*Journal of Inclusion Phenomena and Molecular Recognition in Chemistry* **32:** 107–119, 1998.



# Macrocyclic Ligands in Separations

JOHN D. LAMB* and MARK D. CHRISTENSON
*Department of Chemistry and Biochemistry, Brigham Young University, P.O. Box 25700, Provo, UT 84602–5700, USA*

(Received: 31 July 1997; in final form: 15 September 1997)

**Abstract.** The selectivity of macrocyclic ligands such as crown ethers and cryptands in binding metal and other cations in aqueous and nonaqueous solvents can be exploited to make ion separations. Cations are usually separated by direct interaction with the ligand. In addition, anions associated with the positively charged macrocyclic complexes can be separated in novel separations systems. We have incorporated macrocyclic ligands into high performance ion chromatography, liquid membranes, and solvent extraction separation systems involving coalescence extraction.

**Key words:** macrocyclic ligands, high-performance ion chromatography, cryptand *n*-decyl-[2.2.2], liquid membranes, polymer inclusion membrane, coalescence extraction.

## 1. Introduction

The documented cation selectivity of macrocyclic ligands makes them excellent candidates for incorporation into separations systems. In a recent report [1], the U.S. National Research Council emphasized the need for separations systems of greater selectivity and efficiency. In the report the Council's two highest priority items under "High Priority Research Needs and Opportunities" are to (1) generate improved selectivity among solutes in separations and (2) concentrate solutes from dilute solutions. In both areas, their report emphasized the need for new reagents and processes to make possible a high degree of selectivity toward similar chemical species.

Our laboratory's research into the interesting chemistry of macrocyclic ligands has provided insight into three novel separations methods. These methods are (1) high-performance ion chromatography (HPIC), (2) liquid membranes, and (3) coalescence extraction, a novel mode of solvent extraction. In this paper we present a short review of our laboratory's most significant developments in each of these three areas. Such developments have laid the foundation for future incorporation of new, more complex macrocycles into such separations systems.

* Author for correspondence.

## 2. High-Performance Ion Chromatography [2]

Since the early days of macrocyclic ligand research, macrocycles have been incorporated into chromatography systems. Various laboratories have produced notable achievements in this area. Cram [2] chromatographically separated enantiomers of amino acids using a chiral macrocycle in the mobile phase. In the laboratory of Blasius [2], cations and anions were separated on a resin they developed which contained polymeric crown ethers. Izatt and Bradshaw [2] bound crown ethers to silica particles for the separation of metal cations. However, much of the above work was carried out in a preparative chromatographic mode, in contrast to high-performance analytical separations.

High-performance ion chromatography is a well-established analytical method for the analysis of cations and anions. Samples are injected into a flowing mobile phase, separated on an ion exchange column, and detected, usually conductimetrically. Conductivity detection is commonly implemented by inserting a suppressor module ahead of the detector, thereby lowering the background conductivity by removing eluent ions. We have incorporated macrocyclic ligands (see Figure 1) into chromatography columns by adsorbing hydrophobic macrocycles, such as tetradecyl-18-crown-6 (TD18C6) or cryptand *n*-decyl-[2.2.2] (D222), onto the same styrene/divinylbenzene copolymer used in traditional ion chromatography columns. Since the macrocyclic active site remains on the bead surface, a column can be prepared using a minimal quantity of ligand. Tetradecyl-18-crown-6 columns are capable of generating an excellent separation of nine cations, including alkali metals, common alkaline earth metals ($Ca^{2+}$, $Sr^{2+}$, $Ba^{2+}$), and $NH_4^+$. Figure 2 shows an isocratic separation using a methanesulfonic acid eluent and suppressed conductimetric detection. The separation compares favorably with those achieved by standard HPIC techniques.

When a neutral macrocyclic ligand is used as the active site in a chromatography column, the column can separate anions as well as cations. In this sense, macrocycle-based columns are much more versatile than traditional ion exchange columns. The cation-macrocycle complexes that form on the column serve as anion-exchange sites. Since the macrocycle on the column has varying affinities for different cations, the population of cation-macrocycle complexes will change according to the identity of the cation in the eluent. Column capacity is governed by the degree to which macrocycles on the column are occupied by cations from the mobile phase. Therefore, column capacity can be easily adjusted by changing the mobile phase cation. If the macrocyclic complex is labile, a change in column capacity can be achieved over a short period of time and the chromatographer can exploit this effect to achieve separations. For example, a D222-based chromatography column will retain anions very strongly if a KOH eluent is used, since D222 has a high affinity for $K^+$; therefore, the population of anion-exchange sites on the column will be high. Conversely, if the eluent is switched to LiOH, anion retention

