those of O2. Therefore C2 is shielded by ca. 1 ppm over C1.

A review of the chemical shift data (Tab. 12) reveals that every individual aromatic carbon in the 18-d8 system is shifted to a higher field in comparison to the corresponding carbon in 17-d4. The most shielded aromatic carbon (C6) in 18-d8 is at ca. 111 ppm while 119.5 ppm in 17-d4. The most deshielded aromatic CH resonance in 18-d8 is at ca. 121 ppm while 127.7 ppm in 17-d4. These two high-field shifts are caused by the two key torsional angles being close to 180° in 18-d8 since this increases the electron density in the benzene ring through : i) A better overlap of the oxygen lone pairs with the P orbitals of the benzene ring and ii) The more steric repulsion¹⁰⁵ between C7 and C6 on one hand and C10 and C3 on the other hand.

With respect to the methylene region of the ^{13}C powder spectrum (Fig. 47). The more shielded methylene peak remains intact in the Dipolar Dephased ^{13}C CPMAS spectrum, even without changes in intensity, while the intensity of the other part is considerably reduced. This reveals that the chemical shifts of C8 and C9 (being most remote methylene carbon from the benzene ring), are very close to each other at ca. 70 ppm. The CD_2 signals are clearly divided into two signals separated by 3.9 ppm; C10 at ca. 70 ppm and C7 at ca. 66 ppm. It is noted that this is still only half of the chemical shift difference, 7.7 ppm, observed for C7 and C10 in 17-d4.

It remains to distinguish C7 from C10 and to explain the chemical shift difference between C7 and C10 in contrast to negligible difference for C8 and C9. The first factor is the difference between torsional angles C7-O1-C1-C2 and C10-O2-C2-C1 (Tab. 11, network I). A quick inspection of the LORG calculation diagram of anisole (Fig. 44), shows that the shielding effect for CH_3 carbon increases about 1 ppm as the torsional angle moves from 155° to 174.1° . A steric shielding difference is suggested as another

source; C7 feels more steric shielding by C6 than C10 by C3. Another source of shielding C7 vs. C10 can be extracted from torsional angle differences as shown in the network II (Tab. 11). By submission of two torsional angles 176° and 103.4° for C7-C8-O4-C9' and C10-C9-O3-C8' respectively to the ab initio ^{13}C calculation on methyl ethyl ether[Buchanan,1992,1033](see App. II), one can verify that C7 should be more shielded than C10.

With respect to C8 and C9, it is interesting to note that based on the ab initio ^{13}C calculation on methyl ethyl ether and considering torsional angles in network II, both C8 and C9 are almost equally shielded. The only origin of any chemical shift difference between this carbon couple should result from the difference in O-C-C-O torsional angles 77.3° vs. 164.3° (Tab. 11, network III).

3.4.3.2 : ^2H Solid Phase NMR

As previously mentioned, a large-amplitude Molecular Merry-go Round motion exists in both solid 18-Crown-6 and its malononitrile complex.⁸¹ A logical question is whether such a motion also exists in **18**. So, ^2H NMR was performed on **18-d8** (Fig. 48) and it was found that the introduction of two benzene rings on the 18C6 cycle stops the molecular motion of 18-membered ring in **18**. This is concluded from the ^2H static line shape obtained for CD_2 group with $\Delta V_{xx} = 113.8$, $\Delta V_{yy} = 131.8$, $V_{zz} = 245.6$ KHz, quadrupole coupling constant $\kappa = 163.73$ KHz and asymmetry parameter $\eta = 0.0733$ (Fig. 48).

Fig. 48 : ²H NMR line shape of solid 18-d₈, static CD₂.

3.4.4 : ^{13}C Solid Phase NMR of 20-d4

A close correspondence between the solid phase (Fig. 49a) and LT solution ^{13}C NMR (Fig. 41) was observed. Thus, a starting point for the solid phase assignments is the set of solution assignments in the slow exchange limit [Buchanan, 1987, 4783]. The result of the Dipolar Dephasing ^{13}C CPMAS spectrum of 20-d4 (Fig. 49c) is consistent with this approach since the resonance at ca. 71 ppm, corresponding to C7 and C10, is the only signal observed. It is noted that the chemical shift difference between C7 and C10 at 210K (in solution) is less than 1 ppm. Interestingly, the shift difference between C8 and C9 in 20-d4 in solid phase is 3.8 ppm while 4.3 ppm in solution at 210K.

The relatively big difference between the ^{13}C chemical shifts of C8 and C9 both at solid phase and solution LT ^{13}C NMR in comparison with small difference for C7 and C10 is most likely due to the combination of two factors. i) The difference between torsional angles O3-C8-C7-O1 (-67.4°) and O3-C9-C10-O2 (78.0°) which results in some shielding of C8 vs. C9. ii) The substantial difference between C7-C8-O3-C9 (96.1°) and C10-C9-O3-C8 (127.7°) which deshields C9 by ca. 2 ppm (see ab initio ^{13}C calculations for ethylmethyl ether⁸⁰ and ethylene glycol⁸³ in Appendix II)

Fig. 49 : Normal ^{13}C CPMAS spectra of 20 (a), and 20- d_4 (b).
Dipolar Dephased (c) ^{13}C CPMAS NMR spectrum of 20- d_4 .

Chapter 4

²H Isotope Shifts" in B9C3, DB18C6, and CH9C3"

4.1 : Introduction

The effects of isotopic substitution on the magnetic shielding of nuclei^a have been known for a long time. In 1957, Tiers reported¹⁰⁶ that the ¹⁹F resonance in the CF₂D group of n-C₃F₇D was shifted upfield from that in n-C₃F₇H.

Isotopic substitution changes the dynamic state of a molecule. The modified vibrational and rotational motion of the molecule results in a change in the electronic structure and, hence, the magnetic shielding of the various nuclei.¹⁰⁷ Therefore isotope shifts (ⁱΔC_j)^b can be used as one of the useful probes in understanding of the origins of nuclear shielding.

One of the major problems in this field has always been rationalization of the observed ⁱΔC values.¹⁰⁸⁻¹¹⁰ We were interested to investigate the origins and the conformational dependence of these phenomena in crown ethers 17, 18, and 20.

Since the chemical shift is dependent on the solvent and concentration, the measurements were made on equimolar mixtures of labelled and unlabelled crown ethers

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^aThe expression "isotope shifts" is used for ²H isotope effects on the chemical shifts" throughout this thesis.

^bⁱΔC_j = δC_j(unlabelled) - δC_j(labelled). ⁱΔC_j is used to show the ¹³C chemical shift changes upon substitution of one or more hydrogen with its heavy isotope ²H, i being the number of intervening bonds between ²H and ¹³C. So, positive sign indicates upfield shift and negative sign indicates downfield shift throughout this thesis.

in a range of concentrations as well as in different solvents and average $^1\Delta_C$ values were calculated.

4.2 : Isotope Shifts at RT

The results of isotope shift measurements for **17** in CDCl_3 (at the range of 1.249-0.149 M) and in different solvents (at 0.694 M) by 50.3 MHz ^{13}C NMR are presented in Tables 13 and 14 respectively :

Table 13 : Isotope shifts^a (ppb) for **17** in CDCl_3 at different concentrations.

	1.249 M	0.971 M	0.694 M	0.140 M
$^1\Delta$	746	742	742	742
$^2\Delta$	141	140	140	139
$^3\Delta$	61	59	57	55

^a Uncertainties are ± 10 ppb.

Tab. 14 : Isotope shifts^a (± 10 ppb) for **17** in different solvents (0.694 M solutions).

	CDCl_3	CD_3COCD_3	C_6D_6
$^1\Delta$	742	784	746
$^2\Delta$	140	144	135
$^3\Delta$	57	63	60

^a Digital resolutions are 0.5 Hz/point.

These measurements were also performed for **18** and **20** in the same manner. For

the results of each experiments in these two cases see Appendix II. However, based on the results obtained, the average $^1\Delta_{\text{C}_j}$ values at RT are summarized in Tab. 15 :

Table 15 : Average¹ isotope shifts ($^1\Delta$)(ppb) for 17, 18, and 20 at RT².

	17		18		20	
	a	a'	b	b'	c	c'
$^1\Delta$	743±2	757±19	680±10	670±11	748±4	746±10
$^2\Delta$	140±1	140±4	125±2	118±6	145±2	145±3
$^3\Delta$	58±2	60±3	NR	NR	NR	NR

¹ The uncertainties are standard deviations.

² a, b, and c are the average values in CDCl_3 .

³ a', b', and c' are the averages obtained from different solvents (CDCl_3 , acetone-d6, and benzene-d6 for 17; CDCl_3 , CD_2Cl_2 , and DMSO-d6 for 18; and CDCl_3 , acetone-d6, and DMSO-d6 for 20).

⁴ NR denotes Not Resolved.

Substitution of ^2H at positions 7 and 10 induces i) upfield shifts for the methylene carbons C7 and C8 (i.e. positive $^1\Delta$ and $^2\Delta$) in all the cases and ii) an upfield shift for C1 (i.e. positive $^3\Delta$) in 17.

The largest $^1\Delta_{\text{C}_j}$ observed corresponds to carbons directly attached to deuteriums. Like all CD_2 carbons, C7 and C10 shift high field by more than 700 ppb because of the inductive effect^{111,112} of deuterium owing to the shorter C-D distance caused by a lower zero-point vibration energy¹¹³. The small differences between $^1\Delta$ values in the three systems under study most likely originate from two facts, the "*Hybridization*" and the "C-

D bond length".¹¹⁴ The increased electron density on C_α is partially induced to C_β , in saturated noncyclic systems, causing positive $^2\Delta$. However, the magnitude of $^2\Delta$'s are intensively decreased, relative to $^1\Delta$'s, to a range of 118-145 ppb. $^3\Delta$ is decreased to +60 ppb in 17 system while negligible for 18 and 20. Thus, the order of shielding effects is $^1\Delta > ^2\Delta > ^3\Delta$ at RT.

Inspection of the isotope shift values reveals that they are, in general, more dependent on the nature of the solvent rather than concentration. A logical way to demonstrate the *solvent dependence of isotope shifts*¹¹⁵ is *average $^1\Delta$ values*. The average $^1\Delta$ value in the 17 system at different concentrations in $CDCl_3$ is 743 ± 2 ppb while 757 ± 19 ppb in different solvents.

The major difference between the 17 system and two others is the positive $^3\Delta$. The line broadenings observed are assumed to be due to the small $^3\Delta$. To rationalize these differences, the mechanisms by which positive $^3\Delta$ occurs must be addressed.

