SOLUTE BINDING TO POLYMERS CONTAINING MACROHETEROCYCLIC RINGS

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Abstract—Interactions of macroheterocycles and polymers endowed with such cation binding ligands as pendant groups, with ions or ion pairs are discussed, emphasis being placed on the binding properties of the macrocyclic polyethers or crown ethers. The use of fluorenyl and picrate salts permitted a spectrophotometric investigation of ligand interactions with ion pairs and a determination of ion pair–crown ether structures, which is of importance in the study of ion transport through low polarity media. Conductometric and spectrophotometric studies were carried out to obtain the complex formation constants of bis(crown ethers) (e.g. crown compounds with two crown moieties at opposite ends of a short aliphatic chain) to cations and their picrate tight ion pairs, as a function of the length and structure of the bis(crown ether) chain. Studies of cation binding to homopolymers and styrene copolymers of vinylbenzo-15-crown-5 and of vinylbenzo-18-crown-6 using extraction equilibria, ion transport, conductance and viscosity, demonstrated the formation of 1:1 and 2:1 crown-cation complexes, selectivity of cation binding, the dependence of the complexation constant on the number of cations bound to the chain, and the possibility of intermolecular 2:1 crown-cation complex formation and crosslinking in copolymers with a low crown content. The polymer poly(vinylbenzo-18-crown-6) exhibits unusually strong binding of organic neutral and anionic solutes in aqueous media. Binding of picrate salts, methyl orange, phenolphtaleine and other solutes were studied spectrophotometrically. The hydrophobic adsorption of organic solutes also causes this polymer to catalyze the decarboxylation of 6-nitrobenzisoxazole-3-carboxylate by dehydrating the anion. The reaction is accelerated in the presence of complexable cations, which are bound to the polycrown ether, thereby further enhancing the adsorption of organic anions by electrostatic interactions. The same polymer was found to precipitate polynucleotides in water in the presence of complexable cations such as K^+. It also exerts a strong inhibitory effect on the polyriboadenylate templated elongation of oligodeoxythymidine catalyzed by murine leukemia virions.

INTRODUCTION

The observation that neutral macroheterocycles can form stable complexes with alkali and alkaline earth cations has led to the development of a host of macrocyclic, macrobicyclic and macrotricyclic ligands, some of which show remarkable selectivity in cation complexation. The original work of Pedersen[1,2] was largely focused on the macrocyclic polyethers or crown ethers, but subsequent work by Pedersen[3] and many other investigators[4-10] resulted in the synthesis of compounds with nitrogen or sulfur atoms in the ring as well as that of more complex ligands such as the polyaza-polyoxa macropolycycles reported by Lehn and his coworkers.[10-14] In addition to the cation binding sites in the macroheterocyclic ring cavity, sites can be attached to the ligand at strategic locations in the form of neutral (e.g. $-NH_2$, $-OH$, $-NCH_2CH_2OCH_2CH_2$) or ionic (e.g. $-COO^-$) substituents to further enhance the stability of the complex or the cation selectivity of the ligand. Several such compounds have been reported by Cram *et al.*[15-17] who also synthesized a series of optically active ligands capable of resolving racemic mixtures of α-amino acids and amino esters.[17-21]

While the significance of most of these macroheterocycles derives from their ability to form stable complexes with the alkali and alkaline earth cations, many of which play an important role in organometallic chemistry and biochemical processes, cations such as Hg^{2+}, Pb^{2+} and Ag^+ also interact with macroheterocycles, especially those containing sulfur and nitrogen.[1,2,22] Alkylammonium,[19] arenediazonium and benzoyl cations[23] also bind to macrocyclic polyethers. The cation binding in most instances involves ion dipole interactions with the electronegative donor atoms of the hydrophilic cavity of the macroheterocyclic ligand. The lipophilic exterior of the complex facilitates its solubility in nonpolar solvents. It is this property that renders the macroheterocycles useful as catalysts in many processes involving inorganic salts or organic metallic reagents. It also enhances significantly the solubility of cations in lipophilic membranes, and crown ethers are, therefore, useful in ion separations processes[24-26] and in facilitated ion transport across artificial or natural membranes.[27,28] Another application concerns their use in ion selective electrodes.[29-30]

The most widely studied ligands are the macrocyclic polyethers or crown ethers (for the nomenclature of these compounds, see Ref. 1), some of which are now commercially available. Their application in organic synthesis is related to their ability to solubilize ionic reagents in nonpolar media and to change the structure of the ionic species into a more active (or sometimes a less active) form. For example, interaction with crown ethers can break up aggregated ion pair species, or it may promote formation of reactive loose ion pairs or free ions. In some instances the latter process produces less reactive species, e.g. in reactions where the cation plays a catalyzing role or when cation–anion separation alters the charge density of the reacting anion. Examples of the use of crown ethers or other macroheterocycles in organic synthesis include the oxidation of olefins, alcohols, aldehydes and aralkyl hydrocarbons in benzene by $KMnO_4$-crown ether complex,[31] the conversion of alkyl, acyl or aryl halides to their respectives fluorides in acetonitrile by 18-crown-6 activated potassium fluoride,[32] the reduction of alkoxy salts to sulfonium sulfides with crown complexed sodiumcyanoborohydride[33] and the crown catalyzed alkylation of potassium phenoxide in dioxane.[34] Anionic polymerization of styrene, isoprene, ethylene oxide, propylenesulfide and methylmethacrylate in hydrocarbon and ethereal solvents is greatly accelerated by addition of cation complexable macroheterocycles.[35] Even in polar solvents such as DMSO, crown ether was shown to significantly affect the reactivity of potassium alkoxides.[36] The stereochemical course of a

reaction may also be altered, as demonstrated by alkoxide catalyzed reactions involving carbanion intermediates.[37] Crown ethers are also effective in liquid–liquid and solid–liquid phase transfer catalyses. Examples are the formation of nitriles from benzyl halides with dry potassium cyanide,[38] the synthesis of nitro compounds from the reaction of nitrites with aliphatic and aromatic halides in acetonitrile[30] and the alkylation of aromatic hydrocarbons with acidic hydrogens (e.g. fluorene) in the presence of dibenzo-18-crown-6 and concentrated aqueous sodium hydroxide.[39]

In this paper the behavior of polymers endowed with crown ethers as pendent groups will be discussed. Such polymers, when dissolved in solvents containing complexable cations, behave as typical polyelectrolytes[40] and the ion binding to the macromolecules can be studied by conductance, viscosity, optical spectroscopy and other techniques. The close proximity of the crown moieties affects the cation binding. Both the cation selectivity and binding strength can be altered by varying the spacing between crown units through the use of copolymers.

While crown ethers are specifically designed to interact with cations, some poly (crown ethers) in aqueous solution strongly bind organic anions and neutral solutes in a way similar to that observed for proteins[41] and certain synthetic polymers such as poly (vinyl pyrrolidone). An interesting difference with the latter polymers is the fact that the binding of the organic species can be influenced by crown complexable cations. We have applied this property of the poly (crown ether) to catalyze the decomposition of benzisoxazole-3-carboxylate in water (see below).

Finally, we shall briefly discuss the interaction of poly (vinylcrown ethers) with polynucleotides in the absence and presence of salts. In the latter case, complete precipitation of both polymers occurs at a certain crown to phosphate ratio. The poly (crown ether) also exhibits strong inhibitory effects on the reverse transcriptase activity, even at low salt concentrations.
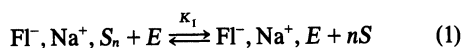
INTERACTION OF IONS AND ION PAIRS WITH MACROCYCLIC POLYETHERS

The two poly(crown ethers) that have been studied in some detail are polymers derived from 4'-vinylbenzo-15-crown-5 and 4'-vinylbenzo-18-crown-6. For a better understanding of the ion binding behavior of these polymers it is illuminating to consider briefly some of the results obtained with their monomeric analogs, 4'-methylbenzo-15-crown-5 (B15C5) and 4'-methylbenzo-18-crown-6 (B18C6), the structures of which are depicted below.

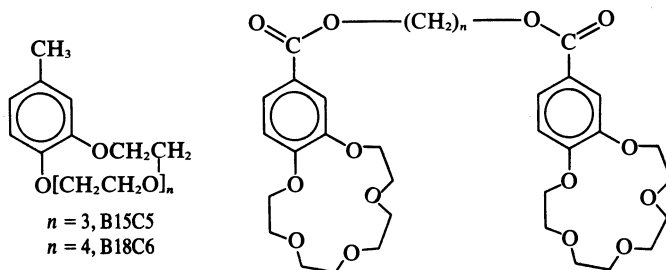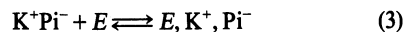Different techniques have been employed to obtain information on crown-cation interactions. Some of the methods that have been reported include u.v. visible spectroscopy,[1,42–45] i.r.,[46] proton and ^{23}Na magnetic resonance,[42,47,48] electron spin resonance,[49] conductance,[50–52] potentiometry,[53] distribution equilibria[1,28,40,54] and calorimetry.[55,56] The results are described in a number of excellent review articles.[2,14,22,57,58] Data on ion pair-crown interactions can be obtained by studying an anion parameter which is sensitive to the interionic ion pair distance, since crown complexation to the cation frequently changes this distance. In much of our own work we have made use of the fluorenyl carbanion as a probe for cation–ligand interactions.[44] Tight and loose ion pairs show distinctly different absorption maxima in the u.v. and visible range of the spectrum, and complex formation constants of crown ethers to these ion pairs can be calculated from the observed optical changes.[43] We recently found that picrate salts exhibit similar optical shifts.[26,59,60] For example, the absorption maxima for the NH$_4$, Na, K, Cs and Ba salts in THF are 351, 351, 357, 362 and 347 nm respectively, while that of the loose ion pair is 378 nm. The picrates have the advantage over carbanion salts of being air and moisture stable and permitting the use of a much wider range of cation chelating agents and solvents, including aqueous and other hydroxylic solvents.

