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**Conformational Analysis of
Some Model Crown Ethers
and Analogues via
 ^1H and ^{13}C NMR Spectroscopy and
X-Ray Crystallography**

by

Mark Reynolds

B.Sc. (Hons.) Carleton University, 1992

***A Thesis Submitted to the Faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
Master of Science***

***Department of Chemistry
Carleton University
Ottawa, Ontario
November, 1994***

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"Conformational Analysis of Some Model Crown Ethers and
Analogues via ^1H and ^{13}C NMR Spectroscopy and
X-Ray Crystallography"

Submitted by Mark Reynolds
in partial fulfilment of the requirements for the
degree of Master of Science

A handwritten signature in dark ink, appearing to read 'G.W. Buchanan', written over a horizontal line.

Dr. G.W. Buchanan
Supervisor

A handwritten signature in dark ink, appearing to read 'James E. Wright', written over a horizontal line.

Chairman
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Abstract

In Part I, four symmetric dicyclohexyl ethylene glycol analogues were synthesized. It has been determined by 100.3 MHz ^{13}C NMR spectroscopy at 210 K that these molecules show a single ring inversion with a conformational free energy of ca. 5.3 kJ/mol in CD_2Cl_2 . To confirm the single ring inversion hypothesis (as opposed to a simultaneous double ring inversion), monocyclic analogues were synthesized. These molecules have conformational free energies of ca. 6.2 kJ/mol in CD_2Cl_2 . In the solvents CD_3OD and CS_2 , the monocyclic molecules have a slightly lower conformational free energy. This is attributed to solvation of the sidechain which increases the population of axial conformers.

In Part II, the structures of dibenzo 15-crown-4 and its sodium iodide complex have been determined via X-ray crystallography. The solution state ^{13}C and ^1H NMR spectra have been assigned unambiguously by HETCOR and NOESY techniques. The sodium iodide complex is a dimer with C_i symmetry. This novel dimerization takes place via bonding of an ethereal oxygen atom to the sodium cation of the adjacent macrocycle, to produce a coordination number of six. The ^{13}C CP/MAS NMR spectra of these materials are discussed in terms of the observed

solid state conformations.

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Introduction

Crown Ethers

Macrocyclic polyethers were first synthesized by Pederson in 1967.¹⁻

⁴ These molecules were termed "crown ethers" since they resemble a crown in shape(Fig. 1).

Figure 1: Crown Structure of 15-Crown-5

Twenty years later, Lehn, Cram, and Pederson received the Nobel Prize for their work in this field. Crown ethers(Fig. 2) have the ability to encapsulate other molecules or atoms. Crown ethers are cyclical molecules, typically comprised of repeating $\text{CH}_2\text{-CH}_2\text{-O}$ units. The electron rich oxygen atoms have the ability to chelate cations and some molecules. Typically, an alkali metal^{5,6}, or transition metal^{7,8} is

encapsulated. Lanthanides^{9,10} may also be guest species. Crown ethers can also chelate with the solvent¹¹, anions¹² or neutral¹³ species. As a result, crown ethers are very useful for solubilization of inorganic salts in an organic medium, and often act as effective phase transfer catalysts.

Figure 2: Various Crown Ethers

a

b

c

d

The chelation strength of a crown ether depends upon two main criteria. The first criterion is the type of heteroatom involved. If the hard oxygen atom is replaced by the softer sulphur(Fig. 2a) or nitrogen heteroatom, complexation with a softer metal will be more likely^{14,15}. Secondly, the size of the cavity is important. Usually, if the cavity size is about the same size as the diameter of the guest(Fig. 3), favourable chelation will occur¹⁶. The favourable wrapping of a crown around a cation is used synthetically. When synthesizing dibenzo 18-crown-6(Fig. 2b), a potassium salt is used as the base. This creates a template effect¹⁷ which biases the reaction to the formation of the crown.

Figure 3: Size of Some Model Crown Ethers and Some Cations

A large guest combined with a smaller host can result in 2:1 (crown:guest) complexes¹⁸⁻²⁰, and small guests in a large host can result in 1:2 complexes²¹⁻²³(Fig. 2c). However, this is not true for all cases. Dibenzo 30-crown-10, which has a much larger cavity than the potassium cation diameter, makes a very stable 1:1 complex²⁴(Fig. 2d). The crown ether wraps itself around the cation in a way that resembles a tennis ball seam.

Over the years, many new crown ether analogues have been synthesized(Fig. 4). A polyether band was strapped across a crown ether and the cryptand²⁵(Fig 4a) was born. A plethora of host molecules were synthesized--such as the spherands²⁶(Fig. 4b), polymeric crowns²⁷(Fig. 4c), and chiral crowns²⁸(Fig. 4d). Recently crown ethers have been used in the fascinating field of self assembly^{29,30}(Fig. 4e).

Figure 4: Some Crown Ether Analogues

Conformational analysis of crown ethers is an area of interesting and copious research. With powerful methods such as nuclear magnetic resonance(NMR) and X-ray crystallography, chemists can now look at how a crown ether complexes a guest. Additionally, one can observe the changes in the conformation of the molecule upon complexation³¹. The flexible O-C-C-O units of a crown ether tend to have specific geometries. The O-C-C-O torsion angle tends to be gauche, whereas the C-C-O-C torsion angle tends to be anti³²⁻³⁴. The O-C-C-O torsion network is approximately 1.7 kJ/mol more stable in the gauche conformer compared to the anti conformer³⁵.

Nuclear Magnetic Resonance^{36,37,38}

Nuclear magnetic resonance(NMR) has been a valuable tool for structure elucidation since its inception^{39,40}. NMR is a spectroscopic method which involves excitation and relaxation of the nuclear spin of an atom. The atom must have a spin quantum number(where $I \neq 0$) for resonance to occur. These are atoms that do not have both an even atomic number and mass number. Consequently, this technique does not work for such nuclei as ^{16}O and ^{12}C .

NMR is a relatively new technique discovered in 1945 independently by two groups. Bloch, Hansen and Packard from Stanford University detected a signal from the protons of water³⁹. Purcell, Torrey and Pound observed the proton signal from paraffin wax⁴⁰. Seven years later Bloch and Purcell were jointly awarded the Nobel Prize.

When active NMR nuclei are placed in a magnetic field, each nuclear spin has $(2I+1)$ possible orientations. The letter I is used to represent the spin quantum number. The nuclear magnetic moment(μ) is directly proportional to the spin I :

$$1) \quad \mu = \gamma I h / 2\pi$$

where h is Planck's constant, and γ is the gyromagnetic ratio. The gyromagnetic ratio is a constant for a given nucleus.

The energy of a nucleus with a magnetic moment in a static magnetic field(B) is:

$$2) \quad E = -\mu B$$

Therefore,

$$3) \quad E = -\gamma h / 2\pi (IB)$$

It is important to realize that this is an energy level(Fig. 5), since I has more than one orientation. For example, a nucleus with a spin of $3/2$ has

the orientations(m_I) of $+3/2$, $+1/2$, $-1/2$ and $-3/2$ which can be determined by

$$-I, -I+1, \dots, I-1, I.$$

It can be easily obtained that the difference in energy between the levels(ΔE) is:

$$\Delta E = \gamma h B / 2\pi$$

Additionally, $\Delta E = h\nu$ defines the frequency of radiation(ν) for a transition to occur, therefore:

$$\nu = \gamma B / 2\pi$$

At this frequency, nuclear magnetic resonance occurs. The radiation frequency is in the radiowave region.

Figure 5: Energy Levels of a Nucleus in a Magnetic Field

NMR is not a sensitive spectroscopic method such as infrared(IR) spectroscopy. This is due to the fact that only a small excess of nuclei are in the lower state. This can be seen by the Boltzmann distribution:

$$7) \quad N_{\beta}/N_{\alpha} = \exp(-h\nu/kT) \quad \text{but since } h\nu \ll kT$$

$$8) \quad \approx 1 - h\nu/kT$$

At thermal equilibrium, and $h\nu = 4.2 \times 10^{-2}$ J (radiofrequency region), this results in the lower state having an excess population of only 1 in 10^5 .

In a magnetic field, the nuclei will precess around the direction of the field with a frequency ω , which is known as the Larmor frequency (Fig. 6). If an observer was at the Larmor frequency looking at the precessing nuclei, then the net number of nuclei in the lower spin state would be a single vector aligned in the same direction as the magnetic field. This mnemonic is known as the rotating frame of reference (Fig. 7). If an alternate pulse of radiofrequency at the Larmor frequency is applied perpendicular to the field (along x axis), then the nuclei will precess around the x-axis. When the irradiation is stopped, the nuclei will start to precess around the bulk magnetic vector. This is known as relaxation.

There are two relaxation processes. The first is spin lattice relaxation (T_1 process). This process is a transfer of energy from the nuclei

to the surrounding environment. Relaxation is finite, and occurs exponentially.

9)
$$M_{y'(t)} = M_{y'(0)} \exp(-t/T_1)$$

After a time $5T_1$ the magnetization left along the y' axis will be 0.007

$M_{y'(0)}$ which is virtually zero.

Figure 6: Larmor Frequency of a Nucleus in a Magnetic Field

Figure 7: The Rotating Frame of Reference

The second relaxation process is spin-spin relaxation, known as T_2 . There is no net change of energy in the system for T_2 relaxation. After the pulse is applied, the spins transfer energy to one another. This causes some to precess at slightly different frequencies. The result is that the spins fan out in the x,y plane (Fig. 8). When all the spins are aligned along the Z axis there will be no spins in the x,y plane.

