THE INTERACTION OF CATIONS WITH CYCLIC ETHERS

Thesis by

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In Partial Fulfillment of the Requirements
For the Degree of
Doctor of Philosophy

California Institute of Technology
Pasadena, California 91109

1974

(Submitted March 7, 1974)

Acknowledgements

I would like to express my great appreciation to Karen Gleason and Edi Bierce for their swift, accurate typing of this thesis.

I wish to express my gratitude to Sunney Chan for his generous assistance, both academic and financial, during my stay at Caltech, for providing a well-equipped laboratory and an unrestricted environment for pursuing scientific endeavors.

I would also like to thank all those others who have, as well, shared their knowledge and ideas with me.

I thank the National Institutes of Health and the Chemistry Department for their financial support.

ABSTRACT

Proton and carbon nuclear magnetic resonance (NMR) have been used to aid in the understanding of solution structure, cation, anion and solvent interactions, and structural aspects of cation specificities of "crown" cyclic polyethers. Investigations were made in water, water-acetone, acetone and chloroform as a function of cation concentration and of anion. Using the effects of the aromatic residues on the molecules we have studied, we have been able to assign the proton and carbon spectra. From the vicinal proton-proton coupling, the electrostatic effect of cation and anion on the proton NMR, and the structural sensitivity of the carbon NMR, we have obtained results on the interaction of Na^+, K^+, Cs^+ and Ba^{+2} with Benzo 18 Crown 6, Dibenzo 18 Crown 6 and Dibenzo 30 Crown 10. Analysis of the cation induced shifts has enabled us in some cases to examine the cation binding as a function of solvent.

The complexes of Benzo 18 Crown 6 and Dibenzo 18 Crown 6 have the same structures in the various solvents as found in the crystal for DB18CR6. However, the solution conformation of the uncomplexed molecules differs from that in the crystal. The K^+, Cs^+ and Ba^{+2} complexes of Dibenzo 30 Crown 10 in solution, have the same configuration reported for the K^+ complex in the crystal. The Na^+ complex does not, and we have proposed an alternate structure. The solvation sphere of a cation is completely removed when it is complexed to the latter crown ether, which is not the case for the 18 membered rings.

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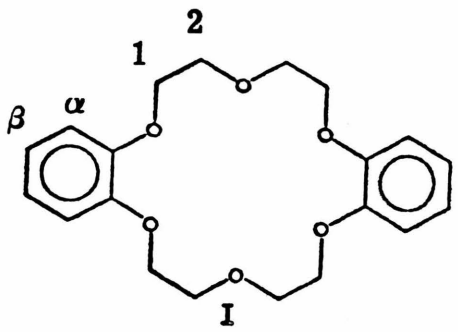
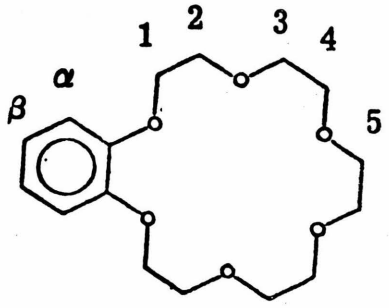
INTRODUCTION

Cyclic ethers, defined as cyclic compounds with the general formula $\text{+O-(CH}_2\text{-CH}_2)_n\text{+}_m$, have been known for some time, 1, 4 dioxane (n = 2, m = 2) being the simplest and most common in the series. It was not until recently, however, when C. J. Pedersen of the DuPont Company isolated compound I in Figure 1 as the product of a side reaction in a synthesis,[1] that the formation of strong, stoichiometric complexes between these molecules and cations was observed. He designated this and the many other cyclic ethers he has made,[1, 2] some of which are illustrated in Figure 2, as crown compounds. Since the IUPAC names for molecules as large as these are rather cumbersome, Pedersen adopted a simplified nomenclature of the general form AAAA-B-Crown-C. AAAA refers to any substituents present on the cyclic ether. B refers to the total number of atoms in the ether ring itself, and C refers to the number of ether oxygens. Compound I is therefore Dibenzo-18-Crown 6. In this work the three cyclic ethers pictured in Figure 1 have been studied and we have adopted a further simplified nomenclature for them given in parentheses under the schematic representation of each molecule. An improved method for synthesizing crown ethers has been recently

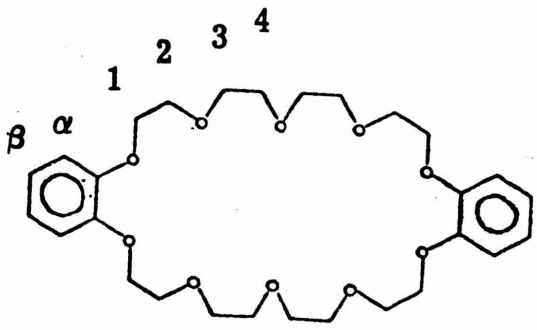
Figure 1. Crown Ethers



Dibenzo 18 Crown 6
(DB18CR6)



Benzo 18 Crown 6
(B18CR6)



Dibenzo 30 Crown 6
(DB30CR6)

reported[3] and bicyclic polyethers have now also been synthesized.[4]

The most striking property of the crown series is their ability to extract alkali ion salts from aqueous into organic phases. This is due to the fact that the crown ethers form a "solvation sphere" around the cation with their polar interior, while the alkane-like exterior makes the complex more soluble in organic media. A consequence of the cation complexation is a reduced tendency for ion pair association which has led to the application of these compounds to the study of cation dependent mechanisms in carbanion reactions.[5] Polymers with cyclic ethers attached to a backbone have been made with efficient desalting capabilities.[6]

It has been found that by changing the substituents on the cyclic ethers one can control the solubility properties and extraction abilities.[7,8,9]

The complexation of crown ethers with various cations in several solvents has been investigated by potentiometric,[10] spectrophotometric[8,11] and calorimetric methods.[12] The general result is that the closer a cation's size is to the size of the crown ether ring, the more stable the complex is. Table 1 gives ring sizes and ionic diameters.[7] In solution only 1:1 stoichiometry has been reported for complexes where the ion is smaller than the ring size.[10,12] For larger ions 2:1 complexes of crown to cation have been observed in

TABLE 1

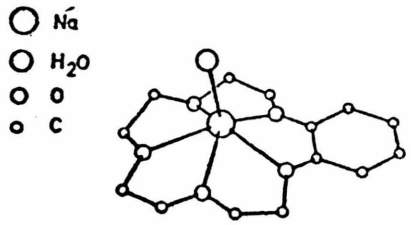
Crown and Cation Diameters (Å)

Polyether	Hole	Ion	Diameter
14 Crown 4	1.2 - 1.5	Li^+	1.36
15 Crown 5	1.7 - 2.2	Na^+	1.94
18 Crown 6	2.6 - 3.2	K^+	2.66
21 Crown 7	3.4 - 4.3	Rb^+	2.94
		Cs^+	3.34
		Ba^{++}	2.68

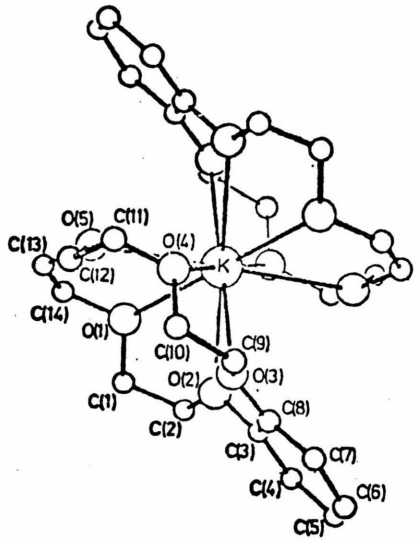
solution and in a crystal (Figure 2).[10] Pedersen suggested such complexes would have a "sandwich" like structure where the cation is held between two cyclic ethers.[13] He was able to obtain crystals of complexes with well-defined stoichiometries greater than 1:1 for ions smaller than the ring size, however X-ray studies of one such system $[(Rb,Na)^{+}NCS^{-}]_2:[DB18CR6]_3$ revealed a unit cell containing one uncomplexed molecule and two complexes (Figure 2).[14] Additional X-ray results have been obtained for free and complexed crown ethers yielding some unusual results (Figure 2). Further interest in the crown compounds has been generated because of the similarity in selectivity and structure of these molecules with compounds such as nonactin and valinomycin (Figure 3) which play an important role in biological ion transport.

Ion selective electrodes using cyclic ethers have been made just as for valinomycin.[21,22] Eisenman has found that crown compounds enhance conductivity in model lipid bilayers,[8,9] but unlike the naturally occurring molecules, their selectivity for ion transport is not the same as the aqueous stability sequence for 1:1 complexes. A detailed discussion of these experiments can be found in reference 23. This problem will be touched on further in the conclusions. Studies on mitochondrial membranes have shown that cyclic ethers interfere with activity at site I on the oxidative phosphorylation chain

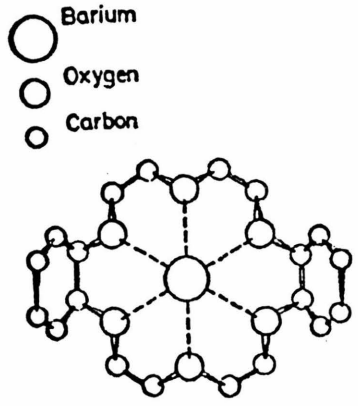
Figure 2. X-ray Structure of Crown Ethers and Their Complexes from References 15, 16, 17, 14, 14, 18, 19, 20, 20, respectively.



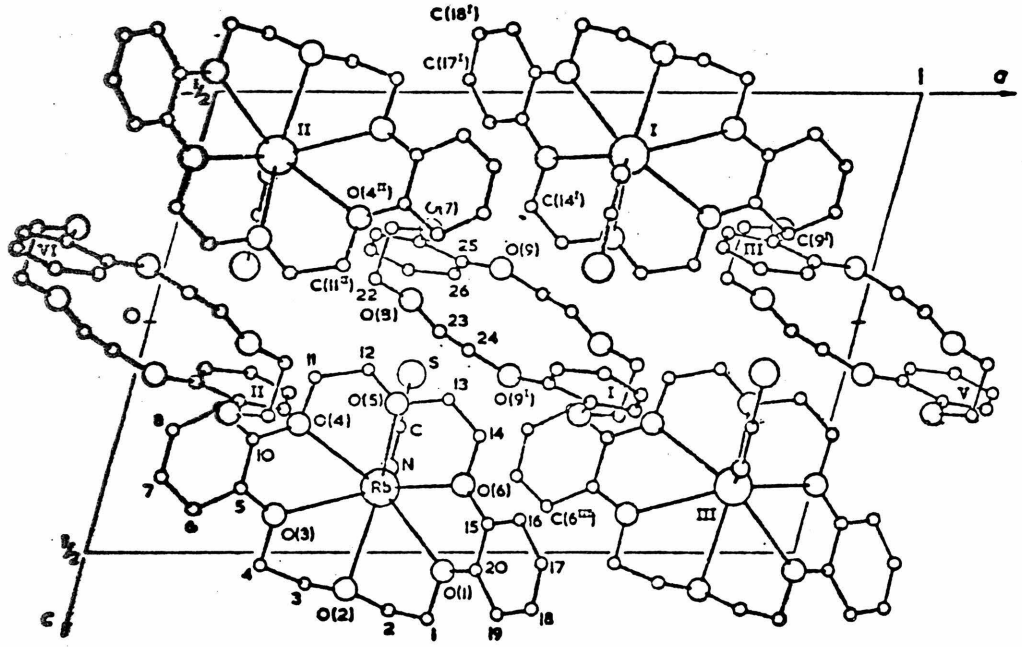
The complex cation of compound (II), NaI(*benzo*-15-*crown*-5),H_2O.



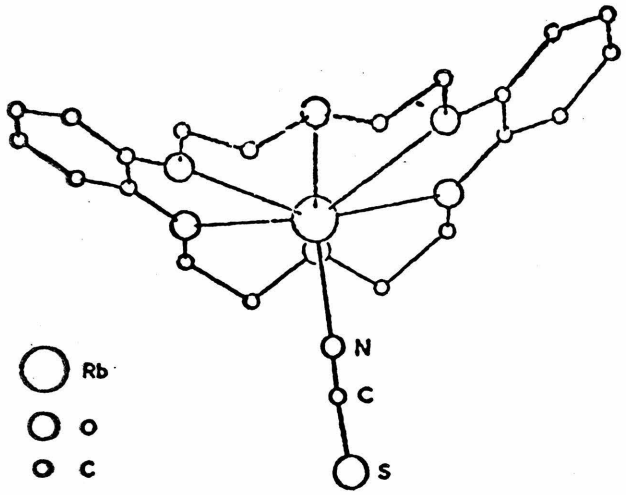
$K,(Benzo\ 15\ Crown\ 5)_2$



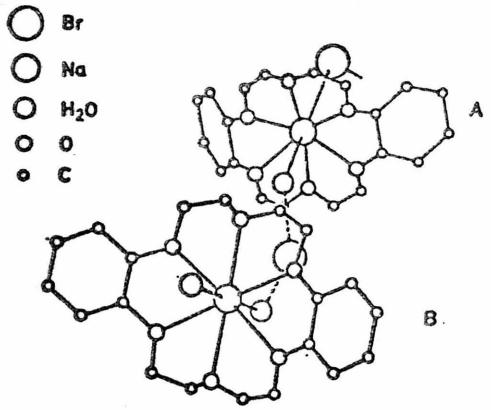
Dicyclohexyl-18-*crown*-6 *(isomer A) complex*



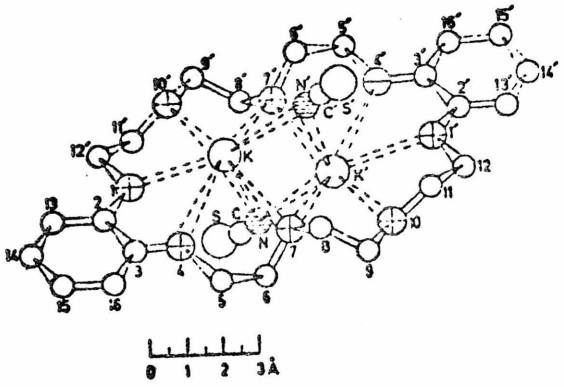
((Rb, Na) NCS)$_2$ (DB18CR6)$_3$



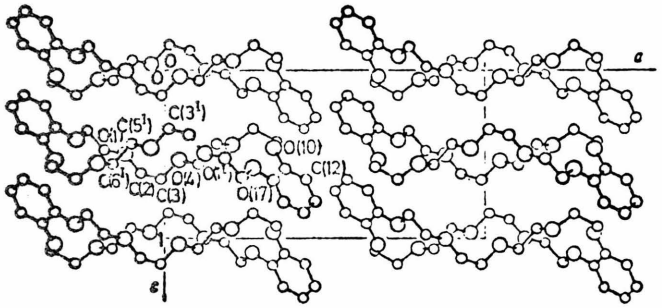
One molecule of the RbNCS(dibenzo-18-crown-6) complex.



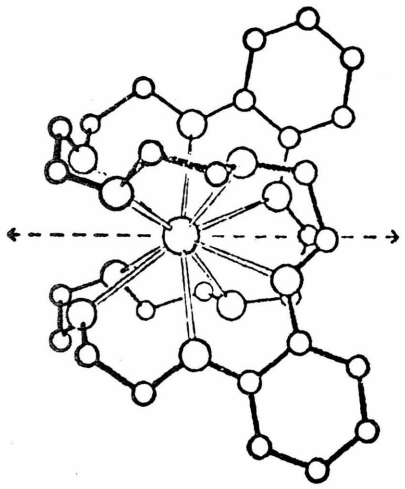
The asymmetric unit of (I), NaBr(*dibenzo*-18-*crown*-6), $2H_2O$. *Broken lines indicate hydrogen bonds between water molecules and bromide ions. The fourth water molecule in the asymmetric unit is not shown; it can be visualised as behind the bromide of Complex A or in front of the nearer water molecule of Complex B.*



One molecule of the complex. Atoms with primes are centrosymmetrically related to those without. ○ = *carbon,* ○ = *oxygen.*

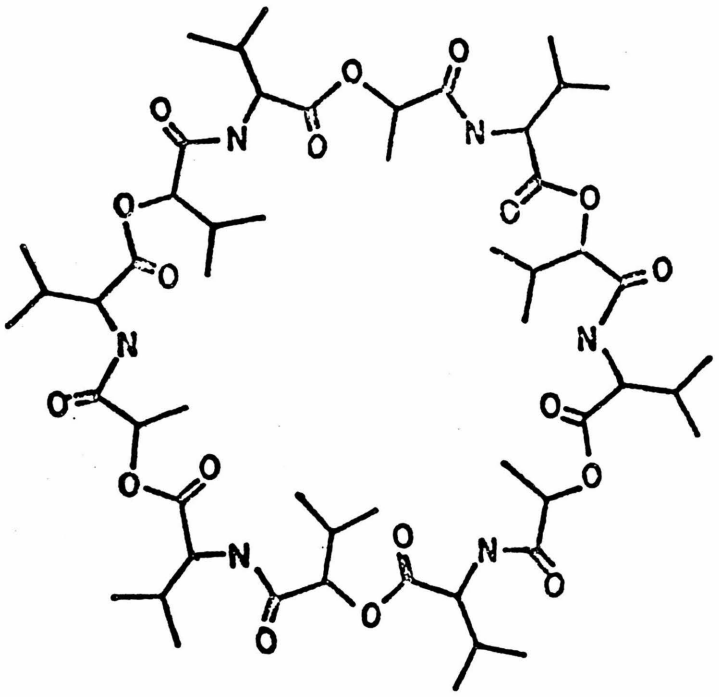


The structure of dibenzo-30-crown-10 projected along **the [b] axis.** The designations of some of the atoms are shown, **those with** Roman numeral superscripts, I, are related to those **without** by the centre of symmetry at 0, $\frac{1}{2}$, $\frac{1}{2}$. Molecules in **heavy** lines have their centres at $y = \frac{1}{2}$, those in lighter lines **have their** centres at $y = 0$

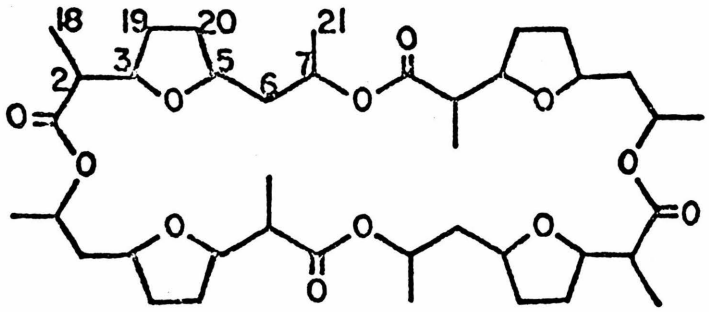


The complex cation of compound (III), KI(*dibenzo-30-crown-10*).

Figure 3. Structures of Nonactin and Valinomycin



VALINOMYCIN



NONACTIN

in a manner similar to valinomycin.[24, 25] The overall details of this complicated process are far from clear.

The availability of many cyclic ethers with a range of ion selectivities and solubilities make them potentially valuable probes for investigating the role of ions and ionophores in living systems. Using these molecules it should be possible to elucidate questions of ion dependent and independent effects and the locus of their action in or on the membrane.

Before the biological and chemical aspects of crown compounds can be understood, it is important to know details of solution conformation, solvent and ion interactions, as well as equilibrium and kinetics of complexation.