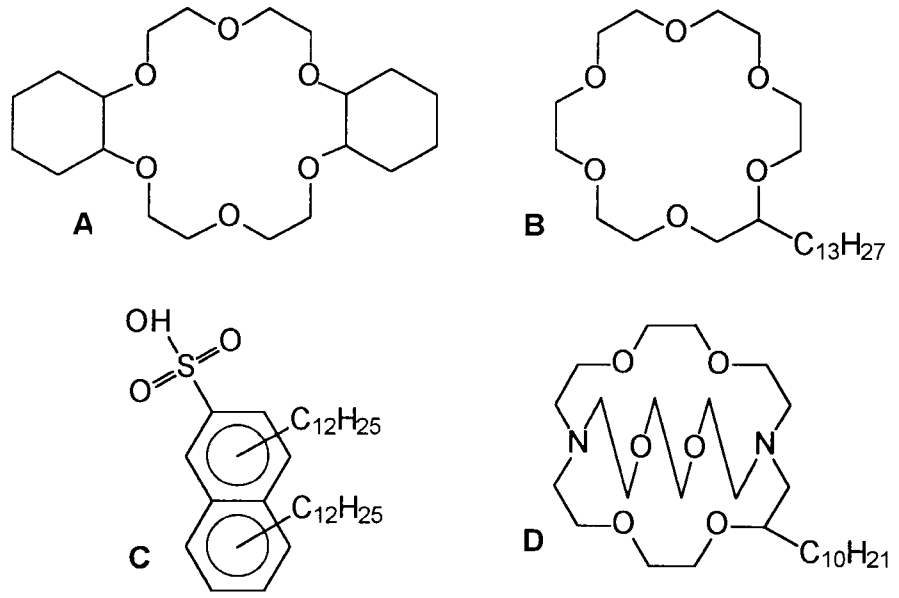


*Figure 1.* Structures of (**A**) dicyclohexano-18-crown-6 (DC18C6), (**B**) tetradecyl-18-crown-6 (TD18C6), (**C**) didodecylnaphthalene sulfonic acid (DDNS), and (**D**) cryptand *n*-decyl-[2.2.2] (D222).

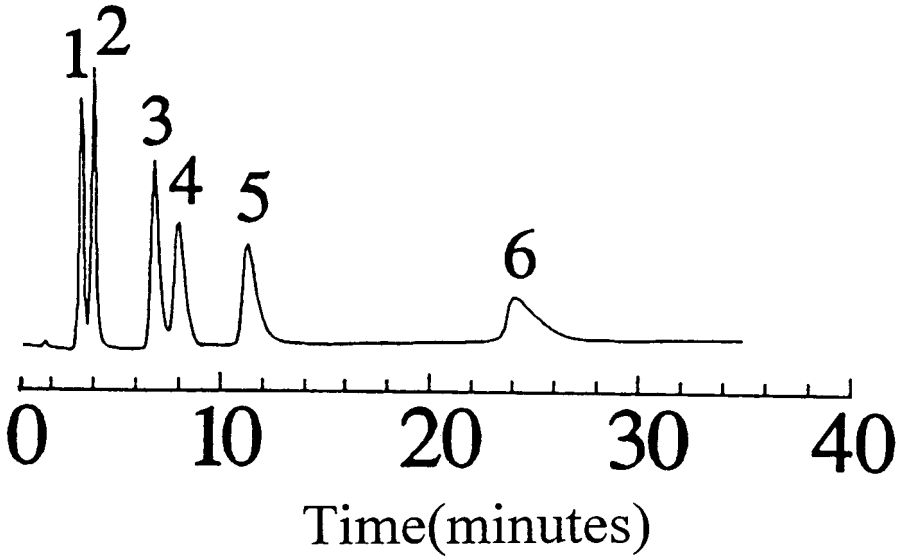


*Figure 2.* An isocratic separation on a TD18C6 column using a 0.25 mM methanesulfonic acid eluent. The peaks are identified as: 1 = $Li^+$, 2 = $Na^+$, 3 = $Cs^+$, 4 = $NH_4^+$, 5 = $Rb^+$, and 6 = $K^+$. All analyte concentrations were 0.1 mM.

will be low. This is because D222 has a low affinity for $Li^+$; hence, the population of anion-exchange sites on the column will be low.