Figure 8: T_2 Relaxation Process

For a ^{13}C NMR spectrum with ^1H decoupling, it is observed that the carbon resonance will have an increased intensity compared to a spectrum with no proton decoupling. This increase in intensity is known as the nuclear Overhauser enhancement (nOe). Clearly, an enhancement in signal must be due to an enhancement in population difference. At equilibrium, it has been shown that:

$$n_\beta/n_\alpha = \exp(-h\nu/kT) \quad \text{but since } h\nu \ll kT$$

$$\approx 1 - h\nu/kT = 1 - \Delta E/kT = 1 - \gamma h B_0 / 2\pi kT$$

so, 10)
$$n_\alpha^\circ - n_\beta^\circ = (N/2)(\gamma h B_0 / 2\pi kT)$$

Therefore for two different spins, A and B, at equilibrium in the same magnetic field and with the same numbers of spins, the different magnetizations is given by:

11)
$$M_A^\circ / M_B^\circ = \gamma_A / \gamma_B$$

If we were to perturb this system, and allow one spin to absorb radiofrequency energy, how will it relax and what effect will this have on the relative populations? It can be determined that the new equilibrium value for nucleus A (^{13}C) when nucleus B (^1H) is decoupled is:

12)
$$\rho(M_A - M_A^\circ) = \sigma M_A^\circ \gamma_B / \gamma_A$$

Rearranging,

$$13) \quad M_A/M_A^0 = 1 + (\sigma/\rho)(\gamma_B/\gamma_A) = 1 + \eta$$

where σ and ρ are different relaxation pathways and η is the nOe. The ratio of σ to ρ is usually 0.5 therefore:

$$14) \quad \eta = 0.5\gamma_B/\gamma_A$$

It can be easily seen that the nOe for ^{13}C NMR spectrum while the ^1H nuclei are decoupled is 2.987 (equation 13), assuming a complete dominance of dipole-dipole relaxation.

Continuous wave (CW) spectroscopy is an absorption technique. The radiofrequency pulse starts at a low (or high) frequency, and slowly changes frequency to high (or low). When the radiofrequency sweep approaches the Larmor frequency of a nucleus, the nucleus absorbs the radiation and resonates, resulting in a signal. Since different protons have different Larmor frequencies, a genuine spectral pattern is generated for each different molecule. CW NMR spectroscopy is now an obsolete method of acquiring NMR spectra. The new method is Fourier transform (FT) NMR.

FT NMR is an emission technique. All the nuclei are excited simultaneously with one pulse. The nuclei begin to relax to equilibrium at

their respective Larmor frequencies. The receiver picks up an exponentially decaying signal(due to T_1 relaxation) with a beat pattern. This is known as the free induction decay(FID). The beat pattern is recorded in a time domain, and by a Fourier transform technique, is transferred into a frequency domain. If the beat pattern has a difference of $0.016\text{s}(62\text{Hz})$, then there will be two signals 62 Hz apart from each other in the NMR spectrum(Fig. 9)!! The nuclei can be excited again, and the process repeated. Signal averaging permits addition of the FID's together until a sufficiently high signal to noise ratio is obtained in the NMR spectrum.

Figure 9: Free Induction Decay of Cyclohexene

Solid State NMR^{36,37,38}

Additional asymmetry may exist in the solid state, and it is for this reason that solid state NMR is a useful technique. Solid state NMR is a powerful method for complementing X-ray crystallographic structures. Solid state NMR differs from solution state NMR in three main areas. The three problems that must be surmounted are:

- i) Dipolar interactions
- ii) Chemical shift anisotropy
- iii) long T_1 times

Dipole-dipole interactions will broaden the line shape of a signal. Since the ^{13}C is only 1.1 % abundant, dipolar interactions for organic molecules are usually limited to ^{13}C - ^1H nuclei. A powerful pulse is applied at the resonance frequency of the protons and this reduces that magnetic moment of the protons to zero. To do this very powerful decouplers are needed--on the order of 100 W. In solution rapid tumbling of the molecule eliminates these interactions.

Since the nuclei are static(in most cases) in the solid state, identical nuclei will be oriented in a different relation to the magnetic field when in powder form. Specific nuclei will have a range of chemical shifts because

of this. For example, a carbonyl carbon will have a different chemical shift if it is aligned with the magnetic field, or perpendicular to it (Fig. 10).

Figure 10: Chemical Shifts of a Static Carbonyl Carbon in a Magnetic Field

The difference in chemical shift (δ) depends upon the angle of the bond with the magnetic field (θ) and the distance (R) between the anisotropic bond and the observed nucleus:

$$\Delta\delta = \Delta\chi(3\cos^2\theta - 1)/R^3$$

$\Delta\chi$ is the magnetic susceptibility difference between parallel and perpendicular orientations. Note that in the solution state, the molecule is tumbling rapidly therefore the chemical shift anisotropy averages out to zero. The chemical shift anisotropy can also have a value of zero when the term $(3\cos^2\theta - 1)$ equals zero. This is true when $\theta = 54.73^\circ$. This angle

is known as the magic angle (Fig. 11), and the process to eliminate chemical shift anisotropy in the solid state is known as magic angle spinning (MAS). In Fig. 11, rapid spinning averages the vectors 1,2 and 3,4 along the magic angle. The vectors represent the same bond at two different times in space. The sample must be spun at a frequency comparable to the frequency range of the observed nucleus at the magic angle if the term is to be reduced to zero. This means the rate of spinning is in the kHz range. This results in the practical limit of spectrometer size (in MHz) for solid state ^{13}C NMR spectroscopy.

Figure 11: Magic Angle Spinning

Due to long T_1 times, even with high power decoupling and MAS, experimental acquisition of a ^{13}C spectrum would take a long time. With the arrival of cross polarization(CP), a solid state spectrum now takes much less time to acquire. Cross polarization is a pulse technique(Fig. 12) which transfers energy from an abundant nucleus(^1H) to a rare nucleus(^{13}C). This is done by spin locking the spins so the Hartmann-Hahn condition is fulfilled:

$$\gamma_{\text{H}}B_{\text{H}} = \gamma_{\text{C}}B_{\text{C}}$$

During the spin lock phase, magnetization from the proton nucleus transfers magnetization to the carbon nuclei. Since the ^1H are much more abundant than ^{13}C nucleus, only a small net loss of magnetization is observed for ^1H and a large gain magnetization for ^{13}C nuclei. The protons are irradiated to eliminate dipolar interactions as the ^{13}C FID is acquired.

Figure 12: Cross Polarization Pulse Technique

A solid state spectrum must have all of the three above techniques if a high resolution spectrum is to be obtained(Fig.13).

Figure 13: Solid State Spectra with High Power Decoupling, Magic Angle Spinning, and Cross Polarization

- a) static spectrum b) only dipolar decoupling
 c) only magic angle spinning(MAS) d) dipolar coupling and MAS
 e) dipolar decoupling, MAS and cross polarization(CP) pulse technique

Dipolar Dephasing

The dipolar-dipolar interaction between ^{13}C and ^1H is inversely proportional to the cube of the distance between the nuclei. Dipolar dephasing is an effective technique to elucidate quaternary carbons in a spectrum. If the power decoupling is turned off for a short time ($40\mu\text{s}$) before acquisition, all carbons attached to protons will broaden out due to dipolar coupling and will be lost in the baseline. The decoupler is then switched on for the purpose of collecting the data. However, if there is motion for all or part of the molecule in the solid state, then the rapid tumbling will eliminate the dipolar effects for those nuclei. The final result is that quaternary carbons and carbons with motion are observed in a ^{13}C dipolar dephased spectrum.

Part I

Synthesis and Mechanism of Ring Inversion for Dicyclohexyl-n-Ethylene Glycols

Introduction

Recently, a new class of molecules has been synthesized⁴¹. The compounds synthesized in this thesis and their numbering scheme is shown below (Fig. 14).

Figure 14: Dicyclohexyl-n-Ethylene Glycols

These molecules are symmetric dicyclohexyl ethers, and their synthetic scheme is represented in Fig. 15.

Figure 15: Synthetic Routes to **1a**, **1b**, **2** and **3**

At low temperature, these molecules have additional minor conformer(s) which can be observed by NMR. At 210K it is assumed that only chair conformations will exist in the cyclohexyl ring. With this assumption, there are three possibilities for ring inversion(Fig. 16):

- a) a single ring inversion(Process I),
- b) a double ring inversion(Process II).
- c) a mixture of a) and b)

Figure 16: Two Processes for Ring Inversion in **1**, **2** or **3**

The equilibrium constant(K) for ring inversion may be calculated by using the relative ^{13}C peak intensities of an equatorial carbon(I_e) compared to an axial carbon(I_a) when the ring inversion process is slow . For a simultaneous double ring inversion, the equilibrium constant values obtained from the ^{13}C NMR spectrum have the formula:

$$K = I_e / I_a$$

However, for single ring inversion of a two ring system, the K values obtained from the ^{13}C NMR spectrum have the following formula:

$$K = (I_e - I_a) / 2I_a$$

Since $I_e > I_a$,

$$K \approx I_e / 2I_a$$

From the calculated equilibrium constants, one can calculate the free energy for ring inversion:

$$-\Delta G = RT \ln K$$

Using ^{13}C peak intensities in solution may not be precise due to T_1 relaxation times and nuclear Overhauser enhancements(nOe) which can affect peak intensities. The effect of T_1 relaxation times can be reduced by using a smaller pulse angle and a longer delay time. The nOe can be reduced to zero by a gated coupling experimental technique.