The compound B15C5 was found to interact with a tight fluorenyl sodium ion pair under formation of a mixture of crown complexed tight ion pairs and crown separated ion pairs:

$$Fl^-, Na^+, S_n + E \underset{}{\overset{K_1}{\rightleftharpoons}} Fl^-, Na^+, E + nS \qquad (1)$$

$$Fl^-, Na^+, E + mS \underset{}{\overset{K_2}{\rightleftharpoons}} Fl^-, E, Na^+, S_m \qquad (2)$$

where E denotes the crown ether and S a solvent molecule. The ratio of the two crown species (characterized by different reactivities, optical spectra and other physical properties) is a sensitive function of the solvent. The tight ion pair complex is favored in low polarity media, e.g. in ethyl ether, the spectrum of the complex is that of a tight ion pair. The constants K_2 in tetrahydropyran and tetrahydrofuran at 25° are 0.52 and 1.8, respectively.[43] Reaction (2) is also exothermic, at least for the system Fl^-, K^+ and B18C6, the ΔH_2 for this system being -3.0 kcal/mol and $\Delta S_2 = -10.4$ e.u.

The ratio of loose to tight crown-ion pair complex is also anion dependent, a more localized charge favoring the tight complex. For example, the B15C5 complex with sodium picrate in THF is a tight ion pair. The same is found when this crown is added to potassium picrate (λ_m changes from 357 nm to 362 nm), but addition of a larger excess of B15C5 forms the 2:1 crown separated ion pair complex,[59] λ_m being 378 nm:

$$K^+Pi^- + E \rightleftharpoons E, K^+, Pi^- \qquad (3)$$

CH$_3$

OCH$_2$CH$_2$
O[CH$_2$CH$_2$O]$_n$

$n = 3$, B15C5
$n = 4$, B18C6

Bis-(crown ether)

$$E, K^+, Pi^- + E \rightleftharpoons E, K^+, E, Pi^-. \qquad (4)$$
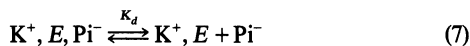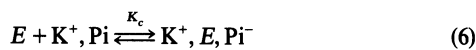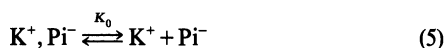
Such cation crown sandwich type complexes are frequently encountered in systems where the cation is larger than the crown cavity, e.g. K^+, Ba^{2+} and NH_4^+ with B15C5, or Cs^+ with B18C6, and have been observed by several investigators.[2,43,54,61] The respective complex formation constants for reactions (3) and (4) in THF at 25°C are 6×10^3 M^{-1} and 2×10^2 M^{-1}.[59] The first value is about the same as that found for Fl^-, K^+ under the same conditions,[43] the second one is ten times lower than for the same reaction with Fl^-, K^+. Charge delocalization in the fluorenyl carbonion facilitates the ion pair separation.

The observation of 2:1 crown–cation complexes and our work on polycrown ethers with variable distances between crown moieties induced us to examine the properties of macrobicyclic polyethers endowed with a benzo-15-crown-5 group at each end of a short aliphatic chain (structure depicted above). A combination of spectrophotometric and conductance measurements permitted us to determine the ion pair dissociation constants and complex formation constants of the following equilibria, all existing simultaneously in THF at 25°C.

$$K^+, Pi^- \overset{K_0}{\rightleftharpoons} K^+ + Pi^- \qquad (5)$$

$$E + K^+, Pi^- \overset{K_c}{\rightleftharpoons} K^+, E, Pi^- \qquad (6)$$

$$K^+, E, Pi^- \overset{K_d}{\rightleftharpoons} K^+, E + Pi^- \qquad (7)$$

$$E + K^+ \overset{K_f}{\rightleftharpoons} E, K^+. \qquad (8)$$

The bis-(crown ether), denoted by E, forms a separated ion pair complex with potassium picrate (λ_m 380 nm). The respective constants for five macrobicyclic polyethers are collected in Table 1. Included are some values obtained with NH_4^+, Pi^-.

Inspection of the data reveal that the dissociation constants, K_d, for the loose ion pair complexes vary only slightly with the structure of the bis-(crown ether), implying that the interionic ion pair distance remains nearly constant. On the other hand, the complex formation constants to ion pair and free cation, K_c and K_f respectively, depend on the length and structure of the chain connecting the crown moieties. CPK models demonstrate that a parallel alignment of the crown rings in the sandwich type complex can be achieved for a distance of 8 Å between the C=O groups. This requires at least 4 or 5 CH_2 groups. A short linkage such as $-CH_2CH_2-$ adversely affects the stability of the complex. Extension of the chain causes loss in conformational

entropy while other chain length dependent variables are known to affect the conformational energy in similar cyclization processes.[62] The highest value was found with five CH_2 groups, but compounds with three, four, six and seven CH_2 groups were not investigated. Replacing a CH_2 group by oxygen enhances K_c by nearly a factor of five (Table 1). Increased chain flexibility is the most probable cause for the higher values. Complex formation constants for NH_4^+, Pi^- are considerably lower than for the potassium salt. Stronger solvation of NH_4^+ by THF and a shorter interionic ion pair distance in the tight ion pair (λ_m of $NH_4^+Pi^-$ is 351 nm as compared to 357 nm for KPi) can account for this.

The ratio K_f/K_c is nearly 400 for both salts. Simultaneous complexation of the cations by the two crown moieties probably requires complete desolvation of the ion. Although more solvent molecules must be removed from the free cation, the strong electrostatic interaction in the tight ion pair is apparently the dominating factor determining the K_f/K_c ratio. These ratios are highly anion dependent because of K_c. For example, in THP at 25°C the ratio is only 2.8 for the system tetraglyme/$NaBPh_4$[63] and 40 for tetraglyme/polystyrl sodium.[64]

Low K_c values for macrobicyclic polyethers may give rise to formation of species such as $E-E$, K^+, Pi^- (the bis-(crown ether) is denoted here by $E-E$). This is expected with compounds where cyclization is hindered by chain stiffness or made less probable by increased chainlength. At higher crown concentration the ion pairs may still separate due to formation of species of the type $E-E$, K^+, $E-E$, Pi^-, similarly as found with B15C5. Polymeric species such as $[K^+, E-E]_n$, Pi_n^- can be visualized at higher concentration of a 1:1 molar mixture of salt and bis-(crown ether). The problem of intra versus intermolecular complexation is also encountered in polymers with B15C5 moieties as pendent groups and will be discussed below.

The compound B18C6 gives 1:1 complexes with both sodium and potassium fluorenyl and picrate salts. With cesium salts the 2:1 complex can be formed but is not very stable in solution. In polymers, however, the complex stoichiometry is clearly two B18C6 moieties for one cesium. In the 1:1 complexes with sodium and potassium one again encounters tight and loose ion pair complexes, depending on the anion. With sodium fluorenyl only crown separated ion pairs are formed with B18C6, both in THF and THP. But sodium picrate in $CHCl_3$ with B18C6 has a λ_m of 362 as compared to 378 nm for the loose ion pair. The crown complexed ion pair in this case may either be a mixture of a crown tight and loose ion pair complex, or a single species with the cation

Table 1. Dissociation constants and complex formation constants of macrobicyclic polyethers with potassium and ammonium picrate in THF at 25°C. (Data taken from ref. 60)

| Bis-(crown ether)*	$K_d \times 10^5$ M	$K_c \times 10^{-3}$ M^{-1}	$K_f \times 10^{-5}$ M^{-1}
Potassium picrate, $K_0 = 9.2 \times 10^{-8}$ M			
$-(CH_2)_2-$	2.4	11	29
$-(CH_2)_5-$	3.2	37	130
$-(CH_2)_8-$	3.7	15	60
$-CH_2CH_2OCH_2CH_2-$	3.5	170	650
$-(CH_2CH_2O)_2CH_2CH_2-$	4.1	72	320
Ammonium picrate, $K_0 = 8.5 \times 10^{-5}$ M			
$-CH_2CH_2OCH_2CH_2-$	3.3	0.19	0.74
$-(CH_2CH_2O)_2CH_2CH_2-$	3.0	0.17	0.60

*For complete structure see text.

slightly protruding from the crown cavity but still close to the anion. It may be stressed at this stage that loose ion pair species with different solvation shells may have identical absorption maxima but different interionic ion pair distances. For example at −60°C in THF fluorenyl sodium itself and its crown complexed ion pair have identical spectra, λ_m being 373 nm. However, the THF separated ion pair has a free ion dissociation constant of $K_d = 4 \times 10^{-6}$ M and the crown separated ion pair a K_d of 0.27×10^{-6} M. The nearly planar conformation of the crown ring permits a much closer approach to the anion than when THF is around the Na$^+$ ion. Dipole measurements such as those reported by Grunwald et al.[65] for crown complexes of potassium p-toluenesulfonate may shed more light on this problem.

