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The Molar Free Energies of Transfer
from Water to Several Nonaqueous
Solvents for DB18C6 and B15C5 and
Proton and Carbon-13 NMR Studies of
Some 18C6 Complexes
presented by

Davette Jones Whitaker

has been accepted towards fulfillment
of the requirements for

Masters degree in Chemistry

A handwritten signature in cursive script, reading "Alexander I. Popov".

Major professor

Alexander I. Popov

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THE MOLAR FREE ENERGIES OF TRANSFER FROM WATER
TO SEVERAL NONAQUEOUS SOLVENTS FOR DB18C6
AND B15C5 AND PROTON AND CARBON-13 NMR
STUDIES OF SOME 18C6 COMPLEXES

By

Davette Jones Whitaker

A DISSERTATION

Submitted to

Michigan State University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

Department of Chemistry

1979

ABSTRACT

THE MOLAR FREE ENERGIES OF TRANSFER FROM WATER
TO SEVERAL NONAQUEOUS SOLVENTS FOR DB18C6
AND B15C5 AND PROTON AND CARBON-13 NMR
STUDIES OF SOME 18C6 COMPLEXES

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The molar free energies of transfer, ΔG_t° , from water to several nonaqueous solvents for DB18C6 and B15C5 were determined by solubility measurements. ΔG_t° of DB18C6 for methanol, acetonitrile, and 1,2-Dichloroethane are -2.1 ± 0.5 , -4.3 ± 0.5 , and -4.8 ± 0.5 Kcal mol⁻¹, respectively and -1.2 ± 0.2 Kcal mol⁻¹ for ΔG_t° of B15C5 for methanol. These values are explained in terms of the solvating ability of the solvent and the solvent structure.

Proton and carbon-13 NMR studies of several alkali metal cations and tetraethylammonium cation complexes of 18C6 were performed. Determination of the formation constants for these complexes was attempted. The results

indicate the insensitivity of proton and carbon-13 NMR as probes in the study of complexation reactions of non-benzo-substituted crown ethers such as 18C6 at low field strengths.

To Clayton and Nicole

ACKNOWLEDGMENTS

The author would like to thank Professor Alexander I. Popov for his patience, guidance, and encouraging words. Thank you Professor Popov.

The help, friendship, and laughter of my brothers and sisters of the group has been deeply appreciated. You will all be missed.

The author acknowledges the financial assistance of the Department of Chemistry, Michigan State University, and the National Science Foundation during the course of this study.

Without the love and constant moral support of my family this study would not be. Therefore, deep and humble appreciation is extended to my Grandmother, brother, and especially to my sister who has indeed been a friend to a friend in need. Finally, I thank my children, Clayton and Nicole for their unquestioning love, to them I dedicate this thesis.

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LIST OF ABBREVIATIONS

DB18C6	Dibenzo-18-crown-6
B15C5	Benzo-15-crown-5
18C6	18-crown-6
MeOH	methanol
An	acetonitrile
1,2-DCE	1,2-Dichloroethane
Ac	acetone
DMSO	dimethylsulfoxide
DMF	dimethylformamide
TMS	tetramethylsilane
DC18C6	Dicyclo-18-crown-6

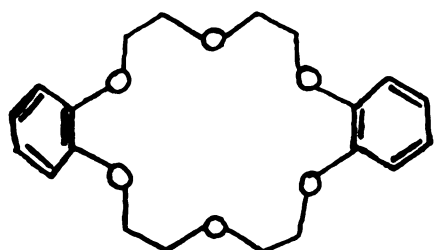
CHAPTER 1

HISTORICAL REVIEW

A. INTRODUCTION

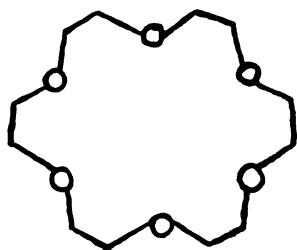
An important and interesting group of macrocyclic compounds is known as crown ethers. The crown ethers were first synthesized and reported by Charles Pedersen in 1967 (1). Pedersen used a trivial nomenclature for these compounds because of their long and complicated IUPAC names. Shown in Figure 1 are some examples of polyether crowns which are identified by their IUPAC and trivial names. The IUPAC names are shortened by using the general scheme of naming the groups attached to the crown ether ring followed by the word "crown" and then the number of oxygen atoms in the crown ether (1,2). According to this scheme ligand I of Figure 1, whose chemical name is 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadiene, can be called dibenzo-18-crown-6, abbreviated in this study to DB18C6.

As seen in Figure 1, the crown ethers are uncharged molecules which contain holes of varying size depending on the number of atoms in the ring. The ring consists of donor oxygen atoms usually separated from each other by two methylene groups, $-\text{CH}_2-\text{CH}_2-$. Pedersen observed that crown ethers displayed complexing properties with some metal cations and especially the alkali and alkaline earth metal cations, by encapsulizing them inside the

**I**

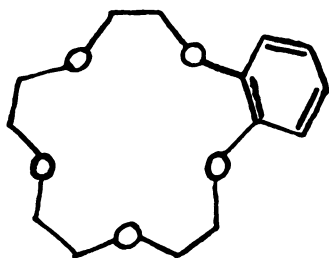
IUPAC name: 2,3,11,12-Dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene

Crown name: Dibenzo-18-crown-6 (DB18C6)

**II**

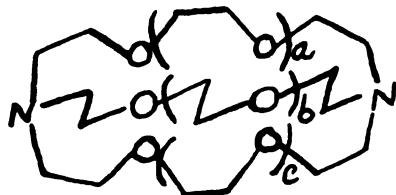
IUPAC name: 1,4,7,10,13,16-hexaoxacyclooctadecane

Crown name: 18-crown-6 (18C6)

**III**

IUPAC name: 2,3-Benzo-1,4,7,10,13-pentaoxacyclopentadeca-2-ene

Crown name: Benzo-15-crown-5 (B15C5)

**IV**

a=b=0, c=1 C211

Cryptand a=b=1, c=0 C221

a=b=c=1 C222

Figure 1. Synthetic macrocyclic polyether ligands.

hole. The crown ethers' ability to solubilize inorganic salts in polar and nonpolar solvents was also demonstrated (1,3-7). Pedersen relates in his account of the discovery of the crown ethers (8) that his and his coworkers' excitement "turned into elation when it was realized that, at long last, a neutral compound had been found capable of forming stable complexes with salts of the alkali metals". The excitement was justified because previously the alkali and alkaline earth metal ions were thought to be inert and unreactive (9).

Since the initial synthesis of the first crown ethers, hundreds of similar macrocyclic compounds have been prepared (10), including various substituted crown ethers and heterocyclic crown ethers in which either nitrogen or sulfur atoms replace the oxygen atoms. Reinhoudt and de Jong (11) and Bradshaw (10) have written excellent reviews with extensive references on the synthesis of these compounds.

Many of the crown ether compounds resemble naturally occurring macrocyclic antibiotics such as valinomycin and nonactin, both in structure and in their ability to form stable complexes with alkali cations. Therefore, the crown ethers have proven to be excellent models for these antibiotics and have even exhibited similar ion transport properties across biological membranes (8,12-15). The importance of macrocyclic ligands in membrane transport

has been summarized by Cockrell et al. (16), Fenton (17), and Morf et al. (18). The use of dicyclohexyl-18-crown-6 in membrane transport is discussed by Grimali and Lehn (19).

Cryptands are another group of macrocyclic compounds that were first synthesized by Lehn and coworkers (20). They are three dimensional macrocyclic polyethers containing three polyether strands joined together by nitrogen bridgeheads (See Figure 1). The polyether strands form a cavity which varies in size depending on the number of ether oxygen groups contained in the strands. The cryptands form very stable three dimensional complexes called cryptates with alkali and alkaline earth metal cations by encapsulizing the cation inside the cryptand cavity. Cryptand compounds are named by stating the word cryptand followed by the number of oxygen atoms in each polyether strand. An example is cryptand 222 which is pictured in Figure 1. The name cryptand is usually shortened to just C222.

There have been many interesting applications developed for the use of macrocyclic ethers based on their complexing ability for and selectivity of different alkali and alkaline earth metal salts. A few examples are: 1) use as anchor groups in ion exchangers developed for the separation of cations with a common anion, or anions with a common cation (21); 2) use as extracting reagents for univalent and bivalent cations (22,23); 3) use in the formation

of transition metal complexes by incorporation of donor atoms or groups into the polyether crowns to improve their complexing ability with the transition metals (24); 4) use in ion-selective electrodes, in which they act as neutral macrocyclic carriers for cations such as K^+ (18,25); 5) use in the determination of K^+ and Na^+ ions in serum (26); 6) use as catalyst for reactions such as nitrogen fixation and organic reactions in which alkali and alkaline earth salts are used with the macrocyclic ligand serving to improve the salts efficiency by increasing their solubility (27); and 7) use of crown ethers in photographic film in which metal complexed crown ethers containing four or more oxygen atoms per molecule are incorporated into pressure sensitive imaging materials and act as color formers in the film (28).

Another interesting application is the use of macrocyclic compounds in the preparation of salts of alkali metal anions (29). The first alkali metal anion salt was synthesized by Dye and coworkers in 1974 (30). This compound is important because it is believed to represent the first example of a new class of compounds. Solvent-free salts of the alkali metal anions are produced by stabilizing the cation by incorporation into a crown ether or cryptand complex.

The above examples demonstrate the great importance and flexibility of macrocyclic compounds. The chemistry

of crown ether complexes in various solvents has been investigated extensively, however, there is little information available concerning the ligands themselves. A study of the relative solvation of the crown ethers in various solvents would be very beneficial because it would provide information concerning the behavior of the crown ethers in the various solvents and may also provide an insight on the structure of the solvents. It is to the end of obtaining information on the solvation of a few selected crown ethers that part of this study was conducted.

The use of nuclear magnetic resonance spectroscopy as an analytical tool for the study of the complexation properties of macrocyclic compounds with alkali and alkaline earth metals is well documented in the literature (31-39). However, most of these studies use alkali and alkaline metal nmr. Therefore, an investigation of the sensitivity of proton and carbon-13 nmr in the study of the stability of the complexes formed by 18C6 with potassium iodide, potassium hexafluorophosphate, and rubidium iodide was conducted.

B. MACROCYCLIC POLYETHERS

1. Introduction

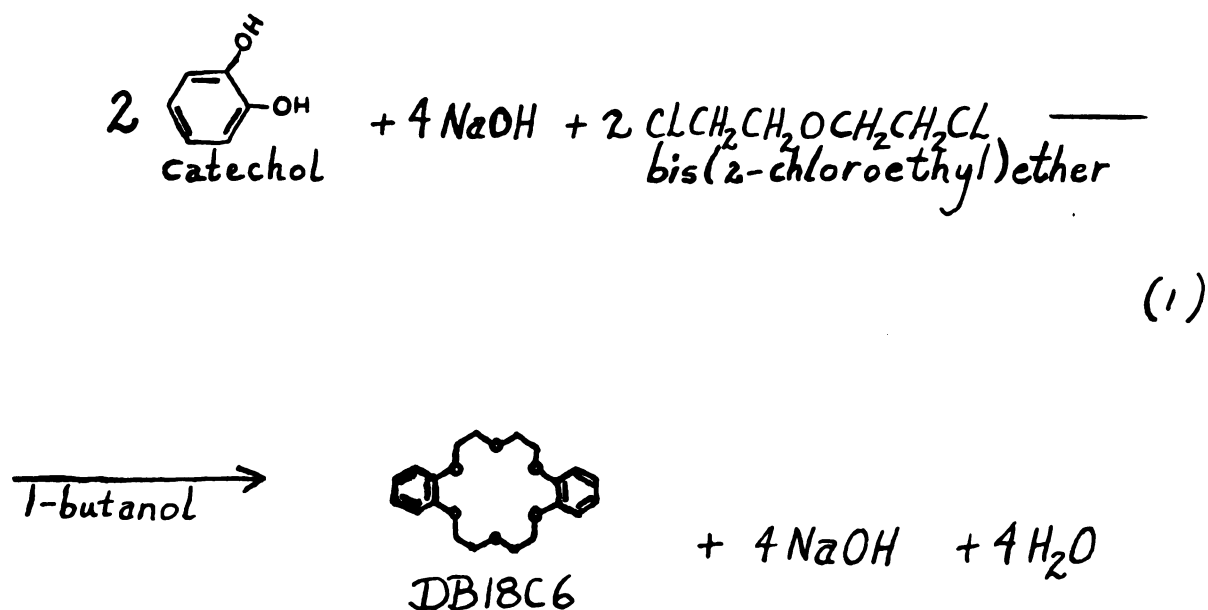
A true understanding of the solvation phenomenon requires some knowledge concerning the nature of the entity which is being solvated. The chemistry of the crown

ether metal complexes has been investigated in water and in various nonaqueous solvents using such methods as proton, carbon-13, and alkali metal nmr, potentiometry, conductance, spectroscopy, and extraction studies. The major interaction between the crown ether and cation is electrostatic in nature. The major factors effecting the cation selectivity and complex stability are 1) number, type, and arrangement of donor atoms, 2) type and charge of the cation, 3) substitution on the macrocyclic ring, 4) type of anion or counterion, and 5) solvent properties. Many reviews exist (1,2,7,27,40-43) that extensively cover this subject. In addition, investigators from this laboratory (44-51) have added significantly to the existing information. Therefore, it is not the intention here to repeat this information. However, as stated earlier, information concerning the ligands themselves is sparse. Following is an attempt to bring together data concerning the general properties of polyether crowns.

Recently there have been three books published about macrocyclic compounds (27,41-42), containing a multitude of references. In no way can this review duplicate the quantity and depth of these works, consequently the reader is directed to these references for any additional information desired.

2. Properties of Polyether Crowns

Macrocyclic crown ethers were first synthesized by the reaction of catechol and α,ω -dihalides or α,ω -ditosylates in the presence of a base with the macrocyclic polyether being obtained by formation of a carbon-oxygen bond in the cyclization step. An example of crown ether preparation is shown below (1)



The polyethers are thermally stable (dibenzo-18-crown-6 can be distilled at 380°C at atmospheric pressure), but must be protected from oxygen at high temperatures. The

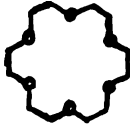
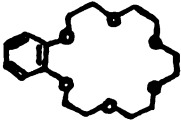
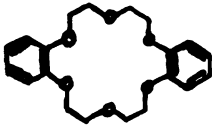
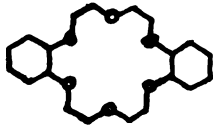
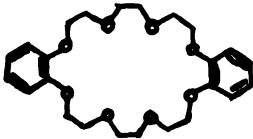
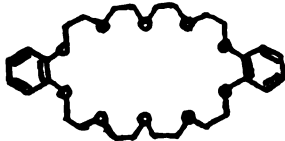
polyether ring is destroyed by reagents which cause the scission of aromatic and aliphatic ethers. Polyether crowns can undergo many substitution reactions to form polymeric products (52).

