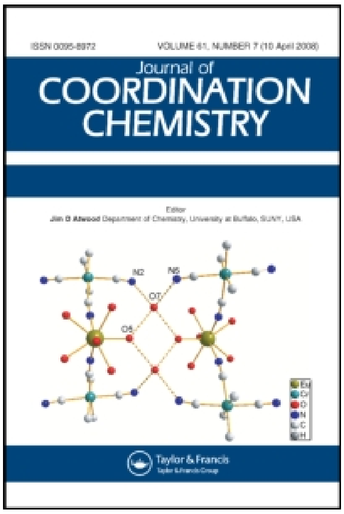

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ANALYTICAL APPLICATION OF FUNCTIONALIZED CROWN ETHER - METAL COMPLEXES

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ANALYTICAL APPLICATION OF FUNCTIONALIZED CROWN ETHER - METAL COMPLEXES

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We have presented the introduction of functional groups such a lipophilic substituents, non-ionic ligating sites, acid-dissociable groups, chromophores, chiral centers, into skeleton of crown ether, and their immobilization through incorporation into polymer matrix in order to modify crown ethers to versatile analytical reagents in chromatography, ion-selective electrode, colorimetry, etc. After a brief summary of recent syntheses of functionalized crown ethers, their applications in analytical chemistry are discussed with emphasis on the behavior of metal-complex formation.

1. INTRODUCTION

Since the discovery of the macrocyclic polyethers known as crown ethers,[1] numerous papers have appeared dealing with various aspects of this class of compounds. However, applications in analytical chemistry are still rather limited in spite of the peculiar affinity of crown ethers for a certain class of metal ions and ammonium ions. Several reviews have been made concerning applications of crown ethers for analytical purposes.[2–6] Crown ethers which carry simply a crown ether function may preclude wider applications because of their limited mode of complexation. In addition, the rather low stability of the complexes may not meet various practical needs. Functionalization of crown ethers is expected to eliminate these restrictions and to provide ample applications in analytical chemistry and related fields. In this review, recent progress in the syntheses of functionalized crown ethers and their applications in chromatography, ion-selective electrode and colorimetry have been discussed.

2. FUNCTIONALIZED CROWN ETHERS

The method of deriving functionalized crown ethers is generally classified into the following seven categories.

a) Introduction of alkyl or lipophilic substituents:

A substituent is introduced through a carbon or nitrogen atom in the crown ether skeleton. Lipophilic crown ethers can be used as a neutral carrier for ion selective electrodes, extractants of alkali and alkaline earth metal ions in ion-pair extraction study, etc.

b) Introduction of non-ionic extra ligating sites:

Extra ligating sites will make the resulting complex more stable. Ion selectivity may also be changed. Bis- and oligocrown ethers are peculiar because the crown ethers themselves constitute "extra" ligating sites.

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c) Introduction of anionic sites such as carboxylic acid and phenol:

Crown ehters with pendent anionic sites interact with cations to form neutral or anionic complexes. These can be used both in aqueous solution and in ordinary solvent extraction as well as in ion transport study through a liquid membrane.

d) Introduction of chromophores:

This may be partially covered under the preceding categories . Chromogenic crown ethers can be used for a colorimetric or fluorimetric determination of alkali and alkaline earth metals.

e) Giving chiral centers on crown ether:

Chiral crown ethers recognize chiral guests such as amino acids. They may be applied to the separation of enantiomers.

f) Immobilization of crown ether through incorporation into polymer matrix.

Immobilized crown ethers can be used as a stationary phase in ion chromatography and as an immobilized phase transfer catalyst in organic synthesis.

To introduce functional groups, either a substitution reaction is carried out on a crown ether or a synthesis from a substituted starting material (*e.g.*, substituted diols) is used to construct an intended crown ether skeleton. Crown ethers thus obtained are conveniently classified into the following three types according to their structural features.

Type 1) Aromatic nucleus-substituted benzocrown ethers and related crown ethers.

Type 2) N-substituted aza- or diaza-crown ethers (monocyclic cryptands).

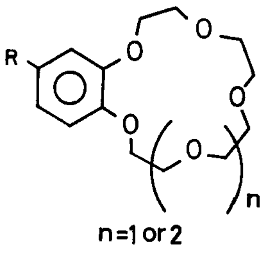
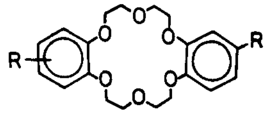
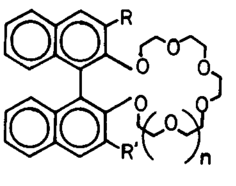
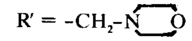
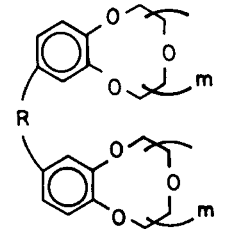
Type 3) Crown ethers with substituents directly bound to the carbon atoms of a crown ether skeleton.

The introduction of functional groups on the aromatic ring of crown ethers is readily accomplished, since substituted catechols are commercially available and the substitution reaction on benzocrown ethers is usually quite straightforward. Most crown ethers of Type 1 are prepared in this manner. For example, 4'-formylbenzo-15-crown-5 and -18-crown-6(**2**; n=1,2) were synthesized from 4-formylcatechol,[7] while 4'-hydroxymethyl-, 4'-hydroxycarbonyl, 4'-nitro-, and 4'-amino-benzo-crown ethers were synthesized via a substitution reaction on benzo-crown ethers.[7-10] Some other functional groups were also introduced on benzo- (or dibenzo-) crown ethers (**6–15**) and binaphtho-crown ethers (**16–18**). These are summarized in Table I.

A large number of useful crown ethers have been derived by further reaction on these functionalized crown ethers. Polymeric benzo-crown ethers were prepared from **6**[20] or from acrylamido derivative of **5**.[21] Colorimetric reagents were also synthesized from **5**[22-25] or **2**.[25] Usually, these substituents on the aromatic nuclei do not play any ligating role on the crown ether-bound cation because of steric restriction, but are supposed to exert some electronic effect on the ethereal oxygen atoms adjacent to the aromatic ring.[7]

Bis-crown ethers **19–22** in which the two benzo-crown enter moieties are bound together through a flexible aliphatic chain can interact with a cation forming a sandwich-like complex, resulting in high metal selectivity and complex formation ability.[18,19] In a similar manner, a functional group which is connected through a long flexible chain can reach the cation trapped on a crown ether.[26] When anionic

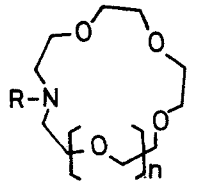
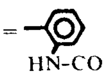
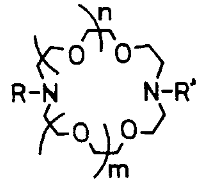
Table I
Functionalized Benzo-crown Ethers

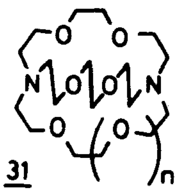
Structure		Reference
	**1** R = $-CH_2OH$	11
	2 $-CHO$	7, 8
	3 $-COOH$	7
	4 $-NO_2$, -Br, -I	7
	5 $-NH_2$	7
	6 $-CH{=}CH_2$	12, 13
	7 $-(CH_2)_3-OH$	14
	8 $-OH$	15
	9 $-COCH_3$	9
	10 $-CHOHCH_3$	9
	11 $-(CH_2)_2-NH_2$	10
	**12** R = $-CHO$	8
	13 $-COCH_3$	9
	14 $-NO_2$	16
	15 $-NH_2$	16
	**16** R, R' = $-CH_2OH$	17
	17 R, R' = $-CH_2OCH_2COOH$	17
	18 R = $-CH_2OCH_2COOH$	17
	R' = $-CH_2-$N O	
	**19** R = $-(OCH_2CH_2)_n-O-$	18
	20 $-O-(CH_2)_6-O-$	18
	21 $-CO-(O-CH_2CH_2)_2-OCO-$	18
	22 $-CH_2-(OCH_2CH_2)_n-OCH_2-$	19

ligating side arms are arranged in a sterically suitable disposition, the crown ether is a particularly favorable complexing agent for alkali and alkaline earth metal ions as exemplified by carboxylic derivatives **17** and **18**, which respectively form quite stable complexes with Sr^{2+} and Ba^{2+}.[17] These complexes do not decompose even in the presence of sulfate ion, which forms "insoluble" salts with alkaline earth metals under ordinary conditions.

N-Substituted azacrown ethers or Type 2 crown ethers are synthesized by the alkylation or acylation of corresponding azacrown ethers, or by the cyclization of N-substituted diethanolamines. Several of them are summarized in Table II. Gokel et al. synthesized azacrown ethers which have extra-polyoxyethylenes, and reported an enhanced complexability.[28,29] An ultimate form of this series of crown ethers may be cryptands (**31**) (*i.e.,* a bicyclic crown ether), which are known as the strongest neutral complexing agents for alkali and alkaline earth metal ions. In contrast to the complicated synthetic procedure involved in cryptands, these N-substituted compounds are easy to prepare.