It was impossible to determine which motion was occurring by studying the dicyclohexyl system alone. The goal of this experiment was to determine whether a double ring inversion or a single ring inversion occurs in the dicyclohexyl compounds. To answer this question asymmetric monocyclohexyl compounds were synthesized (Fig. 17). The synthetic scheme is represented in Fig. 18. If the monocyclohexyl compounds had the same conformational free energies as the dicyclohexyl compounds (including entropic effects) then we conclude that a single ring inversion was occurring at low temperature.

Additionally, both the monocyclic and dicyclic compounds have different chain lengths. There may be a noticeable trend of chain size/ K values for these compounds. Classical conformational theory dictates that the largest substituent will be locked more strongly than the smaller substituents. For instance, the $-\Delta G^\circ$ of methoxy cyclohexane is 3.1 kJ/mol in CF_2Cl_2 at 180 K.⁴² It is expected that the values for $-\Delta G^\circ$ will increase in magnitude (i.e. get more negative) for the compounds synthesized in this thesis since the substituent size is large.

Experiments using different solvents may change the equilibrium values. Different solvents have different viscosities (at low temperature)

and polarities which may change the ratio of the minor:major conformers.

A different solvent may have more of an affinity for the solute in the axial or equatorial form. This would change the equilibrium constants.

Figure 17: Cyclohexyl Ethers

Figure 18: Synthetic Scheme for **4**, **5**, **6**

Results and Discussion

The 100.3 MHz ^{13}C spectrum of the **1a** in CD_2Cl_2 is shown in Fig. 19a. It is clear that five distinct carbons are observed in the room temperature spectrum. This is in accord with rapid conformational interconversion on the NMR timescale. ^{13}C NMR peak assignments for **1a** can be determined by assignments made for methoxycyclohexane⁴³. The C1' deuterated (Fig. 19b) compound, **1b**, shows a collapse at 67 ppm. This is confirmation of the assignment of the ethylene carbons.

Only four additional resonances for **1a** are observed at low temperature (Fig. 20). At low temperature, one would expect to observe 10 additional resonances for the asymmetric conformer in process I (single ring inversion) and 5 peaks for this conformer in process II (double ring inversion). The interpretation of these data suggests that either process II is occurring, or the low temperature chemical shifts for the equatorial substituted ring of the minor conformer are coincident with the resonances of the major conformer. The ^{13}C NMR low temperature data for compounds **1a**, **2**, and **3** are summarized in Table 1. The ethylene carbons have been assigned inductively.

Figure 19a: Room Temperature 100.3MHz ^{13}C Spectrum of **1a**

Figure 19b: Room Temperature 100.3 MHz ^{13}C Spectrum of **1b**

Figure 20: 100.3 MHz ^{13}C Spectrum of **1a** at 210K

If process II was operative, it would suggest there would need to be an unusual interaction between the two terminal cyclohexane rings which either stabilizes the diaxial conformer or destabilizes the monoaxial conformer. Such an interaction would decrease with increasing chain length; therefore one would expect to observe less of the minor conformer

for **3** compared to **1**. However, the the low temperature ^{13}C intensities for **1a**, **2** and **3** are essentially identical(cf. Table 3), indicating that no such interaction exists. Therefore, in accord with fundamental conformational theory, the minor conformations in **1**, **2** and **3** are in the monoaxial forms.

Table 1: Low Temperature 100.3 MHz ^{13}C NMR Data for **1a**, **2** and **3** in CD_2Cl_2

Carbon	1a	2	3
	all values are ± 0.1 ppm		
C1(e)	77.94	77.93	77.84
C1(a)	73.06	73.15	73.07
C2, C6(e)	31.85	31.75	31.95
C2, C6(a)	28.98	28.83	28.81
C3, C5(e)	24.30	24.22	24.20
C3, C5(a)	19.98	19.90	19.89
C4(e)	25.19	25.12	25.10
C4(a)	25.61	25.55	25.52
C1'	66.75	66.30	66.30
C2'	--	70.27	70.31
C3'	--	69.85	69.83 ^a
C4'	--	--	69.74 ^a

^a Represents possible mixed assignments

Table 2: Low Temperature 100.3 MHz ^{13}C NMR Data for **4, **5** and **6** in CD_2Cl_2**

Carbon	4	5	6
	all values are ± 0.1 ppm		
C1(e)	78.58	78.65	77.73
C1(a)	73.92	73.87	72.89
C2, C6(e)	32.53	32.52	31.61
C2, C6(a)	29.67	29.63	28.71
C3, C5(e)	24.98	24.97	24.10
C3, C5(a)	20.65	20.65	19.80
C4(e)	25.87	25.87	24.99
C4(a)	26.29	26.30	25.41
C1'	67.11	67.19	67.03
C2'	72.34	70.71	71.11
C3'	59.24	66.86	66.55
C4'	--	15.59	21.17

Unambiguous assignment of the ^{13}C spectra of 4, 5 and 6 must be known before low temperature thermodynamic information can be obtained from them. The ring carbons for 4, 5 and 6 have very similar chemical shifts as in 1a, 1b, 2 and 3, hence are easily assigned. A HETCOR(Fig. 21) of 5 has been done to distinguish C3' from C1' which both have chemical shifts around 67 ppm. The protons from C3' are a quartet at 3.55 ppm. The quartet is slightly overlapped by the AA' BB' proton system from C1' and C2' . The HETCOR can distinguish C3' from C1' from the connectivity of the quartet to the most shielded of the peak at 67 ppm, which is C3' . Using these data, and the assignments made for 1a, 2 and 3 one can assign the ^{13}C NMR resonances(Table 1).

Figure 21: HETCOR of 5

Ideally, there should be four results for the value of the equilibrium constant at low temperature. However, due to peak overlap, less may be available. Additionally, since the equatorial and axial chemical shifts of C4 are very similar, these peaks overlap somewhat. As a result, that equilibrium constant value will be used in only one case. The values are comparable for **5** only in CS₂. Otherwise, it is consistently shown in the experiments that the delta cyclohexyl carbon has a lower equilibrium constant by about 20%, probably due to the fact that its shift differences between conformers are small, and hence at 210K, the resonances have not reached the stage of being "slow" on the NMR timescale.

For **4**, **5** and **6**, it is observed that the smallest chain length has the smallest equilibrium constant. The low temperature ¹³C NMR spectrum of **4**(Fig. 22) shows an equilibrium constant of 24.0, whereas **5**(Fig. 23) and **6**(Fig. 24) have very similar values of 33.7 and 32.6 respectively. The ¹³C NMR data at low temperature for **4**, **5** and **6** are summarized in Table 2. The energies obtained(-ΔG°) in CD₂Cl₂ from the equilibrium constants are 5.54 kJ/mol for **4**, 6.14 kJ/mol for **5** and 6.08 kJ/mol for **6**(Table 3). This results in an upper limit of approximately 6.1 kJ/mol.

Figure 22: 100.3 MHz ^{13}C Spectrum of **4** at 210 K Figure 23: 100.3 MHz ^{13}C Spectrum of **5** at 210 K

Figure 24: 100.3MHz ^{13}C Spectrum of **6** at 210 K

For **1a**, **2** and **3**, it is observed that the equilibrium constants are similar throughout (Table 3). The values obtained by low temperature ^{13}C NMR for a single ring inversion (Table 3) are 20.3 for **1a** (Fig. 20), 19.4 for **2** (Fig. 25) and 20.5 for **3** (Fig. 26). These data give a result of 5.2 kJ/mol for $-\Delta G^\circ$.

These results support the interpretation of a single ring inversion as the observed process in **1**, **2** and **3**. Since either of the cyclohexane rings of **1**, **2** and **3** can invert to form the minor conformer, this means that the minor conformers have an additional entropy of mixing $R \ln 2$. At 210 K, this translates into a $T\Delta S$ term of 1.2 kJ/mol. This, combined with the $-\Delta G^\circ$ value of 5.2 kJ/mol observed for each of **1**, **2** and **3** leads to the prediction of $-\Delta G^\circ$ values of 6.4 kJ/mol for an $-\text{OCH}_2\text{CH}_2\text{OR}$ moiety, in reasonable agreement with the results obtained for **4**, **5** and **6** (Table 3).

The low temperature ^1H NMR spectrum of **1b** (Fig. 27a) has an equilibrium constant (12.5) which is lower than the value obtained by ^{13}C NMR spectroscopy for **1a** (20.3). The room temperature ^1H NMR spectrum of **1b** is shown in Fig. 27b. This decrease is attributed to the method for obtaining the equilibrium constants (K). The equilibrium constant for the ^1H NMR spectrum is calculated by integration, whereas

peak height is used for the ^{13}C NMR spectra. The minor conformation from the ^{13}C NMR spectrum flattens out due to its tiny resonance. As a result, peak height data will have a higher equilibrium constant than integral data. However, integral values obtained (11.8) from the ^{13}C NMR spectrum of **1a** (Fig. 27c) agree very well with values obtained from the ^1H NMR spectrum (12.5). Consequently, this result confirms the small affect of ^{13}C T_1 relaxation times and the nOe on these compounds. The above equilibrium constants are for a single ring inversion.