Macrocyclic polyethers with aromatic side rings are colorless crystalline compounds while the saturated polyethers are colorless, viscous liquids or solids with low melting points. DB24C8 is known to exist as at least three polymorphs, a glass and two crystalline forms having identical melting points (19).

The melting point for an individual polyether rises with the number of benzo groups attached to the ring. (See References 1,2,7,27,40-43.) Values of molecular weights and melting points of a few selected polyether compounds are shown in Table 1. Diameters of the cavities for a few representative cyclic polyethers are shown in Table 2.

Spectral data obtained from nmr, uv, and ir spectroscopy are used to identify crown ethers. The protons on the carbon attached to the ether oxygen and those on the aromatic moiety give characteristic nmr spectra with observed intensities that are close to the theoretical number of protons (1). Nmr spectra of crowns in deuteriochloroform confirm the absence of terminal groups such as hydroxyl or alkoxy which may be suspected to be present considering the synthesis reactants.

Table 1. Molecular Weights and Melting Points of Some Polyether Crowns.^a

Ligand	Molecular Weights (g/mole)	Melting Points (°C)
B15C5 	268	79 - 79.5
DB15C5 	316	113.5 - 115
18C6 	264	39 - 40
B18C6 	312	43 - 44
DB18C6 	360	164
DC18C6 	372	68.5 - 69.5
DB24C8 	448	113 - 114
DB30C10 	536	106 - 104.5

^aReference (1).

Table 2. Diameters of Cavities in Some Cyclic Polyethers.

Polyether	Cavity Size (Å)
14C4	1.2 - 1.5 (a)
15C5	1.7 - 2.2 (a)
DB15C5	2.7 (b)
18C6	2.6 - 3.2 (a)
DB18C6	4.0 (b)
21C7	3.4 - 4.3 (a)
DB24C8	>4.0 (b)
DB30C10	>4.0 (b)

(a) Reference (1).

(b) Reference (7).

All cyclic polyethers containing benzo groups have a characteristic uv absorption maximum in methanol at 275 nm. This absorption band is characteristic of compounds derived from catechol. In general, molar absorptivities, ϵ , of crown ethers containing benzo groups depend on the number of benzo groups attached to the crown ether. Crown ethers with one, two, three, and four benzo groups and derived from catechol have molar absorptivities of approximately 2100 - 2300, 4400 - 5200, 6300 - 7200, and 8400 respectively. Those crowns derived from 4-t-butylcatechol show molar absorptivities of 2700 for one attached benzo group and 5000 - 5200 for those containing two groups (1). Saturated crown ethers such as 18C6 and DC18C6 do not show any absorption above 200 nm, and consequently, cannot be studied by uv spectroscopy since absorption below 200 nm is out of the range of most commercial uv spectrometers. Table 3 shows characteristic features of uv spectra of some crown ethers.

Ultraviolet spectra can be used as a qualitative detection of the complexation of the crown ethers with metal cations. For example, DB18C6 in methanol shows one peak at about 275 nm. On complexation with some metal cations such as Na^+ , Li^+ , K^+ , Ca^{+2} , and Ba^{+2} , a shoulder forms on this peak. In some cases the resolution of the shoulder shows a dependence on the concentration of the cation and becomes more resolved with increasing cation

Table 3. UV Spectrometric Characteristics of Some Poly-ether Crowns.

Ligand	Solvent	Peak Wavelengths (nm)
DB18C6	Cyclohexane	278 (ϵ 4700) (a)
		274 (ϵ 4400) shoulder
		283 (ϵ 3600) shoulder
	Methanol	274 (ϵ 5200) (a)
	Water	273.5 (a)
		279 shoulder
	Water	273 (ϵ ~5400) (b)
		278 shoulder
B15C5	Methanol	275 (a)

(a) Reference (1).

(b) Reference (53).

concentration. It is suggested that the increase in resolution of the shoulder is an indication of the stability of the complex formed such that the more resolved the peak the more stable the complex (1). However, if the shoulder does not appear on addition of a metal cation to a crown ether solution, it cannot be definitely concluded that complexation does not occur.

Infrared spectra has been used to confirm the absence of a hydroxyl group. The ether linkage is confirmed by strong, broad bands centering near 1235 cm^{-1} for an aromatic - o - aliphatic linkage and near 1130 cm^{-1} for an aliphatic - o - aliphatic ether linkage (1). Therefore, ir spectra for saturated crowns have a characteristic band near 1130 cm^{-1} and aromatic crown ethers have characteristic bands near 1130 and 1235 cm^{-1} . The ir spectrum will change on complexation displaying band shifts corresponding to the change in the bonding character of the ligand.

Solubility of Macrocyclic Ethers

The solubility of macrocyclic crown ethers tends to be lower the higher the melting point. In general, complex formation of the crown ethers with metal cations increases their solubility in solvents of high dielectric constants and decreases it in solvents of low dielectric constants (1). Benzo groups attached to the ring decrease the solubility in water, alcohols, and many other

solvents at room temperature, but, the benzo-substituted crown ethers are readily soluble in methylene chloride and chloroform. Saturated cyclic polyethers are much more soluble in all solvents than the corresponding benzo compounds. Table 4 lists the available solubilities from the literature. DB18C6 has been studied quite extensively, but there are little data on the other crown ethers.

Heats of Solution

The heat of solution gives information concerning the behavior of a solute in a particular solvent. The difference in the heats of solution of a solute in its standard states in two solvents, where one solvent is designated the reference solvent, gives the enthalpy of transfer, ΔH_t° from the reference solvent to the other solvent. This relationship can be expressed as follows:

$$\Delta H_{\text{soln.}}^\circ(\text{solvent},s) - \Delta H_{\text{soln.}}^\circ(\text{ref. solvent}) = \Delta H_t^\circ(\text{ref.} \rightarrow \text{solvent},s) \quad (2)$$

Arnett and Moriarity (52) have measured the heats of solution at 25°C for DC18C6 as a mixture of isomers in

Table 4. Solubilities of Some Crown Ethers.

Ligand	Solvent	Method	Solubility (moles/liter)
DC18C6	water		0.036 @ 26°C (a)
	water		0.022 @ 53°C (a)
	water		0.010 @ 82°C (a)
DB18C6	water	gravimetric	0.00009 @ 26 ± 0.5°C (a)
	water	uv	0.0000128 @ 25 ± 1°C (b)
	methanol	gravimetric	0.0011 @ 30°C (a)
	carbon tetra- chloride	uv	0.005 @ 25 ± 1°C (b)
	carbon tetra- chloride	gravimetric	0.005 @ 26 ± 0.5°C (a)
	cyclohexane	gravimetric	0.00067
	benzene	"	0.018
	chloroform	"	0.21
	ethyl acetate	"	0.01
	tetrahydrofuran	"	0.022
1-Butanol	pyridine	"	0.001
	acetone	"	0.12
	ethanol	"	0.0092
	formic acid	"	0.0089
		"	1.06

Table 4. Continued.

Ligand	Solvent	Method	Solubility (moles/liter)
DB18C6	dimethylformamide	gravimetric	0.056 @ 26 ± 0.5°C (a)
	nitromethane	"	0.047 "
	dimethylsulfoxide	"	0.048 "
	acetonitrile	"	0.079 "
	acetophenone	"	0.07 @ 25°C (c)
	aniline	"	0.222 "
	benzonitrile	"	0.12 "
	benzyl alcohol	"	0.075 "
	m-Cresol	"	0.19 "
	phenethyl alcohol	"	0.025 "
	benzaldehyde	"	0.073 "
	nitrobenzene	"	0.194 "
	2-Chloroaniline	"	0.163 "
	2-Bromobutyric acid	"	0.290 "
	2,2,2-Trichloro-ethane	"	0.710 "
	2,4-Xylenol	"	0.367 "

(a) Reference (1).

(b) Reference (53).

(c) Reference (54).

THF, DMSO, and AC and for the individual isomers (cis-syn-cis and cis-anti-cis isomers) in AC by calorimetric titration. The heats of solution, heats of complexation, and the enthalpy of transfer for the crown ethers complexed with various alkali metal and ammonium salts in the above solvents were also determined. Values for the ligands were 6.30 ± 0.19 , 7.58 ± 0.42 , and 7.32 ± 0.24 kcal mol⁻¹ for the isomer mixture in THF, DMSO, and AC respectively. The isomer labelled A (melting point 54.5 - 61.5°C) had a heat of solution of 8.57 ± 0.27 kcal mol⁻¹ where isomer B (melting point 81 - 83°C) had a heat of solution of 10.0 ± 0.27 kcal mol⁻¹. Based on the positive values of the heats of solution, the solution process is endothermic. It is interesting that the order of the dielectric constants for the solvents, 45, 20.7, and 7.58 for DMSO, AC, and THF respectively, follow the order of the heats of solution values. This suggests that the lower the dielectric constant of the solvent the less energy required to dissolve the ligand.

Conformations of Crown Ethers

Crystallographic data (55-58) show that the angles and bond lengths of the cyclic ethers do not change significantly on complexation, but that there are conformational changes. For example, in the uncomplexed DB18C6 ligand, the center of the ligand is at the crystallographic center

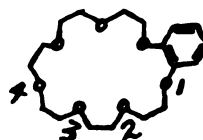
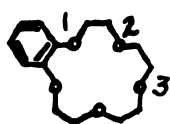
of symmetry and the six oxygen atoms are not coplanar, while in the ligand, complexed with rubidium thiocyanate, the six oxygen atoms are almost coplanar and the molecule has C_2 symmetry (55). Bush and Truter (57) determined the crystal structures of DB18C6 complexed with NaBr, B15C5 complexed with NaI, and DB30C10 complexed with KI. The structures show that in the cases of the DB18C6 and B15C5 complexes, the cations are coordinated not only to the ligand, but to water molecules and/or the respective anions as well.

However, in the case of DB30C10, the ligand is able to enclose the cation by wrapping itself around it and to completely replace the hydration sphere of the alkali metal cation. It was concluded that while large ring systems can completely replace the hydration sphere of the alkali metal, the small rings can only partially replace this sphere allowing additional interactions between the solvent, or anions, or other ligands and the cation. They further conclude that the accessibility of the complexed cation to additional ligands probably accounts for the variation of selectivity with the anion and solvent used.

Shamsipur (50) also showed the ability of large crown ethers to form three dimensional "wrap around" complexes. He found that the ligands' ability to form such complexes, with the same cation, decreases with the size of the ligand such as DB30C10 > DB24C8 > DB21C7.

Basicity of Crown Polyethers

Lockhart et al. (59) used a lanthanide shift reagent as a Lewis acid to study the basicity of the oxygen atoms in the asymmetrical ligands B15C5 and B21C7. A clear differentiation in the behavior for sets of hydrogen nuclei of the crown ethers was observed. This behavior was ascribed to differential basicity of the individual oxygen atoms and their selective coordination to the lanthanoid shift reagent. The oxygens nearest (on a time-averaged basis) the site of the strongest lanthanoid interaction are the most basic. These oxygens are located directly opposite the benzo group, oxygen number three for B15C5 and oxygen number four for B21C7 if the first oxygen next to the benzo ring is considered as oxygen number one.



Dale and Kristiansen (60) found that all the oxygen atoms in more symmetrical crown ethers are equivalent.

Shchori et al. (33) concluded that the basicity of four oxygens in the macrocyclic ring of DB18C6 may be affected by the introduction of electron-withdrawing or

electron-donating substituents into its aromatic rings. Introduction of the electrophilic NO_2 group into the benzo ring of DB18C6 caused a five fold decrease of the formation constant of the sodium ion complex in DMF solution.

In summary, 1) the asymmetrical ligands show differential basicity in the individual oxygen atoms where the more symmetrical ligands display equivalent basicity in their oxygen atoms, and 2) ring substitution can influence the basicity of the oxygen atoms of crown ethers.

Complex Formation

Crown ethers form mostly one to one (1:1), cation to ligand complexes, but they can also form complexes of different cation to ligand ratios. Shamsipur (50) found the presence of three sodium DB30C10 complexes, $\text{Na}_2(\text{DB30C10})$, $\text{Na}(\text{DB30C10})_2$, and $\text{Na}(\text{DB30C10})$ in nitromethane and acetonitrile solutions. The capability of the crown polyethers of forming more than just 1:1 complexes results when the diameter of the cation to be complexed with the ligand is either smaller or larger than the diameter of the ligand (See Table 2). The 2:1 complexes are called "sandwich" compounds where the cation is located between two molecules of crown ether; and the 3:2 complexes are called "club sandwich" complexes where the two cations are layered between three ligands (ligand:cation:ligand:cation:ligand) (34,45,61). The existence of the 2:1 complex has been

confirmed by Mallenson and Truter (61) by x-ray crystallography. The existence of the 3:2 complex is still unconfirmed. The conformational rearrangement of the ligand during complexation occurs so as to allow for the greatest interaction between the oxygens of the crown ether and the cation. This interaction usually results in the cation being equi-distance from each oxygen atom in the ligand cavity. The cation may lie either in the plane of the cavity, slightly above or slightly below the cavity. Therefore, the incomplete enclosure of the cation by the ligand due to size differences of the ligand and cation (See Tables 2 and 5) or the inability of the ligand to completely "wrap around" the cation results in possible interactions between the cation and solvent molecules, counterions, and other ligands and may result in the formation of the "sandwich" or "club sandwich" complexes.

Toxicity of Cyclic Polyethers

All new compounds must be treated with respect. Little is known about the toxicity of cyclic polyethers, but from the information available these compounds should definitely be handled with the upmost care to guard against immediate as well as any possible long-delayed harmful action.

The strong complexing ability of the crown ethers with the alkali, alkaline earth, and some transition metal

Table 5. Ionic Diameters of Alkali Metal Cations.

