REVIEW

CROWN ETHERS IN ANALYTICAL CHEMISTRY

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Crown ethers can selectively form complexes with alkali and alkaline earth metal ions, and sometimes other cations by ion-dipole interaction. Taking advantage of the cation binding selectivity, they have been widely used in analytical chemistry in the separation and the analyses of metal ions. In this review, general features of crown ethers and their analytical applications are described.

The discovery of a crown ether was quite fortuitous. In 1967, Pedersen recognized a minute quantity of white crystals as a by-product in the process of condensation of catechol and dichloroethyl ether, attempted with the synthesis of the compound [1] in mind, and confirmed it to be macrocyclic polyether [2].

[1]

[2]

He found out that the compound [2] forms stable complexes with alkali and alkaline earth metal salts and that these complexes can be dissolved in nonpolar organic solvents. This discovery led to the synthesis of a series of macrocyclic polyethers, which were designated "crown" ethers from their stereochemical configurations. The number of crown ether type compounds synthesized has become very large and their application spheres have reached out to every field of chemistry. The utilization of activated anion (naked anion), based on the prominent feature of crown ethers that make inorganic salts soluble in organic solvents, has brought about great developments in the field of organic chemistry; in the realm of analytical chemistry, developments in practical applications including analytical separation of alkali and alkaline earth metal ions, spectrophotometry and analyses based on use of ion selective electrodes where such crown ethers are utilized are outstanding.

In this review, general features of crown ethers will be described and examples of our recent studies based on their analytical applications will be cited.

ION SELECTIVITY OF CROWN ETHERS

The complex stability of crown ethers with metal ions is mainly governed by the following factors: i) relative sizes of metal ions and cavity of crown ethers, ii) type, number and placement of hetero atoms at their binding sites in the crown ring, iii) conformational flexibility of the ring, iv) electrical charge of metal ions, and v) ion-solvent interaction.

Pedersen examined the complex stability of various crown ethers which he himself had synthesized by way of solvent extraction. He interpreted the ion selectivity of crown ethers in terms of factor i). Thus 14-crown-4 derivatives showed selectivity to Li^+ , 15-crown-5 derivatives to Na^+ , and 18-crown-6 derivatives to K^+ . Of course, the ion selectivity of crown ethers is subjected to the effect of all factors i) - v), integrated, but the adaptability of the metal ion to the cavity is no doubt a particularly important factor. Crown ethers normally form 1 : 1 complexes with metal ions, but sometimes form 2 : 1 (ring/ion) complexes with the metal ions which are a little larger than the cavity; sometimes two metal ions are known to be incorporated into a single cavity. A crown ether called poly- or bis(crown ether) has been synthesized with an eye to the formation of 2 : 1 complexes. In such a crown ether, stable 2 : 1 (ring/ion) complexes are formed with the metal ions which are larger than the cavity by cooperative action of the two adjacent crown ether units, thereby developing higher selectivity to the metal ions than the corresponding monocyclic crown ethers¹⁾⁻³⁾. For example, poly- and bis(15-crown-5) show selectivity to K^+ among alkali metal ions, and their 18-crown-6 derivatives to Cs^+ , the former's K^+ selectivity being particularly prominent.

The stability constant for the complexation of crown ethers with metal ions may be considered a measure of ion selectivity. Dependence of the stability constant on solvents is very large.