The effect described above can be used to cause the capacity of a column to change rapidly during the course of separation and overcome the general elution problem. The general elution problem can be described thus: sometimes if a separations system is optimized for good resolution of early eluting peaks, late peaks will come out too slowly and broadly. On the other hand, if the system is optimized for good resolution of the later eluting peaks, the earlier peaks are not separated. The traditional solution to this general elution problem is to form a gradient by gradually increasing the strength of the eluent during the course of the separation, causing later peaks to elute more quickly. The same effect can be achieved in macrocycle-based anion chromatography, not by changing the strength of the eluent, but by lowering the capacity of the column. For example, during the course of a separation using a D222-based column, the eluent can be changed from NaOH to LiOH in either a stepwise or gradient mode. This change causes the population of anion exchange sites on the column to gradually decrease. This decrease provides early eluting species with a column of fairly high capacity, while later eluting species are exposed to a column of low capacity. For example, using a D222 column for an isocratic separation of anions with a LiOH eluent, all of the anions elute in a short time, but with very poor resolution. Conversely, when an NaOH eluent is used, early eluting anions are well separated, but strongly retained anions elute too slowly. The chromatogram in Figure 3 represents a capacity gradient separation in which the eluent is changed from NaOH to LiOH. This gradient generates good separations among both early and late eluting peaks. An advantage of capacity gradients over traditional gradients is its stable baseline. With conductimetric detection traditional gradients cause baseline distortion. However, in a capacity gradient, the ionic strength, and hence the conductivity of the eluent, changes very little. Consequently, the baseline remains stable during the course of the separation.

A capacity gradient can also be achieved by changing the temperature of a column instead of the eluent cation. Since the enthalpy change of metal ion complexation in solution for macrocyclic ligands is usually exothermic, the value of the binding constant is temperature dependent (i.e., the degree of complex formation drops rapidly with temperature). As the capacity of the column drops as the temperature of the column is raised, the same capacity gradient effect is achieved.

We recently investigated the application of capacity gradients to macrocycle-based anion chromatography in the separation of mono-, di-, and oligosaccharides. We achieved good separations of mono- and disaccharides on a D222-based column. The same column was also successful in separating a homologous series of maltooligosaccharides (see Figure 4). Macrocycle-based gradient capacity separations have the distinct advantage over other oligosaccharide separations in that a much lower background ionic strength is required. This is advantageous when

