association energies are much smaller than to molecules where one metallic atom already is present. This differentiates hypermetalated species, which enjoy both metal-metal and metal-central atom bonding of substantial magnitudes, from relatively weak complexes.

Since the principle of hypermetallic bonding is general,[1-3] compounds of the alkali metals with most if not all the other elements in the periodic table are expected. Alloys, surface complexes,[20] and definable entities in the solid state[7] are more familiar manifestations of the same phenomenon. Many small cluster molecules of this type have already been detected in the gas phase,[1-5,8] and should be observable in matrix isolation. Hypermetalated species already are known in condensed phases.[7,25] The $\Delta H_f{}^\circ{}_{298}$ (Na_3O, crystal) value[26] is 2.5 kcal/mol more favorable than that for Na_2O.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the National Science Foundation and benefited from a Special Award (to J.A.P.) by the Alexander von Humboldt Foundation. We thank Professor A.W. Castelman for information prior to publication and Dr. A. Sawaryn for his adaptation of the GAUSSIAN 82 program to the Erlangen CDC computer.

Note Added in Proof. The nature of the bonding in hypermetalated molecules has now been analyzed by Gopinathan and Jug[27] and by Reed and Weinhold;[28] both groups concur with our conclusions.

Registry No. 1, 87331-12-2; **2**, 89091-90-7; **3**, 92285-05-7; **4**, 92285-06-8; O_2, 7782-44-7.

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Lipophilic Crown-4 Derivatives as Lithium Ionophores

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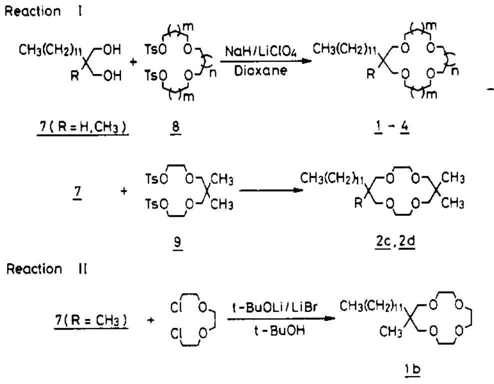
Abstract: Crown-4 derivatives of 13- through 16-member rings bearing a long aliphatic chain have been synthesized in an effort to obtain highly selective ionophores for lithium ions. The measurements of potentiometric selectivity coefficients for polymeric membranes containing the crown ethers indicated that their lithium selectivities can be explained primarily in terms of the size-fit concept, the 14-crown-4 and 15-crown-4 derivatives being much more selective for lithium than the larger and the smaller macrocycles. It was found that incorporation of a methyl group geminal to the long aliphatic chain prevents formation of sandwich-type 2:1 crown ether-metal complexes with alkali metal ions other than lithium and, therefore, enhances the lithium selectivity of the original crown ether. Some of the lipophilic 14-crown-4 derivatives possess remarkably high preference of lithium over sodium which bears importantly upon their applications.

Increasing attention is being focussed on Li^+ ionophores as tools for biological applications as well as for analyses and separation of the ion. Several Li^+ ionophores have been designed which are based on dioxadiamide derivatives.[1-4] Some of them have been applied for neutral carriers of polymeric membrane Li^+-selective electrodes,[1,2] which are very convenient tools for monitoring of Li^+ activity in environmental and biological systems. The others have been tested for Li^+ transport activity through a biological membrane.[3,4] The selectivity ratio of Li^+ over Na^+, one of the most essential factors for Li^+ ionophores, has proved to range from 10 to 100. Ionophores with still higher Li^+ selectivity are desirable for the practical applications.