Several techniques have been used to determine equilibrium data as mentioned earlier. Kinetic data have been obtained with temperature jump methods,[26, 34] Na^{23} nuclear magnetic resonance,[27, 28, 29] and in one case where the anion gave rise to a large chemical shift, proton magnetic resonance.[11]

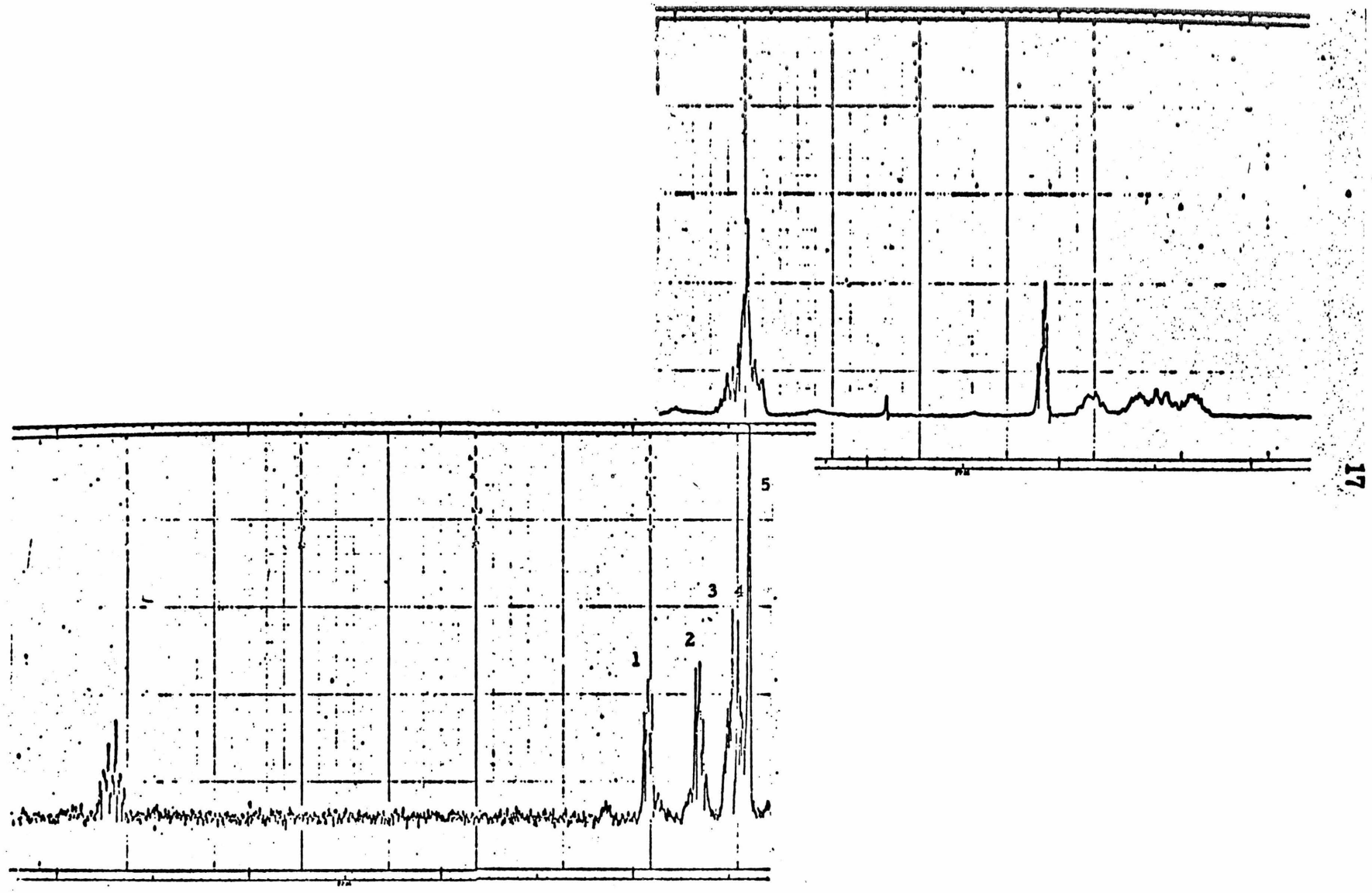
Proton and Carbon Nuclear Magnetic Resonance (PMR and CMR, respectively) are potentially valuable methods for investigating all of these aspects. Changes in resonance position at various ratios of crown to cation can be used to determine overall equilibrium

constants. The magnitude of these shifts as well as coupling constants reveal information of solvent, cation and anion interaction as well as solution conformation. Linewidth (T_2) changes as well as spin lattice relaxation times (T_1's) can give information on kinetics and molecular dynamics. PMR has been avoided in studies of polyethers in the past because of the small complex induced shifts.[27] This problem can be surmounted by using a high field Nuclear Magnetic Resonance (NMR) spectrometer operating at 220 MHz where the shifts in Hz are greater than for conventional 100 MHz and 60 MHz instruments.

CMR is very responsive to conformational changes and has been used by others to some extent, however, it is relatively insensitive and cannot reveal the absolute configuration. The two NMR techniques together, however, provide a powerful means of determining the results we seek.

The benzo substituted crown compounds were chosen for study because the aromatic moiety, through its magnetic anisotropy, separates the resonances of the ether protons, allowing assignment of the PMR and CMR spectra, and permitting a straightforward analysis of the ether proton-proton coupling constants. The latter provides valuable structural information. Figure 4 illustrates the advantages to the NMR experiment of having an aromatic group present in the molecule. A further reason for choosing these

Figure 4. Spectra of dicyclohexyl-18-crown-16 (upper) and benzo-18-crown-6 (lower) positioned to retain the proper shifts relative to TMS. Spectra were taken in acetone at 15°C on an HR-220.


1
2
3
4
5

compounds was that nuclear coordinates were available or being determined for DB18CR6 and DB30CR10.

Water is clearly a logical choice for a solvent to work with, but because of the low solubility of most of the compounds studied in this medium, and the low cation binding constants, it was difficult to use it as a general solvent. Acetone and acetone-water mixtures were therefore used to simulate a dipolar high dielectric medium in which both salts and crown-ethers were independently sufficiently soluble to carry out PMR and in some cases CMR investigations. Chloroform provided a readily available low dielectric organic medium.

In the results reported here, there are three major effects which are relied on heavily in drawing conclusions.

The first is the magnetic anisotropic effect of aromatic groups which is in large part responsible for our being able to get useful information from the PMR data. In a semi-classical model, this is considered to arise from the circulation of the π electrons in two circular current loops[30] which have been empirically chosen to be 0.7Å above and below the plane of the aromatic ring. Waugh and Fresenden[31] and Johnson and Bovey[32] calculated shielding effects on the basis of this model.

The equation derived is

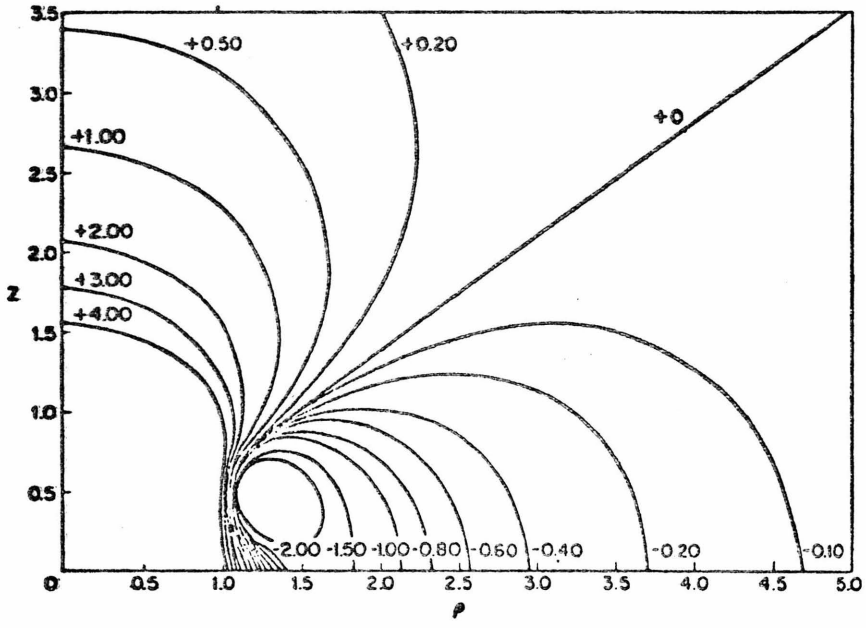
$$\delta = 3.2266\left[\frac{1}{[(1+r)^2 + z_1^2]^{1/2}} \cdot \left(K + \frac{1 - r^2 - z_1^2}{(1-r)^2 + z_1^2} E\right) + \frac{1}{(1+r)^2 + z_2^2} \cdot \left(K + \frac{1 - r^2 - z_2^2}{(1-r)^2 + z_2^2} E\right)\right] \quad (1)$$

where δ is the chemical shift effect, E and K are complete elliptic integrals of the first and second kind respectively with modulus $k^2 = \left(\frac{4r}{(1+r)^2 + z^2}\right)$, r is the horizontal coordinate in units of ring radii (1.39 Å) and z_1 and z_2 are the vertical coordinates, in ring radii, (z + 0.33) and (z - 0.33). (This takes into account the two current loops.) For the purposes of this work, Eq. (1) was programmed to be solved by computer; values of z and r obtained from crystal structure data, Drieding models and CPK models were used to calculate expected shifts.

A plot of some shielding values is shown in Figure 5. In the cyclic ethers, the general trend is that as the number of bonds between the aromatic ring and the protons decrease, the resonance moves to lower field.

The second effect is the relation of the vicinal proton-proton coupling constants to the dihedral angles betwen C–H bonds on adjacent carbon atoms. On the basis of theoretical and empirical

Figure 5. Shielding from a benzene ring.
Center of ring at origin (from reference 32).


+0.50
+0.20
+0
+1.00
+2.00
+3.00
+4.00
-2.00
-1.50
-1.00
-0.80
-0.60
-0.40
-0.20
-0.10
z
ρ
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0

considerations Karplus [33] derived Eqs. (2) and (3) relating these two parameters

$$J = J^0 \cos^2 \theta - C \qquad 0 \leq \theta \leq 90° \qquad (2)$$

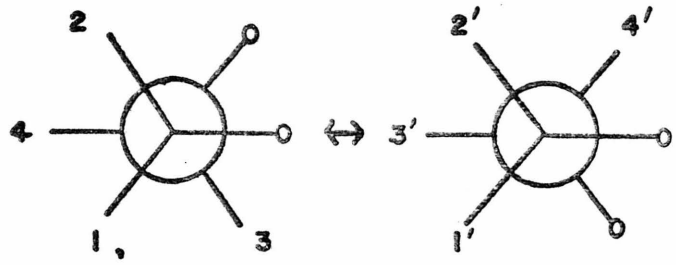
$$J = J^{180} \cos^2 \theta - C \qquad 90 \leq \theta \leq 180° \qquad (3)$$

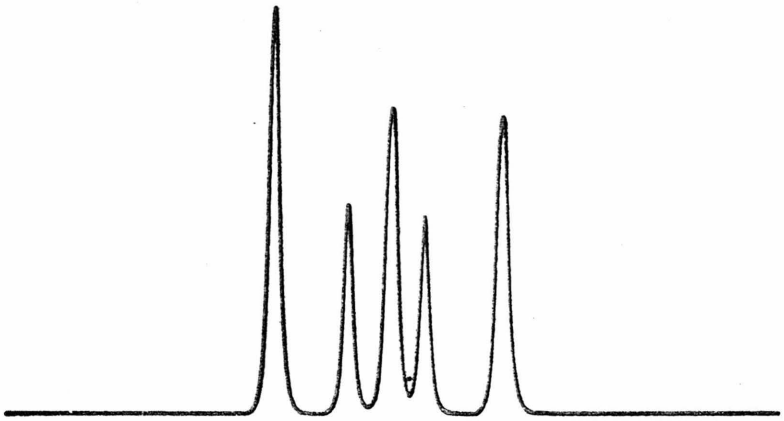
For typical systems $J^0 = 8.5$ Hz, $J^{180} = 9.5$ Hz and $C = -0.3$ Hz. This equation produces quite reasonable results for a large number of compounds.

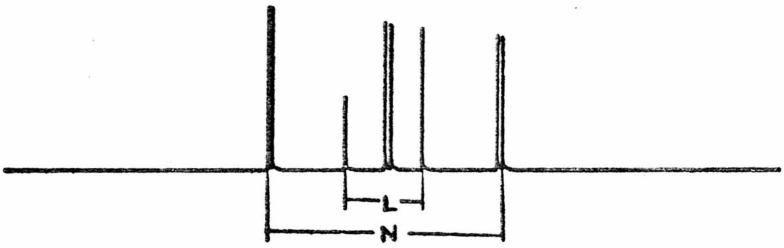
The coupling is largest when the dihedral angle is 0° or 180° and decreases to a minimum at 90°. These equations do not predict the coupling constants for cyclic ethers very well, but the best agreement between experimental and simulated spectra is obtained when the coupling constants are calculated for rapidly inverting + and - gauche rotamers. The perturbation caused by substituent electronegativities for fragments of the type $X-CH_2-CH_2-Y$ and in cyclic ethers has been considered. [34] Relations for the vicinal coupling constants in the various rotational isomers in terms of the sum of electronegativities for X and Y have been determined. These equations are in Figure 6. The results of these equations are in good agreement with the experimental values. Implicit in these equations is the assumption of a fixed, presumably pure gauche or trans form .

Figure 6. Determination of vicinal proton-proton coupling constants from an aa′ xx′ pattern.

L = 2.9 N = 9.1 equations from references 34 and 35.







$L = J_{ab} + J_{ab'}$ $\quad N = J_{ab} - J_{ab'}$

$J_{ab} = J_{a'b'} = (J_{13} + J_{1'3'}) / 2$

$J_{a'b} = J_{ab'} = (J_{14} + J_{1'4'}) / 2$

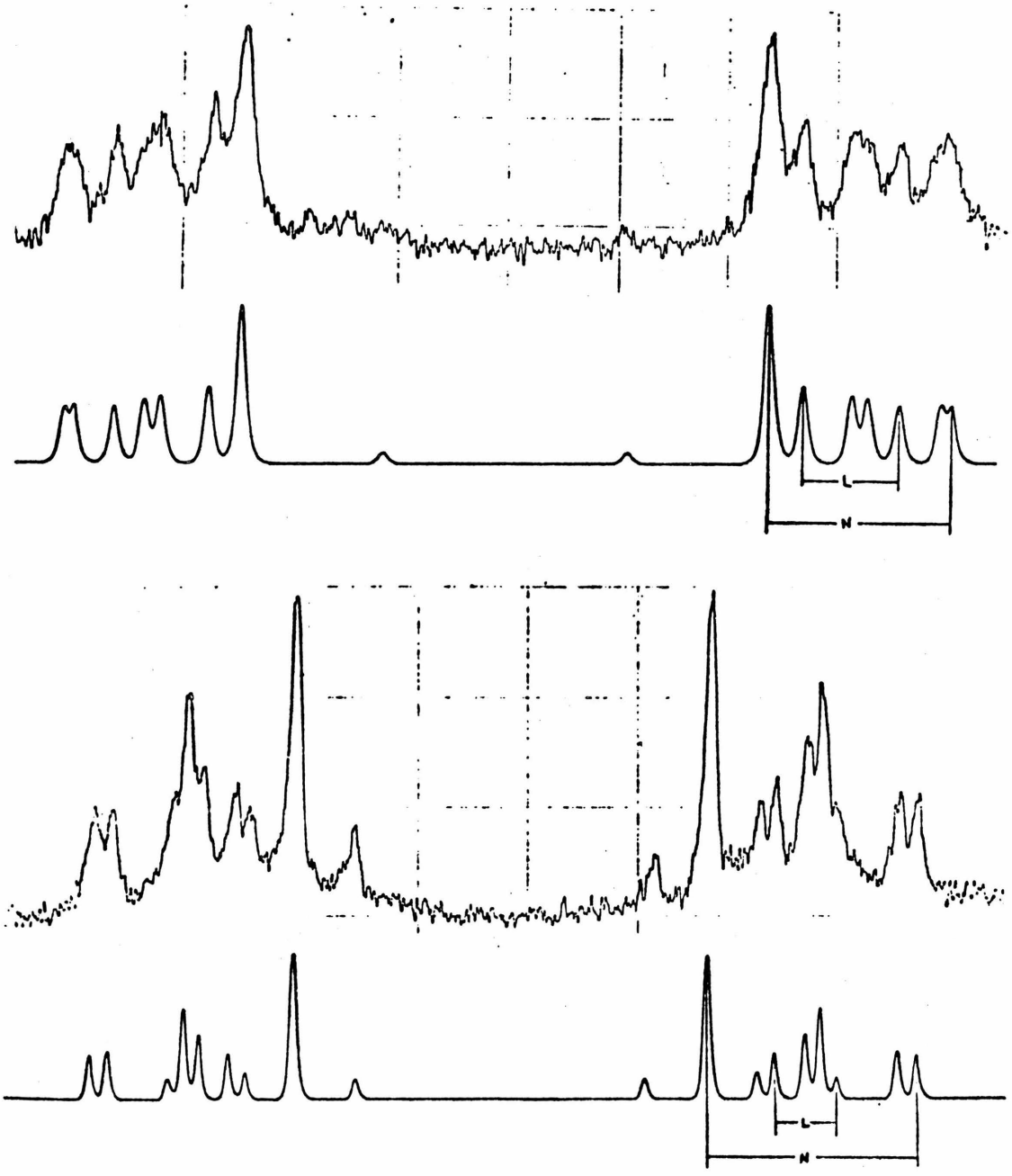
$J_{ab} = 2J_g^g / 2 = 8.94 - 0.94 \Sigma E_n$

$J_{ab'} = (J_g^t + J_g^{g'}) / 2 = 26.92 - 2.03 \Sigma E_n$

$J_g^{g'} = 10.45 - 1.43 \Sigma E_n$

$J_g^t = 16.47 - 0.60 \Sigma E_n$

Figure 7. Observed and simulated spectrum of B18CR6 (lower) and K^+, B18CR6 (upper). For lower simulation $\Delta\delta = 26.9$, $J_{12} = -10.2$, $J_{13} = 6.1$, $J_{14} = 3.4$, $J_{23} = 3.4$, $J_{24} = 6.1$, $J_{34} = -11.0$. For upper simulation $\Delta\delta = 31.3$, $J_{12} = -11.0$, $J_{13} = 6.4$, $J_{14} = 2.0$, $J_{23} = 2.0$, $J_{24} = 6.4$, $J_{34} = -11.0$.


L
N
L
N

The protons of the $-O-CH_2-CH_2-O-$'s give rise to aa′bb′ patterns depending on the separation of the two multiplets.

In Figure 7 are the observed and simulated spectra for the protons at position 1 and 2 of B18CR6 in a free state and when complexed to K^+. These spectra were taken at high resolution at 100 MHz where the patterns are in the aa′bb′ class. As the multiplets approach each other the sensitivity of the individual components to coupling constants increases; the fit to a simulated spectrum is therefore more precise. From the parameters [5] used in these two fits, several important conclusions can be drawn. The equivalence of the chemical shifts for atom a and a′ and for b and b′ when they are not a priori in magnetically equivalent positions, particularly with respect to the aromatic ring, indicates rapid averaging of the shift. The chemical shift equivalence has been checked at 300 MHz on several of the molecules studied here and still holds. The equality of $J_{ab'}$ and $J_{a'b}$ means that there is, on a rapid time scale, conversion between the two gauche and the one trans rotamer or just between the two gauche rotamers. The coupling constants including electronegativity effects and the results of the Karplus relation indicate the latter. The great similarity of these results with the coupling constants 1, 4 dioxane (Table 3) [35] where + gauche - gauche inversion is known to occur supports this conclusion. When the multiplets get close together it is necessary to resort to computer simulation.

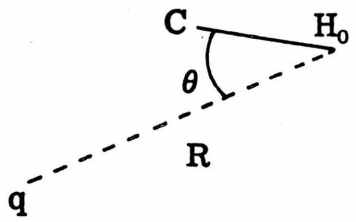
However for the majority of the spectra done at 220 MHz these patterns approach the aa'xx' appearance, and the vicinal coupling constants can be directly calculated as shown in the simulation in Figure 6. The values in Figure 7 are typical for the ether coupling in their respective bound and complexed states. The mathematical details aa'bb' and aa'xx' pattern can be found elsewhere.[36]

There is in the spectra studied here (Fig. 8) another AA'BB' system of quite different appearance. This is due to the four aromatic protons (Fig. 8). A detailed analysis of the pattern can also be found in standard NMR texts.[36] This multiplet does not give any conformational information since the proton positions are fixed. The coupling constants observed in this region are those expected for disubstituted benzenes.[37] For the cyclic ether case these coupling constants do not change from cyclic ether to cyclic ether or on complexation, to within our experimental accuracy.

The third effect is the shift of a proton resonance when an electrostatic field is present. Buckingham[38] has derived an expression for predicting this effect

$$\delta = A\vec{E}\cos\theta - B\vec{E}^2 \qquad (4)$$

where δ is the shift, A and B are constants, $\vec{E}$ is the electric field at the proton and θ is given below



Various values of the constants have been suggested, the ones used here have been determined from experiment,[39] giving

$$\delta = 12.5 \times 10^{-6} \frac{q}{R^2} \cos\theta - 17 \times 10^{-6} \frac{q^2}{R^4} \qquad (5)$$

where q is the charge in units of electronic charge and R is the charge to proton distance in Å. In the present work the values predicted for complexation of a +1 charged cation are generally several times too big, however when calculating the incremental shift caused by replacing a ion of +1 charge with a +2 charged species of similar dimensions, the equation gives reasonably accurate results. This implies that Eq. (5) is reasonably accurate, but that there are other effects, independent of the electric field, contributing to the complexation shift.

MATERIALS AND METHODS

DB18CR6, CsI, $(DB18CR6)_2$, B18CR6 and DB30CR10 were a generous gift of H. K. Frensdorf of the DuPont Company and were used as received. B18CR6 gave peculiar binding curves that were linear but which reached the limiting shifts at 90% of the expected value of salt added. This was attributed to a 10% by weight impurity and all results were corrected for this. This sample was checked by Atomic Absorption Spectroscopy for Na^+ and K^+ and neither was found, although the Na^+ results were ambiguous because of contamination from the glassware. There is some evidence in the PMR spectrum of an organic impurity.