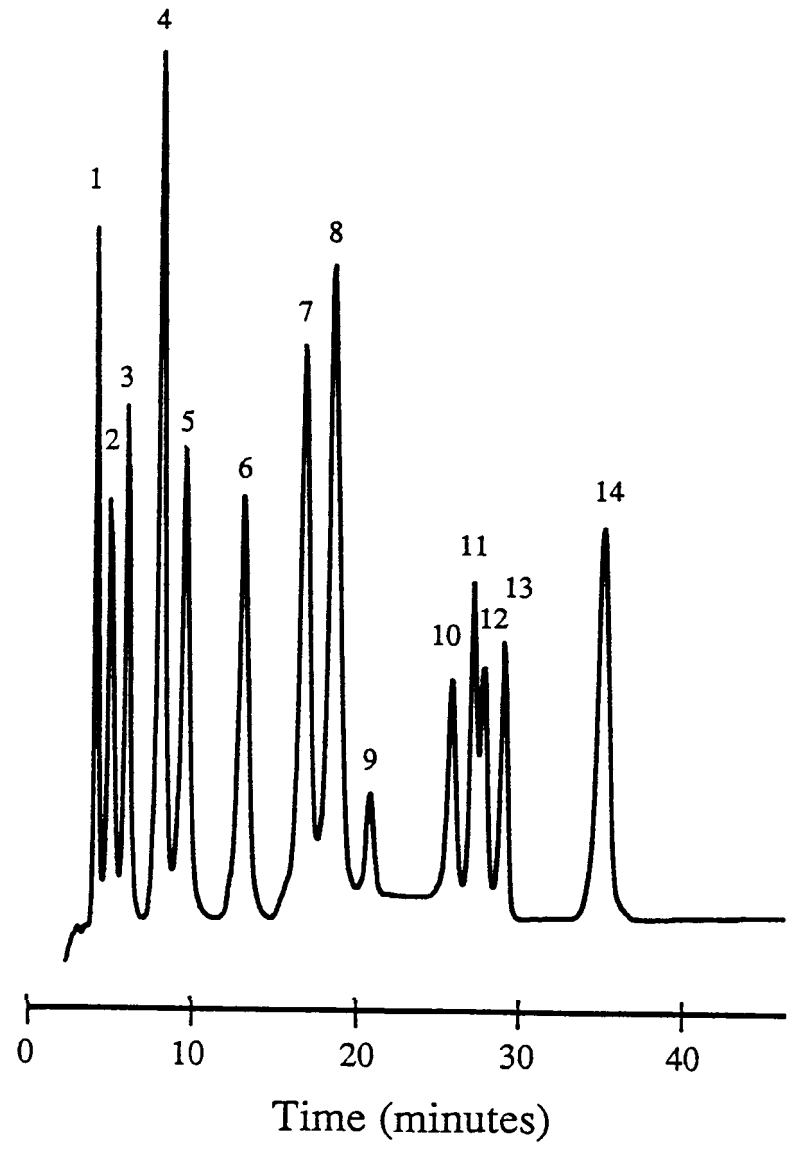


*Figure 3.* A gradient separation on a D222-based column. The gradient was 30 mM Na-LiOH over 20 min. The peaks are identified as: 1 = $F^-$, 2 = Acetate, 3 = $Cl^-$, 4 = $NO_2^-$, 5 = $Br^-$, 6 = $NO_3^-$, 7 = $SO_4^{2-}$, 8 = Oxalate, 9 = $CrO_4^{2-}$, 10 = $I^-$, 11 = $PO_4^{3-}$, 12 = Phthalate, 13 = Citrate, and 14 = $SCN^-$. All concentrations were 10 ppm except $F^-$ was 1.5 ppm and $Cl^-$ was 3.0 ppm.

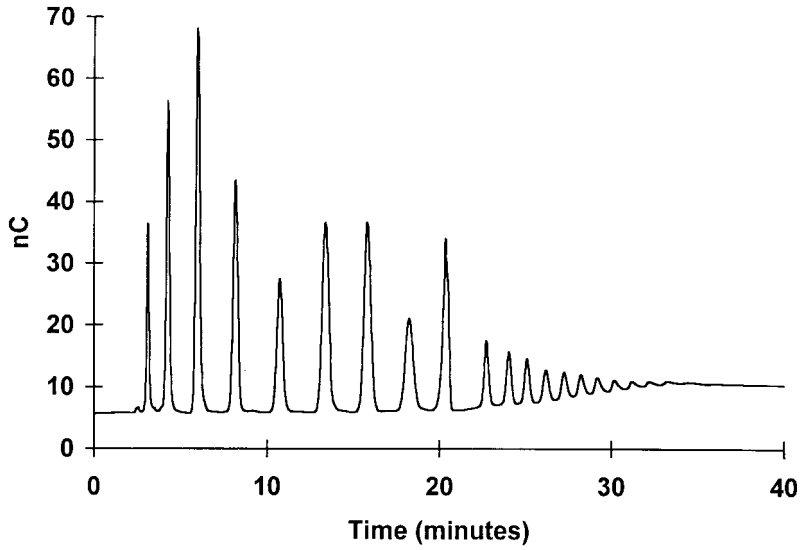


*Figure 4.* Capacity gradient separation of a maltodextrin homologous series on a D222-based column. Conditions: 100 mM KOH with a step at 5 min to 100 mM LiOH.

collection, purification, or further use of the individual polysaccharide peaks is needed, or when mass spectrometric analysis is required.

## 3. Liquid Membranes [3]

A membrane is "a semi-permeable barrier between two phases" that prevents intimate contact between these phases [4]. A membrane's semi-permeable nature allows species to be separated by their different rates of transport across the membrane. A liquid membrane is composed of a liquid (albeit sometimes viscous) which permits diffusion from a source phase to a receiving phase. Macrocyclic ligands, when included in a hydrophobic liquid membrane, can selectively extract metal ions from the source phase and facilitate their transport to the receiving phase, thereby achieving separations. If the macrocyclic ligand in the membrane is neutral, anions from the source phase must accompany cations through the membrane. Under this mechanism, cations are forced through the membrane against their concentration gradients either by introducing a complexing agent into the receiving phase or by the resulting chemical potential from the difference in anion concentrations between the two water phases. If the ligand is acidic, its acidic proton can be exchanged at the source phase/membrane interface for another monovalent cation. The resulting metal-ligand complex moves through the membrane as a neutral species. At the membrane/receiving phase interface the macrocycle exchanges its metal cation for a proton. This counter transport of protons can be used to force cations through the membrane against their concentration gradients when there is a proton gradient from receiving to source phase.

By these means, selective separation and concentration of specific metal ions can be achieved.

In our laboratory, we have introduced macrocyclic ligands into membranes of four types.