Scheme I



Crown ether	m	n	R
1a	0	0	H
1b	0	0	CH_3
2a	0	1	H
2b	0	1	CH_3
2c	0	1	H
2d	0	1	CH_3
3a	1	0	H
3b	1	0	CH_3
4a	1	1	H
4b	1	1	CH_3

Macrocyclic polyethers, referred to as crown ethers or cryptands, can complex various alkali and alkaline earth metal ions, and their ion-selectivities often depend on their cavity size. The cyclic polyethers, when dissolved in organic solvents or incorporated into membranes, can behave as ionophores selective for particular metal ions. Especially, highly lipophilic derivatives, e.g., crown ethers and cryptands bearing a long aliphatic chain(s),[5-10] may be efficient ionophores. Most of the crown ethers contain 5 or 6 oxygen atoms in the crown ring, thus being suited for preferential complexation with Na^+ or K^+. Very few crown ethers selective for Li^+ have appeared so far. In addition to cryptand [2.1.1],[11] crown

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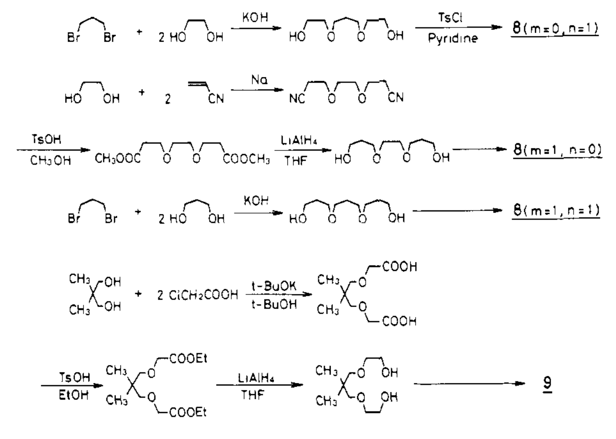
Scheme II



ethers containing 4 oxygen atoms, what they call crown-4 derivatives, although a little more difficult to synthesize than the larger macrocycles, may be expected to exhibit Li^+ selectivity on complexation of alkali and alkaline earth metal ions. Li^+ selectivities of some crown-4 derivatives have been evaluated by the solvent extraction technique[12] and EMF measurements of polymeric membrane electrodes.[13-15] The Li^+ selectivities, however, are still insufficient, because the Li^+/Na^+ selectivity ratios do not exceed a value of 10. Our goal, therefore, is to obtain efficient, selective Li^+ ionophores while investigating the relationship between the Li^+ selectivity and the ring size of crown-4 derivatives. To this end, we have synthesized a series of highly lipophilic crown-4 derivatives with 13- through 16-member rings, **1** through **4**. Herein, we wish to describe the syntheses of such crown-4 derivatives and to report on their Li^+ selectivities which were determined here by EMF measurements of polymeric membrane electrodes based on the Li^+ ionophores. Some comparison with benzo-13-crown-4 and 12-crown-4 derivatives possessing a similar lipophilic chain is also described.

Results and Discussion

Syntheses. The syntheses of a series of lipophilic crown-4 derivatives with 13- through 16-member rings are based mainly on the cyclization reaction of 2-dodecyl- or 2-dodecyl-2-methylpropane-1,3-diol with an appropriate polyoxaalkanediol ditosylate in the presence of NaH as the base, as represented as Reaction I in Scheme I. As a template of the cyclization,[16,17] $LiClO_4$ was added in excess to the reaction systems, in such a way that some part of the added salt remained insoluble during the reaction. This type of reaction, however, failed to produce any detectable amount of dodecylmethyl-14-crown-4, **1b**. The crown ether **1b** was, therefore, produced by means of a tedious cyclization reaction of the propanediol derivative and triethylene glycol dichloride with the aid of *t*-BuOLi and LiBr (Reaction II).[18] Reaction II was also attempted for the preparation of the other crown-4 derivatives (**1–4**, except **1b**), but it proved less suitable than Reaction I for our purpose. Only for the synthesis of **1b** did Reaction II exceed Reaction I in the cyclization yield. The reason for the reactivity difference is not yet understood. Thus, Reaction I was applied to the syntheses of most of the crown-4 derivatives, **1–4**, with the exception of **1b** which was prepared successfully through Reaction II. The dodecyl- or dodecylmethylpropanediol was prepared by the $LiAlH_4$ reduction of the easily accessible diethyl malonate derivative. The polyoxyalkanediol ditosylates were obtained according to the procedures illustrated in Scheme II.