Cation	Diameter ^a
Li^+	1.86
Na^+	2.34
K^+	2.98
Rb^+	3.28
Cs^+	3.66

(a) Reference (62).

cations, makes these compounds suspect to possible interferences in the vital processes in which the cations participate (8). It should be remembered that some of the polyether crowns are being used to determine K^+ and Na^+ in serum (26).

An approximate lethal dose for dicyclohexyl-18-crown-6 for ingestion by rats is 300 mg/kg and causes death in 11 minutes. However, in a 10-day subacute oral test of 60 mg/kg/day, the compound did not exhibit any cumulative oral toxicity to male rats and a dose of 200 mg/kg was not lethal in 14 days. Dicyclohexyl-18-crown-6 also produced some generalized corneal injury, some iritic injury, and conjunctivitis when introduced in propylene glycol. It is readily absorbed through the skin of test animals and was fatal when absorption reached 130 mg/kg level (8).

Leong (63-64) reported that vapors of 12C4 caused testicular atrophy when inhaled by rats. Gad (65) reported that rats and mice given 18C6 i.p. at 20 - 160 mg/kg/day showed aggression, tremors, muscle weakness, and degradation of some reflexes. Rabbits given i.v. 6.0 mg/kg/day 18C6 displayed tremors, hyperactivity, unsteady gait, and stereotypic behavior. For all cases, acclimation was observed when the dose was maintained constant and the symptoms disappeared when the treatment was discontinued. The possible dangers of the polyether crowns is therefore emphasized.

C. TRANSFER ACTIVITY COEFFICIENTS (FREE ENERGY OF TRANSFER)

1. Introduction

The transfer activity coefficient, designated by γ_t , has been called the medium effect, medium activity coefficient, primary medium effect, partition coefficient, and the distribution coefficient (66). Regardless of how it is labelled this quantity represents a measure of the effect of changing the medium or solvent of a solute. It is defined as a measure of the difference between the partial molal free energies of the solute in its standard states in a solvent s , and in a reference solvent, r . This difference is known as the molal free energy of transfer, ΔG_t° for the solute (67-69). This relationship is shown in Equation (3)

$$\Delta G_t^\circ = {}_s\bar{G}_1^\circ - {}_r\bar{G}_1^\circ = RT \ln \gamma_t \quad (3)$$

The chemical activity of a solute is defined by Lewis (70) in terms of the chemical potential. If the reference solvent is chosen as water, the chemical potential or partial molal free energy for the solute in its aqueous and non-aqueous standard states can be written as

$$\bar{G}_1 = {}_w\bar{G}_1^\circ + RT \ln A_1 \quad (4)$$

and

$$\bar{G}_i = {}_s\bar{G}_i^\circ + RT \ln A_i^* \quad (5)$$

where

$\bar{G}_i$ = partial molal free energy of solute i;

${}_w\bar{G}_i^\circ$ and ${}_s\bar{G}_i^\circ$ = standard free energy of solute i in water and in solvent s, respectively.

A_i and A_i^* = activity of solute i in water and in solvent s, respectively

The activities of solute i in water and in the nonaqueous solvent can be represented as

$$A_i = m_i {}_w\gamma_i \quad (6)$$

and

$$A_i^* = m_i {}_s\gamma_i \quad (7)$$

where

m_i = molality of solute i;

${}_w\gamma_i$ = activity coefficient referred to an aqueous standard state; and

${}_s\gamma_i$ = activity coefficient referred to a standard state in solvent s.

In order to compare the activity of a solute in different solvents, a single reference state for the solute must be chosen. If henryan standard states are assumed, then in the limit as the molality of solute i approaches zero, the activity coefficient of solute i in solvent s, ${}_s\gamma_i$, approaches unity. However, the activity coefficient of solute i, ${}_w\gamma_i$, in water approaches unity in water only. In any other solvent s, as the molality of solute i approaches zero, the activity coefficient referred to the aqueous standard state, ${}_w\gamma_i$, will approach the transfer activity coefficient, γ_t .

$$\lim_{m \rightarrow 0} {}_s\gamma_i \rightarrow 1 \quad \text{in solvent s} \quad (8)$$

$$\lim_{m \rightarrow 0} {}_w\gamma_i \rightarrow 1 \quad \text{in water only} \quad (9)$$

$$\lim_{m \rightarrow 0} {}_w\gamma_i \rightarrow \gamma_t \quad \text{in any other solvent} \quad (10)$$

Therefore, when referred to an aqueous standard state the activity coefficient of solute i in a nonaqueous

solvent can be represented as the product of the salt activity coefficient, ${}_s\gamma_i$, which represents the effect of electrostatic ion-ion interactions and the transfer activity coefficient, γ_t , which represents the difference in ion-solvent or interparticle interactions in the two solvents (66).

$${}_w\gamma_i = {}_s\gamma_i \gamma_t \quad (11)$$

Multiplying both sides of Equation (11) by the molality of solute, i , m_i , Equation (12) can be obtained

$$A_i = A_i^* \gamma_t \quad (12)$$

Finally, combining Equations (4) and (5) with Equation (12) results in the defining Equation (3).

$$\Delta G_t = {}_s\bar{G}_i^o - {}_w\bar{G}_i^o = RT \ln \gamma_t \quad (3)$$

The transfer activity coefficient, γ_t , will therefore equal unity by definition in the reference solvent.

2. Determination of Transfer Activity Coefficients

Determination of transfer activity coefficients has been reviewed in detail by Popovych (68-69) and by Bates (67). It is possible to measure accurately the

transfer coefficients of nonelectrolytes and electrically neutral electrolytes. However, transfer activity coefficients for single ions are not experimentally measurable since it would be necessary to measure some process which transfers the single charged species into or out of the solution (70). This constitutes the transfer of ionic charge Z , across the interface of two solvents where a potential difference, ψ , exists. This process would result in an additional term in Equation (3) of ψZF .

$$\Delta G_t^\circ = {}_s\bar{G}_1^\circ - {}_w\bar{G}_1^\circ = RT \ln \gamma_t + \psi ZF \quad (13)$$

Ionic transfer activity coefficients presented a challenge to chemical ingenuity that has been dealt with by the age old process of estimation, namely the use of "extra thermodynamic" assumptions which have met with a great degree of success. The literature which amply covers this subject includes reviews (67-69,71-77) which discusses the various assumptions, their merits, and the importance of single ion transfer activity coefficients. Consequently, there will be no further discussion here since this work deals with the transfer activity coefficients of nonelectrolytes.

The three methods that are most often used for the determination of transfer activity coefficients of solutes are solubility measurements, calculation from standard

potentials of a galvanic cell reversible to its ions, and vapor pressure measurements. The solubility method is most often used as it can be applied to nonelectrolytes and electrolytes alike. These three methods are discussed below.

a. Solubility Studies

When a saturated solution of solute i, in water (or in other reference solvents) and in another solvent, S is in equilibrium with solid solute i, the partial molar free energies of solution are equal (See Equations (3-5)). Therefore, the value of the free energy of transfer from water to solvent S is given by

$$\Delta G_t^\circ = \frac{s\bar{G}_i^\circ - w\bar{G}_i^\circ}{RT} = \ln \frac{(A_i)_{\text{saturated}}}{(A_i^*)_{\text{saturated}}} \quad (14)$$

and the transfer activity coefficient is given by

$$\ln \gamma_t = \ln \frac{(A_i)_{\text{saturated}}}{(A_i^*)_{\text{saturated}}} \quad (15)$$

Solubility measurements can be used to determine γ_t for electrolytes and nonelectrolytes and is given by

$$\gamma_t = \frac{{}_sK_{sp}}{{}_wK_{sp}} \quad (\text{for electrolytes}) \quad (16)$$

$$\gamma_t = \frac{{}_wS_1}{{}_sS_1} \quad (\text{for nonelectrolytes}) \quad (17)$$

where ${}_wK_{sp}$ and ${}_sK_{sp}$ are the solubility products of an electrolyte in water and in solvent S, and ${}_wS_1$ and ${}_sS_1$ are the solubilities of a nonelectrolyte in water and in solvent S. In the case of electrolytes the salt activity coefficients are usually treated in one of two ways:

1) ignored or assumed to be unity in the case of low solubilities, or 2) corrected for by the use of the Debye-Hückel or a similar equation (66).

The methods used in the determination of solubilities are classified as "synthetic" or "analytic". Synthetic refers to methods applied to a system of solute and solvent in which the temperature or the pressure or both are varied until the solute just dissolves. The analytical methods, in general, consist of obtaining a saturated solution and determining the concentration of the resulting solution by a suitable method (78).

Many methods are described in the literature that utilize a variety of simple and complex apparatus (78-82). It seems though, that in all systems, regardless of the

method employed there are three important factors that affect all solubility measurements, purity of reagents, temperature regulation, and especially establishment of equilibrium.

It is generally assumed that equilibrium conditions are established when repeated analyses of a solution give constant results. The time required to reach equilibrium depends on the solute and the solvent. It can range from minutes to several weeks. Other factors to be considered are the possibility of hydrolysis in aqueous systems, the stability of the solution, the inertness of the solubility vessel toward the components of the solution, the tendency of some solutes toward colloidal formation at concentrations at, or slightly above, saturation, and particle size.

In some systems investigations of the above factors could be very difficult if not impossible. Atomic absorption or emission can be used to verify the inertness of the solubility vessel by testing for metals such as sodium. Particle size can be controlled by grinding.

Measurement of the resulting saturated solution depends on the solute and solvent involved. Some of the major techniques suggested and used in various studies are gravimetric or residual weight, chemical analysis; electrical methods such as conductometry, electromotive force, polarography, and pH determinations; optical methods including colorimetry, spectrophotometry, turbidimetry,

nephelometry, refractometry, interferometry, polarimetry, and microscopy; radioactive tracer methods and some special application methods.

b. Determination by Measurement of the Standard Potentials of a Galvanic Cell Reversible to its Ion

Measurement of the standard potential of an electrolyte in a galvanic cell reversible to its ions, in a reference solvent and another solvent s , and application of the following equations to the resulting potentials, can yield the transfer activity coefficients for the electrolyte (68).

$$\Delta G_t^\circ = -nF\Delta E_{\text{cell}}^\circ \quad (18)$$

$$\log \gamma_t = \frac{(E_i^\circ - E_i^\circ)}{K} \quad (19)$$

$$K = RT \ln 10/F$$

When problems such as poor solubility of a salt arise in the standard potential measurements, polarographic half-wave potentials are substituted in Equation (19). This causes errors of its own because the half-wave potential values are measured in the presence of supporting

electrolytes in cells with liquid junctions. Even with reproducible conditions the half-wave potential value is only an approximation of the corresponding standard potential (68).

c. Vapor Pressure Measurements

In this method either the partial pressures of a volatile solute or volatile solvent can be measured. Measurements for a volatile solute are based on the same principle as that for solubility measurements. If two phases are in equilibrium with the same third phase they have equal chemical potentials. Therefore, as with solubility measurements, equation (20) can be derived.

$$\gamma_t = \frac{A}{A^*} \quad (20)$$

A = activity of the solute referred to infinite dilution in water,

A^* = activity of solute referred to infinite dilution in a nonaqueous solvent.

If the partial pressures of a volatile solute above aqueous and nonaqueous solutions are measured the transfer activity coefficients may be obtained from Equation (21) (68).

$$\gamma_t = \frac{P^* A}{PA^*} \quad (21)$$

where P and P* are the partial pressures of a volatile solute above the aqueous and the nonaqueous solutions and A and A* have been defined above. For equal activities in both solutions, Equation (21) becomes

$$\gamma_t = \frac{P^*}{P} \quad (22)$$

This method at present is the least popular of the three methods discussed for the determination of transfer activity coefficients. However, with the advancements in the technology of gas chromatography, more reliable quantitative information may be obtained.

3. Ligand-Solvent Interactions

Differences in the transfer activity coefficients are caused by the nonspecific effects due to the differences in the dielectric constants of the solvents and by the specific interactions between the solute and the solvents (66). These two factors are interrelated and the values of the transfer activity coefficients must be interpreted with this interrelationship in mind.

A positive value of the logarithm of the transfer activity coefficient for the transfer of a solute from

some reference solvent to another solvent indicates that the solute is more solvated by the reference solvent than by the other solvent. Hydrogen-bond accepting solutes would be more solvated in water than in a nonaqueous solvent, but a hydrogen-bond donor would be more strongly solvated by the more basic solvents such as dimethylformamide and dimethylsulfoxide.

Thermodynamic quantities such as the free energy, enthalpy, and entropy of transfer for the transfer of inert solutes from water to other solvents can be interpreted in terms of the perturbation by the solute of the solvent structure. In the solvation process of a nonpolar molecule there are several major contributions to the solvation energy: 1) formation of a cavity for the solute in the solvent; 2) solute-solute dispersion interactions; 3) the energy change for the transfer of a molecule from its standard state in the gas phase to its standard state in a solution; and 4) the possible structure making or structure breaking energies in highly structural solvents like water (68). Solvation of nonpolar species is energetically unfavorable in water as compared to the less structured solvents because of a large entropy loss due to "icebergs" or "cages" of water structure around the solutes (68).

Jolicoeur and Lacroix (82) investigated nonpolar or hydrophobic solutes in light and heavy water. Their

objective was to establish whether the geometry of a series of isomeric ketones, which included saturated, unsaturated, and polycyclic varieties, some with varying degrees of branching, had a significant influence on their thermodynamic properties, especially on those properties which are commonly assigned to the structural effects. They proposed that the free energy of transfer can be broken down into several contributions:

$$\Delta G_t^\circ = \Delta G_t^\circ(\text{CAV}) + \Delta G_t^\circ(\text{SOL}) + \Delta G_t^\circ(\text{STR}) + \Delta G_t^{\text{Ex}^\circ}(\text{HI}) \quad (23)$$

These terms represent the solvent isotope effect of light and heavy water on the free energy that is due to:

- CAV : process of cavity formation in the solvent;
- SOL : solvation of the polar group of the molecule
(dipole-dipole interactions, hydrogen bonding);
- STR : structural rearrangement of the solvent around
the cavity enclosing the solute; and
- HI : solute-solute interactions (hydrophobic interactions).

Millen (83) calculated a solvent structure parameter for protic and dipolar aprotic solvents, by considering the work of creating a liquid surface equal to the surface of a spherical solute of radius r . The free energy is

given by,

$$\Delta G_h^\circ = 4\pi r^2 \sigma \quad (24)$$

where

r = radius of spherical cavity; and

σ = free energy per square centimeter of liquid surface.