One may propose "*Positive Hyperconjugation*",¹¹⁶ as the dominant mechanism for $^3\Delta$. If this was true, one would expect downfield shift (negative $^3\Delta$) for C1 because a C-D bond acts as a poorer electron donor than a C-H bond under the conditions of high electron demand in (+)Hyp.^{116,117} However, a negative $^3\Delta$ was not observed in any of the crown ethers studied indicating that this is not the dominant mechanism. The second possible mechanism is the simple through-bond inductive effect. Majerski, et.al.¹¹⁸ have used this rational to define the origin of positive $^3\Delta$ in a number of protoadamantanes. Although this might be a minor contributing factor, it is not the dominant mechanism since it is not a conformationally dependent mechanism.

"*Negative Hyperconjugation*", (-)Hyp.¹¹⁹ is deemed to be the main factor, with the

inductive effect as well as the Dipolar mechanism¹¹⁸, being minor factors contributing to the positive $^3\Delta$ in 17. (-)Hyp. in the 17 system is schematically shown below :

Fig. 50 : The negative hyperconjugation in 17 and 17-d4.

According to (-)Hyp., a C-D bond is a poorer electron acceptor than a C-H bond.^{117,120} Therefore less electron density is injected into the backbone of an anti C-D bond relative to a C-H bond by oxygen lone pairs. Therefore, the relatively greater positive charge on oxygens O1 and O2 in 17 is induced to the adjacent carbons C1 and C2 causing more deshielding. It is for this reason the C-D bond in 5,5-dimethyl- 1,3-dioxane-2-d1 (Fig. 51) prefers the equatorial position by about 50 cal/mol while this preference is just 6.3 cal/mol in Cyclohexane-d₁.¹¹²

Fig. 51 : Reverse Anomeric Effect in deuterated 5,5-dimethyl 1,3-dioxane.

In fact, the conformer **A2** is more stabilized by (-)Hyp. due to a greater interaction between an anti oxygen lone pair and *axial* H over that with *axial* D. Anet¹¹² has named this effect as the "*reverse anomeric effect*".

In order to find out why $^3\Delta$ in **17** is larger than in **18** and **20**, the i) availability of oxygen lone pairs in (-)Hyp. ii) conformational dependence of (-)Hyp., and iii) possible competition of (+)Hyp. with (-)Hyp. have to be considered. The complicating factor, here, is that $^1\Delta$ values at RT are average values due to the rapid conformational changes in the 9 and 18 membered crown rings hence there is no access to the individual values of each of three above factors. This complex situation doesn't exist in **20** at low temperature since the ring inversion is slow on the NMR time scale.

4.3 : Isotope shifts at 225K

The cis-cyclohexyl-9-crown-3 **20** system at 225K provides a unique chance to explore the origins of $^3\Delta$ since its X-ray data are available. The results of isotope shifts at 225K as well as RT are presented below :

Fig. 52 : $^1\Delta$ values (± 6 ppb) in **20** at 225K (bold values) and RT (in brackets)

The two substantially different isotope shifts for C1 and C2 at 225K (i.e. 140 and 62 ppb) confirm the angular dependency of $^3\Delta$. The (-)Hyp. in this system is shown below :

Fig. 53 : The scheme for negative hyperconjugation in **20**.

where stronger arrows indicate better electron donation, and therefore stronger (-)Hyp. This, in turn, requires that the both C10-H10A and C10-H10B bonds adopt more of an anti conformation with respect to the O2 lone pairs than the C7-H7A and C7-H7B bonds with respect to O1 lone pairs.

The Newman projections shown in Fig. 54 clearly show that the C10-H10B(D) bond is suitably aligned with one of the O2 lone pairs in an anti conformation while the C7-H7A(D) and C7-H7B(D) bonds are eclipsed with respect to the O1 lone pairs.

Fig. 54 : The Newman projection of C1-O1-C7-H vs. C2-O2-C10-H in **20**.

As has been discussed by Pross et.al.¹²⁰ a direct consequence of hyperconjugation is that the interacting C-H bonds are lengthened compared to those of a non-interacting C-H bonds. Thus, the longer C10-H10B bond (1.15 Å) vs. 1.03 Å for C10-H10A bond is supporting evidence for the postulated (-)Hyp.

The +60 ppb shielding for C1 might not be fully explained by (-)Hyp. since no suitable orientation was found in the H-C7-O1-LP network. The direct through-bond inductive shielding effect as well as dipolar mechanism might be other contributing mechanisms here.

The long range downfield shift Δ , is -17 ppb for C3 whereas 0 for C6. This is likely due to the steric repulsion effect.^{121,122} A comparison between dihedral angles C10-O2-C2-C3 and C7-O1-C1-C6 (117° vs. 161.1°) reveals that there is more steric repulsion between H10 hydrogens and H3 in comparison with that between H7 hydrogens and H6. X-ray data of **20** reveal that the distance between H7A and H6 is about 4.03 Å while 2.91 Å between H10A and H3. So, the chemical shift of C3 is sterically more sensitive than C6. The downfield shift of C3 in **20-d4**, relative to the corresponding carbon in **20**, most probably is caused by the reduction of the steric repulsion effect on C3 in **20-d4**.

Chapter 5

"Model Crown Ethers, Dicyclohexoxy-n-Oxaalkanes"

5.1 : Introduction

A new class of compounds, *Dicyclohexoxy-n-Oxaalkanes*, with the general structure depicted below are components of the conformationally isomeric dicyclohexano-3n-crown-n ether systems.

Fig. 55 : Chemical structure of the model crown ethers.

Since both simple and double ring inversion processes have been detected in these crown ethers,¹²³ it is of interest to investigate the temperature dependent dynamic NMR of the model compound **22** in solution to determine if it possesses any conformational equilibria detectable by NMR at low temperature. Additionally the equilibrium constant **K** and the free energy difference ΔG° between observed conformations may be amenable to measurement.

5.2 : Synthesis of 1,5-Dicyclohexoxy-3-oxapentane, 22

The model crown ether **22** was synthesized according to the following scheme :

Fig. 56 : Synthetic scheme of 22.

High resolution MS and elemental analysis were furnished in order to identify 22. No molecular ion was observed in MS spectrum. However, the result of elemental analysis was consistent with the formula $C_{16}H_{30}O_3$.

5.3 : The number of conformers of 22

The conformational equilibria in 22 may involve three conformers, namely equatorial-equatorial (major), axial-equatorial (minor) and axial-axial (minor) which are generated through the following interconversions. This assumes that all interconversions between preferred anti-diethylene glycol conformers are averaged on the NMR timescale even at 173K.

Fig. 57 : Three possible conformers of 22.

Fig. 58 : Temperature dependent ^{13}C NMR (100 MHz) spectra of 22 in CD_2Cl_2 .

The ee conformer is assumed to have the lowest free energy of any of three above conformers followed by ae and aa conformers, if one uses simple monosubstituted cyclohexanes as models. The introducing of the intervening diethylene glycol unit, however, may alter these preferences.

5.4 : Dynamic solution ^{13}C NMR study

The numbering scheme for **22** at 300K is as in Fig. 57 while temperature dependent solution ^{13}C NMR spectra, (100 MHz), are shown in Fig. 58. The observation of six ^{13}C resonances at 300K is consistent with a situation in which all conformational interconversions are rapid on the NMR timescale. Based on the known β , γ , and δ effect in monosubstituted cyclohexanes,^{87,90} the cyclohexane methylene peaks can easily be assigned. Assignment for the methylene carbons C5 and C6 are straightforward and follow from the ^{13}C spectral analysis of **21** as shown in Fig. 59 :

Fig. 59 : ^{13}C NMR spectra of **21** in CDCl_3 .

Methylene carbon C5 ($\delta=67.5$ ppm) is more shielded than C6 ($\delta=71.4$ ppm) in both **21** and **22** most probably because of the 2γ C's, from cyclohexane ring, for C5 in comparison with just one γ Carbon for C6.

As the temperature was lowered, each of the C1, C2, C3 cyclohexane resonances showed extensive broadening and finally split into doublets of relative intensity of about 16:1 at 210K as depicted in Fig. 58.

The multiplicity of cyclohexane carbon signals observed at 210K (Fig. 58) could be interpreted in two ways. The first, is a double ring inversion (*ee* $\rightleftharpoons$ *aa*) to a symmetric conformer, where only four cyclohexyl carbon resonances are expected for each conformer. The second more likely possibility, is a single ring inversion (*ee* $\rightleftharpoons$ *ae*) with the interconversion *ee* $\rightleftharpoons$ *aa* being negligible. In this case the four intense ^{13}C peaks must correspond to the three equatorially substituted rings of *ee* and *ae* conformers while the four weak peaks are due to the axially substituted ring of the *ae* conformer.

This interpretation demands that the resonances of the equatorially substituted ring of the *ae* conformer must be coincident with the lines of the major conformer *ee*. Such a result may not be surprising because the ^{13}C peaks of -OCH₂-CH₂- methylenes (C5 and C6) of **22** have not reached the coalescence temperature even at 210K which means that the resonances of C5' and C5'' as well as C6' and C6'' are very close to each other.

The ^{13}C assignments and the chemical shift differences ($\Delta\delta_{\text{Ci}}$) of cyclohexane carbons of **22** are presented in Tab. 16 and the $\Delta\delta_{\text{Ci}}$ values are compared to the corresponding values of methoxycyclohexane :

Tab. 16 : ^{13}C chemical shifts of 22 at 300 and 210K; and $\Delta\delta\text{Ci}^a$ (ee $\rightleftharpoons$ ae) of 22 and methoxycyclohexane.

T (K)		C1' , C1''	C2' , C2''	C3' , C3''	C4' , C4''
300	δCi	78.1	32.6	24.5	26.3
210	δCi	77.9 , 73.1	31.7 , 28.8	24.2 , 19.8	25.1 , 25.5
210	$\Delta\delta\text{Ci}$	4.8	2.9	4.4	-0.4
180	$\Delta\delta\text{Ci}^b$	4.8	3.3	4.4	-0.4

^a $\Delta\delta\text{Ci} = \delta\text{Ci}(\text{ee}) - \delta\text{Ci}(\text{ae})$, upfield shifts are positive.

^b For 20% methoxycyclohexane in CFCl_3 at 180K, Ref. 90.

The axial vs. equatorial substituent effect on the chemical shifts of cyclohexane carbons of 22 at 210K was found to be similar to methoxycyclohexane; i.e. high-field shifts in most of the cases.

If the minor conformation is indeed the unsymmetrical ae form, then the average relative intensities shown in Fig. 58 cannot be used in the calculation of the equilibrium parameters^a, K and $-\Delta G^\circ$. Such an average, in fact, is larger than the real K value by a factor close to two and needs to be corrected. The relative intensities for each pair of ^{13}C signals (i.e., C1' and C1'') and K values are collected in Tab. 17.

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^a $K = n_{\text{ee}} / n_{\text{ae}}$, where n_{ee} and n_{ae} are populations of the major (ee) and the minor (ae) conformers respectively. ΔG° is the free energy difference for the equilibrium ee $\rightleftharpoons$ ae (see the related dynamic process in Fig. 58).

Tab. 17 : The C_i'/C_i'' and K values for 22 at 210K.