CROWN ETHERS AS A SOLVENT EXTRACTANT⁴⁾ AND CHROMOGENIC REAGENT

Ion pair extraction

When making quantitative analysis by extraction of alkali and alkaline earth metals, picric acid is often used as the anion paired to such metal ions. This is because metal ions are readily subjected to ion pair extraction to organic layer with the picric acid ion and also because it enables the colorimetric determination of metal ions at high efficiency, since it shows a strong absorption band in the visible region. As an example, the colorimetric determination of Na^+ in blood serum based on the use of Na^+ selective cryptand [2.1.1] has been carried out⁵⁾. In this method, K^+ ions in amounts up to 350 times as much as Na^+ do not interfere with the determination of Na^+ ; so the K^+ coexisting in blood serum is not troublesome. Polyvalent metal ions can be masked by addition of EDTA. As the paired anion for used in ion pair extraction, fluorescent organic anions are also utilized. For example, fluorescent determination has been conducted by subjecting K^+ in blood serum to the ion pair extraction with 18-crown-6, using tetrabromofluorescein (Eosine)⁶⁾. The working curve gives a straight line at 0.01 - 1 ppm K^+ concentration, suggesting that the determination may be made by this method at substantially higher sensitivity than by the conventional methods of K^+ determination.

When any metal element is contained in a paired anion as complexed ion, this method may be utilized in order to analyze such a metal ion. In this regard, Yoshio et al.⁷⁾ have achieved favorable results with cobalt-thiocyanate and copper-zincon complexes.

Crown ethers having chromophoric functional groups

The colorimetry of metal ions with crown ethers having a chromophore, namely crown ether dyes, is very interesting⁸⁾. Results for the benzo crown ether having a picrylamino group show that, when the metal ion is taken into its cavity, the picrylamino group undergoes proton dissociation; as a result, an intramolecular ion pair is formed, which is readily extracted into the organic layer⁹⁾. Further, with the dissociation of the picrylamino group, the absorption spectrum of the chromophore undergoes a red shift, thus permitting colorimetric determination. When making solvent extraction in chloroform-water system, a high concentration of amine must be added for promotion of dissociation to counter the high pKa (=10.6) of the picrylamino group. For this reason, some efforts were exerted for decreasing pKa by introducing a bromo group or a nitro group into 5'-position of the benzo crown ether. While spectral overlap between the crown ether dye and its complex presented a problem, an attempt has been made to expand the red shift in the spectrum when making the proton dissociation with picrylamino group¹⁰⁾ by replacing one of the nitro groups by a cyano group or a trifluoromethyl group. In the absorption spectrum in the presence of various alkali metal salts in a chloroform-pyridine solution of the dye of crowned dinitrophenyl azophenol, a notable red shift is recognized only in the presence of Li^+ salt. This is considered due to the strong interaction between the oxygen atom of phenol and Li^+ which occurs when forming the complex¹¹⁾.

On the other hand, Ueno et al.¹²⁾ have synthesized N-(2-hydroxy-5-nitrobenzyl)-aza-15-crown-5 as a Li^+ selective chromogenic reagent. This has a structure with an acid dissociative group introduced in such a way that the anion center is brought to the position where it can interact with the Li^+ taken into the crown ether. Thus as the complex is formed, the phenolate oxygen forms a chelate ring with the Li^+ taken into the crown ring.

The crown ethers having uncharged, coordinating, and flexible side chains, which are considered as an intermediate type between the chelate type and the ion pair type of picrylamino benzo crown ether, are Na^+ selective and applicable for the determination of Na^+ in blood serum¹³⁾¹⁴⁾. Further, the compounds (a) - (b) shown in Fig. 1 are Ca^{2+} selective, and the compound (c) is Ba^{2+} selective. The compound (d)

a) $m=1, n=2, X = -\text{NO}_2$

b) $m=2, n=2, X = -\text{NO}_2$

c) $m=3, n=3, X = -\text{NO}_2$

d) $m=2, n=2, X = -\text{N}=\text{N}-\text{C}_6\text{H}_3(\text{NO}_2)_2$

provides a colorimetric reagent with high sensitivity to Ca^{2+} ($\epsilon=80,000$)¹⁵⁾. Fig. 1 Crown ether-based extraction photo-metric reagents for Ca^{2+} and Ba^{2+} .