Hermann (84) found a correlation between the solubility of hydrocarbons and their surface area which has been used as evidence for the importance of the $G^\circ(\text{CAV})$ term in the free energy of solvation. If Equation (24) and the above correlation are assumed, an equation for estimating $G^\circ(\text{CAV})$ is given by,

$$G^\circ(\text{CAV}) = 4\pi r^2 \sigma^\circ \quad (25)$$

where σ° is the bulk surface tension and r the radius of a spherical cavity (82).

It has been postulated that non-polar or hydrophobic solutes in water can promote some hydrogen-bonded structure in the surrounding solvent. This structure-making effect has been supported in part by large entropy losses upon dissolution of inert gases in water. Jolicoeur and

Lacroix came to the following conclusions: 1) the differences in the observed values for ΔG_t° for the different ketones originates in the structural part of ΔG_t° ; 2) the magnitudes of ΔG_t° and ΔH_t° of large hydrophobic solutes are strongly influenced by the structure of these solutes; and 3) the solvent isotope effect on the thermodynamic quantities for the solvent appears to be an important contribution to both ΔG_t° and ΔH_t° .

Lucas (85) studied the effect of the size of some nonpolar solutes on their transfer from one solvent to another solvent. The free energies of transfer were computed by use of the scaled particle theory (SPT) advanced by Reiss et al., Pierotti, and Wilhelm and Battimo (86). This theory is also used to predict solubilities, heats of solution, and partial molar volumes of simple gases in nonpolar solvents. In the SPT the solvent molecules are considered to be hard spheres which are related to the real solvent molecules in that the hard-sphere diameter is as close as possible to the true solvent molecular diameter of the solvent. Plots of the free energy of solution from the gaseous state for a nonpolar solute in the various solvents versus solute diameter shows that a nonpolar solute with a diameter of approximately 4 Å, is more soluble in a nonpolar solvent than in water. Calculations of ΔG_t° from SPT shows that the negative values of ΔG_t° for the transfer from water to a nonpolar solvent results mainly

from the fact that the nonpolar solvent molecules used in the study have a larger size than the water molecules. It is also shown that the importance of dispersion forces relative to cavity energy effects increases with solute size and further that solvent dimensions are important in determining the sign of the free energy of transfer for a nonpolar solute from one solvent to another.

Vesala (87) determined ΔG_t^0 for some nonelectrolytes such as sulfur dioxide, variously substituted benzenes and amines, and phenanthrene from light to heavy water by solubility measurements. The main criterion for solute selection was that they did not contain any exchangeable hydrogen atoms. Two linear correlations were found, one between the free energy of transfer of the corresponding nonelectrolytes from the gas phase to a hypothetical one aquamolal solution in water, and another between the free energy of the nonelectrolytes from light to heavy water and the heats of melting, ΔH_m , of the various compounds. Values found for ΔG_t^0 for the nonelectrolytes were small and varying in sign, ranging from +192 cal mol⁻¹ and +158 cal mol⁻¹ for phenanthrene and methoxybenzene, respectively, to -50 cal mol⁻¹ and -45 cal mol⁻¹ for argon and tributylamine, respectively.

Dahlberg (88) determined the free energy and enthalpy of transfers from light to heavy water of several ketones and alcohols that were representative of aliphatic, cyclic,

and aromatic compounds such as acetone, cyclohexanone, benzene, naphthalene, toluene, and benzyl alcohol. The free energies of transfer were determined by solubility measurements. Free energies of transfer were zero for most of the nonelectrolytes studied. Exceptions occurred for some cyclic compounds with side groups such as toluene with a ΔG_t° value of $+25 \pm 15 \text{ cal mol}^{-1}$, while benzene has a ΔG_t° value of $0 \pm 15 \text{ cal mol}^{-1}$. The results were explained in terms of solvent structure-breaking and solvent structure-making spheres of influence with polar groups being structure breakers, while nonpolar groups are structure makers. If the polar and nonpolar groups of structural influence overlap, their ability to alter solvent structure decreases as they tend to cancel one another. This effect is termed the concept of overlapping spheres. Values of ΔG_t° for benzene and acetone were near zero while values for toluene, nitrobenzene, and cyclohexanone were $+25 \text{ cal mol}^{-1}$, $+157 \text{ cal mol}^{-1}$, and $+52 \text{ cal mol}^{-1}$ respectively. This difference was explained to be caused by addition of side chains to the ring compounds. Compound shape itself was also shown to be an important influence on the values of ΔG_t° .

Cox (89) used vapor pressure measurements as well as solubility measurements to obtain the free energies, enthalpies, and entropies of transfer of nonelectrolytes from water to mixtures of water with dimethyl sulfoxide,

acetonitrile, and dioxan. Large increases in both the enthalpy and entropy with correspondingly small changes in the free energy were found.

Ahrland (90) points out that the ratio of the dielectric constant to the dipole moment, ϵ/μ can reflect the relative degree of solvent structure. Water, whose high degree of structural order due to hydrogen bonding, has an exceptionally high ϵ/μ ratio. Methanol which displays weaker hydrogen bonding has a lower ϵ/μ ratio than water, but a higher ratio than for other aprotic solvents. A comparison of these ratios with values found for the free energy of transfer of a solute for the same solvent would prove interesting if the order of the magnitudes were the same. This relationship could lead perhaps to the use of ϵ/μ ratios as an indication of the relative values of $\Delta G_t^\circ(\text{STR})$ for the various solvents.

These selected illustrations demonstrate the importance and use of the magnitudes and signs of the free energies of transfer as a diagnostic tool for solvent structure elucidation, solute influence on solvent structure, and solute-solute interactions. The separation of the free energy of transfer into individual contributions can aid in at least differentiating if not isolating the important factors influencing the solvation process.

D. PROTON AND CARBON-13 NMR STUDY OF 18C6 WITH SOME
POTASSIUM AND RUBIDIUM SALTS

1. Introduction

About half of the known nuclei possess spin or angular momentum which generates a magnetic moment along the axis of spin. If the spinning nuclei are placed in an external magnetic field H_0 , their magnetic moments align either with the field or against the field. (This is a simplistic view. For further detail see References 91-93). Energy must be absorbed in order to "flip" the spinning nuclei into a higher energy level or excited state - one anti-parallel to the field H_0 in the case of protons and carbon-13 (92). A radio frequency (rf) field H_1 , can be applied to the system to provide the energy necessary to "flip" the nuclei. Either a constant magnetic field H_0 , can be applied and the rf field H_1 , is varied as described above or a constant rf field H_1 , is applied and the magnetic field H_0 , is varied. In either case the energy is varied until it matches the energy required to cause transition of the spinning nuclei which produces the observed absorption signal.

The frequency at which the nuclei absorbs depends on the magnetic field strength that the nuclei experiences. This field strength is different from the applied field strength due to the chemical environment of the nuclei

and is called the effective field strength. The effective field strength can be expressed by

$$H = H_0(1 - \sigma) \quad (26)$$

where σ is the screening or shielding constant. The shielding constant σ , is generally the sum of two terms, a paramagnetic term (shielding) σ_p , and a diamagnetic term (deshielding) σ_d .

$$\sigma = \sigma_d + \sigma_p \quad (27)$$

The diamagnetic term σ_d , depends on the circulation of local electrons induced by the applied field about the nucleus. The paramagnetic term σ_p , depends on several factors such as the energy difference between the ground and excited states, electron density in the outer p orbitals of the nucleus, and the distance between the nuclei and the outer p orbital is inversely proportional to the excitation energy and directly proportional to atomic number (94). In proton nmr σ_d is the important factor in the shielding constant while σ_p is the important factor in carbon-13 nmr (94) and in multinuclear nmr in general.

Separate absorption bands occur for nuclei of the same molecule that are in different chemical environments.

"Chemical shift" is the term used to describe the differences in resonance conditions required for the same isotope in different chemical environments. The absorption bands found for the nuclei are referred to as the chemical shifts for the nuclei.

The chemical shifts are expressed with reference to an arbitrary standard. Tetramethylsilane (TMS) is the most common reference chosen for proton and carbon-13 nmr because its' nmr signal appears near one of the extreme ends of the carbon-13 shielding range for neutral molecules. The chemical shift of TMS is referred to as upfield (0 Hz or 0 ppm). The nmr signal of a proton or carbon-13 nuclei that is less shielded than the nuclei of TMS will appear downfield from the TMS nmr signal.

2. Proton and Carbon-13 NMR of Polyether Complexes of Alkali and Alkaline Earth Metals

Proton NMR has been used to identify macrocyclic polyethers (1). Lockhart (95) used proton NMR as one method of characterizing the structures of some newly synthesized crown ethers. Both proton and carbon-13 NMR shieldings are very sensitive to variations in molecular structure (94). When a change in molecular structure occurs changes in the chemical shifts and vicinal coupling constants, important in conformational determination, may also be

observed depending on the resolution power, and therefore on the operating field strength of the NMR instrument used. Complexation of a compound causes a change in molecular structure and consequently causes spectral changes that can be analyzed to give important conformational information about the compound. This is the case in the complexation of crown ethers with metal cations. The addition of a metal cation to the crown ethers induces two major spectral changes: 1) a change in the vicinal coupling constants, and 2) a change in the chemical shifts. By appropriate choice of crown ethers and the use of a high field NMR spectrometer, the assignment of protons in the ether region is possible and the vicinal coupling constants can be obtained.

The use of proton and carbon-13 NMR techniques have been fundamental in the elucidation of the structure of some crown ethers in solution. Live and Chan (38) analyzed proton and carbon-13 NMR spectra to ascertain the solution structures of B18C6, DB18C6, and DB30C10 complexes with Na^+ , K^+ , Cs^+ , and Ba^{2+} in water, water-acetone mixture, and chloroform. Benzo-substituted crown ethers were chosen because the benzene groups, due to their ring current magnetic anisotropy, causes the separation of the ether resonances and deduction of the spatial relationship between the ether protons and the aromatic group leading to less complex spectra. Also with the increased spectral

resolution the ether vicinal coupling constants were readily extracted. A high field NMR spectrometer was used to take the proton spectra operating at 220 MHz and carbon-13 spectra operating at 55.3 MHz. Carbon-13 and proton chemical shifts were referred to internal tetramethylsilane. DB18C6 with four nonequivalent hydrogens gave the simplest proton spectrum. B18C6 and DB30C10 with seven and six nonequivalent hydrogens respectively, produced spectra that were more complex. Chemical shifts were small. For example, proton NMR shifts were all less than 0.5 ± 0.002 ppm. From a detailed analysis of the proton and carbon-13 NMR spectra, the proton-proton vicinal coupling constants, and the salt-induced chemical shifts Live and Chan concluded that the complexes of B18C6, DB18C6, and DB30C10 in the various solvents are in syn- and anti-gauche conformations with rapid rotamer interconversion. X-ray crystallographic



Gauche Conformation

data of DB18C6 show the presence of both trans and gauche rotamers. The K^+ , Cs^+ , and Ba^{2+} complexes of DB30C10 have conformations in solution that are consistent with KI-DB30C10 complex in the crystal. However, the Na^+ -DB30C10 complex is different from the others which demonstrates

the ability of DB30C10 to adapt itself to different-sized cations.

Formation constants derived for the complexes were consistent to those derived by other workers (43,50). For example, $\log K_f$ (formation constant) for DB30C10CS⁺ complex in AC was 4.23, Shamsipur (50) found an average for $\log K_f$ of 4.0 for DB30C10CS⁺ complexes with various anions.

Lockhart, et al. (39) used proton NMR to study the conformations of B15C5 and B21C7 in solution as free ligands and as complexed ligands with alkali-metal iodides or thiocyanates. Deuterated methanol (CD₃OD) was used as the solvent. Most of the spectra were obtained at 90 MHz on a Bruker Spectrospin HFK-6, but some spectra were obtained at 60 MHz and spectra for free B15C5 and its NaI complex were obtained at 220 MHz. The results indicate that the gross conformations of the B15C5 and B21C7 complexes in solution are similar to the conformations found in the crystal forms of the complexes. The possibility of the use of proton NMR spectra as a diagnostic tool in the investigation of complex formation stoichiometry was indicated as a result of the following observations. The proton signals for ligand:cation combinations expected to give 1:1 complexes were downfield from those of the free crown at all crown:cation ratios investigated, while proton signals for ligand:cation combinations expected to give 1:1 and 2:1 complexes, the

chemical shifts were upfield from free crown for crown: cation ratio of 2:1 or more and downfield at low crown cation ratios. Chemical shifts observed in the study were small as expected, with all shifts being less than 0.2 ppm and a majority of them less than 0.1 ppm with a precision of ± 0.002 ppm.

Alkali metal NMR has been shown to be a powerful tool for the investigation of the complexation of macrocyclic polyethers with alkali metal cations because it is very sensitive to the immediate chemical environment of the alkali metal cations (31-37). As shown above, proton and carbon-13 NMR are powerful tools for conformational elucidation of the crown ether complexes in solution. However, proton and carbon-13 NMR have been considered unsuitable for complexation studies, especially in the determination of formation constants, of the macrocyclic polyethers because of the small chemical shifts observed between complexed and uncomplexed forms of the ligands (32) and because the spectra of cyclic polyethers can be quite complex (38). As mentioned above, Live and Chan (38) reported some formation constants obtained in their study from carbon NMR data. It is to be remembered however, the chemical shifts involved were obtained with a high field NMR spectrometer with the chemical shifts good to within ± 0.5 Hz ($\sim \pm 0.002$ ppm) for protons and ± 1 Hz ($\sim \pm 0.02$ ppm) for carbon and also that benzo-substituted crowns which lead to better

resolution of the NMR data was used.

It is the purpose of this part of the study to investigate the sensitivity of proton and carbon-13 NMR instruments of low operating fields (proton-60 MHz, carbon-13-20 MHz) in the complexation of the saturated unsubstituted crown ether 18C6, with potassium iodide, potassium hexafluorophosphate, and rubidium iodide salts.

CHAPTER II

EXPERIMENTAL MATERIALS AND METHODS

A. MATERIALS

1. Ligands

B15C5 was purified by recrystallizing at least three times from reagent grade n-heptane (Fisher); vacuum dried at least 24 hours at room temperature prior to use; melting point 80.5°C; literature 79 - 79.5°C (1).

DB18C6 was purified by recrystallizing at least three times from reagent grade benzene (Fisher); vacuum dried at least 24 hours at room temperature prior to use; melting point 164.5 - 165.5°C, literature 164°C (1).