KCNS, $KClO_4$ and NaCNS were reagent grade from Mallincrodt Co. KI and NaI were reagent grade from Baker Co. Reagent grade $NaClO_4$ (anhydrous) was purchased from G. Fredrick Smith Co., and 99.9% $CsClO_4$ from ROC/RIC Co. $Ba(ClO_4)_2$ was made here by George Rossman and was in excess of 99% pure.

Acetone-d_6 was purchased from Diaprep and Merck Co., chloroform -d was purchased from Merck and the D_2O was from Columbia Organic Co. Initially care was taken to dry the acetone-d_6 with $CaSO_4$ or molecular seives. It was found, however, that using

this solvent directly from the manufacturers' sealed vials gave the same results. Any contribution of water from the salts was negligible. When acetone and chloroform are referred to as NMR solvents in this work it is the deuterated form that is meant.

With the exception of the two spectra in Figure 7 which were done on a Varian XL-100 at 30°C, all others were taken on a Varian HR-220 equipped with a Fourier Transform accessory for ^{1}H and ^{13}C. The proton spectra were taken at 220 MHz either in the CW or FT mode at ~15°C. The carbon spectra were all done in the FT mode at 55.3 MHz and at ~47°C. Noise and CW proton decoupling were used. A Varian 620i computer with 16K memory (8K for FT data) was employed to carry out the Fourier transform. T_1's were determined by progressive saturation and 90°-90°-180° inversion recovery sequence.[40] Peak intensities were determined by weighing them and the accuracy of the T_1 values is 20%. Chemical shifts are good to within ±0.5 Hz for protons and ±1 Hz for carbon, vicinal proton-proton coupling constants are good to ±0.2 Hz. A positive shift is a downfield shift.

Spectrum simulation was done on an IBM 370/155 with the LAOCOON III program[41] and on the Varian 620i computer system using a Varian supplied program.

Errors in the binding curves are denoted by the size of the symbols used.

All crown ethers and salts were independently soluble enough in acetone to perform the PMR experiments. Complexes in $CDCl_3$ were made by evaporating the acetone and redissolving the crystalline complex in $CDCl_3$ where possible.

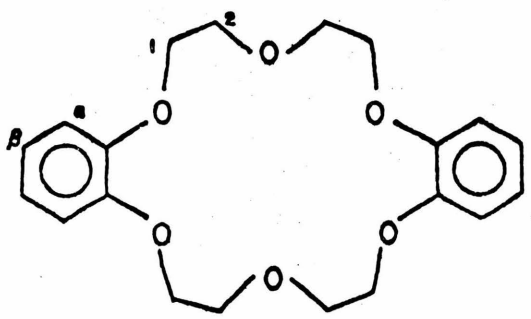
With the exception of the DB18CR6, Cs^+ binding curve where the Cs^+ concentration was kept constant and the ether concentration varied, all other binding curves were determined at constant ether concentration by varying the concentration of the salt in question.

RESULTS AND DISCUSSION

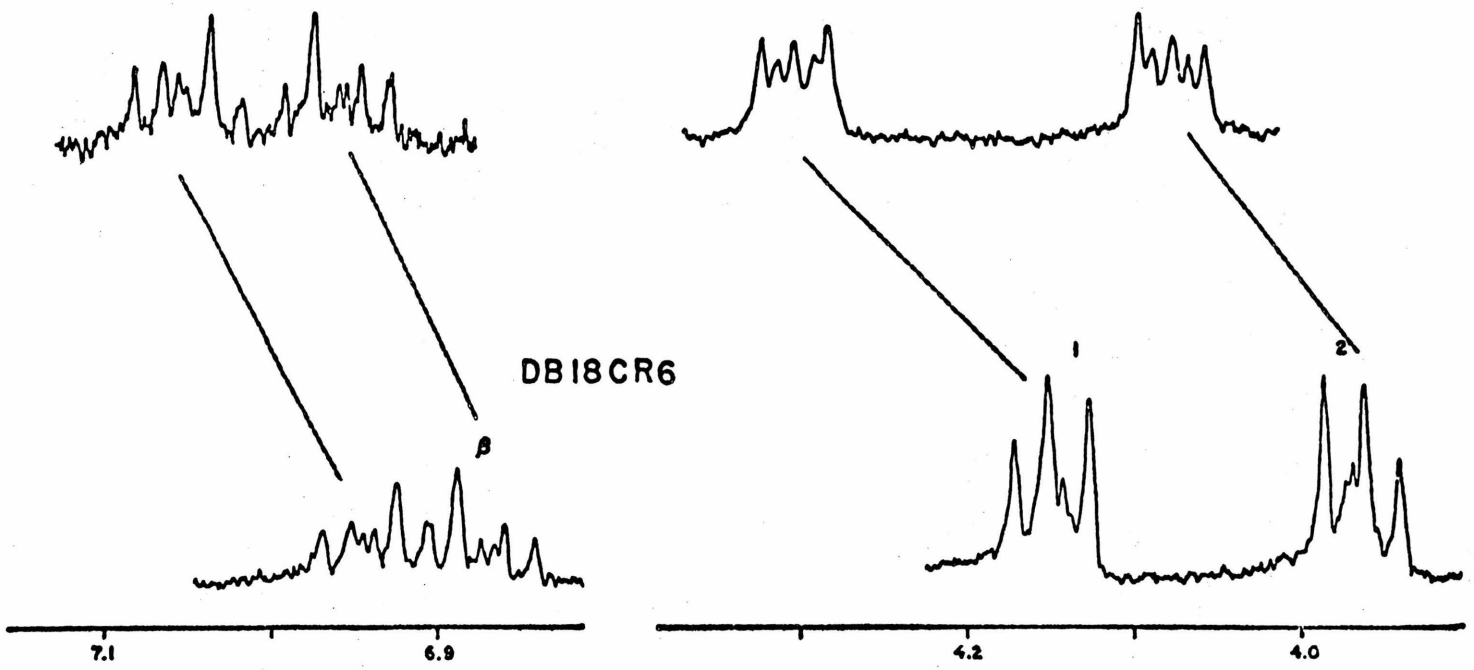
PMR Spectra of DB18CR6

Because of the molecular symmetry and rapid ring inversion, DB18CR6 has the simplest spectrum of the cyclic ethers studied here. A spectrum is shown in Figure 8 and chemical shifts and coupling constants are given in Tables 2 and 3. The assignment of the protons in the ether region can be made on the basis of their proximity to the aromatic moiety. The proton closest to the ring is deshielded the most and occurs at the lowest field. At conditions of optimum resolution the lower field ether multiplet is slightly broader than the upper field ones, and the lower field portion of the aromatic resonance is also broadened. Long range spin-spin coupling through five bonds with coupling constants up to 0.8 Hz has been reported for methoxy benzenes [39] (between methyl and aromatic protons). On this basis the lower field portion of the aromatic resonances is assigned to the α benzo position. It should be emphasized that even though the sixteen protons responsible for the ether resonances are not a priori magnetically equivalent, they collapse into two sharp multiplets with a pattern characteristic of a system rapidly inverting between the two gauche rotamers. There is further evidence supporting

Figure 8. PMR spectrum of DB18CR6 and K^+, DB18CR6 in acetone.



K^+, DB18CR6



DB18CR6

PPM from TMS

TABLE 2

Proton Chemical Shifts for DB18CR6[a]

Conc.	Solvent	Position	1	2	$\alpha + \beta/2$	$\alpha - \beta(H_3)$
4.6×10^{-3} 1.07×10^{-1}	$CDCl_3$		4.177	4.041	6.888	≥ 5
5×10^{-3}	C_3D_6O		4.147	3.965	6.910	15

[a] relative to TMS in ppm

TABLE 3

Vicinal Coupling Constants for DB18CR6

Ether Region

Solvent	$J_{13}(H_3)$	$J_{14}(H_3)$
$CDCl_3$	3.3	5.7
C_3D_6O	3.5	5.8
1, 4 Dioxane[a]	2.7	6.05
Calculated[b]	1.8	5.5
Calculated[c]	2.36	6.55

Aromatic Region

$J_{AA'} = 0.2$

$J_{AB} = 8.0$

$J_{AB'} = 1.6$

$J_{BB'} = 7.4$

---

[a] from ref. 35

[b] from eqs. 2 and 3

[c] from eq. in fig. 6

rapid inversion from the CMR T_1's [42] which will be discussed later. On the basis of differences in chemical shifts for the individual protons derived from ring current shielding calculations, and the linewidths, a lower limit for the rate of inversion of ~1000 sec^{-1} can be estimated.

In Table 4 it can be seen that the agreement between the observed ether multiplet separations and coupling constants and those derived from the X-ray data is not very good. We attribute this to a difference between the solution and crystal conformation of the uncomplexed molecule, and we have proposed a solution conformation which better fits the data (Figure 9). For all the crown ethers examined here, and in dioxane [35] as well, there is one set of coupling constants characteristic of the ether region, and which are in agreement with the X-ray results for DB30CR10. [20] In both of these instances the $O-CH_2-CH_2-O$ fragments are in + and - gauche conformation, presumably undergoing rapid conversion, and do not have trans arrangements as found in the crystal results for DB18CR6. The crystal conformation of DB18CR6 was determined in a mixed crystal containing DB18CR6 and (Rb,Na)NCS, DB18CR6. [14] The presence of ions will set up local electric fields which may interact with the ether dipoles and distort the structure. The DB30CR10

TABLE 4

Ether Multiplet Separation (Hz)

Observed	
$CDCl_3$	30
C_3D_6O	40
Calculated	
from x-ray results	62
from proposed structure	49

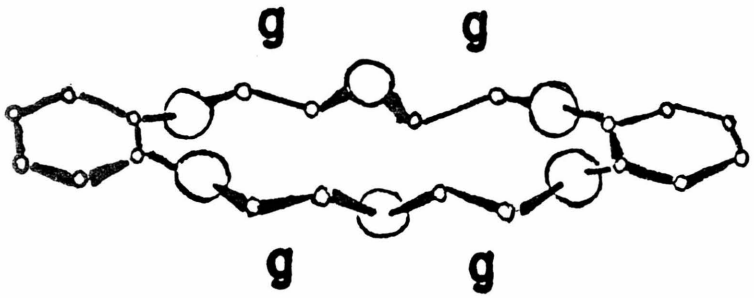
Coupling Constants (Hz)

Calculated[a]	J_{13}	J_{14}	J_{23}	J_{24}
from x-ray data	7.14	2.88	12.05	7.14
from proposed structure	2.36	6.55	6.55	2.36

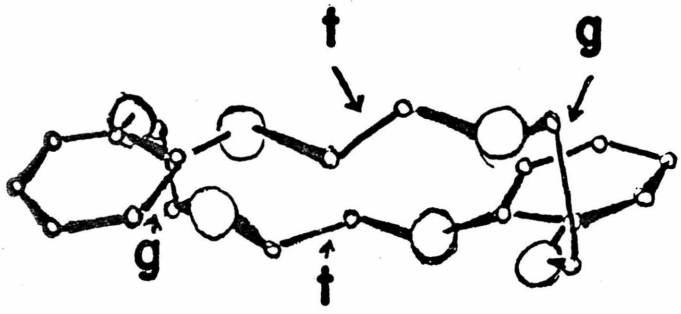
[a] from eq. in fig. 6 and ref. 34

Figure 9. Proposed structure (a) and X-ray determined structure [14] (b) of DB18CR6.

a



b

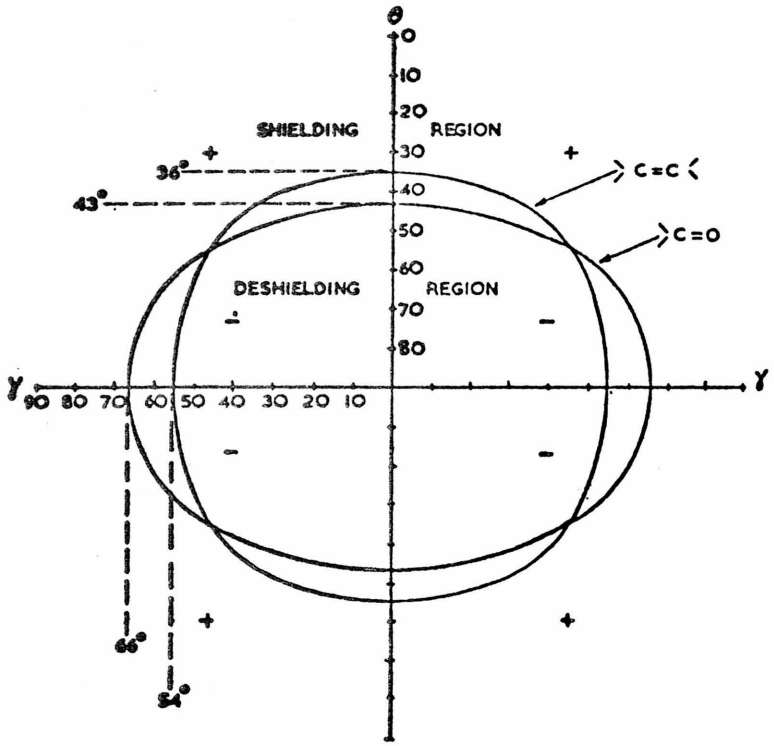


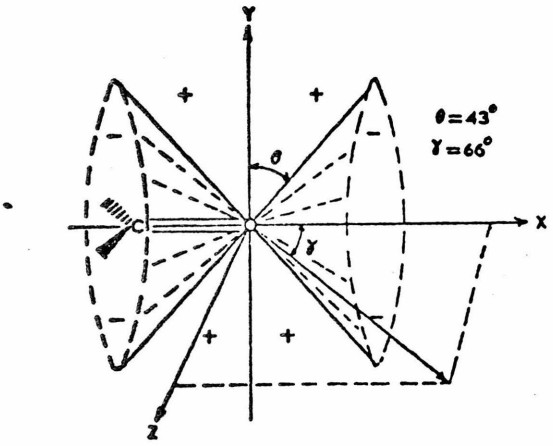
structure was done in a pure crystal. There is an apparent solvent effect in chemical shifts of DB18CR6 in $CDCl_3$ and acetone. This can be caused by a conformational change that would change the relative position of protons and the aromatic ring. This is ruled out because the ether proton vicinal coupling does not change with solvent (Table 3). Also if a comparison of the solvent effect for DB18CR6 and for B18CR6 (Table 12) and DB30CR10 (Table 20) is made, it is seen that the protons farther away from the aromatic ring have the greatest solvent shift and that the effect for positions 2, 3, and 4 on these molecules are roughly the same. The latter is also the value observed for position 2 in DB18CR6.

Another conformational change could be the reorientation of the ether dipoles and hence a change in their electric field effect. The consistency of the coupling constants shows that this is not the case either.

This leaves the possibility of a solvent-solute dipole-dipole interaction between the ether groups and the carbonyl groups of acetone which would cause the dipoles to line up anti-parallel to each other. The gas phase dipole moments of dimethyl ether, which we will use as a model, is 1.3 D and for acetone is 2.88 D.[43] The acetone molecule has a chemical shift effect shown in Figure 10,[44] and an anti-parallel arrangement could then provide a shielding effect.

Figure 10. Anisotropic effect of a carbonyl group from reference 44.


θ
0
10
20
30
40
50
60
70
80
SHIELDING REGION
DESHIELDING REGION
36°
43°
C=C
C=0
γ
90 80 70 60 50 40 30 20 10
66°
54°
+
−


Y
θ=43°
γ=66°
θ
γ
X
Z
C
+
−

The greater availability of protons further from the benzo group to solvent interactions explains the variation of the shift with position. $CDCl_3$ has a smaller dipole moment, 1.02 D,[43] as well as a smaller shift anisotropy and would not be expected to exhibit a solvent interaction.

DB18CR Cation Complexes in Acetone

Although DB18CR6 has been found to complex a large variety of cations, the emphasis here is on some of the alkali metal ions because of their biological importance.

Stability constants for DB18CR6 with Na^+ and K^+ have been measured by nmr in acetone, and the results are shown in Figure 11. The solid lines in Figure 11 are solutions, for a particular η value, to the equation

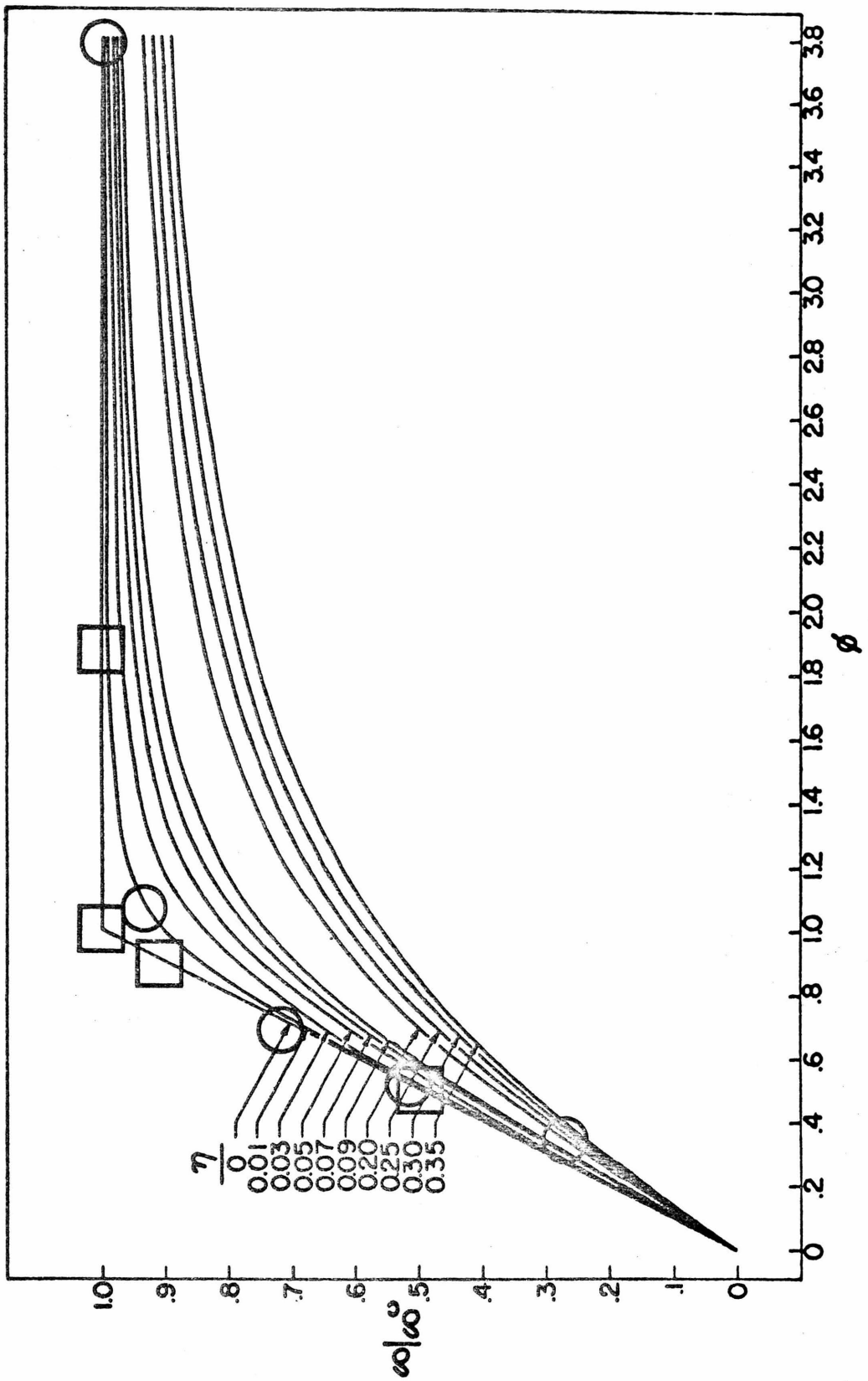
$$|\delta - \delta_0| = \frac{1}{2}[(1 + \eta + \Phi) - \sqrt{(1 + \eta + \Phi)^2 - 4\Phi}] \qquad (6)$$

which represents the behavior of the chemical shifts of a molecule undergoing the reaction

$$A + B \underset{}{\overset{K}{\rightleftharpoons}} AB.$$

A in this case is the ion and B the crown ether. δ is the shift induced at a ratio Φ of total ion to total crown, δ_0 is the limiting induced shift,

Figure 11. Normalized cation induced shifts for K^+ (squares) and Na^+ (circles) with DB18CR6 in acetone. The average of the normalized shifts for the ether and aromatic resonance were plotted. For the K^+ plot KCNS was the salt and the crown concentration was 6.67×10^{-3} M $K_{K^+} > 2 \times 10^4$ L M^{-1}. For the Na^+ result $NaClO_4$ was the salt and the crown concentration was 2.5×10^{-3} M, $K_{Na^+} \sim 4 \times 10^4$ L M^{-1}.