Figure 25: 100.3 MHz ^{13}C Spectrum of **2** at 210 K

Figure 26: 100.3 MHz ^{13}C Spectrum of 3 at 210 K Figure 27a: 400.6MHz ^1H Spectrum of 1b at Room Temperature

Figure 27b: 400.6 MHz ^1H Spectrum of **1b** at 210 K

Figure 27c: 100.3 MHz ^{13}C NMR Spectrum of **1a** at 210 K

The values for 1, 2 and 3, and 5 and 6 are the same within the error limits. Therefore, we conclude that a single ring inversion occurs at low temperature for 1, 2 and 3. This is in accord with a recently synthesized ditelluride compound(Fig. 28), which also has a predicted single ring inversion.⁴⁴

Figure 28: Dicyclohexyl Ditelluride Compound:

Table 3: Equilibrium Constants(K) of **1a**, **2**, **3**, **4**, **5** and **6** in CD₂Cl₂

Compound	K _{raw}	K _{average}	K _{SRI}	-ΔG (kJ/mol)
1a	40.50 40.62	40.6±0.1	20.3±0.1	5.26±0.01
2	35.48 42.00	38.7±3.3	19.4±1.6	5.2±0.2
3	41.10 41.25 40.48	40.9±0.3	20.5±0.2	5.27±0.02
4	24.64 24.13 23.30	24.0±0.6	-----	5.55±0.05
5	37.12 34.35 34.38	35.3±1.3	-----	6.22±0.07
6	33.12 33.04	33.7±0.9	-----	6.14±0.05

K_{raw}: Equilibrium Constants from raw data

K_{average}: Calculated average equilibrium constant from raw data. Errors are standard deviations from the mean.

K_{SRI}: Calculated equilibrium constant for a single ring inversion

The low intensity of the minor conformation would create a large error on any T_1 calculation. This is due to the fact that most of the peaks would have a very small peak height and some would be lost in the baseline of a T_1 experiment. Consequently, the precision for a low temperature T_1 experiment would be low and would not distinguish any significant differences in T_1 between an axial or equatorial carbon. Additionally, a gated decoupling experiment at low temperature to suppress nOe would not work because the low intensities created by the experiment cannot be detected in a reasonable time period.

The low temperature spectra for **4**, **5** and **6** in CD_3OD are shown(Fig. 29, 30 and 31 respectively), and the low temperature spectrum for **5** in CS_2 is shown in Fig. 32. There is a slight drop in $-\Delta G$ for **4**, **5** and **6** when the solvent is changed to CD_3OD (Table 4). The $-\Delta G$ for **5** also is decreased in the solvent CS_2 (Table 4). This may be attributed to the differing solvation of the equatorial vs. axial sidechains in the above solvents with the oxygen lone pair electrons(Fig. 33). These effects are small(about 1/20th of a hydrogen bond).

Table 4: Equilibrium Constants of **4**, **5** and **6** in CD₃OD and CS₂

Compound	Solvent	K _{raw}	K _{average}	-ΔG (kJ/mol)
4	CD ₃ OD	11.85	11.6±0.2	4.28±0.03
		11.61		
		11.38		
5	CD ₃ OD	9.47	11.2±1.3	4.2±0.2
		12.14		
		12.74		
		10.37		
6	CD ₃ OD	20.72	20.5±0.6	5.3±0.1
		19.54		
		21.09		
5	CS ₂	15.39	12.9±2.0	4.4±0.3
		10.19		
		11.88		
		14.08		

K_{raw}: Equilibrium Constants from raw data

K_{average}: Calculated average equilibrium constant from raw data. Errors are standard deviations from the mean.

Figure 30: 100.3 MHz ^{13}C Spectrum for 5 in CD_3OD at 210K

Figure 31: 100.3 MHz ^{13}C Spectrum for **6** in CD_3OD at 210K

Figure 32: 100.3 MHz ^{13}C Spectrum for **5** in CS_2 at 210K

Figure 33: Solvation Effects of the Sidechain which Affect the Equilibrium Constant

S=Solvent Molecules

Part II

Solid State and Solution Stereochemistry of Dibenzo-15-Crown-4 Ether and its Sodium Iodide Complex as Studied by X-Ray Crystallography and ^1H and ^{13}C NMR

Introduction

Crown ethers derived from bis(2-hydroxyphenyl)methane were first reported by Vogtle⁴⁵. These molecules may have interesting complexation properties due to the steric crowding of the benzylic group in the crown cavity(Fig. 34).

Figure 34: Vogtle's Crown Ether

This effect may prevent complexation of some cations or enhance selectivity for others. In this thesis dibenzo 15-crown-4(7) and its NaI complex(8) have been synthesized and its structures are shown below(Fig 35a and 35b respectively). The synthetic scheme to 7 and 8 is shown in Fig. 36.

Figure 35a: Dibenzo
15-Crown-4

Figure 35b: Dibenzo
15-Crown-4(NaI)

There has been great interest in the conformational adjustment of crown ethers to cations upon complexation. If the crown cavity is too small then 1:2 cation:crown complexes²¹⁻²³ may form(Fig 37a). Also, 3:2 club sandwich complexes have been postulated but not isolated(Fig. 37b)⁴⁶. Dobler and Phizackerley have synthesized a sandwich dimer held

Figure 36: Synthetic Scheme for the Dibenzo 15-Crown-5 Analogue and its Sodium Iodide Complex

together by bonding through ions(Fig. 37c)⁴⁷. Herein is reported a new method of complexation for sodium to crown ethers(Fig, 37d). The sodium cation is coordinated to the four oxygen atoms of one crown unit and one oxygen of a neighbouring crown ether molecule, resulting in a dimer.

Figure 37: Various Stoichiometries of Crown Ethers with Guests

Also included are the solid phase ^{13}C NMR, solution state ^{13}C and ^1H NMR, and X-ray crystallographic structures for the free crown ether(7) and the sodium iodide complex of the crown ether(8). Solution NMR shift assignments are based on NOESY and HETCOR results.

Results and Discussion

(i) Solution NMR Assignments

^{13}C and ^1H NMR assignments of **7** can unambiguously be made by the use of NOESY(Fig. 38) and $^{13}\text{C}^1\text{H}$ HETCOR(Fig. 39) spectra. The only NOESY connection is between the aromatic and the aliphatic protons arises from H18, H8(aromatic) and H1, H6(aliphatic). This connectivity was used as a starting point to assign all protons, and the corresponding carbons could be assigned from the J1 HETCOR (Table 5). The only carbons not assigned by this method are the quaternary carbons and the benzylic carbon which can be assigned from known chemical shifts of 2-methylanisole in the literature⁴⁸. The AA'XX' proton spin system(Fig. 40a) from C1(C5) and C2(C6), and the aromatic ABCD proton system(Fig. 41a) has been analyzed iteratively(Fig. 40b and 41b respectively). The coupling constants of the protons from C1(C6) and C2(C5) are consistent with a rapid rotamer system with O-C-C-O *gauche* torsion angles. The proton shifts and coupling constants are summarized in Table 6.

Figure 38: NOESY of 7 Figure 39: HETCOR of 7

Figure 40a: 400MHz ^1H NMR of the Methylene AA'XX' Spin System of **7**(Experimental)

Figure 40b: 400MHz ^1H NMR of the Methylene AA'XX' Spin System of **7**(Simulated)

Figure 41a: 400MHz ^1H NMR of the ABCD Aromatic Spin System of **7**(Experimental)

Figure 41b: 400MHz ^1H NMR of the ABCD Aromatic Spin System of **7**(Simulated)

Table 5: ^{13}C NMR Chemical Shifts for **7** and **8** in Parts per Million(ppm)

	7(sol'n)*	7(solid)	8(sol'n)**	8(solid)
C1	68.1	68.5	69.1	64.1
C2	69.6	68.5	69.9	66.5
C3	70.1	72.5	70.4	66.5
C4	70.1	72.5	70.4	66.5
C5	69.6	68.5	69.9	66.5
C6	68.1	68.5	69.1	64.1
C7	156.6	157.3	157.6	155.4
C8	111.9	110.2	113.1	114.1
C9	126.9	128.2	127.9	(130.0) ^a
C10	120.5	118.8	121.1	125.5
C11	130.4	128.2	130.9	(131.5) ^a
C12	130.1	128.2	130.7	127.2
C13	28.9	27.5	29.4	32.2
C14	130.1	128.2	130.7	129.3
C15	130.4	128.2	130.9	(131.5) ^a
C16	120.5	118.8	121.1	125.5
C17	126.9	128.2	127.9	(130.3) ^a
C18	111.9	111.7	113.1	112.5
C19	156.6	157.5	157.6	154.4