18C6 was purified by first forming the solid acetonitrile 18C6 complex. The adduct was precipitated from an 18C6 solution in acetonitrile by cooling it in an ice-acetone bath. The solution was filtered rapidly and acetonitrile was removed under vacuum; melting point 37-38°C, literature 39°C (96).

2. Salts

Benzoic acid (Mallinkrodt) was purified and dried by John Hoogerhede (46).

Potassium iodide (Mallinckrodt) was dried in the vacuum oven for 72 hours at 60°C (48).

Potassium hexafluorophosphate (Pflaltz and Bauer) was dried in the vacuum oven for 48 hours at room temperature prior to use.

Rubidium iodide (Fisher) was purified by recrystallizing from methanol and dried for 48 hours in the oven at 110°C.

Sodium perchlorate (G. F. Smith) was oven dried for several days at 150°C.

Sodium tetraphenylborate (J. T. Baker) was vacuum dried at 50°C for several days.

Tetraethylammonium perchlorate (Eastman) was vacuum dried several days at room temperature.

3. Solvents

Methanol (Mallinckrodt, Fisher) was refluxed over magnesium turnings (approximately 20 g/l) and iodine (0.1 g/l) for ~24 hours and then distilled under nitrogen atmosphere. Distillate was allowed to stand over activated molecular sieves (heated at approximately 500°C for at least 24 hours) for at least 24 hours and redistilled from the sieves under nitrogen atmosphere.

Water was used as received from the laboratory of Dr. M. Weaver. The water, labelled Milli-Q water, was

purified by a system of Milli-pore filters which produces water of conductance of 5.88×10^{-8} mhos/cm.

Acetonitrile (Matheson, Coleman and Bell or Fisher)

Method 1. Acetonitrile was refluxed over calcium hydride for ~ 24 hours; distilled onto activated molecular sieves; allowed to stand over the molecular sieves for at least 24 hours; and redistilled from the molecular sieves.

Method 2. (97) Acetonitrile was refluxed over anhydrous aluminum chloride (15 g/l) for one hour followed by rapid distillation; refluxed over potassium permanganate (10 g/l) and lithium carbonate (10 g/l) for fifteen minutes followed by rapid distillation; refluxed over potassium bisulfate (15 g/l) for one hour followed by rapid distillation; refluxed over calcium hydride (2 g/l) for one hour followed by careful fractionation onto activated molecular sieves; redistilled from the molecular sieves. The middle 80% fraction was retained. Both methods resulted in a solvent with a uv cutoff of approximately 210 nm and a water content of less than 100 ppm. Therefore, Method 1, which is considerably shorter, was subsequently used.

1,2-Dichloroethane (Fisher) was washed with 0.1 N NaOH solution and distilled water; refluxed over calcium chloride for at least 24 hours (98); distilled onto activated molecular sieves; allowed to stand over the molecular sieves

for at least 24 hours and then redistilled from the molecular sieves.

Acetone (Drake Brothers) was refluxed over calcium sulfate for at least 24 hours; distilled onto activated molecular sieves; allowed to stand over the molecular sieves for at least 24 hours and then redistilled from the molecular sieves.

Dimethylsulfoxide (Fisher) was refluxed over calcium hydride for approximately 24 hours under reduced pressure and distilled onto activated molecular sieves; allowed to stand over the molecular sieves for at least 24 hours and then redistilled from the molecular sieves.

Dimethylformamide (Fisher) was vacuum distilled over phosphorus pentoxide onto activated molecular sieves; allowed to stand over the molecular sieves for at least 24 hours and then redistilled from the molecular sieves.

Acetone-d₆, acetonitrile-d₃, dimethylsulfoxide-d₆ (Stohler Isotope Chemicals) deuterated solvents were used as received. Live and Chan (38) used acetone-d₆ in their proton nmr studies and found that using this solvent as it came directly from the manufacturer's sealed vials gave the same results as when the solvent was carefully dried with calcium sulfate or over activated molecular sieves.

Molecular sieves (Davison) were 3 Å pore size, 8-12

mesh, and were activated by heating at approximately 500°C for at least 24 hours under a flow of dry nitrogen after being washed with distilled water and dried in an oven at 110°C overnight.

The above drying methods for the solvents produced solvents with less than 100 ppm water content as measured by Karl Fisher analysis. Purity of the solvents were checked by gas chromatography.

Table 6 lists some pertinent properties of the solvents used in the molar free energy of transfer study. The solvents were chosen because they represent: 1) a wide range of dielectric constants; 2) solvents whose uv cutoff value does not interfere with the crown's absorption spectra; and 3) both protic (strong and weak H-bonding characteristics for water and methanol respectively) and aprotic with acetonitrile being an anoxic solvent. No solvent representing an aprotic oxidic solvent such as dimethylsulfoxide could be found which was suitable for study by uv spectroscopy.

Table 7 lists properties of solvents used in the nmr study of potassium and rubidium complexes of 18C6.

The ligands used in the molar free energy of transfer study were chosen because they contained benzo groups and could therefore be studied by uv spectroscopy. Melting points and IR spectra were obtained periodically on the ligands remaining in the flasks after the solubility determinations to check for contamination of the ligands

Table 6. Properties of Solvents Used in the Study of the Free Energy of Transfer of Some Polyether Crowns.

Solvent	Dielectric Constant	Donor Number ^a	Dipole Moment	$\frac{\text{Dielectric Constant}}{\text{Dipole Moment}}$	UV Cut Off Wavelength ^b
Acetonitrile	38.8	14.1	3.92	9.90	210 nm
1,2-dichloro- ethane	10.36		1.19	8.71	230 nm
Methanol	32.7	25.7	1.70	19.24	210 nm
Water	78.4	33.0	1.85	42.38	190 nm

(a) Reference (99).

(b) Reference (92).

Table 7. Pertinent Properties of Solvents Used in the Proton and Carbon-13 NMR Study of Potassium and Rubidium Complexes of 18C6 and Magnetic Susceptibility Correction Factors.

Solvent	Dielectric Constant	Donor Number ^a	Magnetic Susceptibility Corrections ^b
Acetone	20.7	17.0	-0.545
Acetonitrile	38.8	14.1	-0.390
Dimethylformamide	36.7	26.6	-0.308
Dimethylsulfoxide	46.7	29.8	-0.241
Methanol	32.7	25.7	-0.429
Water	78.4	33.0	0

(a) Reference (99).

(b) Reference (100).

and hydrate formation.

B. METHODS

1. Spectroscopy

Ultraviolet Spectroscopy

All UV measurements were carried out on a Cary 17-909 Spectrophotometer which was converted to a Cary 17 D by the addition of a digital readout system. Spectra were obtained in the range of 310 - 200 nm using 0.1, 1.0, and 2.0 cm quartz cells as necessary for optimum absorbance measurements.

Nuclear Magnetic Resonance

Proton NMR spectra were obtained on a Varian T-60 NMR Spectrometer. All chemical shifts were referred to TMS (tetramethylsilane) which was used as an internal standard. Carbon-13 NMR spectra were obtained on a Varian CTF-20 Spectrometer with a magnetic field of 18.7 kilogauss and resonance frequency of 20 MHz. Samples in 8 mm NMR tubes were placed inside 10 mm NMR tubes containing a 50% deuterium oxide-acetone mixture. Deuterium oxide served as an external lock with acetone serving as the secondary external standard. Complete proton

decoupling was employed. Chemical shifts were corrected for bulk diamagnetic susceptibility according to the relationship of Live and Chan (100) for a nonsuperconducting spectrometer. Downfield chemical shifts from the free ligand and TMS are paramagnetic (deshielding) shifts. Upfield chemical shifts from the free ligand are diamagnetic (shielding) shifts.

Infrared

Infrared spectra in the range of $4000 - 600 \text{ cm}^{-1}$ were obtained on a Perkin-Elmer 457 Grating Infrared Spectrophotometer. A standard of polystyrene was used for wavelength calibration. Nujol mulls were made of the solid samples and run on sodium chloride mull plates.

2. Other Analyses

Solvent Purity

The purity of the various solvents was checked by the use of a Varian Aerograph Model 920 Gas Chromatograph with a porapak QS 80/100 mesh column and helium carrier gas. An Omniscribe recorder (Houston Instruments) was used to record the spectra and a Hamilton 702 NWG microliter syringe was used for sample injections.

Water Analysis

Water analyses were performed on a Karl Fisher Photo-volt Aquatest II Titrimeter.

Melting Point Analysis

Melting point analyses were performed on a Fisher-Johns melting point apparatus.

3. NMR Data Handling

Complex formation constants of the 18C6 complexes were obtained by computer fitting the chemical shift-mole ratio data using a CDC 6500 computer program system and a non-linear least squares curve fitting program, KINFIT 4 (101, 9,50).

4. Solubility Measurements

Experimental Technique and Instrumentation

All reagents were purified and dried for each experiment as described above. The ligands were crudely weighed to ensure that enough ligand was added to each solvent to produce a saturated solution. The minimum amount to be added was previously determined by adding ligand from a weighed amount to a known volume of solvent until saturation

was reached and then reweighing the remaining ligand. The solvents were added to 50 ml Erlenmeyer flasks containing the ligand in an inert atmosphere (N_2) dry box except in the case of water. The solutions were sealed first with teflon tape and then with parafilm to prevent moisture contamination from the atmosphere and the shaker bath liquid.

The solutions were placed in a Wilkins-Anderson shaker-bath equipped with a Precision Scientific Micro Set Thermoregulator which controlled the temperature of the shaker-bath to within $\pm 0.5^\circ C$. The temperature was initially set for 12-24 hours approximately $10^\circ C$ above the final equilibrium temperature and then reset to the equilibrium temperature in an attempt to reduce the time required to reach equilibrium. Equilibrium was considered to be reached after two consecutive concentration measurements yielded the same results within experimental error. The shaking of the solutions was stopped at least one hour before samples were taken for concentration determination.

Samples of the solutions were removed by pipeting through a medium size pore filter stick attached to the pipet by a small piece of tygon tubing. A vacuum pump was employed to provide suction. This procedure was performed as quickly as possible to prevent moisture contamination. However, as was found later, the solubility of the ligands studied in water was small enough to be considered

negligible as compared to their solubility in the other solvents used. The solutions were resealed after removal of each sample and shaking was resumed. The filtered samples were then diluted to suitable concentrations for measurement.

Concentration measurements were made by UV Spectroscopy. Molar absorptivities of the ligands in the various solvents were determined by use of Beer's Law (92).

$$A = \epsilon bc \quad (28)$$

A = measured absorbance

ϵ = molar absorptivity

b = cell path length (cm)

c = concentration (moles liter⁻¹)

Known concentrations of the ligands were prepared and their absorbances measured. The molar absorptivity was determined at each concentration and averaged. This procedure was repeated until a molar absorptivity was obtained that was reproducible within experimental error.

5. Validity of Method

The use of uv spectroscopy in the determination of the solubility of different substances is well documented in the literature (78-81). The system chosen to test the

accuracy of the experimental technique used in this study was that of benzoic acid in water. This system was chosen because it lends itself to study by other techniques as well. The solubility of benzoic acid was determined by the gravimetric and titrometry methods as well as by uv spectroscopy for comparison.

Saturated solutions of benzoic acid in water at $25 \pm 0.5^{\circ}\text{C}$ were obtained by the method previously described. Three one milliliter samples were taken from each of the saturated solutions. One sample being diluted and measured by uv spectroscopy, another being diluted and measured potentiometrically, and the third sample being placed in weighed vials which were dried for several days at approximately 35°C . In the gravimetric method the vials, after removal from the oven, were dried further by placing in a vacuum oven overnight and then into a dessicator for at least a half hour before weighing the resulting residues. A carbonate free solution of sodium hydroxide, standardized with a primary standard potassium acid phthalate solution, was used as the titrant in the potentiometric titration (102). The molar absorptivity of benzoic acid in water was determined to be $876 \text{ cm}^{-1} \text{ liter}^{-1} \text{ moles}$ at λ_{max} of 273 nm and a pH value of $4.0 < \text{pH} > 3.0$. Literature values of $933 \text{ cm}^{-1} \text{ liter}^{-1} \text{ moles}$ at pH 1-3 and $794 \text{ cm}^{-1} \text{ liter}^{-1} \text{ moles}$ at pH 4.0 were found also at λ_{max} of 273 nm (103).

Table 8 shows the results of the determinations at

Table 8. Solubility of Benzoic Acid as Determined by UV Spectroscopy, Titration, and Gravimetric Methods.

Sample	Solubility of Benzoic Acid (M)		
	UV Spectroscopy	Titration	Gravimetric
1	0.023	0.026	0.005
2	0.024	0.024	-----
3	0.023	-----	0.001
4	0.023	-----	0.002
5	0.023	0.026	0.003
Blank	0.0	0	0
Average	0.023 ± 0.001	0.025 ± 0.001	0.003 ± 0.002

$25 \pm 0.5^{\circ}\text{C}$. The average values of the determinations $0.023 \pm 0.001 \text{ M}$ and $0.025 \pm 0.001 \text{ M}$ for uv and titration methods respectively are identical within experimental error. However, the average value found for the gravimetric method of 0.003 ± 0.002 is smaller than the other values obtained by ten fold. The results found in Table 8 and the average value of the solubility for benzoic acid by the gravimetric method shows both the inaccuracy and unreproducibility of the method. Literature value for the solubility of benzoic acid in water is 0.0278 M (104) at 25°C .

It can be concluded that the solubility data obtained by the solubility method utilizing uv spectroscopy should result in reliable values.

CHAPTER III

RESULTS AND DISCUSSION

A. MOLAR FREE ENERGIES OF TRANSFER FROM WATER TO SEVERAL
NONAQUEOUS SOLVENTS FOR DB18C6 AND B15C5

The ultraviolet characteristics and solubilities for DB18C6 and B15C5 in various solvents are listed in Table 9. Transfer coefficients and molar free energies of transfer from water, the reference solvent, to several non-aqueous solvents are given in Table 10. The errors in the molar absorptivity values were determined by calculation of the variances of at least three separate determinations. The large error in the molar absorptivity value of DB18C6 in water is due to its low solubility which resulted in low absorbance values. (~ 0.1 absorbance units at saturation). This error is carried into the solubility calculated for DB18C6 in water and therefore, into values of the transfer activity coefficients and molar free energies of transfer. The error in the solubility values for DB18C6 and B15C5 in the various solvents was calculated from the relative standard deviations in the molar absorptivities and absorbance measurements. The maximum error in the molar free energies of transfer for DB18C6 is estimated to be $\pm 0.5 \text{ Kcal mol}^{-1}$.

