Anion Separation and Preconcentration with Cyclen and Cyclen-Resorcinarene Derivatives

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Abstract

N-undecyl cyclen and a resorcinarene bowl bearing four cyclen arms have been applied as anion exchangers in ion chromatography by strong adsorption to a reversed-phase column. The column loaded with the resorcinarene bowl cyclen tetramer exhibited significantly better performance in anion separation than that with *N*-undecyl cyclen monomer in isocratic elution mode. Both columns were tested for polarizable anion preconcentration or removal. By changing the eluent type from sodium bicarbonate to sodium hydroxide, the degree of protonation of the cyclen molecules could be modified, and the column capacity for anion retention adjusted thereby. Capacity gradient elution was successfully applied to removing sample matrix ions in the preconcentration of perchlorate and perrhenate ions as example analytes.

Introduction

Anion analysis is important in environmental and biological studies (1,2). Some polarizable anions such as perchlorate (ClO_4^-) and pertechnetate (TcO_4^-) have attracted special attention in recent years. ClO_4^- occurs naturally in the environment and can also be released as a byproduct of the manufacture of explosives and rocket fuels. ClO_4^- has been found at trace levels in drinking water in California and other US states, and prolonged uptake into the body can cause serious health problems, principally related to thyroid gland function (3). The radioisotope TcO_4^- is found in nuclear waste and used in cancer treatment. The analysis and recovery of trace amounts of TcO_4^- in nuclear waste remains a challenge (4). Determination of trace amounts of these anions is especially difficult in the presence of a high sample anion matrix concentrations (5,6). High-performance ion chromatography (IC) has been used for this purpose with some success, and a common strategy for overcoming the effect of interfering anions in IC is to preconcentrate the target anions prior to analysis (7–10).

The conventional stationary phase in IC usually contains quaternary amine groups as anion exchangers (11–13). Al-though these anion exchangers are very stable in different kinds of eluent media, the retention times of polarizable anions like ClO_4^- and perrhenate, are usually quite long. As a result, stationary phases based on novel anion exchangers could be of benefit for better separation or preconcentration of these and other anions. Novel exchangers may be found among the variety of anion receptors synthesized in various laboratories in recent years (14–19). Among these receptors, cyclen (1,4,7,10-tetraazacyclododecane) is of particular interest to this work because of its ability to bind transition metal and other cations very strongly in aqueous solution, forming complexes which can in turn attract anions (20,21).

In this paper, we report the application of cyclen derivatives in the separation of common anions and in the preconcentration or removal of ClO_4^- and perrhenate, a non-radioactive analog of TcO_4^-, which is commonly used as a surrogate in related studies. A novel type of anion host macromulticycle is employed, in which multiple cyclen units are preorganized on a macrocyclic scaffold to provide an electrophilic cavity for anion sequestration. The approach in testing the effectiveness of the new macromulticycle-based columns involves comparing the performance of the IC column containing an analogous macrocyclic monomer (*N*-undecyl cyclen) to that of the column containing the tetrameric macromulticycle cyclenbowl (Figure 1). *N*-undecyl cyclen consists of a single macrocyclic subunit with a long aliphatic "tail" designed to facilitate strong adsorption to the hydrophobic IC resin in aqueous solution. Cyclenbowl contains four cyclen subunits held in proximity to each other by a resorcinarene bowl-shaped scaffold. Cyclenbowl also bears four alkyl chains, ensuring strong adsorption to the IC resin. We have successfully adopted this

Figure 1. *N*-undecyl cyclen and cyclenbowl.