### 3.1. BULK LIQUID MEMBRANES

These membranes are stirred layers of unsupported, hydrophobic organic liquid. Two aqueous phases sit atop the membrane and are separated by a barrier. Bulk liquid membranes have little potential for practical application, but are useful to screen membrane carriers for cation selectivity.

### 3.2. EMULSION LIQUID MEMBRANES

These membranes are formed in two steps. First, an aqueous receiving phase is emulsified with a hydrophobic liquid membrane which contains a surfactant to stabilize the emulsion. Then the resulting emulsion is stirred into the aqueous source phase. This kind of liquid membrane suffers from instability; however, pilot scale systems have been developed and tested. In such systems, the membrane is continually recycled (i.e., broken down after a short time and regenerated for repeated use).

### 3.3. SUPPORTED LIQUID MEMBRANES

In these membranes, liquid is wicked by capillary action into the pores of an inert, porous polymer sheet, such as polypropylene. The resulting thin, plastic sheet has the appearance of a traditional membrane. However, only a fraction of the sheet's surface area is actually composed of liquid membrane. These membranes can be implemented for practical separations in a spiral-wound flat sheet or a high-surface-area, hollow-fiber bundle format. Both formats achieve good selectivity and flux; however, the membrane suffers from instability as membrane solvent gradually leaches from the pores.

### 3.4. POLYMER INCLUSION MEMBRANES (PIMS)

These membranes are formed by mixing a polymer (such as cellulose triacetate), a macrocyclic carrier, and a large amount of plasticizer (an organic liquid such as *ortho*-nitrophenyloctyl ether (NOE), which serves as the "liquid" of the liquid membrane) in a volatile solvent, such as dichloromethane. This solution is then allowed to sit on a flat, glass plate and evaporate, to form a celluloid-type film. The resulting membrane has the following approximate composition by weight: 18% polymer, 9% carrier, and 73% plasticizer.

We have shown that PIMs function mechanistically as true liquid membranes, despite their mechanical strength and amorphous-solid appearance. They are quite stable and for this reason are the most promising candidates for implementing macrocyclic ligand chemistry in membrane separations. Our laboratory has carried out experiments for over ninety days without membrane deterioration or change in permeability. Furthermore, the same membrane has been used in repeated experiments with reproducible performance. A macrocycle's selectivity for a given cation is reflected by the rate of the cation's flux through the membrane. This has also been observed in other kinds of membranes, the exception being when the stability of the macrocycle-cation complex is so high that it limits cation release into the receiving phase.

The separation of cations by liquid membranes is of special interest to the nuclear industry. The U.S. Department of Energy is interested in the potential of applying macrocycle-containing membranes to the removal and concentration of toxic, radioactive metals from nuclear waste. For this reason we have focused our research on $Pb^{2+}$, $Sr^{2+}$, and $Cs^{+}$. Our results show that the permeability for $Pb^{2+}$ of a membrane containing *bis*-tert-butylcyclohexano-18-crown-6 is consistent over a period of twenty days, and that the $Pb^{2+}$ cation is selectively transported over $Na^{+}$, even when $Na^{+}$ is present at a concentration higher by several orders of magnitude.

Metal ion transport through PIMs is a first order kinetic process based on the diffusion of the ligand-metal complex through the membrane. Membrane selectivity, on the other hand, is determined by the degree of extraction of a metal ion at the source phase/membrane interface. The transport mechanism is shown below, where subscript *s* indicates the source phase, *r* the receiving phase, and *membr* the membrane. (1) The uptake of metal cations and source phase anions with a ligand into the organic phase, (2) the diffusion from the source to the receiving interface, and (3) the reverse equation for the breakup of the complex into the receiving phase.

$$J_{in} = k_1[M]_s[A]_s^n[L]_{membr,s} \tag{1}$$

$$J_{diff} = \frac{D_{membr}}{l_{membr}}([MLA]_{membr,s} - [MLA]_{membr,r}) \tag{2}$$

$$J_{out} = -k_1[M]_r[A]_r^n[L]_{membr,r} + k_{-1}[MLA_n]_{membr,r}. \tag{3}$$

The flux ($J$) through the membrane can be represented by the equation

$$J = \frac{D_{MLA}}{l}[MLA]_{org}, \tag{4}$$

where $J$ is the flux, $D$ is the diffusion coefficient, and $l$ is the thickness of the membrane. Figure 5 shows the first order kinetic plot for the diffusion of $Pb^{2+}$ through a liquid membrane of this type.