η
0
0.01
0.03
0.05
0.07
0.09
0.20
0.25
0.30
0.35
σ/σ₀
ϕ
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1.0
0
.2
.4
.6
.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8

that of the particular resonance in the complexed AB state, and $\eta = 1/KB$, where K is the equilibrium constant, and B is the total concentration of crown. The close correlation of the observed data with these curves indicates a 1:1 complexation of cation to crown ether. Additional evidence of stoichiometry and high binding constant can be found in the lack of concentration dependence in the shift of a 1:2 ratio of K^+ to DB18CR6 in Table 5. Potentiometric measurements in methanol show 1:1 complexation and stability constants of 2.29×10^4 M L^{-1} and 1.0×10^5 M L^{-1} for Na^+ and K^+, respectively.[10] Studies using Na-23 nmr in dimethyl formamide also show 1:1 complexation.[27] There is no observed variation of binding constant with anion.

The limiting shifts are given in Table 5 and the coupling constants for the complexes are in Table 6. With the possible exception of the NaCNS complex there is no anion shift dependence. Because of the variety in size and shape of the anions used, this is evidence that the ions are dissociated. Ion pairing in acetone of NaI, NaCNS and $NaClO_4$ has been studied by Na^{23} nmr,[56] and in the concentration range used here $NaClO_4$ shows no ion pairing while NaI and NaCNS do, with NaI showing the greatest tendency. The presence of a crown molecule should reduce the tendency of ion pairing by shielding the cation; the degree of this reduction will be dependent on the anion

TABLE 5

Limiting Shifts[a] and Induced Shifts[b] for DB18CR6 Complexes in Acetone

Crown conc.	Salt	Position	1	2	β	α	$\alpha - \beta$ (Hz)
1×10^{-3}	KI		4.283	4.069	7.047	6.956	20
			(30.3)	(23.0)	(22.6)	(17.5)	
6.67×10^{-3}	KCNS		4.295	4.085	7.061	6.961	21
			(32.8)	(26.2)	(18.7)	(25.8)	
1×10^{-2}	$KClO_4$		4.295	4.062	7.062	6.962	21
			(32.5)	(21.2)	(18.9)	(18.9)	
2.5×10^{-3}	NaI		4.255	4.010	7.031	6.940	20
			(23.7)	(9.9)	(19.1)	(14.0)	
1×10^{-2}	NaCNS		4.222	4.041	6.998	6.916	18
			(16.5)	(16.6)	(11.9)	(8.8)	
5×16^{-3}	$NaClO_4$		4.255	4.002	7.035	6.966	20
			(23.7)	(8.1)	(19.9)	(14.8)	
4.3×10^{-3}	$Ba(ClO_4)_2$		4.497	4.110	7.161	7.048	25
			(77.1)	(41.8)	(47.8)	(37.1)	
KCNS:DB18CR6 = 1:2							
8.6×10^{-3}			4.209	4.011	7.004	6.914	17.5
			(13.7)	(10.1)	(11.3)	(9)	
1.74×10^{-3}			4.210	4.005	6.990	6.912	17.5
			(13.9)	(9.8)	(10.0)	(7.9)	

[a] in ppm from TMS

[b] in Hz

TABLE 6

Ether Proton Coupling Constants
for DB18CR6 Complexes in Acetone

Salt	J_{13}	J_{14}
KI	1.9	6.3
KCNS	2.1	6.2
$KClO_4$	2.0	6.4
NaI	2.3	6.3
NaCNS	2.2	6.2
$NaClO_4$	2.2	6.2
$Ba(ClO_4)_2$	2.2	6.2
Calculated from eqs. 2 + 3 using x-ray data		
	0.85	5.8

TABLE 7

Calculated Induced Shifts (Hz)

	1	2
Ring current effect[a]	+ 8	+ 3
$\vec{E}$ effect for +1 ion		
+0.94 Å	+91.4	+22.4
+0.54 Å	+92.2	+43.2
+0.0 Å	+88.8	+62.1
-0.54 Å	+79.5	+72.1
-0.94 Å	+70.0	+74.5
Incremental shift for replacing +1 ion with +2 ion		
+0.94 Å	+71.0	-21.7
+0.54 Å	+69.6	- 3.6
Mid	+63.9	+23.7
-0.54 Å	+54.5	+41.9
-0.94 Å	+45.0	+50.0
Observed incremental shift	+45	+19
Observed incremental shift B18CR6	1 and 4[b]	2 and 3[b]
	+42	+29

---

[a] Comparison of proposed structure for free molecule and x-ray structure for complex.

[b] Average.

and cannot be readily estimated, but may explain the NaCNS, DB18CR6 result. In agreement with our conclusions, infrared studies of K^+ and Na^+ DB18CR6 complexes in dimethylsulfoxide and pyridine with different counterions indicate an 8-fold coordination consisting of the six ether oxygens and either two solvent molecules or a solvent and an anion in axial positions. The crown-cation interaction was found to be independent of anion.

Estimates of the cation induced shifts on complexation were made considering changes in ring current and electrostatic contributions (Table 7). The conformation used for these calculations was that for [(Rb, Na)NCS]$_2$(DB18CR6) since the proton positions were given. This is the same ether conformation found for NaI DB18CR6 done in a pure crystal. Various cation positions were used to calculate induced shift since, Rb^+ is found 0.94 Å above,[14] and Na^+ can vary between 0.54 Å above to 0.27 Å below the plane of the six ether oxygens.[18] (Below the ring is defined as the side toward which the aromatic rings are bent.) Using these theoretical results to establish the cation position is risky because of the poor agreement between the predicted and observed shifts. The validity of Eq. (5) can be checked by comparison of the incremental shift due to replacing K^+ with Ba^{+2}. The Ba^{+2} ion is chosen for comparison since it is only 0.04 Å larger than K^+ and should therefore provide the least disturbance on

substitution. The coupling constant for the Ba^{+2} complex as well as the high binding constant reinforces this assumption. The incremental shift is predicted well for a central in plane location of both ions. Tsatsas et al.[45] concluded for the infrared data that K^+ and Na^+ were located centrally in the ether oxygen plane in DMSO and pyridine. The question then remains as to what causes the error in the absolute magnitudes of the shifts.

A possible explanation is the variation in the ether proton-ether dipole orientation when a complex is formed; the change in coupling constants, and the X-ray results[14] suggest such a change. Because of the rapid inversion of the ether ring and the molecular symmetry the effect of the ether dipole at positions 1 and 2 in any given crown configuration is the same, but the magnitude of the effect is different in the bound and complexed conformation. It is also expected that the acetone-crown solvent interaction would change since the ether dipoles are no longer available to the solvent. There are probably two axially coordinated acetone molecules in the complex. In this position they should also have some effect on the ether resonances.

The change of the coupling constants on complexation indicates, from Eqs. (2) and (3), a small increase in the dihedral angle between the C—O bonds while retaining the + gauche - gauche inversion. It can be readily seen from these equations and Figure 6 that this will

result in an increase in the parameter L while N will decrease. The X-ray data for NaI and (Rb, Na) NCS complexes of DB18CR6 indicate dihedral angles greater than 60° when complexed. Results for 1, 4 dioxane [46] and uncomplexed DB30CR10 [20] indicate average dihedral angles of 60°. The effective electronegativity of the oxygens may also increase when complexation occurs. From the equations in Figure 6 it can be seen that this too will change the coupling constants in the way observed, however, this contribution would not be large enough to explain the observed changes.

The multiplet pattern requires fast ring inversion so that there is an equal distribution in time of + and - gauche conformations in a period of $\sim 10^{-3}$ sec. This can be accomplished by rapid cation exchange between solvent and crown. From Na^{23} nmr [27, 28] the reaction

$$Na\ (solvent)_n + crown \underset{k_r}{\overset{k_f}{\rightleftharpoons}} Na^+\ (crown) + n\ (solvent)$$

has been shown to be the primary exchange process in dimethyl formamide, methanol and dimethoxyethane. $k_f = 3.2 \times 10^8\ M^{-1}\ sec^{-1}$ and $k_r = 1.4 \times 10^4\ sec^{-1}$ at 25°C in methanol. These rates are sufficient to put the system in the fast exchange limit.

Na^+ and K^+ DB18CR6 Complexes in $CDCl_3$

Even though there is less solvent interaction between $CDCl_3$ and crown ethers, the complexation shifts in a low dielectric constant medium are in general complicated by ion pairing. It can be seen for the KCNS, NaCNS and $NaClO_4$ DB18CR6 complexes that the ether resonances coalesce into a single sharp line (Table 8). For NaI and KI complexes this unusual effect is not what is observed, and the induced shifts are similar to the acetone results (Table 8). I^- can interact with $CDCl_3$ allowing for anion solvation. There is one obvious manifestation of this in the yellow-orange color of the cation iodide complexes. In the gas phase in an analogous system, Cl^-, $CHCl_3$ a strong hydrogen bond is formed.[47] Assuming a similar complex in solution, the ion pairing tendency should be reduced by the diffusion of the negative charge over a large complex. There is a NCS^-, $CDCl_3$ interaction, presumably of the same nature as that with I^- since the color is the same, but somewhat weaker since it cannot remove the ion pairing in this instance. In DB30CR10 where ion pairing should be weaker, it does have the strength to eliminate ion pairing.

When I^- is the anion it is assumed that the cation-DB18CR6 complex is tumbling in a spherical cavity with the I^-—$CDCl_3$ complex somewhere on the surface, or even further away, therefore the ether protons feel an electrostatic effect from the cation and from an anion

TABLE 8

Limiting[a] and Induced Shifts[b] for DB18CR6 Complexes in $CDCl_3$

Salt	Position	1	2	$\alpha + \beta/2$	$\alpha - \beta$ (Hz)
KI[c]		4.300 (27.0)	4.191 (33.0)	6.890 (0.5)	22
KCNS[c]		4.169 (2.0)	4.169 (28.2)	6.894 (1.3)	18
NaI[d]		4.342 (36.2)	4.169 (+28)	6.927 (4.0)	20
$NaClO_4$		4.175 (-0.6)	4.175 29.4	6.905 (4.0)	16
NaCNS		4.152 (-5.4)	4.152 (24.6)	6.875 (-2.4)	20
$\frac{1}{2}$ Cr KCNS	J_{13} 2.3 J_{14} 6.4	4.173 (0.8)	4.105 (14)	6.888 (~0)	12.5

[a] in ppm from TMS

[b] numbers in parentheses are shifts relative to DB18CR6 in $CDCl_3$

[c] ether resonances ~3 Hz wide

[d] J_{13} 2.3 J_{14} 6.4

positioned randomly over a sphere around the molecule. When considering the effect with Eq. (5) this causes the linear term in the electric field to go to zero. The quadratic term does not, and gives rise to an upfield shift. This term in the limit of rapid tumbling which holds here, is proportional to r^{-4} averaged over all orientations. The effect of this term will drop off rapidly with distance as a proton is moved further inside the solvent cage; only those protons close to the anion complex would have a significant upfield shift.

The aromatic moieties are at the extremities of the crown complex as can be seen in Figure 2, and they would roughly determine the diameter of the solvent cage. The ether protons are further inside the cavity and are protected from much of an upfield influence. The resulting shifts are then more like what is observed in acetone, and are in the direction expected from the cation electric field effect. The coupling constants, where they can be observed, are consistent with those for the complex in acetone. We can now see whether ion pairing can in fact explain the spectra of the other complexes in $CDCl_3$. This can be done by calculating the electric field effect for point negative charges at various positions. These results are given in Table 9 for positions axial to the ether ring. From experiment it is observed that the H-1's are shifted much further upfield than the H-2's compared to KI and NaI complex shifts. This behavior can be

TABLE 9

Negative Ion Effect (Hz)

Calculated (DB18CR6)	1	2
-4.5	- 7.3	-42
-4.0	-13	-48
-3.5	-20.4	-54.8
-3.0	-30.8	-62.5
+3.0	-69.9	-23.7
+3.5	-60.0	+32.0
+4.0	-51.0	+35.5
+4.5	-43.0	+35.2
Average of +4.5 Å and -4.5 Å	-25.1	- 3.5
Average of +4.0 Å and -4.0 Å	-32	- 3.5
Average of +3.5 Å and -3.5 Å	-40	-11
Average of +3.0 Å and -3.0 Å	-51	-20
DB18CR6 observed shift of KCNS relative to KI	-25	- 5
Average observed shift of NaCNS and $NaClO_4$ relative to NaI	-38	- 6
B18CR6 Average of observed shift of NaCNS and $NaClO_4$ relative to NaI	1 and 4[a]	2 and 3[a]
	- 3	-18
Average of observed shift for KCNS and $KClO_4$ relative to KI	- 8	-23

[a] average of shifts at both positions

qualitatively explained by the presence of an anion above the ring as in the (RbNCS)DB18CR6 crystal structure (Figure 2), or by a distribution where an anion spends some time above and below the ring. The quantitative value of these calculations is limited by the approximation of the ions in question as point charges.

The splitting of the aromatic multiplets increases on complexation just as it did in acetone.

In the KI and KCNS complexes in $CDCl_3$ the natural linewidth is several Hz wide. This is a result of a slow rate of ring inversion. In a solvent such as $CDCl_3$ where the cation cannot be solvated, ring inversion is then probably achieved through a collision-exchange process with another complex or with an uncomplexed crown molecule if there is an excess rather than by a crown solvent ion exchange. When this rate falls below $\sim 10^3$ sec^{-1} broadening will begin to appear. This should be considerably slower than the fast decomplexation reaction mentioned earlier which cannot occur in this solvent. The 1:1 stoichiometry of the complex can be shown in $CDCl_3$ by the linear dependence of the induced shift on the fraction of ion to crown present (Table 8).

DB18CR6-Cs^+ Complexes

The cesium DB18CR6 complexes are treated separately because the cesium ion is larger than the ring hole size (Table 1), giving rise to unusual behavior. This is seen in Figure 12. The solid curves are calculated shifts using the equilibrium constants for 1:1 and 2:1 Cs, DB18CR6 complexes reported by Frensdorf[10] for methanol. These are $K_{1:1}$ = 3,550 L M^{-1} and $K_{2:1}$ = 850 L M^{-1}. The limiting values for the calculation were determined by taking the second and last experimental points and fitting them to Frensdorf's equilibrium constants. The justification for using the binding constants in methanol for acetone is found in the similarity of these numbers in both solvents for the complexes we have examined. The agreement of experiment with the curves indicates the same equilibrium and stoichiometry in acetone as in methanol. The concentration dependence of the chemical shift also indicates that this is the case (Table 10).

A noteworthy feature, which is qualitatively obvious from the spectra directly, is that there is at least one species whose limiting shift is upfield from that of the uncomplexed molecule. In the analysis here for the 2:1 crown to Cs complex stoichiometry, H-1 has a limiting shift of -6.0 Hz and H-2 is -20.0 Hz. All the 1:1 complexes studied up to this point have shown downfield shifts. The 1:1 version

FIGURE 12

Binding of Cs^+ to DB18CR6.

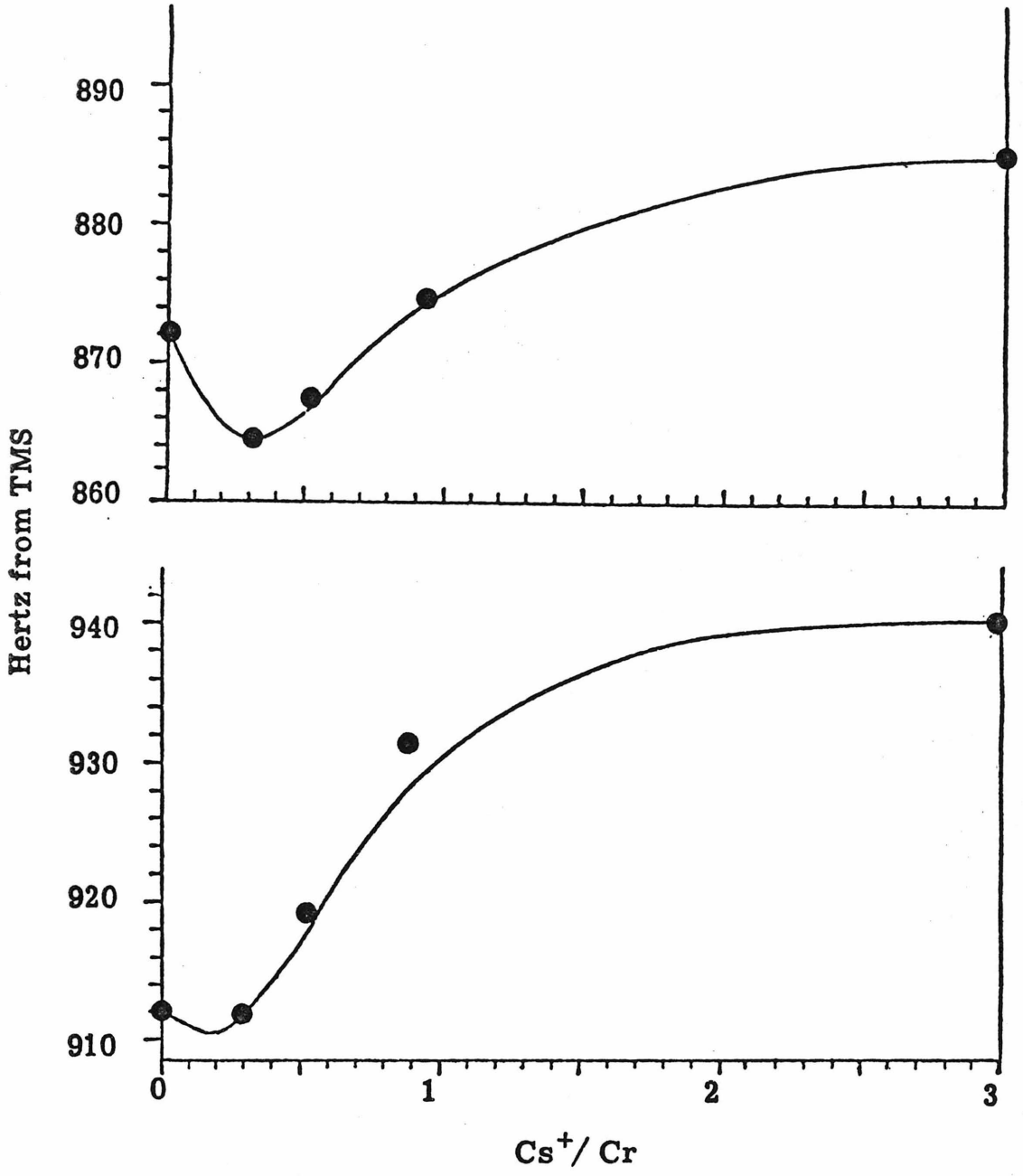

890
880
870
860
940
930
920
910
Hertz from TMS
0
1
2
3
Cs+/ Cr

TABLE 10

Concentration Dependence of CSI, $(DB18CR6)_2$ Shifts and Coupling Constants[a]

Solvent	Conc.	Position	1	2	$\alpha+\beta/2$	$\alpha-\beta$ (Hz)
Acetone	9.9×10^{-3}		4.147	3.910	6.939	5
			(-12.1)	(+0.2)	(+6.5)	
	4.95×10^{-3}		4.154	3.920	6.945	6
			(-10.0)	(+1.6)	(8.0)	
	1.02×10^{-3}		4.193	3.965	6.945	13
			(-0.2)	(+10.2)	(8)	
$CDCl_3$	4.87×10^{-2}[b]		3.994	3.847	6.849	37
			(-42.7)	(-40.4)	(8.6)	
	1.02×10^{-3}		4.136	3.958	6.886	20
			(-18.2)	(-9)	(+0.5)	

Ether Vicinal coupling constants (Hz)

		J_{13}	J_{14}
Acetone	4.9×10^{-3}	2.3	6.3
	1.02×10^{-3}	2.3	6.3
	9.9×10^{-3}	2.4	6.4
$CDCl_3$	1.02×10^{-3}	2.5	6.0

[a] shifts in ppm from TMS, induced shifts in Hz below

[b] ether resonances ~3 Hz wide

of this complex does as well (Table 11). It is obvious from Figure 13 that if two rings are parallel with enough space between them to fit a Cs^+ ion some protons would feel a strong shielding influence due to the benzo groups. If the assumption is made that the conformation of the individual DB18CR6 molecules is the same in the 1:1 and 2:1 complexes and that the electrostatic effects are similar, then, for the arrangement pictured in Figure 13, the relative shifts of 2:1 and 1:1 complexes can be estimated from the additional ring current contribution, and are in agreement with the observed values.

Rotation of the two cyclic ether molecules relative to each other would decrease the effect on the ether protons and shift the aromatic resonances to higher field, as opposed to what is observed. Such rotation would be hindered, by steric interference of the benzo groups.