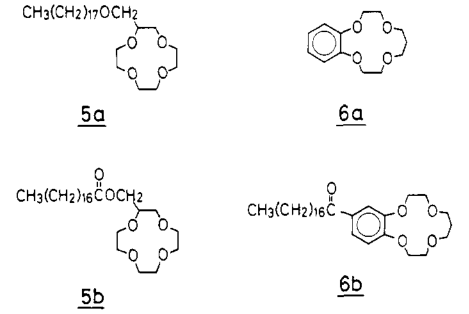


Figure 1. Benzo-13-crown-4 and 12-crown-4 derivatives employed for comparison.

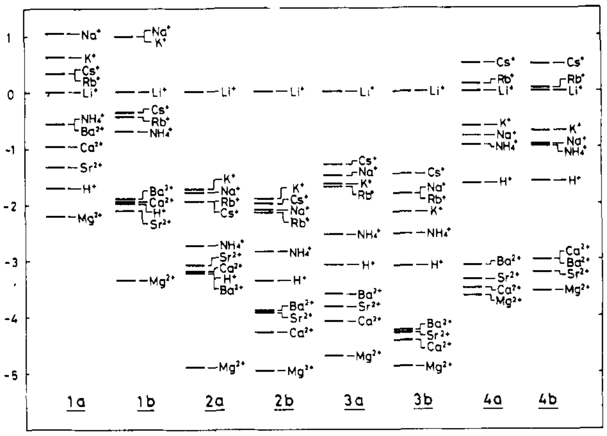


Figure 2. Selectivity coefficients log k^{Pot}_{LiM} for PVC membranes containing lipophilic crown-4 derivatives **1–4**.

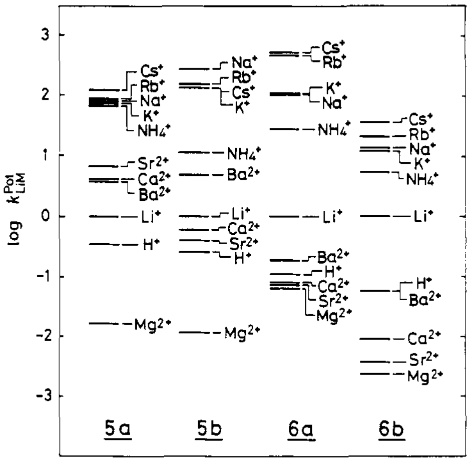


Figure 3. Selectivity coefficients log k^{Pot}_{LiM} for PVC membranes containing benzo-13-crown-4 and 12-crown-4 derivatives **5** and **6**.

The yields of analytically pure products in the cyclization reactions, although not optimized, seem rather low in comparison to those for most of the larger crown ethers including more than 4 ring oxygen atoms synthesized thus far. One main reason for the modest yield is the smaller macrocycles which generally possess greater ring strains than larger ones. Also, the dodecyl methyl derivatives **1b** through **4b** possess better cyclization yields than the corresponding dodecyl derivatives **1a** through **4a**, in the cyclization of which proton release at the tertiary carbon of the dodecylpropanediol occurs easily as a side reaction.[19] It is of much interest to note that the yields of dodecyl-methyl-crown-4 deriv-

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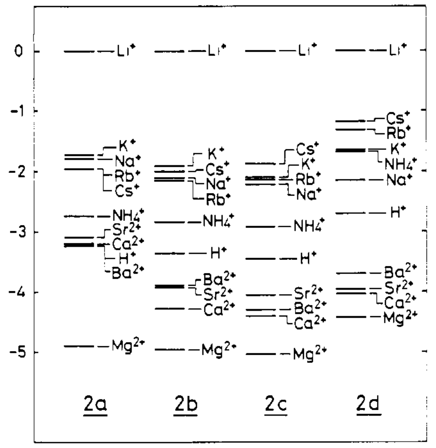

Figure 4. Selectivity coefficients log k_{LiM}^{Pot} for PVC membranes containing lipophilic crown-4 derivatives **2a–2d**.

atives **1b–4b** are roughly reflected in their Li^+ selectivities which is described later. Thus, it appears that the Li^+ template effect works well during the cyclization. Dodecyl-methyl-14-crown-4 **2b**, which will prove highly Li^+ selective and useful for the applications, can be obtained in a rather good yield.