	1', 1''	2', 2''	3', 3''	K
C_i'/C_i''	15.9	17.5	16.0	8.3 ± 0.3

The coalescence temperature for C4 is too low to permit a return to a slow exchange spectrum for this carbon at 210K, hence the relative C4 intensities are not included in average K calculation.

Since the intensity of a ^{13}C signal is dependent on a number of factors, especially T_1 and nOe, much care is required to obtain reliable equilibrium constants through ^{13}C measurements for the cyclohexane ring inversion process. The T_1 problem can be overcome by increasing the delay time to permit all the ^{13}C nuclei involved to fully relax. Although the nOe problem is removable by the suppressed nOe experiment, the intensity of the ^{13}C signals considerably decrease under such conditions, making detection of the minor conformer difficult. However, one way to circumvent the problem is to use ^1H NMR spectroscopy, although the extensive ^1H peak overlap may make this method inappropriate in some cases.

5.5 : Dynamic solution ^1H NMR study

The solution ^1H NMR (500 MHz) spectra at 304.1 and 205.5K are shown in Fig.60. The key point, in terms of K calculation, is finding the proper ^1H signals. The best peak here is the methine proton (CH) at 3.22 ppm (at 300K). This peak is split into two multiplet peaks at 205.5K. The axial CH is obviously observable at about 3.15 ppm

Fig. 60 : 500 MHz ¹H NMR spectra of **22** in CD₂Cl₂ at 304.1 (a) , and 205.5K (b).

while the equatorial one is hidden under the very intensive doublet ether protons centred at about 3.45 ppm.

That the axial CH is more shielded than equatorial CH has been recently¹²⁴ confirmed by the 210K ^1H NMR of the compound **23** as shown in Fig. 61.

Fig. 61 : Solution ^1H NMR (400 MHz) of **23** at 300 and 210K.

Therefore ^1H NMR of **22** does not aid in the solution of the present problem. Substitution of ether protons of **22** with ^2H would remove the problem of ^1H signal overlap and provide more reliable results.

Although no data have been reported for ring inversion in any other monosubstituted dicyclohexane system, it is of interest to compare the present results with those reported for *trans*-1,2-Cyclohexyl crown ether **24** shown in Fig. 62.¹²⁵

Fig. 62 : Cyclohexane ring inversion process in 24

The average $-\Delta G^\circ$ value for dicyclohexoxy 22 has been compared with the corresponding values, obtained via ^{13}C NMR, of 24 and methoxycyclohexane in Tab. 18 :

Tab. 18 : The $-\Delta G^\circ$ values for cyclohexane ring inversion in 22, 24 and methoxycyclohexane ($\text{CH}_3\text{O}-\text{CH}$).

	22 (CD_2Cl_2)	24 ^a (CD_2Cl_2)	$\text{CH}_3\text{O}-\text{CH}^b$ (CFCl_3)
$-\Delta G^\circ$	3.7 ± 0.1	6.2	3.1 ± 0.2

a : Ref. 125, b : Ref. 90.

The substitution of the methyl in methoxycyclohexane by a more bulky group $-\text{OCH}_2\text{CH}_2-\text{OCH}_2\text{CH}_2-\text{C}_6\text{H}_{13}$, increases $-\Delta G^\circ$ by about 0.6 kJ/mol. The reason $-\Delta G^\circ$ in the case of 24 is much greater than our findings for 22 is that in the aa conformer of 24, two axial substituents are bonded to one cyclohexane ring. It is also noted that some other factors such as crown ring constraint and the repulsion between two equatorial oxygens in ee conformer of 24 perturb the ring inversion equilibrium.

Further work in this area is needed to unambiguously prove that the minor conformer of **22** is indeed the *ae* form. Experiments to measure the conformational free energies ($-\Delta G^\circ$) for the series of molecules $C_6H_{13}-OCH_2CH_2-OR$, where R is CH_3 , Et and *n*-Pr. are in progress¹²⁴. If the present conclusions are correct, the $-\Delta G^\circ$ values for these substituents should increase as R increases in size and should all exceed the value for the CH_3 group.

Conclusions

Monomer 3 is not homopolymerizable either under the radical polymerization condition using benzene as solvent, AIBN as initiator, and 3 days heating at 70 °C or the anionic polymerization method at -70 °C using n-BuLi. This is most probably due to steric repulsion between adjacent 24-membered rings. The copolymerization of monomer 3 with styrene results in a copolymer with molecular weight of 16,000. The efficiency of this copolymer in extraction of Ra^{2+} (4 ng/l) from water into $CHCl_3$ is only 10%.

An intrinsic partial motion exists in the B24C8 derivatives in the solid phase as confirmed and evaluated by ^{13}C CPMAS and solid phase ^2H NMR. The motion is retarded upon complexation of 8 with K^+ . A phase change at about 0 °C occurs for 14 as first detected by ^2H NMR and confirmed by DSC experiments. This is attributed to the intermolecular hydrogen bonding between two carboxylic functional groups.

Selective incorporation of the ^2H isotope at the ethereal methylene carbons in 17, 18, 19, and 20 when coupled with COSY, NOESY, HETCOR, and DEPT experiments has proven to have an important role on the analysis of the complex ^1H and ^{13}C (solution and solid phase) spectra of the crown ethers 17, 18, 19, and 20. The chemical shifts of the crown ethers 17, 18, 19, and 20 are very sensitive to the conformation of their crown rings, and to the -O-C-C-O- and -C-O-C-C- torsion angles. When the crown ring size is large enough to allow the crown ring to adopt a trans-coplanar conformation, the similarity between solution and solid phase ^{13}C spectra is increased and the aromatic ^{13}C resonances shift upfield.

$^3\Delta$ isotope shifts in 17, 18, and 20 are dominated by negative hyperconjugation

when positions 7 and 7' are deuterated.

The model crown ether **22** shows a single cyclohexane ring inversion at 210K. The equilibrium constant (K) for $ee \rightleftharpoons ae$ in **22** is 8.3 ± 0.3 and ΔG° is 3.7 ± 0.1 kJ/mol.

Chapter 6

Experimental

6.1 - Synthesis

The general synthetic scheme and the codes for the key compounds are shown in Figures 63 and 64. Unless otherwise specified, all the starting materials used in this study were purchased from Aldrich, and used without further purifications, as follows:

1) 3,4-Dihydroxybenzaldehyde, 97%.	13) Lithium aluminium deuteride, 98 atom % D.
2) 2-Chloroethoxy ether, 99%, .	14) Ethyldiazoacetate.
3) Di., and Triethylene glycol, 99%.	15) Boron trifluoride etherate.
4) 1,2-Bis(2-Chloroethoxy) ether, 97%.	16) Triphenyl phosphate, 99%.
5) 2-(2-Chloroethoxy) ethanol, 99%.	17) Barium perchlorate, 99%.
6) Sodium hydride, 57%, (Alfa Inorganic Venton).	18) Sodium perchlorate, 99%.
7) 3,4- Dihydro-2H-pyran, 97%.	19) Sodium thiocyanate, 98%, Fluka.
8) p-toluenesulfonyl chloride, 99%.	20) Potassium thiocyanate, Fisher.
9) Thionyl chloride, 99%.	21) Sodium iodide, 99%.
10) Ethylene glycol-d ₄ , 97 atom % D.	22) Potassium iodide.
11) Ethylene glycol-d ₆ , 98% atom % D (MSD).	23) Catechol, 99%.
12) Silver(I) oxide, 99%.	24) Phenol.

Fig. 63 : General synthetic scheme for the molecules described in chapters 2, 3, 4, and 5.

Fig. 64 : Structures of the synthesized key compounds.

6.1.1 : 4-Formylbenzo-24-crown-8 ether; 2

Heptaethylene glycol

A 1 L round bottom 3-necked flask, equipped with a condenser and a dropping funnel, was charged with diethylene glycol(660.0g, 6.2 moles), crushed pellets of sodium hydroxide(80g, 2 moles) and heated to 110 °C while stirring under a nitrogen atmosphere for 2h until the most of the base was dissolved. 1,2 Bis (2-chloroethoxy)ethane(187.07g, 1 mole) was dropwise added to the mixture over the period of 2h keeping the temperature at about 120 °C. The reaction mixture was refluxed at 120 °C for 4h and then cooled to room temperature. The water produced was removed by evaporation at reduced pressure and the concentrated mixture, containing some solid, was diluted with CH₂Cl₂(200 mL) and the NaCl removed by filtration. The filtrate was dried over anhydrous Na₂SO₄, the CH₂Cl₂ removed by rotary evaporation, and finally fractional distillation was applied to purify the crude product. The fraction 240-250 °C at 0.7 mmHg was collected as pure liq. heptaethylene glycol and weighed to be 135.0g (41.4%).

¹³C NMR(CDCl₃), δ_c : 72.43, 70.30, 70.10, 61.27

CIMS : M+1 at 327 (100%), other peaks at 353 (22%), 283 (30%), 239 (55%), 177 (40%), 149 (100%), and 133 (83%).

1,20-dichloro-3,6,9,12,15,18-hexaoxadodecane; 1

Thionyl chloride(52.5 mL, 0.72 moles) was added dropwise over a period of 90 min. with stirring to cooled heptaethylene glycol(108.6 g, 0.33 moles) under nitrogen. The mixture was stirred at room temperature for 14 h, then refluxed for 26 h. The excess thionyl chloride was removed at reduced pressure, the residue was cooled and poured into ice(50 g) and then washed with CH₂Cl₂(3x100 mL). The combined extracts were washed

with saturated NaHCO_3 (3x20 mL), saturated NaCl (30 mL), water (2x30 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed by evaporation at reduced pressure and fractional distillation was applied on the viscous crude product. The fraction boiling at 190-200 °C at 0.4 mmHg (60 g, 50%) was collected as pure product.

^{13}C NMR(CDCl_3), δ_c : 71.28, 70.58, 70.53, 42.74 CIMS : M+1 at 363 (62%), other peaks at 195 (20%) and 149 (100%).

Heptaethylene glycol ditosylate

A 250 mL round bottom 2-necked flask equipped with a dropping funnel and a magnetic stirrer was charged with anhydrous pyridine (25 mL) and heptaethylene glycol (16.32g, 0.05 moles) and was stirred under nitrogen in an ice-water salt bath for 15 min. To this, tosyl chloride (20.97g, 0.11 moles) dissolved in anhydrous pyridine (100 mL) was dropwise added over a period of 45 min. The mixture was stirred for further 2h and subsequently was poured into a beaker containing ice (200 g) and was acidified by HCl (6M) to pH 2, then extracted with dichloromethane (3x150 mL). The combined extracts were washed with saturated NaHCO_3 (2x30 mL), saturated NaCl (20 mL), water (30 mL), and dried over anhydrous magnesium sulphate. The solvent was removed by evaporation at reduced pressure. The resulting oil (22 g) was then purified by flash chromatography on silica gel (grade 60, mesh 230-400) using dichloromethane/ethyl acetate (2:1) as eluent to get 20 g (63%) oily heptaethylene glycol ditosylate.