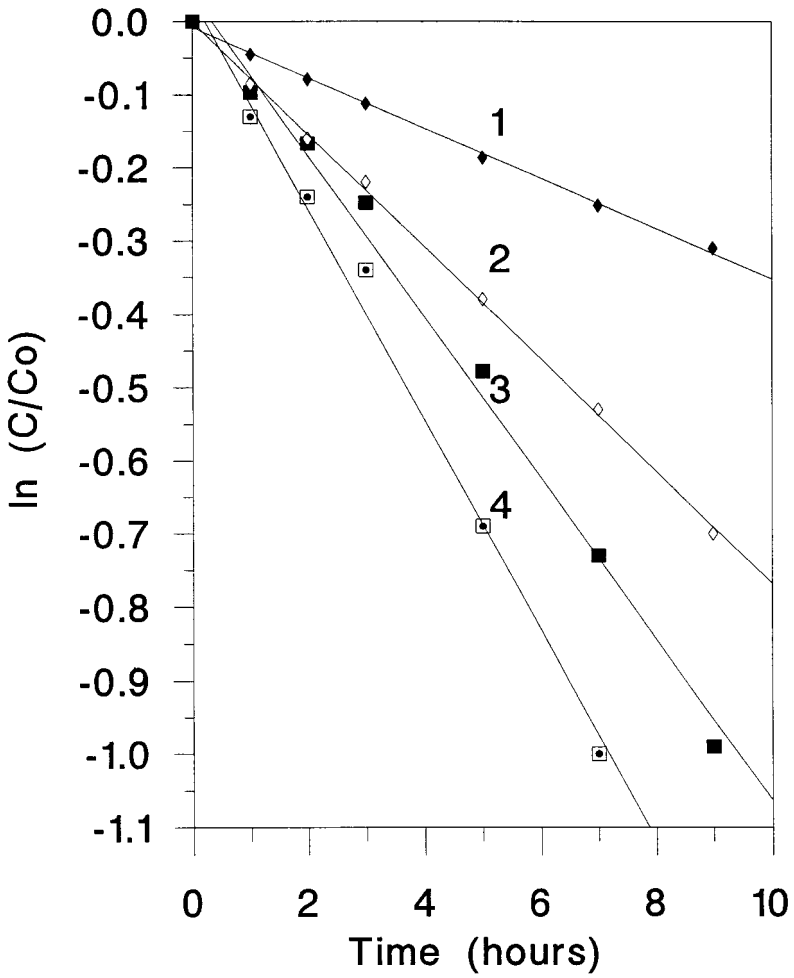


*Figure 5.* First order kinetics of $Pb^{2+}$ transport through PIMs. Conditions: 5 mM EDTA in receiving phase, source and receiving phases with equal picrate concentrations of (1) 0.5 mM, (2) 1.0 mM, (3) 2.5 mM, and (4) 4.0 mM.

The incorporation of a hydrophobic counter ion into the organic phase can lower the energy requirement for extracting the metal cation from the source phase into the membrane. When a hydrophobic counter anion such as didodecylnaphthalene sulfonic acid (DDNS) (see Figure 1) is used, a synergistic effect is achieved. Table I shows the permeability of a membrane to $Sr^{2+}$ in the presence of (1) DDNS alone, (2) dicyclohexano-18-crown-6 alone, and (3) when both DDNS and dicyclohexano-18-crown-6 are present. There is clearly a synergistic effect when both carrier and counter ion are present.

Membrane selectivity is highly dependent on the degree of metal ion extraction from source to membrane phase. We measured the distribution ratios of $Pb^{2+}$ and

*Table I.* The permeability (P) of a PIM to $Sr^{2+}$ in the presence of didodecylnaphthalene sulfonic acid (DDNS) alone, dicyclohexano-18-crown-6 (DC18C6) alone, and when both are present

| | DDNS | DC18C6 | DDNS and DC18C6 |
|---|---|---|---|
| $P_{Sr}$ ($10^{-7}$ m $s^{-1}$) | 0.34 | 0.93 | 13 |

[a] Source phase: 0.1 M $HNO_3$, 2M $NaNO_3$, and 1 mM $Sr(NO_3)_2$. Receiving phase: 20 mM $Na_4EDTA$.