The equations used in the calculation of the transfer activity coefficients and the molar free energies of

Table 9. Ultraviolet Characteristics and Solubilities of DB18C6 and B15C5 in Various Solvents at $25 \pm 0.5^\circ\text{C}$.

Ligand	Solvent	$\lambda_{\text{max}} \pm 1 \text{ nm}$	Molar Absorptivity	Absorbance	Dilution Factor ^a	Equilibrium time ^b	Solubility (M) ^c
DB18C6	H ₂ O	273	$3 \times 10^3 \pm 1.5 \times 10^3$	0.09 ± 0.02	None	~4 weeks	$3.0 \times 10^{-5} \pm 1.6 \times 10^{-5}$
	AN	275	5777 ± 484	0.480 ± 0.007	1:500	~5 weeks	0.042 ± 0.004
	MeOH	274	5109 ± 131	0.206 ± 0.006	1:25	~2½ weeks	0.0010 ± 0.0001
	1,2-DCE	276	5505 ± 93	0.430 ± 0.009	1:1250	~4 weeks	0.098 ± 0.003
B15C5	H ₂ O	273	2555 ± 30	0.64 ± 0.12	1:250	~3 weeks	0.06 ± 0.01
	MeOH	277	2459 ± 67	0.44 ± 0.05	1:2500	~6 weeks	0.44 ± 0.05

(a) Dilutions made to give appropriate absorbance values.

(b) Equilibrium times shown are from the time the samples were placed into the shaker bath until the time the last concentration measurement was made.

(c) Determined by Beer's Law.

Table 10. Transfer Activity Coefficients and Free Energies of Transfer of DB18C6 and B15C5 from Water to Various Solvents.

Ligand	Solvent	γ_t ($H_2O \rightarrow$ nonaqueous solvent)	ΔG_t° ($H_2O \rightarrow$ nonaqueous solvent)
DB18C6	Water ^(a)	1	0
	MeOH	-3.5 $\pm$ 0.9	-2.1 $\pm$ 0.5 Kcal mole ⁻¹
	AN	-7.2 $\pm$ 0.9	-4.3 $\pm$ 0.5 Kcal mole ⁻¹
	1,2-DCE	-8.1 $\pm$ 0.7	-4.8 $\pm$ 0.5 Kcal mole ⁻¹
B15C5	Water	1	0
	MeOH	-2.0 $\pm$ 0.3	-1.2 $\pm$ 0.2 Kcal mole ⁻¹

(a) Reference solvent.

transfer for DB18C6 and B15C5 are given below.

$$G_t^{\circ}(1)_{H_2O \rightarrow \text{solvents}} = RT \ln \frac{w_{S_i}}{s_{S_i}} \quad (14)$$

and

$$\ln \gamma_t = \ln \frac{w_{S_i}}{s_{S_i}} \quad (15)$$

Table 11 shows a comparison of solvent properties and free energies of transfer for DB18C6 and B15C5. The ratio of the dielectric constant to the dipole moment of the solvents, ϵ/μ , as mentioned earlier, gives a qualitative measurement of solvent structure (90).

The dielectric constant measures qualitatively the dipolar orientations of a solvent. The greater the dipolar orientations of the solvent the more "structure" the solvent is expected to exhibit and consequently, the more difficult it should be to make a "hole" in the solvent for a symmetrical nonelectrolyte solute such as DB18C6. Therefore, the solubility of DB18C6 would be expected to increase as the dielectric constant of the solvent decreases. However, the results show that this is not the case. The values for the ϵ/μ ratio follow the order water > methanol > acetonitrile > 1,2-Dichloroethane (See Table 12). The solubilities of DB18C6 increases in the reverse order and

Table 11. Comparison of Solvent Properties and Molar Free Energies of Transfer, ΔG_t° from Water to the Various Solvents.

Ligand	Solvent	Dielectric Constant, ϵ	Dipole Moment, μ	ΔG_t° Kcal/mole	$\frac{\text{Dielectric Constant}}{\text{Dipole Moment}}, \epsilon/\mu$
DB18C6	H ₂ O	78.4	1.85	0	42.38
	MeOH	32.7	1.70	-2.1 $\pm$ 0.5	19.24
	AN	38.8	3.92	-4.3 $\pm$ 0.5	9.90
	1,2-DCE	10.36	1.19	-4.8 $\pm$ 0.5	8.71
B15C5	H ₂ O	78.4	1.85	0	42.38
	MeOH	32.7	1.70	-1.2 $\pm$ 0.2	19.24

Table 12. Comparison of Solubilities and ΔG_t° ($H_2O \rightarrow$ Solvents) of DB18C6 with the ϵ/μ Ratio.

Solvent	Solubility $\underline{M}$	ΔG_t° ($H_2O \rightarrow$ Solvents) Kcal mol ⁻¹	ϵ/μ
H ₂ O	$3.0 \times 10^{-5} \pm 1.6 \times 10^{-5}$	0	42.38
MeOH	0.0010 ± 0.0001	-2.1 ± 0.5	19.24
AN	0.042 ± 0.004	-4.3 ± 0.5	9.90
1,2-DCE	0.098 ± 0.003	-4.8 ± 0.5	8.71

indicates that the less structured the solvent the more soluble the ligand as expected, but the ϵ/μ ratio gives a better indication of solvent structure than does the dielectric constant alone.

All values of the molar free energies of transfer were negative indicating that the ligands are more solvated by the nonaqueous solvents than by water. The order of the values for the free energies of transfer for DB18C6 parallel that of the ϵ/μ ratio. The lower the ϵ/μ ratio the more negative values of ΔG_t^0 for DB18C6 becomes, again indicating that the less structure there is in the solvent the greater is its ability to solvate the DB18C6 ligand. The magnitudes of ΔG_t^0 ($H_2O \rightarrow MeOH$) for DB18C6 and B15C5 of -2.1 ± 0.5 and -1.2 ± 0.2 Kcal mol⁻¹ respectively, are as expected because of the smaller size of B15C5 which would not be expected to cause as great of a disturbance to the structure of the solvent in cavity formation as DB18C6 and should result in a smaller free energy of solvation. Therefore, the difference in the free energies of solvation for B15C5 in water and methanol should be smaller than for DB18C6 as the results indicate.

Attainment of equilibrium conditions for the systems investigated was extremely difficult. The equilibrium times required varied from approximately 2-1/2 weeks to 6 weeks as measured from the time the samples were prepared to the time the last concentration determination was made

(See Table 1).

When two consecutive concentration determinations resulted in the same value, equilibrium was considered to be reached. The length of time required to reach equilibrium greatly limited the quantity of data acquired. In addition to the problem of equilibrium times, uv scattering due to solvent contamination or solute particles and sample contamination during concentration determinations, especially in the cases of low solubilities, often caused the need for repeated duplication of measurements. Extreme care had to be exercised in the cleaning of glassware to prevent any contamination of the samples and especially contamination by substances that might complex with the ligands. Blanks, which were treated in the same manner as the samples, were checked periodically to aid in the detection of the possible uv scattering.

In summary, the values of the molar free energies of transfer from water to the nonaqueous solvents investigated for DB18C6 and B15C5 indicate that the ligands are more strongly solvated by the nonaqueous solvents than by water. Also the parallel order of the values of the ϵ/μ ratio and the molar free energies of transfer suggest that the ratio, used as a solvent structure gauge, may be a good qualitative indicator of the order of the free energies of transfer for the crown ethers.

B. PROTON AND CARBON-13 NMR of 18C6 COMPLEXES OF SOME
ALKALI METAL SALTS

1. Proton NMR

The chemical shifts obtained at 60 MHz from proton nmr mole ratio studies of 18C6 complexed with NaClO_4 in deuterated acetone (AC-d_6), and with KPF_6 in deuterated solvents of acetone (AC-d_6), acetonitrile (AN-d_6), and dimethylsulfoxide (DMSO-d_6) are shown in Table 13. A constant concentration of 0.05 M of 18C6 was used and the concentrations of the salts was varied to yield the different mole ratios shown. Chemical shifts were good to approximately ± 2 Hz. The results show that there is virtually no change in the chemical shift of 18C6 on complexation with either salt in any solvents used. Also samples of uncomplexed 18C6 in methanol and in dimethylsulfoxide and of 18C6 in dimethylsulfoxide with a 25 fold excess of KPF_6 were obtained at 180 MHz. The results are shown in Table 14. The higher field did produce larger changes in the chemical shifts. The 29.54 Hz difference in the chemical shifts for 18C6 in methanol and dimethylsulfoxide reflect the difference in solvation of the ligand in the different solvents. However, there is only a 2.05 Hz difference in the chemical shifts between the free and complexed forms of 18C6.

Table 13. Proton NMR Chemical Shift-Mole Ratio Data for
18C6 Complexation Studies ($C_{18C6} = 0.05 \text{ M}$;
60 Hz = 1 ppm).

Salt: NaClO_4 Solvent: AC-d_6			Salt: KPF_6 Solvent: AC-d_6		
$\frac{C_{\text{Na}^+}}{C_{18C6}}$	δ (± 2 Hz)	δ (ppm)	$\frac{C_{\text{K}^+}}{C_{18C6}}$	δ (± 2 Hz)	δ (ppm)
0	212	3.53	0	212	3.53
0.31	212	3.53	0.76	212	3.53
0.47	212	3.53	1.01	214	3.57
0.63	214	3.57	1.26	214	3.57
0.78	212	3.53	1.52	214	3.57
0.94	215	3.58	1.77	214	3.57
1.10	215	3.58	2.53	214	3.57
1.25	213	3.55			

Salt: KPF_6 Solvent: AN-d_3			Salt: KPF_6 Solvent: DMSO-d_6		
$\frac{C_{\text{K}^+}}{C_{18C6}}$	δ (± 2 Hz)	δ (ppm)	$\frac{C_{\text{K}^+}}{C_{18C6}}$	δ (± 2 Hz)	δ (ppm)
0	209	3.48	0	210	3.50
0.25	209	3.48	0.25	208	3.47
0.50	209	3.48	0.50	207	3.45
0.75	211	3.52	0.76	208	3.47
1.00	212	3.53	1.01	210	3.50
1.25	212	3.53	1.52	212	3.53
1.50	211	3.52	2.02	211	3.52
2.00	210	3.50	2.53	210	3.50

Table 14. Proton NMR Chemical Shift Data Obtained at 180 MHz for 18C6 and 18C6·K⁺ in MeOH and DMSO.

Solvent	Salt	δ (Hz)
MeOH	None	733.15
DMSO	None	762.69
DMSO	KPF ₆ ^a	764.64

^a25 Fold excess salt.

Live and Chan (38) observed changes in the chemical shifts for benzo-substituted crown ethers as big as 89.4 Hz on the complexation of DB30C10 with Ba(ClO₄)₂ in acetone and 36.2 Hz for the complexation of DB18C6 with NaI in deuterated chloroform. The spectra were obtained at 220 MHz. The higher field used and the presence of the benzo groups on the crown ethers are the factors responsible for these large chemical shifts.

Calculation of formation constants for the complexation of crown ethers with metal cations from nmr-mole ratio data requires changes in the chemical shifts of the free and complexed ligand that are large enough to be measured accurately and have a small standard deviation. Formation constants for DB18C6, B18C6, and DB30C10 complexed with various alkali and alkaline earth metal cations were reported in the Live and Chan study. Formation constants could not be obtained from the results presented here.

It is concluded that proton nmr operated at 60 and 180 MHz does not provide accurate enough data for the quantitative investigation of the complexation of nonbenzo-substituted crown ethers such as 18C6 with alkali metal cations.

2. Carbon-13 NMR

Results of the carbon-13 nmr chemical shift-mole ratio studies for the complexation of 18C6 and Na^+ , K^+ , Rb^+ , and Et_4N^+ cations are shown in Table 15. Chemical shift data of an 18C6 concentration study in DMSO given in Table 16 shows that the chemical shift of the free 18C6 ligand is concentration independent.

In the following discussion all carbon-13 nmr chemical shifts are referred to TMS which is upfield (0 ppm). The more deshielded the nuclei becomes the more downfield the chemical shifts are and the more shielded the nuclei becomes the more upfield the chemical shifts. Comparisons are made to results obtained by Shih (48) from potassium-39 nmr for some $18\text{C}6 \cdot \text{K}^+$ complexes in various solvents. Explanation of the carbon-13 and potassium-39 nmr conventions for chemical shift data is shown below.

Table 15. Carbon-13 NMR Chemical Shift-Mole Ratio Data for 18C6 Complexation Studies.

Salt: KPF_6 $C_{18C6}=0.05 \text{ M}$		Salt: NaBO_4 $C_{18C6}=0.06 \text{ M}$	
Solvent: DMSO		Solvent: DMSO	
$\frac{C_{K^+}}{C_{18C6}}$	δ (± 0.05 ppm)	$\frac{C_{Na^+}}{C_{18C6}}$	δ (± 0.05 ppm)
0	71.19	0	71.21
0.23	71.08	0.23	71.11
0.46	70.99	0.55	70.94
0.70	70.88	0.69	70.86
0.93	70.82	0.83	70.86
1.16	70.84	0.92	70.82
1.39	70.82	1.15	70.75
1.86	70.83	1.38	70.72
		1.61	70.65
Salt: Et_4NClO_4 $C_{18C6}=0.06 \text{ M}$		Salt: RbI $C_{18C6}=0.05 \text{ M}$	
Solvent: DMSO		Solvent: DMSO	
$\frac{C_{\text{Et}_4\text{N}^+}}{C_{18C6}}$	δ (± 0.05 ppm)	$\frac{C_{\text{Rb}^+}}{C_{18C6}}$	δ (± 0.05 ppm)
0	71.27	0	71.27
0.23	71.27	0.26	71.08
0.45	71.26	0.48	71.01
0.68	71.27	0.72	70.88
1.13	71.26	0.96	70.78
1.58	71.21	1.45	70.73
2.64	71.19	1.93	70.78
3.52	71.20		

Table 15. Continued.