^{13}C NMR(CDCl_3), δ_c : 144.76, 132.87, 129.80, 127.82, 70.50, 70.43, 70.38, 70.33, 69.30, 68.46, 21.45 (methyl) .

^1H NMR(CDCl_3), δ_H 7.69(d, 4H), 7.24(d, 4H), 4.04(m, 4H) (-CH₂-OTS), 3.56-3.46(m,

24H)(O-CH₂-CH₂-O), 2.33(s, 6H)(methyl).

CIMS : M+1 at 635 (14%), other peaks at 547 (4%) and 149 (100).

4-formylbenzo-24-Crown-8 ether; 2

3,4-Dihydroxy benzaldehyde(2.35g, 0.017 moles) and 18-Crown-6 (0.1g, 0.0003 moles) were dissolved with stirring in anhydrous acetonitrile(500 mL) in a 1L round bottom 2-necked flask, equipped with a condenser under an N₂ atmosphere. K₂CO₃(7.05g, 0.051 moles) and **1** (6.20g, 0.017 moles) were added to the flask and the reaction mixture was refluxed for 5 days. Upon cooling, the mixture was filtered, the solvent was removed by rotary evaporation and finally the crude product was purified by column chromatography on silica gel(grade 60, 230-400 mesh). Elution with ethyl acetate yielded 3.6g (50%) light yellow oily **2**.

¹³C NMR(CDCl₃), δ_c : 191.2(CHO), 154.87, 149.57, 130.55, 127.13, 112.67, 111.92; 71.68, 71.54, 71.25, 71.19, 71.06, 69.95, 69.80, 69.64(O-CH₂-CH₂-O).

¹H NMR(CDCl₃), δ_H : 9.84(s, 1H, CHO), 7.45(d of d, 1H), 7.40(d, 1H), 6.98(d, 1H); 4.22(m, 4H), 3.94(m, 4H), 3.81(m, 4H), 3.73(m, 4H), 3.68(broad s, 8H), 3.65(broad s, 4H)(O-CH₂-CH₂-O).

CIMS : M+1 at 429 (100%), other peaks at 503 (6%) and 149 (100%).

6.1.2 : 4- Carboxybenzo-24-Crown-8 ether; 8

Ag₂O(5g, 0.022 moles) was dissolved in 500 mL NH₄OH(0.73 M) in a 1000 mL Erlenmayer flask covered by aluminium foil and stirred for 5 min. To this solution, **2** (5.0 g, 0.012 moles) dissolved in absolute ethanol(10 mL) was dropwise added. After 30 min.,

the mirror started to form. The mixture was stirred for 16h at room temperature, filtered, then washed with CH_2Cl_2 (6x50 mL). Evaporation of the solvent of the organic phase gave 1.5g of mostly unreacted starting aldehyde. The aqueous phase was acidified (pH=2), and washed with CH_2Cl_2 (4x100 mL). The combined extracts were dried over anhydrous MgSO_4 and the solvent was removed by rotary evaporation. The solid residue was kept under vacuum with gentle occasional warming to yield 3.0 g, (56.3%) **8**, mp 87-89 °C.

^{13}C NMR(CDCl_3), δ_c : 170.64(COOH), 153.74, 148.57, 124.95, 122.58, 115.27, 112.61; 71.52, 71.45, 71.13, 71.95, 71.13, 70.95, 70.35, 69.95, 69.79, 69.64, 69.41(O- CH_2 - CH_2 -O).

^1H NMR(CDCl_3) (400 MHz), δ_H : 11.3(broad s, 1H, COOH), 7.88(d of d, 1H), 7.61(d, 1H), 6.91(d, 1H); 4.24(m, 4H), 3.97(m, 4H), 3.83(m, 4H), 3.75(m, 4H), 3.71(broad s, 8H), 3.68(broad s, 4H)(O- CH_2 - CH_2 -O).

CPMAS δ_c : 173.77, 154.46, 148.42, 125.58, 118.88, 112.02, 111.11, 72.28, 71.81, 70.92, 68.11.

High resolution MS : m/z for $\text{C}_{21}\text{H}_{32}\text{O}_{10}$ (M^+), Calc.: 444.1996; Found: 444.1967(12.9%), other peaks at 180 (100%) and 165 (28%).

6.1.3 : 4- Vinylbenzo-24-Crown-8 ether, monomer 3

Triphenylmethyl phosphonium bromide

This compound was prepared by the method outlined in Vogel¹²⁶ as follows:

A dry 1 L stout-walled wide-necked glass bottle was charged with 99% benzene(60 mL), and triphenyl phosphine(0.25 moles, 69.4g) and was cooled in an ice-salt bath for 15 min. with stirring. To this, methyl bromide(2M in diethyl ether)(0.35 moles, 175 mL) was added and the bottle was sealed and removed from the ice-bath and left for one day. The

added and the bottle was sealed and removed from the ice-bath and left for one day. The white precipitate was filtered and washed with fresh cold benzene(20 mL) and kept under vacuum for 2h with occasional gentle warming to yield 86g (96%) triphenylmethyl phosphonium bromide.

To obtain the monomer **3**, a mixture of anhydrous 1,2-dimethoxyethane(250 mL), triphenylmethyl phosphonium bromide(0.016 moles, 5.71g), and sodium hydride(57% suspension)(0.016 moles, 0.67g) was heated at 65 °C in a dry 500-mL, three-necked round bottom flask, equipped with a magnetic stirrer, a condenser, and dropping funnel for 1h. The yellowish mixture was subsequently cooled to 40 °C. Then, dropwise addition of **2** (0.011 moles, 4.71g) dissolved in anhydrous 1,2-dimethoxyethane(50 mL) was carried out over a period of 10 min. The mixture was refluxed for 2h, then cooled, filtered, and the solvent was removed by rotary evaporation. The yellow-reddish residue oil was dissolved in dichloromethane(100 mL) and washed with water(2x30 mL) followed by saturated sodium chloride(30 mL), then dried over magnesium sulphate and the solvent was removed by evaporation at reduced pressure. The resulting oil was subsequently dissolved in hot n-hexane and left at room temperature overnight. The precipitate triphenylphosphine oxide (2g) was filtered, the solvent was removed by rotary evaporation, and the remaining oil was purified by flash chromatography on silica gel(grade 60, 230-400 mesh) using ethylacetate/dichloromethane(1:1) as eluent to yield 3.1 g (66%) oily **3**.

^{13}C NMR(CDCl_3), δ_c : 148.90, 136.32(vinyl methine), 131.26, 120.03, 114.04, 111.99(vinyl methylene), 111.86; 71.14, 70.91, 70.84, 70.73, 69.83, 69.38, 69.31(O-CH₂-CH₂-).

5.14(d, 1H), 4.18(m, 4H), 3.91(m, 4H), 3.79(m, 4H), 3.72(m, 4H), 3.68(broad s, 8H), 3.66(s, 4H).

High resolution MS : m/z for $C_{22}H_{34}O_8$ (M^+), Calc.: 426.2254; Found: 426.2192(5.3%), other peaks at 162 (100%), 100 (100%) and 143 (30%). Also, molecular ion with m/z 427 was observed by CI method.

6.1.4 : Copolymer 4

A one-necked flask, equipped with O-ring stopcocks, was charged with benzene(60 mL), monomer 3 (1.28g, 0.003 moles), styrene(2.31g, 0.022 moles), and azobis(isobutyronitrile)(AIBN)(0.01g, moles) and degassed using four freeze-pump-thaw cycles under high vacuum. The flask was sealed under vacuum and heated to 70 °C for 3 days, then cooled down to room temperature and the clear benzene solution was poured slowly into the n-hexane(500 mL) with vigorous stirring. Some sticky semisolid precipitated. The semisolid was filtered and reprecipitated by dissolving it in dichloromethane(4 mL) and pouring dropwise into the n-hexane(500 mL) to get 1.0 g white precipitate as 4.

^{13}C NMR(CDCl_3), δ_c : 145.6, 138-140, 128.0-128.9, 126.0, 120-121.0, 114.0-114.1 (aromatic); 71.0, 70.7, 70.2, 70.0, 69.7, 69.6 (O-CH₂-CH₂-); 42-46, 40.6 (CH, CH₂ benzylic) ppm.

^{13}C CPMAS NMR δ_c : Broad peaks at 140-150, 120-135, 67-75, 38-40 ppm.

^1H NMR (CDCl_3), δ_H : 6.1-7.1(aromatic, 20 H); 3.0-4.2(O-CH₂-CH₂-); 0.9-2.1(CH, CH₂ benzylic, 14H) ppm.

6.1.5 : Copolymers 6 and 7

2- (2-bromoethoxy) tetrahydro-2H-pyran

62.5g (0.50 moles, 41.9 mL) of 2-bromoethane was dissolved in 50 mL THF and cooled in an ice-bath. 50.1 mL of 3,4-dihydro-2H-pyran(46.2g, 0.54 moles) was added dropwise to it over 1h with stirring. The ice-bath was removed and the mixture was stirred overnight at room temperature, then the excess of 3,4-dihydro-2H-pyran and the solvent were removed by rotary evaporation. The residue was left under vacuum for 3h with gentle occasional warming and the residual oil was used for the next step without further purification.

^{13}C NMR (CDCl_3), δ_c : 99.4 (acetal), 68.1 ($\text{BrCH}_2\text{CH}_2\text{O-}$), 62.7 ($\text{BrCH}_2\text{-}$), 31.3, 30.9, 25.8, 19.7 ppm.

^1H NMR (CDCl_3), δ_H : 4.7 (acetal, 1H), 3.5-3.6 (broad m, 6H), 1.3-2.0 (m, 6H) ppm.

3,4-di[2-(2-tetrahydro-2H-pyranoxy)lethoxy benzaldehyde

3,4-dihydroxybenzaldehyde(27.6g, 0.2 moles), 18-crown-6(1.0g)(as catalyst), and all of the crude 2- (2-bromoethoxy) tetrahydro-2H-pyran obtained in the previous step were dissolved in acetone(700 mL). To this, K_2CO_3 (64.1g, 0.5 moles) was added and the mixture was refluxed for 60h, then cooled down to room temperature, filtered, and the solvent was removed by rotary evaporation to get 102g of a crude oil. The crude oil was purified by flash chromatography on silica gel(grade 60, mesh 230-400) to get 70g pure product.

^{13}C NMR(CDCl_3), δ_c : 191.16, 154.88, 149.67, 130.62, 126.93, 113.04, 112.57, 99.16, 68.98, 68.88, 65.93, 65.81, 62.24, 30.80, 25.77, 19.57 ppm.

^1H NMR(CDCl_3), δ_{H} : 9.87(s, 1H, -COH), 7.1-7.6(m, 3H, aromatic), 4.7(m, 2H), 3.5-4.5(m, 12H), 1.3-1.9(broad m, 12H) ppm.