TABLE II
N-Substituted Azacrown Ethers

Structure		Reference
	**23** R = $-CH_2PO_3H_2$	27
	24 $-(CH_2CH_2)_m$-OMe	28, 29
	25 R, R' =  HN-$COCH_2CH_2COOH$	30
	**26** R = $-COC_{11}H_{23}$ R' = $-CH_2COOH$	31
	27 R, R' = $-CH_2PO_3H_2$	27
	28 R, R' = $-CH_2COOH$	27, 32, 33
	29 $-CH(CH_3)COOH$	32
	30 $-(CH_2)_2COOH$	34



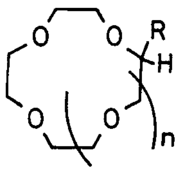
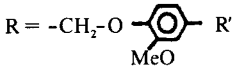
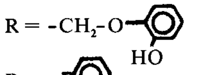
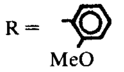
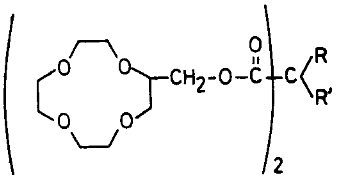
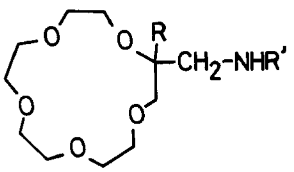
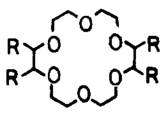
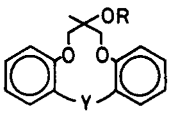
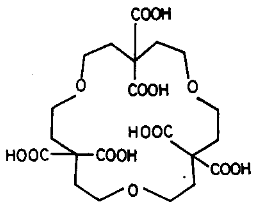
31

It is also possible to introduce anionic groups such as carboxylates, phosphonates, phenolate on the nitrogen atom of the N-substituted azacrown ethers (*e.g.*, **23–30**). Aminocarboxylic acid derivatives (**28–30**) are a kind of complexanes and are macrocyclic analogues of EDTA or EGTA. Their complexing behavior with transition and lanthanide metals revealed both characteristics of crown ether and complexane.[32–34]

There is no known synthetic reaction for direct substitution of hydrogen on the crown ether skeletal carbon. Therefore, in order to obtain crown ethers of Type 3 one has to use substituted or functionalized oligoethyleneglycol derivatives. In spite of this difficulty in the synthesis, many C-substituted crown ethers have been synthesized.[35–57] They are summarized in Table III. Among those compounds, **32** ($R=CH_2OH$) are useful precursors for derivation to further the variety of crown ethers by using the hydroxymethyl side arm as a derivation site. The hydroxy oxygen does not seem to interact with the crown ether-bound metal and thus does not contribute to enhance the stability of complexes.[35,37] Compound **32** was immobilized to polystyrene through this side arm.[39] **32** ($n=1$) was also converted to bis-crown ethers **38**, which were utilized as extractants and as neutral carriers for ion-selective electrodes.[56] Many crown ethers with a neutral polyethyleneglycol side arm were studied by Gokel et al.,[37,38,42,43,45] and have been named "lariat ether" because their structure visually resembles a lariat.

The introduction of carboxylic side arms to a crown ether ring was achieved by Bartsch et al.[52,53,57] Some of these compounds **46** were applied to the transport of cation through liquid membranes.[58,59] Tetracarboxylate **42** or **43** forms a stable complex with K^+, and the stability constant is 10^4 times greater than that of

TABLE III
Skeletal-C-substituted Crown Ethers

Structure		Reference
	**32** R = $-CH_2OH$, $n = 1$	35
	$n = 2$	36, 37, 38
	$n = 3$	36, 39
	$n = 4$	40, 41
	$n = 5$	40
	33 R = $-CH_2-O-C_mH_{2m+1}$ $n = 2$	35-39, 41-44
	34 R = $-CH_2-(OCH_2CH_2)_m-OR'$ $n = 2.3$	37, 38, 42, 43, 45
	35 	38, 46
	36 	47
	37 	46
	**38** R = $-CH_3$, R' = $-C_{12}H_{25}$	55
	**39** R, R' = H	48
	40 R = CH_3, R' = $-C_6H_{13}$	43
	41 R = H, R' = $-C_mH_{2m+1}$	49
	**42** R = $-COOH$	50, 51
	43 R = $-CONH\underset{\displaystyle COO^-}{CH}-CH_2-$(3-Indolyl)	50, 51
	44 R = $-CONH-CH_2COO^-$	50, 51
	**45** R = H, Y = $-(OCH_2CH_2)_nO-$	52, 53
	46 R = $-\underset{\displaystyle R'}{CH}COOH$, Y = $-(OCH_2CH_2)_nO-$	52, 53
	**47**	54

18-crown-6.[50,51] This compound has a possibility of being utilized as a potassium ion buffer reagent.

Tabushi et al. synthesized the hexacarboxylic acid derivative of crown ether **47**.[54] This compound was designed for extracting uranyl ion, but no details are yet available.

3. APPLICATION IN CHROMATOGRAPHY

The selective interaction of crown ethers with alkali or alkaline earth metal ions enables them to be applied in ion chromatography. From an operational point of view, there can be two types of approach to chromatography.

(a) Crown ethers used in a mobile phase.

A mobile phase (eluting solvent) contains crown ethers (Cr). The complex cations in solution form with appropriate anions (A^-) lipophilic ion pairs (M^+ Cr A^-), which are distributed to a lipophilic stationary phase (Figure 1-a).

(b) Crown ethers immobilized in a stationary phase.

A stationary phase is loaded with crown ethers (dynamically or covalently), which form complexes with cations in a mobile phase (Figure 1-b). Cations are thus distributed between a mobile phase and a stationary phase.

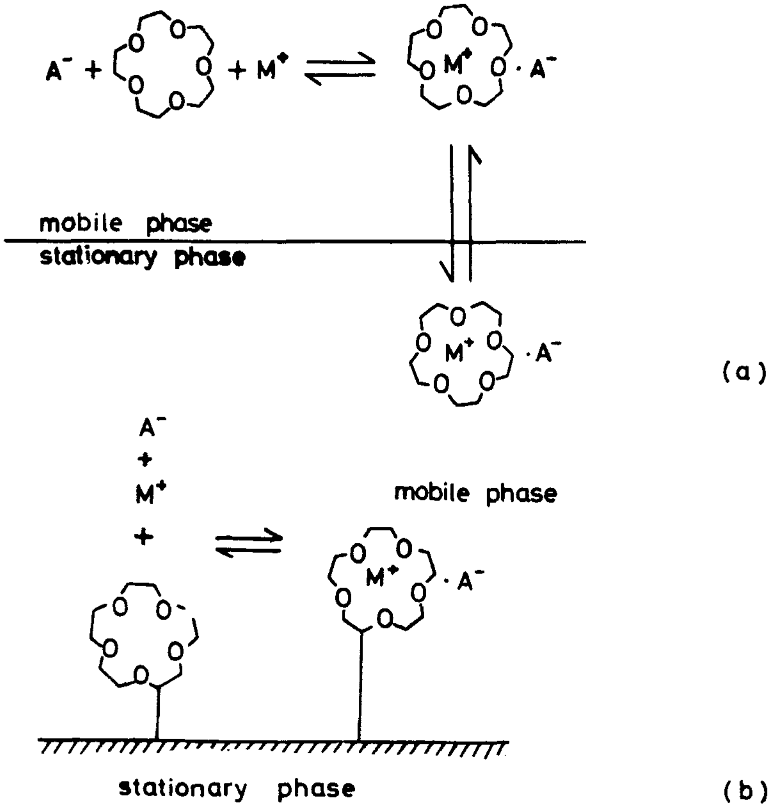
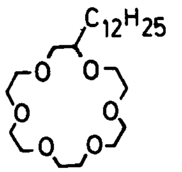


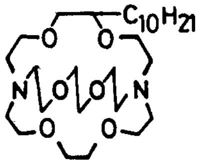
FIGURE 1 Separation scheme in ion chromatography.

Since a relatively large quantity of crown ether reagent, often quite expensive, is needed for type (a), not many papers have dealt with this approach. Cram et al. reported the separation of racemic amines with the use of an optically active crown ether.[60]

In approach type (b), the method or manner of crown ether immobilization is the first concern. Two methods are adopted to immobilize crown ethers into a stationary phase. i) Crown ether is bound on support material dynamically (*i.e.*, physically adsorbed). ii) Crown ether is bound on supports through a covalent bond. The former is easy to exercise since it is free from chemical manipulations on both crown ethers and stationary phase material. The latter has an advantage in a longer lifetime of the column along with higher reproducibility of analytical data.



48



49

3.1 Ion Chromatography on Dynamically-bound Crown Ethers

Shono et al. reported the chromatographic separation of alkai metal ions by using dynamically bound crown ethers.[61] Lipophilic crown ethers **48** or **49** were coated on ODS (octadecyl-silanized silica). Chromatography of alkali metal ions was carried out with methanol – water (50:50) as an eluent. The retention time was found to increase in the order of $Li^+ < Na^+ < Cs^+ < Rb^+ < K^+$ (Figure 2). This

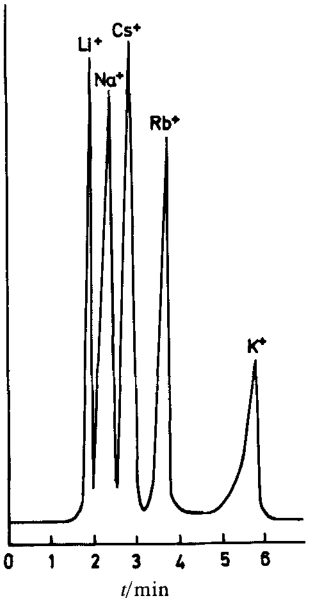
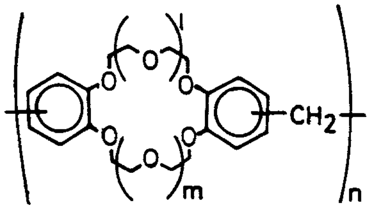


FIGURE 2 Chromatography of alkali metal iodides on **48**-coated ODS-silica. eluent: $MeOH-H_2O$ (1:1) (reference 61)

reflects the order of stability of the metal complexes with crown ethers. Retention time is also affected by the nature of counter anions. Thus, salts with lipophilic anions are retained longer. The problem in this chromatography is the desorption of crown ether, especially when a higher methanol content is used in the eluting solvent.



