Journal of Chromatography, 546 (1991) 73–88
Elsevier Science Publishers B.V., Amsterdam

CHROMSYMP. 2117

Review

Application of macrocyclic ligands to ion chromatography

JOHN D. LAMB* and ROBERT G. SMITH
Department of Chemistry, Brigham Young University, Provo, UT 84602 (U.S.A.)

ABSTRACT

Macrocyclic ligands such as crown ethers and cryptands are highly selective in binding metal and other cations and have been employed in a variety of separation technologies, including solvent extraction, membranes and chromatography. In recent years, groups have succeeded in applying these ligands to high-performance ion chromatography. Typically, crown ethers have been adsorbed, covalently bonded or polymerized on particulate substrates. In some instances, excellent separations among alkali and other metal ions have been achieved. As many macrocycles are uncharged and are insensitive to pH, cations, together with their accompanying anions, may be eluted using pure solvents such as water or methanol as eluents. Further, anions may be separated through the formation of ion pairs with the bound cations. The latter effect has been refined to make possible a unique form of gradient anion chromatography. When metal hydroxide eluents are used for anion chromatography, the capacity of a macrocycle column is determined by the stability constant of the metal ion complexation reaction. If the eluent cation is changed during the course of a single chromatogram so that the column capacity drops, a wide range of anions can be separated with excellent resolution. Little baseline perturbation is experienced since the eluent (OH^-) concentration remains constant throughout the gradient.

CONTENTS

0021-9673/91/$03.50

1. INTRODUCTION

Macrocyclic ligands have been studied for over two decades because of their unique cation-complexing characteristics [1]. A variety of macrocycles have been described, including crown ethers, cryptands, spherands, calixarenes and tetraaza ligands, with specific research emphasis on their potential for affecting a variety of separations. All are characterized by a cyclic carbon structure containing heteroatoms such as oxygen, nitrogen and sulfur, which provide an electron-rich environment for cations, some of which may fit into the central cavity of the molecule forming stable complexes. The best characterized synthetic macrocycle is 18-crown-6, a planar, cyclic polyether with an eighteen-membered ring containing six oxygen atoms (Fig. 1a). Another class of particular interest in this paper, the cryptands, provides a three-dimensional cavity for metal cation entrapment. The basic structure of cryptands is illustrated by the ligand 2.2.2 (Fig. 1b). The crown ethers, cryptands and other macrocycles have been used to separate both cations and anions by high-performance ion chromatographic and other methods [2–5].

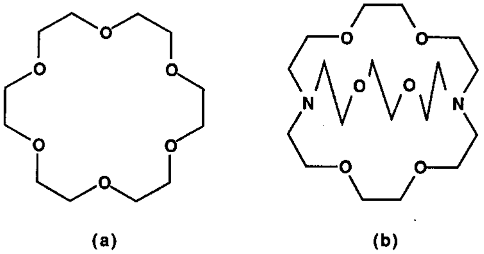

Fig. 1. Basic structures of typical macrocycles used in ion chromatography: (a) 18-crown-6; (b) cryptand 2.2.2.

The selectivity of macrocycles for cations is often determined by the ability of the cation to fit into the central cavity of the macrocycle. The dramatic variation of cryptand selectivities with the size of alkali metal cations is illustrated in Fig. 2. Because macrocycles are usually neutral molecules, an anion is often associated with the resulting cationic complex in order to maintain electrical neutrality, especially in low-dielectric media. As macrocycles are generally hydrophobic, they can be used to extract both cations and anions from aqueous into hydrophobic environments. Thus, macrocycle-based chromatographic columns can be used to separate not only cations with a common anion, but also anions with a common cation.

2. CHARACTERISTICS OF MACROCYCLE-BASED ION CHROMATOGRAPHY

Macrocycles were first used in chromatography by Cram and co-workers [6–8] to separate amino acid isomers. Since then, the use of macrocycles in chromatography to separate cations and anions has been an active area of research. Most applications of macrocycles to ion chromatography involve their incorporation into the stationary phase. The practical aspects of how this and other types of applications are

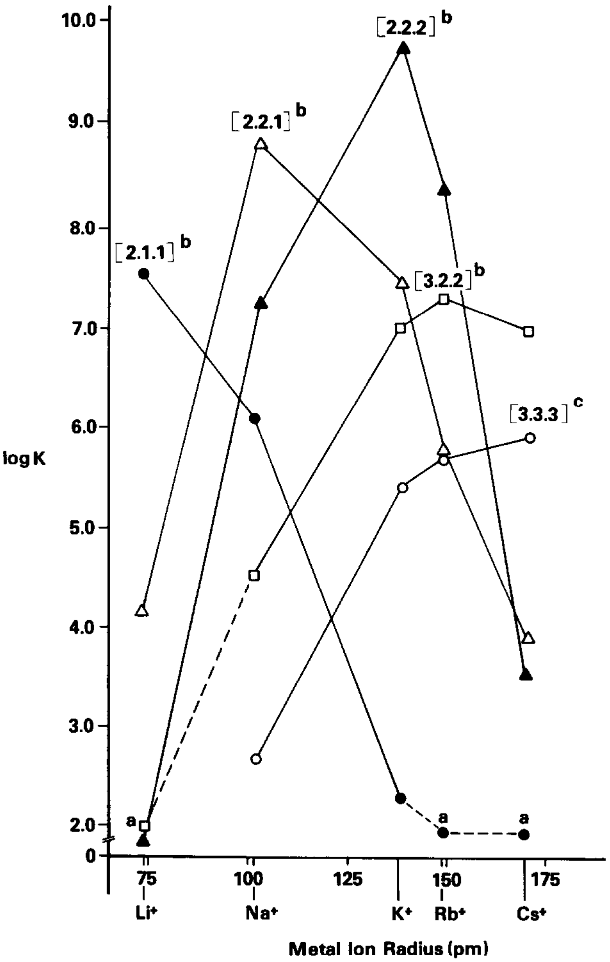

Fig. 2. Selectivities, given in terms of binding constant, *K*, of several cryptands among alkali metal cations. (a) Reported <2.0; (b) in 95% methanol; (c) in methanol.

accomplished is described in Section 3. The use of macrocycles as stationary phase exchange sites in ion chromatography offers several unique features. First, because macrocycles are commonly uncharged, cations can be eluted from the column without the addition of ionic eluents, making possible a very low background conductivity and concomitant increased sensitivity. Further, waste disposal is greatly simplified if the eluent consists only of solvents.