The order of stability of crown complexes with respect to a series of cations is solvent dependent. For example, optical measurements[42] reveal that in an equimolar mixture of Fl$^-$, Na$^+$ and Fl$^-$, K$^+$ in THF, B18C6 is complexed to Fl$^-$, Na$^+$. In oxetane, where Fl$^-$, Na$^+$ is a loose ion pair at 25°C as compared to a tight ion pair in THF, the B18C6 under the same conditions is complexed to Fl$^-$, K$^+$. The latter species is a tight ion pair in both solvents. In aqueous media, complexation to K$^+$ is stronger than to Na$^+$, due to differences in hydration energies.[53] This is the main reason why the extraction equilibrium constant for potassium picrate with B18C6 in H$_2$O/CHCl$_3$ is 2.4×10^5 M^{-2} and only 2.3×10^3 M^{-2} for the sodium salt.[26] This difference permits separation of Na$^+$ and K$^+$ ions by means of CHCl$_3$ as a barrier. Transport measurements for a mixture of the two alkali picrates with chloroform as the barrier between two aqueous phases give a flux ratio K$^+$/Na$^+$ of 50, very close to the ratio of the two extraction equilibrium constants.[26] This ratio is anion dependent, as the species transported through the chloroform layer are crown complexed ion pairs and their structure depends on the anion. The flux ratio for the two chlorides was found[26] to be 24.

The number of thermodynamically and chemically distinct complexes is even larger when crown ether interact with ion pairs of divalent cation such as strontium or barium.[66] Barium and potassium have about the same ionic radius, and it is not surprising, therefore, that B15C5 has a strong tendency to form 2:1 complexes with salts such as barium difluorenyl. The tight ion pair† spectrum of Ba^{2+}, Fl$_2$$^{2-}$ (λ_m 347 nm) converts to that of a loose ion pair Fl$^-$, E, Ba^{2+}, E, Fl$^-$ (λ_m 373 nm) in THF on addition of B15C5, the complex formation constant being 1.3×10^8 M^{-2}. This value is higher than for Fl$^-$, K$^+$, which was found to be 1×10^7 M^{-2} (the product K_1K_3 in Ref. 43). However, the reverse is found for picrates. Potassium picrate readily forms a loose ion pair in THF with bis-(crown ether), but even a large excess of the same compound could not fully convert the tight barium picrate ion pair. The tightness of the ion pair, which, of course, is different for the fluorenyl and picrate salts, becomes a very important factor in the divalent salts, especially in the second dissociation step.

Complex formation of B18C6 with Ba^{2+}, Fl$_2$$^{2-}$ in THF produces a mixed tight-loose ion pair complex of the type Fl$^-$, Ba^{2+}, E, Fl$^-$, the optical spectrum being identical to that of an equal molar mixture of tight and loose fluorenyl ion pairs.[66] This ion pair is electrostatically more stable

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†In the divalent salts we are using the term ion pair of species such as Ba^{2+}, Fl$_2$$^{2-}$ although we realize that it actually resembles a nonconducting triple ion.

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than one in which the Ba^{2+} cation is centered in the crown cavity at equal distances from the anion. The optical spectrum of the mixed ion pair remains essentially unchanged between 25 and −70°C. This is not the case with the strontium salt. Addition of dibenzo-18-crown-6 (and B18C6 would probably behave the same) to SrFl$_2$$^{2-}$ again forms the asymmetrically complexed 1:1 tight-loose ion pair complex in THF at 25°C, but the spectrum changes on lowering the temperature, and only the 373 nm absorption maximum is found at −70°C. The reaction

$$\text{Fl}^-, \text{Sr}^{2+}, E, \text{Fl}^- + n\,\text{THF} \rightleftharpoons \text{Fl}^-, \text{THF}_n \text{Sr}^{2+}, E, \text{Fl}^- \tag{9}$$
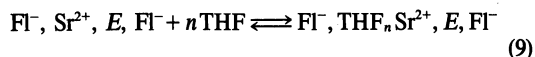
has a $\Delta H = -5.7$ kcal/mol, ΔS being −25 e.u. The interaction between Sr^{2+} and THF apparently is strong, as evidenced by a $\Delta H = -12.3$ kcal/mole for the reaction[67]

$$\text{Sr}^{2+}, \text{Fl}_2{}^- + n\,\text{THF} \rightleftharpoons \text{Fl}^-, \text{Sr}^{2+}, \text{THF}_n, \text{Fl}^-. \tag{10}$$

The second dissociation step to the fully separated ion pair Fl$^-$∥Sr^{2+}∥Fl$^-$ is more difficult than for the mixed crown complex shown in eqn (9), the ΔH being only −2.8 kcal/mol. The probable reason for this difference lies in the shorter interionic distance between Sr^{2+} and Fl$^-$ in the crown complex as compared to the THF separated ion pair. Another interesting observation is that the ion pair Fl$^-$, THF$_n$, Sr^{2+}, E, Fl$^-$ on dissociation into free ions does not produce the species Fl$^-$, E, Sr^{2+}, THF$_n$ but Fl$^-$, Sr^{2+}, E. The conversion of the former into the latter species is endothermic ($\Delta H = +2.6$ kcal/mol), the ΔS being +11 e.u. These thermodynamic quantities are nearly identical to those found for the conversion of a crown separated fluorenyl potassium ion pair into a crown complexed contact ion pair, a process resembling the interconversion of the two positively charged strontium fluorenyl species.

Suffice to say that the above examples demonstrate the complexity of crown intractions with ion pairs, especially those of divalent cations. The stability of the various crown ion pair complexes for a particular crown–cation system is a sensitive function of the solvent, temperature and anion, and it is to be expected that the effect of crown ethers on the mechanism of reactions in which ion pairs are the reactive species will be equally sensitive to these parameters.

CROWN MONOMERS AND POLYMERS

The polymers most frequently used in our work are 4′-vinyl derivatives of benzo-15-crown-5 and benzo-18-crown-6. The monomers were prepared with cathecol as starting material.[40] This was converted to 3,4 dihydroxyacetophenone via the catecholdiacetate. The ketone was then reacted with Cl(CH$_2$CH$_2$O)$_n$CH$_2$CH$_2$Cl to form the 4′-acetobenzo crown ether, which was reduced to the alcohol and subsequently dehydrated to the vinyl derivative. The 4′-acetobenzocrown ether can also be obtained by acetylation of benzocrown ether with acetylchloride and HF.[68] Another method for producing the vinyl compound starts with 3,4 dihydroxybenzaldehyde, converting this to the corresponding crown ether, which then can be reacted with methyl magnesium iodide to form the alcohol and, by dehydration, the vinyl compound.[69]

The vinylbenzocrown ether can be polymerized to high molecular weight polymers by a radical initiator in the conventional way.[40] Copolymers with styrene were also prepared, the composition being nearly identical to that of

the starting monomer feed and independent of conversion, indicating that the two reactivity ratios are close to unity. Living polymers are formed by polymerizing the vinyl monomers in THF with α-methylstyrene tetramer as catalyst as long as the temperature is kept at about $-80°C$. Block copolymers can be synthesized by adding monomers such as styrene, ethylene oxide, methylmethacrylate or vinylpyridine to the living crown polymer, or vice versa. The homopolymer, poly (vinylbenzo-15-crown-5) (P15C5) and poly (vinylbenzo-18-crown-6) (P18C6) are soluble in solvents such as aromatic hydrocarbons, THF, $CHCl_3$ and CH_2Cl_2. The solubility decreases considerably in more polar media, but P18C6 has a remarkable solubility in water (8 g/100 ml), especially at lower temperatures.[40] The intrinsic viscosity of P18C6 in water is low ($\eta = 0.1$ for $M_n = 100,000$), and the molecules apparently are highly coiled. This leads to some interesting phenomena when this polymer and certain organic compounds are mixed in water (see below).

Other monomers can be prepared from crown ethers such as 4'-hydroxymethyl- and 4'-carboxy benzocrown ether (obtained by reduction and oxydation, respectively, of the crown benzaldehyde). Reaction of the hydroxymethyl derivative with methacryloyl chloride produces crown esters of methacrylic acid which can be polymerized radically to high molecular weight polymers. The two 4' derivatives can also be utilized to carry out reactions on polymers with functional groups, such as poly(methacryloylchloride) or polyethyleneimine.

Another interesting class of crown monomers are macrocyclic polyethers bearing one or two spiro-oxetane rings.[70] They can be synthesized in one step from poly(ethylene glycol) and 3,3 bis(halomethyl)oxetanes, and polymerize cationically through the oxetane ring. The presence of three carbon atoms separating two of the oxygen atoms of the crown ring appears to considerably lower the stability of the crown cation complexes.

Polymers with crown ethers in the backbone have been prepared by polymerizing iso- and terephtaloyl chloride with diaminobenzo-18-crown-6 in hexamethylphosphoramide or dimethylacetamide.[71] The resulting polyamides can be cast into films from hexafluoro isopropanol and exhibit interesting cation binding properties.