* The solvent was CDCl_3

** The solvent was CD_3COCD_3

^a Represent possible mixed assignments

Table 6: ^1H NMR Chemical Shifts and Coupling Constant Data

	$\nu\text{H} + (0.001)$	^2J	^3J	^4J
	τ^*	δ^{**}	Coupling constants for τ^*	
H1	4.114	4.121	-10.8	6.9, 2.3
H1'			-10.8	6.9, 2.3
H2	3.816	3.785	-10.8	6.9, 2.3
H2'			-10.8	6.9, 2.3
H3	3.711	3.660		
H4	3.711	3.660		
H5	3.816	3.785	-10.8	6.9, 2.3
H5'			-10.8	6.9, 2.3
H6	4.114	4.121	-10.8	6.9, 2.3
H6'			-10.8	6.9, 2.3
H8	6.822	6.931		6.9, 1.5
H9	7.148	7.154		6.9, 2.3
				7.6
H10	6.863	6.847		7.6, 1.5
				7.2
H11	7.065	7.036		7.2, 2.3
H13	4.103	4.068		
H15	7.065	7.036		7.2, 2.3
H16	6.863	6.847		7.2, 1.5
				7.6
H17	7.148	7.154		7.6, 2.3
				6.9
H18	6.822	6.931		6.9, 1.5

* The solvent was CDCl_3 ** The solvent was CD_3COCD_3

(ii) Solid State NMR

From the ORTEP of **7**(Fig 42) it is clear that there is no symmetry present in this system. Hence, one could expect to observe 19 unique resonances in the solid state ^{13}C CP/MAS spectrum with the absence of peak overlap and crystal packing effects⁴⁹. There is, however extensive overlap in the solid state spectrum(Fig. 43a) with only C7, C19 and C8, C18 pairs being resolved. The shift difference between these carbons may be due in part to slightly different electronic effects from oxygens 4 and 1. The solid state ^{13}C CP/MAS assignments are summarized in Table 5. These oxygens differ in how they donate electron density to the phenyl ring. This difference can be ascertained from the X-ray structure. The torsion angles(Table 11a) of C1-O1-C19-C18(C14) are averaged to 3.6° out of plane compared with the torsional angles C6-O4-C7-C8(C12) which are averaged to 5.8° out of plane. It is believed from these data that O1 donates more electron density to the phenyl ring than O4. Due to resonance, C19 is assigned as being more shielded than C7, and C18 is assigned to be more shielded than C8 in the ^{13}C CP/MAS spectrum. The dipolar dephased spectrum(Fig. 43b) distinguishes C12 and C14 from C9 and C17.

Figure 42: ORTEP Plot of **7**

Figure 43a: ^{13}C CP/MAS Spectrum of **7**

Figure 43b: Dipolar Dephased Spectrum of **7**

The ethereal region of the CP/MAS spectrum shows only 2 distinct resonances. Due to steric crowding from H9 and H19, carbons 1 and 6 are assigned as being most shielded.

For **8**, the X-ray crystal structure of one half of the dimer(Fig. 44a) shows lack of any elements of symmetry. This is reflected in the ^{13}C CP/MAS spectrum(Fig. 45a) which shows 13 of 19 possible resonances. The ^{13}C solid state CP/MAS NMR data for **8** are summarized in Table 5. The difference in carbon resonances can be attributed to two main factors: first, the ability for O1 and O4 to donate electron density to the phenyl ring, and second the chelation strength of the oxygen to the sodium cation. The latter is easily determined by bond distances from the sodium to the appropriate oxygen. There is a bond distance difference of approximately $0.34\text{\AA}$ between O1-Na($2.442\text{\AA}$) and O4-Na($2.779\text{\AA}$)! Coupled with the fact that the torsion angles C6-O4-C7-C8(C12) are out of plane with the phenyl ring by an average of 12.2° , compared with the C1-O1-C19-C14(C18) torsional angle being out of plane by an average of 17.2° . It appears from these data that O4 contributes more electron density to the aromatic ring than O1 in the complex. Therefore C8, C10 and C12 are shielded relative to their counterparts(C18, C16 and C14 respectively)

Figure 44a: ORTEP Plot of **8** as Half a Dimer

Figure 44b: ORTEP Plot of **8** as a Dimer

Figure 45a: ^{13}C CP/MAS Spectrum of **8**

Figure 45b: Dipolar Dephased Spectrum of **8**

and C7 is deshielded relative to C19. The dipolar dephased spectrum of **8** (Fig. 45b) distinguishes C12 and C14 from C9 and C17.

There is a considerable deshielding chemical shift difference (6.7 ppm) in C10(16) when the crown is complexed. This is attributed to a considerable decrease in conjugative electron release from O1 and O4. This is due to electron donation of O1 and O4 to the sodium cation. Logically, C8(C18) should also be affected by this. It is believed that the interaction with C8(18) and C6(C1) significantly overcomes the resonance effect and thereby provides an extra shielding mechanism.

The aliphatic region of the spectrum reveals 2 distinct carbon resonances in the ratio of approximately 2 to 1. Carbons 1 and 6 are assigned as the only two carbons being most shielded at 64.1 ppm due to the steric crowding of H8 and H18.

(iii) X-ray Crystal Structures

The crystallographic data for **7** and **8** are summarized in Table 7. Table 8 displays atomic parameters. Tables 9, 10 and 11 include bond lengths, bond angles and torsion angles respectively for **7**(Tables a) and **8**(Tables b). The X-ray structure shows that **7**(Fig. 42) has *gauche* O-C-C-O torsion angles which is normal in crown ethers³²⁻³⁴. However, in **7** two of these angles are expanded to 72.6°(O1-C1-C2-O2) and 79.1°(O3-C5-C6-O4) respectively. The remaining O2-C3-C4-O3 torsion angle is -61.6°. The C-C-O-C torsion angles in crown ethers are typically *transoid*³²⁻³⁴. However, the C5-O3-C4-C3 torsion angle is orthogonal at 92.4°. The C3-O2-C2-C1 moiety has a slightly contracted torsion angle of -165.7°. The remaining torsion angles are -170.8°(C19-O1-C1-C2), 174.5°(C2-O2-C3-C4), -175.1°(C4-O3-C5-C6), and 179.3°(C7-O4-C6-C5).

For the X-ray structure of **8**(Figs. 44) the oxygen atoms all form a tetragonal plane due to complexation with the sodium cation. Upon complexation, two major conformational changes occur in the crown ring. First, all the oxygen atoms must be oriented on the same side of the cavity and point to the sodium cation for full complexation to occur. It can be seen that O2 flips around to the other side of the ring and points

Table 7: Crystallographic Data of **7** and **8**

	Free Crown	Complexed
Crown		
Formula	$C_{19}H_{22}O_4$	$C_{19}H_{22}O_4NaI$
Crystal System	triclinic	monoclinic
Space Group	P-1	P-21/c
a(Å)	9.4072(18)	10.003(4)
b(Å)	11.677(4)	16.639(4)
c(Å)	8.3147(24)	12.059(4)
alpha	106.58(3)	90.0
beta	105.800(1)	108.02(3)
gamma	100.516(21)	90.0
Z(molecules/cell)	2	4
D_c, g/cm	1.292	1.616
F(000)	336.14	925.62
mu(mm-1)	0.08	1.70
Crystal dimensions, mm³	0.2x0.2x0.2	0.2x.02x0.2
Volume(Å³)	808.0(4)	1908.7(10)
Radiation(λ, Å)	MoKα (0.70930)	MoKα (0.70930)
Octants measured	<i>h</i> (-11 to +10) <i>k</i> (0 to +13) <i>l</i> (-9 to +9)	<i>h</i> (-11 to +11) <i>k</i> (0 to +19) <i>l</i> (0 to +14)
Max 2θ	49.9	49.9
Temperature(°C)	-100	-110
No. of reflection measured	2995	3556
No. of unique reflections	2813	3356
No. of observed reflections	2419	2733
No. of atoms	45	47
No. of variables	296	227
R_f(significant refl)	0.047	0.045
R_w(significant refl)	0.065	0.070
R_f(all refl)	0.065	0.070
R_w(all refl)	0.065	0.070
Goodness-of-fit	2.01	1.82

to the sodium cation. Secondly, O3 translates toward the centre of the crown cavity, while C5 moves out of the crown cavity. The above motions(Fig. 46) have marked effects on the torsion angles furthest from the aromatic ring system. Two of the six crown C-C-O-C torsion angles contract to an expanded gauche conformation of -74.2° (C2-O2-C3-C4) and -71.3° (C4-O3-C5-C6), while the rest remain in the anti conformation. Also, the C5-O3-C4-C3 torsion angle expands from its orthogonal conformation of 92.4° to an anti conformation of 168.1° .

Figure 46: Change of Conformation of **8** compared to **7**

The O-C-C-O torsional angles all contract upon complexation by 4° , 11° and 21° for the O1-C1-C2-O2, O2-C3-C4-O3 and O3-C5-C6-O4 respective networks. This contraction is expected since there is a tendency for a planar 5-membered chelate to form⁵⁰.

Since O2, O3 and C5 move dramatically upon complexation, it is not surprising that bond angles involving those atoms would change when complexed. There is an expansion of 6.0° and 3.5° for the O2-C3-C4, and O3-C5-C6 respective bond angles. There is a contraction of 4.1° for the O3-C4-C3 bond angle.

The complex is a dimer of C_i symmetry in the solid state which can be seen in the ORTEP diagram(Fig. 44b). The atom O2 is chelated to two sodium cations! The dimerization of the crown ether complex may result from two factors. Firstly, the benzylic group forces the sodium cation further away from the centre of the crown ring. This steric hindrance is reflected in the short internuclear distance of $2.39\text{\AA}$ between H13B and the sodium cation. Consequently, the sodium cation cannot coordinate to O1 and O4 equally. This effect is manifested in the O1-Na distance($2.44\text{\AA}$) and the O4-Na distance($2.78\text{\AA}$). Secondly, sodium prefers a coordination number of six. The only way this can occur is if the sodium cation

complexes to an intermolecular atom of an adjacent crown unit.