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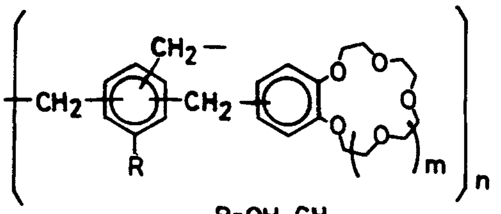


51

R=OH, CH_3

3.2 *Ion Chromatography on Covalently-bound Crown Ethers*

Blasius et al. synthesized crown ether polymers **50** by condensing dibenzo-crown ethers with formaldehyde.[62,63] Benzocrown ethers were also poly-condensed with formaldehyde in the presence of phenol, toluene, or xylene to achieve **51**. The polymer particles were packed in a chromatographic column and used for the ion chromatography of alkali, alkaline earth, and some transition metal salts.[64] Alkali metal thiocyanates were satisfactorily separated on the column of **50**(l=1, m=2) (Figure 3).[62]

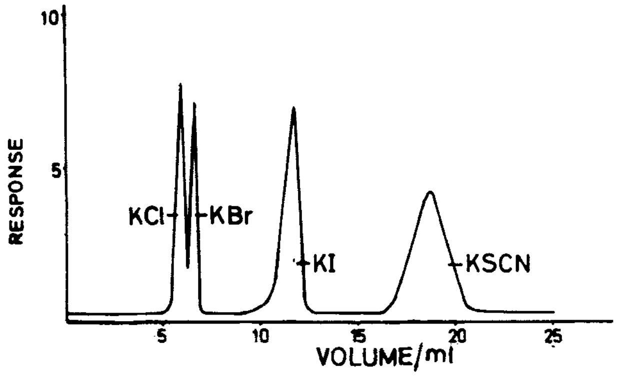
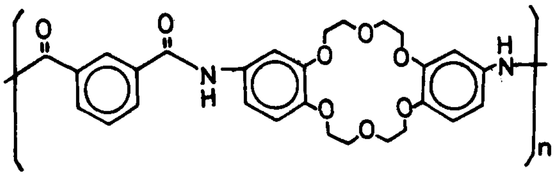


FIGURE 3 Chromatography of potassium salts on **50**(l=1, m=2). eluent: H_2) (reference 62)

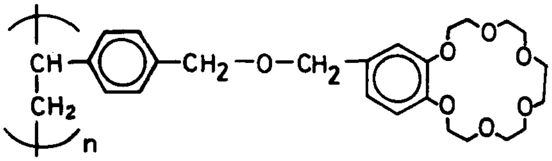
As expected, the stability of each metal complex involved is reflected in the retention behavior of the above-mentioned chromatographies. However, since these chromatographies are based on ion-pair formation in the stationary phase, the retention, *i.e.*, the separation, is strongly affected by the nature of counter anions. In accordance, when a mixture of salts with a common cation is analyzed, the anions are separated from each other as shown in Figure 3.[62] In this case, there is no difference in metal complex stabilities (single complex species involved), but there are differences in the extent of formation of ion-pairs in the mobile phase as well as in the stationary phase (ion-pair "extraction").

Schchori et al. synthesized polyamide type crown ether **52**.[65] Igawa et al. used this polymer for ion chromatography.[66] Sodium and potassium ions were separated through a column of **52**. A good separation of lithium from other alkali metal ions was attained when 10% methanol in water was used as eluent. However, the peaks of Na^+ and K^+ were broad because of their high distribution to the stationary phase.[67]

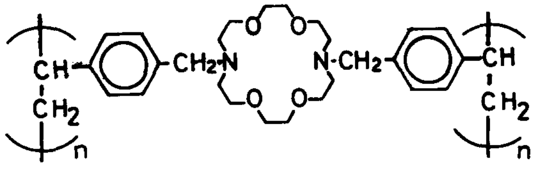


52

The immobilized crown ether is also prepared by introducing crown ethers into cross-linked polymer, *e.g.* styrene-divinylbenzene copolymer. Blasius et al. synthesized polymer supported crown ethers **53** and **54** by the reaction of chloromethylated polystyrene with 4'-hydroxymethylbenzocrown ethers and diazacrown ethers (cryptand-2,2).[62–64] Similarly, Cram et al. prepared polystyrene resin loaded with an optically active crown ether **55**.[68] They used the resin to separate racemic amines, and a good enantiomer separation was achieved (Figure 4).

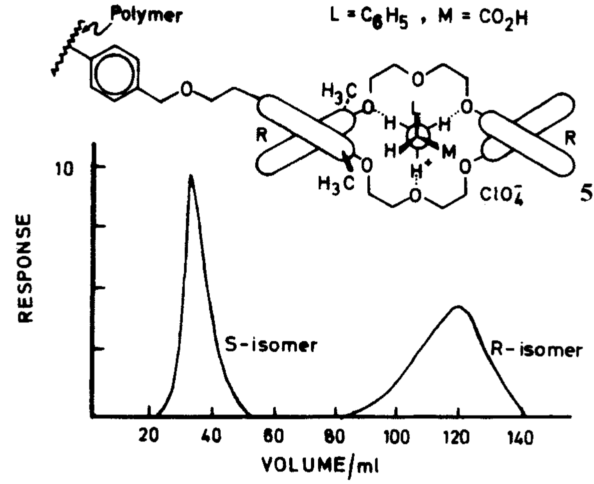


53



54

Because the resins mentioned above are physically soft, they are not suitable for high performance liquid chromatography (HPLC). Shono et al. used microparticulated silica for hard support durable under high operational pressure.

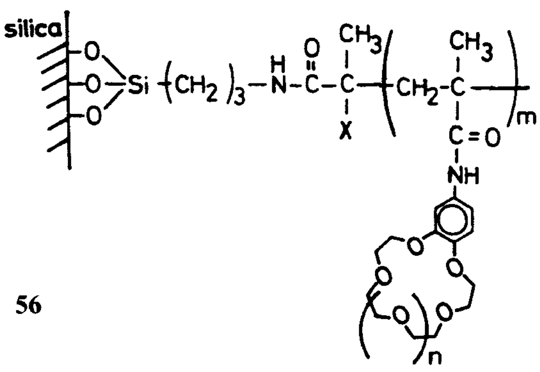


55

FIGURE 4 Chromatography of DL-phenylalanine on optically active carrier column

They synthesized an oligomer of benzo-15-crown-5, which was covalently bound to silica support to give **56** (n=1).[69] The "modified silica" was used in the HPLC separation of alkali metal salts. When water was used as an eluent, the separation of alkali metal chlorides or iodides was poor, probably because of the low distribution of these salts to the stationaly phase. The addition of an organic solvent such as methanol (10%) to the eluent improved separation. Obviously, lowering the dielectric constant of the eluent helped increase the formation of ion-pair (association of complex electrolytes). The retention time increased in the order of LiCl < NaCl < CsCl < RbCl < KCl, and this is in agreement with the interaction of metal ions with ordinary crown ethers.

When monomeric benzo-crown was attached to silica support, no retention of metal salts was observed.[69] This means that an interaction between the supported monomeric benzocrown ethers and metal ions is negligible. When dimeric or bis-crown ethers were introduced on silica (bis-crown ether **57** (n=1)), the separation of alkali metal chlorides was possible.[70] The separation behavior was almost the same as that of **56**. Thus, the presence of at least two adjoining crown ether functions is required for good chromatographic performance.



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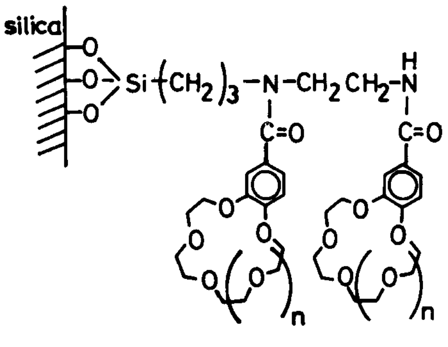

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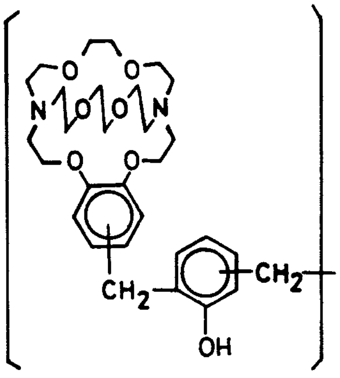
As with other immobilized crown ethers mentioned previously, the separation of alkali or alkaline earth metal salts is possible on the columns of modified silica **56** (n=1) and **57** (n=1).

The columns of 18-crown-6 derivatives **56** (n=2) and **57** (n=2), were also reported.[71] With this type of poly- or bis-crown ether- modified silica, the retention of alkali metal cations was found to increase in the order of $Li^+ < Na^+ < Rb^+ < K^+ < Cs^+$. It is thought that poly- or bis-crown ethers form a sandwich-type 2:1 (ligand to metal) complex with a relatively large alkali metal cation such as Cs^+. Thus, Cs^+ is most greatly retained among alkali metal ions. These are summarized in Table IV.