Introduction of fluorescent groups as a proton-dissociable chromogenic group will give fluorometric reagents, which facilitate the extraction-fluorometry with high sensitivity of alkali and alkaline earth metals. The compounds formed by introducing 4-methyl umbelliferone into aza-crown ethers show a maximum of emission spectrum at 440 nm. Fluorometric determination of Li^+ , K^+ and Ca^{2+} is practicable by utilizing these compounds¹⁶⁾.

CROWN ETHERS AS ION CARRIERS IN ION SELECTIVE ELECTRODES

The function of liquid membrane type electrodes using a neutral carrier may be interpreted as some sort of ion transport phenomenon by the ionophore. For ions to be transferred effectively, the following three processes must be balanced in action: i) complexation of the ionophore and the metal ion, ii) dissolution and diffusion into organic liquid film of the ionophore metal ion complex, and iii) release of the metal ion from the complex.

As for i), the complexing ability of the ionophore must be strong and selective. In order to rapidly perform the process of ii), appropriate lipophilicity must be conferred on the ionophore molecule. As the molecular volume increases, the lipophilicity will augment, but to have smooth diffusion, the ionophore molecule should not be too large. Then for the purpose of rapidly liberating the metal ion as defined in iii), the decomplexation rate must be fast.

With natural occurring ionophores, K^+ or NH_4^+ selective electrodes using valinomycin or nonactin derivatives are known. The ion selectivity of the K^+ electrode using valinomycin is excellent and interference with it from Na^+ is very little, with $K_{\text{KNa}}^{\text{Pot}}$ being 10^{-3} - 10^{-4} . This electrode is sensitive to Rb^+ so much that it is usable as a Rb^+ selective electrode; but this is regarded as a disadvantage. Since Rb^+ only rarely coexists in the actual sample, this raises no serious problem. Most of K^+ selective electrodes presently commercialized are the valinomycin type electrodes.

Crown ethers are also used as neutral carriers, and performances of the liquid film type, PVC film type and coated wire type electrodes have been examined. The K^+ selectivity of the electrodes using various monocyclic crown ethers is mostly on the order of 10^{-2} . Even dibenzo-30-crown-10 derivatives which manifest a conformation analogous to that of valinomycin when forming a complex with K^+ gave relatively high K^+ selectivity as $K_{\text{KNa}}^{\text{Pot}} = 2.2 \times 10^{-3}$, but this is no match for the valinomycin's. Generally, the ion selectivity of monocyclic crown ethers is not appreciably high and their electrodes seem to be naturally limited in ion selectivity. However, the ion selectivity in the complex formation of naphtho-15-crown-5 is not appreciably high, but in the K^+ selective electrode using this crown as a neutral carrier, some evidence that $K_{\text{KNa}}^{\text{Pot}}$ decreases with increasing concentration of the crown ether in the liquid film is reported¹⁷⁾. The bis(crown ether)s shown in Fig. 2 show better ion selectivity than the corresponding monocyclic crown ethers, and the K^+ - or Cs^+ -PVC film electrodes using A(n=1) or A(n=2) in Fig. 2 also exhibit excellent ion selectivity¹⁸⁾¹⁹⁾. Particularly, the K^+ selective electrode using B(n=2) in Fig. 2 as a neutral carrier²⁰⁾ shows remarkable selectivity, $K_{\text{KNa}}^{\text{Pot}} = 2 \times 10^{-4}$, which is comparable to that of the valinomycin electrode, and in the former electrode, the interference from Rb^+ which is apparent in the latter electrode

Fig. 2 Examples of bis(crown ether) derivatives.

is found to be relatively slight. A(n=1) in Fig. 2 forms similarly a stable complex with Tl^+ as with K^+ , and therefore, is usable as a Tl^+ selective electrode²¹⁾. B(n=1) in Fig. 2 is bis(crown ether) designed as a carrier for a Na^+ selective electrode, which forms with Na^+ a stable intramolecular 2 : 1 (ring/ion) complex²²⁾. This Na^+ selective electrode giving the ion selectivity, $K_{\text{KNa}}^{\text{Pot}} = 9 \times 10^{-3}$, is a little inferior to conventional glass electrodes, but does not require periodic conditioning which is indispensable with glass electrodes, and is excellent in responsiveness and stability in potential and durability.