A second feature of macrocycle-based stationary phases is the variety of selectivities available. In ion chromatography with traditional fixed ionic exchange sites, cation selectivity is rather inflexible, although it may be influenced to some extent by altering the mobile phase conditions. With macrocycle-based stationary phases, on the other hand, the cation selectivity of the column differs from one macrocyclic ligand to another. By employing different macrocycles or combinations of macrocycles, the selectivity can be varied over a wide range, allowing considerable flexibility in the types of separations that can be performed. Also, because cation affinities fall within a relatively narrow range, Group I and II and other metal cations may be separated isocratically, the preferred method for compatibility with conductivity detection.

A third characteristic of macrocycle-based stationary phases is their ability to separate both cations and anions. Cations are retained by complexation with the exchange site ligand. Anions are retained along with macrocycle-bound cations when the complex is positively charged, *i.e.*, when the unbound macrocycle is neutral.

Each of these features is treated in detail below.

2.1. *Cation selectivity and retention*

The retention of a cation by a macrocycle-based column depends on how strongly it is bound by the macrocycle and by the rate of ligand exchange. These factors, in turn, are determined by how well the cation's coordination requirements are met by the macrocycle relative to the solvent. One criterion that influences this featue is how well the cation fits into the central cavity of the macrocycle. Cations that are too small cannot interact with all of the heteroatoms in the ring without considerable ring distortion and are retained less strongly than those which fit better. Cations which are too large to fit in the cavity may form complexes by sitting on the ring, or by being sandwiched between two rings. The best fit, and hence the greatest degree of retention, is often exhibited by those cations which most closely approach an ionic radius/macrocyclic cavity radius ratio of 0.8 [2,9]. This size criterion is most significant among cations that have few geometric constraints in their coordination properties, such as the alkali and alkaline earth cations. For 18-crown-6, K^+ (ratio 0.9) fits most closely among the alkali metals, followed by Rb^+(1.02), Cs^+(1.20), Na^+(0.67) and Li^+(0.47). This order is reflected in the values of stability constants for complex formation [10,11].

Early work by Blasius and co-workers [2,12] showed that in macrocycle-based chromatography, cations elute in order of increasing binding constants. For example, the binding constants of dibenzo-18-crown-6 increase in the order $Li^+ < Na^+ < Cs^+ < Rb^+ < K^+$. This is also the experimentally observed elution order of the alkali metals. Among the alkaline earths the binding constants and elution order are $Mg^{2+} < Ca^{2+} < Sr^{2+} < Ba^{2+}$. These results illustrate that the mechanism of retention is based on ligand exchange rather than ion exchange. In fact, it is generally possible to predict the retention behaviour of cations with a particular macrocycle by referring to tabulated binding constants. The constants for a wide variety of macrocycles have been measured [10,11].

The retention of cations by one of the smallest macrocycles, 12-crown-4 and its derivatives, is of the order $Na^+ > K^+ > Rb^+ > Cs^+ > Li^+$ [9,13]. The selectivity for lithium, rubidium and cesium is very low, but a good separation of lithium, potassium and sodium is observed (Fig. 3a). Thus, the 12-crown-4 macrocycles show a higher affinity for sodium cations than for potassium cations, the opposite of the retention order in standard ion exchange.

Several derivatives of 15-crown-5 ethers have been applied to chromatography. While each has slightly differing properties, including cation retention times and resolutions, the retention order is generally $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$ (Fig. 3b). This ligand serves to illustrate the principle that when no one cation offers an ideal

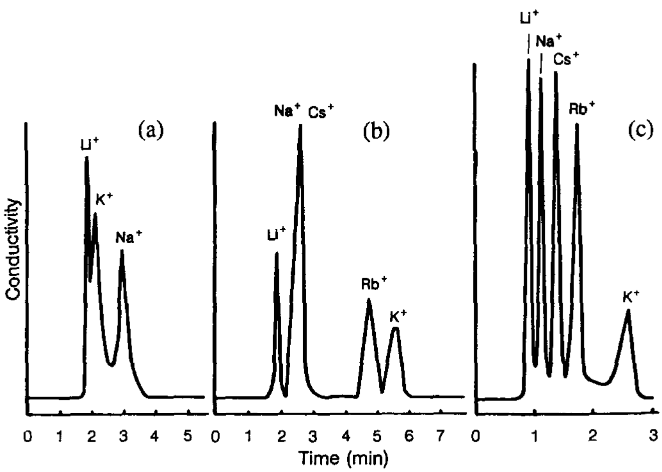

Fig. 3. Alkali metal cation separation (as iodides) on C_{18}-bonded silica dynamically coated with (a) dodecyl-12-crown-4, (b) dodecyl-15-crown-5 and (c) dodecyl-18-crown-6, using methanol–water (50:50) as eluent and conductivity detection (from ref. 9).

fit in the ligand cavity, other factors predominate in determining selectivity. Even Na^+ is slightly too large to fit ideally the 15-crown-5 cavity. In this instance, the desolvation energy of the cation couples with cation/ligand size considerations to determine the selectivity.