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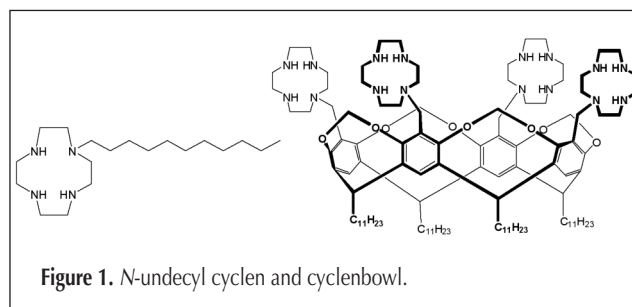
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alkyl column adsorption strategy in the past in developing columns which incorporate crown ether and cryptand moieties and found that the columns are very stable over long periods of time (22,23). Our goal with the present work is to establish the selectivity of the macrocyclic compounds as applied to IC so that we can identify those macrocycles which show promise for eventual application in matrix elimination or analyte concentration applications. While resorcinarenes have been used previously by other laboratories in high-performance liquid chromatography separations of neutral organics (24,27), we believe this is the first report of ion chromatographic separations using columns based on resorcinarene macromulticycles with cation-binding pendant arms.

Experimental

Reagents

Potassium ClO_4^- used in the study was obtained from Accustandard (New Haven, CT). All other anions were reagent-grade potassium salts obtained from Sigma-Aldrich (Milwaukee, WI). The hydroxide eluent was prepared from Fisher (Pittsburgh, PA) analytical reagent-grade 50% sodium hydroxide. Water used in making all standards and eluents was purified to 18 Megaohm/cm resistivity with a Milli-Q water purification system (Millipore, Billerica, MA). All eluents were degassed by helium sparging before use.

Synthesis of macrocyclic compounds

N-undecyl cyclen. The preparation of *N*-undecyl cyclen followed a previously reported method (28) with slight modifications. Bromoundecane (0.47 g, 2.0 mmol) in 60 mL of dry acetonitrile was added dropwise under nitrogen to a solution of cyclen (0.69 g, 4.0 mmol) in 120 mL of acetonitrile with anhydrous K_2CO_3 (1.38 g, 10.0 mmol) at 57°C. The reaction mixture was stirred for six days at the same temperature. After cooling down to room temperature, the excess of cyclen and K_2CO_3 in the reaction mixtures was filtered, and acetonitrile was removed under vacuum to produce a yellow oil. The oil was then extracted by 10 mL of diethyl ether. After evaporating diethyl ether, 0.61 g of light yellow oil was obtained (94%). Electrospray ionization mass spectrometry, *m/z*: calculated 326.3, found 327.3 $(M+H)^+$. ^1H-NMR ($CDCl_3$, 500 MHz): δ = 2.79 (t, J = 5.0 Hz, 2H, NCH_2), 2.63 (t, J = 4.5 Hz, 2H, NCH_2), 2.57 (t, J = 5.5 Hz, 2H, NCH_2), 2.52 (t, J = 4.5Hz, 2H, NCH_2), 2.40 (t, J = 7.5 Hz, 2H, NCH_2), 1.98 (brs, 3H, NH), 1.48–1.44 (m, 2H, CH_2), 1.25 (brs, 16H, C_8H_{16}), 0.88 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 500 MHz): δ = 54.757, 51.756, 47.263, 46.367, 45.406, 32.141, 29.873, 29.782, 29.593, 27.721, 27.546, 22.911, 14.351.

Cyclenbowl. The preparation of cyclenbowl has been reported elsewhere (29).

Column preparation

The stationary phase was provided by Dionex Corporation (Sunnyvale, CA). The resin consisted of conventional 55% cross-linked styrene–divinylbenzene polymeric macroporous substrate beads with an average pore size of 100–150 Å and a surface area of 350 m²/g. The average particle size of the raw resin was 5 μm.

The macrocyclic compounds were loaded onto the columns by the following procedure: 95.2 mg (0.292 mmol) of *N*-undecyl cyclen or 138 mg (0.073 mmol) of cyclenbowl was dissolved in 2.0 mL of methanol. Resin (1.30 g) was weighed and mixed with the methanol solution and then air-dried in the hood. The coated dry resin was dispersed in 30 mL of 0.5 M NaOH solution to make a slurry. A 4 × 200 mm blank PEEK column was connected to a packing device and the resin slurry was poured into the packing reservoir. The column was then packed at 60°C and 5000 psi with a packing pump for 15 min. When the packing was finished, MilliQ water was flushed through the column at a flow rate of 0.5 mL/min to remove the remaining NaOH. The column was then installed on the ion chromatograph for anion analysis.