EXTRACTION EQUILIBRIA

Significant information on ion binding to crown compounds has been gained from studies of extraction equilibria in solvent mixtures such as $H_2O/CHCl_3$, H_2O/CH_2Cl_2 and $H_2O/toluene.$[2,26,27,40,54] Picrate salts again offer an advantage, not only experimentally, but also because ion pair structures can be identified by analyzing the optical spectra. This aids significantly in the interpretation of both extraction and ion transport data.

The heterogeneous extraction equilibrium can be represented by:

$$M^+(aq) + Pi^-(aq) + n\text{Crown} * \overset{K_e}{\rightleftharpoons} M^+, Pi^-, \text{Crown}_n *$$
(11)
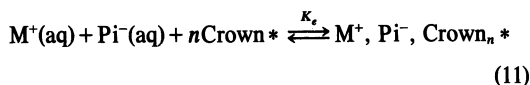
where the asterisk refers to species in the organic phase. We already pointed out that the structure of the ion pair complex is dependent on the particular crown/cation combination and the solvent. While in chloroform (dielectric constant 4.80) the free ion concentration is very low (K_d for B18C6/KPi is in the order of 10^{-9} M and the complex concentration $>10^{-5}$ M), it cannot be neglected in

Table 2. Extraction equilibrium constants of sodium* and potassium picrate for H_2O–$CHCl_3$ at 20°C with crown ethers† dissolved in $CHCl_3$‡

Crown§	$K_e \times 10^{-3}$ M^{-2}	
	Sodium picrate	Potassium picrate
B15C5	3.7	0.42
P15C5	5.5	2.3
P15C5 (20%)	4.1	45
B18C6	2.3	240
P18C6	5.6	550
P18C6 (20%)	1.7	150

*Picrate concentration in H_2O was 10^{-2} M for NaPi and $10^{-3} - 3 \times 10^{-3}$ M for KPi.

†Crown concentration varied from 10^{-4} to 4×10^{-4} M (for polymers expressed in terms of crown units).
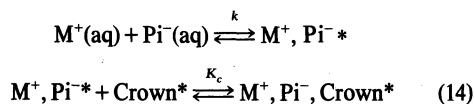
‡Data taken from Ref. 26.

§P15C5 (20%) refers to a copolymer with styrene containing 20% of the 15C5 moiety on a molar basis. Same for P18C6 (20%).

methylene chloride (dielectric constant 9.08).[27,40,54] With only ion pairs present and n equals unity, the extraction equilibrium constant is given by

$$K_e = \frac{[\text{complex}]}{\gamma \pm^2 [M^+][Pi^-]\{[\text{crown}]_0 - [\text{complex}]\}}$$
(12)

where $\gamma_\pm$ denotes the mean activity coefficient of the salt in water. This equation is applicable in most of our systems except for B15C5/KPi* at higher B15C5 concentrations, since, in addition to the 1:1 tight ion pair complex, a 2:1 crown complex is formed (see previous section). However, spectral data prove that under our experimental conditions (low B15C5 concentration) the only species formed is B15C5, K^+, Pi^-. With P15C5 and P15C5 (20%) (the percentage following the polymer notation refers to the mol % of crown monomer in the styrene—vinylcrown ether copolymer) the ion pair complexes are of the separated kind, with K^+ sandwiched in between two B15C5 moieties (λ_m 378). However, the complexation is intramolecular, (see, however, the section on viscosity), and equation (12) is applicable with the modification that the free crown concentration in (12) is given by $[\text{crown}]_0 - 2[\text{complex}]$.

The data for the respective picrate-crown systems are given in Table 2 (in most cases two or six extractions at different picrate and crown concentrations were carried out to determine K_e). The results demonstrate that replacing the crown compound by its polymer does not affect K_e to any great extent when the cation forms a 1:1 complex with the crown (Na/B15C5, Na/B18C6 and K/B18C6). This is not surprising if the extraction is viewed in terms of the following equilibria:

$$M^+(aq) + Pi^-(aq) \overset{k}{\rightleftharpoons} M^+, Pi^- *$$

$$M^+, Pi^-* + \text{Crown}* \overset{K_c}{\rightleftharpoons} M^+, Pi^-, \text{Crown}*$$
(14)

where $K_e = kK_c$. Any difference in K_e for a particular salt only depends on K_c. Although no K_c values were measured in chloroform, potentiometric measurements of complex formation constants of B18C6 and P18C6 to K^+(KCl) in water/THF reveal only small differences. However, direct measurements in solvents such as THF are needed to confirm this. Differences between monomeric crown and polymer can be expected when the polymer exhibits a significant tendency to bind anions or,

in the case of copolymers, when the second monomer contributes to the binding of either cations or anions. An example is found in the system P18C6/H2O, where cation binding to the crown moiety appears to be higher for potassium picrate than for potassium chloride, due to hydrophobic bonding of picrate anions to P18C6 (see below).

Another interesting observation is the sharp decrease in K_e for P18C6/KPi in CHCl3 as the population of ion pairs along the chain increases. In fact, the ratio of complexed crown to total crown does not exceed 0.5 even at high picrate to crown ratio's. Although B18C6 is not known to form a 2:1 complex with K$^+$, the K_e value is constant when the free crown concentration in equation (12) is given by [crown]0 − 2[complex]. Apparently the binding constant rather abruptly decreases when more than half the crown moieties contain a K$^+$ ion either because of electrostatic repulsion or steric hindrance. The ratio complexed crown to total crown does approach unity when the B18C6 moieties are spaced farther apart such as in P18C6 (20%), where K_e is constant. The ratio also approaches unity for P18C6 and K$^+$ when the complex formation constant is very high, such as for fluorenyl potassium in THF.[72] Whether the binding constant of P18C6 to the Na$^+$ ion also depends on the degree of cation binding could not be ascertained from the limited extraction data, but conductance measurements with P18C6 in acetone solutions of KBPh4 and NaBPh4 indicate that this is the case.

When 2:1 crown–cation complexes are formed, polymers are more effective than their monomeric analogs, at least at low crown concentrations. This is shown by comparing the extraction of KPi by B15C5 with that by P15C5 or P15C5 (20%). The latter two crown species can best be compared with the bis-(crown ethers), but no extraction data are available on these compounds. Note the considerably higher K_e value for P15C5 (20%) as compared to P15C5. Squeezing a K$^+$ ion in between two B15C5 moieties is likely to be more difficult for the already compact P15C5 polymer. Spectrophotometric measurements on KPi in THF with P15C5 copolymers of different crown content may yield more definitive data on the binding of K$^+$ ions as a function of the spacing between crown moieties.

The K_e values are strongly solvent dependent,[26,40,54] since equilibria (13) and (14) are affected by the polarity of the medium. This effect is particularly pronounced when complexation results in ion pair separation as in 2:1 crown cation complexes. In a low polarity solvent such as CHCl3 the K_e value for P15C5/KPi is nearly hundred times lower than that in methylene chloride.[26] On the other hand 1:1 crown-ion pair complexes may either be of the tight or loose kind, depending on the solvent. In these systems, K_e values in CHCl3 and CH2Cl2 are not very different, although formation of free ions in CH2Cl2 results in a significant increase in the total amount of picrate extracted.

ION TRANSPORT

Ion transport across natural and synthetic membranes can be augmented by antibiotics such as monactin or valinomycin.[27,28] Ionic permeability can also be induced by synthetic carriers such as macrocyclic polyethers. A liquid hydrocarbon phase (containing the carrier) interposed between two aqueous phases has frequently been utilized as a model for facilitated ion transport through natural membranes.[25,27,28] In our work we used a Schulman

bridge to study ion migration through a chloroform layer.[26] The bridge essentially consists of a U-tube with the aqueous phases in the two side arms separated by chloroform which contains the crown compound or the polymer. One of the aqueous phases contains a salt or mixture of salts. Both picrates and chlorides were used. In the former case the flux of salt through the stirred chloroform layer can be calculated by measuring spectrophotometrically the accumulated picrate salts as a function of time. For chlorides, a conductometric method was used,[25] while for mixtures of two alkali salts the concentration of each cation was determined by emission spectroscopy.[26]

Spectra of the stirred chloroform layer reveal that picrate transport (and certainly also chloride transport) through this medium occurs by means of ion pair crown complexes. The rate controlling step in the migration of picrates and chlorides was shown to be the diffusion of the ion pair complex through the thin chloroform layer separating the interphase from the steady state region of the chloroform, after rapid establishment of the distribution equilibrium across the two H2O/CHCl3 boundary layers. The steady state flux, F, for such a migration is given by

$$F = D(C_e - C_s)\mathrm{l} \tag{15}$$

where D denotes the diffusion constant of the ion pair complex, l is the thickness of the diffusion barrier (found to be 47μ) and C_e and C_s are the concentrations of the complex at the interphase and in the steady state region of the chloroform respectively. From linear plots of accumulated salt versus time the flux densities for the migration of sodium and potassium picrate for four crown species were determined. The results are listed in Table 3.

Assuming identical diffusion constants for the two B18C6–MPi complexes, the ratio of the extraction equilibrium constants of the two salts and the B18C6–NaPi complex can be determined from the respective flux densities. The value is found to be 118, very close to the ratio of 104 found for $K_e(\mathrm{K}^+)/K_e(\mathrm{Na}^+)$ from extraction experiments. This demonstrates that indeed the distribution equilibrium across the boundary is maintained during the salt transport.