TABLE IV
Separation of Metal Salts by immobilized Crown Ether

Crown ether	Salts (in the order of elution)	Reference
50 (l = 1, m = 1)	$Y(NO_3)_2$, $Sr(NO_3)_2$	62
	$BaCl_2$, $RaCl_2$	62
	$CdCl_2$, $ZnCl_2$	62
	$CrCl_3$, $FeCl_3$	62
	$SrCl_2$, $EuCl_2$, $BaCl_2$	62
	LiSCN, NaSCN, KSCN	62
(l = 2, m = 1)	KCl, Kbr, KI, KSCN	62
(l = 1, 2, m = 1.2)	other salts	63, 64
51	NaCl, NaBr, NaI, NaSCN	62
	NH_4Cl, RbSCN	62
	$HgCl_2$, $CdCl_2$, $ZnCl_2$	63, 64
52	LiCl, NaCl, KCl	67
54	NaOH, KOH	62
58	LiCl, NaCl, KCl	62
	CsCl, RbCl, KCl	62
59	LiCl, NaCl, KCl	62
	CsCl, RbCl, KCl	62
60	$MgCl_2$, $CaCl_2$, $SrCl_2$, $BaCl_2$	63, 64
	$BaCl_2$, $RaCl_2$	63, 64
56(n = 1)	LiCl, NaCl, CsCl, RbCl, KCl	69
	LiI, NaI, CsI, RbI, KI	69
56 (n = 2)	LiCl, NaCl, RbCl, KCl, CsCl	70, 71
	LiBr, NaBr, RbBr, KBr, CsBr	70, 71
57 (n = 2)	LiCl, NaCl, RbCl, KCl, CsCl	70, 71
	NaCl, NaBr, NaI, NaSCN	70, 71
	$MgCl_2$, $SrCl_2$, $BaCl_2$	70, 71
	$CaCl_2$, LiCl, $SrCl_2$, $BaCl_2$, NaCl, CsCl	70, 71



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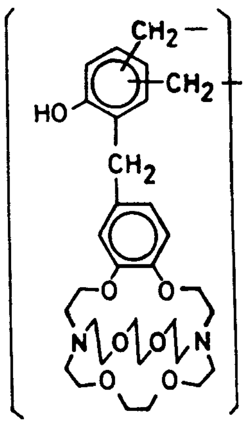

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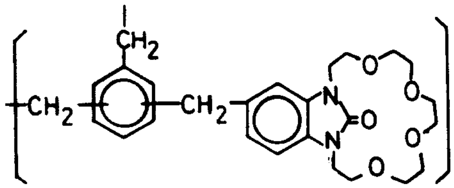

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4. APPLICATION IN ION-SELECTIVE ELECTRODE

Most of the so-called neutral carriers such as crown ethers, valinomycin and noncyclic polyethers are usable as ion-selective components (ion carriers) in liquid membrane electrodes. Numerous macrocyclic or acyclic carriers have been tested. There are two types of liquid membrane electrodes according to construction: a) a membrane which contains an ion carrier divides internal and external (sample) solutions. This is a standard membrane electrode construction, illustrated in Figure 5-a. b) Silver wire is coated with PVC (polyvinyl chloride) membrane, which contains an ion carrier (coated wire electrode, CWE, Figure 5-b).

The type (a) electrode contains an internal electrode Ag/AgCl, and therefore, an internal solution is a chloride salt of a target metal. A difference in electrochemical potential of target metal ions across the membrane appears as membrane potential.

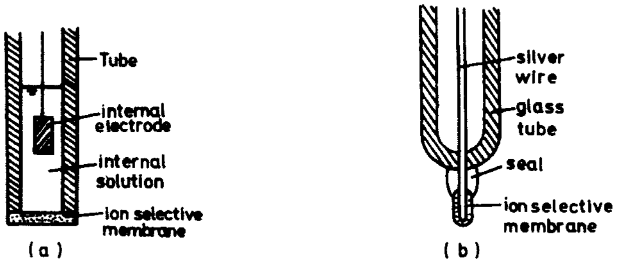


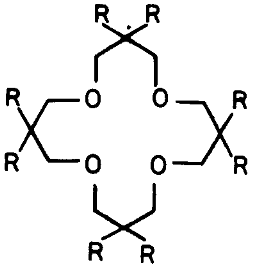
FIGURE 5 Construction of ion selective electrodes: (a) standard type; (b) coated wire electrode (CWE).

In type (b) electrodes, the mechanism of potential development between the silver wire and electrolyte solution can not be precisely described, but the ion-selective potential which develops at the membrane-electrolyte solution interface is somehow transduced to the potential on the metal wire. In each case, the membrane potential or electromotive force (EMF) is measured against a standard calomel electrode (SCE) or an Ag/AgCl electrode as reference.

4.1 Lithium-Selective Electrode

Lithium-selective electrodes based on crown ethers were reported by Aalmo et al.[72] They used an electrode system given below:

$$\mathrm{Hg/Hg_2Cl_2 : KCl \,\|\, sample\ solution \,|\, membrane \,|\, LiCl: AgCl/Ag} \tag{1}$$



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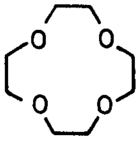

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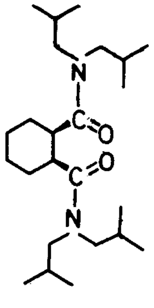
A 16-crown-4 derivative **61** (R=H or R=CH_3) was used in the membrane. They obtained a linear response over the activity range from 10^{-4} to 1 M Li^+ solution with a near Nernstian slope (59 mV potential change per ten times activity change of Li^+ ion, 25 °C).

Gadzekpo et al. studied a similar electrode system using 12-crown-4 (**62**) instead of 16-crown-4.[73] In both cases, selectivity towards the proton surpassed Li^+ so that the pH of the sample solution had to be adjusted above 5.[73] Furthermore, since selectivity to Li^+ is no more than 10 with respect to ammonium ion and other alkali metal ions, somewhat interference from NH_4^+ or Na^+ could not be avoided.

Imato et al. has shown that an addition of organophosphorus compound to the membrane enhanced the Li^+ selectivity of dibenzo-14-crown-4 - PVC membrane electrode.[74] From a practical point of view, electrodes based on crown ethers are still inferior to those based on noncyclic amides such as **63**, for which an Li^+ selectivity factor as high as 100 is described against Na^+ or NH_4^+.[75] However, quite recently, Kimura and coworkers reported a 16-crown-4 type neutral carrier **64** (R=CH_3) which gave a Li^+ selectivity over 100 against Na^+.[76]



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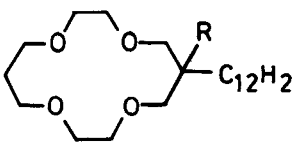

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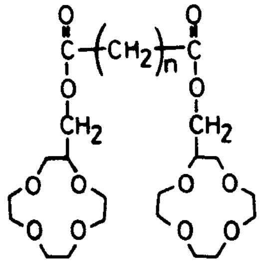
4.2 Sodium-Selective Electrode

Shono et al. showed that bis(12-crown-4) derivatives are suitable neutral carriers for Na^+-selective PVC membrane electrode.[77] The compounds they used are bis(12-crown-4) derivatives **65** and **38**. The performance of the electrodes is, as with other liquid membrane electrodes, affected by the PVC plastisizer. Usually *o*-nitrophenyl octyl ether gives the best results.[77] When this membrane was applied to the type (a) electrode in Figure 5-a, good sodium selectivity was observed with a nearly ideal Nernstian response.



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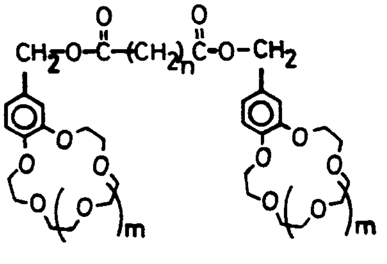
Shono et al. also studied CWE, Ag/AgCl: KCl|Sample solution|PVC membrane| Ag, with the same carriers **5** and **38**.[78] The electrodes are easy to construct and inexpensive, but their performance is comparable to electrodes of standard construction. The CWE based on crown ether **38** was successfully applied to the determination of Na^+ in human urine and serum. The lifetime of the electrode was quite long. No deterioration was indicated even after 300 measurements.[56] The selectivity factor and response slope did not change during this period.

4.3 Potassium-Selective Electrode

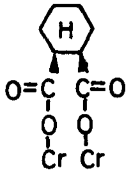
Bis(15-crown-5)s are useful for K^+-selective membrane electrodes. Wong et al. synthesized bis(benzo-15-crown-5) (**22**)[19] and applied this to PVC membrane electrode (Figure 5-a type).[11] The selectivity and response to K^+ varied with the length of the linking polyoxyethylene chain. The electrode using **22** (m=3, n=0) showed a near Nernstian response in the range of 10^{-5} - 0.1 M K^+, and a good selectivity, 4000 times over Na^+, was indicated. The selectivity to K^+ may be explained by the formation of a stable 2:1 (crown ether: metal) sandwich-type complex.

Shono et al. studied diester type bis(benzo-15-crown-5)s (**66**) (n=1,3,5,7).[79] The electrode performance is influenced by the plastisizer in the PVC membrane, and *o*-nitrophenyl octyl ether (NPOE) gave a better response (a near Nernstian slope and rapid response time) than diphenyl phthalate. For the electrode based on **66** (n=5) (NPOE-PVC), the selectivity of K^+ over Na^+ was close to that of valinomycin system.[80]

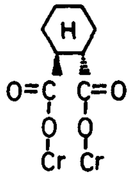


66 m = 1
68 m = 2

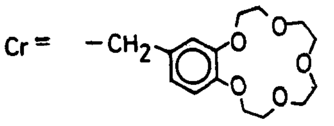
66 ($n=5$) was also applied to CWE, which was used for the determination of K^+ in practical samples.[56] However, due to the slow dissolution of the carrier from the membrane, the response slope and ion selectivity gradually decreased. More lipophilic bis-crown ether **67** was thus tested.[81] The coated wire electrode based on **67**-cis was similar to **66**($n=5$) in response and selectivity, but was superior in stability and lifetime. The geometry of the bis-crown ether is quite important; **67**-trans or 1,4-cis type of **67** gave a poor electrode performance.