Instrumentation

A Dionex DX 600 ion chromatograph with an ED 50 electrochemical detector and a GP 50 gradient pump was used throughout this work. Eluent flow rate was set at 0.5 mL/min. An ASRS-Ultra 4 mm suppressor was used in all separations in the recycle mode. Sample automation was performed using a Dionex AS 40 automated sampler. All data were collected and analyzed using a Dionex PeakNet chromatography workstation.

Results and Discussion

In a study to characterize the potential of cyclenbowl for anion binding, the ligand was found to bind four Zn^{2+} ions and found to attract anions selectively (29). ^1H NMR titrations showed that the $Zn_4 2^{8+}$ complex binds more than one anion in the host cavity. The anion association constants for the tetramer were larger than those for the monomeric cyclen analog, which indicates better anion recognition with the preorganized macromulticycle structure. This paper describes the use of cyclenbowl and its monomeric analog uncomplexed to any metal ion as a first step toward characterizing the use of such ligands in chromatography, relying on the protonation of the cyclen moieties to provide the electrophilic pocket for anion binding. Future work will investigate the use of metal-bound macromulticycle in such applications.

Effect of eluent pH on anion retention

Sodium hydroxide, potassium hydroxide, sodium bicarbonate, or a combination of sodium bicarbonate and carbonate were tested as eluents for anion separations using these cyclen-based macrocycles. Sodium hydroxide (1.0–10.0 mM) and sodium bicarbonate (1.0–10.0 mM) were chosen for anion analysis because they provided a good baseline and consistent results. When the eluent concentration was increased further, the baseline became unstable and not suitable for analysis.

For both macrocycle columns (one incorporating *N*-undecyl cyclen, the other incorporating cyclenbowl) we found that when NaOH was used as the eluent in isocratic elution mode,

six common anions co-eluted quickly from the columns and ClO_4^-/perrhenate were not retained strongly on the columns (for example, Figure 2A). The longer retention time of ClO_4^- or perrhenate than the other six anions derives from their participation in water-structure-enforced ion pairing with the ion exchange sites (30). When the eluent was $NaHCO_3$, the six common anions showed a degree of separation on both columns and the separation efficiency was significantly affected by the eluent strength and the column type (Figures 2B–2E). ClO_4^- and perrhenate were not eluted.

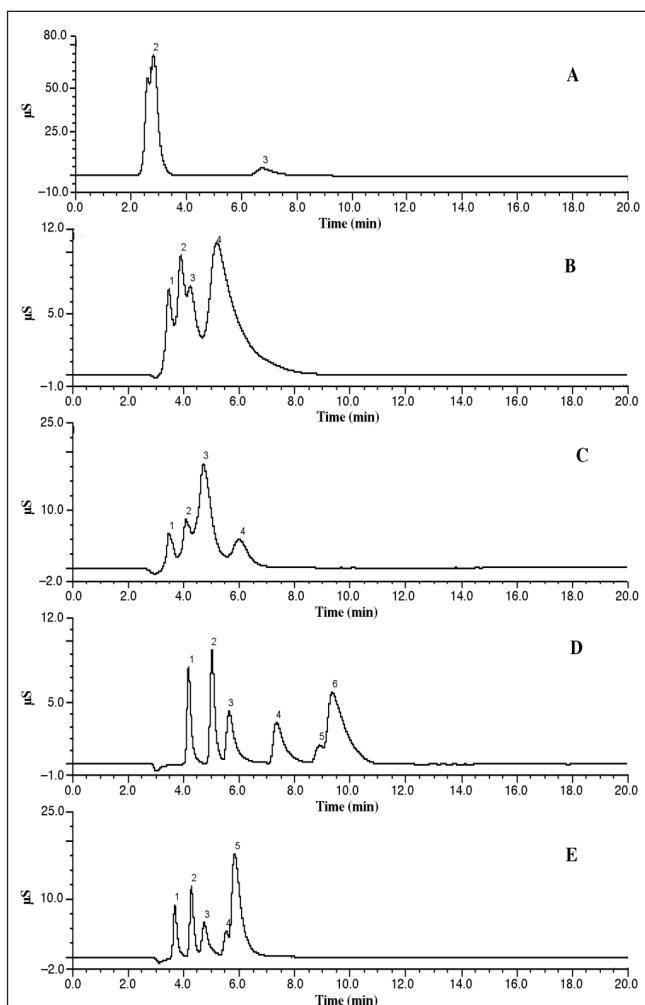Because anions are retained by the protonated macrocyclic sites, the eluent effect on anion retention was a result of the degree of protonation of the cyclen molecules in aqueous solution. The first protonation constant (pK$_a$) for cyclen is as large as 10.6 (31,32). This keeps cyclen protonated even in slightly basic solution. In 10 mM $NaHCO_3$ eluent (pH = 7.6–8.0), for example, the majority of cyclen molecules are protonated and can strongly attract anions. Different anions have different affinities for the protonated binding sites; hence the anions displayed a range of retention times. By comparison, protonation of cyclen does not occur when the eluent is 10 mM NaOH (pH = 12). And in the absence of charged binding sites, anions pass through the column unretained. Under these circumstances, even though cyclen can bind Na^+ to form charged complexes on the resin surface, the binding is very weak (log K = 2.7). So, in this case, the anions are not strongly retained on the columns and no significant separation is achieved.