The diameter of the binding cavity can be found by determining the average diagonal distance of oxygen atoms ($4.08\text{\AA}$) and subtracting twice the van der Waals radius of the oxygen atom ($2 \times 1.4\text{\AA}$). The diameter of the binding cavity is approximately $1.3\text{\AA}$. The effective diameter of the sodium cation is $1.9\text{--}2.4\text{\AA}^{51}$ hence the cation does not fit into the plane defined by the four oxygen atoms.

Finally, there is contraction of the ring upon complexation which can be seen by the decrease in the O1-O4 distance. The free crown has a O1-O4 distance of $3.57\text{\AA}$, compared to $3.28\text{\AA}$ in the complex.

Table 8a: Atomic Parameters x,y,z and Biso for **7**

	x	y	z	Biso
O1	0.76395(16)	0.42841(14)	0.31381(19)	2.20(7)
O2	0.48311(16)	0.49788(14)	0.27706(20)	2.26(7)
O3	0.26390(17)	0.32534(14)	-0.04936(20)	2.29(7)
O4	0.48885(15)	0.17735(13)	-0.05575(21)	2.20(7)
C1	0.73325(23)	0.51276(20)	0.4540(3)	2.15(9)
C2	0.63319(23)	0.58306(19)	0.3739(3)	2.13(9)
C3	0.38458(24)	0.53980(20)	0.1590(3)	2.26(10)
C4	0.23783(24)	0.43432(21)	0.0551(3)	2.30(10)
C5	0.2175(23)	0.23978(20)	0.0411(3)	2.16(10)
C6	0.32913(22)	0.13498(20)	-0.0741(3)	2.17(10)
C7	0.54664(23)	0.09345(19)	-0.1501(3)	1.87(9)
C8	0.46012(24)	-0.02418(20)	-0.2726(3)	2.31(10)
C9	0.5286(3)	-0.10106(21)	-0.3660(3)	2.65(10)
C10	0.6840(3)	-0.06238(22)	-0.3384(3)	2.79(11)
C11	0.77094(25)	0.05472(21)	-0.2138(3)	2.42(11)
C12	0.70694(23)	0.13411(19)	-0.1164(3)	1.90(9)
C13	0.80266(23)	0.25936(19)	0.0246(3)	1.95(9)
C14	0.85662(21)	0.25705(19)	0.2132(3)	1.85(9)
C15	0.93057(23)	0.16977(20)	0.2505(3)	2.25(10)
C16	0.98111(24)	0.16621(22)	0.4223(3)	2.59(11)
C17	0.95961(24)	0.25104(23)	0.5592(3)	2.71(11)
C18	0.88738(24)	0.34011(22)	0.5272(3)	2.48(10)
C19	0.83518(22)	0.34253(19)	0.3547(3)	1.96(9)
H1A	0.679(3)	0.4644(21)	0.513(3)	2.5(5)
H1B	0.826(3)	0.5719(22)	0.542(3)	2.8(5)
H2A	0.6269(22)	0.6640(18)	0.477(3)	0.9(4)
H2B	0.675(3)	0.6174(22)	0.299(3)	2.6(5)
H3A	0.437	0.5650(23)	0.074(3)	3.3(6)
H3B	0.361(3)	0.6165(20)	0.234(3)	2.1(5)
H4A	0.169(3)	0.4617(22)	-0.030(3)	2.7(5)
H4B	0.184(3)	0.4133(21)	0.139(3)	2.5(5)
H5A	0.196(3)	0.2075(22)	0.063(3)	2.7(5)
H5B	0.374(3)	0.2892(22)	0.162(3)	2.6(5)
H6A	0.317(3)	0.0581(22)	-0.034(3)	2.7(5)

Table 8a: Continued

H6B	0.265(3)	0.1051(23)	-0.205(3)	3.0(5)
H8	0.346(3)	-0.0505(25)	-0.228(4)	3.8(6)
H9	0.463(3)	-0.1899(24)	-0.460(4)	3.6(6)
H10	0.731(3)	-0.1214(24)	-0.407(3)	3.5(6)
H11	0.875(3)	0.0819(22)	-0.199(3)	2.8(5)
H13A	0.896(3)	0.2879(20)	-0.015(3)	2.1(5)
H13B	0.746(3)	0.3239(23)	0.029(3)	3.2(5)
H15	0.943(3)	0.1083(21)	0.145(3)	2.3(5)
H16	1.029(3)	0.1032(23)	0.440(3)	2.9(5)
H17	1.000(3)	0.2520(23)	0.677(3)	3.2(6)
H18	0.874(3)	0.3977(21)	0.619(3)	2.3(5)

Biso is the mean of the principal axes of the thermal ellipsoid

Table 8b:

	x	y	z	Biso
I1	0.33478(5)	0.67196(3)	0.22228(4)	2.667(18)
Na1	0.4995(3)	0.53127(15)	0.34529(22)	2.08(10)
O1	0.7526(4)	0.5234(3)	0.4419(4)	1.79(17)
O2	0.5467(4)	0.4142(3)	0.4700(4)	1.81(18)
O3	0.3773(5)	0.4201(3)	0.2418(4)	2.23(19)
O4	0.5998(5)	0.4770(3)	0.1679(4)	2.17(19)
C1	0.7841(6)	0.4574(4)	0.5264(5)	1.8(3)
C2	0.6868(6)	0.3907(4)	0.4755(5)	1.8(3)
C3	0.4428(7)	0.3532(4)	0.4231(6)	2.0(3)
C4	0.4081(8)	0.3436(4)	0.2938(6)	2.5(3)
C5	0.3701(7)	0.4216(5)	0.1218(6)	2.8(3)
C6	0.5148(8)	0.4122(5)	0.1050(6)	2.7(3)
C7	0.7352(7)	0.4831(4)	0.1598(5)	2.0(3)
C8	0.7970(8)	0.4229(4)	0.1121(6)	2.6(3)
C9	0.9322(8)	0.4330(5)	0.1063(6)	2.9(3)
C10	1.0049(7)	0.5041(5)	0.1454(6)	2.5(3)
C11	0.9429(7)	0.5634(5)	0.1920(5)	2.3(3)
C12	0.8077(7)	0.5554(4)	0.2006(5)	2.0(3)
C13	0.7456(7)	0.6237(4)	0.2519(5)	1.8(3)
C14	0.8338(6)	0.6432(4)	0.3757(5)	1.7(3)
C15	0.9168(7)	0.7101(5)	0.3994(6)	2.4(3)
C16	1.0038(8)	0.7281(5)	0.5129(6)	2.8(3)
C17	1.0089(7)	0.6753(4)	0.6027(6)	2.2(3)
C18	0.9275(7)	0.6054(5)	0.5814(6)	2.2(3)
C19	0.8404(6)	0.5899(4)	0.4680(5)	1.4(3)
H1A	0.893	0.438	0.549	2.5
H1B	0.765	0.475	0.609	2.5
H2A	0.718	0.334	0.526	2.3
H2B	0.692	0.377	0.387	2.3
H3A	0.476	0.297	0.469	2.5
H3B	0.345	0.371	0.442	2.5
H4A	0.319	0.302	0.257	2.7
H4B	0.498	0.316	0.272	2.7
H5A	0.298	0.376	0.071	3.3

Table 8b: Continued

H5B	0.328	0.481	0.084	3.3
H6A	0.507	0.413	0.011	3.6
H6B	0.558	0.353	0.138	3.6
H8	0.738	0.367	0.078	3.2
H9	0.984	0.384	0.073	3.4
H10	1.113	0.513	0.136	3.1
H11	1.003	0.618	0.222	3.0
H13A	0.734	0.676	0.197	2.3
H13B	0.640	0.605	0.253	2.3
H15	0.919	0.752	0.328	3.0
H16	1.068	0.782	0.529	3.3
H17	1.080	0.688	0.691	3.1
H18	0.929	0.565	0.653	2.7

Biso is the mean of the principal axes of the thermal ellipsoid

Note: To obtain parameters for the other half of the dimer use the formula;

$$x_a + x_b = 1; \quad y_a + y_b = 1; \quad z_a + z_b = 1$$

where x_a , y_a and z_a are given above and x_b , y_b and z_b are the parameters for the other half of the dimer.