67 -cis



67 - trans

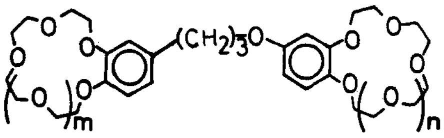


4.4 *Miscellaneous*

The bis-crown ethers of larger ring size (*e.g.*, **68**(n=3,5, or 7)) are carriers for cations of larger ionic size than K^+. Shono et al. constructed a Cs^+-selective electrode by using **68** (n=3,5, or 7).[82] Ikeda et al. synthesized unsymmetrical bis-crown ethers **69**, and the membrane electrode using **69** ($m=1$, $n=2$) was found to be selective to Rb^+.[83] The behavior of larger ring size bis(crown ether) **69**($m=2$, $n=2$) was almost the same as **68**(n=3,5, or 7) in Cs^+ selectivity.[83]

A thallium-selective PVC membrane electrode was reported in which **66**(n=3,5 or 7) was used in a similar manner to K^+ electrode.[84]

Ion selectivity coefficients of the PVC membrane electrodes are listed in Table V.



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5. APPLICATION IN COLORIMETRY

Ion-selective chromogenic (colorimetric, photometric) reagents have long been known and have been of practical importance since as early as 1940 for most of the metal ions. However, attempts to develop alkali metal selective reagents remained unsuccessful until the late 1970s. The discovery of crown ethers in 1967[1] opened a way to develop alkali metal- as well as alkaline earth metal-selective chromogenic reagents.[6]

Strategy in designing alkali or alkaline earth metal selective colorimetric reagents are, in principle, not much different from those used to develop traditional chromogenic chelating agents such as PAR (pyridylazoresorcinol). However, the stability of crown ether-metal complexes is extremely low in aqueous solutions, and this posed a problem in designing crown ether reagents for colorimetry in aqueous solutions. Extraction photometry or photometry in non-aqueous media was therefore adopted as an alternative. For extracting alkali and alkaline earth metal ions, crown ether dyes carrying respectively one and two, dissociable protons were synthesized by a method similar to those discussed previously in section 1.

TABLEV
Ion Selectivity Coefficients of PVS Membrane Electrode

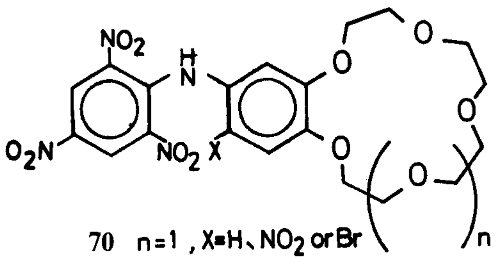
Carrier	Plastisizer[a]	H^+	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	NH_4^+	Ref.
61 (R=H)	TEHP	4.7	1	0.1	0.02	0.014	0.013	1.7×10^{-3}	1.4×10^{-3}	1.2×10^{-3}	1.2×10^{-3}	0.34	72
61 (R=CH_3)	TEHP	3.5	1	0.99	0.029	0.015	0.014	3.5×10^{-3}	9.5×10^{-3}	9.5×10^{-3}	1.6×10^{-3}	0.32	72
63	*o*-NPOE	4	1	0.01	0.01	0.003	0.01	10^{-3}	10^{-3}	10^{-3}	10^{-3}	10^{-3}	75
62	TINTM	2.2	1	0.12	0.66	—	0.15	1.6×10^{-4}	3.1×10^{-4}	—	9.5×10^{-7}	0.09	73
dibenzo-14-crown-4	TOPO	—	1	0.027	0.044	0.048	0.082	—	—	—	—	—	74
64 (R=CH_3)	*o*-NPOE	5×10^{-4}	1	0.008	0.01	0.007	0.01	[c]	[c]	[c]	[c]	0.001	76
65 (*n*=1)	*o*-NPOE	—	—	1	0.04	0.04	0.04	[c]	[c]	[c]	[c]	0.02	77
38	*o*-NPOE	—	0.001	1	0.009	0.004	0.01	[c]	[c]	[c]	[c]	0.001	77
38	*o*-NPOE[b]	—	0.001	1	0.01	0.01	0.03	[c]	[c]	[c]	[c]	0.006	78
22 (*m*=3, *n*=0)	DBP	—	1.0×10^{-4}	2.6×10^{-4}	1	0.016	3.2×10^{-3}					8.7×10^{-3}	11
66 (*m*=1, *n*=5)	*o*-NPOE	—	—	3.0×10^{-4}	1	0.2	0.01					0.01	80
66 (*m*=1, *n*=5)	*o*-NPOE[b]	—	—	3.0×10^{-4}	1	0.3	0.4					0.08	78
67	*o*-NPOE	—	—	5.0×10^{-4}	1	0.05	0.005					0.2	81
69 (*m*=1, *n*=1)	*o*-NPOE	—	—	5.0×10^{-4}	1	0.2	0.006						83
69 (*m*=2, *n*=1)	*o*-NPOE			0.02	0.2	1	0.6						83
69 (*m*=2, *n*=2)	*o*-NPOE			0.001	0.06	0.04	1						83
22 (*m*=4, *n*=2)	DBP		1.7×10^{-4}	0.013	0.028	0.05	1						11
68 (*n*=3, 5, 7)	*o*-NPOE	—	—	0.001	0.08	0.08	1					0.009	82

[a] DBP: di-*n*-butyl phthalate, TEHP: Tris(2-Ethylhexyl)phosphate, *o*-NPOE: *o*-nitrophenyl octyl ether, TINTM: triisononyl trimellitate, TOPO: Trioctyl phosphine oxide

[b] coated wire electrode

[c] $<2 \times 10^{-4}$

In the concept of reagent design, the function of metal binding and the function of its detection may be separately carried out by crown ether and protonic chromophore, respectively. However, the anionic chromophore can more or less contribute to the metal binding ability of the crown ether, and thus, in actual reagents, the two functions can not be separated from each other.



70 n=1, X=H, NO$_2$ or Br

71 n=2, X=H or NO$_2$

5.1 *Monoprotonic Crown Ethers*

The first crown ether dyes synthesized according to the principle mentioned above were 4'-picrylamino-15-crown-5 derivatives (**70**) described by Takagi, Nakamura, and Ueno.[22,23] The crown ether **70** (HL) is quite lipophilic, and its distribution between water and chloroform is strongly in favor of the latter. When a chloroform solution of **70** was brought into contact with an alkaline solution of alkali metal salts, K^+ and Rb^+ were extracted into chloroform solution. The color of the chloroform solution then changed from orange (for HL species) to blood red (for L^- species), indicating the formation of ML (metal complex) species in the organic solution (Figure 6-a). Sodium

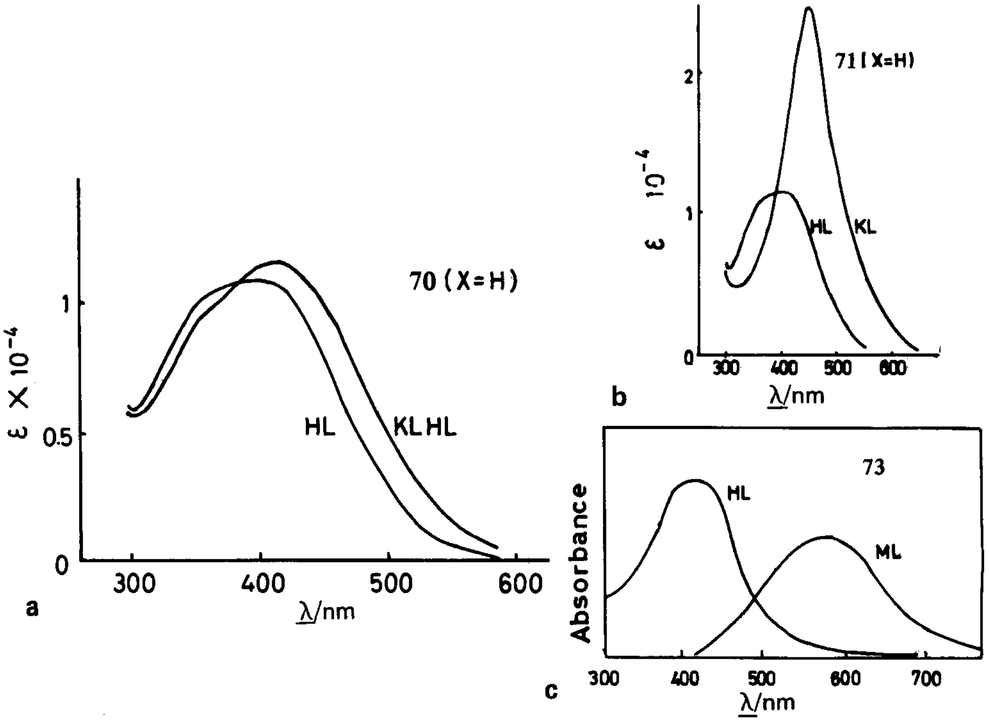


FIGURE 6 Electronic spectra of typical chromogenic crown ether dyes and their alkali metal complexes.

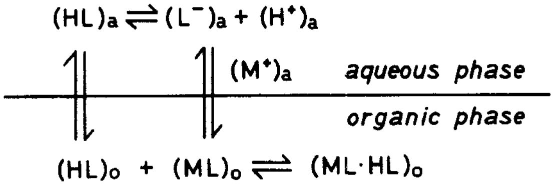


FIGURE 7 Extraction scheme of alkali metal ion by monoprotonic crown ether dye

was poorly extracted, and there was no extraction of Li^+. Typical absorption spectra are shown in Figure 6, and the reactions involved are illustrated in Figure 7.