*Table II.* The distribution constant, $K_d$, for $Pb^{2+}$ and $Sr^{2+}$ between water and *bis*-tert-butylcyclohexano-18-crown-6 in an NOE-based PIM

| | log $K_d$ | |
|---|---|---|
| $[HNO_3]$ M | $Pb^{2+}$ | $Sr^{2+}$ |
| 0.16 | 3.4 | 1 |
| 0.32 | 2.8 | 0.9 |
| 0.48 | 2.9 | – |
| 0.64 | 2.8 | 1.3 |
| 0.83 | 2.9 | – |
| 1.28 | 2.9 | 1.5 |

$Sr^{2+}$ with *bis*-tert-butylcyclohexano-18-crown-6 in NOE. The results are shown in Table II. It is clear from the data that such a membrane should be selective for $Pb^{2+}$ over $Sr^{2+}$, as borne out in membrane experiments. Selectivity is only slightly dependent on the nitric acid concentration in the source phase. This result is significant because many nuclear waste solutions have a high background concentration of nitric acid. The selectivity of these membranes and their dependence on the source phase anion has been investigated. It is clear that there is a very strong selectivity for $Pb^{2+}$ over $Sr^{2+}$ and $Na^+$, even in the presence of a very high background of $Na^+$. The ligand *bis*-tert-butylcyclohexano-18-crown-6 is currently used in a solvent extraction system known as SREX [5] to separate $Sr^{2+}$ from nuclear waste. For both the membrane and SREX processes to function effectively, any $Pb^{2+}$ present in the waste matrix must be taken into account.

In summary, PIMs effectively exploit the selectivity of macrocyclic ligands in both separation and concentration. They have the mechanical strength of an amorphous solid and the chemical transport characteristics of a true liquid membrane. They demonstrate long-term stability, ease of preparation, and a high active surface area-to-volume ratio.

*Table III.* Properties of solvents (coalescing solvents in bold) and partition constants of *cis-syn-cis*-DC18C6[b]

| Solvent | Dielectric constant | Solubility in water | Solubility of water in solvent | $P_{DC18C6}$[a] | |
|---|---|---|---|---|---|
| | | | % | Mole ratio | |
| chloroform | 4.9 | 0.7 | 0.072 | 0.0048 | 2500 |
| benzyl alcohol | 13.1 | 3.9 | – | – | 306 |
| benzonitrile | 25.2 | 0.2 | 1 | 0.05 | – |
| **butyronitrile** | 23 | 3.35 | 1.99 | 0.08 | 51 |
| **adiponitrile** | 32.5 | 5.5 | 5.9 | 0.40 | 14.6 *16*(*1*) |
| **glutaronitrile** | – | 10.5 | 10 | 0.57 | 11.5 *10*(*1*) |
| **succinonitrile** | 57.3 | 11 | 8.5 | 0.41 | 17 |
| **malononitrile** | 46.3 | 11.8 | 12 | 0.50 | 700 (*>400*) |

[a] NMR data are shown in italics.
[b] Some data taken from references [6–11].

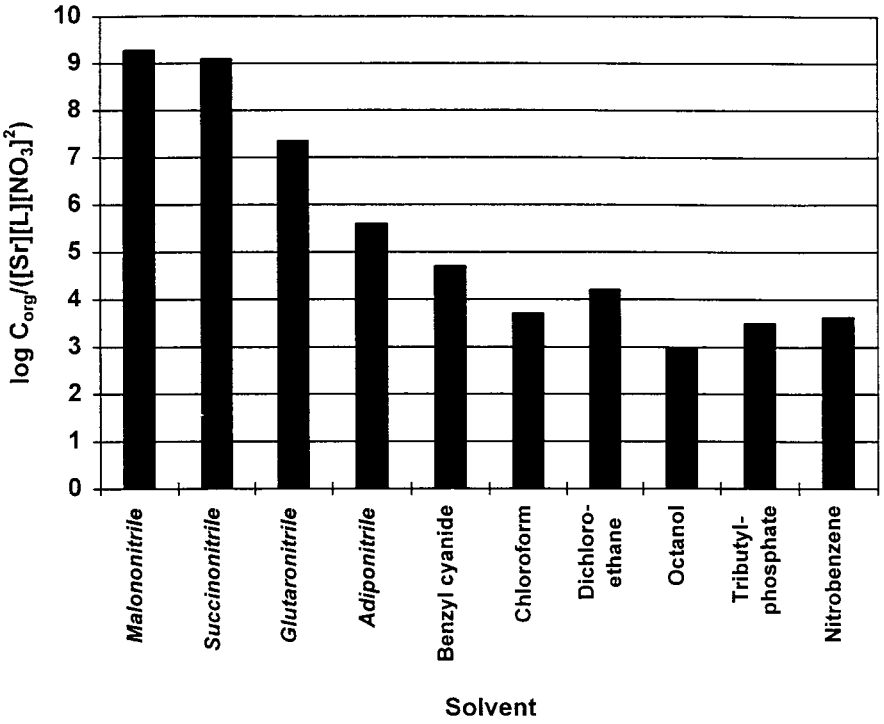


*Figure 6.* Extraction constants of various coalescing and non-coalescing solvents using DC18C6. Coalescing solvents are in italics.