We have recently developed²³⁾²⁴⁾ new neutral carriers which show good selectivity to Li^+ and Ca^{2+} . Their structural formulae and selectivities are depicted in Fig. 3.

CROWN ETHERS IN LIQUID CHROMATOGRAPHY

Utilization of crown ethers as a component of the mobile phase of liquid chromatography has been examined. As the crown ether is added to the mobile phase in reverse phase chromatography of aromatic amines, amino acids and amides, the separation behavior is greatly altered, depending on the complex stability with ammonium ions²⁵⁾. In the case of the amides which make no strong interaction with the crown ether, it exerts almost no influence on the chromatogram. In view of the fact that the crown ether has a stronger interaction with a primary ammonium ion than a secondary one, the chromatographic separation of primary and secondary amines is possible by making use of the mobile phase containing the crown ether²⁶⁾.

As a packing material for liquid chromatography, insoluble resins including crown ethers and cryptands have been synthesized²⁷⁾. Then in order to obtain fundamental knowledge on the separation behavior in liquid chromatography using these resins, metal ion adsorbability of the crown ether resins in batch system was examined. The results show that the ion adsorbability of the crown ether resins is largely influenced not only by the type of metal ions, but by paired anions or solvents as well. As a general tendency, the resins of 15-crown-5 and 18-crown-6 derivatives strongly adsorb K^+ , among alkali metal ions, and the 24-crown-8 resin takes in Cs^+ , and the 21-crown-7 resin favors Rb^+ . All resins prefer Ba^{2+} among alkaline earth metal ions. Although the effect of paired anions on metal ion adsorbability differs somewhat, depending on the crown ether resins used, generally, the metal ion tends to be readily adsorbed, if accompanied by a paired anion with

Fig. 3 Potentiometric selectivity coefficients $\log k_{\text{LiM}}^{\text{Pot}}$ and $\log k_{\text{CaM}}^{\text{Pot}}$ for PVC-NPOE membranes containing lipophilic crown ethers 1), 2) and 3).

high polarizability [polarizability of anions F^- (0.81), Cl^- (2.98), Br^- (4.24), and I^- (6.45), $\times 10^{-24} \text{ cm}^3$]. The effect of solvents is especially large: substitution of methanol with water results in a sharp drop in adsorbability of the resins.

A stationary phase of silica-gel for high performance liquid chromatography which was chemically modified with poly(crown ether) was synthesized; with it, liquid chromatography of metal ions was studied²⁸⁾. These crown ether resins were obtained by first introducing vinyl group into silica-gel with 3 - 10 μm particle diameter by chemical bonding, and thereafter, copolymerizing it with the corresponding crown ether monomer. The crown ether resins show high adsorbability to alkali and alkaline earth metal ions and K^+ or Rb^+ which is readily adsorbed is not eluted out of column when pure methanol is used as the mobile phase. In this chromatographic system, generally favorable separation can be achieved by using water with a small amount of methanol added as the mobile phase. The metal ion retention time in poly(12-crown-4) modified silica is longer in the order of $\text{Li}^+ < \text{Cs}^+ < \text{Rb}^+ < \text{K}^+ < \text{Na}^+$, and in poly(15-crown-5) modified silica in the order of $\text{Li}^+ < \text{Na}^+ < \text{Cs}^+ < \text{Rb}^+ < \text{K}^+$. In poly(18-crown-6) modified silica, the elution order of salts is $\text{Li}^+ < \text{Na}^+ < \text{Rb}^+ < \text{K}^+ < \text{Cs}^+$. Such a separation behavior well reflects the stability of each poly(crown ether)-cation

complex. For the separation of alkaline earth metal ions, in all crown ether modified silica, the retention time is longer in the order of $\text{Mg}^{2+} < \text{Ca}^{2+} < \text{Sr}^{2+} < \text{Ba}^{2+}$. On the other hand, a stationary phase of chemically bonded silica-gel with benzo-15-crown-5 was synthesized by Blasius²⁹⁾. Its chromatographic behavior resembles that of poly(15-crown-5) modified silica, but no notable separation between K^+ and Rb^+ is recognized.