Extractabilities of alkali metal ions are quantitatively estimated by extraction constants. Two constants $K_{ex}{}^1$ and $K_{ex}{}^2$ are defined in Eqs. (2)-(5), the former being for the extraction of 1:1 (crown ether:metal) complex, and the latter for 2:1 complex. Suffixes "a" and "o" denote aqueous and organic phases, respectively. From spectrophotometric analysis of extraction equilibria, it was found that crown ether **70** extracts K^+ by forming a 2:1 complex (probably with a sandwich-like structure).

$$(HL)_0 + (M^+)_a \rightleftharpoons (ML)_0 + (H^+)_a \tag{2}$$

$$K_{ex}{}^1 = \frac{[(ML)_0][(H^+)_a]}{[(HL)_0][(M^+)_a]} \tag{3}$$

$$2(HL)_0 + (M^+)_a \rightleftharpoons (ML\cdot HL)_0 + (H^+)_a \tag{4}$$

$$K_{ex}{}^2 = \frac{[(ML\cdot HL)_0][(H^+)_a]}{[(HL)_0]^2[(M^+)_a]} \tag{5}$$

Similar reagents **71** were also synthesized from benzo-18-crown-6.[25] They extracted K^+ most effectively (Figure 6–b), and the composition of the extracted complex was found to be 1:1.[24] Table VI summarizes the extraction constants of **70** and **71** for alkali metals. Proton dissociation constants (K_a) are also included. Introduction of a nitro group in the 5′-position of benzo-crown ether causes an increase in acidity of the picryl-amino proton. Since the extraction constants implicitly involve the proton dissociation process of the reagent, the increase in the proton dissociation constant leads to the increase in the extraction constant, which in turn means that the extraction of metal can take place at a lower pH region.

In the practical use of these crown ether reagents for extraction photometric determination of K^+, considerably high pH conditions (*ca.* 11–12 for crown ethers without an added 5′-nitro group) are required to increase the extraction efficiency (sensitivity of determination)[†]. It is best to use the Li^+ salt of EDTA as a pH buffering

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[†] It should be emphasized that unlike conventional extraction photometric reagents for ordinary multivalent metal ions the extraction of alkali metal with these and forthcoming crown ether reagents is usually not quantitative. Thus, calibration curves are linear only under limited determination conditions, and the sensitivity of determination depends not only on the spectral characteristics such as molar absorptivity of the metal-reagent complex but also on the extent to which metal ions are extracted from aqueous to organic phase.

TABLE VI
Extraction of Alkali Metal Ions by Chromogenic Benzo-crown Ethers

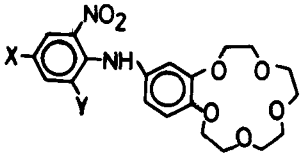
Reagent		pK_a[a]	−log K_{ex}[1b]					Complex (reagent: metal)	Reference
			Li^+	Na^+	K^+	Rb^+	Cs^+		
70	X=H	10.55	–	10	7.55	8.5	10.4	2:1[b]	22, 23, 84
	X=NO_2	8.63	–	8	7.1	7.9	8.3	2:1[b]	22, 23, 84
71	X=H	10.58	–	12.5	10.52	10.90	11.28	1:1[c]	24
	X=NO_2	8.79	–	–	9.13	9.42	9.54	1:1[c]	24
72		10.22		–	7.5	8.3	–	2:1[c]	87
73		12.38		–					87
74		11.45	–	–	9.44	10.4	–	2:1[c]	87

[a] K_a: proton dissociation constant in 10% dioxane-water (v/v), 25°C.
[b] Extraction solvent: 14% triethylamine – chloroform (v/v), 25°C
[c] Extraction solvent: chloroform, 25°C

agent, which also serves to remove interferences from multivalent metals. Potassium in sea water and Portland cements was successfully determined without interference from high levels of Na^+, Mg^{2+} and Ca^{2+}.

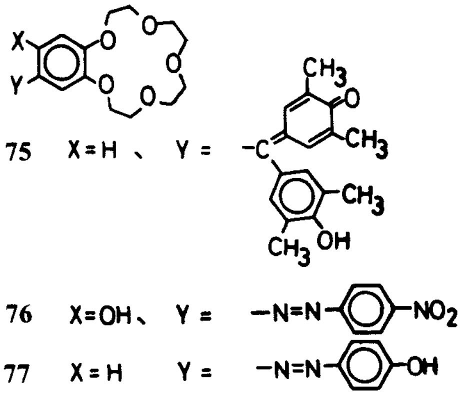
In colorimetry, the spectral overlap between reagent and complex species should be as small as possible, because high concentration of reagent, which is sometimes required to increase the extent of extraction, makes a spectral separation of the complex rather difficult. Since the first reagent **70** suffers a relatively large spectral overlap, the determination limit of K^+ does not go below 40 ppm.

Pacey et al. described some variations of **70** type reagents, in which one of the nitro group was replaced by a cyano or trifluoromethyl group.[85–87] The crown ether reagents **72–74** have physico-chemical properties similar to **70** except that they have higher pK_a values and, importantly, less spectral overlap than those of **70** (Figure 6-b). It is reported that with reagent **72** the calibration graph gave a linear range of 5 – 700 ppm K^+ even in the presence of 3000 ppm Na^+.[86]

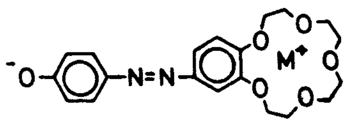


72 X=NO_2 , Y=CF_3
73 X=CF_3 , Y=NO_2
74 X=CN , Y=NO_2

Several other monoprotonic chromogenic crown ethers have been derived from benzocrown ethers.[25] However, few of them have proved to be useful as a colorimetric reagent. **75** was found to have a large molar absorptivity along with a small spectral overlap, but the metal extraction ability is rather low and the dye is prone to be air-oxidized. Crown ethers **76** and **77** do not extract alkali metal ions, probably because the anionic phenolate group is too strongly hydrated when the metal complex is extracted as "intramolecular ion-pair" **78**. A successful extraction of alkali metal ions with picrylamino-type crown ethers suggests that the ion-pair complexes **79** from this type of crown ethers are more stabilized than those complexes from other crown ethers



75–77. Efficient charge delocalization over entire nitro groups and a steric hindrance to hydration at amino nitrogen seem to contribute to minimizing hydration at the anionic site (picrylamino moiety) of the ion-pair complex **79**.



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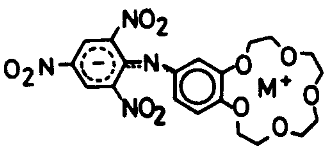

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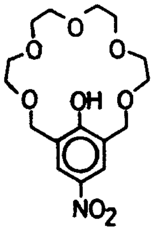
McKervey and Mulholland described a crown ether **80** which incorporate a hindered phenol structure within a crown ether skeleton.[88] **80** forms a stable Na^+ complex, in which Na^+ may be positioned in the crown ether ring in such a way that the phenolate anion part can interact directly with Na^+ (**81**). However, they have not referred to any further study on the complexation property nor its analytical application. On the other hand, Kaneda et al. reported an azophenol analogue **82** (n=1) which was found to cause a color change from yellow to purple when solid lithium salts were added to the chloroform solution of **82** in the presence of pyridine.[89] Other alkali metal salts were reported not to induce such a color change. Akiyama et al. applied this system to the spectrophotometric determination of 25 to 250 ppb Li^+. The interferences from other alkali (except for Na^+) and alkaline earth metal ions were appreciable and these cations had to be removed before determination.[90,91] Fluorescent reagent **83** is also synthesized.[92]



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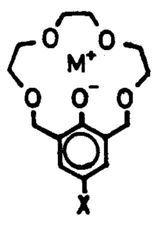

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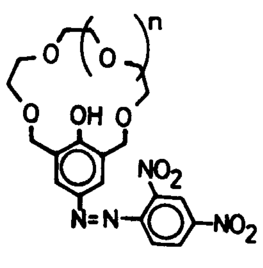

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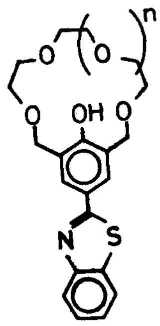

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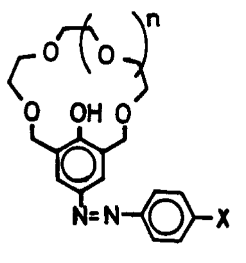
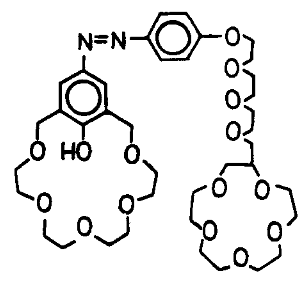


84 X=OMe, -SO$_2$NMe$_2$



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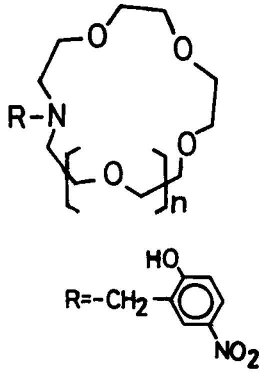
Azophenol type crown ethers (**84**) were tested for extraction photometry of alkali and alkaline earth metals.[93] **84** (n=1) extracted Ba^{2+} into chloroform most effectively, the order of extractability being $\mathrm{Ba}^{2+} > \mathrm{Sr}^{2+} > \mathrm{Li}^{+} > \mathrm{Na}^{+} > \mathrm{K}^{+}$. Introduction of another crown ether (**85**) did not affect the metal selectivity. Two molecules of the reagent should be involved in the extraction of Ba^{2+} or Sr^{2+}, probably with two crown ether rings cooperating, but no detailed equilibrium study was performed.