Monomer 5: 3,4-di[2-(2-tetrahydro-2H-pyranoxy)]ethoxy styrene

A Wittig reaction was performed on 39.5g (0.1 moles) of 3,4-di[2-(2-tetrahydro-2H-pyranoxy)]ethoxy benzaldehyde using the same conditions as for 2 to get 42.16g (60%) of product.

^{13}C NMR(CDCl_3), δ_{C} : 149.57, 136.86, 131.83, 120.55, 115.14, 113.04, 112.31, 99.24, 69.30, 69.23, 66.32, 66.22, 62.31, 30.92, 25.87, 19.68 ppm.

^1H NMR(CDCl_3), δ_{H} : 6.81-6.98(m, 3H, aromatic), 6.5(dd, 1H), 5.5(d, 1H), 5.0(d, 1H), 4.6(broad s, 2H), 3.5-4.3(m, 12H), 1.3-1.9(broad m, 12H) ppm.

The copolymers 6 and 7 were synthesized via the same conditions as for copolymer 4 with the exception of taking 3.5g (0.009 moles) of monomer 5, 4.5g (0.043 moles, 4 mL) styrene, and 0.017g AIBN in 74 mL benzene. Fractional precipitation yielded two precipitates as copolymer 9 (0.1 g) and 10 (0.2 g).

copolymer 6 :

M.W = 47000; m.p = 55-63 °C; $n/n' = 12$ (n for styrene); ^1H NMR(CDCl_3), δ_{H} : 6.1-7.1(aromatic, 63 H), 4.7(broad s, acetal, 12H), 3.3-4.2(broad m, 12H), 0.9-2.1(broad m, 48 H) ppm; ^{13}C NMR(CDCl_3), δ_{C} : 145.2-145.7, 125.6-129.1, 125.5, 120.1, 115.0 (aromatic), 98.9(acetal), 68.5, 65.9, 61.8(-OCH₂CH₂O-), 44.0, 40.5(CH, CH₂ benzylic), 30.5, 25.5, 19.4(CH₂ of THP) ppm.

copolymer 7 :

M.W = 44000; m.p = 50-60 °C; $n/n' = 2$; ^{13}C NMR(CDCl_3): similar to that of copolymer

6; ^1H NMR(CDCl_3): similar to that of copolymer 6 but with different relative intensities as : δ_{H} : 6.1-7.1(13H), 4.7(2H), 3.3-4.2(12H), 0.9-2.1(21H) ppm.

6.1.6 : 4-carboxybenzo-24-Crown-8 ether(13, 13'-d4); 10

1,20-Dichloro-3,6,9,12,15,18-Hexaoxa-dodecane(10,11-d4); 9

A 500 mL round bottom 3-necked flask, equipped with a condenser and a dropping funnel, containing 250 mL tert-butanol was charged with a 57% suspension of sodium hydride (4.88g, 0.116 moles) at room temperature under a nitrogen atmosphere and stirred for 20 min. A mixture of ethylene glycol- d_6 (4.00g, 0.058 moles) and 1,2 bis (2-chloroethoxy)ethane(112.24g, 0.600 moles) was added dropwise to the flask over one min. and the reaction mixture was refluxed for 5 days. The solution was then cooled to room temperature, dissolved in water(200 mL) and extracted with CH_2Cl_2 (3x100 mL). The organic phase was dried over anhydrous Na_2SO_4 , the solvent removed by rotary evaporation, and finally fractional distillation was applied to purify the crude product. The fractions 180-210 C(0.5-0.7 mmHg) were collected and subsequently column chromatography on silica gel(grade 60,230-400 mesh) was applied to get 2.57 g (12.9%) pure liq. product.

^{13}C NMR(CDCl_3)(100.6 MHz), : 71.37, 70.70, 70.68, 70.61, 70.54, 69.74(quintet) 42.73.

CIMS : M+1 at 367 (42%), other peaks at 199 (82%), 151 (100%), and 107 (48%).

Deuterated crown ether 10, was synthesized in the same manner as for nondeuterated counterpart using 9, mp= 87-89 °C.

^{13}C NMR(CDCl_3)(100.6 MHz), δ_{C} : 170.86, 153.60, 148.41, 124.81, 122.32, 115.20, 112.51, 71.30, 71.22, 70.89, 70.87, 70.79, 70.77, 69.74, 69.58, 69.45, 69.21.

^1H NMR(CDCl_3)(400 MHz), δ_{H} : 11.12(broad, 1H), 7.71(d of d, 1H), 7.60(d, 1H), 6.90(d, 1H), 4.22(m, 4H), 3.93(m, 4H), 3.81(m, 4H), 3.72(m, 4H), 3.68(broad s, 8H).

High resolution MS : m/z for $\text{C}_4\text{H}_{28}\text{O}_{10}\text{D}_4$ (M^+), Calc.: 448.2247; Found: 448.2244(4.6%), other peaks at 180 (100%) and 143 (25%).

6.1.7 : 4-carboxybenzo-24-Crown-8 ether(11, 11'-d4); 14

1,2-Bis(ethyl acetoxy) ethane; 11

Ethylene glycol(3.1 g, 0.05 moles) and ethyldiazoacetate(10.5 mL, 0.10 moles) were dissolved in CH_2Cl_2 (spectral grade)(100 mL) and the solution was cooled in an ice-bath while stirring. Then, 3 drops of $\text{BF}_3\cdot\text{O}(\text{Et})_2$ as catalyst was added. An exothermic reaction occurred. The N_2 gas evolved was allowed to escape. Stirring was continued, for 30 min., until no further gas evolved. This was followed by the stirring at Room Temperature for 30 min. The solvent was removed by rotary evaporation and column chromatography on silica gel(grade 60, 230-400 mesh.) was applied on the 11.5 g crude product using 1:1 hexane:diethyl ether as eluant to get 8.0 g (68.4%) pure oily product.

$^1\text{H}(\text{CDCl}_3)$, δ_{H} : 4.21(quartet,4H), 4.16(s,4H), 3.78(s,4H), 1.29(triplet,6H)

$^{13}\text{C}(\text{CDCl}_3)$, δ_{C} : 170.33, 70.91, 68.63, 14.20.

CIMS : M+1 at 235 (100%), other peaks at 181 (38%), 147 (70%) and 131 (82%).

Triethylene glycol(1,8-d4)

For this reaction, the required glassware was dried in an oven at 110 °C overnight. Subsequently, a 1 L three necked round bottom flask charged with 500 mL anhydrous THF was equipped with a condenser, a strong magnetic stirrer and a dropping funnel. Then, anhydrous lithium aluminium deuteride (2.0 g,0.048 moles) was added to the flask

while the THF was being stirred vigorously under N_2 atmosphere. The flask was cooled by salt-ice bath and diester **11** (11.8 g, 0.050 moles) dissolved in 20 mL of anhydrous THF was added dropwise to the heterogenous reaction mixture over the period of 45 min. Two additional 50 mL aliquots of dry THF were added to the reaction mixture to reduce the viscosity. The ice bath was removed and the temperature was raised to room temperature followed by warming up to 40 °C. The mixture was stirred for 30 min. at 40 °C, then cooled. The excess of lithium aluminium deuteride was neutralized by slow addition of 1 mL of water. Dilute sulphuric acid (18 mL, 20%) was added dropwise to break down the complex formed. The clear upper layer was separated and added to the 300 mL THF resulting from washing the lower viscous slurry layer with fresh THF (3x50 mL). The solvent was removed by rotary evaporation, the resulting crude product was dissolved in water (50 mL) and washed with CH_2Cl_2 (20 mL). The water was removed by evaporation at reduced pressure and the residue was left under vacuum (3 h) with gentle occasional warming to yield 6.2 g (80%) Triethylene glycol(1,8-d4).

1,8-dichloro-3,6-dioxaoctane(1,8-d4): 12

A 100 mL three necked round bottom flask equipped with a condenser, a dropping funnel, N_2 inlet and a magnetic stirrer, was charged with triethylene glycol(1,8-d4)(6.0 g, 0.039 moles) and the flask was cooled in an ice-bath. Thionyl chloride(7.3 mL, 0.100 moles) was added dropwise over the period of 30 min. The temperature was raised up to reflux and the reaction mixture was left to be refluxed for 24 h. The excess of thionyl chloride was removed at reduced pressure and the residue was poured onto ice (15 g) and extracted with dichloromethane (3x50 mL). The combined organic extracts were washed

with saturated sodium bicarbonate (2x10 mL), saturated sodium chloride (1x20 mL), and water (2x20 mL), then dried over anhydrous sodium sulphate. The solvent was removed by evaporation at reduced pressure to obtain 5.92 g (80%) of a light yellow liquid 12.

^{13}C NMR(CDCl_3), δ_c : 71.19, 50.58, 40.27(quintet).

1,20-Dichloro-3,6,9,12,15,18-hexaoxo-dodecane(7,14-d4); 13

Compound 13 was synthesized similar to 1 using 12 as starting material.

^{13}C NMR(100 MHz)(CDCl_3), δ_c : 71.35, 70.68, 70.61, 70.51, 70.47, 69.91(quintet), 42.74.

CIMS : M+1 at 367 (88%), other peaks at 243 (28%), 197 (100%) and 153 (100).

Deuterated crown ether 14 was synthesized in the same manner as for nondeuterated counterpart using 13 as starting material.

^{13}C NMR(CDCl_3)(100.6 MHz), δ_c : 170.89, 153.46, 148.23, 124.72, 122.14, 114.92, 112.23, 71.27, 71.19, 70.80, 70.79, 70.76, 69.71, 69.56, 69.43, 69.18.

^1H NMR(CDCl_3)(400 MHz), δ_H : 11.10(broad, 1H), 7.72(d of d, 1H), 7.60(d, 1H), 6.90(d, 1H), 4.22(m, 4H), 3.94(m, 4H), 3.80(m, 4H), 3.77(m, 4H), 3.70(s, 4H), 3.67(s, 8H).

High resolution MS : m/z for $\text{C}_{21}\text{H}_{28}\text{O}_{10}\text{D}_4$ (M+), Calc.: 448.2247; Found: 448.2260(7.7%), other peaks at 180 (100%) and 119 (19%).

6.1.8 : $\text{Ba}(\text{ClO}_4)_2$, NaSCN, and KSCN Complexes of 8

Seven separate sample vials were charged with $\text{Ba}(\text{ClO}_4)_2$ (1.0008 g, 0.003 moles), NaSCN(0.243 g, 0.003 moles), KSCN(0.292 g, 0.003 moles), LiSCN(0.195 g, 0.003 moles), NaClO_4 (0.367 g, 0.003 moles), KI(0.498g, 0.003 moles) and NaI(0.450 g, 0.003 moles). The salts were dissolved in a minimum amount of absolute methanol via heating

in a water bath. To each of the sample vials, **8** (1.332 g, 0.003 moles) dissolved in ethyl acetate(2 mL) was added dropwise with stirring while heating, in the 50 °C water bath, and left aside at Room Temperature. The $\text{Ba}(\text{ClO}_4)_2$ complex precipitated after 12h while KSCN and NaSCN complexes formed after 3 days. The precipitates were filtered off, washed with dichloromethane(5 mL), and dried under vacuum to get :

0.7 g (30%) light yellowish solid of $\text{Ba}(\text{ClO}_4)_2$ complex, mp : 245-250 °C.