Lithium Selectivities of Lipophilic Crown-4 Derivatives. The lithium selectivities of the crown ethers **1** through **4** were evaluated as potentiometric selectivity coefficients of polymeric membranes based on them. For comparison, 12-crown-4 derivatives **5** and benzo-13-crown-4 derivatives **6** were also employed. The polymeric membrane consists of poly(vinyl chloride) (PVC) as the support, *o*-nitrophenyl octyl ether (NPOE) as the membrane solvent, and a crown ether as the ionophore. The membranes also contain a small quantity of potassium tetrakis(*p*-chlorophenyl)borate (KTpClPB) for the purpose of reducing the membrane resistance and suppressing permeation of counteranions in aqueous phases into the membrane phase. The potentiometric selectivity coefficients, which were determined by a mixed solution method,[20] are illustrated in Figures 2–4. The selectivity coefficient given as k_{LiM}^{Pot} represents the preference of the PVC membranes containing the crown ether for Li^+ over other metal ions (M). It should be kept in mind that the smaller the k_{LiM}^{Pot} value, the higher the Li^+ selectivity of the crown ether based PVC membrane. Generally, the 13-member ring macrocycles **1** are much less selective for Li^+ than 14- and 15-member ring ones **2** and **3**. The 12-member ring model compounds **5** hardly showed any Li^+ preference over other alkali metal ions in the potentiometric measurement. Benzo-13-crown-4 derivatives **6** also exhibited only poor Li^+ selectivity, although **6a** seems rather selective for Li^+ in the extractability for alkali and alkaline earth metal picrates[12] and forms stable crystalline complexes with the ion.[21] It is, therefore, concluded in our case that all of the 12-crown-4, 13-crown-4, and benzo-13-crown-4 derivatives prefer the other alkali metal ions to Li^+. Further ring expansion to 14- or 15-member ring macrocycles **2** and **3** augmented the Li^+ selectivities drastically. In the largest macrocycles, 16-crown-4 derivatives **4**, the Li^+ selectivity was again dropped as compared with **2** and **3**. Examination of CPK space-filling models for the crown-4 derivatives reveals that Li^+ fits into the 15-crown-4 and more favorably into the 14-crown-4 ring. Therefore, the remarkably high Li^+ selectivity of **2** and **3** may be explained appreciably in terms of the size-fit concept.