Very high metal extraction ability is achieved with N-substituted-azacrown ethers if deprotonated anion in the side arm can interact directly with the metal ion bound in the crown ether ring.

Nakamura, Takagi, Ueno, and coworkers described azacrown ethers which contain p-nitrophenol and 4-methylumbelliferone chromophores linked to nitrogen by a methylene group.[94,95] The reagents **86** and **87** distribute predominantly in organic solution (water – 1,2-dichloroethane). Under basic conditions, phenolic protons dissociate into an aqueous phase, and alkali metal ions in turn are extracted into an organic phase. This causes color (**86**) or fluorescence (**87**) changes in the organic phase. The reactions involved are quite similar to those in scheme I. Kitazawa et al. synthesized bis(aza-15-crown-5) type reagent **88**.[93] Table VII summarizes metal extraction constants and proton dissociation constants of these reagents.

Comparing Table VI and Table VII, one may notice for azacrown ethers a small increase in extraction constants and a diminished metal selectivity in general. However, a selective extraction of Li^{+} by **86** (n=1) and **87** (n=1) is notable. The affinity of these 15-crown-5 type reagents to Li^{+} suggests the chelate-forming (coordination) interaction between Li^{+} and the anionic reagent. Extraction-photometric and -fluorimetric determinations of ppm level Li^{+} are possible by using **86** (n=1) and



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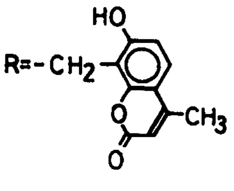

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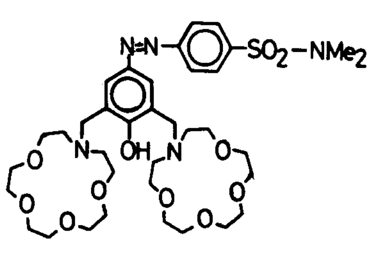


88

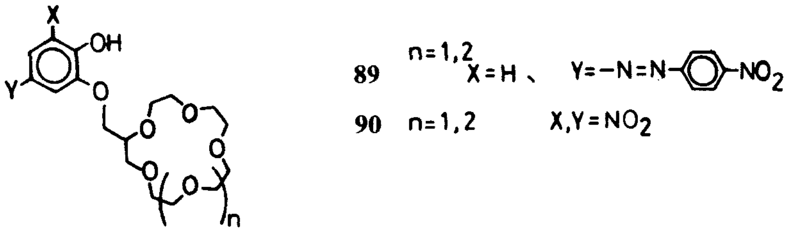
TABLE VII
Extraction of Alkali Metal Ions by Chromogenic Azacrown Ethers

Reagents		pK_a [a]	$-\log K_{ex}^{1}$ [b]					Reference
			Li^+	Na^+	K^+	Rb^+	Cs^+	
86	$n = 1$	5.79, 9.79	9.15	9.76	9.86	–	–	94
	$n = 2$	5.77, 9.59	10.29	9.46	8.93	9.63	10.62	94
87	$n = 1$	6.29, 10.46	9.70	10.30	11.50	–	–	95
	$n = 2$	6.45, 10.49	10.30	10.25	10.00	10.05	–	95
88		3.55	11.0	10.6	11.7			93

[a] K_a: proton dissociation constant in 10% dioxane-water (v/v), 25°C.
[b] Extraction solvent: 1,2-dichloroethane, 25°C.

87 (n=1), respectively. Crown ethers **86** (n=2) and **87** (n=2), which are the derivatives of aza-18-crown-6, are selective to K^+.[94,95] Bis-crown ether **88** derived from aza-15-crown-5 is selective to Na^+.[93]

Since C-substituted crown ether derivatives are free from amino nitrogen in the crown ring, the features different from those of azacrown derivatives can be rendered to them: the affinity to transition metals becomes less and the number of proton-dissociable functional groups is reduced owing to the lack of weakly acidic NH^+ group in the ring.



89 n=1,2 X=H、 Y=–N=N–⟨⟩–NO_2

90 n=1,2 X,Y=NO_2

Crown ethers **89** and **90** are prepared by three-step reactions starting from commercially available guaiacol glyceryl ether via **35** (R′=H) and **36**.[47,96] These reagents are, as other reagents mentioned before, quite lipophilic in their undissociated form. However, the lipophilicity (extractability) of their salts or metal complexes greatly depends on the nature of metal ions. Thus, when cations which fit the crown ether cavity are present in the aqueous phase, those cations are extracted to an organic phase as the pH is raised, giving the absorption of proton-dissociated reagent species in the

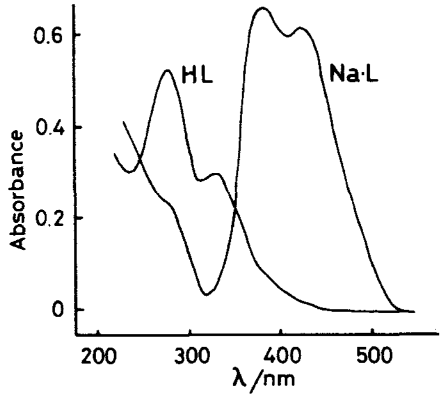


FIGURE 8 Electronic spectra of **89** and its Na^+ complex.

TABLE VIII
Extraction of Alkali Metal Ions by Skeletal-C-substituted Crown Ethers

Reagent		$pK_a{}^a$	$-log\ K_{ex}{}^{1b}$					Reference
			Li^+	Na^+	K^+	Rb^+	Cs^+	
89	$n = 1$	7.51	9.8	8.40	9.20	9.55	>10	47
	$n = 2$	7.54	8.8	8.32	7.11	7.75	>10	47
90	$n = 1$	3.16	>5.6	3.60	4.15	4.76	5.6	47
	$n = 2$	3.27	4.8	4.01	2.22	2.68	3.76	47
94	$n = 1$	–	7.4	6.19^c	5.86^c	6.5^c	7.64^c	48
95	$n = 2$	–	7.1	7.41	6.1	8.0	7.3	48

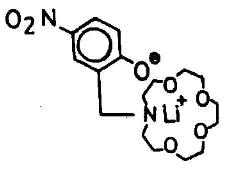
[a] K_a: proton dissociation constant in 10% dioxane-water (v/v), 25°C.
[b] Extraction solvent: 1,2-dichloroethane, 25°C.
[c] Extraction of a 2:1 (reagent:metal) complex. Refer to eq. 6.

organic phase. If cations do not fit the crown ether reagents, the salt is not extracted and the reagents are then partially or totally transferred from the organic to the aqueous solution as the pH is raised. Typical spectral behavior is shown in Figure 8 for **89** (n=1). Tetramethylammonium ion is the least extractable cation, and it is conveniently used as a cationic component of pH buffer in this type of extraction study.

Extraction constants are summarized in Table VIII for crown ethers **89** and **90**. 18-Crown-6 type reagents **89** (n=2) and **90** (n=2) are selective to K^+ in accordance with the generally accepted metal selectivity of 18-crown-6 derivatives. For 15-crown-5 type reagents, both **89** (n=1) and **90** (n=1) prefer Na^+. It should be recalled here that aza-15-crown-5 type reagents **86** (n=1) and **87** (n=1) preferred Li^+. Obviously, some structural factors on changing from **86** to **90** contributed to change the selectivity from Li^+ to Na^+. A chelate ring in **91** (including phenolate oxygen, amino nitrogen, and Li^+) is six-membered, while those chelates formed analogously with **89** or **90** are eight-membered. Five or six-membered chelate rings are supposed to be the most stable in ordinary coordination compounds, but eight-membered chelate rings are considerably unstable. Thus, compound **89** (n=1) and **90** (n=1) would not be favorable in the extraction of Li^+, because for Li^+ complexes a chelate formation between the metal and phenolate oxygen with somewhat covalent interaction (**92**) seems to be essential for its stabilization in organic solvent. A contribution of ion-pair-like interaction for Na^+ (schematically shown in **93**) combined with a fitness of crown ether ring size seems to account for the preferred extraction of Na^+ by **89** (n=1) and **90** (n=1).

Both reagents **89** and **90** are useful in the extraction photometric determination of ppm level Na^+ (n=1) and K^+ (n=2). Reagent **90** (n=1) was successfully used for the determination of Na^+ in human blood serum.[47]

Pacey et al. introduced a picrylamino group into aliphatic crown ethers. Aminomethyl crown ethers **39** (n=1,2) reacted with picryl chloride and l-trifluoromethyl-2-chloro-3,5-



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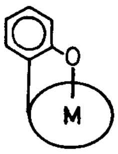

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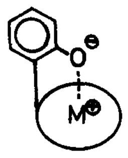

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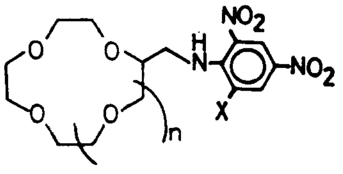


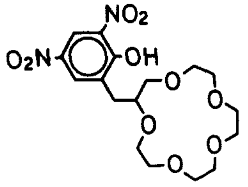
94 n=1, X=CF_3

95 n=2, X=NO_2

dinitrobenzene to achieve chromogenic lariat-type crown ethers **94** and **95**.[48] The extraction constants for alkali metals are included in Table VIII.