Using an ODS column (20% carbon, 6x100 mm), we executed a dynamic coating of the crown ether such as dodecyl-18-crown-6 which has high lipophilicity. As an example, the separation profile (mobile phase, $\text{H}_2\text{O}/\text{MeOH} = 50/50$) of the alkali metal salts using a column coated with 59 mg of the crown ether is shown in Fig. 4³⁰⁾.

Utilizing the resin immobilized such an optically active crown ether as binaphtho crown ether, chromatographic resolution of amino acids may be made³¹⁾.

Fig. 4 Chromatographic separation of alkali metal iodides on dodecyl-18-crown-6 coated ODS-silica.

MEMBRANE SEPARATION USING CROWN ETHERS

Transport reverse to the concentration gradient (active transport) of alkali or alkaline earth metals utilizing potentials inside and outside the membrane is essential in biological system.

In the liquid membrane transport using monensin, the active transport of alkali metals is conducted by causing a structure change and utilizing the proton concentration difference. For concentrating (desalting) of salt by such transport, utilization of acid-base, oxidation-reduction or light energy may be contemplated to provide the potential difference inside and outside the membrane. In monensin, the conformational change of cyclic-noncyclic structure in conjugation with formation and cleavage in response to pH of hydrogen bonding between terminal hydroxyl group and carboxyl group takes place. If both sides of the liquid film containing monensin are water phases containing 0.1M NaOH and 0.1M NaCl + 0.1M HCl, when taking Na^+ in the acidic side from the basic side, it functions as a cyclic ionophore. Active transport of Na^+ is performed by liberating the ion from inside the membrane and restoring it to a noncyclic form³²⁾.

The system devised by Shinkai³³⁾ takes advantage of photochemically induced cis $\rightleftharpoons$ trans isomerization. Thus it has in its cis form the ability to form a sandwich-shaped complex because the crown rings approach each other.

We have synthesized the crown ether polymer shown in Fig. 5, which was derived from an alternate copolymer of ethylene and maleic anhydride and hydroxymethyl crown ether. We conducted active transport of Na^+ , K^+ and Cs^+ using a membrane formed by mixing it with polyvinyl alcohol. In performing the transport experiment, pH was adjusted using tris(hydroxymethyl)aminomethane - hydrochloric acid buffer solution

Fig. 5 Crown ether polymer derived from poly(ethylene-co-maleic anhydride).

on the basic side and phosphoric acid - triethanolamine buffer solution on the acidic side in a glass cell partitioned at its center with a membrane. This membrane (containing 12-crown-4) functioned like an active transport system and showed the selectivity to alkali metal ions³⁴⁾ shown in Fig. 6.

Fig. 6 Proton-driven transport of alkali metal ions through a membrane formed from 12-crown-4 polymer. $[M^+]_t / [M^+]_0$ refer to metal ion concentration at times $t = t$ and 0.

CONCLUSION

In analytical chemistry, incessant studies are being pursued in search of highly sensitive method along with high selectivity.

The crown ethers discussed in this review are the complexing reagents dependent on the relationship between the cavity size and the relative size of metal ions, which has never been contemplated with usual chelate reagents. Accordingly, taking account of the type, number and placement of hetero atoms inside the crown rings and also their interaction with solvent molecules, innumerable combinations are

feasible, so that emergence of new organic reagents which provide for high selectivities to specific ions is probable. I am looking forward to further developments in this field.

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