Among 18-crown-6 analogues, there is a deviation from the normal order $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$, shown in Fig. 3c [9,12,14,15], when bis- or polymeric crown ether stationary phases are used. Specifically, the latter retain Cs^+ longer than K^+. This result is probably due to the fact that the Cs^+ cation, being too large to fit into the macrocyclic cavity, commonly forms 2:1 macrocycle–cation complexes with this ligand which are more stable [16].

Blasius and Janzen [2] synthesized polymers of large macrocycles such as 21-crown-7 and 24-crown-8 for use in chromatography. Both of these macrocycles show the same elution order, $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$. These macrocycles exhibit high selectivity for the Cs^+ cation. The Cs^+: (21-crown-7 cavity) ratio is 0.89. This selectivity can be exploited to perform the separation of cesium from complex ionic solutions, a separation of interest in the nuclear industry [2].

Little work has been done on chromatographic cation separations using cryptands, which encapsulate the cation better than planar macrocycles. The measured binding constants for the cryptands are often several orders of magnitude higher than the constants for crown ethers, and the chromatographic retention of cations on cryptand-based columns is considerably longer and less efficient than for the corresponding crown ethers. For the cryptand 2.2.2 the selectivity is slightly different from that for the similar 18-crown-6 ligand, with the retention decreasing in the order $K^+ > Rb^+ > Na^+ > Cs^+ > Li^+$ [17].

2.2. Mobile phase options

One potential advantage of using macrocyclic sites in the stationary phase is that the addition of salts to the mobile phase is not necessary to elute analytes from the column. Thus, pure water or another pure solvent can be used as the mobile phase. It is generally true that the stability constants of cation–macrocycle complexes are higher in methanol and other organic solvents than in water [10]. Methanol and methanol-containing mobile phases reflect this higher stability, as the retention of cations and anions increases with increasing methanol content (Fig. 4) [9,14,16]. It is noteworthy that the addition of other organic solvents to the mobile phase may not have the same effect. Macrocycle–cation binding constants in acetonitrile and tetrahydrofuran are also higher than in pure water. However, it has been observed that retention decreases on addition of those solvents to the mobile phase in certain systems [14]. No explanation of this phenomenon was given, although these solvents may have affected the resin-based stationary phase used in these experiments.

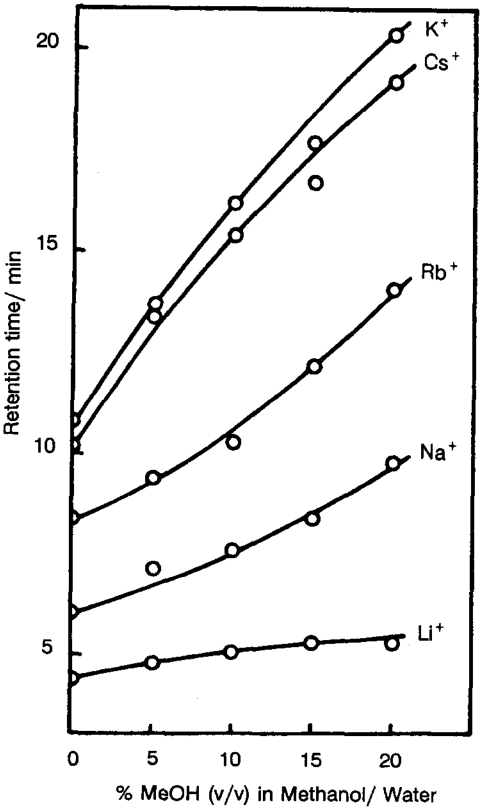

Fig. 4. Effect of methanol (MeOH) content in mobile phase on retention of alkali metal cations (as chlorides) on benzo-18-crown-6 covalently attached to silica. Analytes: 0.05 *M* metal chlorides. Flow-rate' = 0.5 ml/min (from ref. 14).

2.3. *Temperature effects*

The complexation of cations with macrocycles is usually an exothermic process. The stability of the macrocycle–cation complex is lower at higher temperature in this instance. Increasing the temperature in chromatographic separations with macrocycles has two effects: the efficiency increases because the mobile phase become less viscous, allowing better diffusion, and Iwachido *et al.* [14] showed that the retention decreases as temperature increases, owing to the weaker cation–macrocycle interactions. However, resolution is not lost because of the increase in efficiency [16]. Another paper in this volume describes our own work on this topic [18].

2.4. *Anion separations*

In low-dielectric media, positively charged macrocyclic complexes exist in close associaton with anions to maintain electrical neutrality. Thus, in reversed-phase macrocycle chromatographic systems, the anion is included in the cation retention equilibrium. Those anions which facilitate extraction, such as iodide or thiocyanate, increase the retention of cations [12,16,19,20]. This anion dependence can lead to difficulties with cation peak identification if more than one anion is present in a sample.

The anion effect described above has been exploited to separate anions in the presence of a common cation. The retention order of anions is generally independent of macrocycle type, namely $SCN^- > I^- > NO_3^- > Br^- > Cl^- > F^- > SO_4^{2-}$. This selectivity is different from that of traditional ion exchange, in which divalent anions such as sulfate are more strongly retained. Cations which experience greater retention on a given macrocycle column increase the degree of retention of accompanying anions. For example, on 18-crown-6-based columns, mixtures of potassium salts show improved anion separations over mixtures of sodium salts [12,15] (Fig. 5). This effect is even more dramatically illustrated in Fig. 6, described below. Difficulties in separation arise if more than one type of cation is present, with multiple peaks possible for the same anion [20].