Isocratic mode for anion separations

To elucidate the anion selectivity of the new macrocycles, the two columns were tested for separation of a suite of anions in isocratic elution mode. Both columns were made and used in an identical fashion except that the number of moles of macrocycle was normalized between the two columns to ensure that both contain the same number of cyclen subunits. Specifically, because each resorcinarene bowl molecule contains four cyclen subunits, only one-fourth as much of this molecule was loaded onto its column.

Figures 2B and 2C show the chromatograms obtained from the isocratic separation of seven anions, including perrhenate, on the *N*-undecyl cyclen column. The separation of the anions is poor, and the result was not improved when the eluent strength was increased from 4 mM to 10 mM $NaHCO_3$. However, under these latter conditions, the elution order of the oxoanions was changed, with NO_3^- eluting after SO_4^{2-} and PO_4^{3-}. In comparison, the cyclenbowl column was able to achieve a baseline separation of F^-, Cl^-, NO_2^-, and NO_3^- using 4 mM $NaHCO_3$ as the eluent (Figure 2D). As is shown in Figure 2E, increasing the eluent strength with the cyclenbowl column significantly shortened the retention time of the polyvalent anions while the elution order remained unchanged. These results indicate that the cyclenbowl column yields better anion retention and selectivity than the *N*-undecyl cyclen column. The difference may arise from the preorganized arrangement of the macrocyclic subunits in the cyclenbowl, a feature which is absent with the monomer.

It is noteworthy that even at a higher eluent concentration (10 mM $NaHCO_3$), ClO_4^- or perrhenate could not be eluted from either column. These two anions share a very strong affinity for the binding sites when the sodium bicarbonate eluent is used.

Capacity gradient mode for preconcentration of anions

As described in the "Effect of eluent pH on anion retention" section, changing the eluent type can modify the column capacity with these systems. This makes it possible to achieve capacity gradient elution (22,23,33,34) of ClO_4^- or perrhenate. And using this capacity gradient technique, the chromatograms in Figures 3–5 illustrate how the columns studied might be used in preconcentration of the target anions. We performed multiple injections of anion mixtures containing either

Figure 2. Isocratic analysis of seven anions on *N*-undecyl cyclen and cyclenbowl columns. Sample anions: 5 mg/L F^-, 9 mg/L Cl^-, 12 mg/L NO_2^-, 16 mg/L NO_3^-, 24 mg/L SO_4^{2-}, 24 mg/L PO_4^{3-}, and 63 mg/L ReO_4^-.