Salt: KPF_6 Solvent: AC $C_{18C6}=0.06 \text{ M}$		Salt: KI Solvent: MeOH $C_{18C6}=0.05 \text{ M}$	
$\frac{C_{K^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$	$\frac{C_{K^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$
0	70.50	0	70.59
0.25	70.38	0.25	70.37
0.50	70.28	0.49	70.31
0.73	70.13	0.74	70.24
1.00	70.05	0.99	70.17
1.22	69.99	1.23	70.16
1.50	70.01	1.48	70.17
2.0	70.00	1.72	70.17
2.5	69.97	1.97	70.17
Salt: KPF_6 Solvent: DMF $C_{18C6}=0.05 \text{ M}$		Salt: KI Solvent: H_2O $C_{18C6}=0.05 \text{ M}$	
$\frac{C_{K^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$	$\frac{C_{K^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$
0	70.98	0	70.92
0.23	70.88	0.25	70.96
0.46	70.75	0.50	70.99
0.69	70.66	0.75	71.03
0.92	70.56	1.00	71.07
1.39	70.52	1.50	71.08
1.85	70.51	2.01	71.13
2.77	70.52	3.01	71.15
3.70	70.50	3.51	71.17
		4.01	71.17

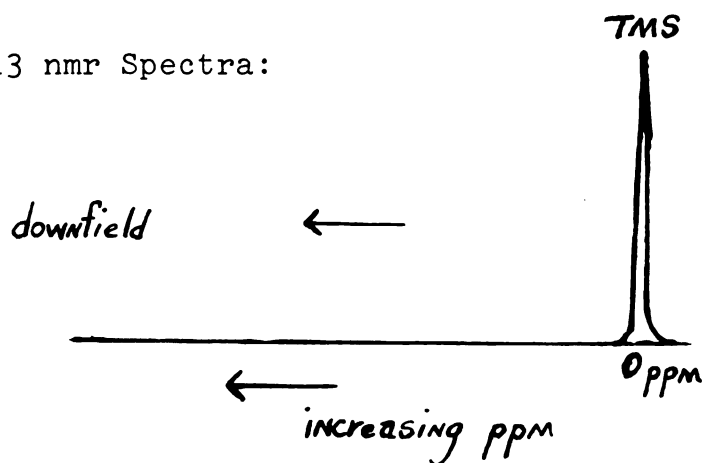
Table 15. Continued.

Salt: RbI Solvent : MeOH $C_{18C6}=0.05 \text{ M}$		Salt: RbI Solvent : AN $C_{18C6}=0.025 \text{ M}$	
$\frac{C_{Rb^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$	$\frac{C_{Rb^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$
0	70.59	0	70.73
0.2	70.46	0.24	70.59
0.4	70.40	0.40	70.56
0.6	70.29	0.46	70.51
1.0	70.12	0.55	70.44
1.4	70.12	0.80	70.38
2.0	70.13	0.96	70.30
		1.2	70.22
Salt: KI Solvent: DMSO $C_{18C6}=0.05 \text{ M}$			
$\frac{C_{K^+}}{C_{18C6}}$	$\delta (\pm 0.05 \text{ ppm})$		
0	71.27		
0.22	71.13		
0.43	71.07		
0.65	70.97		
0.86	70.89		
1.08	70.84		
1.51	70.82		
1.94	70.82		
3.02	70.83		
3.88	70.84		

Table 16. $^{18}\text{C6}$ Concentration Study Data in DMSO Obtained by Carbon-13 NMR.

$\text{C}_{18}\text{C6}$ (<u>M</u>)	δ (± 0.05 ppm)
0.011	71.26
0.021	71.23
0.043	71.23
0.086	71.24
0.129	71.23
0.214	71.23

Carbon-13 nmr Spectra:



Upfield shift results from an increase in electron density of the carbon nuclei causing a diamagnetic (shielded) chemical shift.

Downfield shift results from a decrease in electron density of the carbon nuclei causing a paramagnetic (de-shielded) chemical shift.

Potassium-39 nmr Spectra:

Upfield shift results from a decrease in electron density of the potassium ion nuclei causing a diamagnetic (shielded) chemical shift.

Downfield shift results from an increase in electron density of the potassium ion nuclei causing a paramagnetic (deshielded) chemical shift.

The limiting chemical shifts, δ_{lim} , which are the chemical shifts of the complexes, the chemical shifts of

the free ligand, δ (M.R. = 0), and log of the formation constants, $\log K_f$, calculated by the KINFIT computer program, are shown in Table 17. The range of chemical shifts from the free ligand to the complexed ligand is less than 0.55 ppm in all cases except for $18C6 \cdot Rb^+$ complex in AN for which the results may be suspect because the mole ratio values investigated were small due to the low solubility of the salt. Potassium iodide was used to complex 18C6 in water and methanol because the complex formed with hexafluorophosphate is insoluble and the solubility of the potassium hexafluorophosphate salt is low in methanol. Pyridine was a solvent of interest because of its low dielectric constant and high dipole moment, but salt solubility was too low in this solvent. According to potassium-39 nmr results of Shih (48), increasing the concentration of potassium halide salts produces paramagnetic (deshielded) chemical shifts in various solvents while an increase in the concentration of potassium salts with an anion such as PF_6^- causes diamagnetic (shielded) chemical shifts. DeWitte (105) found no concentration dependence of the ^{19}F nmr chemical shift on potassium hexafluorophosphate solutions indicating the absence of ionic association in these solutions. The chemical shift changes indicate ionic association of the salt due to the donicity and dielectric constant of the solvent. As shown in Figures 2 and 3 both anions I^- and PF_6^- gave the same paramagnetic chemical shifts in

Table 17. Carbon-13 NMR Limiting Chemical Shifts and Log K_f of $^{18}\text{C}_6\cdot\text{K}^+$ and $^{18}\text{C}_6\cdot\text{Rb}^+$ Complexes in Various Solvents.

Salt	Solvent	δ_{ligand} (ppm)	δ_{lim} (ppm)	$\log K_f^a$
KI	H ₂ O	70.92	71.23±0.02	1.4±0.1
	MeOH	70.59	70.15	-----
	DMSO	71.27	70.83	-----
KPF ₆	DMSO	71.19	70.81±0.02	-----
	DMF	70.98	70.51±0.01	-----
	AC	70.50	69.98±0.04	-----
	AN	70.73	70.39	-----
RbI	MeOH	70.59	70.15	-----
	AN	70.73	68.94±0.85	1.2±0.7
	DMSO	71.27	70.74±0.02	-----
	H ₂ O	70.90	70.88	~0

(a) Computer generated formation constants resulted in standard deviations greater than or near the value calculated for the formation constant in cases of complexes considered to be strong due to the fact that their chemical shift-mole ratio plots can be represented as two intersecting straight lines at M.R. of one.

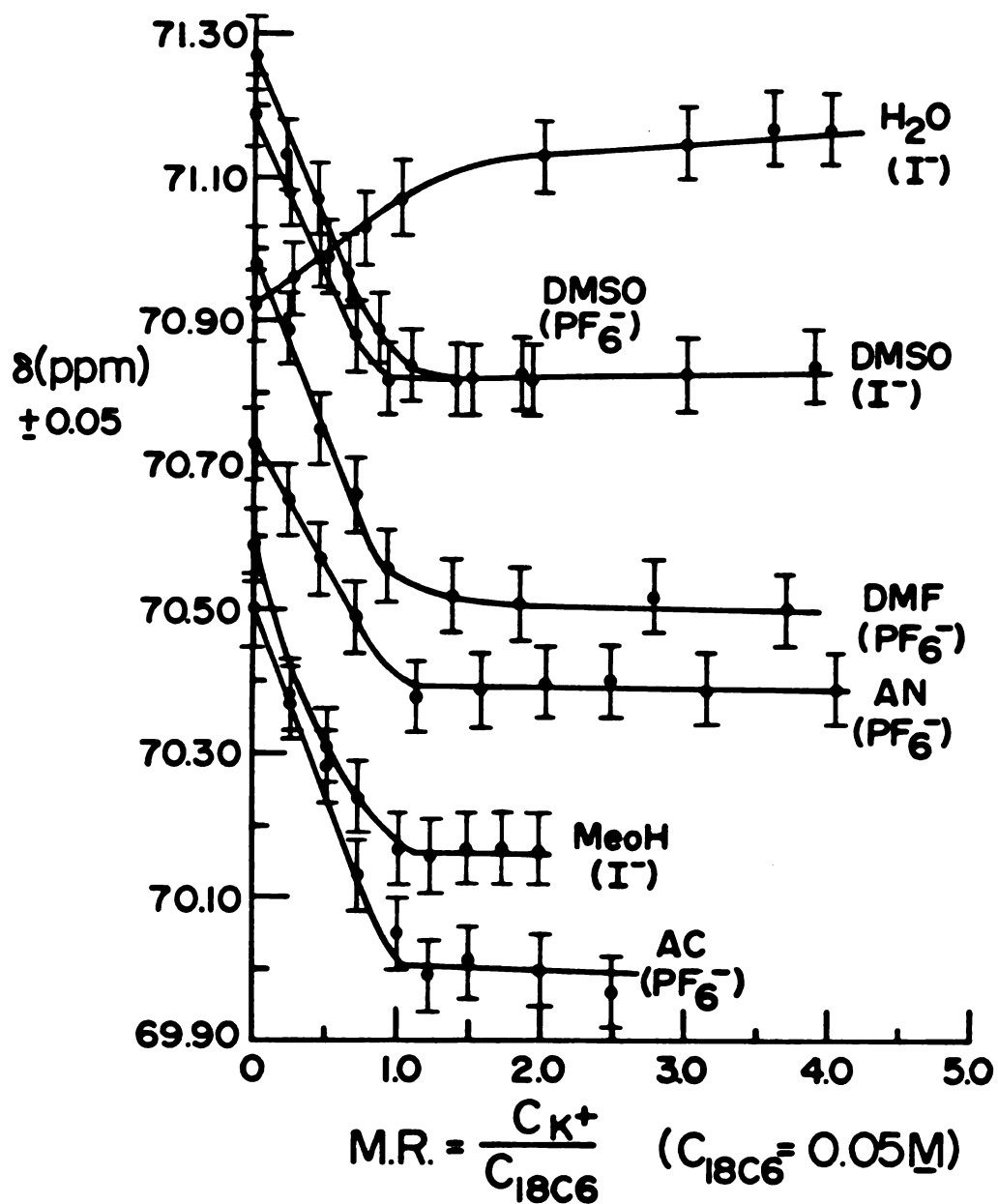


Figure 2. Carbon-13 chemical shifts vs. $K^+/18C_6$ mole ratio in various solvents.

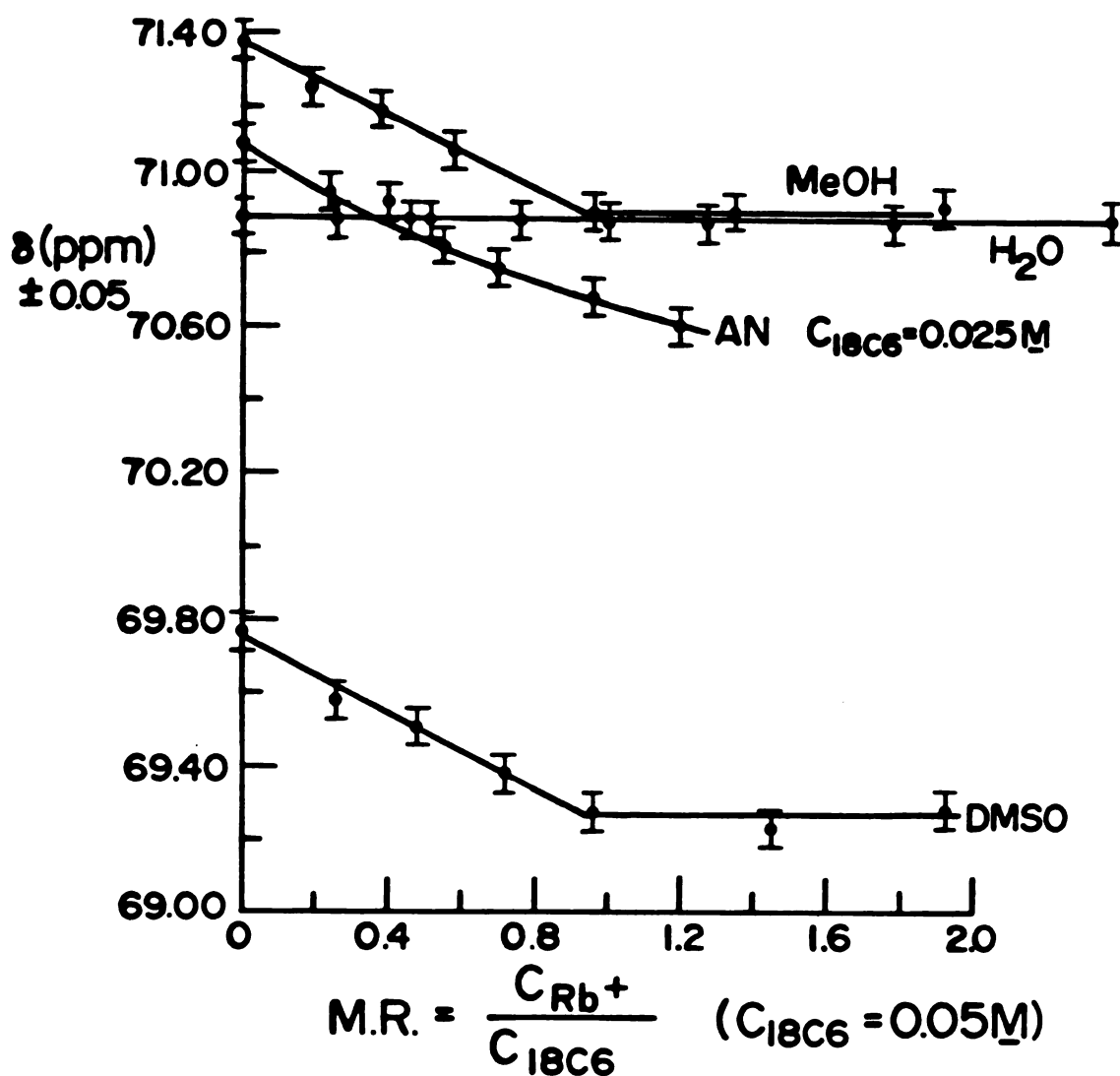


Figure 3. Carbon-13 chemical shifts vs. $Rb^+/18C6$ mole ratio in various solvents.

in DMSO which suggest that the chemical shift changes observed are not due to ionic association of the salts. Shih also found that the chemical shift of the $18C6 \cdot K^+$ complex is concentration independent which indicates the absence of ion pairing between $18C6 \cdot K^+$ and the anion.