For the 2:1 complexes the splitting of the aromatic resonances decreases compared to the uncomplexed form. The proposed arrangement would explain this because the α protons would experience a larger shielding effect than the β protons from the aromatic residues on the other DB18CR6 in the complex. Pedersen put forth the concept of such a sandwich complex some time ago [13] and X-ray results have shown this is what occurs for K^+ (benzo 15 crown 5)$_2$ [16] (Figure 2). Shifts of a similar nature to those observed here for the 2:1

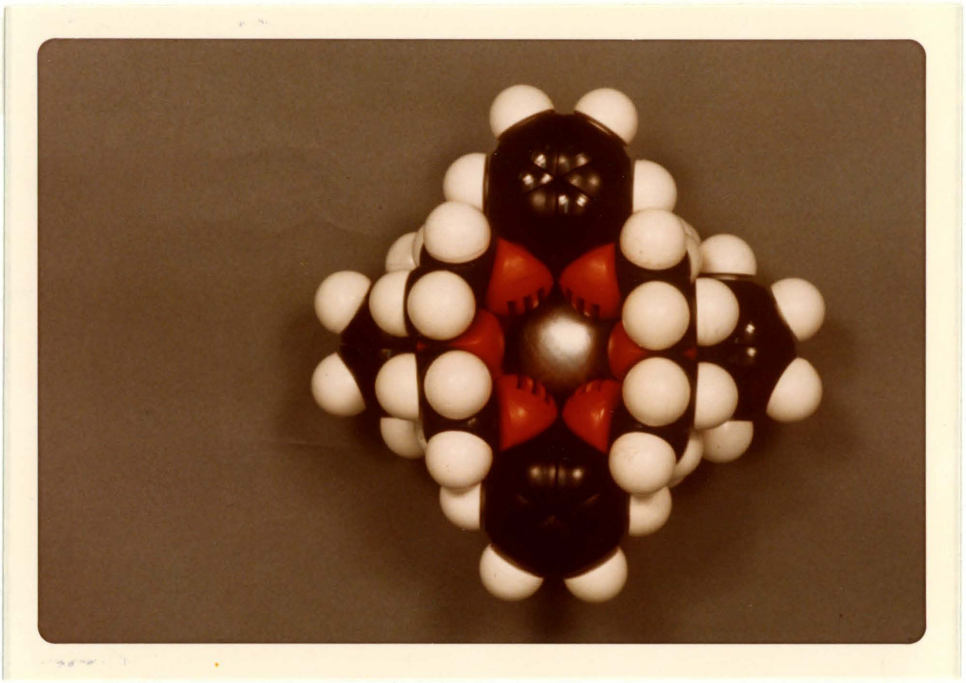
TABLE 11

Limiting Induced Shifts (Hz) for Cs, DB18CR6 Complexes in Acetone

Complex (Cr/Cs)	Position	1	2	α	β
1:1		+40.0	+19.7	+16.9	+20.1
2:1		- 6.0	-20.0	+0	+20

FIGURE 13

Photograph of CPK model realization of proposed arrangement of 2:1 crown:Cs complex.



complex were found in complexes where the aromatic fluorenyl anion was used and ion pairs formed placing the anion over the ether ring [11].

On the basis of the limiting shifts of the 1:1 complex and the ether proton coupling constants the DB18CR6 molecule should have a structure somewhat similar to what is seen for the K^+ and Na^+ DB18CR6 complexes.

In $CDCl_3$ the spectrum of $CsI(DB18CR6)_2$ has a concentration dependence indicating varying stoichiometry, the shifts indicate a greater than 1:1 complexation. The coupling constants are the same as in acetone. A striking feature of Table 10 is the large upfield shifts relative to the complexes in acetone. In our model for this complex the ether protons are near the extremities of the complex they may be feeling some of the effects of the quadratic term of Eq. (5) in line with our hypothesis about iodide ion in $CDCl_3$.

The broadening observed particularly in the ether proton at the higher concentrations is probably due to a reduced exchange rate in this solvent and the presence of various stoichiometries.

The inability to isolate 1:1 Cs, DB18CR6 complexes that would dissolve in $CDCl_3$ prevented us from studying a variety of crown to cation ratios.

B18CR6

The DB18CR6 molecule and its complexes are ideal for nmr study because of the existing X-ray data and the simplicity of the spectrum. It is important, certainly from the point of view of understanding the biological implications of these molecules, to find out whether when substituents which effect solubilities and transport by several orders of magnitude are changed, the structure of the complex changes as well. B18CR6 allows us to investigate this since the removal of the second benzo group greatly increases its solubility as well as the solubilities of its complexes in water, acetone and $CDCl_3$. It retains, however, an aromatic residue which as mentioned before simplifies the interpretation. This molecule also is very useful in understanding the spectrum of DB30CR10.

The spectrum of B18CR6 is given in Figure 14. The chemical shifts in various solvents are given in Table 12 and coupling constants are in Table 13. There are more peaks in the ether region than in DB18CR6 as would be expected when the molecular symmetry is lowered. The solvent effects have been discussed in the previous section.

The proton shifts for positions 1 to 4 in acetone and in $CDCl_3$ are essentially the same as those observed for positions 1 to 4 in DB30CR10 in the same solvents (Table 20). The cmr shifts for the

FIGURE 14

PMR spectrum of B18CR6 in acetone in free and complexed form.

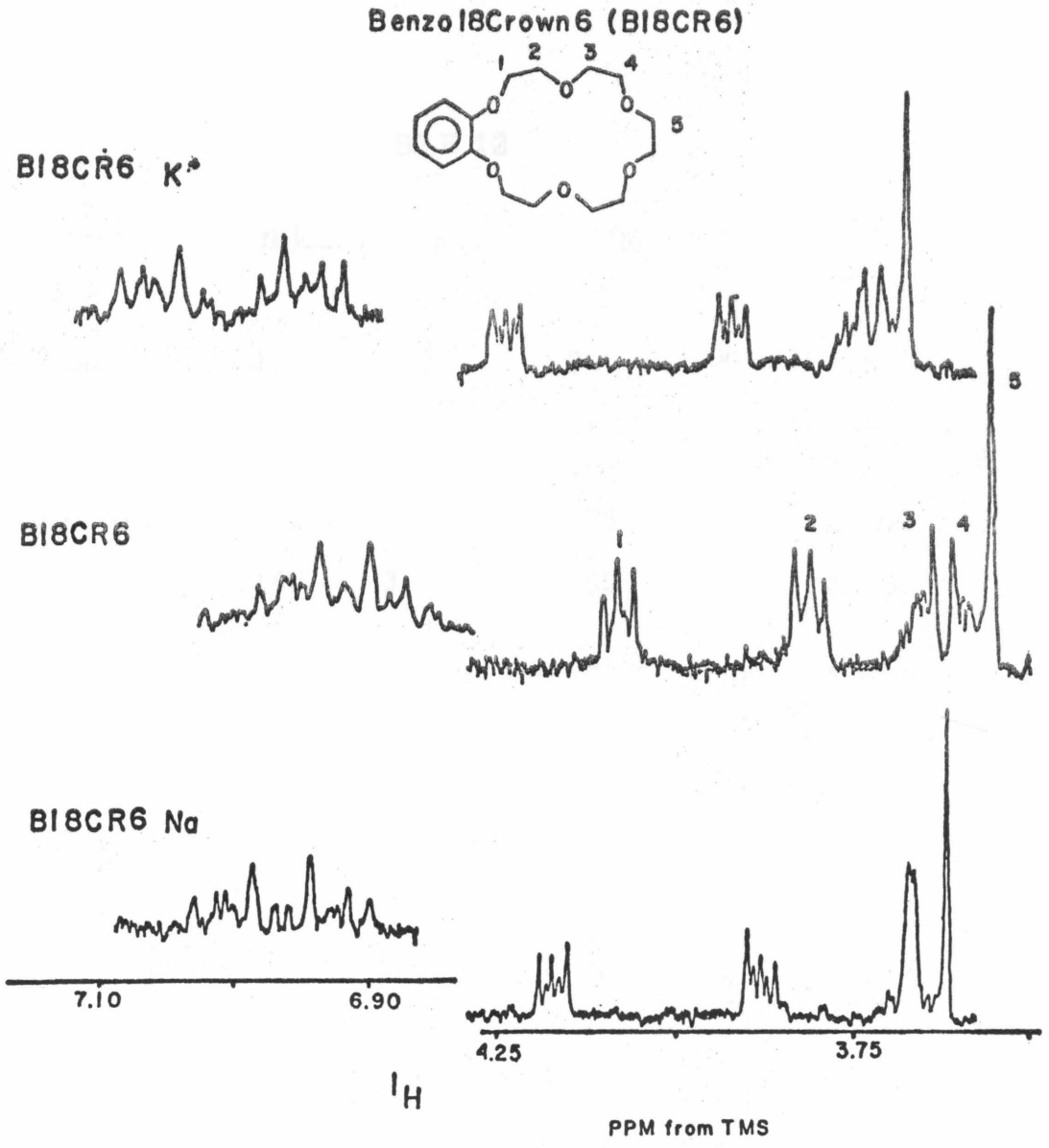

Benzo18Crown6 (B18CR6)
1
2
3
4
5
B18CR6 K+
B18CR6
B18CR6 Na
5
1
2
3
4
7.10
6.90
4.25
3.75
1H
PPM from TMS

TABLE 12

Chemical Shifts for B18CR6

Solvent	Conc.	1	2	3	4	5	$\frac{\alpha+\beta}{2}$	$\alpha-\beta$ (Hz)
Acetone[a]	2×10^{-2}	4.1236	3.852	3.700	3.633	3.596	6.916	15
$CDCl_3$[a]	5×10^{-2}	4.163	3.930	3.776	3.722	3.692	6.896	~4
29 Mole % D_2O in Acetone	5×10^{-3}	4.149	3.879	3.752	3.688	3.688	7.014	8
D_2O[b]	5×10^{-3}	4.223	3.900	3.727	3.709	3.661	6.936	17

[a] relative to TMS in ppm

[b] relative to DSS in ppm

TABLE 13

Ether Vicinal Proton-Proton Coupling Constants (H_3)

Solvent	Positions 1 and 2		Positions 3 and 4	
	J_{13}	J_{14}	J_{13}	J_{14}
Acetone	3.3	6.1	3.3	6.1
$CDCl_3$	3.2	6.1	3.2	6.2
29 Mole % D_2O in Acetone	2.9	6.1	3.0	6.1
D_2O	1.8	6.2	-	-

carbons are also very similar for both (Tables 19 and 26). Applying the calculated ring current shifts from the DB30CR10 crystal structure (Table 21) there is good agreement between the observed and predicted ether multiplet separation, except for position 3 which appears about 20 Hz to higher field than predicted. (The agreement is also reasonable with values from our proposed DB18CR6 structure.) Such a change could be explained by rotations about C–O bonds that would not affect the proton coupling constants and would tend to flatten the curvature in the ether chain. Such a flattening would make the conformations more favorable to the smaller B18CR6. The significance of the coupling constants has been considered in the previous section. Rapid inversion occurs in this molecule.

Na^+, K^+ and Ba^{+2} Complexes in Acetone

Binding curves for Na^+ and K^+ B18CR6 are shown in Figure 15 along with the stability constants. Although no other stability constants for B18CR6 are available, these are expected to be and are similar to those reported for the other 18 membered ring ethers is and to within the limits that we can measure they are.[10]

The induced shifts are given in Table 14. They are similar in magnitude to those for DB18CR6, and the same general analysis applies. The variation in limiting shifts particularly in the sodium

TABLE 14

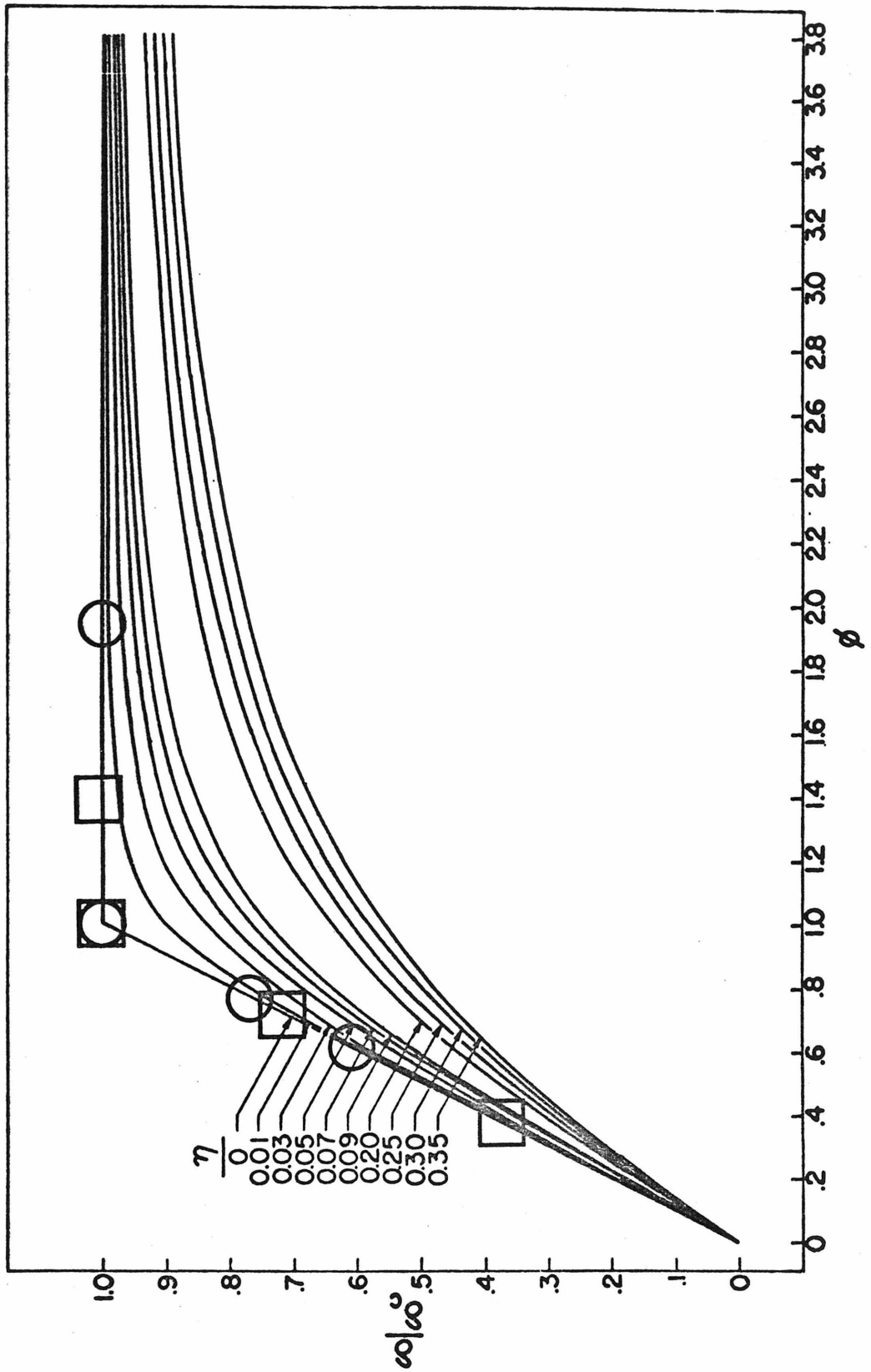
Limiting and Induced Shifts for Cation Complexes of B18CR6 in Acetone[a]

Salt	Conc.	Position	1	2	3	4	5	$\alpha+\beta/2$	$\alpha-\beta$ (Hz)
KI	2.6×10^{-3}		4.291	3.964	3.795	3.745	3.722	7.064	20
			(37.2)	(24.6)	(21.1)	(24.8)	(27.3)	(25.4)	
KCNS	1×10^{-2}		4.278	3.960	3.788	3.734	3.714	7.061	25
			(34)	(23.5)	(19.5)	(22.2)	(25.8)	(24.8)	
$KClO_4$	3.2×10^{-3}		4.277	3.947	3.780	3.730	3.712	7.055	23
			(33.8)	(20.7)	(17.8)	(21.5)	(25.4)	(23.4)	
NaI	3.7×10^{-3}		4.223	3.931	3.736	3.705	3.666	7.010	17
			(21.8)	(17.4)	(8.1)	(15.8)	(16.1)	(13.7)	
NaCNS	2×10^{-2}		4.218	3.943	3.744	3.698	3.664	7.002	17
			(20.8)	(20.1)	(9.7)	(14.4)	(14.8)	(17.5)	
$NaClO_4$	5×10^{-3}		4.221	3.927	3.734	3.688	3.666	7.009	17
			(21.5)	(16.2)	(7.6)	(12.5)	(15.4)	(13.3)	
$Ba(ClO_4)_2$	1×10^{-2}		4.440	4.071	3.945	3.945	3.945	7.174	30
			(69.6)	(48.0)	(54.1)	69.0	77	(49.6)	
Incremental Shift[b]			35	25	34	47	51		

[a] in ppm from TMS

[b] for replacing K^+ with Ba^{+2}

Figure 15. Binding curve for K^+, B18CR6 (□) as 2×10^{-2} M crown concentration and Na^+, B18CR6 (○) at 1×10^{-2} M in acetone. $K_{K^+} > 10^4$ L M^{-1}; $K_{Na^+} > 10^4$ L M^{-1}.


η
0
0.01
0.03
0.05
0.07
0.09
0.20
0.25
0.30
0.35
ω/ω'
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
0
.2
.4
.6
.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
φ

complexes between the protons near the aromatic ring and those at the other end of the molecule may be due to a structural adjustment in the more flexible end to reduce the Na–O distances, or by a tight solvent binding. The K^+ to Ba^{+2} incremental shift is in fairly good agreement with values calculated from the DB18CR6 structure (Table 7). For comparison position 1 and 4 should follow position 1 of DB18CR6 and position 2 and 3 should follow the value for H-2 of DB18CR6. The behavior of the aromatic resonances follows the DB18CR6 data. The ether proton vicinal coupling constants are the same as for the previous complex studied and are the same for position 1 and 2, and 3 and 4 (Table 15). This indicates that the second aromatic ring does not perturb the complex structure significantly. There is also support for this from cmr results which will be discussed later. The available X-ray structures for Na^{+}[48] and Ba^{+2}[17] complexes of dicyclohexyl-18-crown-6 and those for DB18CR6 show that they are very similar. It is reasonable therefore that B18CR6 should follow this pattern.

The shifts for the $NaClO_4$ complex of B18CR6 have been checked over two orders of magnitude from 2×10^{-3} to 2×10^{-1} M and no evidence for aggregation or deviation from 1:1 stoichiometry is observed. The fast inversion for the ether ring holds for this system.

TABLE 15

Ether Proton Vicinal Coupling Constants for B18CR6 Cation Complexes

Solvent	Salt	Position 1 and 2		Position 3 and 4	
		J_{13}	J_{14}	J_{13}	J_{14}
Acetone					
	KI	2.0	6.5	2.1	6.3
	KCNS	1.9	6.5	2.4	6.2
	$KClO_4$	2.1	6.5	2.4	6.2
	NaI	2.2	6.2	2.4	6.2
	NaCNS	2.3	6.3	-	-
	$NaClO_4$	2.3	6.3	-	-
	$Ba(ClO_4)_2$	2.4	6.5	-	-
$CDCl_3$					
	KI	2.2	6.2	2.1	6.1
	KCNS	2.2	6.5	2.1	6.2
	$KClO_4$	2.1	6.4	2.0	6.0
	NaI	2.2	6.2	2.0	6.4
	NaCNS	2.0	6.0	2.1	6.3
	$NaClO_4$	2.4	6.4	2.1	6.4

Na^+ and K^+ Complexes in $CDCl_3$

The shifts for various complexes of B18CR6 in $CDCl_3$ are given in Table 16. Those with ClO_4^- and NCS^- counterions behave differently from the complexes with I^- ions. A comparison of the shifts of these two classes of anion shows a greater upfield shift for positions 2 and 3 than for positions 1 and 4 when ion pairs are formed (Table 16). Using the values calculated for DB18CR6 in Table 9, correlating H-2 and H-3 with H-2 of DB18CR6 and H-1 and H-4 with H-1 of DB18CR6, positioning an anion above the ring fits best. The proton-proton coupling constants are the same for B18CR6 complexes in $CDCl_3$ as they were in acetone, and as they are for DB18CR6 complexes in $CDCl_3$ and acetone. The separation of the aromatic multiplet for complexes in $CDCl_3$ follows the same trend for both molecules. The additional similarity of the cmr for B18CR6 complexes in acetone and $CDCl_3$ and with the KNCS DB18CR6[42] complex in CH_2Cl_2 (Table 19) indicates that Na^+ and K^+ complexes of DB18CR6 and B18CR6 are very much alike in the solvents studied. The KI, B18CR6 and NaI, B18CR6 complexes have been studied over a concentration of 2×10^{-3} M to 2×10^{-1} M in $CDCl_3$, and there is no evidence of aggregation or stoichiometry changes. 1:1 stoichiometry is indicated by the linear dependence of the shift and crown to cation ratio.