(**A**): *N*-undecyl cyclen column. Eluent: 4.0 mM NaOH. Peaks: 1 and 2 = F^-, Cl^-, NO_2^-, NO_3^-, SO_4^{2-}, and PO_4^{3-}; 3 = ReO_4^-.

(**B**): *N*-undecyl cyclen column. Eluent: 4.0 mM $NaHCO_3$. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-, SO_4^{2-}, and PO_4^{3-}; ReO_4^- did not show up.

(**C**): *N*-undecyl cyclen column. Eluent: 10.0 mM $NaHCO_3$. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-, SO_4^{2-}, and PO_4^{3-}; 4 = NO_3^-; ReO_4^- did not appear.

(**D**): 2 column. Eluent: 4.0 mM NaHCO3. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-; 5 = SO_4^{2-}; 6 = PO_{43}^-; ReO_4^- did not appear.

(**E**): Cyclenbowl column. Eluent: 10.0 mM $NaHCO_3$. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-; 5 = SO_4^{2-} and PO_4^{3-}; ReO_4^- did not appear.

ClO_4^- or perrhenate in addition to a matrix of common anions. After each injection, we performed an isocratic elution of the common anions using a weak bicarbonate eluent, with the expectation that the ClO_4^- or perrhenate would be retained. After the final injection, a capacity gradient elution was performed by
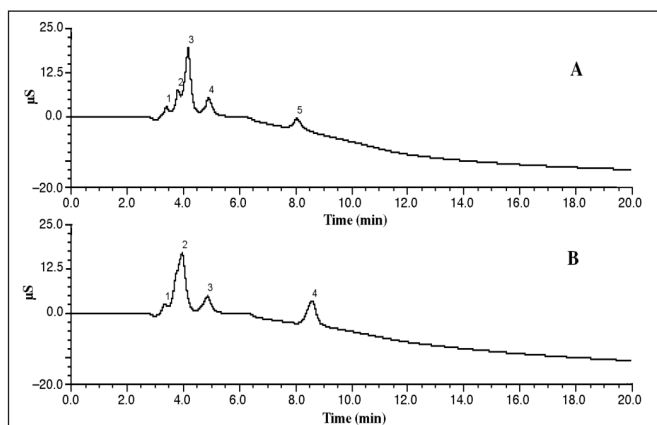

Figure 3. Preconcentration of perchlorate on N-undecyl cyclen column. Sample anions: 2 mg/L F^-, 4 mg/L Cl^-, 6 mg/L NO_2^-, 9 mg/L NO_3^-, 13 mg/L SO_4^{2-}, 11 mg/L PO_4^{3-}, and 14 mg/L ClO_4^-. Procedure:
   (A): single injection using a linear gradient elution. Eluent: 0 min, 10.0 mM $NaHCO_3$; 0–7 min, gradual change from 10.0 mM $NaHCO_3$ to 10.0 mM NaOH; 7–20 min, 10.0 mM NaOH. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-, SO_4^{2-}, and PO_4^{3-}; 4 = NO_3^-; 5 = ClO_4^-.
   (B): Made one injection and ran with 10 mM $NaHCO_3$ in isocratic mode for 15 min, then repeated. Made third injection and ran with the linear gradient. Peaks: 1 = F^-; 2 = Cl^-, NO_2^-, SO_4^{2-}, and PO_4^{3-}; 3 = NO_3^-; 4 = ClO_4^-.

switching to sodium hydroxide eluent to drive the concentrated ClO_4^- or perrhenate from the column, essentially by removing the anion capacity of the column.

N-undecyl cyclen column. The *N*-undecyl cyclen column was first tested for preconcentration of ClO_4^-. Figure 3A demonstrates that a linear gradient program successfully elutes the ClO_4^-. In this program, the strength of $NaHCO_3$ is gradually decreased, and NaOH is gradually increased during a period of 11 min. A step gradient elution program (changing immediately from 100% of $NaHCO_3$ to 100% NaOH) was also tested. However, there was no appreciable difference between the two results. Figure 3B shows the elution of ClO_4^- after three successive injections of the sample, where short isocratic bursts of bicarbonate eluent followed the first two injections to remove the common anions but leave the ClO_4^- retained. The peak area of ClO_4^- after preconcentration in 3 successive injections is three times that of the single injection. Another anion, perrhenate, tends to remain on commercial columns longer than ClO_4^-. As expected, perrhenate eluted from the *N*-undecyl cyclen column at a longer time than ClO_4^- (10–11 min) using the same linear gradient program described previously for ClO_4^-. The ReO_4^- peak was a little bit broader than ClO_4^- in keeping with a stronger retention on the column. The peak area of ReO_4^- in the preconcentration step was also three times that of the single injection.