Figures 2 and 3 show chemical shift-mole ratio plots for the complexation of $18C6$ with potassium and rubidium salts in various solvents. Mole ratio plots give an indication of the relative strength of the complex by the amount of curvature in the plot. The greater is the curvature the stronger is the complex. Plots that result in or that can be represented as the intersection of two straight lines at mole ratio of one within the standard deviations, are indicative of the formation of a very strong complex. The KINFIT computer program used in the calculation of the limiting chemical shifts and formation constants, cannot be used to calculate formation constants of these very strong complexes. All plots, except in the cases of $18C6 \cdot K^+$ and $18C6 \cdot Rb^+$ in water and $18C6 \cdot Rb^+$ in AN, can be represented as two intersecting straight lines within the error bars shown. Consequently, formation constants for these "strong" complexes could not be determined.

As mentioned before, the interaction of the alkali metal cation and crown ether is electrostatic in nature. Therefore, it could be deduced that the free $18C6$ ligand contains a partial negative charge on the oxygen atoms and a partial

positive charge on the carbon atoms due to the greater electronegativity of oxygen. On complexation, the electron density of the carbon should decrease further due to the interaction of the oxygen atoms with the metal cation causing a greater deshielding and therefore, a paramagnetic chemical shift of the carbons in the complex than the carbons of the free ligand. However, diamagnetic chemical shifts were observed in all solvents except $18C6 \cdot K^+$ and $18C6 \cdot Rb^+$ complexes in water. This can be interpreted as the carbon nuclei of the solvated complexed $18C6$ receiving more electron density than the nuclei of the free solvated ligand. Truter (58) suggests that when the K^+ ion is inside the cavity there is a repulsive interaction between the K^+ ion and the oxygen atoms on the crown ether causing a deshielding of the K^+ ion and subsequently causing an increase in electron density of the carbon atoms. In the case of $18C6 \cdot K^+$ complex in water, hydrogen bonding between the oxygen atoms of the ligand and water decreases the electron density of the carbon nuclei and cause the paramagnetic shift observed. As for the horizontal straight line observed for the $18C6 \cdot Rb^+$ complex, which indicates no complex formation, hydrogen bonding and the repulsive forces mentioned above could just cancel each other. Another explanation may be that the hydration of Rb^+ ion may be strong enough to prevent the formation of the complex. However, K^+ ion, whose charge density is greater than that of Rb^+

ion, is more hydrated and in this case, prevention of interaction between the ligand and K^+ ion should be even greater, but the chemical shift data shows the opposite to be true. Izatt (106) found $\log K_f$ for $18C6 \cdot Rb^+$ in H_2O of 1.56 by calorimetry. Lichter and Roberts (107) suggests that repulsion of the C-H bonding electrons towards the carbon nucleus results in a shortening of the average radius of that orbital, thus increasing the average of the inverse cube of the effective orbital radius term of the Ramsey equation (94), $\langle 1/r^3 \rangle$, and inducing a paramagnetic shift in the carbon-13 nmr spectra.

Shih (48) found potassium-39 paramagnetic shifts for the $18C6 \cdot K^+$ complex in water and DMSO and diamagnetic shifts in AC and DMF. These results indicate that DMSO and water are better electron donors than the ligand and that the ligand is a better donor than AC and DMF. Carbon-13 nmr data show that the complexation of the 18C6 ligand with K^+ and Rb^+ ions all results in an increase in electron density of the carbon atoms, except perhaps the $18C6 \cdot Rb^+$ complex in H_2O .

Table 18 shows the results for different 18C6-cation complexes in DMSO. The ionic diameter of the cations (except for Et_4N^+ which is assumed to be the largest) is listed to provide a comparison with the limiting chemical shifts for the complexes. The limiting chemical shift in ppm follows the order of the ionic diameters, the larger

Table 18. Comparison of Carbon-13 NMR Limiting Chemical Shifts of Various Salt Complexes of 18C6 in DMSO with Ionic Diameter of the Cations.

Salt	Ionic Diameter ^a	δ_{lim} (ppm)
NaBO ₄	2.34	69.07
KPF ₆	2.98	70.81±0.02
KI	2.98	70.83
RbI	3.28	70.74±0.02
Et ₄ NClO ₄	---- ^b	71.20 ^c

(a) Reference (62).

(b) Diameter assumed to be greater than other cations.

(c) No complexation takes place.

the diameter the smaller the diamagnetic shift from the free ligand. The horizontal straight line resulting from the interaction of Et_4N^+ and 18C6 (See Figure 4) indicates that no complex is formed because the Et_4N^+ ion is too large for the cavity of 18C6. These results indicate the importance of the size and therefore the charge density of an ion in the determination of the cation-ligand interaction.

Tables 19 and 20 compare the solvent properties with the limiting chemical shifts of $18\text{C}6 \cdot \text{K}^+$ and $18\text{C}6 \cdot \text{Rb}^+$ complexes respectively. No linear correlations could be determined from the results.

Formation constants for some of the $18\text{C}6 \cdot \text{K}^+$ and $18\text{C}6 \cdot \text{Rb}^+$ complexes in various solvents are shown in Table 21. Table 22 shows a comparison of formation constants for the $18\text{C}6 \cdot \text{K}^+$ complex obtained by carbon-13 nmr and potassium-39 nmr (48). A strong cation-ligand interaction is expected between K^+ cation and 18C6 because the diameter of K^+ is just right to fit inside the 18C6 cavity; however, solvents of high donicity will highly solvate the K^+ ion and thus prevent a strong interaction. AC with the lowest donicity would be expected to support the strongest interaction between 18C6 and the K^+ ion. The order of formation constants would be expected to be $\text{AC} > \text{DMF} > \text{DMSO} > \text{H}_2\text{O}$. Formation constants determined from potassium-39 nmr data follows this order but, those obtained by carbon-13 do not reflect

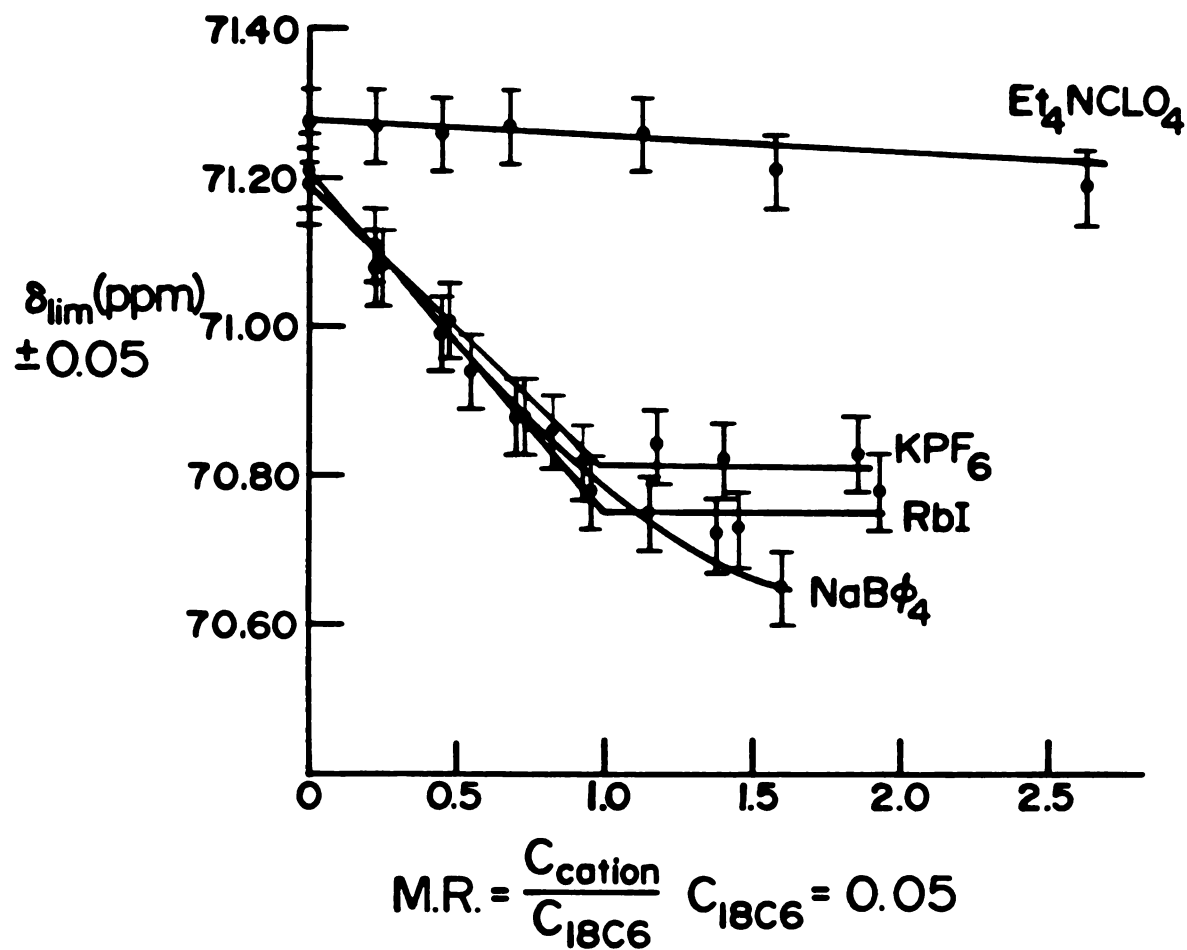


Figure 4. Carbon-13 chemical shifts vs. cation/18C6 mole ratio in DMSO.

Table 19. Comparison of the Carbon-13 NMR Limiting Chemical Shifts of $^{18}\text{O}6\cdot\text{K}^+$ Complexes and Solvent Properties.

Salt	Solvent	Dielectric Constant	Donor No.	δ_{lim} (ppm)
KPF_6	AC	20.7	17.0	69.98 ± 0.041
	AN	38.8	14.1	70.39
	DMF	36.7	26.6	70.51 ± 0.01
	DMSO	46.7	28.9	70.81 ± 0.02
KI	DMSO	46.7	28.9	70.83
	MeOH	32.7	25.7	71.15
	H_2O	78.5	33	71.23 ± 0.02

Table 20. Comparison of the Carbon-13 NMR Limiting Chemical Shifts of the $^{18}\text{C}_6\cdot\text{Rb}^+$ Complex^a and Solvent Properties.

Solvent	Dielectric Constant	Donor No.	δ_{lim} (ppm)
MeOH	32.7	25.7	70.12
AN	38.8	14.1	68.94 $\pm$ 0.85
DMSO	46.7	28.9	70.74 $\pm$ 0.02
H ₂ O	78.5	33	70.88

(a) RbI used.

Table 21. Formation Constants of $18C6 \cdot K^+$ and $18C6 \cdot Rb^+$ Complexes in Various Solvents.

Salt	Solvent	Log K_f
KI	H ₂ O	1.40±0.10
	MeOH	-----
	DMSO	-----
KPF ₆	DMSO	-----
	DMF	~3
	AC	~3
	AN	-----
RbI	MeOH	-----
	AN	1.24 0.65
	H ₂ O	~0
	DMSO	-----

Table 22. Comparison of Formation Constants Determined From ^{13}C and ^{39}K NMR for $18\text{C6}\cdot\text{K}^+$ Complex^a in Various Solvents.

Solvent	Log K_f - $^{13}\text{C}_{\text{NMR}}$	Log K_f - $^{39}\text{K}_{\text{NMR}}$ ^b
Ac	~ 3	>4
DMF	~ 3	2.70 ± 0.04
DMSO	---	2.19 ± 0.23
H ₂ O	1.40 ± 0.10	2.17 ± 0.13^c

(a) KPF_6 used except KI used in H₂O.

(b) Reference (48).

(c) Log K_f of 2.03 was found by Izatt (Reference 106).

this order as well. Alkali metal nmr chemical shift changes reflect the competition between the crown ether and the solvent for the metal cation while those of carbon-13 nmr reflects the competition between the solvent and cation for the ligand and is therefore at best, only an indirect or qualitative indication of the former competition. An example of a formation constant determined by the computer KINFIT program for a complex whose chemical shift-mole ratio plot can be represented as two intersecting straight lines is 4123 ± 3420 or $\log K_f = 3.61 \pm 3.53$ for the $18C6 \cdot K^+$ complex with DMF. Lin (51) also reports that $\log K_f$ for this complex in DMF could be greater than three from carbon-13 NMR data. $\log K_f$ for $18C6 \cdot K^+$ in DMF is reported as 2.70 ± 0.04 from potassium-39 nmr data (See Table 22). However, close agreement between the formation constants obtained from carbon-13 and potassium-39 nmr data for the $12C4 \cdot K^+$ complex was found (48). Cation-ligand interaction is expected to be weak in this complex because the diameter of the K^+ ion is too large for the cavity of the $12C4$ ligand. Values of $\log K_f$ for the $12C4 \cdot K^+$ complex obtained by potassium-39 nmr were 1.79 ± 0.18 , 2.18 ± 0.16 , and 0.31 ± 0.04 in AC, AN, and DMSO respectively. Values of $\log K_f$ obtained by carbon-13 nmr were 1.87 ± 0.07 , 2.26 ± 0.07 , and 0.67 ± 0.14 in AC, AN, and DMSO respectively.

The results indicate that the carbon-13 nmr method is

unable to differentiate the relative strengths of complexes that are expected to display strong cation-ligand interactions. However, formation constants obtained for complexes expected to have weak cation-ligand interactions agree well with those obtained by alkali metal nmr as shown above. The minimum value of the formation constant of a complex for which carbon-13 nmr data can be expected to provide an accurate value as compared to values obtained by alkali metal nmr has not been determined. It is concluded that carbon-13 nmr is not a sensitive enough probe for quantitative determinations of complexation strength. An increase in field strength to provide larger chemical shift with less error may increase the sensitivity and usefulness of this method.

Future Work

This study only touches the surface in the investigation of transfer activity coefficients for the crown ethers. Much more data are needed on the solubilities of the crown ethers in order to continue. Transfer activity coefficients for the crown ether complexes in various solvents will also give valuable information concerning their solvation in the solvents. However, a suitable method for the determination of the solubilities of the complexes must be found.

Proton nmr does not seem promising as a method of

investigating the complexation reactions of the crown ethers except at high field strength. Such studies should continue to be investigated by use of metal nuclei nmr.

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