Table 9a: Atomic Bond Distances(Å) for **7**

O1-C1	1.430(3)	O1-C19	1.374(3)
O2-C2	1.429(3)	O2-C3	1.417(3)
O3-C4	1.426(3)	O3-C5	1.429(3)
O4-C6	1.444(2)	O4-C7	1.363(3)
C1-C2	1.502(3)	C3-C4	1.514(3)
C5-C6	1.497(3)	C7-C8	0.389(3)
C7-C12	1.418(3)	C8-C9	1.382(3)
C9-C10	1.393(3)	C10-C11	1.391(3)
C11-C12	1.385(3)	C12-C13	1.513(3)
C13-C14	1.521(3)	C14-C15	1.393(3)
C14-C19	1.398(3)	C15-C16	1.392(3)
C16-C17	1.368(4)	C17-C18	0.390(3)
C18-C19	1.394(3)		

Table 9b: Atomic Bond Distances(Å) for **8**

Na1-I	2.980(3)	Na1-O1	2.442(5)
Na1-O2	2.417(5)	Na1-O2a	2.575(5)
Na1-O3	2.352(5)	Na1-O4	2.779(5)
O1-C1	1.464(7)	Na1a-O2	2.575(5)
O1-C19	1.388(7)	O2-C2	1.437(7)
O2-C3	1.437(8)	O3-C4	1.409(8)
O3-C5	1.426(8)	O4-C6	1.436(8)
O4-C7	1.392(8)	C1-C2	1.479(9)
C3-C4	1.497(10)	C5-C6	1.530(10)
C7-C8	1.391(10)	C7-C12	1.413(10)
C8-C9	1.386(11)	C9-C10	1.392(11)
C10-C11	1.374(10)	C11-C12	1.395(9)
C12-C13	1.516(10)	C13-C14	1.516(8)
C14-C15	1.365(10)	C14-C19	1.408(9)
C15-C16	1.408(10)	C16-C17	1.382(10)
C17-C18	1.398(10)	C18-C19	1.400(9)

Table 10a: Atomic Bond Angles(°) for **7**

C1-O1-C19	117.46(16)	O4-C3-C12	115.19(18)
C2-O2-C3	114.00(16)	C8-C7-C12	120.12(19)
C4-O3-C5	113.49(16)	C7-C8-C9	120.33(20)
C6-O4-C7	116.66(16)	O1-C1-C2	108.37(17)
C8-C9-C10	120.60(20)	C9-C10-C11	118.99(21)
O2-C2-C1	106.97(17)	C10-C11-C12	122.18(20)
C7-C12-C11	117.75(19)	C7-C12-C13	120.03(18)
O2-C3-C4	107.03(17)	C11-C12-C13	122.20(18)
O3-C4-C3	112.49(17)	C12-C13-C14	113.93(17)
O3-C5-C6	108.85(18)	C13-C14-C15	120.77(19)
O4-C6-C5	108.10(16)	C13-C14-C19	121.42(18)
O4-C7-C8	124.69(18)	C15-C14-C19	117.80(20)
C14-C15-C16	121.67(21)	C15-C16-C17	119.63(21)
C16-C17-C18	120.28(21)	C17-C18-C19	120.00(22)
O1-C19-C14	116.30(18)	C14-C19-C18	120.61(20)
O1-C19-C18	123.08(20)		

Table: 10b: Atomic Bond Angles(°) for **8**

Il-Na1-O1	127.72(14)	Il-Na1-O2	156.11(15)
Il-Na1-O2a	86.22(12)	Il-Na1-O3	103.74(14)
Il-Na1-O4	98.51(12)	O1-Na1-O2	71.68(15)
O1-Na1-O2a	92.48(16)	O1-Na1-O3	120.18(19)
O1-Na1-O4	77.39(15)	O2-Na1-O2a	78.40(16)
O2-Na1-O3	70.45(16)	O2-Na1-O4	99.75(17)
O2a-Na1-O3	127.22(18)	O2a-Na1-O4	169.71(17)
O3-Na1-O4	62.67(16)	Na1-O1-C1	109.9(3)
Na1-O1-C19	123.7(4)	C1-O1-C19	117.1(4)
Na1-O2-Na1a	101.6(2)	Na1-O2-C2	104(3)
Na1-O2-C3	110.2(4)	Na1a-O2-C2	119.3(3)
Na1a-O2-C3	106.8(3)	C2-O2-C3	113.7(5)
Na1-O3-C4	117.9(4)	Na1-O3-C5	112.3(4)
C4-O3-C5	113.7(6)	Na1-O4-C6	110.8(4)
Na1-O4-C7	128.4(4)	C6-O4-C7	116.6(5)
O1-C1-C2	107.5(5)	O2-C2-C1	108.8(5)
O2-C3-C4	113.1(5)	O3-C5-C6	112.3(5)
O4-C6-C5	106.5(6)	O4-C7-C8	122.9(6)
O4-C7-C12	116.3(6)	C8-C7-C12	120.8(6)
C7-C8-C9	119.9(7)	C8-C9-C10	120.1(7)
C9-C10-C11	119.6(7)	C10-C11-C12	122.2(7)
C7-C12-C11	117.4(6)	C7-C12-C13	123.4(6)
C11-C12-C13	119.3(6)	C12-C13-C14	112.1(5)
C13-C14-C15	120.8(6)	C13-C14-C19	120.9(6)
C15-C14-C19	118.1(6)	C14-C15-C16	122.0(7)
C15-C16-C17	119.3(7)	C16-C17-C18	120.4(6)
C17-C18-C19	118.9(6)	O3-C4-C3	108.4(6)
O1-C19-C14	116.9(5)	O1-C19-C18	121.8(6)
C14-C19-18	121.3(6)		

Table 11a: Torsion Angles(°) for **7**

C19-O1-C1-C2	-170.8(2)	C1-O1-C19-C18	-4.6(1)
C2-O2-C3-C4	174.5(2)	C4-O3-C5-C6	-175.1(2)
C6-O4-C7-C8	5.9(1)	O1-C1-C2-O2	72.6(1)
O3-C5-C6-O4	79.1(1)	O4-C7-C12-C13	3.8(1)
C8-C7-C12-C13	-176.5(2)	C10-C11-C12-C13	177.4(2)
C11-C12-C13-C14	-94.6(2)	C12-C13-C14-C19	-129.6(2)
C13-C14-C19-C18	-179.1(2)	C15-C14-C19-C18	0.4(1)
C17-C18-C19-C14	-0.9(1)	C1-O1-C19-C14	176.8(2)
C3-O2-C2-C1	-165.7(2)	C5-O3-C4-C3	92.4(1)
C7-O4-C6-C5	179.3(2)	C6-O4-C7-C12	-174.4(2)
O2-C3-C4-O3	-61.6(1)	O4-C7-C8-C9	177.9(2)
C12-C7-C8-C9	-1.8(1)	O4-C7-C12-C11	-177.4(2)
C8-C7-C12-C11	2.2(1)	C7-C8-C9-C10	0.3(1)
C8-C9-C10-C11	0.7(1)	C9-C10-C11-C12	-0.1(1)
C10-C11-C12-C7	-1.3(1)	C7-C12-C13-C14	84.1(1)
C12-C13-C14-C15	51.0(1)	C13-C14-C15-C16	179.9(2)
C19-C14-C15-C16	0.4(1)	C13-C14-C19-O1	-0.4(1)
C15-C14-C19-O1	179.1(2)	C14-C15-C16-C17	-0.7(1)
C15-C16-C17-C18	0.2(1)	C16-C17-C18-C19	0.6(1)
C17-C18-C19-O1	-179.5		

Table 11b: Torsion Angles(°) for **8**

C19-O1-C1-C2	-174.5(6)	C1-O1-C19-C18	-18.4(3)
C2-O2-C3-C4	-74.2(5)	C4-O3-C5-C6	-71.3(5)
C6-O4-C7-C8	-11.5(4)	O1-C1-C2-C2	-68.6(4)
O3-C5-C6-O4	-58.3(4)	O4-C7-C12-C13	0.5(3)
C8-C7-C12-C13	179.2(8)	C10-C11-C12-C13	-179.4(8)
C11-C12-C13-C14	-59.3(5)	C12-C13-C14-C19	-70.4(5)
C13-C14-C19-C18	176.4(7)	C15-C14-C19-C18	1.1(4)
C17-C18-C19-C14	0.2(3)	C1-O1-C19-C14	164.0(6)
C3-O2-C2-C1	-179.3(6)	C5-O3-C4-C3	168.1(7)
C7-O4-C6-C5	-176.7(7)	C6-O4-C7-C12	167.2(7)
O2-C3-C4-O3	-50.6(4)	O4-C7-C8-C9	179.8(8)
C12-C7-C8-C9	1.2(4)	O4-C7-C12-C11	-179.2(8)
C8-C7-C12-C11	-0.6(4)	C7-C8-C9-C10	-1.6(4)
C8-C9-C10-C11	1.3(4)	C9-C10-C11-C12	-0.7(4)
C10-C11-C12-C7	0.3(4)	C7-C12-C13-C14	121.0(7)
C12-C13-C14-C15	104.9(6)	C13-C14-C15-C16	-177.5(8)
C19-C14-C15-C16	-2.1(4)	C13-C14-C19-O1	-6.0(3)
C15-C14-C19-O1	178.6(7)	C14-C15-C16-C17	2.0(4)
C15-C16-C17-C18	-0.7(4)	C16-C17-C18-C19	-0.4(4)
C17-C18-C19-O1	-177.3(7)		

Conclusions

In Part I, the dicyclohexyl ethylene glycol derivatives **1,2**, and **3** undergo a cyclohexane ring inversion with a conformational free energy ($-\Delta G^\circ$) of 5.3 kJ/mol at 210 K. As expected from entropic considerations, the $-\Delta G^\circ$ values of the cyclohexyl ethylene glycol derivatives **4**, **5** and **6** are ca. 1.2 kJ./mol higher than for **1,2**, and **3**. These results suggest that the conformational process observed in **1,2**, and **3** is a single ring inversion.