Note that under identical conditions the flux of sodium picrate in the presence of P18C6 (20%) is about six times

Table 3. Flux density of sodium and potassium picrate across a CHCl3 membrane containing a crown ether†

Crown	[Picrate]0 ($\times 10^3$ M)	[Crown]0 ($\times 10^3$ M)	Flux ($\times 10^7$ M hr^{-1} cm^{-2})
	Sodium picrate		
B18C6	20.0	1.00	1.36
	20.0	2.03	2.90
	20.0	4.06	5.85
P18C6 (20%)	20.0	1.00	0.272
	20.0	1.71	0.300
	20.0	3.42	0.600
	Potassium picrate		
B18C6	2.00	1.00	2.02
	2.00	2.03	4.21
	2.00	4.06	8.20
P18C6 (20%)	2.00	1.00	0.706
	2.00	1.71	1.05
	2.00	3.42	1.38

†Data taken from Ref. 26.

slower than for B18C6, although the K_e values for the two crown species are nearly identical (Table 2). A decrease of about four is found for the potassium salt. The lower diffusion constant for the polymeric ion pair complexes must be the reason for this. This constant is likely to depend on the ion pair population along the chain and decreasing as fewer cations are bound.

Experiments with a mixture of sodium and potassium picrate in the presence of B18C6, B15C5 and P15C5 yields selectivity ratios for K^+/Na^+ (i.e. the ratio of the concentrations of accumulated salt) of 50, 0.14 and 0.55, respectively. This compares with calculated ratio's (from K_e values) of 104, 0.11 and 0.14, respectively. The ratio for B15C5 increases at higher crown concentration as relatively more K^+ migrates due to formation of the 2:1 crown-KPi complex. Chloride transport shows a K^+/Na^+ selectivity ratio of 24.0. This ratio is generally expected to be anion dependent as both k and K_c depend on the nature of the anion. It should also be solvent dependent, but it is interesting to note that only small differences in selectivity ratios are found with carriers that completely sequester the cations, such as is the case with macrotetralide actin antibiotics.[27] The ion pair complexes are probably all of the separated kind, while with crown ethers sodium and potassium salts may yield different ion pair structures.

CONDUCTANCE MEASUREMENTS

Although a quantitative treatment of conductance data of polyelectrolytes is frequently a cumbersome task, some insight can be gained when this technique is applied to the study of polycrown ether–salt solutions. Addition of crown ether to a solution of free and complexable cations changes the conductance when the cation ligand has a mobility different from that of the solvated cation. In solutions of ion pairs the conductance is affected not only by the cation mobility but also by the change in ion pair dissociation constant. The new crown-ion pair complex may have a lower or higher dissociation constant, depending on its structure relative to that of the original ion pair (see previous sections). Complex formation constants for dicyclohexyl-18-crown-6, dibenzo-18-crown-6 and some of its derivatives to ion pairs and free ions of alkali tetraphenylborons and chlorides were obtained in acetonitril, methanol, dimethylformamide and dimethoxyethane.[73,74]

A simple conductometric titration can often establish the composition of the complex.[3] Using tetraphenylboron salts in acetone and methyl ethyl ketone we measured the change in equivalent conductance of a 10^{-3} M salt solution on addition of crown ether. At 10^{-3} M salt concentration only free ions are present in these solvents and it can easily be shown that for $K_f[M^+] \gg 1$ (K_f being the complex formation constant to the free cation M^+) the equivalent conductance Λ is given by

$$\Lambda = \Lambda^- + (\Lambda^+)' - \{(\Lambda^+)'' - (\Lambda^+)'\}[\text{crown}]_0/[\text{salt}] \quad (16)$$

where $(\Lambda^+)'$ and $(\Lambda^+)''$ denote the equivalent conductances at 10^{-3} M for the cation and its crown complex, respectively. Plots of Λ vs [crown]$_0$/[salt] are straight lines with a rather sharp break at a crown to salt ratio equal to the composition of the complex. For small values of $K_f[M^+]$ a curve is obtained from which the complex formation constant K_f can be calculated.[73] When complexes of different composition exist simultaneously the equation for Λ will, of course, be more complex.

Several conductance plots for tetraphenylboron salts in the presence of crown ethers and their polymers are depicted in Figs. 1 and 2. As expected, 1:1 complexes are formed for B18C6/K^+, B15C5/Na^+ and dicyclohexyl-18-crown-6/K^+. Other 1:1 complexes not shown are bis-
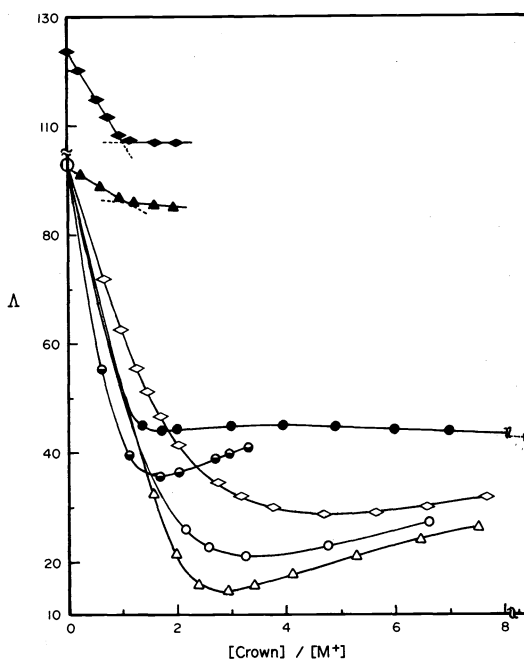

Fig. 1. Change in equivalent conductance of a 10^{-3} M solution of alkali tetraphenylboron in methyl ethyl ketone at 25°C in the presence of crown ethers as a function of the crown to cation ratio (for clarity, a number of experimental points below a crown to cation ratio of two are not shown on the drawings). ◆ B18C6/K^+ (Solvent: acetone); ▲ B15C5/Na^+; △ P18C6/Cs^+; ○ P18C6/K^+; ◇ P18C6/Na^+; ◓ P18C6 (20%)/K^+; ● P18C6 (5%)/K^+; ■ Polystyrene added to show viscosity effect.
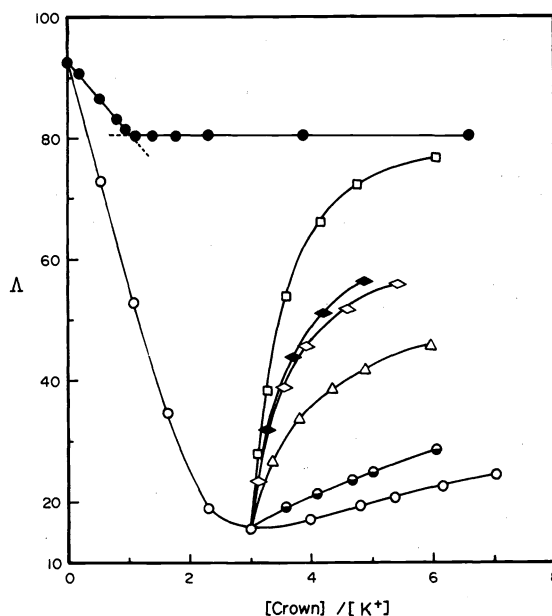

Fig. 2. Change in equivalent conductance of a 10^{-3} M solution of KBPh$_4$ in methyl ethyl ketone at 25°C in the presence of P15C5. The following crown ethers were added at the minimum conductance of the solution: □ dicyclohexyl-18-crown-6; ◆ B18C6; ◇ (B15C5) COOCH$_2$CH$_2$OCH$_2$CH$_2$OOC (B15C5); △ dibenzo-18-crown-6; ◓ B15C5; ○ P15C5 only; ● dicyclohexyl-18-crown-6 without P15C5.

(crown ether)/K$^+$ and B18C6/Na$^+$. Also not shown are 2:1 complexes found for B15C5/K$^+$ and B15C5/Rb$^+$.[40] The decrease in Λ for the polycrown ethers is, of course, much larger due to the low mobility of the polycation and the decrease in the fraction of free counterions contributing to the conductance. The actual value of Λ is a complicated function of the fraction, γ, of free counterions, the degree of cation binding, q, and polymer-solvent interactions. An expression relating Λ to these variables:

$$\Lambda = \gamma[\Lambda^- + A(\gamma q/\eta\alpha)] \qquad (17)$$

was developed by MacFarlane and Fuoss[75] for partially quaternized poly(vinylpyridine). In this equation, applied to our polymers (assuming all cations are bound), γ and q are defined as above, Λ^- is the equivalent conductance for the negative ion, η the solvent viscosity, α refers to Flory's expansion factor for polyelectrolytes and A is a constant for a given polymer. Not only does γ depend on the ratio of complexed crown to total crown but so does α. The polymer coil expands as more cations are bound to the polymer.

Since B18C6 strongly complexes to K$^+$ and Na$^+$ one expects a break in the conductance plot for P18C6/K$^+$ and P18C6/Na$^+$ at a crown to salt ratio of unity. Instead, a minimum is observed for P18C6/K$^+$ at a crown to salt ratio of three and even higher for Na$^+$. This implies a dependence of the complex formation constants on the fraction of complexed crown units in a chain, a conclusion supported by extraction data. A more detailed study is required to establish more exactly the correlation between the binding constants of cations to P18C6 and the degree of cation binding. Note that the minimum conductance reflects the composition of the complex more closely when the B18C6 moieties are spaced farther apart such as in P18C6 (20%).