Cyclenbowl column. The cyclenbowl column was evaluated in a study parallel in design to that described previously for ClO_4^- using the *N*-undecyl cyclen column, but testing for perrhenate concentration using the cyclenbowl column. Again, we observe proof of principle in using this column for target anion preconcentration.
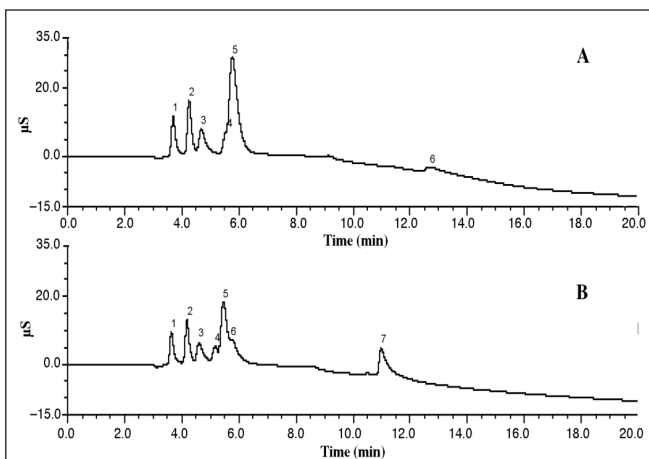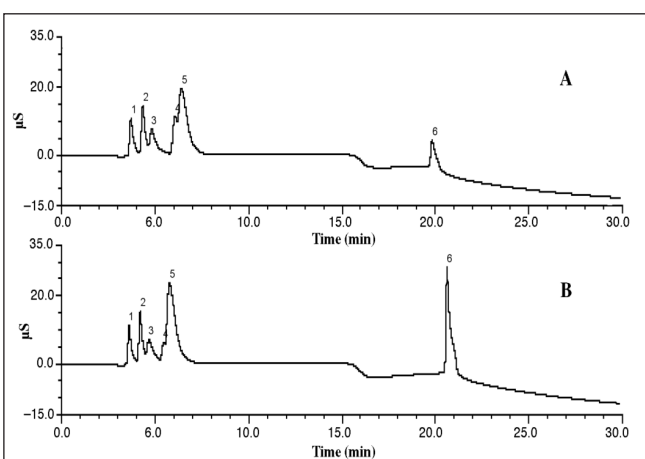

Figure 4. Preconcentration of perrhenate on cyclenbowl column. Sample anions: 5 mg/L F^-, 9 mg/L Cl^-, 12 mg/L NO_2^-, 16 mg/L NO_3^-, 24 mg/L SO_4^{2-}, 24 mg/L PO_4^{3-}, and 63 mg/L ReO_4^-. Procedure:
   (A): single injection with a linear gradient elution. Eluent: 0 min, 10.0 mM $NaHCO_3$; 0–11 min, linear change from 10.0 mM $NaHCO_3$ to 10.0 mM NaOH; 11–20 min, 10.0 mM NaOH. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-; 5 = SO_4^{2-} and PO_4^{3-}; 6 = ReO_4^-.
   (B): Made one injection and ran with 10 mM $NaHCO_3$ in isocratic mode for 15 min, then repeated. Made third injection and ran with the linear gradient. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-; 5 and 6 = SO_4^{2-} and PO_4^{3-}; 7 = ReO_4^-.