In Part II, the X-ray crystal structures of dibenzo 15-crown-4 and its sodium iodide complex reveal a novel NaI crown dimer(**8**) of C_2 symmetry. This dimerization is caused by three main factors. First, the benzylic protons force the sodium cation to the far edge of the crown cavity. This, in turn, allows the sodium cation to complex with an adjacent macrocycle to produce the preferred coordination number of six. Thus the lack of the preferred number of coordination sites in one crown unit "forces" the sodium to seek a complexation site in a neighbouring crown ether moiety.

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Experimental

Tosylation

All tosylated materials were prepared by a common tosylation procedure from the appropriate alcohol.⁵²

Hydrogenation

The starting product(0.4-1g) was dissolved in ethanol(30mL) and 5% rhodium on alumina was added(200-600 mg). The mixture was hydrogenated at a hydrogen pressure of 600 psi and a temperature of 35°C for 24-36 hours.

The mixture was filtered by gravity and was extracted with dichloromethane(3x30 mL). The organic layer was dried over magnesium sulphate and the solvent removed. Typical yields were 90%.

Synthesis of 1a

1,2 diphenoxyethane(2.0g, 9.3mmol) was partially dissolved in 40mL of absolute ethanol with 100mg of rhodium on alumina catalyst.

This was hydrogenated in a high pressure bomb at a hydrogen pressure of

600psi and 40°C for 20 hours. The catalyst was filtered, and the solvent removed to yield 1,2- dicyclohexoxyethane(2.0g, 8.9mmol, yield 95%, b.p 90°C @ 0.3mmHg).

Synthesis of **1b**

Phenol(2.2g, 20mmol) was dissolved in 200mL anhydrous acetonitrile. 10g of powdered anhydrous potassium carbonate was added and the solution stirred vigorously. d4 Ethylene glycol ditosylate(2.2g, 5.8mmol) was added and the mixture was refluxed for 10 days. The mixture was diluted with 0.1m sodium hydroxide solution(300mL), and was extracted with dichloromethane (3x100mL). The organic phase was dried over magnesium sulphate and removed and the product was recrystallized in ethanol to give 1,2 diphenoxy-d4-ethane(1.5g, 5.6 mmol, yield 97%, mp. 95-97°, lit.mp. 94-96°C(non-deuterated)) which was hydrogenated.

Preparation of **2**

Phenol(4.0g, 0.04mol) was dissolved in 250mL of anhydrous acetonitrile in a 3 necked 500mL flask. Powdered potassium carbonate(8g)

was added. 1,2 Bis(2-chloroethoxy)ethane (2.7g, 0.015mol) was dissolved in 50mL of anhydrous acetonitrile and added dropwise to the stirred mixture which was refluxed for 12 days. The mixture was diluted with 0.1M sodium hydroxide solution(400mL) and extracted with dichloromethane(3x150mL). The organic phase was dried over magnesium sulphate and removed to give a brown crude oil which was purified by flash chromatography using 1:1 dichloromethane, ethyl acetate and recrystallized in ethanol to give O,O (diphenyl) triethylene glycol(4g, 0.013mol, yield 87%, mp 42°C). The pure aromatic product was hydrogenated and purified by bulb to bulb distillation at an oven temperature of 150°C at 0.3 mmHg.

Preparation of **3**

Phenol(10g, 0.11mol) was dissolved in 300mL of anhydrous acetonitrile in a 500mL 3 necked flask. The solution was stirred and powdered potassium carbonate(15g) was added. Tetraethylene glycol ditosylate(17g, 0.034mol) was slowly added. The reaction was complete after 11 days. The mixture was diluted with 500mL of 1M sodium hydroxide solution and extracted with dichloromethane(3x 150mL). The

organic phase was dried and removed to give the aromatic product(8.0g, 0.023mol, yield 68%), which was hydrogenated and purified by vacuum distillation at 190°C at 0.3 mmHg.

Synthesis of **4**

Phenol(5g, 0.053 mol) was dissolved in 200 mL of anhydrous acetonitrile. Powdered potassium carbonate(10 g, 0.072 mol) was added and the solution was stirred. 2-Bromoethyl methyl ether(5g, 0.036) was added dropwise to the mixture. The mixture was refluxed and stirred for two days.

The mixture was filtered by gravity, and the solvent was removed to give a crude product(4.5 g, 0.03 mol). The crude product was purified by vacuum distillation to give pure product(1.4g, 26% yield), which was hydrogenated. A high resolution mass spectrum of **4** gave a molecular formula of $C_9H_{18}O_2$, and n_D^{22} of 1.4423.

Synthesis of **5**

Phenol(8.0g, 0.085 mol) was dissolved in 200 mL of anhydrous acetonitrile. Powdered potassium carbonate(14g, 0.1 mol) was added and

the solution was stirred. 2-Bromoethyl ethyl ether (7.5 g, 0.05 mol) was added dropwise to the mixture. The mixture was refluxed and stirred for two days.

The mixture was filtered by gravity, and the solvent was removed to give a crude product (7g, 80% yield). The crude product was purified by vacuum distillation to give a pure product (2.5g, 30% yield) which was characterized. High resolution mass spectrum of **5** gave a molecular formula of $C_{10}H_{20}O_2$.

Synthesis of **6**

NaH (2.4 g, 0.1 mol) was added slowly to reagent grade isopropanol (150 mL). The mixture was stirred for 10 minutes. 2-Bromophenethanol (10 g, 0.05 mol) was added. The mixture was refluxed for two days.

The mixture was diluted with 500 mL of distilled water and extracted with dichloromethane (3x100 mL). The organic layer was dried over magnesium sulphate and removed to give a crude product (7.5g, 83% yield) which was vacuum distilled (2.3g, 26% yield). The product was hydrogenated and purified by column chromatography using 1:10

ether/hexane as the eluent.

Synthesis of **7**

Bis(2-hydroxyphenyl) methane (2.00g, 10mmol) was dissolved in 300mL of anhydrous acetonitrile then LiH(160mg, 20mmol) was slowly added. This mixture was allowed to stir for fifteen minutes. Triethylene glycol ditosylate(4.6g, 10mmol) was dissolved in 150mL of acetonitrile and slowly added dropwise to the mixture. After refluxing for three days in inert and anhydrous conditions the white precipitate was filtered by gravity and washed with dichloromethane(50mL). The filtrate was removed by rotoevaporation and purified by flash chromatography using 1:1 ethyl acetate/petroleum ether. Fractions 8-20 were recrystallized in ether to give compound **7** in 60% yield(1.9g, 6mmol, mp. 82-84°C)

The NaI complex(**8**) was prepared by dissolving sodium iodide(120mg, 0.8mmol) in the minimum amount of hot methanol and in a separate container dissolving compound **7**(250mg, 0.8mmol) in 10mL of ethyl acetate. The ethyl acetate solution was added to the methanol solution and hot methanol was added dropwise until all compounds were dissolved. Crystals of compound **8**(260mg, 0.56mmol, mp. decomposed

before melting) were obtained in 70% yield.

(ii) Spectra

Solution NMR Spectra

All spectra were recorded using a Bruker AMX-400 spectrometer equipped with a 4-mm inverse probe and an Aspect X32 computer. An Aspect 3000 processing controller was employed and by standard microprograms used are in the Bruker Software Library

For the $^1\text{H}^{13}\text{C}$ HETCOR experiments, the free induction decay were typically acquired over 1024 data points for each of the 512 values of the evolution time, with a digital resolution of ca. 8 Hz/point in F2 and 4 Hz/point in F1. The raw data were zero filled in F1 prior to transformation using the qsine window function for both F1 and F2. the proton relaxation delays were set at 1 s. Delays were chosen to emphasize coupling of 135-140 Hz. NOESY spectra were obtained with mixing times of 0.3 s.

Solid Phase ^{13}C Spectra

The ^{13}C CP/MAS solid phase spectra were recorded at 45.3 MHz on

a Bruker CXP-180 instrument. Cross polarization (CP) times were typically 3ms with the radio frequency field amplitude being 60 kHz with a recycle time of 4-8s. 2K data points were collected with zero filling to 8K before Fourier transformation. Magic angle spinning(MAS) rates of ca. 3 kHz were obtained using Kel-F spinners of the Andrew-Beams type. For the dipolar dephased spectra, the ^1H decoupler was gated off for a period of 40 μs during the delay before the ^{13}C acquisition. Chemical shifts were measured relative to external solid hexamethylbenzene (HMB) and converted to the TMS scale via the factor of 16.9ppm, which is the chemical shift for the CH_3 group of HMB.

(iii) Crystallographic Structures and Structure Solutions

A summary of the crystal data is given in Table 7. All measurements were made on a Rigaku diffractometer with Mo K α radiation. The $\theta/2\theta$ scan technique with profile analysis⁵² was employed at a speed of $4^\circ/\Omega$. The space group was determined by systematic absences. Unit cell parameters were obtained by refining the setting angles of 25 reflections with 2θ angles in the range of 40-50°. Lorentz and polarization factors were applied but no correction for absorption was made.

The structure was solved by direct methods plus Fourier maps and

were refined by full-matrix least squares analysis with weights based on counting statistics. All the atoms were refined anisotropically except the hydrogen which were calculated by differences in Fourier maps. Weights based on counting statistics were used. All the calculations were performed using the NRCVAX crystallographic software package⁵³ by Corrine Bensimon.

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53) Scattering Factors from Int. Tab. Vol. 4

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