Recrystallization from CH_3OH gave 0.3 g of $\text{Ba}(\text{ClO}_4)_2$ complex, mp : 260-263 °C.

0.4 g (26%) NaSCN complex, mp: 140-150 °C. Recrystallization failed in this case.

0.5 g (37%) KSCN complex, mp: 107-110 °C.

$\text{Ba}(\text{ClO}_4)_2$ complex of **8** :

^{13}C NMR($\text{DMSO}-d_6$)(100.6 MHz), δ_c : 167.09, 152.32, 147.76, 123.51 123.37, 114.32, 112.69 (aromatics); 70.31, 70.26, 70.04, 70.00, 69.03, 68.90, 68.79, 68.61 (O- CH_2 - CH_2 -) ppm.

^1H NMR($\text{DMSO}-d_6$)(400 MHz), δ_H : 7.55(dd, 1H), 7.46(d, 1H), 7.05(d, 1H) (aromatic); 4.17(m, 4H), 4.13(m, 2H), 3.78(m, 4H), 3.64(m, 4H), 3.57(m), 3.53(s), 3.52(s) (O- CH_2 - CH_2 -) ppm.

FAB MS : m/z, 681.1 (100%) and 1125.4 (19.5%) for 1:1 ($\text{C}_{21}\text{H}_{32}\text{O}_{14}\text{BaCl}$) and 2:1 ($\text{C}_{42}\text{H}_{64}\text{O}_{24}\text{BaCl}$) complexes respectively, other peaks at 581.1 (27.0%) and 427.2 (44.3%).

NaSCN complex of **8** :

^{13}C NMR($\text{DMSO}-d_6$), δ_c : 167.0, 152.2, 147.6, 123.5, 123.1, 114.1, 112.5 (aromatic); 70.2, 69.9(broad), 68.9, 68.8, 68.6, 68.5 (O- CH_2 - CH_2 -) ppm.

^1H NMR(DMSO- d_6), δ_{H} : 7.6(d, 1H), 7.5(s, 1H), 7.1(d, 1H) (aromatic); 4.2(m, 4H), 3.8(m, 4H), 3.4-3.6(broad m, 20H) (O-CH₂-CH₂-) ppm.

FAB MS : m/z, 467.2 (100%) and 911.4 (5.5%) for 1:1 (C₂₁H₃₂O₁₀Na) and 2:1 (C₄₂H₆₄O₂₀Na) complexes respectively, other peaks at 577.2 (40%) and 427.3 (42.3%).

KSCN complex of 8 :

^{13}C NMR(DMSO- d_6)(100.6 MHz), δ_{C} : 166.9, 152.2, 147.6, 123.2 123.4, 114.6, 112.9 (aromatic); 69.7, 69.6, 69.5, 69.4, 68.7, 68.6, 68.5, 68.2 (O-CH₂-CH₂-) ppm.

^1H NMR(DMSO- d_6)(400 MHz), δ_{H} : 7.57(dd, 1H), 7.50(d, 1H), 7.09(d, 1H) (aromatic); 4.20(m, 2H), 4.16(m, 2H), 3.80(m, 4H), 3.64(m, 4H), 3.58(m), 3.56(s), 3.55(s), 3.54(s), 3.49(m) (O-CH₂-CH₂-) ppm.

FAB MS : M⁺, 483.3 (100%) and 927.5 (13.6%) for 1:1 (C₂₁H₃₂O₁₀K) and 2:1 (C₄₂H₆₄O₂₀K) complexes respectively, other peaks at 522.2 (26%) and 965.5 (7.7%).

6.1.9 : B9C3-d4, DB18C6-d8, and 4-NO₂-B9C3; 17-d4, 18-d8, and 19-d4.

Diglycolic acid methyl ester, 15

17.4 g (0.13 moles) of diglycolic acid was dissolved in 100 mL absolute methanol and 22 mL (0.30 moles) thionyl chloride was added dropwise over the period of 10 min. while the solution was being stirred by a magnetic stirrer. The reaction is strongly exothermic and care should be taken to prevent explosion. The solvent was then removed by rotary evaporation. The resulting viscous liquid turned to a semi-solid upon standing. The crude product was used for the next step without further purification. yield: 20.84 g, 98%.

^{13}C NMR(CDCl_3), δ_c : 170.16, 68.05, 52.33.

Diethylene glycol(1,5-d4)

This compound was synthesized via a procedure identical to that for triethylene glycol-d4, yield : 11.9 g (95%).

^{13}C NMR(CDCl_3), δ_c : 72.2, 60.6(q).

1,5-dichloro-3-oxapentane(1,5-d4); 16

Diethylene glycol(1,5-d4) was chlorinated via the same procedure as for triethylene glycol(1,8-d4) to obtain 12.3 g, 76% **16**.

^{13}C NMR, δ_c : 71.1, 42.1(quintet).

To obtain **17-d4** and **18-d8**, a 2-L round bottom flask equipped with a condenser and a magnetic bar was charged with water (1700 mL), catechol (16.3 g, 148 mmol), and lithium hydroxide (12.42 g, 296 mmol) and stirred for 5 min. The deuterated **16** (21.7 g, 148 mmol) was added to the mixture, brought to reflux and left for 86 h at 110 °C. The mixture was acidified to pH=2 with dilute sulphuric acid and extracted with dichloromethane (3x200 mL). The combined organics were washed with sodium hydroxide (5%, 3x100 mL), water (3x100 mL), and saturated sodium chloride (1x100 mL), then dried over anhydrous sodium sulphate. The solvent was removed by evaporation at reduced pressure and the resultant reddish slurry was purified by column chromatography on silica gel (grade 60, 230-400 mesh) with mixture of dichloromethane and diethyl ether (50:50) to yield 10g, 33% **17-d4**; mp 69-71 °C.

^{13}C NMR, δ_c : 151.46, 124.04, 122.95, 73.43(q, $-\text{CD}_2-$), 72.30. ^1H NMR(CDCl_3), δ_H : 6.9-

7.0(m, 4H)(aromatic), 3.9(s, 4H, $-\text{CH}_2-$) ppm.

^{13}C CPMAS NMR, δ_c : 151.4, 149.0(tert. aromatic); 127.7, 125.0, 122.3, 119.5(aromatic methine); 76.2(broad m, $-\text{CD}_2-$); 73.3; 70.7; 68.5(broad m, $-\text{CD}_2-$) ppm.

High resolution MS : m/z for $\text{C}_{10}\text{H}_8\text{O}_3\text{D}_4$ (M^+), Calc.: 184.1038; Found: 184.1047(100%), other peaks at 138 (75%), 122 (62%), and 80 (55%).

18-d8 : yield: 1 g, 1.6%; mp 162.5-164 °C. ^{13}C NMR, δ_c : 148.80, 121.27, 113.46, 69.82, 68.08(q, $-\text{CD}_2-$). ^1H NMR(CDCl_3), δ_H : 6.88(s, 8H)(aromatic); 4.02(s, 8H, $-\text{CH}_2-$) ppm.

^{13}C CPMAS NMR, δ_c : 148.29, 147.43 (tert. aromatic); 120.85, 111.14 (aromatic CH); 69.66(broad), 65.82(d) ($-\text{OCH}_2\text{CD}_2-$) ppm.

High resolution MS : m/z for $\text{C}_{20}\text{H}_{16}\text{O}_6\text{D}_8$ (M^+), Calc.: 368.2075; Found: 368.2080(87.1%), other peaks at 184 (12%), 138 (100%) and 122 (75%).

To synthesize 19-d4, the method reported for 6-nitrodibenzo-18C6 by W.M. Fiegenbaum[W.M. Fiegenbaum 1970] was closely followed.

Initially, 3.3g (0.0179 moles) of 17-d4 was dissolved in a mixture of CH_2Cl_2 (70 ml) and glacial CH_3COOH (50 ml) and one drop 96% H_2SO_4 was added with stirring. To this solution was added 70% HNO_3 (8 ml) and the mixture was stirred at room temperature for 15 min. followed by refluxing for 3h. The reaction mixture was cooled and the acidic solution was neutralized by addition of Na_2CO_3 while keeping the mixture cool in an ice bath. The solution was then extracted with CH_2Cl_2 , backwashed with saturated NaHCO_3 and H_2O , dried over MgSO_4 and rotary evaporated. A yellow crude solid was obtained which, upon recrystallization from absolute EtOH yielded 2.4g (58%) pure 19-d4; mp 93.5-95 °C.

^{13}C NMR(CDCl_3), δ_c : 157.01, 150.28, 142.41, 121.83, 120.08, 119.90, 74.47(q, $-\text{CD}_2-$), 72.46, 71.38, 71.07(q, $-\text{CD}_2-$). ^1H NMR(CDCl_3), δ_H : 7.88(d, 1H), 7.85(dd, 1H), 6.99(d, 1H), 3.91(s, 2H), 3.89(s, 2H).

^{13}C CPMAS NMR δ_c : 157.67, 147.51, 139.90, 121.72, 120.91, 76.63, 73.05, 70.05, and 68.82.

High resolution MS : m/z for $\text{C}_{10}\text{H}_7\text{O}_5\text{N}_1\text{D}_4$ (M^+), Calc.: 229.0888; Found: 229.0926(100%), other peaks at 267 (25%), 183 (95%), and 143 (51%).

6.1.10 : Cis-Cyclohexyl-9-Crown-3(d4); 20-d4

17-d4 (1 g, 4 mmol) was dissolved in methanol (40 mL), acetic acid (0.5 mL) and 50% rhodium on alumina catalyst (0.2 g) were added to the solution and the hydrogenation was performed with use of American Instrument Co. 50,000 psi maximum pressure high pressure apparatus at 40 °C under 5 atm. pressure of hydrogen for 6 h. The mixture was filtered, then the solvent was removed at reduced pressure. The crude product was dissolved in 100 mL CH_2Cl_2 and washed with saturated sodium chloride (2x10 mL), and water (20 mL). After drying over anhydrous sodium sulphate, the solvent was removed by evaporation at reduced pressure. The resultant viscous oil was purified by recrystallization from n-hexane to yield 0.8 g, 80% 20-d4; mp 41-42.5 °C.

^{13}C NMR(CDCl_3), δ_c : 78.88, 75.63, 70.10(q), 28.95, 22.00.

^1H NMR(CDCl_3), δ_H : 3.92(s, 2H), 3.86(s, 2H), 3.67(d, 2H), 1.3-1.8(m, 8H) ppm.