Macrocycles have been used to separate anions through an ion-exchange mechanism rather than a ligand-exchange mechanism [21,22]. This type of separation has been accomplished by the use of a mobile phase containing the hydroxide of a cation that is retained by the macrocycle. As mobile phase cations form complexes with the stationary phase macrocycle, anion-exchange sites are formed in equilibrium with free eluent cation in the mobile phase. Sample anions are eluted by hydroxide ion, which can in turn be chemically suppressed as in standard ion chromatography. The identity of the mobile phase cation greatly affects the column capacity under these conditions. Using a column loaded with decyl-2.2.2, little anion retention is observed with a lithium hydroxide eluent (Fig. 6a), whereas a sodium hydroxide eluent yields significant anion retention (Fig. 6b). The efficiencies observed with this system approach those of traditonal ion-exchange chromatography. Also, with the relatively high concentration of eluent cation in the mobile phase, the effects of analyte concentration and of sample counter ion are largely eliminated. A gradient in column capacity can be achieved by changing the eluent from sodium hydroxide to lithium hydroxide during the course of a chromatogram. Fig. 6c shows how such a gradient combines the desirable properties of each eluent used isocratically. During the course of the gradient, only the cation identity changes. As the eluent concentration does not

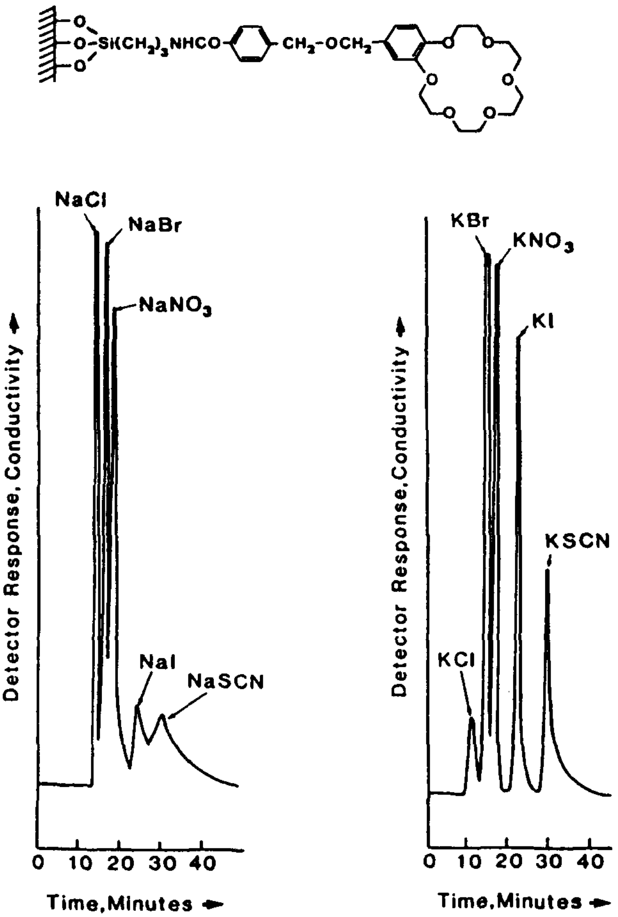

Fig. 5. Separations of anions in the presence of a common cation on silica-based benzo-18-crown-6 resin (top) using a water mobile phase and conductivity detection. Analytes: 0.1 *M*, 20 ml (from ref. 15).

change, little baseline distortion occurs, and system turnaround time is minimized. Such gradients can be used to perform efficient separations of a wide variety of anions.

3. METHODS OF APPLICATION

Macrocycles can be incorporated in the ion chromatographic system in the mobile phase or in the stationary phase. Incorporation in the stationary phase has been achieved in one of three ways: physical adsorption on a solid support; polymerization to form a stationary phase; or covalently bonding to either a polymeric or silica solid support.

3.1. Mobile phase applications

Crown ethers were first used as an additive to the mobile phase by Sousa *et al.* [6],

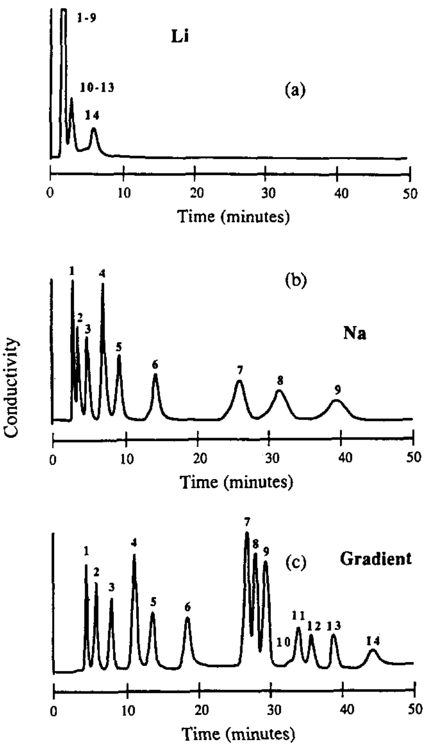

Fig. 6. Separation of fourteen common anions under three different chromatographic conditions: (a) with 20 m*M* LiOH as eluent (isocratic); (b) with 20 m*M* NaOH as eluent (isocratic); (c) with a 20 m*M* NaOH–20 m*M* LiOH gradient over 20 min. Chemically suppressed conductivity detection (from ref. 22).

who used a dinaphthal-18-crown-6 in the mobile phase to separate amino acid isomers. Common cations and anions can also be separated by this approach [21], in addition to protonated amine cations [23–25], amino acids and peptides [26] and β-lactam antibiotics [27]. Brugman and Kraak [28] used crown ether complexes of K^+ in the mobile phase to facilitate ion-pair retention of various sulfonic acids on reversed-phase columns. Similarly, Miyashita and Yamashita [24] used a crown ether complex of a protonated alkylamine as an ion-pairing agent for the retention of I^-. Separations of this type have been limited because of the need for soluble macrocycles, limiting the types that can be used and by the expense of using large amounts of these relatively costly reagents.