TABLE 16

Cation Induced Shifts for B18CR6 Complexes in $CDCl_3$[a]

Salt	Position	1	2	3	4	5	$\alpha+\beta/2$	$\alpha-\beta$ (Hz)
KI		4.218	4.045	3.855	3.727	3.740	6.900	24
		(12.2)	(25.2)	(17.8)	(1.2)	(10.6)	(+0.8)	
KCNS		4.214	3.969	3.802	3.716	3.715	6.906	17
		(11.2)	(8.4)	(+5.7)	(-1.3)	(+5.2)	(+2.1)	
$KClO_4$		4.195	3.927	3.762	3.698	3.687	6.893	13
		(7.2)	(0.6)	(-3.2)	(-1.3)	(3.4)	-0.8	
NaI		4.216	4.115	3.879	3.733	3.725	6.900	24
		(13.8)	(40.8)	(22.6)	(2.5)	(7.3)	+0.8	
NaCNS		4.170	4.028	3.795	3.705	3.688	6.898	18
		(1.6)	(21.4)	(4.2)	(-3.8)	(-1.8)	(0.4)	
$NaClO_4$		4.195	4.009	3.795	3.705	3.690	6.905	14
		(7.2)	(17.4)	(+4.2)	(-3.8)	-1.3	(+1.8)	

[a] in ppm from TMS. numbers in parentheses are induced shifts in Hz.

TABLE 17

Limiting and Induced Shifts and Coupling Constants for B18CR6 Complexes in 29 Mole % D_2O in Acetone[a]

Salt	Conc.	Position	1	2	3	4	5	$\alpha+\beta/2$	$\alpha-\beta$ (Hz)
KCNS	5×10^{-3}		4.281	3.966	3.789	3.743	3.718	7.007	24
			(29)	(14.0)	(19.6)	(24.3)	(27)	(22.1)	
$NaClO_4$	5×10^{-3}		4.218	3.943	3.754	3.704	3.673	6.972	17
			(15.2)	(9.4)	(12)	(12)	(15.6)	(14.5)	

Ether Vicinal Proton Coupling Constants

	Position 1 and 2		Position 3 and 4	
	J_{13}	J_{14}	J_{13}	J_{14}
KCNS	2.2	6.4	2.1	6.3
$NaClO_4$	2.2	6.4	2.1	6.3

[a] in ppm relative to TMS, induced shifts in parentheses.

B18CR6 in D_2O and D_2O-Acetone

B18CR6 is soluble enough in water to allow PMR and CMR investigation and a comparison of the medium with acetone. The shift for B18CR6 in D_2O and 29 mole per cent D_2O in acetone are given in Table 12. In the mixed solvent the shifts are to slightly higher field than in pure acetone, and the coupling constants are the same. This small shift is attributable to a solvent-crown interaction as opposed to a solvent reference interaction, since the limiting complex shifts are the same in mixed solvent and in acetone. The small downfield shift and increased splitting of the aromatic resonances is consistent with an increased dipole-dipole interaction with the solvent. There is no detectable change in the cation binding constant between the pure and mixed solvent.

The situation in pure D_2O is somewhat different. For pure B18CR6 the coupling constants in this medium are reminiscent of the bound form of B18CR6. The interaction is not a hydrophobic one since a conformation with these coupling constants would expose the aliphatic region more to the solvent than would the uncomplexed configuration observed before. It is probably a direct interaction between the D_2O molecule and the ether oxygens. OH_3^+-Dicyclohexyl 18 Crown 6 complexes have been isolated and studied by infrared spectroscopy,[49] but the existence of such a species in appreciable

quantities when B18CR6 is dissolved in neutral H_2O is not likely since no pH change is observed. A more reasonable interaction is the formation of a hydrogen bond with the ether oxygens. An analogous bond has been postulated for the HBr, DB18CR6 complex in $CDCl_3$.[50]

Complexes in D_2O

Complexes of KCl and $Ba(ClO_4)_2$ with B18CR6 have been studied in D_2O. Stability constants of approximately 10^2 L M^{-1} and 5×10^3 L M^{-1}, respectively, have been observed for these complexes. These numbers are close to those reported for dicyclohexyl 18 crown 6 complexes of these ions in water.[10, 12] Limiting shifts and coupling constants are given in Table 18. The incremental shift for replacing K^+ with Ba^{+2} is much smaller than that predicted from the DB18CR6 X-ray structure. This could be due to a different complex structure, or to the ability of water because of its small size and high Ba^{+2} solvation energy to change the solvent interaction with the complex. The coupling constants are similar to those for the complexes in acetone and $CDCl_3$, indicating that the complex conformation may be the same in D_2O as in the organic solvents. No aggregation effects have been observed up to a concentration of 2×10^{-1} M for either B18CR6 or the KCl complex.

TABLE 18

Limiting and Induced Shifts and Coupling Constants for B18CR6 Complexes in D_2O[a]

Crown conc.	Salt	Position	1	2	3	4	5	$\alpha + \beta/2$	$\alpha - \beta$ (Hz)
2×10^{-2}	KCl		4.267	3.918	3.766	3.730	3.704	7.067	9.0
			(9.7)	(4.0)	(8.6)	(4.6)	(3.5)	(11.9)	
	$Ba(ClO_4)_2$		4.334	4.000	3.841	3.845	3.805	7.095	10.0
			(23.5)	(22)	(29)	(25)	(16)	(18)	
Incremental Shift			13.8	18	20.4	19.9	8.5	18	

Ether Vicinal Coupling Constants

	Position 1 and 2	
	J_{13}	J_{14}
KCl	1.9	6.2
$Ba(ClO_4)_2$	2.3	6.5

[a] in ppm relative to DSS

CMR of B18CR6 and DB18CR6

The present knowledge of C^{13} shifts does not permit their accurate prediction or the prediction of incremental contributions from conformational changes, though the positions of peaks 1 and 2 and 3, 4, and 5 are in qualitative agreement with what is observed with what is observed for substituted benzenes (Table 19). The ordering of the α and β aromatic resonances also follows what is known for such systems. It is interesting to note that the α carbon changes more on complexation than does the β, just as was observed for the analogous protons.

Some work has been done on the electric field effects on CMR resonances using an approach like Buckingham's.[51] To first order it has been found that the induced shift is proportional to the projection of the electric field along C–C, or in this case C–O bonds. If the X-ray results for DB18CR6 apply in solution to the 18 membered ring systems we have studied, then the geometry indicates that the electrostatic effect of the cation on the C^{13} shifts should be small, and the spectral changes should be primarily structural in origin. This can be seen in Figures 16 and 17 where the spectrum of pure B18CR6 in water resembles that for the B18CR6 complexes in acetone and $CDCl_3$ more than it does the free molecule in those solvents. This is exactly what was suggested by the proton coupling constants. An anion situated

TABLE 19

CMR Shifts and T_1's for B18CR6 and DB18CR6[a]

	Solvent	Salt	1	2	3, 4, 5	α	β
B18CR6	Acetone		70.25	70.49	71.57, 71.5, 71.5	115.6	122.3
	$CDCl_3$		69.44	69.87	70.2, 70.2, 70.2	114.9	121.6
	$CDCl_3$	KCNS	67.1	68.9	70.14, 70.14, 70.14		
	$CDCl_3$	KI	67.25	68.94	70.15, 70.13, 70.05	111.7	121.6
	$CDCl_3$	NaI	67.07	68.78	69.27, 69.44, 69.68	112.50	121.87
	$CDCl_3$	$NaClO_4$	66.76	68.59	69.12, 69.28, 69.52	112.28	121.69
	Acetone	KI	68.29	69.78	70.90, 70.74, 70.74	112.35	122.3
	Acetone	$NaClO_4$	67.424	69.623	70.23, 70.52, 70.52	112.37	121.88
DB18CR6	$CDCl_3$		69.39	70.19			
	CD_2Cl_2[b]		68.8	70.2		113.5	121.3
	T_1 (sec)		(1.24)	(1.19)		(1.72)	(1.73)
	CD_2Cl_2[b]	KCNS	67.5	69.2		111.6	121.5
	T_1 (sec)		(0.5)	(0.5)		(0.9)	(1.0)

[a] in ppm relative to TMS. There is a solvent effect in the reference signal of ~0.6 ppm between $CDCl_3$ and Acetone.

[b] Shifts and T_1's from ref. 42. Assignments made by analogy to our results.

Figure 16. CMR spectrum of the ether region of B18CR6 and complexes in $CDCl_3$ (left-hand side) and acetone (right-hand side).

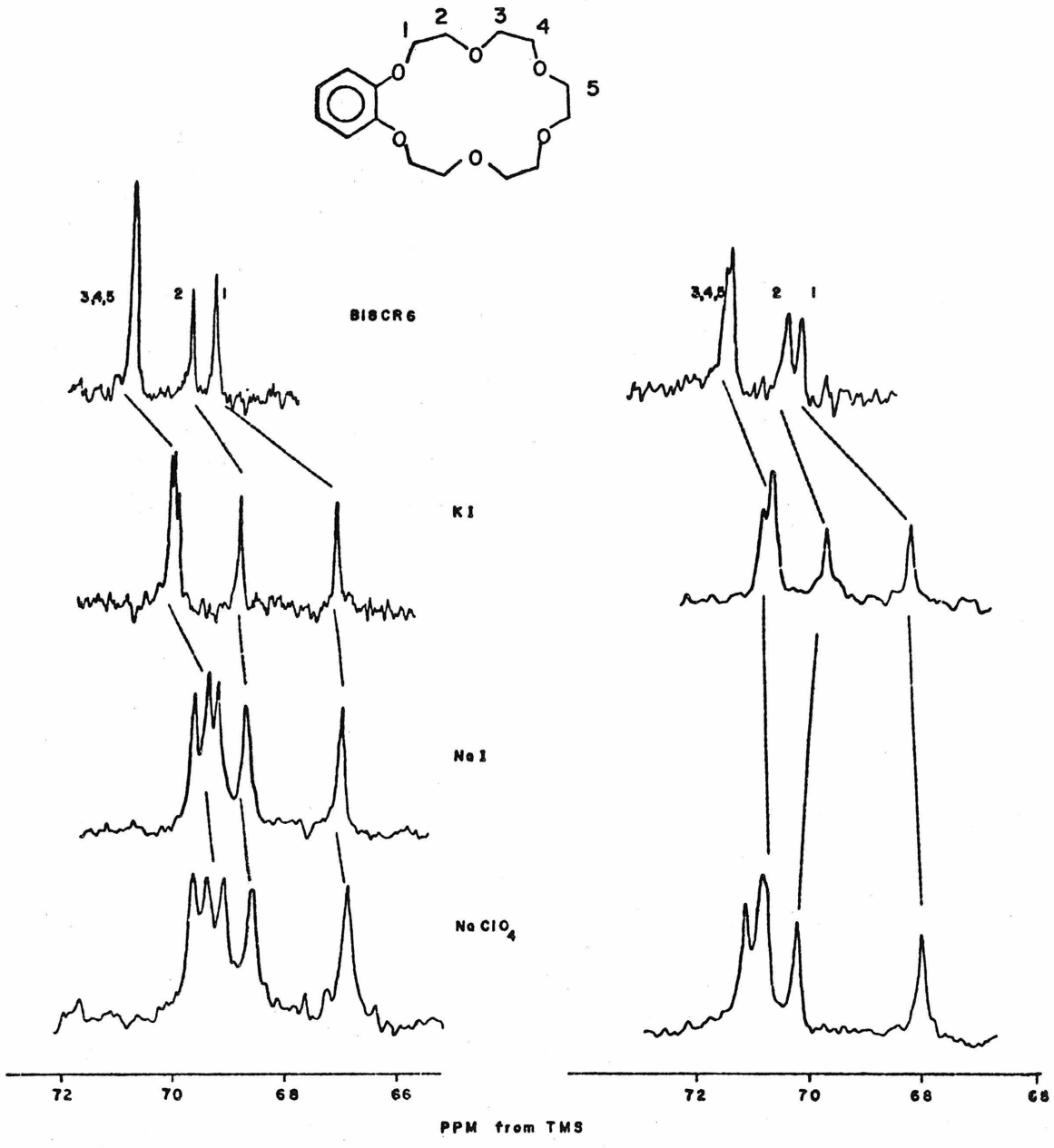
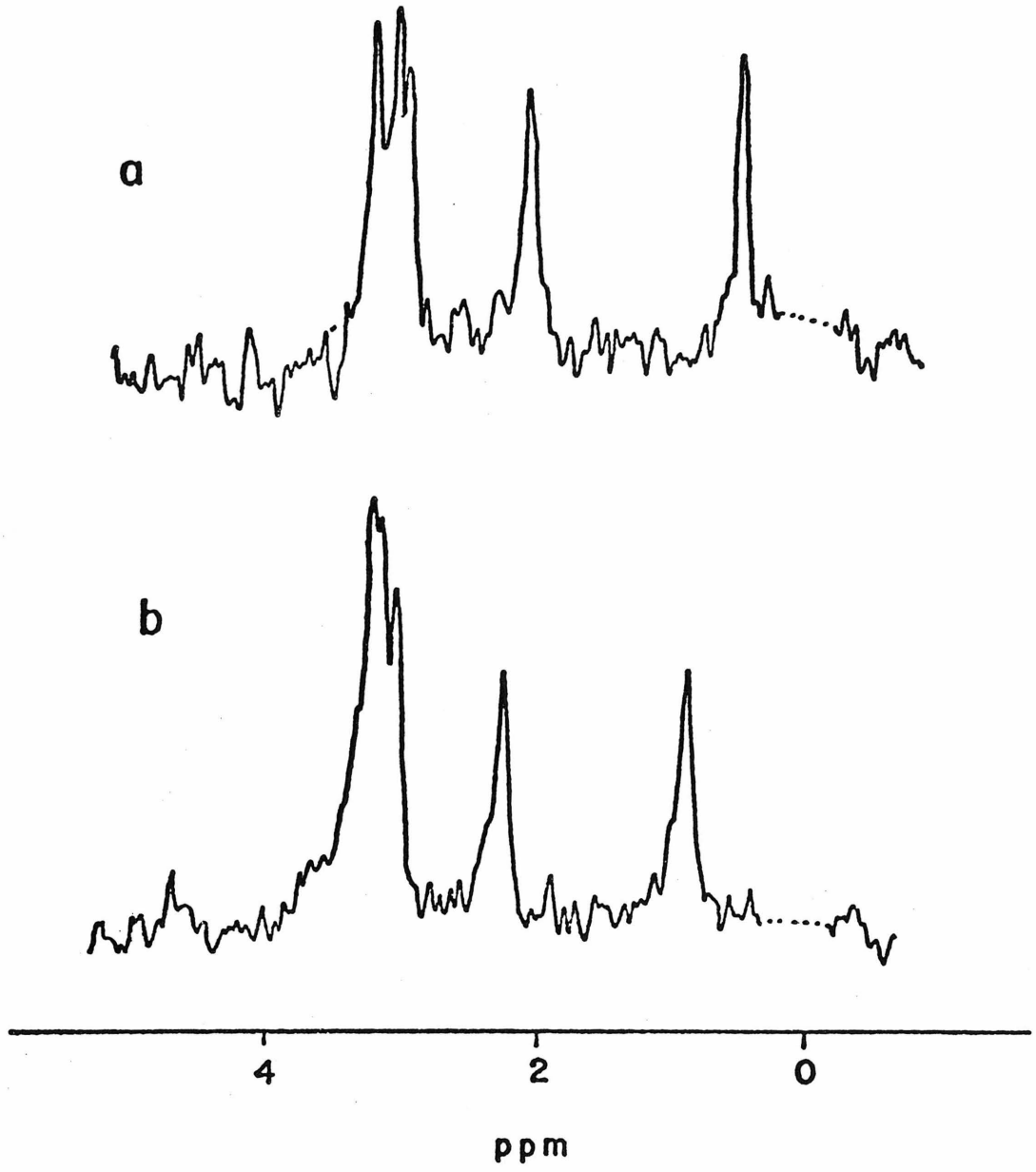

1
2
3
4
5
O
3,4,5
2
1
B15CR6
KI
NaI
NaClO4
72
70
68
66
PPM from TMS

Figure 17. CMR spectrum of KCl, B18CR6 (a) and B18CR6 (b) in D_2O. Concentration of crown is 0.2 M. Dioxane was used as a reference.


a
b
4
2
0
ppm

axially to the ether ring would also not have much of an electrostatic effect on the resonances. This is born out in the similarity of the spectra of the $NaClO_4$ and NaI, B18CR6 complexes in $CDCl_3$. It is reasonable to conclude that the CMR shift for DB18CR6 and B18CR6 are structure dependent, and therefore we can use them for fingerprints of the free and complexed structures where the PMR results are obscured by other effects. We can then deduce from Figure 16, 17 and Table 19, that the free B18CR6 and DB18CR6 conformation is the same in acetone and $CDCl_3$, and that this differs from the B18CR6 conformation in D_2O. The latter is rather like the configuration of the complexes for K^+ and Na^+ in acetone and $CDCl_3$ and the K^+ complex in D_2O.

The ~0.6 ppm shift difference between acetone and $CDCl_3$ appears to be due to variation of the TMS reference peak with solvent.

C^{13} T_1 data have also been determined for DB18CR6 and dicyclohexyl-18-crown-6, [42] and they have been interpreted in terms of segmental motion of the ether chains in the uncomplexed form, and a rigid structure for the complex. The segmental motion may arise from inversion of the gauche rotamers which is expected to be more rapid in the free molecule than in the complex where decomplexation would be required to accomplish this. The complex therefore appears to be fixed on the time scale of the Larmor precession frequency,

even though from the PMR spectrum, rapid ring inversion is occurring.

DB30CR10

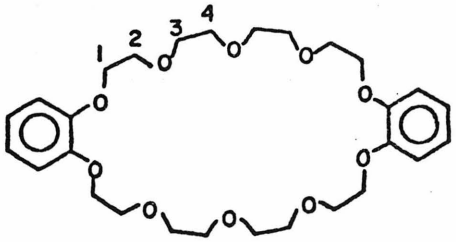
The PMR and CMR spectra and the proton-proton coupling constants are almost identical for DB30CR10 in B18CR6 with the exception of the resonance due to position 5 in B18CR6. It was therefore concluded, by the arguments in the previous section, that the conformation of the molecule was like the X-ray structure for the free molecule with the curvature of the ring slightly flattened. The shifts and coupling constants are given in Table 20 and Figure 18. The spectra in Figure 18 indicate rapid ring inversion. The spin lattice, T_1, relaxation time of the ether carbons indicates an even greater segmental motion than for the 18 membered ring. This is reasonable since the longer ether chain should be floppier.

Na^+, K^+, Cs^+ and Ba^+ Complexes of DB30CR10

As can be readily observed in Figure 18 and Table 22 the cation induced shifts for K^+ and Cs^+ are very different from those for Na^+. If the K^+, Cs^+ and Ba^{+2} complexes are analyzed with the data from the crystal structure of the KI, DB30CR10 complex the predictions in Table 23 are obtained. The agreement for the electric field and ring current effects are poorer than for the two cases previously

Figure 18. PMR spectrum of DB30CR10 and complexes in acetone.