^{13}C CPMAS NMR δ_c , δ_c : 82.05, 78.44, 76.59, 74.68, 70.88, 30.00, 28.28, 25.73, 19.49 ppm.

High resolution MS : m/z for $\text{C}_{10}\text{H}_{14}\text{O}_3\text{D}_4$ (M^+), Calc.: 190.1507; Found: 190.1527(100%),

other peaks at 146 (42%) and 119 (78%).

6.1.11 : B9C3, DB18C6, 4-NO₂-B9C3, CH9C3; 17, 18, 19, and 20

These four crown ethers were synthesised via exactly the same procedure as described for deuterated analogues using nondeuterated reagents.

17 : mp = 68-70 °C. ¹³C NMR(CDCl₃), δ_c : 151.4, 123.9, 122.8, 74.0, 72.3 ppm. ¹H NMR(CDCl₃), δ_H : 6.9-7.1(m, 4H, aromatic); 4.3(m, 4H), 3.8(m, 4H) (-OCH₂CH₂O-) ppm.

18 : mp = 162.164 °C. ¹³C NMR(CDCl₃), δ_c : 148.5, 121.5, 114.0(aromatic); 70.1, 69.0 (-OCH₂CH₂O-) ppm. ¹H NMR(CDCl₃), δ_H : 6.93(s), 6.89(s) (8H, aromatic); 4.16(m, 8H), 4.05(m, 8H) (-OCH₂CH₂O-) ppm.

19 : mp = 93-95 °C. ¹³C NMR(CDCl₃), δ_c : 157.3, 150.6, 142.6, 122.1, 120.3, 120.1, 75.4, 72.8, 72.0, 71.7. ¹H NMR(CDCl₃), δ_H : 7.90(d, 1H), 7.86(dd, 1H) 7.01(d, 1H), 4.65(m, 2H), 4.31(m, 2H), 3.92(m, 4H).

20 : mp = 40-42 °C. ¹³C NMR(CDCl₃), δ_c : 79.0(methine CH); 75.8, 70.8 (-OCH₂CH₂O-); 28.9, 22.0 (cyclohexane -CH₂-) ppm. ¹H NMR(CDCl₃), δ_H : 3.92(s, 2H), 3.86(s, 2H), 3.67(d, 2H), 1.3-1.8(m, 8H, cyclohexane -CH₂-).

6.1.12 : 5-cyclohexoxy-3-oxapentane 1-ol

5-phenoxy-3-oxapentane 1-ol, 21

A 200 mL round bottom flask was charged with phenol (1.9 g , 0.02 moles) , NaOH (0.8 g, 0.02 moles), and water (100 mL) and stirred for 5 min. at Room Temperature followed by addition of 5-chloro-3-oxapentane-1-ol (2.5 g, 0.02 moles). The mixture was refluxed for 3 days. Upon cooling, the mixture was extracted with CH₂Cl₂ (3x30 mL) and the combined extracts were dried over anhydrous MgSO₄. The solvent was removed by rotary evaporation and the yellowish crude product was purified by column

chromatography on silica gel (grade 60, 230-400 mesh) using CH_2Cl_2 as eluant to yield 1.2g; 32% 5-phenoxy-3-oxapentane-1-ol.

^{13}C NMR(CDCl_3), δ_c : 158.61, 129.45, 120.97, 114.57, 72.68, 69.59, 67.25, 61.62.

5-cyclohexoxy-3-oxapentane-1-ol

5-phenoxy-3-oxapentane-1-ol was hydrogenated under conditions similar to B9C3 to obtain **21** with 44% yield.

^{13}C NMR(CD_2Cl_2), δ_c : 78.14, 72.61, 70.79, 67.29, 61.78, 32.13, 25.73, 24.14.

6.1.13 : 1,5-dicyclohexyloxy-3-oxapentane; 22

1,5-diphenoxy-3-oxapentane

A 200 mL round bottom flask was charged with phenol (3.76 g , 0.04 moles) , anhydrous THF (100 mL), and a 57% suspension of sodium hydride (0.84 g , 0.02 moles). This was stirred for 15 min. at room temperature followed by addition of 1,5-dichloro-3-oxapentane (1.43g , 0.01 moles) and the mixture was refluxed for 3 days. Upon cooling, the mixture was filtered and the solvent was removed by evaporation at reduced pressure. The residue was dissolved in 100 mL CH_2Cl_2 and treated with 5% NaOH (3x50 mL). The yellowish crude product was purified by column chromatography on silica gel (grade 60, 230-400 mesh) using CH_2Cl_2 as eluent to yield 2.06g (80%) 1,5-diphenoxy-3-oxapentane, mp 65-66 °C (lit.¹²⁷ 66 °C).

^{13}C NMR(CDCl_3), δ_c : 158.69, 129.39, 120.86, 114.60, 69.92, 67.32.

To obtain **22**, 1,5-diphenoxy-3-oxapentane was hydrogenated under conditions similar to **17** in 88% yield.

^{13}C NMR(CD_2Cl_2), δ_c : 78.13, 71.36, 67.50, 32.63, 26.26, 24.53.

High resolution MS : no molecular ion was observed.

CIMS : M+1 at 271 (70%), other peaks at 189 (92%) and 107 (100%).

Anal. Calc. for $\text{C}_{16}\text{H}_{30}\text{O}_3$: C, 71.07; H, 11.18. Found : C, 70.39; H, 10.87.

6.2 : NMR

The solution ^{13}C spectra were recorded on Varian Gemini XL-200, Bruker AMX-400, and AMX-500 spectrometers at 50.3, 100.6, and 125.8 MHz respectively. The concentrations of the samples for the normal 50.3 MHz ^{13}C and 200 MHz ^1H spectra were approximately 0.2 and 0.1M in CDCl_3 respectively. TMS was used as internal reference in 5 mm o.d. tubes. Routinely ^{13}C spectra were obtained with complete ^1H noise decoupling. Normal operating conditions for ^{13}C at 50.3 MHz were as follows : pulse width 16 μs (90°), and 30K data points with a repetition rate of 1.0 s. The number of accumulations for the low temperature spectra was typically 1000-2000 and the temperatures were calibrated using a copper-constantin thermocouple in a dummy NMR tube.

Normal operating conditions for the ^{13}C and ^1H spectra, at 100.6 and 400.1 MHz, were : pulse widths 6 and 7 μs (90°) with 32 and 30K data points respectively.

^1H NMR spectra of 8, 10, and 14 (Fig. 31) were recorded at 400 MHz using acquisition time 2.7s with 30K data points and the Line Broadening of 0.12 Hz while the corresponding ^{13}C NMR spectra (Fig. 30) were obtained at 100.3 MHz under the conditions of : acquisition time 12.9s, LB 0.013 Hz, and 65K data points.

^{13}C spin-lattice relaxation times (T_1) were determined at 50.3 MHz via the inversion recovery method,¹²⁸ (i.e. 180° pulse followed by 90° pulse after suitable recovery time), with typical delay times, τ , of 0.01, 0.02, 0.03, 0.04, 0.06, 0.08, 0.09, 0.10, 0.3, 0.5, 3.0, and 5.0 s. The standard XL-200 software was employed to process the data obtained. The 0.25 M solutions of **8** in CDCl_3 and DMSO-d_6 as well as 0.25 M of **8**/potassium complex in DMSO-d_6 were degassed by bubbling with helium gas before use.

The $\{^1\text{H}\}^{13}\text{C}$ nOe experiment was performed on a 0.5 M CDCl_3 solution of **8** at 50.3 MHz using delay time of 6 s and 6000 accumulations.

The Room Temperature isotope shifts ($^1\Delta\text{C}_j$) measurements for **17**, **18**, and **20** were conducted at 50.3 MHz (with digital resolution of 0.5 Hz/point) by using equimolar mixtures of deuterated and nondeuterated crown ethers under two conditions : a) in different solvents CD_2Cl_2 , CDCl_3 , acetone- d_6 , C_6D_6 , and DMSO-d_6 b) at different level of concentration in the range of 0.35-1.249 M, in CDCl_3 . The 225K isotope shifts ($^1\Delta\text{C}_j$) measurements for **20** were also performed at 100.6 MHz (with digital resolution of 0.6 Hz/point) using a 0.175M sample in CD_2Cl_2 . In order to determine the signs of the $^1\Delta\text{C}_j$ values, at least one nonequimolar mixture of labelled and unlabelled was tested in each case.

The dynamic NMR study for the model crown ether **22** was carried out from 300 to 210K by both ^1H (at 500 MHz) and ^{13}C (at 100 MHz) to measure the equilibrium constant **K**. The experiment was performed on a 0.3 M CD_2Cl_2 solution sample using 2 and 3 μs pulses respectively and a delay time of 2s.

The ^{13}C CPMAS spectra were recorded at either 45.3 MHz on a Bruker CXP-180 or at 50.3 MHz MSL-200 spectrometers. Cross Polarization times were typically 2-3 ms,

with the radio frequency field amplitude 60 KHz and sweep width 20 KHz. Satisfactory of S/N ratios were obtained after a maximum of 400 spectral accumulations. Magic-angle spinning rates of ca. 3 KHz were obtained with use of Kel-F spinners of the Andrew-Beams type. Chemical shifts were measured relative to the external solid hexamethylbenzene (HMB) and converted to the TMS scale via the factor of 16.9 ppm, which is the chemical shift of the methyl group of HMB. Other parameters for some of the samples were as follow:

17-d4 by 45.3 MHz : delay time 100s and pulse width ^{13}C 3 μs .

19-d4 by 50.3 MHz : delay time 80s and pulse width ^{13}C 4 μs .

Copolymer 4 by 45.3 MHz : delay time 2s, pulse width 5 ms, and data points 0.6K.

10 and 14 by 50.3 MHz : delay time 1.6s and pulse width ^{13}C 4 μs .

8/ K^+ complex by 45.3 MHz : delay time 4s, pulse width ^{13}C 5 μs , and data points 1K.

The ^2H NMR powder spectra were recorded either on Bruker CXP 180 spectrometer at 27.63 MHz (for 18-d8), or on Bruker AMX 300 at 46.1 MHz (for 10, and 14) at various temperatures using a variable temperature N_2 gas-flow probe with a Bruker B-VT-1000 temperature controller. A phase alternated quadruple echo pulse sequence¹²⁹ was used with a delay time of 35 μs between X and Y pulses of 2.6-3.0 μs in all cases.

6.3 : MS, GPC, IR, and DSC

The MS spectra of all intermediate compounds were recorded on a VG 7070E Mass Spectrometer by either electron impact at 70 eV, 6 kV accelerating; or chemical

ionization using diethyl ether as the reagent gas. The Fast Atomic Bombardment(FAB) method was applied for Ba^{2+} , K^+ , and Na^+ complexes using Cs^+ as reference. For the new compounds, the high resolution MS on a KRATOS CONCEPT II H with the resolution of 8000 and Ionization of 70 eV was scanned by 10 sec./dec, and ac voltage 8kV using perfluorokerosene(PFK) as reference.