The increase in Λ at higher crown to salt ratios results from a lower positive charge density on the polymer coil. This causes γ to increase and it lowers α. For the same reason, the overall drop in Λ for P18C6 (20%) and P18C6 (5%) is less than for the homopolymer. The γ for the 5% copolymer is probably close to unity. Its Λ value above a crown to salt ratio larger than unity approaches 46 (the slight decrease at higher ratios is caused by increased viscosity of the solution). This compares with a Λ^- value of 42 for BPh$_4^-$ at 10^{-3} M (obtained from measurements on triisoamylbutylammonium tetraphenylboron by assuming that $\Lambda^- = \Lambda^+$ at 10^{-3} M). The difference represents the mobility of the polycation, which for this polymer must be very small since only a few cations are bound to a chain of approximately 400 units above crown to cation ratios of four.

Formation of 2:1 crown–cation complexes is evident with P18C6/Cs$^+$ (Fig. 1) and P15C5/K$^+$ (Fig. 2). The minimum conductance is close to two, especially if experiments are carried out at a salt concentration of about 5×10^{-3} M (the condition $K_f[M^+] \gg 1$ may not be fulfilled at 10^{-3} M).

A simple method to determine qualitatively the cation binding efficiency of a series of crown ethers is depicted in Fig. 2. A mixture of P15C5 and KBPh$_4$ in acetone or methyl ethyl ketone is prepared with a crown to salt ratio such that the conductance of the solution is at its minimum. When a low molecular weight crown ether such as B18C6 is added it competes with P15C5 for the K$^+$. If the cation is transferred to B18C6 the equivalent conductance will increase due to a higher cation mobility

and the increase in the fraction of non-bound counterions. The rate of increase as a function of the crown to salt ratio depends on the cation binding strength of the crown ether relative to that of the polymer. Notice that the Λ with dicyclohexyl-18-crown-6 rapidly approaches the Λ value of its 1:1 complex with KBPh$_4$ in the absence of polymer. Neglecting small differences in mobilities of the respective cation-crown complexes one finds that the order in the ability to bind K$^+$ ions is dicyclohexyl-18-crown-6 > B18C6 $\approx$ bis-(crown ether) (–CH$_2$CH$_2$OCH$_2$CH$_2$–) > dibenzo-18-crown-6 > B15C5.

VISCOSITY OF POLY(CROWN ETHER)-SALT SOLUTIONS

We shall only briefly discuss some of the viscosity data obtained with poly(crown ethers). The addition of complexable cations to a solution of poly(vinylbenzo crown ether) converts the neutral polymer into a polyelectrolyte, with the reduced viscosity versus dilution plot showing the characteristic behavior of polyelectrolytes. For example, the reduced viscosity of a mixture of P18C6 and CsCl (crown to cation ratio equal to 2) in THF/CH$_3$OH increases to more than 3.0 on dilution while the neutral polymer itself has an $[\eta]_0$ of only 0.2.[40] For many systems maxima are found in plots of reduced viscosity versus the salt to crown ratio at constant polymer concentration. The higher charge density as more cations become bound to the polymer rapidly expands the polymer coil, but this is eventually counterbalanced by the increase in the fraction of bound counterions.

When 2:1 complexes are formed (e.g. P15C5/K; P18C6/Cs) the two crown moieties may be on the same or on different chains. The probability of intermolecular complex formation (and, therefore, a high viscosity) is expected to increase as the crown moieties are spaced farther apart. Plots of reduced viscosity versus polymer concentration for different copolymers of P18C6 and P15C5 in the presence of Na, K and Cs salts of tetraphenylboron are depicted in Fig. 3. Nearly normal viscosity plots are observed in systems where 1:1 complexes are formed, e.g. P18C6 (5%)/K$^+$, P15C5 (2%)/Na$^+$ and other such combinations. Similar plots are found for KBPh$_4$ and P15C5 and its copolymers down to a crown content of 20%, implying that the 2:1 complexes in these polymers are intramolecular in nature. However, a very strong enhancement in the viscosity is found with KBPh$_4$ for the 5% copolymer of styrene and vinylbenzo-15-crown-5. The solution becomes extremely viscous, and it is obvious that considerable crosslinking by K$^+$ ions takes place. For the same weight of polymer the increase is less with the 2% crown copolymer as the number of possible crosslinking sites has decreased. A similar behavior is found for copolymers of P18C6 with Cs$^+$.

SOLUTE BINDING AND POLYMER CATALYSIS IN AQUEOUS SOLUTIONS OF P18C6

Macroheterocycles such as crown ethers are noted for their effective chelation of cations. However, we recently found that P18C6 in water (in which it is quite soluble and probably highly coiled, see above) strongly interacts with neutral and anionic organic solutes.[76] This binding was first observed in aqueous solutions of picrate salts. Addition of P18C6 ($\approx 2 \times 10^{-3}$ M) to a 2×10^{-4} M solution of sodium or potassium picrate induces a bathochromic shift in the absorption maximum of the picrate anion from 354 nm to 380 nm. The latter spectrum is identical to that of a free picrate anion or of that of a solvent separated
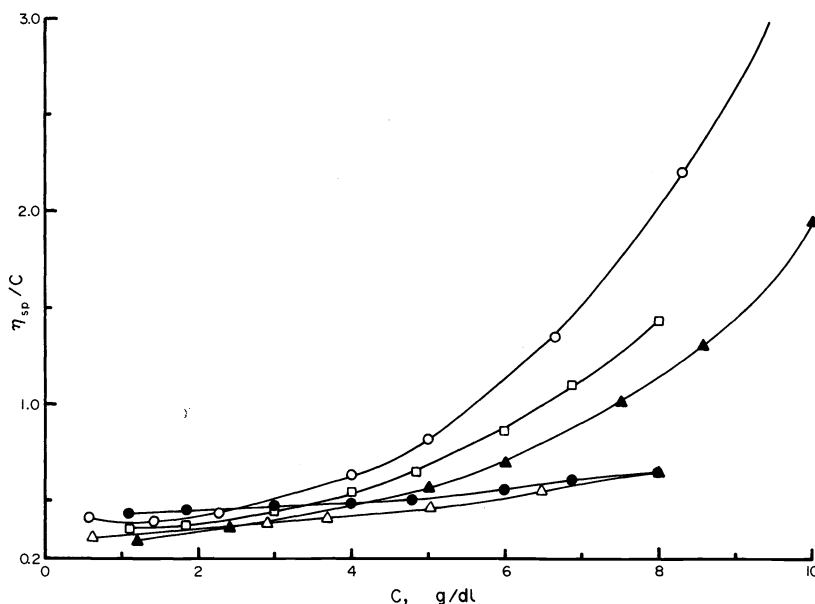
Fig. 3. Plots of reduced viscosity vs polymer concentration in methyl ethyl ketone at 25°C for the following systems: ○ P15C5/KBPh₄; □ P18C6 (5%)/CsBPh₄; ▲ P15C5 (2%)/KBPh₄; ● P18C6 (5%)/KBPh₄; △ P15C5 (2%)/NaBPh₄. The salt concentration is the same for all systems at each polymer concentration, and adjusted such that for the 2% copolymer the crown to salt ratio is 2:1, and for the 5% copolymer 5:1.

picrate ion pair in a solvent such as THF. The shift is apparently the result of a loss of water around the picrate anion as it becomes hydrophobically bonded to P18C6. This type of bonding of organic solutes in water has been reported for several natural and synthetic polymers such as poly(vinylpyrrolidone),[77–79] bovine serum albumin,[80,81] crosslinked polylysine[82] and chemically modified polymers with hydrophobic side chains.[83,84]

Following the approach outlined by Klotz[80] we obtained for the system sodium picrate—P18C6 in water a straight line plot from the rearranged Langmuir isotherm. The first order binding constant, K, was found to be $3000\,M^{-1}$, or $K = 8.6 \times 10^5$ when calculated on the basis of $10^5\,g$ of polymer (a unit frequently used in the literature). Equilibrium dialysis measurements show that binding of picrate to poly(vinylpyrrolidone) is much less than to P18C6. Binding of methyl orange to P18C6 is comparable to that of picrate. This means that our polycrown ether is considerably more effective in binding this dye than is bovine serum albumin,[85] and comparable or better than most of the chemically modified synthetic polymers.[83,84]

An interesting difference between P18C6 and other polymers concerns the effect of added electrolyte on the binding of anionic solutes. Although binding of K^+ to P18C6 in water is considerably less than of the picrate anion (potentiometric measurements yield a K of about $35\,M^{-1}$ for KCl), addition of a sufficient amount of a KCl significantly increases the degree of picrate binding. Figure 4 shows that addition of $10^{-2}\,M$ of KCl to a solution containing $5 \times 10^{-4}\,M$ P18C6 and $1 \times 10^{-4}\,M$ of KPi enhances the fraction of bound picrate from 0.45 to more than 0.80. The increase is nearly proportional to the increase in the fraction of K^+ ions bound to P18C6. At $10^{-2}\,M$ KCl nearly half of the crown moieties are complexed to a K^+ ion, which may be the maximum number of cations that can be bound to P18C6 in water (see earlier discussion). As expected, salts of organic anions such as KBPh₄ show the reverse effect. The BPh₄⁻

ion easily replaces the picrate anion, and the 354 nm peak of Pi⁻ in water reappears.