Figure 5. Preconcentration of perrhenate on cyclenbowl column by step gradient. Sample anions: 5 mg/L F^-, 9 mg/L Cl^-, 12 mg/L NO_2^-, 16 mg/L NO_3^-, 24 mg/L SO_4^{2-}, 24 mg/L PO_4^{3-}, and 63 mg/L ReO_4^-. Procedure:
   (A): single injection with step gradient elution. Eluent: 0–11 min, 10.0 mM $NaHCO_3$; 11–30 min, 10.0 mM NaOH. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-; 5 = SO_4^{2-} and PO_4^{3-}; 6 = ReO_4^-.
   (B): Made one injection and ran with 10 mM $NaHCO_3$ in isocratic mode for 15 min, then repeated. Made third injection, ran with the step gradient. Peaks: 1 = F^-; 2 = Cl^-; 3 = NO_2^-; 4 = NO_3^-; 5 = SO_4^{2-} and PO_4^{3-}; 6 = ReO_4^-.

Table I. Anion Preconcentration Recovery from Cyclen Column N-Undecyl Cyclen and Cyclenbowl Columns*

	N-undecyl cyclen column	Cyclenbowl column
ClO_4^-	96.3%	80.5%
ReO_4^-	99.8%	98.1%

* After 3 sequential injections, as described in the text; recovery is defined here as [peak area in the preconcentration step / (3 × peak area in the single injection step)] × 100%. Peak areas used in the calculation were reproducible to ±3%.

The chromatograms in Figure 4 were obtained from a linear gradient elution program and those in Figure 5 were obtained from a step gradient elution program. Comparing the chromatograms in Figure 4 and 5 indicates that the step gradient program is more effective in anion preconcentration with this column, as the peak of ReO_4^- is narrower and sharper, which can lead to a determination with higher sensitivity and accuracy. The disadvantages of using the step gradient over the linear gradient program are that the baseline shift is more dramatic and the elution time of the ReO_4^- (~20 min) is relatively long. Preconcentration studies of ClO_4^- on the cyclenbowl column yielded a very similar result with a shorter retention time than found for perrhenate. The retention times of ClO_4^- and perrhenate peaks from batch to batch were very consistent. The reproducibility was very good (± at most 5%).

The peak areas of ClO_4^- and perrhenate recovered after three injections of the sample yielded high recovery of the analyte of interest with simultaneous elimination of common matrix anions. Figures 3, 4, and 5 illustrate how the ClO_4^- or perrhenate peaks grow with multiple injections, while those of common matrix ions do not because unlike the anions to be concentrated, they are eluted by the weaker eluent. The percent recovery of the anion in typical concentration experiments for both columns is shown in Table I.

To be useful as preconcentration columns, the macrocycle-based columns should allow even large amounts of interfering ions in the sample matrix to elute without significantly affecting the functionality of the anion of interest. The effect of sample matrix ion concentration on the anion preconcentration was studied by adding 1000 mg/L sodium chloride to a solution of the ion of interest (i.e., 14 mg/L ClO_4^- or 63 mg/L ReO_4^-). Under isocratic conditions using 10 mM $NaHCO_3$ as the eluent, a huge chloride peak eluted out while the target anion stayed on the column. After the matrix ions had eluted, a step gradient to 10 mM NaOH was then made, and the target anion eluted at its normal time under these new eluent conditions. A further study was performed with 2500 mg/L sodium chloride added to the sample solution. No adverse effect on the functionality of the columns and recovery of the ion of interest at this concentration was observed.

With regards to column stability, the columns prepared from these macrocycles have been used for hundreds of injections over a six month period and no deterioration of performance both in terms of retention time and peak shape has been observed.

Conclusions

The two types of macrocycle-based columns studied, N-undecyl cyclen and cyclenbowl, are capable under mild basic conditions of separating and preconcentrating ClO_4^- and perrhenate ions. The cyclenbowl column exhibits better anion separation and preconcentration properties than the monomeric N-undecyl cyclen column. We propose that this is due to the preorganization of the anion receptor sites of cyclenbowl. These columns are stable over long periods of time. We foresee potential for using columns based on these compounds or their analogs in separations and preconcentration applications in IC.

Acknowledgements

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