Dibenzo 30 Crown10 (DB30CR10)



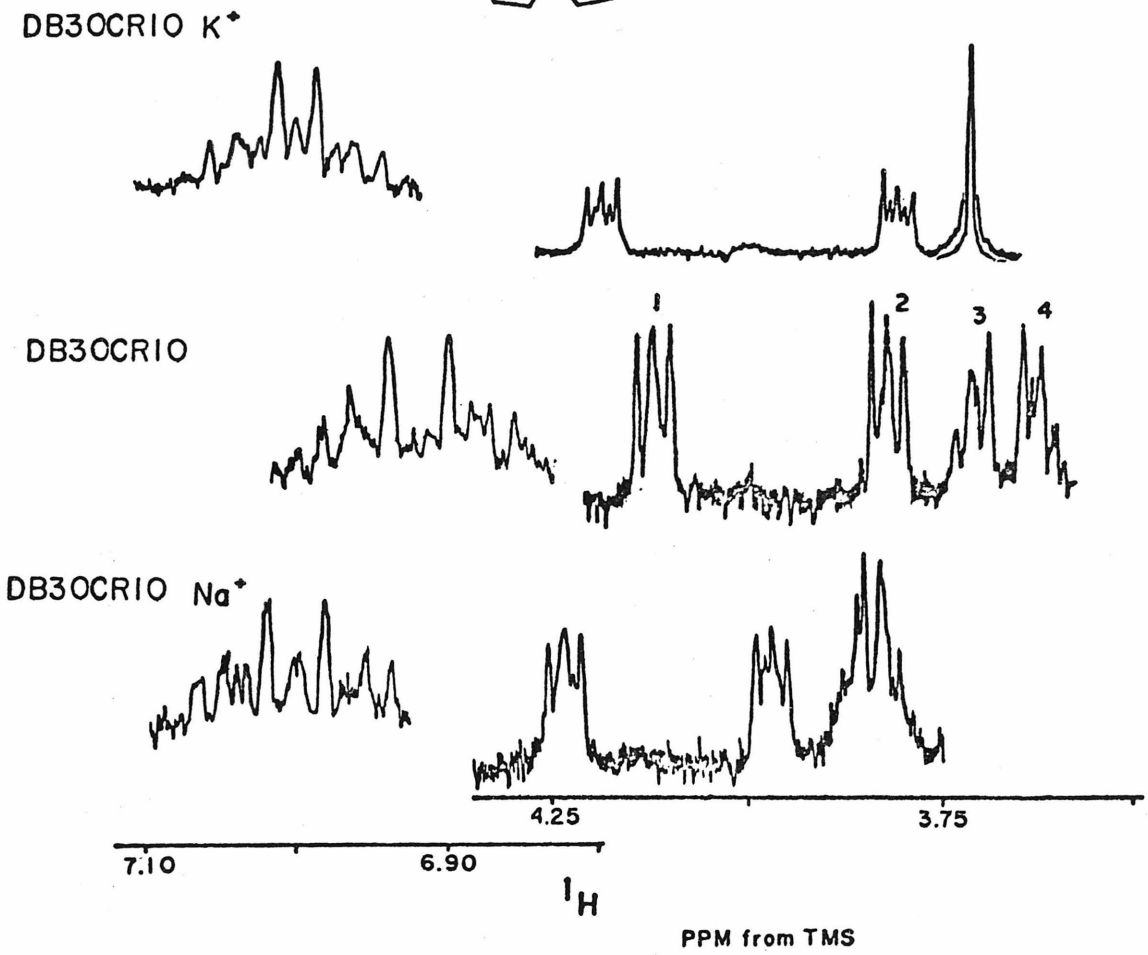


TABLE 20

Chemical Shifts of DB30CR10[a]

Solvent	Position	1	2	3	4	$\alpha+\beta/2$	$\alpha-\beta$ (Hz)
Acetone		4.131	3.826	3.712	3.632	6.916	16
$CDCl_3$		4.153	3.887	3.799	3.698	6.890	4
29 Mole % D_2O in Acetone		4.148	3.859	3.734	3.661	6.936	17.6

Ether Vicinal Coupling Constants

	Position 1 and 2		Position 3 and 4	
	J_{13}	J_{14}	J_{13}	J_{14}
Acetone	3.1	6.2	3.3	6.0
$CDCl_3$	3.0	6.0	3.3	6.0
29 Mole % D_2O in Acetone	3.0	6.1	3.2	6.0

[a] in ppm relative to TMS

TABLE 21

Calculated and Observed Ether Multiplet Separation for DB30CR10 and B18CR6

	Position 1 to 2	2 to 3	3 to 4
Calculated[a]	61	12	26
Observed (DB30CR10)			
Acetone	67	25.2	16.6
$CDCl_3$	58.4	21.6	20
Observed (B18CR6)			
Acetone	59.8	33.4	14
$CDCl_3$	57.2	33.8	12

[a] from coordinates in ref. 20

TABLE 22

Limiting and Induced Chemical Shifts for DB30CR10 Complexes in Acetone[a]

Salt	Crown conc.	Position	1	2	3	4	$\alpha+\beta/2$	$\alpha-\beta$ (Hz)
KI	3.5×10^{-3}		4.195	3.805	3.719	3.719	6.998	11
			(14.2)	(-4.8)	(+1.6)	(+19.2)	(18.9)	
KCNS	3.3×10^{-3}		4.205	3.810	3.719	3.719	7.001	11
			(16.2)	(-3.6)	(+1.6)	(+19.2)	(18.6)	
$KClO_4$	2.8×10^{-3}		4.197	3.807	3.718	3.718	7.000	11
			(14.6)	(-4.2)	(+1.4)	(19.0)	(18.4)	
KCNS[b]	4.9×10^{-3}		4.186	3.814	3.715	3.715	7.001	15
			(+8.4)	(-10)	(-4)	(+12)	(18.6)	
$NaClO_4$	3.3×10^{-3}		4.237	3.968	3.868	3.815	6.985	15.5
			(23.3)	(31.2)	(34.5)	(40.3)	(15.0)	
$CsClO_4$	1.5×10^{-3}		4.142	3.805	3.717	3.690	7.005	13
			(2.5)	(-4.8)	(+1.6)	(12.8)	(19.4)	
$Ba(ClO_4)_2$	2.5×10^{-3}		4.495	4.008	4.008	4.008	7.532	24
			(80.1)	(39.9)	(65.1)	(82.7)	(69.4)	

[a] Shifts in ppm. Induced shifts (Hz) below in parentheses.

[b] In 29 Mole % D_2O in Acetone.

TABLE 23

Calculated and Observed Complexation Shifts for Potassium DB30CR10 Complex (Hz)[a]

	1	2	3	4
Calculated				
Ring Current	-11	-60	-12	-13
$\vec{E}$ Field	+90	+74.2	+64	+87
Total	+59	+14	+52	+100
Observed	+15	-4.2	+16	+19.1
Incremental Shift (Ba^{+2} - K^{+})				
Calculated	68	33	48	41
Observed	64	44	63	63

[a] from coordinates in ref. 20

TABLE 24

Ether Vicinal Coupling Constants for DB30CR10 Complexes (Hz)

Solvent	Salt	Position 1 and 2		Position 3 and 4	
Acetone		J_{13}	J_{14}	J_{13}	J_{14}
	KI	2.4	6.4		
	KCNS	2.2	6.4		
	$KClO_4$	2.0	6.6		
	$NaClO_4$	2.3	6.4	2.0	6.3
	$CsClO_4$	2.3	6.4		
	$Ba(ClO_4)_2$	2	6		
$CDCl_3$					
	KI	2.0	6.5		
	KCNS	2.0	6.4		
29 Mole % D_2O in Acetone					
KCNS		2.0	6.3		

examined. The difficulty in predicting the shifts for this complex lies in the rather large scale reorientation of the internal dipoles on complexation. The incremental shift for replacing a monovalent cation with a divalent one is in good agreement with prediction. The reduction rather than increase in the separation of the aromatic resonances is consistent with the crystallographic results, because the α proton positions are shielded in the complex by the other aromatic group. The coupling constant changes are the same as they are for the 18 membered rings studied. The x-ray data for DB30CR10 indicate , as we concluded for the 18 membered rings, an average increase of 5° in the C – O dihedral angle. H-3 and H-4 show an unusual behavior because they become equivalent on complexation with K^+. This result is not predicted from calculation, but must be a coincidence of the structure. When Ba^{+2} is substituted for K^+ there is a small splitting of the line which may be due to a difference in the incremental electrostatic effect for these two positions rather than a large structural change. In the complex with the much larger Cs^+ ion there is a greater splitting. In this instance the molecule has to adapt its shape to accommodate the significantly larger Cs^+ ion. The solvent does not appear to affect this shift since this resonance appears as a single line at the same place in $CDCl_3$ when the anion is I^- or NCS^- (Table 25). An effect of the solvent interaction on the uncomplexed molecule can be observed in the comparison of the induced shifts of H-3 and H-4 in acetone and $CDCl_3$ relative to their initial states in those solvents (Tables 22 and 25). The absence

TABLE 25

Limiting and Induced Shifts for

DB30CR10 Complexes in $CDCl_3$

Salt	Position	1	2	3	4	$\frac{\alpha+\beta}{2}$	$\alpha-\beta$(Hz)
KI		4.051	3.764	3.713	3.713	6.860	26
		(-21.6)	(-26.7)	(-16.8)	(+3.2)	(-6.6)	
KCNS		4.059	3.764	3.715	3.715	6.864	25
		(20.6)	(-27.2)	(-16.4)	(+3.6)	(-5.8)	
$KClO_4$		4.123	3.859	3.750	3.691	6.086	5
		(-6.6)	(-6.2)	(-8.6)	(1.6)	(+0.2)	

of a solvent shift or an anion effect for KI and KNCS complexes in $CDCl_3$ indicates that these atoms are well inside the solvent cage of the molecule. The stability constants of KCNS and $CsClO_4$ DB30CR10 complexes are given in Figure 19. These values are in reasonable agreement with the values reported in methanol of 3.98×10^4 and 1.7×10^4 LM^{-1} respectively. The plots agree with 1:1 stoichiometry. Rapid ring inversion is observed for these complexes. Chock[26] has reported rates for the complexation reaction

$$M^+ + \text{Crown} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} M^+ \text{Crown}$$

of $k_f \sim 7 \times 10^8$ and $k_r = 1.6 \times 10^4$ for K^+ and 4.7×10^4 for Cs^+. This would be fast enough for the inversion rate seen.

The induced shifts for the Na^+ complexes are more after the pattern observed for 18 membered rings in acetone. The magnitude of the shift increases on going from position 1 to 4, however the aromatic splitting does not increase substantially.

The interior ether cavity of the KI, DB30CR10 structure cannot be made small enough to fit the Na^+ ion tightly, so we have proposed a different structure which would be more consistent with the observed. This is pictured in Figure 20. This structure would allow an energetically more favorable Na – O interaction with four oxygens, with four more oxygens loosely interacting with the ion. The effect on the proton shifts would decrease as one moved away from the ion and the aromatic rings could no longer provide the

FIGURE 19

Binding curves for K^+ (□) and Cs^+ (∇) with DB30CR10. $K_{K^+} = 2 \pm 0.5 \times 10^4$ LM^{-1} crown concentration = 3.3×10^{-3} M. $K_{Cs^+} = 1.7 \pm 0.5 \times 10^4$ LM^{-1} crown concentration 1.5×10^{-3} M.

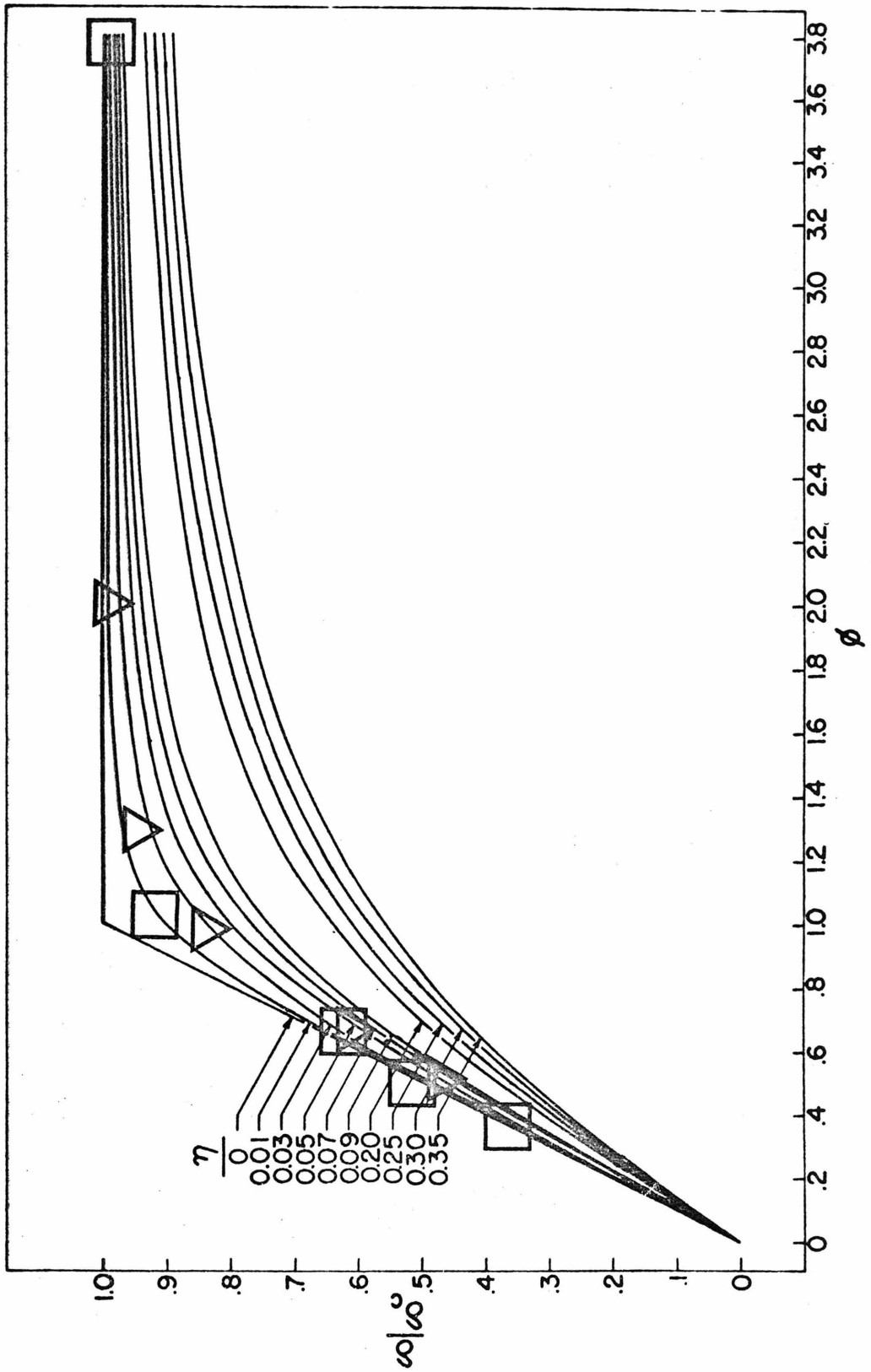
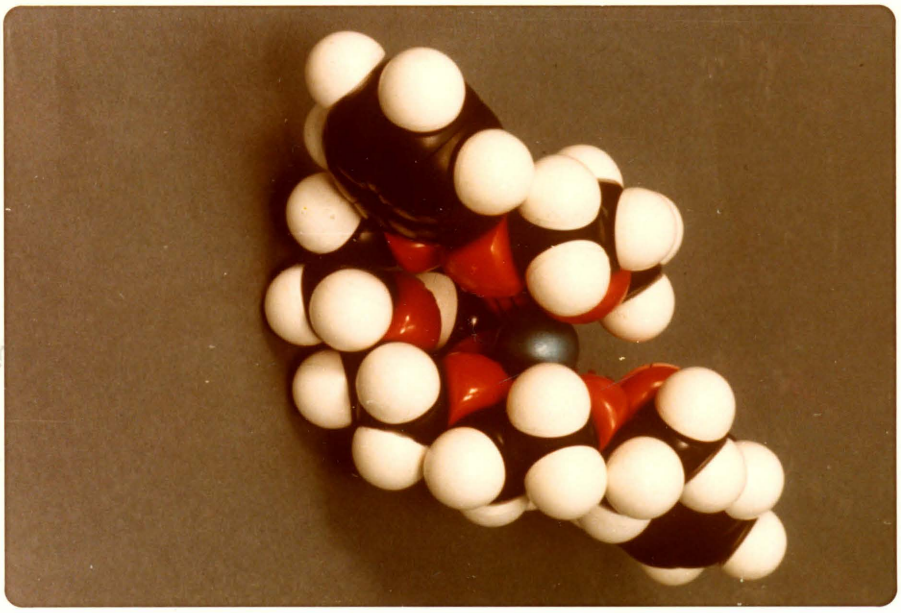

η
0
0.01
0.03
0.05
0.07
0.09
0.20
0.25
0.30
0.35
ω/ω₀
φ
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
1.0
0
.2
.4
.6
.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8

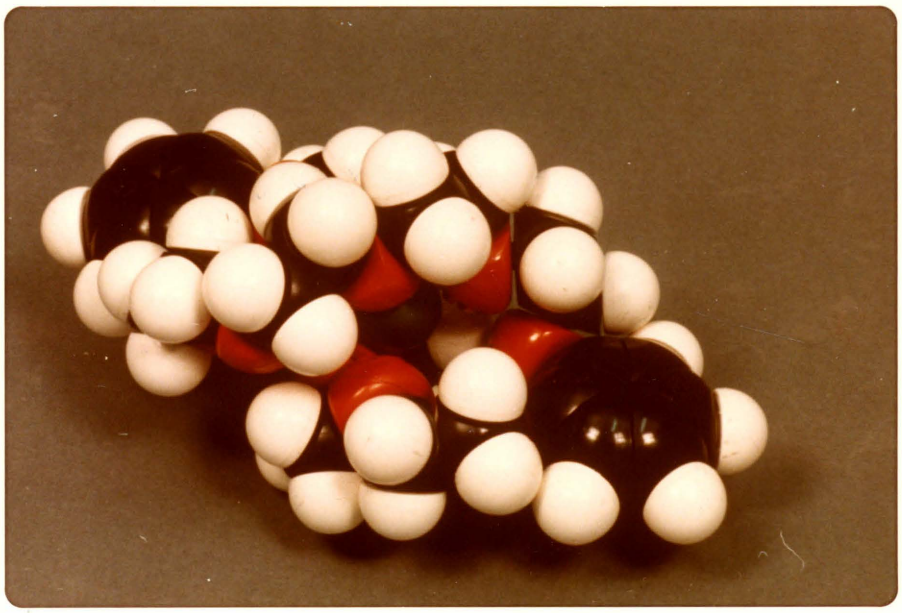
FIGURE 20

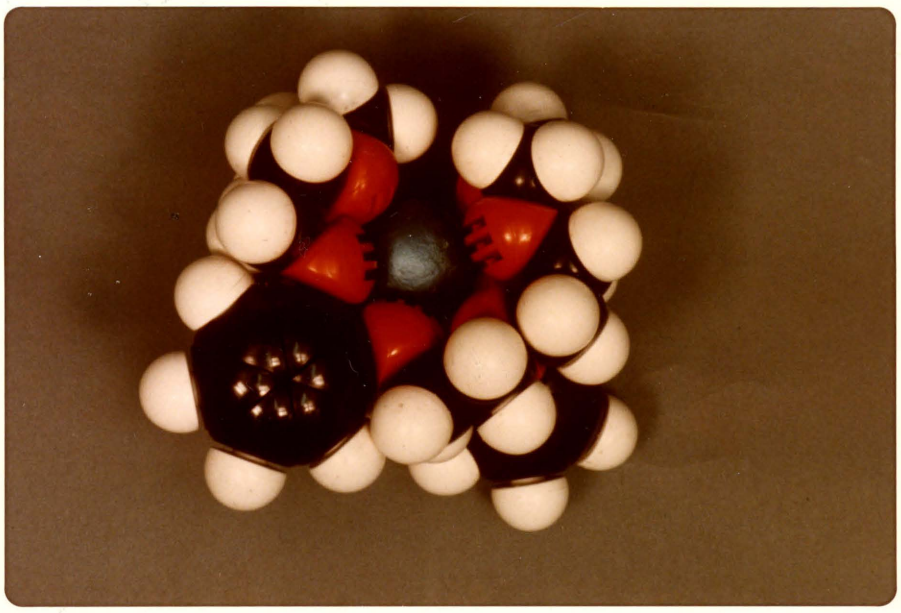
Two views of proposed Na^+, DB30CR10 conformation (a, b), and X-ray determined K^+, DB30CR10 structure (c).

a



b





c

shielding effect that tends to reduce the induced shifts for the K^+ complex.

Figure 21 illustrates the binding curve of Na^+ and DB30CR10 in acetone. The binding constant is $3.5 \pm 0.75 \times 10^2$ LM^{-1}. The value reported in methanol is 100 LM^{-1}.[10, 26] A lower binding constant for Na^+ than for K^+ is expected as a result of the fewer ion-oxygen interactions.

The proposed model does not allow room for solvent-ion interaction and therefore the conformation would be due to an ion size effect rather than a solvation effect. This is confirmed by the result that the binding constants for K^+, Cs^+, and Na^+ are all reduced by approximately an order of magnitude in a 40 mole % D_2O in acetone solvent compared to dry acetone.

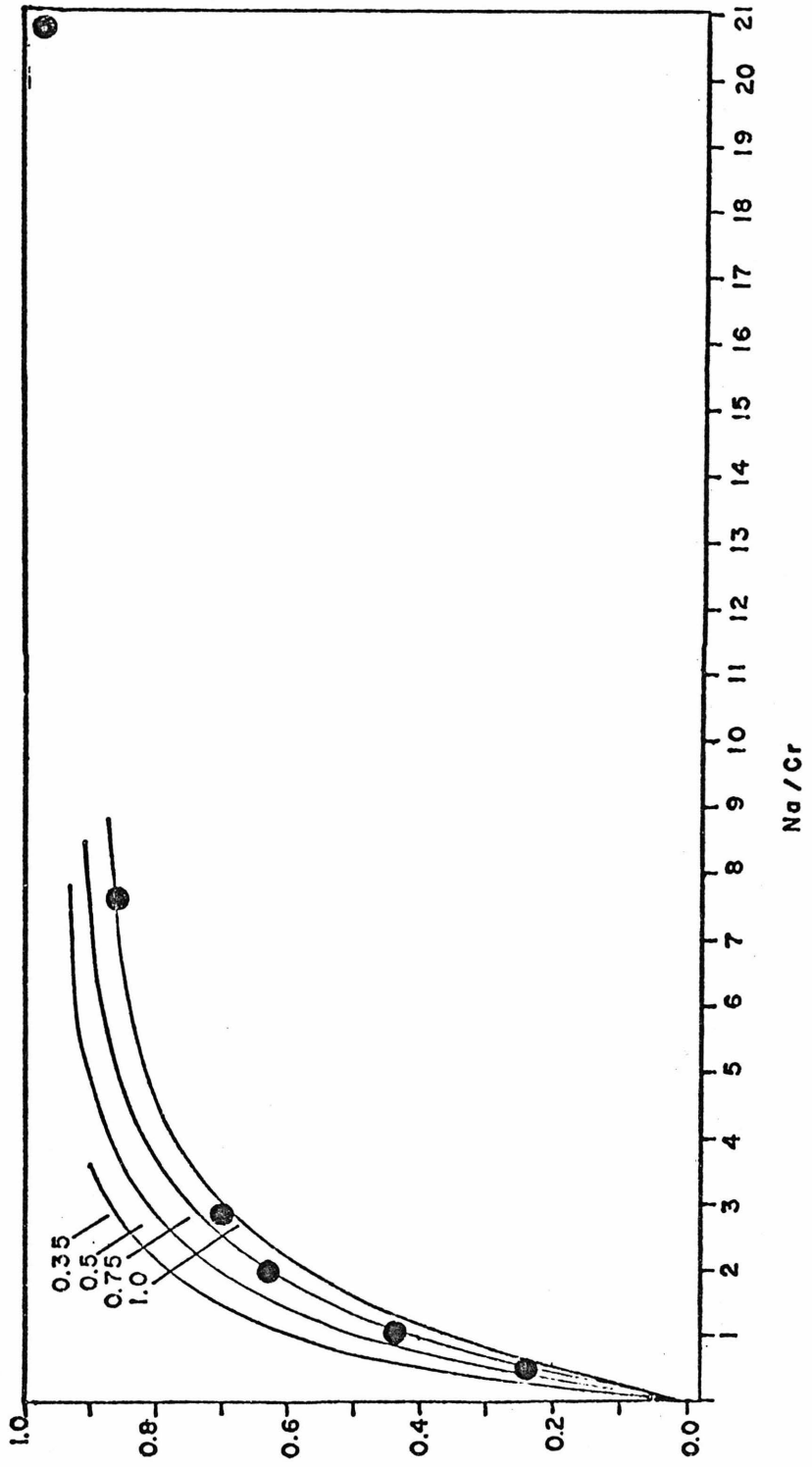
The limiting shifts and coupling constants are the same in both wet and dry acetone, indicating that the individual ion and not the hydrated ion is being complexed and that the free energy of the complex is the same in both solvents.