3.2. Physical adsorption on a solid support

Kimura's group pioneered the technique of macrocycle adsorption on silica-based C_{18} columns or polystyrene–divinylbenzene packings [9]. Appropriate macrocycles usually have a hydrophobic "tail" or other moiety that promotes strong adherence to the stationary phase. Specifically, Kimura and co-workers [9,17] adsorbed dodecyl-substituted 12-crown-4, 15-crown-5 and 18-crown-6 ligands on silica-based C_{18} columns, and also the cryptand decyl-2.2.2. Typical separations of cations achieved using these modified stationary phases are shown in Fig. 3. Lamb and co-workers [21,22] used decyl-2.2.2 adsorbed on several types of reversed-phase columns for anion and cation separations.

The preparation of adsorbed macrocyclic stationary phases is straightforward and free from the difficulties involved in polymerization or covalent attachment. A water–methanol solution containing just enough methanol to dissolve the desired amount of the macrocycle is recycled through the column for several hours. The capacity of the column can be controlled by the amount of macrocycle loaded onto the column. A potential disadvantage to the adsorption method is the loss of the macrocycle from the stationary phase with time. Kimura *et al.* [9] showed that when a pure water eluent or eluents of low methanol concentration are used, the stationary phase is stable for long periods of time. We have observed that even with millimolar hydroxide eluents, the capacity of such columns remains unchanged after several weeks of use. However, if the methanol concentration is greater than 40%, the macrocycle is quickly eluted from the column. However, even after 50 h of continuous use at 80°C, no decrease in column capacity was detected in our laboratory [18].

Shinbo *et al.* [30] used a chiral crown ether dynamically coated on a reversed-phase packing to separate amino acid enantiomers. Racemic mixtures of almost all common amino acids were resolved using a dilute perchloric acid eluent. A typical chromatogram is shown in Fig. 7. Daicel Chemical Industries market analytical and preparative columns for amino acid enantiomer separations based on chiral crown ether exchange sites [31]. Joly and Gross [32] also reported the resolution of amino acid enantiomers on a C_{18}-bonded silica column containing an adsorbed optically active crown compound.

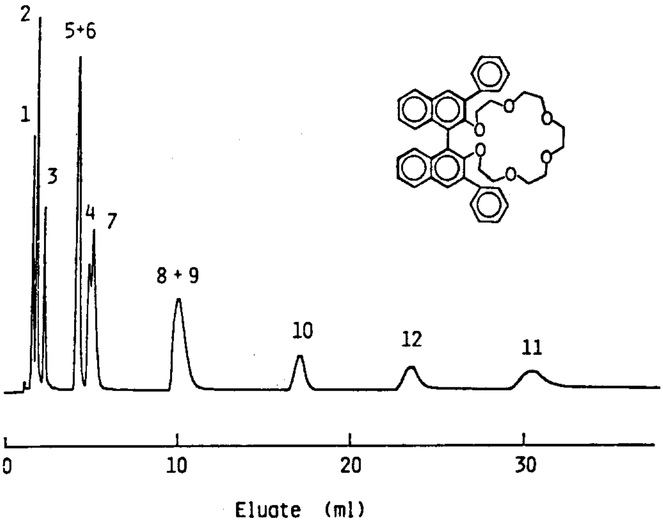

Fig. 7. Separation of six racemic amino acids at 2°C on a reversed-phase packing dynamically coated with the crown ether shown. Elution sequence: 1 = L-alanine; 2 = L-glutamic acid; 3 = D-alanine; 4 = D-glutamic acid; 5 = L-methionine; 6 = L-phenylglycine; 7 = L-leucine; 8 = D-methionine; 9 = D-leucine; 10 = L-phenylalanine; 11 = D-phenylglycine; 12 = D-phenylalanine. Eluent = 0.01 *M* perchloric acid. UV detection. Flow-rate = 0.5 ml/min (from ref. 30).

3.3. Polymeric macrocycle stationary phases

The development and use of polymeric crown ether stationary phases was pioneered by Blasius and co-workers [2,12,33–36]. These polymeric stationary phases have several advantages, *e.g.*, they are stable to a wide variety of solvents. For example, Blasius and co-workers used pure methanol as the mobile phase to perform separations of both cations and anions. As the stability constants of cation–macrocycle complexes can vary widely with the solvent, this stability provides another powerful variable that can be used to modify chromatographic performance.

Polymeric crown ether stationary phases can be formed in two different ways: formation of solid polymer particles or coating a macrocycle polymer on a solid support. Stationary phases were first formed by packing columns with particles of the polymeric resin generated by cross-linking benzo- or dibenzo-crown ethers in formic acid with formaldehyde, so that methylene bridges connected crown moieties [12]. Dibenzo-18-crown-has been the most common polymeric resin. This resin was used by Blasius and co-workers to perform a wide variety of separations, *e.g.*, HCl from NaCl, NaOH from KOH and Na_2SO_4 from NaCl. Separations of alkylammonium chlorides and of anions were also performed on this resin using methanol as the eluent (Fig. 8). Blasius and Janzen [2] also obtained a cesium-selective exchanger by forming a condensation polymer with dibenzo-24-crown-8, potentially useful for separating cesium from high-activity nuclear waste solutions. Polymeric polyamide-18-crown-6 was used by Igawa *et al.* [20] to perform separations. This resin was not successful in separating cations, and very little separation of anions was observed. Suh *et al.* [37] and Jung *et al.* [38] grafted nitrogen-containing crown ethers to styrene–divinylbenzene copolymer and demonstrated separations among lanthanides, Cu^{2+} and $UO_2{}^{2+}$.