## 4. Coalescence Extraction [6]

Solvent extraction is a traditional approach used to apply ligand selectivity in separations. Our laboratory has pioneered a novel method of solvent extraction called coalescence extraction. Coalescence extraction takes advantage of non-aqueous solvents that are immiscible with water at one temperature, but become completely miscible with water at a lower or higher temperature. The advantage of this type of extraction is that chemical equilibrium is rapidly achieved since the extraction diluent and the aqueous solution are intimately mixed. This mixing occurs when a diluent containing a macrocycle is added to an aqueous matrix of interest, stirred, and heated, to cause the two solutions to coalesce into one. Because the two phases coalesce, no interfacial boundary layers must be crossed for the extractant to encounter the species to be extracted, as is the case in traditional solvent extraction. Therefore, equilibrium is rapidly achieved. When the resulting solution is cooled and phase separation occurs, the ions of interest remain bound to the extractant in the organic phase while other ions return to the newly reconstituted aqueous phase.

Table III shows the physical properties of some coalescing and non-coalescing solvents we have compared in our laboratory. In all cases the degree of extraction by coalescing solvents is at least as good as that achieved using the

same macrocyclic ligands in more traditional non-coalescing solvents, such as chloroform.

We observed an interesting and unanticipated feature of extraction behavior when using coalescing solvents containing nitrilo groups. Dinitrilo solvents show both coalescing behavior and give improved extraction constants, as illustrated in Figure 6. For example, when $Sr^{2+}$ is extracted using dicyclohexano-18-crown-6 in malononitrile, the extraction constant is six orders of magnitude higher than when chloroform is the solvent. However, not all coalescing solvents exhibit this behavior. The improvement observed when using dinitrile solvents may result from a mixed complex between the macrocycle, the dinitrile solvent, and the metal cation. Dinitrilo solvents have an acidic hydrogen on their $\alpha$-carbon, which makes hydrogen bonding to macrocycles possible. We have deduced x-ray crystal structures of various complexes between macrocycles and dinitrile solvents, which support this hypothesis. Overall, dinitrilo solvents offer excellent potential for making good metal cation separations using coalescence extraction.

## Acknowledgements

Appreciation is expressed to the United States Department of Energy, Office of Basic Energy Sciences, Chemical Science Division, which funded this research through grant number DE–FG02–86ER13463.

## References

1. *Separation and Purification: Critical Needs and Opportunities* (Report to the National Research Council by the Committee on Separations Science and Technology, Chairman C.J. King), National Academy, Washington, DC, (1987).
2. J.D. Lamb and R.G. Smith: *The Application of Macrocyclic Ligands to High Performance Ion Analysis*: In J.L. Atwood, J.E.D. Davies, D.D. McNicol and F. Vögle (eds.), *Comprehensive Supramolecular Chemistry*, Pergamon (1996) and references cited therein, pp. 78–112.
3. R.T. Peterson and J.D. Lamb: *Design of Macrocyclic Carriers for Liquid Membranes*: In R.A. Bartsch and J.D. Way (eds.), *Chemical Separations with Liquid Membranes*, Washington, DC, (1996) and references cited therein, pp. 57–74.
4. R.D. Noble: *Sep. Sci. Tech.* **22**, 731 (1987).
5. E.P. Horwitz, M.L. Dietz and D.E. Fisher: *Sol. Extr. Ion. Exch.* **8**, 557 (1990).
6. J.D. Lamb and R.T. Peterson: *Sep. Sci. Tech.* **30**(17), 3237 (1995) and references cited therein.
7. Y. Markus and A.S. Kertes: *Ion Exchange and Solvent Extraction of Metal Complexes*, Wiley Interscience, New York, pp. 927–935 (1969).
8. V.V. Kafarov: *Solubilities of Inorganic and Organic Compounds*, Vol. 1; Pergamon, London (1963).
9. R.K. Freier: *Aqueous Solutions*, Vol. 1; Walter de Gruyter, Berlin (1976).
10. E. Buncel, H.S. Shin, R.A.B. Bannard and J.G. Purdon: *Can. J. Chem.* **62**, 926 (1984).
11. N.A. Lipkovska, A.Y. Nazarenko, V.V. Sukhan and A.A. Chukio: *Russ. J. Anal. Chem.* **47**, 1033 (1992).