There is clearly from the data in Tables 20 and 12 a change in the crown solvent interaction with the two solvents, but that is probably of little or no effect since in both B18CR6 and DB30CR10 this is observed, but only in the latter do we see any effect on the equilibrium.

We did not observe a change in the binding constant of cation to B18CR6 in wet as opposed to dry acetone, although it does drop in pure water. However the experiment was done at a concentration

FIGURE 21

Binding curve for Na^+-DB30CR10 in acetone. $K_{Na^+} = 3.5 \pm 0.5 \times 10^2\ LM^{-1}$. Crown concentration = 3.3×10^{-3} M.


0.35
0.5
0.75
1.0
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
Na / Cr

such that only a lower limit on the binding constant could be established for either wet or dry acetone. An analogous experiment for DB18CR6 where the binding constant appears to be just below our limit for dry acetone, does not indicate a change in the equilibrium either. From the experiments of Eyal and Rechnitz[22] on valinomycin in wet and dry methanol, and Prestegard and Chan[54] on wet and dry acetone it appears that on the average about one molecule of water is in the inner solvation sphere of the cation at the level of water present in our experiment. This molecule binds more strongly than the methanol or acetone, lowering the free energy of the ion. When the total solvation sphere is removed, as is presumed to be the case for valinomycin and nonactin, the binding constant drops. For the open ring cyclic ethers one and possibly two solvent molecules can remain in contact with the cation in the complex. In the wet solvents this would be one or two water molecules. Therefore it is only after three or more water molecules are in the solvation sphere of the cation that a drop in binding constant will be observed in this system. We can deduce from the drop in the binding constant for DB30CR10 in wet acetone that the ion loses all direct contact with the solvent for the three cases we have examined.

K^+ Complexes in $CDCl_3$

Due to problems in crystallization and solubilities only the K^+ complexes could be studied in $CDCl_3$. The chemical shifts for KI, KNCS and $KClO_4$ complexes are in Table 25. The similarity of

the coupling constants in acetone and $CDCl_3$ (Table 24) as well as the retention of the equivalence of the H-3 and H-4 resonances (Table 25) suggests the same structure in both solvents. These latter are the same as those in acetone. The anion dependence of the shifts for the first two salts means that in this case both of these anions are solvated sufficiently to remove specific anion complex interaction. The upfield complexation shifts observed in $CDCl_3$ should be due to the quadratic term in Eq. 5. It can be seen that $KClO_4$ results do not conform with those for the other two salts. The equivalence of H-3 and H-4 is not retained. Since there is no evidence for a $CDCl_3$-ClO_4^- interaction it is likely that there is a specific anion complex interaction which would explain these effects.

1:1 stoichiometry in $CDCl_3$ is shown by the linear dependence of the shift in the ratio of crown-ether to K^+.

The spectrum of DB30CR10 and KNCS, DB30CR10 has been observed between 2×10^{-3} M and 2×10^{-1} M and no suggestion of aggregation of different stoichiometries is observed.

CMR of DB30CR10

The CMR spectrum for KCNS, DB30CR10 is shown in Figure 22 along with the KI, B18CR6 for comparison. The shifts are in Table 26. It is readily observed that the shifts caused by complexation are entirely different for the two molecules. This is an additional conformation of the large structural differences between the complexes. The T_1 relaxation times have been measured

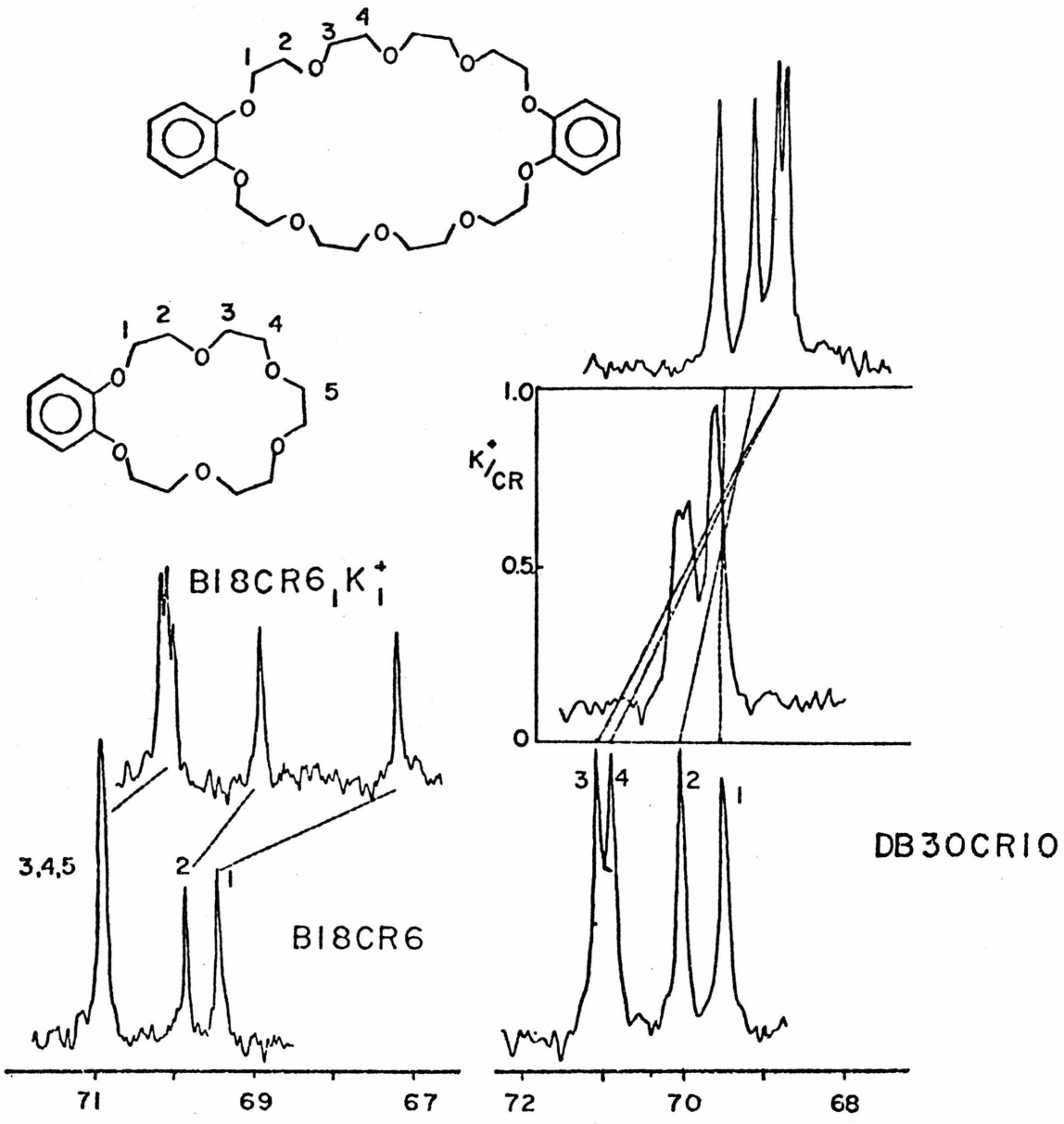
TABLE 26

CMR of DB30CR10 in $CDCl_3$

	1	2	3	4	α	β
DB30CR10	69.5	70.3	71.06	70.89	115.22	121.75
T_1 (sec)	1.18	1.05	0.95		1.01	0.96
KCNS, DB30CR10	69.4	69.07	68.84 68.80		116.5	123.0
T_1 (sec)	0.82	0.77	0.73		1.4	1.4

FIGURE 22

Comparison of B18CR6 and DB30CR10 CMR spectra in free and complexed forms.


1
2
3
4
5
B18CR6, K+
3,4,5
2
1
B18CR6
71
69
67
1.0
K*CR
0.5
0
3
4
2
1
DB30CR10
72
70
68
PPM vs TMS
13C

for the ether carbons in both the complexed and free forms (Table 26), these can also provide some structural information.

In the extreme narrowing limit, with isotropic motion where the relaxation mechanism is dipolar, the equation

$$\frac{1}{T_1} = \frac{C\gamma_H^2\gamma_C^2\hbar^2}{2\pi r^6}\tau_c N \qquad (7)$$

is a good approximation.[52] γ_H and γ_C are the gyromagnetic ratios of the H^1 and C^{13} nuclei, τ_c is the molecular correlation time, r is the C – H internuclear distance and N is the number of protons attached to the carbons. If the above conditions are met the T_1's should be inversely proportional to the number of protons of a carbon. Fedarko has found that the relaxation is dipolar in origin for the 18 membered rings, and this should be true here, therefore any deviation from this formula should be due to anisotropic motion or a lack of rigidity. For the K^+, DB30CR10 complex the T_1's have the ratio $T_{1CH}/T_{1CH_2} = 2$ to within experimental accuracy. This is consistent with a spherical shape and a rigidity of the complex on the time scale of $10^{11} \times \sec^{-1}$. For the unbound molecule the ratio of the T_1's for the CH's and CH_2's is one. This deviation from the equation 7 is probably not due to anisotropic tumbling since both α and β carbons in the aromatic groups have the same relaxation time. It can be the result of segmental motion in the ether chain. From the coupling constants we know there is ring inversion, and if the barrier is low enough this can occur fast enough to affect the T_1. Fedarko[42] has concluded that this is the

case for the uncomplexed 18 membered rings, however her contention that the complexes are rigid has to be modified as mentioned above. One would, in fact, expect the barrier to motion in the ether chain to be higher when the molecule is complexed.

CONCLUSION

In non-hydrogen bonding solvents the $O\diagup CH_2-CH_2 \diagdown O$ fragments of the cyclic ethers adopt a gauche conformation with a low barrier to + gauche, - gauche rotamer conversion. This is observed in the more restricted, 1, 4 dioxane as well as in DB30CR10 where there is a great deal of conformational freedom, indicating that this is the favored arrangement. In water and possibly in other solvents that can easily form hydrogen bonds this interaction leads to a structural change in which the dihedral angles of the C – O bonds on adjacent carbons increases. This interaction decreases the free energy of the uncomplexed molecule and would therefore contribute to the reduced complex stability in water.

When cation crown complexes are formed the dominant effect is the ion-dipole interaction, and the reorientation of the oxygens changes to minimize the energy, this structure is independent of solvent. In the system examined here this seems to require an increase in the C – O dihedral angles. The larger rings can adapt themselves to ions in a variety of ways to compensate for ion size effects. Even though substituents can have large effects on the solubility of the complexes they do not seem to affect the structure of the ether ring in the complex. There does not seem to be a solvent effect on the complex structure. No direct anion effect on the cation-crown interaction is observed. Stoichiometries greater than 1:1 crown to cation only occur when the cation is larger than

the size of the ether ring hole. In this case the arrangement is a "sandwich" complex. When ions are smaller than the ring the rule is that 1:1 complexes are formed. Neither free nor complexed molecules show any aggregation over a range of two orders of magnitude in concentration up to 0.2 M. Ion exchange either with solvent or with another crown molecule occurs in general at a rate greater than 10^3 sec^{-1}, giving rise to rapid ring inversion.

In general the binding constants are sufficiently high and the shifts sufficiently small that we are at or approaching the limit for measuring equilibrium constants with the PMR method.

Ion Selectivity

The selectivity of the crown ethers has been considered in terms of their ability to form complexes with ions in a variety of solvents, to extract alkali ions from aqueous solutions, and to enhance ion permeability or conductance through lipid bilayers. For the crown molecules it has been found that all of these properties do not follow the same ion sequence

For valinomycin and nonactin, on the other hand, all these properties do follow the same sequence. We can now shed some additional light on this contrasting behavior [53] from the structural results we have obtained.

The valinomycin-nonactin class of ionophores appears to bind cations in a single configuration, and only with 1:1 stoichiometry. This configuration prevents direct anion or solvent interaction with

the cation. Under such conditions it can be shown that the properties mentioned above are proportional to the complex stability in aqueous solutions or whatever other solvent the association is taking place in.[23]

For the crown complexes with their variety of size and flexibility as well as their exposure, in some cases, of the cation to the solvent, the interactions do not follow such a simple proportionality.

18 Membered Rings

In the 18 membered rings we have shown that although solvent and anion do not seem to affect the structure of the ether in the complex, they can nevertheless interact with the cation in the complex. When a monovalent ion forms a complex one of the following equations holds, depending on whether there is ion pairing

$$I^+(\text{solvent})_n + \text{crown} \rightleftharpoons I^+\,\text{crown}(\text{solvent})_2 + n - 2\ (\text{solvent})$$

or

$$I^+A^-(\text{solvent})_n + \text{crown} \rightleftharpoons I^+\,\text{crown}\,A^-(\text{solvent}) + n - 1\ (\text{solvent})$$

Considering the first of the above equations, one finds that the stability of the complex depends on the energy gained in complexation, and the energy lost by partial removal of the solvent molecules.

Since our results indicate that the geometry of the complexes for ions that can fit in the ring are the same, the ion selectivity for the open ring system is determined by the fraction of the solvation energy required to remove the necessary number of solvent

molecules. Even though this is a varying fraction of the total ion solvation energy because of changes in solvation numbers with ion size, the differences between the solvation energies of the small ions in question are such that the complexation equilibrium follows qualitatively the inverse of the total solvation energy. The solvation energy is approximately proportional to the ionic radius, so as the ions get bigger the energy loss on desolvation decreases while the ion-dipole interaction with the cyclic ether stays approximately the same. Therefore as the size of an ion increases up to the ether ring size for the open ring systems the stability of the complex will increase.

When the complication of ion pairing arises the relative cation-anion and solvent-anion interactions in the complexed and uncomplexed conditions have to be considered. There is no straightforward approach to estimating these effects and it has been found that inconsistent selectivity sequences are observed when comparing results of complexes in solvents with different ion pairing tendencies.[11] The existence and variation of this effect is clearly reflected in the variation of our PMR results with anion in $CDCl_3$.

When an ion is bigger than the size of the ether ring then the conformation of the complex will vary from ion to ion and there is no standard ion-dipole interaction energy to compare with.

In addition to the presence of a variety of stoichiometries, extraction equilibria can be used as a way of measuring stability since the overall extraction equilibrium constant is given by

$$K_e = P_e P_c K$$

where P_e and P_c are the partition coefficients for uncomplexed and complexed molecules respectively and K is the complex formation constant in the solvent from which the extraction was made. In order for there to be strict proportionality between extraction and complex stability, the partition coefficient must be the same for all complexes. In the nonactin-valinomycin case they are the same since the complexes have basically the same geometry and the same solvent and anion interaction from cation to cation.[23, 54] The exposure of the cation to the solvent can lead to differences in solvent interaction from complex to complex and to differences of anion-cation attraction as we have shown. The latter should certainly be the case for extraction into CH_2Cl_2 or n-hexane from aqueous solution, where there are some data available for dicyclohexyl-18-crown-6. The larger ion complexes have the additional complication of a difference in the tendency for higher stoichiometries in the two media in question. The sequences for extraction from H_2O to n-hexane and CH_2Cl_2 using the picrate anion are K $\rangle$ Rb $\rangle$ Na $\rangle$ Cs $\rangle$ Li and K $\rangle$ Rb $\rangle$ Cs $\rangle$ Na $\rangle$ Li, respectively. The aqueous formation constants go as K $\rangle$ Na $\rangle$ Rb $\rangle$ Cs.[8, 9]

The conductance and permeability of model lipid bilayers should be a function of the extraction equilibrium and the mobility of the complex. For complexes like nonactin and valinomycin which are isosteric, the former two properties are, just as the extraction equilibrium is, proportional to the aqueous binding constants. This

prediction again does not apply for the open cyclic ethers. In the appropriate concentration range one can get the conductance and permeability ratios to agree, but they do not agree with the extraction or aqueous complexation equilibria.[8, 9]

The conductance of di(t-butylcyclohexyl)-18-crown-6 varies as a function of polyether concentration between the first and third powers of the ether concentration.[8] All the properties discussed up to now have had first power dependence on the ether concentration except in the presence of Cs^+. The peculiar result for conductance has been rationalized in terms of the function of 1:1, 2:1 and 3:1 complexes in the model membrane systems. The question is why do we not observe such features with Na^+ or K^+ in low dielectric bulk systems? In a low dielectric medium the anion in general wants to be close to the cation, this would tend to prevent the formation of non 1:1 complexes. For ions that are bigger than the ether hole, that prefer longer ion-oxygen distances, the energy gained by complexing to a second crown is enough to make up for the increased distance to the anion; the results for the Cs^+, DB18CR6 show this to be the case. The situation is different in lipid bilayer films since in this system at concentrations below 5×10^{-5} M, the space charge effects that cause ion pairing are negligible,[55] and consequently complexes can be sustained at this concentration in such an environment without an anion present. This concentration is high enough to explain the conductance behavior. In this instance it would be helpful to have 2:1 and 3:1 complexes since the more the ion was

surrounded by ethers, the lower the electric field energy required to transfer the complex into a low dielectric medium. The preference for such complexation would drop off as the preferred cation-oxygen distances do with ionic size, and thus the sequence observed for conductance and permeability is $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$.[8] The observation of such postulated sandwich structures in solution strongly supports this hypothesis.

In contrast to the bilayer conductance data, the ion selectivity of a bulk phase liquid membrane electrode follows the same sequence as the aqueous formation constants for DB18CR6, dicyclohexyl 18 crown 6 and benzo 15 crown 5.[21]

The selectivity for induction of ATP hydrolysis by 18 membered crown molecules in mitochondrial membranes is K > Rb > Cs which is also the formation constant sequence.[24, 25] This suggests that the model bilayer results are not applicable to this system or that a process other than ion transport is involved. The overall results for the effects on mitochondria of polyethers as a function of ions and other ionophores present are confusing,[25] implying several different modes of operation for these molecules.

It is possible that cations already at an active site in the membrane could be complexed. Our observation that hydrogen bonding can occur between water and crown molecules suggests that they may interact with protein bound water in a membrane. Preliminary results from this laboratoryindicate that cyclic ethers can enhance the diffusion of water through lipid bilayer vesicles

and also disturb their structure.

Further studies on simpler systems such as axons are needed to sort out direct ion transport from other interactions before the role of crown ethers in mitochondrial membranes can be understood.

DB30CR10

The results we have obtained on DB30CR10 indicate a much greater similarity between it and nonactin and valinomycin than applies to the 18 membered rings. Most notable is the removal of the ion from solvent and anion interaction when it is complexed.

No extraction or bilayer conductance results are available for this compound, however liquid membrane electrode studies have been done and the selectivity follows that in dry and wet acetone and in methanol.[21] Valinomycin shows such a relation to its stability constants in wet and dry methanol.[20]

It is expected on the basis of our structural results for K^+ and Cs^+, and probably for Rb^+ which we have not studied that the bilayer effects of this compound should follow the formation constant sequence as well. For Na^+ however the isosteric approximation[23] may break down because of the different shape of the complex.

The limited data available on the biological activity of dicyclohexyl 30 crown 10 show a specificity for K^+ and Rb^+ in inducing ATP hydrolysis, and some effect in uncoupling of oxidative phosphorylation in the presence of K^+.[29] These results are too

sketchy for making any conclusions.

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