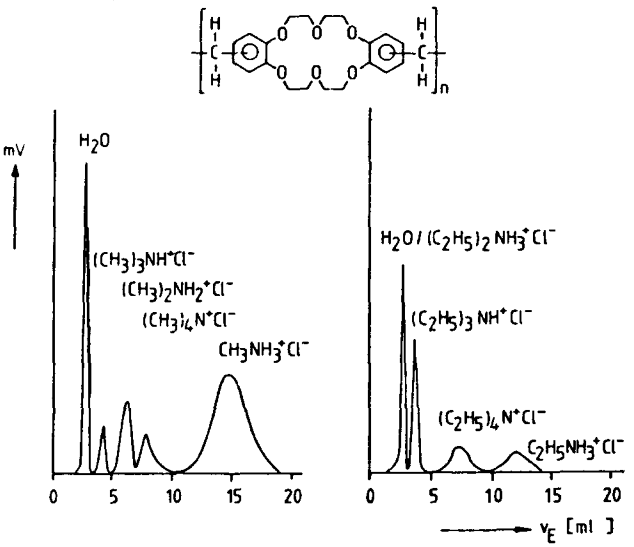

Fig. 8. Separation of alkylammonium chlorides on polymeric dibenzo-18-crown-6 (top) using methanol as eluent (from ref. 2).

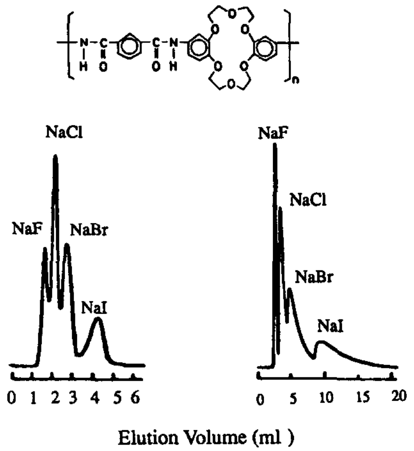

Fig. 9. Separation of sodium halides using the polyamide crown resin shown: (a) alone (flow-rate 0.15 ml/min) and (b) coated on silica particles (flow-rate 0.30 ml/min). Eluent: water. Conductivity detection (from ref. 20).

The polymeric crown ether resins are soft and unable to withstand the high pressures of typical high-performance liquid chromatographic (HPLC) environments. The separations performed with the resins were done at very low flow-rates of 0.05–0.1 ml/min to reduce compression. Hence, the separations are very long, requiring as much as 6 h. The efficiencies of the separations are also poor. To overcome this problem, the same polymeric crowns were coated on hard solid supports. Igawa *et al.* [20] coated polymeric polyamide-dibenzo-18-crown-6 on silica particles by dissolving the resin in N-methyl-2-pyrrolidone, adding silica particles and evaporating. This stationary phase showed superior separations over the polymeric resin alone (Fig. 9).

Blasius and co-workers also coated solid supports with polymeric resins either statically or by polymerization with functional groups on the solid support. The dibenzo-crown ether polymers were reacted with the silanol groups or with chloromethylated polystyrene to form an anchored polymeric resin [2,33–35]. Improved efficiencies at higher flow-rates were achieved over the polymer particles. In addition to separating inorganic anions, Blasius *et al.* [36] also showed that a series of short-chain carboxylic acids could be separated with these resins. Kimura *et al.* [39] were able to separate organic amines and phenols on a similar stationary phase.

3.4. Covalently bound macrocyles

Monomeric macrocycles have been covalently bonded to both silica and polymeric HPLC packings [12,15,16,19,40,41]. These stationary phases exhibit the higher efficiencies of adsorbed crowns and are easier to synthesize than the polymeric crowns. Much of the more recent research in macrocycle-based ion chromatography has been focused on the attachment of crown ethers to solid supports such as silica and polystyrene HPLC resins.

Blasius *et al.* [12] first bonded benzo-15-crown-5 to silica gel and used the resulting resin to separate alkali metals (Fig. 10a). The crown–silica linkage was

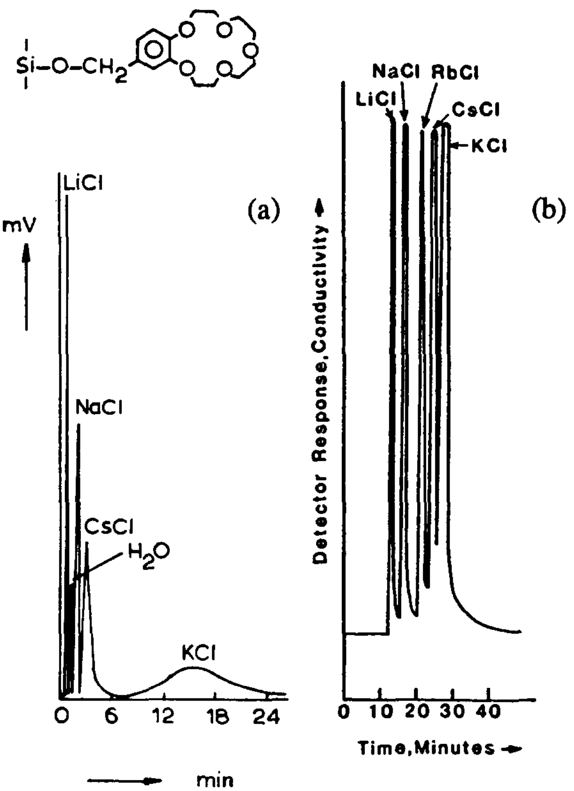

Fig. 10. Separation of alkali metal chlorides. (a) On benzo-15-crown-5 covalently bound to silica particles. Eluent: methanol. Conductivity detection. Flow-rate: 5 ml/min (from ref. 12). (b) On silica-based benzo-18-crown-6 resin, structure as shown in Fig. 5. Eluent: water. Conductivity detection. Flow-rate: 0.16–0.26 ml/min (from ref. 15).

Si–O–CH_2–, which is hydrolyzed by water. Hence methanol (containing less than 0.01% of water) was used as the mobile phase.