Many other solutes such as p-nitrophenol, p-nitrophenolate, phenolphtaleine and chrysophenine are adsorbed to P18C6. In many instances dissociation equilibria are affected. A $5.10^{-5}\,M$ solution of sodium p-nitrophenolate contains approximately equal fractions of the phenolate anion and the non-dissociated p-nitrophenol ($K_a = 8 \times 10^{-8}\,M^{-1}$). On addition of a small amount of P18C6 the 400 nm absorption maximum of the anion nearly completely disappears, while the 318 nm band of the phenol is increased. The same is found for phenolphtaleine, where the purple color of the anion in a solution of pH = 11.3 completely disappears on addition of P18C6, although the pH remains nearly the same. Studies are being carried out to determine whether the shift in equilibrium is caused by preferential binding of the undissociated form.

The observed dehydration of anions by P18C6 can be applied in an interesting way by studying the decomposition of 6-nitrobenzisoxazole-3-carboxylate anion in water. The rate of decarboxylation of this anion according to:
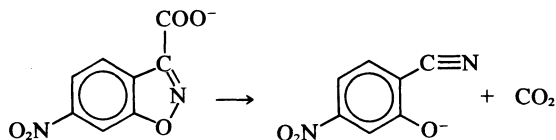
is known to be very slow in water but accelerated in aprotic solvents such as benzene, acetonitrile, acetone, DMSO and HMPA.[86] We have found that the decarboxylation is significantly accelerated by addition of P18C6, as shown in Table 4. At a 50:1 crown to carboxylate ratio the first order rate constant is comparable to that found in benzene (with tetramethylguanidine as base).[86] The carboxylate apparently is dehydrated on binding to P18C6, causing the decomposition to accelerate. The
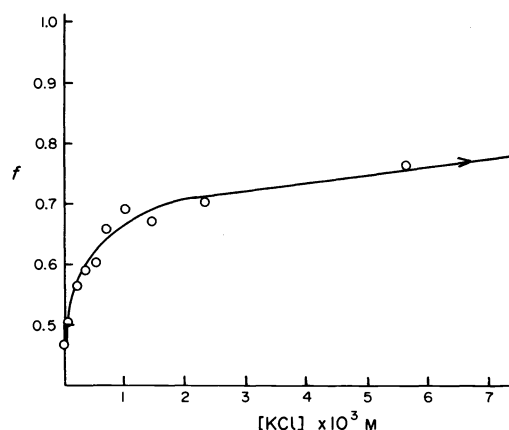
Fig. 4. Plot of fraction, f, of total amount of picrate bound to P18C6 as a function of potassium chloride concentration.

Table 4. Decomposition of 6-nitrobenzisoxazole-3-carboxylate in water in the presence of poly(vinylbenzo-18-crown-6); Concentration of carboxylate 2×10^{-4} M; $T =$ 25°C

Ratio of crown to carboxylate	Ratio of salt to carboxylate	$k \times 10^5 \text{ sec}^{-1}$
2		11
2	10:1 NaCl	16
2	10:1 KCl	45
5		45
20		111
50		198

binding is considerably weaker than found for picrate, since the rate constant continues to go up even at concentrations of 5×10^{-2} M P18C6. Note also the effect of added electrolyte. A significant rate enhancement is found on addition of KCl, due to the conversion of the neutral polycrown ether into a polycation. Sodium chloride is less effective, as binding of Na^+ to P18C6 is not as strong as for K^+. The behavior of P18C6 in some respects resembles the micellar catalysis of this decarboxylation reaction with cationic soaps,[87] although in the latter case electrostatic effects play a much more important role. Other reactions are presently being investigated, including the catalytic behavior of copolymers of P18C6.

INTERACTIONS OF P18C6 WITH POLYNUCLEOTIDES AND ITS INHIBITORY EFFECT ON REVERSE TRANSCRIPTASE ACTIVITY

Poly(vinylbenzo-18-crown-6) has been found to exert a remarkable inhibitory effect on reverse transcriptase activity, both of the virions of murine leukemia and of E. coli polymerase I.[88] The reaction studied in considerable detail concerns the polyriboadenylate templated elongation of oligodeoxythymidine using a suspension of murine leukemia virions. Other components added to the mixture were sodium and manganese chloride, trihydroxymethylmethylamine hydrochloride, dithiothreitol, detergent Triton X-100 and deoxyribothymidinetriphosphate as the substrate.

In a solution containing polynucleotides one may expect interactions between this poly anion and a polymer such as P18C6 when crown complexable cations are present. Indeed, mixtures of poly(rA) and P18C6 in the

presence of potassium chloride form precipitates. Complete precipitation occurs when the mixture has a composition of two crown units per polynucleotide phosphate and at 0.2 M KCl. The results can be rationalized in terms of complex formation between poly cations and poly anions. Since the binding constant of KCl to P18C6 in water is approximately 35 M^{-1}, the fraction of crown moieties complexed to a K^+ ion should approach 0.9. It is plausible that the lowest solubility of the complex is attained when positive and negative charges on the two polymers balance. The stoichiometry of two crown units per phosphate residue implies, therefore, that only one-half of the crown units contain a K^+, a conclusion which is supported by findings reported earlier in this paper.

At KCl concentrations of 2 M and higher, the precipitate redissolves. Apparently, at these high salt concentrations more K^+ ions can be complexed to P18C6, and the complex becomes positively charged, thereby increasing its solubility. No precipitation is found with monobenzo-18-crown-6, while divalent cations such as Mn^{2+} and Mg^{2+} only precipitate poly (rA), leaving the P18C6 in solution. This is not surprising since the latter two cations are only weakly bound to P18C6.

The mechanism of inhibition of nucleic acid polymerases by P18C6 was studied by systematically varying the concentrations of the different components in the reaction mixture. Changing the NaCl concentrations enhances inhibition, while increasing the amount of poly(rA) causes the inhibition to start at higher P18C6 concentrations. Reversal of inhibition occurs when additional poly-(rA) is added to a poly(crown ether) inhibited reaction after 15 min. of reaction time. Addition of K^+ (not an activator in the enzymatic reaction) does not affect the reaction in the presence of P18C6.

The combined studies suggest that the inhibition by P18C6 is not caused by binding of enzyme, Na^+, K^+ or Mn^{2+} to this polymer, but that the poly(crown ether) interacts with poly(rA), thereby rendering the polynucleotide template unavailable for the enzymatic reaction. The inhibition, also found for synthetic polymers such as poly(9-vinyladenine), compares favorably with that exerted by polynucleotides.

There is no direct spectral evidence for an interaction between P18C6 and poly(rA) in the absence of salt. However, the interaction which probably is largely hydrophobic in nature can be indirectly demonstrated by passing P18C6 through a column of Sepharose beads to which poly(rA) is attached. The poly(crown ether) is strongly adsorbed on these beads, even in the absence of added electrolyte, while adsorption to Sepharose beads only is negligibly small.

REFERENCES

[1](a) C. J. Pedersen, J. Am. Chem. Soc. **89**, 7017 (1967). (b) C. J. Pedersen, J. Am. Chem. Soc. **92**, 391 (1970).
[2]C. J. Pedersen and H. K. Frensdorff, Angew. Chem. Int. **11**, 16 (1972).

[3]C. J. Pedersen, *J. Org. Chem.* **36**, 254 (1971).

[4]J. R. Dann, P. P. Chiesa and J. W. Gates, *J. Org. Chem.* **26**, 1991 (1961).

[5]J. C. Lockhart, A. C. Robson, M. E. Thompson, S. D. Furtado, C. K. Kaura and A. R. Allan, *J. Chem. Soc. Perkin I*, 577 (1973).

[6](a)J. S. Bradshaw, J. Y. Hui, B. L. Haymore, J. J. Christensen and R. M. Izatt, *J. Heterocyclic Chem.* **10**, 1 (1973). (b) J. S. Bradshaw, J. Y. Hui, Y. Chan, B. L. Haymore, R. M. Izatt and J. J. Christensen, *J. Heterocyclic Chem.* **11**, 45 (1974).

[7]D. St. C. Black and I. A. McLean, *Tetrahedron Lett.* 3961 (1969).

[8]F. Vogtle and M. Zuber, *Tetrahedron Lett.* 727 (1972).

[9]M. Newcomb, G. W. Gokel and D. J. Cram, *J. Am. Chem. Soc.* **96**, 6810 (1974).

[10](a) B. Dietrich, J. M. Lehn and J. P. Sauvage, *Tetrahedron Lett.* 2885 (1969). (b) B. Dietrich, J. M. Lehn and J. P. Sauvage, *J. Chem. Soc. Chem. Comm.* 1055 (1970).

[11]B. Dietrich, J. M. Lehn and J. P. Sauvage, *J. Chem. Soc. Chem.* **15**, (1973).

[12]J. M. Lehn, J. Simon and J. Wagner, *Angew. Chem. Int.* **12**, 579 (1973).