The molecular weights of copolymers synthesized was measured on a Waters GPC using 0.4%(g weight) solution of copolymers in spectral grade THF. Both U.V(269 nm) and differential refractometer indices were used as detector.

The solution IR spectra were recorded on Perkin Elmer 1600 Series FT-IR spectrometer using 0.25 M solutions of **8** in solvents CDCl_3 and DMSO-d_6 in 250 μL cells.

Carbonyl stretching in CDCl_3 : 1685.9 cm^{-1}

Carbonyl stretching in DMSO-d_6 : 1692.8 cm^{-1}

The DSC plots were recorded on a Seiko SSC5200 differential scanning calorimetry with a heating rate of 10°C per minute from -50 to 110°C and a Nitrogen flow rate of 50 mL per minute. The cooling rate was 5°C per minute. Sample **14** was analyzed in crimped aluminium sample pan with an aluminium + lid as reference. The samples were kept under vacuum, while gently heating, for one hour to remove any trace of solvents left. 5.7 mg of **14** was used in two trials to perform phase change measurements.

APPENDIX I

Spectra

Appendix I contains solution ^1H and ^{13}C NMR; solid phase ^{13}C NMR; IR; MS; and GPC spectra. The codes H, C, S, and D are defined as follows :

- H   400 MHz solution ^1H NMR spectra.
- C   100.6 MHz solution ^{13}C NMR spectra.
- S   45.3 MHz Solid Phase CPMAS ^{13}C spectra.
- D   45.3 MHz Dipolar Dephased ^{13}C spectra.

The rest of the solution ^1H , and ^{13}C spectra were recorded at 200 and 50.3 MHz respectively, TMS used as an internal reference.

List of spectra :

- ^1H and ^{13}C solution NMR and MS of 3.
- ^1H and ^{13}C solution NMR and GPC of copolymer 4.
- ^1H and ^{13}C solution NMR and GPC of copolymer 6.
- Solution IR (CDCl_3 , and DMSO-d_6) of 8.
- ^{13}C solution NMR and MS of 4.
- ^1H and ^{13}C solution NMR, MS, and ^{13}C CPMAS NMR of 10.
- ^1H and ^{13}C solution NMR of 12.
- ^{13}C solution NMR and MS of 13.
- ^1H and ^{13}C solution NMR, MS, and ^{13}C CPMAS NMR of 14.
- ^1H and ^{13}C solution NMR, and MS of 8/ $\text{Ba}(\text{ClO}_4)_2$ complex.
- ^1H and ^{13}C solution NMR, and MS of 8/ NaSCN complex.
- ^1H and ^{13}C solution NMR, and MS of 8/ KSCN complex.
- 210K HETCOR, and COSY of 19.
- 210K HETCOR, and COSY of 20.
- 210K HETCOR, and COSY of 20-d4.
- 210K ^{13}C ^1H (^3J)HETCOR and NOESY of 20.
- ^{13}C solution NMR of 21 and its unlabelled counterpart.

4-Vinylbenzo-24-crown-8 ether

4-Vinylbenzo-24-crown-8 ether/Styrene copolymer

GPC Plot

SOLUTION IR SPECTRA OF 8

1,20-dichloro-3,6,9,12,15,18-hexaoxadodecane (10,11-d₄) 142

4-Carboxybenzo-24-crown-8 ether (13,13'-d₄)

72636 Scan 46 RT=11.28 100%=126932 mv 21 Jul 93 9:37
HRP +EI

4-Carboxybenzo-24-crown-8 ether (13,13'-d₄)

1,8-Dichloro-3,6-dioxaoctane ($1,8-d_4$)

4-Carboxybenzo-24-crown-8 ether (11,11'-d₄)

7/25/93 Scan 11 RT=2:38 100%=1529% mv 16 Jun 93 14:22
HRP +EI 207

4-Carboxybenzo-24-crown-8 ether (11,11'-d₄)

712415 Scan 16 RT=3.30 100%=58372 mv 14 May 93 8:37
LRP +FAB 169

4-Carboxybenzo-24-crown-8 ether /NaSCN complex

712400 Scan 3 RT=0.39 100%=143566 mv 7 May 93 8:54
LRP +FAB 156

HETCOR **7 10** **COSY**

^{13}C NMR

APPENDIX II

Appendix II contains the following:

- 1)   **LORG of methyl ethyl ether and ethylene glycol.**
- 2)   **ORTEP of 17, 19, and 20.**
- 4)   **Six tables containing ^2H isotope shifts of 17, 18, and 20 at different solvents and a range of concentrations.**

LORG θ vs. C1, C3, C4 Shifts of EtOMe θ vs. ^{13}C Shift of Ethylene Glycol

* absolute scale (CH_4 , 221 ppm); TMS appears at ca. 119 ppm

Isotope shifts^{a,b} (ppb) of B9C3 in CDCl₃ at different concentrations.

δC_i	Conc. Crown	1.249 M	0.971 M	0.694 M	0.140 M
δC_1	B9C3	151.397	151.407	151.490	151.421
	B9C3-d4	151.336	151.348	151.433	151.366
	³ Δ	061	059	057	055
δC_4	B9C3	123.880	123.886	123.996	123.477
	B9C3-d4	123.880	123.886	123.996	123.477
	⁴ Δ	0	0	0	0
δC_3	B9C3	122.823	122.843	122.926	122.876
	B9C3-d4	122.823	122.843	122.926	122.876
	⁵ Δ	0	0	0	0
δC_7	B9C3	73.976	74.026	74.113	74.121
	B9C3-d4	73.230	73.284	73.371	73.379
	¹ Δ	746	742	742	742
δC_8	B9C3	72.263	72.308	72.393	72.376
	B9C3-d4	72.122	72.168	72.253	72.237
	² Δ	141	140	140	139

^a $\Delta C_i = \delta C_i(\text{B9C3}) - \delta C_i(\text{B9C3-d4})$, i being the number of intervening bonds between ²H and ¹³C. All ¹ Δ 's in ppb.

^b δ is the chemical shift with respect to the TMS as an internal reference.

Isotope shifts of B9C3 in different solvents (0.694M).

δC_i	Solv. Crown	$CDCl_3$	CD_3COCD_3	C_6D_6
δC_1	B9C3	151.490	152.460	151.938
	B9C3-d4	151.433	152.397	151.882
	$^3\Delta$	057	063	060
δC_4	B9C3	123.996	123.470	123.326
	B9C3-d4	123.996	123.470	123.326
	$^4\Delta$	0	0	0
δC_3	B9C3	122.926	123.470	123.326
	B9C3-d4	122.926	123.470	123.326
	$^5\Delta$	0	0	0
δC_7	B9C3	74.113	74.354	74.063
	B9C3-d4	73.371	73.570	73.317
	$^1\Delta$	742	784	746
C_8	B9C3	72.393	72.864	71.974
	B9C3-d4	72.253	72.720	71.839
	$^2\Delta$	140	144	135

Isotope shifts of DB18C6 in CDCl_3 at various concentrations.

δC_i	Conc. Crown	0.140 M	0.070 M	0.035 M
δC_1	DB18C6	148.954	148.908	148.452
	DB18C6-d8	148.954	148.908	148.452
	$^3\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_3	DB18C6	114.028	113.984	113.987
	DB18C6-d8	114.028	113.984	113.987
	$^4\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_4	DB18C6	121.452	121.393	121.446
	DB18C6-d8	121.452	121.393	121.446
	$^5\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_7	DB18C6	69.030	68.986	69.012
	DB18C6-d8	68.349	68.294	68.345
	$^1\Delta$	<u>681</u>	<u>692</u>	<u>667</u>
δC_8	DB18C6	70.081	70.037	70.090
	DB18C6-d8	69.954	69.914	69.964
	$^2\Delta$	<u>127</u>	<u>123</u>	<u>126</u>

Isotope shifts of DB18C6 in different solvents at concentration 0.035 M.

δC_i	Solv. Crown,	$CDCl_3$	CD_2Cl_2	CD_3SOCD_3
δC_1	DB18C6	148.452	149.077	147.880
	DB18C6-d8	148.452	149.077	147.880
	$^3\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_3	DB18C6	113.987	113.219	112.303
	DB18C6-d8	113.987	113.219	113.303
	$^4\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_4	DB18C6	121.446	121.315	112.589
	DB18C6-d8	121.446	121.315	112.589
	$^5\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_7	DB18C6	69.012	68.579	67.485
	DB18C6-d8	68.345	67.894	66.826
	$^1\Delta$	<u>667</u>	<u>685</u>	<u>659</u>
δC_8	DB18C6	70.090	70.213	68.844
	DB18C6-d8	69.964	70.094	68.731
	$^2\Delta$	<u>126</u>	<u>114</u>	<u>113</u>

Isotope shifts of CH9C3 in different solvents (0.402M) at RT.

δC_i	Solv. Crown	$CDCl_3$	CD_3COCD_3	CD_3SOCD_3
δC_1	CH9C3	78.975	79.306	78.157
	CH9C3-d4	78.975	79.306	78.157
	$^3\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_3	CH9C3	28.911	29.572	28.689
	CH9C3-d4	28.911	29.572	28.689
	$^4\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_4	CH9C3	21.969	22.632	21.778
	CH9C3-d4	21.969	22.632	21.778
	$^5\Delta$	<u>0</u>	<u>0</u>	<u>0</u>
δC_7	CH9C3	70.838	71.205	71.147
	CH9C3-d4	70.073	70.473	69.396
	$^1\Delta$	<u>755</u>	<u>732</u>	<u>751</u>
δC_8	CH9C3	75.810	76.029	75.064
	CH9C3-d4	75.668	75.885	74.914
	$^2\Delta$	<u>142</u>	<u>144</u>	<u>150</u>

Isotope shifts of CH9C3 in CDCl₃ at various concentrations at RT.

δC_i	Conc. Crown	0.941 M	0.671 M	0.402 M	0.134 M
δC_1	CH9C3	78.871	78.871	78.975	78.903
	CH9C3-d4	78.871	78.871	78.975	78.903
	³ Δ	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
δC_3	CH9C3	28.877	28.861	28.911	28.857
	CH9C3-d4	28.877	28.861	28.911	28.857
	⁴ Δ	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
δC_4	CH9C3	21.928	21.924	21.969	21.909
	CH9C3-d4	21.928	21.924	21.969	21.909
	⁵ Δ	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
δC_7	CH9C3	70.751	70.747	70.838	70.751
	CH9C3-d4	70.005	70.003	70.073	70.003
	¹ Δ	<u>746</u>	<u>744</u>	<u>755</u>	<u>748</u>
δC_8	CH9C3	75.700	75.700	75.810	75.719
	CH9C3-d4	75.555	75.555	75.668	75.573
	² Δ	<u>145</u>	<u>145</u>	<u>142</u>	<u>146</u>

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