Several other types of bonded silica gel macrocycles were prepared by Kimura and co-workers [19,41,42]. The bis- and poly-crown-5 resins gave baseline separations of alkali metals using aqueous mobile phases. Nakajima *et al.* [16] also achieved the separation of a mixture of alkali metals and alkaline earths with these resins. The monomeric forms, while exhibiting some separating ability, provided less separation than the bis- and poly-crown resins. The 18-crown-6 resins showed better ability to separate cations than the 15-crown-5 derivatives [16].

Iwachido *et al.* [14] prepared silica-based resins with 15-crown-5, 18-crown-6 and 21-crown-7. The alkali and alkaline earth metal separations with the 15-crown-5 and 18-crown-6 resins were similar to those obtained by Kimura and co-workers. However, the 21-crown-7 resins showed selectivity toward Rb^+ and Cs^+.

Lauth and Gramain [15,43] also attached benzo-18-crown-6 to silica through a slightly different linkage (see Fig. 5). Anions and alkali and alkaline earth metal cations were separated. This resin showed a higher efficiency than that originally obtained by Blasius and co-workers (see Fig. 10b). Szczepaniak and Szymanski [44] also used silica-bound macrocycles containing nitrogen to separate various phenolic compounds. Josic and Reutter [45] used nitrogen-containing crowns bound to silica to separate nucleic acids and proteins in the presence of K^+ ions.

Most of the above resins are based on benzo derivatives of crown ethers. These benzocrowns bind cations more weakly than the parent crown structures. Bradshaw *et al.* [46] prepared crown ether-modified silica resins that do not contain the aromatic ring in the crown structure. These resins show nearly the same cation-binding equilibrium constants as the unbound macrocycles, leading to the conclusion that cation complexation occurs in the aqueous phase. These resins have been applied with great efficacy to sample cation concentration and separation rather than to high-performance ion chromatographic separations. Samples are loaded onto packed columns, then stripped with EDTA, thiosulfate or some other appropriate complexer depending on the ion(s) to be recovered. A variety of macrocycles have been used in this fashion. Oxygen-only crowns have been used to concentrate alkali metal, alkaline earth metal, Pb^{2+} or Tl^+ cations according to size [46,47]. Nitrogen-containing macrocycles were used to concentrate Ag^+ and Hg^{2+} [47–49] and sulfur-containing macrocycles for gold(III), palladium(II), Ag^+ and Hg^{2+} [50]. Many of these separations were accomplished in the presence of very high concentrations of acid and/or completing cations. These phases are now available commercially through IBC (Provo, UT, U.S.A.). Separation of enantiomers has also been proposed for cationic organic amines using chiral crowns bound to silica in this way [51].

Diaza-crown ethers, in which two nitrogen atoms replace two crown oxygen atoms, have also been attached to silica [52]. These resins have been used in a preparative scale to separate transition metals, and show some promise for analytical separations. Recently two groups have reported the use of crown ethers loaded on solid supports for Cs^+, Sr^{2+} and Ba^{2+} separations of interest to the nuclear industry [53,54].

Very little work has been done to bond crown ethers to polymeric resins. Iwachido *et al.* [14] bonded a benzo-18-crown-6 to a –COOH-type gel through an amide linkage. The results were similar to those found for silica-based stationary phases, but with poorer resolution.

The covalent bonding of macrocycles to silica or other HPLC resins provides several advantages. The efficiencies are better than those observed for similar polymeric resins. They are easier to synthesize and show better mechanical stability. Most of the linkages are stable with respect to water and methanol, so mixed mobile phases that would elute adsorbed crowns from the column can be used. Lack of stability to basic solutions is a problem for silica-based resins.

4. ACKNOWLEDGEMENTS

The authors express appreciation to Dionex for a graduate fellowship to R.G.S.

REFERENCES

1 C. J. Pederson, *J. Am. Chem. Soc.*, 89 (1967) 7017–7036.
2 E. Blasius and K. P. Janzen, *Top. Curr. Chem.*, 98 (1981) 163–189.
3 K. Kimura and T. Shono, *J. Liq. Chromatogr.*, 5 (1982) 223–255.
4 T. Shono, *Jpn. Soc. Anal. Chem.*, 33 (1984) E449–E458.

5 M. Takagi and H. Nakamura, *J. Coord. Chem.*, 15 (1986) 53–82.

6 L. R. Sousa, D. H. Hoffman, L. Kaplan and D. J. Cram, *J. Am. Chem. Soc.*, 96 (1974) 7100–7101.

7 G. Dotsevi, Y. Sogah and D. J. Cram, *J. Am. Chem. Soc.*, 92 (1975) 1259–1261.

8 G. Dotsevi, Y. Sogah and D. J. Cram, *J. Am. Chem. Soc.*, 98 (1976) 3038–3041.

9 K. Kimura, H. Harino, E. Hayata and T. Shono, *Anal. Chem.*, 58 (1986) 2233–2237.

10 R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb and J. J. Christensen, *Chem. Rev.*, 85 (1985) 271–339.

11 A. Bajaj and N. Poonia, *Coord. Chem. Rev.*, 87 (1988) 55–213.

12 E. Blasius, K. P. Janzen, W. Klein, H. Klotz, V. B. Nguyen, T. Nguyen-Tien, R. Pfeiffer, G. Scholten, H. Simon, H. Stockemer and A. Toussaint, *J. Chromatogr.*, 201 (1980) 147–166.