The extraction by picrylamino-type 12-crown-4 reagents **94** involves a 2:1 (reagent:metal) complex for most alkali metal ions. This seems reasonable in view of the small cavity size of the crown ether. On the other hand, the extraction by 15-crown-5 reagent **95** all takes place with a 1:1 complex in contrast to the corresponding crown ethers **70**, which preferred a 2:1 complex. This suggests that the picrylamino side arm in **95** takes a chelate-like conformation in a similar manner to the reagents of the type **86** or **89**. The steric bulkiness of picrylamino group, however, seems to preclude a direct interaction of amino nitrogen or nitro-group oxygen with the metal in the crown ether cavity. Thus, the extraction selectivity of **95** is favorable to K^+ rather than Na^+ or Li^+. It is also possible that well-delocalized anionic charge on picrylamino group is simply unfavorable to coordinate to metals.

The importance of steric factor associated with ligating side arm was also exemplified in the M^+-**96** series for Li^+, Na^+, and K^+, where the order of extraction selectivity was observed $K^+ > Na^+ > Li^+$.[97] In **96** an appropriate approach for coordination of phenolate group to the metal centered in the crown ring is apparently hindered sterically when the assumed structure is inspected on CPK molecular model. In the Li^+-complex it can be assuemd that the crown ring chelate is rigid enough to hold Li^+, but the extraction selectivity is the poorest. Therefore, in this series, the highest K^+ extraction selectivity is interpreted in terms of the less contribution from the ring chelate structure but the more enhanced contribution from the intramolecular ion-pair formation. The intermediate character of the Na^+-complex should be interpreted similarly.



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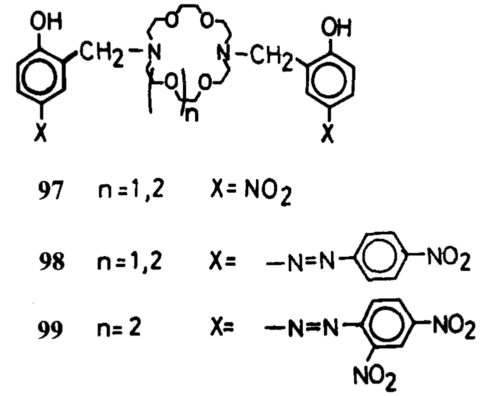
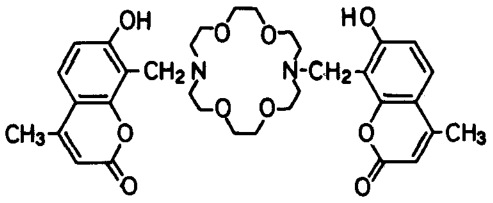
5.2 *Diprotonic Crown Ether Dyes*

The introduction of two-proton-dissociable chromophore into crown ethers gives dyes which are expected to selectively extract divalent metals, particularly alkaline earth metals.

p-Nitrophenol-type reagents **97** (*n*=1,2) as well as *p*-(*p*-nitrophenylazo)phenol-type reagents **98** and **99** (*n*=1,2) were readily derived from diaza-crown ethers.[98,99] These showed an excellent extraction ability toward alkaline earth metal ions. Bis-(picrylamino)-substituted dibenzo-18-crown-6 (**102**), however, was found not to extract divalent metals, probably because the charge separation involved in the extraction is too large: the two anionic centers are separated too far to interact together with a double-charged central metal cation.[25]





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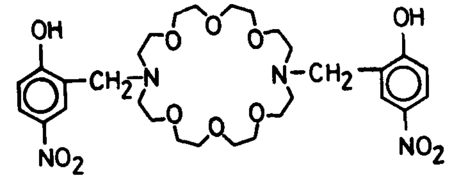

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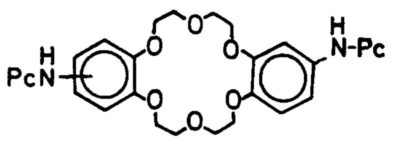

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The extraction of alkaline earth metal ions by reagents **97–101** is described by eqs. 6–7 and Figure 9. These reagents are again soluble in organic solvents and do not distribute into aqueous solution.

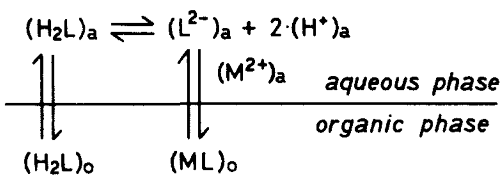


FIGURE 9 Extraction scheme of alkaline earth metal ion by diprotonic crown ether dye

$$(H_2L)_0 + (M^{2+})_a \rightleftharpoons (ML)_0 + 2(H^+)_a \tag{6}$$

$$K_{ex} = \frac{[(ML)_0][H^+)_a]^2}{[(H_2L)_0][(M^{2+})_a]} \tag{7}$$

The extraction constants and proton dissociation constants are summarized in Table IX for reagents **97–101**. Alkali metal ions do not interfere the extraction of divalent metals at all.[98] Metal extraction selectivity is $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$ for **97** (n=1,2), **98** (n=1,2) and|**99**. **97** (n=2) extracts calcium most effectively and can be used to the determination of Ca^{2+} in blood serum. 4-(2,4-Dinitrophenylazo)phenol-type reagent **99** is one of the most sensitive reagents to Ca^{2+}, the molar absorptivity of the extracted complex being 81,000 in 1,2-dichloroethane.

Fluorimetric reagent **100** can be synthesized in the same manner as **87**, and the fluorimetric determination of ppm level Ca^{2+} is possible.[95] *p*-Nitrophenol-type 24-crown-8 reagent **101**, which is derived from diaza-24-crown-8, is a quite selective extraction photometric reagent for Ba^{2+}.[6]

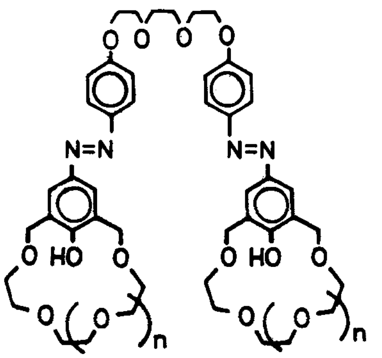
These crown ether reagents, however, tend to suffer interferences from other divalent metal ions such as Cu^{2+}, Pb^{2+}, Cd^{2+}, and Zn^{2+}, since these metals also form stable complexes with the crown ether reagents. Pb^{2+} complex of **97** (n=2) is particularly stable, and in fact this reagent may be used as a Pb^{2+}-selective extraction photometric reagent. These interferences can be removed by using masking agents such as nitrilotriacetic acid (NTA) and sarcosine dithiocarbamate.[99]

TABLE IX
Extraction of Alkaline Earth Metal Ions by Diprotonic Diazacrown Ethers

Reagent		pK_a[a]			$-\log K_{ex}^2$[b]				Reference
					Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	
97	n = 1	–	–	–	–	15.0	16.8	18.4	99
	n = 2	4.03,	6.56,	9.8	–	12.54	13.50	15.14	99
98	n = 1	–	–	–	–	17.6	18.9	20.4	99
	n = 2	5.52,	9.00,	10.9	–	16.6	17.9	19.1	99
99		5.01,	8.72,	10.3	–	15.0	16.3	18.5	99
100		4.28,	7.23,	10.38	–	14.72	16.11	17.10	6
101		4.7,	6.7,	9.5	–	17.7	17.0	14.3	6

[a] K_a: proton dissociation constant in 10% dioxane-water (v/v), 25°C
[b] Extraction solvent: 1,2-dichloroethane, 25°C

Kitazawa et al. reported a different type of diprotonic crown ether dyes **103**.[93] The reagent extracted Ba^{2+} most effectively, but details of extraction were not described. However, from a qualitative estimation, the Ba^{2+} selectivity over other alkaline earth metal ions seems not better than that of **101**.[93]



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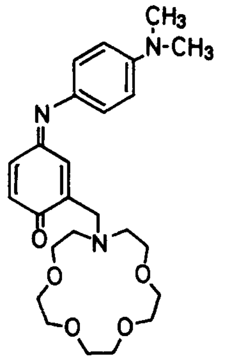
5.3 *Uncharged Crown Ether Dyes*

Vögtle et al. described an interesting family of uncharged crown ethers, which change color on interaction with alkali and alkaline earth metal ions.[100–103] These crown ether dyes have electron donor and acceptor sites within the molecule, and an absorption of visible light (electronic excitation) is accompanied by an electronic charge transfer from the donor to the acceptor. The crown ether structures are incorporated in such a way that the metal ion bound in crown ether simultaneously interacts with either the donor site or the acceptor site of the molecule to influence the energy level of electrons involved in light absorption. Typical crown ethers with donor and acceptor sites are shown by **104** and **105**.



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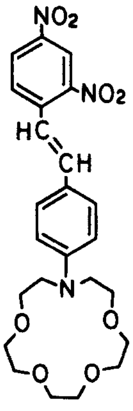

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Spectral change on the complex formation is sometimes very sharp. The complex species show high molar absorptivity and small spectral overlap. However, the reaction is limited in the organic solvent such as acetonitrile, and the metal salt are used as solid in excess of the crown ethers. Experimental data so far have been presented are not enough to allow detailed consideration of the metal-reagent equilibria. In spite of intriguing features of this class of crown ethers one still has to wait for further investigations of use in analytical purposes.

6. CONCLUSION

A tremendous number of functionalized crown ether derivatives have been synthesized and the number is still increasing. However, most of them have come from more or less purely scientific interest, and relatively few laboratories have been involved in analytical applications of this novel class of compounds. As has been discussed in this paper, the applications are already fruitful in the ion chromatography, ion-selective electrodes, and colorimetry of alkali metals; some applications, *e.g.*, Na^+-selective electrodes, have become indispensable in routine field analysis. Further investigations in this field can be expected with more fruitful and rewarding results.

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