[13]J. M. Lehn and J. Simon, *Angew Chem. Int.* **13**, 406 (1974).

[14]J. M. Lehn, *Structure and Bonding* **16**, 1 (1973).

[15]R. C. Helgeson, J. M. Timko and D. J. Cram, *J. Am.* **95**, 3023 (1973).

[16]M. Newcomb and D. J. Cram, *J. Am. Chem. Soc.* **97**, 1257 (1975).

[17]D. J. Cram and J. M. Cram, *Science* **103**, 183 (1973).

[18]R. C. Helgeson, K. Koga, J. M. Timko and D. J. Cram, *J. Am. Chem. Soc.* **95**, 3021 (1973).

[19]J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel and D. J. Cram, *J. Am. Chem. Soc.* **96**, 7097 (1974).

[20]L. R. Sousa, D. H. Hoffman, L. Kaplan and D. J. Cram, *J. Am. Chem. Soc.* **96**, 7100 (1974).

[21]G. Dotsevi, Y. Sogah and D. J. Cram, *J. Am. Chem. Soc.* **97**, 1259 (1975).

[22]J. J. Christensen, J. O. Hill and R. M. Izatt, *Science* **174**, 459 (1971).

[23]G. W. Gokel and D. J. Cram, *J. Chem. Soc. Chem. Comm.* 481 (1973).

[24]E. L. Cussler and D. F. Evans, *Separation Purification Methods* **3**, 399 (1974).

[25]C. F. Reusch and E. L. Cussler, *Am. Inst. Chem. Eng. J.* **19**, 736 (1973).

[26]K. H. Wong, K. Yagi and J. Smid, *J. Membrane Biol.* **18**, 379 (1974).

[27]S. C. A. McLaughlin, G. Szabo, S. Ciani and G. Eisenman, *J. Membrane Biol.* **9**, 3 (1972).

[28](a)G. Eisenman, S. M. Ciani and G. Szabo, *Fed. Proc.* **27**, 1289 (1968). (b) D. C. Tosteson, *Fed. Proc.* **27**, 1269 (1968). (c) H. Lardy, *Fed. Proc.* **27**, 1278 (1968).

[29]G. A. Rechnitz and E. Eyal, *Ana Chem.* **44**, 370 (1972).

[30]O. Ryba and J. Petránek, *Electroanal. Chem. Interfac. Electrochem.* **44**, 423 (1973).

[31]D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.* **94**, 4024 (1972).

[32]C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.* **96**, 2250 (1974).

[33]H. D. Durst, J. W. Zubrick and G. R. Kieczykowski, *Tetrahedron Lett.* 1777 (1974).

[34]L. M. Thomassen, T. Ellingsen and J. Ugelstad, *Acta Chem. Scand.* **25**, 3024 (1971).

[35](a)S. Boileau, B. Kaempf, J. M. Lehn and F. Schué, *J. Polymer Sci.* **B12**, 203 (1974). (b) P. Hemery, S. Boileau, P. Sigwalt and B. Kaempf, *J. Polymer Sci.* **B13**, 49 (1975).

[36]M. Maskornick, *Tetrahedron Lett.* 1797 (1972).

[37]J. N. Roitman and D. J. Cram, *J. Am. Chem. Soc.* **93**, 2231 (1971).

[38]J. W. Zubrick, B. I. Dunbar and H. Dupont Durst, *Tetrahedron Lett.* 71 (1975).

[39]M. Makosza and M. Ludwikow, *Angew Chem. Int.* **13**, 665 (1974).

[40]S. Kopolow, T. E. Hogen Esch and J. Smid, *Macromolecules* **6**, 133 (1973).

[41]J. Steinhardt and J. A. Reynolds, *Multiple Equilibria in Proteins.* Academic Press, New York (1969).

[42]K. H. Wong, G. Konizer and J. Smid, *J. Am. Chem. Soc.* **92**, 666 (1970).

[43]U. Takaki, T. E. Hogen Esch and J. Smid, *J. Am. Chem. Soc.* **93**, 6760 (1971).

[44]J. Smid, *Angew. Chem. Int.* **11**, 112 (1972).

[45]P. B. Chock, *Proc. Nat. Acad. Sci., U.S.A.* **69**, 1939 (1972).

[46]A. T. Tsatsas, R. W. Stearns and W. M. Risen, *J. Am. Chem. Soc.* **94**, 5247 (1972).

[47]E. Shchori, J. Jagur-Grodzinski and M. Shporer, *J. Am. Chem. Soc.* **95**, 3842 (1973).

[48]A. M. Grotens, J. Smid and E. de Boer, *Chem. Comm.* 760 (1971).

[49]M. T. Watts, M. L. Lu and M. P. Eastman, *J. Phys. Chem.* **77**, 625 (1973).

[50]E. Shchori and J. Jagur Grodzinski, *Isr. J. Chem.* **11**, 243 (1973).

[51]D. F. Evans, S. L. Wellington, J. A. Nadis and E. L. Cussler, *J. Sol. Chem.* **1**, 499 (1972).

[52]T. E. Hogen Esch and J. Smid, *J. Phys. Chem.* **79**, 233 (1975).

[53]H. K. Frensdorff, *J. Am. Chem. Soc.* **93**, 600 (1971).

[54]H. K. Frensdorff, *J. Am. Chem. Soc.* **93**, 4684 (1971).

[55]R. M. Izatt, D. P. Nelson, J. H. Rytting, B. L. Haymore and J. J. Christensen, *J. Am. Chem. Soc.* **93**, 1619 (1971).

[56]E. M. Arnett and T. C. Moriarity, *J. Am. Chem. Soc.* **93**, 4908 (1971).

[57]C. Kappenstein, *Bull. Soc. Chim.* 89 (1974).

[58]J. J. Christensen, D. J. Eatough and R. M. Izatt, *Chem. Rev.* **74**, 35 (1974).

[59]K. H. Wong, M. Bourgoin and J. Smid, *Chem. Comm.* 715 (1974).

[60]M. Bourgoin, K. H. Wong, J. Y. Hui and J. Smid, *J. Am. Chem. Soc.* **97**, 3462 (1975).

[61]P. R. Mallinson and M. R. Truter, *J. Chem. Soc. Perkin II*, 1818 (1972).

[62]V. Prelog, *J. Chem. Soc.* 420 (1950).

[63]M. Shinohara, J. Smid and M. Szwarc, *Chem. Comm.* 1232 (1969).

[64]M. Shinohara, Ph.D. Thesis, State University of New York, Syracuse, New York (1969).

[65]Ting-Po I and E. Grunwald, *J. Am. Chem. Soc.* **96**, 2879 (1974).

[66]U. Takaki and J. Smid, *J. Am. Chem. Soc.* **96**, 2588 (1974).

[67]T. E. Hogen Esch and J. Smid, *J. Am. Chem. Soc.* **94**, 9240 (1972).

[68]J. Harwood, Private communication.

[69]B. El Haj and J. Smid, To be published.

[70]C. G. Krespan, *J. Org. Chem.* **39**, 2351 (1974).

[71]W. M. Feigenbaum and R. H. Michel, *J. Polymer Sci.* A1, **9**, 817 (1971).

[72]S. Kopolow, Z. Machacek, U. Takaki and J. Smid, *J. Macromol. Sci.* A7, 1015 (1973).

[73]D. F. Evans, S. L. Wellington, J. A. Nadis and E. L. Cussler, *J. Solution Chem.* **1**, 499 (1972).

[74]E. Shchori and J. Jagur Grodzinski, *Isr. J. Chem.* **11**, 243 (1973).

[75]R. MacFarlane, Jr. and R. M. Fuoss, *J. Polymer Sci.* **28**, 403 (1957).

[76]J. Smid, S. Shah, L. Wong and J. Hurley, *J. Am. Chem. Soc.* **97**, 5932 (1975).

[77]P. Molyneux and H. P. Frank, *J. Am. Chem. Soc.* **83**, 3169 (1961).

[78]M. L. Fishman and F. R. Eirich, *J. Phys. Chem.* **75**, 3135 (1971).

[79]P. Bandyopadhyay and F. Rodriguez, *Polymer* **13**, 119 (1972).

[80]I. M. Klotz, F. M. Walker and R. B. Pivan, *J. Am. Chem. Soc.* **68**, 1486 (1946).

[81]T. Takagishi, K. Takami and N. Kuroki, *J. Polymer Sci., Polymer Chem.* **12**, 191 (1974).

[82]I. M. Klotz and J. U. Harris, *Biochemistry* **10**, 923 (1971).

[83]I. M. Klotz and A. R. Sloniewsky, *Biochem. Biophys. Res. Comm.* **31**, 3 (1968).

[84]T. Takagishi, Y. Nakata and N. Kuroki, *J. Polymer Sci. Polymer Chem.* **12**, 807 (1974).

[85]I. M. Klotz and K. Shikama, *Arch. Biochem. Biophys.* **123**, 551 (1968).

[86]D. S. Kemp and K. Paul, *J. Am. Chem. Soc.* **92**, 2553 (1970).

[87]C. A. Bunton, M. Minch and L. Sepulveda, *J. Phys. Chem.* **75**, 2706 (1971).

[88]J. Pitha and J. Smid, *Biochim. Biophys. Res. Comm.*, **31**, 3 (1968).