13 M. Nakajima, K. Kimura, E. Hayata and T. Shono, *J. Liq. Chromatogr.*, 7 (1984) 2115–2125.

14 T. Iwachido, H. Naito, F. Samukawa and K. Ishimaru, *Bull. Chem. Soc. Jpn.*, 59 (1986) 1475–1480.

15 M. Lauth and P. Gramain, *J. Chromatogr.*, 395 (1987) 153–158.

16 M. Nakajima, K. Kimura and T. Shono, *Bull. Chem. Soc. Jpn.*, 56 (1983) 3052–3056.

17 K. Kimura, H. Hayata and T. Shono, *J. Chem. Soc., Chem. Commun.*, (1984) 271–272.

18 R. G. Smith, P. A. Drake and J. D. Lamb, *J. Chromatogr.*, 546 (1991) 139–149.

19 K. Kimura, M. Nakajima and T. Shono, *Anal. Lett.*, 13(A9) (1980) 741–751.

20 M. Igawa, K. Saito, J. Tsukamoto and M. Tanaka, *Anal. Chem.*, 53 (1981) 1942–1944.

21 J. D. Lamb and P. A. Drake, *J. Chromatogr.*, 482 (1989) 367–380.

22 J. D. Lamb, P. A. Drake and K. E. Woolley, in P. Jandik and R. M. Cassidy (Editors), *Advances in Ion Chromatography*, Vol. 2, Century International, Franklin, MA, 1990, pp. 215–231.

23 M. Wiechmann, *J. Chromatogr.*, 235 (1982) 129–137.

24 T. Nakagawa, H. Murata, A. Shibukawa, K. Murakami and H. Tanaka, *J. Chromatogr.*, 330 (1985) 43–53.

25 S. Iwagami and T. Nakagawa, *J. Chromatogr.*, 369 (1986) 49–58.

26 T. Nakagawa, A. Shibukawa, A. Kaihara, T. Ita-Mochi and H. Tanaka, *J. Chromatogr.*, 353 (1986) 399–408.

27 T. Nakagawa, A. Shibukawa and T. Uno, *J. Chromatogr.*, 239 (1982) 695–706.

28 W. J. T. Brugman and J. C. Kraak, *J. Chromatogr.*, 205 (1981) 170–178.

29 M. Miyashita and S. Yamashita, *J. Liq. Chromatogr.*, 9 (1986) 2143–2151.

30 T. Shinbo, T. Yamaguchi, K. Nishimura and M. Sugiura, *J. Chromatogr.*, 305 (1987) 145–153.

31 *CROWNPAK, CHIRALPAK, CHIRALCEL: Chiral HPLC Columns for Optical Resolution*, Daicel Chemical Industries, Tokyo, 1989.

32 J. P. Joly and B. Gross, *Tetrahedron Lett.*, 26 (1989) 4231–4234.

33 E. Blasius and K. P. Janzen, *Isr. J. Chem.*, 26 (1985) 25–34.

34 E. Blasius, K. P. Janzen, H. Luxenburger, V. B. Nguyen, H. Klotz and J. Stockemer, *J. Chromatogr.*, 167 (1978) 307–320.

35 E. Blasius, K. P. Janzen, H. Simon and J. Zender, *Fresenius' Z. Anal. Chem.*, 320 (1985) 435–438.

36 E. Blasius, K. P. Janzen and J. Zender, *Fresenius' Z. Anal. Chem.*, 325 (1986) 126–128.

37 M. Suh, T. Eom and I. Suh, *Bull. Korean Chem. Soc.*, 8, No. 5 (1987) 2–8.

38 O. Jung, H. Jung and J. Kim, *J. Korean Chem. Soc.*, 32 (1988) 358–370.

39 K. Kimura, H. Harino and T. Shono, *Chem. Lett.*, (1985) 747–750.

40 T. G. Waddell and D. E. Leyden, *J. Org. Chem.*, 46 (1981) 2406–2407.

41 M. Nakajima, K. Kimura and T. Shono, *Anal. Chem.*, 55 (1983) 463–467.

42 K. Kimura, M. Nakajima and T. Shono, *J. Polym. Sci.*, 23 (1985) 2327–2331.

43 M. Lauth and P. Gramain, *J. Liq. Chromatogr.*, 8 (1985) 2403–2415.

44 W. Szczepaniak and A. Szymanski, *Chem. Anal. (Warsaw)*, 32 (1987) 273.

45 D. Josic and W. Reutter, *J. Chromatogr.*, 476 (1989) 309–318.

46 J. S. Bradshaw, R. L. Breuning, K. E. Krakowiak, J. B. Tarbet, M. L. Breuning, R. M. Izatt and J. J. Christensen, *J. Chem. Soc., Chem. Commum.*, (1988) 812–814.

47 R. M. Izatt, R. L. Bruening, M. L. Bruening, B. J. Tarbet, K. E. Krakowiak, J. S. Bradshaw and J. J. Christensen, *Anal. Chem.*, 60 (1988) 1825–1826.

48 J. S. Bradshaw, K. E. Krakowiak, B. J. Tarbet, R. L. Bruening, J. F. Biernat, M. Bochenska, R. M. Izatt and J. J. Christensen, *Pure Appl. Chem.*, 61 (1989) 1619–1624.

49 R. M. Izatt, R. L. Bruening, B. J. Tarbet, D. Griffin, M. L. Bruening, K. E. Krakowiak and J. S. Bradshaw, *Pure Appl. Chem.*, 62 (1990) 1115–1118.

50 J. S. Bradshaw, K. E. Krakowiak, R. M. Izatt, R. L. Bruening and B. J. Tarbet, *J. Heterocycl. Chem.*, 27 (1990) 347–349.

51 J. S. Bradshaw, R. M. Izatt, J. J. Christensen, K. E. Krakowiak, B. J. Tarbet, R. L. Bruening and S. Lifson, *J. Inclus. Phenom. Mol. Recog. Chem.*, 7 (1989) 127–136.
52 V. Dudler, L. F. Lindoy, D. Sallin and C. W. Schlaepfer, *Aust. J. Chem.*, 40 (1987) 1557–1563.
53 N. Y. Kremliakova, A. P. Novikov and B. F. Myasoedov, *J. Radioanal. Nucl. Chem. Lett.*, 145 (1990) 23–28.
54 E. Peimli, *J. Radioanal. Nucl. Chem. Lett.*, 144 (1990) 9–15.