Another point is the effect of the methyl substituent attached to the quaternary carbon of the crown-4 derivatives on the Li^+ selectivity. Obviously, the dodecyl methyl derivatives of the 14- and 15-member ring macrocycles are superior to the corresponding dodecyl derivatives in the Li^+ preference, particularly over Na^+ and K^+. This implies that the methyl group on the crown ring causes some steric effect on complexation with metal ions. Since Na^+ and K^+ exceed in size the cavities of the crown-4 derivatives, there is a possibility of forming sandwich-type 2:1 complexes of the crown ethers and the ions, as realized in the 15-crown-5 and 18-crown-6 complex systems.[22-24] Figure 5, which depicts the dependence of crown ether concentration in the PVC membrane upon the selectivity coefficients, may afford some information concerning the 2:1 complexes of the 14-crown-4 derivatives. According to a bi-ionic potential theory of liquid membranes containing neutral carriers,[25] the value of selectivity coefficient k_{XY}^{Pot} ought to be independent on the neutral carrier concentration in the membrane if both X and Y ions form only 1:1 complexes. In the dodecyl-methyl-14-crown-4 (**2b**) membrane system the selectivity coefficient of Li^+ relative to Na^+ and K^+ was hardly altered with an increase in the crown ether concentration. In contrast, in the dodecyl-14-crown-4 (**2a**) system a drastic increase of the selectivity coefficients, which in turn stands for a decrease of Li^+ selectivity over Na^+ and K^+, was observed in the higher concentration of it. This finding suggests that the dodecyl-14-crown-4 is able to complex Na^+ and K^+ with 2:1 stoichiometry of crown ether and ions as well as with 1:1 stoichiometry, while the dodecyl methyl derivative has difficulty in forming sandwich-type complexes with the ions even in the high crown ether concentrations. Also, preference of crown ether for a certain metal ion over other ions which tend to give only 1:1 complexes is often enhanced by the formation of the sandwich-type complexes. Actually, bis(crown ether) derivatives, a macrocyclic polyether containing two crown ether rings at a short aliphatic chain, possess higher selectivities for particular ions which slightly exceed the crown ether ring size of the corresponding monocyclic analogues.[26-31] The bis(crown ether) effect is mainly because of cooperative action of two adjacent crown ether rings,[32-34] sometimes being drastic.[26,28] This is also the case with bis(12-crown-4) derivatives,[35] which surpass the monocyclic model compounds in Na^+ selectivity. Returning to the crown-4 derivatives in this work, the formation of 2:1 crown ether–metal complexes with Na^+ and K^+ lowers their Li^+ selectivity in the opposite sense. That is to

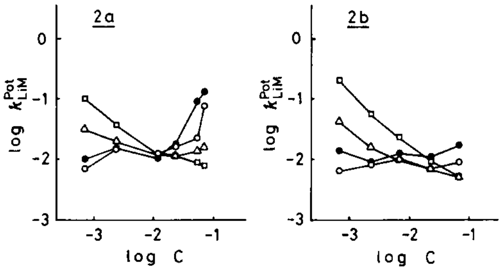

Figure 5. Dependence of log k_{LiM}^{Pot} values on crown ether concentration in PVC membranes of **2a** and **2b**. M: Na^+(○), K^+(●), Rb^+(△), Cs^+(□).

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Table I. Values of Selectivity Coefficients $k_{\mathrm{LiNa}}^{\mathrm{Pot}}$ and $k_{\mathrm{NaLi}}^{\mathrm{Pot}}$ of PVC Membranes Based on Crown-4 Derivatives

selectivity coeff	**1a**	**1b**	**2a**	**2b**	**2c**	**2d**	**3a**	**3b**
$k_{\mathrm{LiNa}}^{\mathrm{Pot}}$	$1._7 \times 10$	$9._8$	$1._6 \times 10^{-2}$	$6._9 \times 10^{-3}$	$6._2 \times 10^{-3}$	$7._2 \times 10^{-3}$	$3._2 \times 10^{-2}$	$1._5 \times 10^{-2}$
$k_{\mathrm{NaL}}^{\mathrm{Pot}\ a}$	$9._1 \times 10^{-2}$	$1._0 \times 10^{-1}$	$6._2 \times 10$	$1._4 \times 10^{2}$	$1._6 \times 10^{2}$	$1._4 \times 10^{2}$	$3._2 \times 10$	$6._6 \times 10$

selectivity coeff	**4a**	**4b**	**5a**	**5b**	**6a**	**6b**
$k_{\mathrm{LiNa}}^{\mathrm{Pot}}$	$1._7 \times 10^{-1}$	$1._1 \times 10^{-1}$	$8._1 \times 10$	$2._8 \times 10^{2}$	$8._7 \times 10$	$1._3 \times 10$
$k_{\mathrm{NaLi}}^{\mathrm{Pot}\ a}$	$5._8$	$8._7$	$1._2 \times 10^{-2}$	$3._6 \times 10^{-3}$	$1._1 \times 10^{-2}$	$7._4 \times 10^{-2}$

[a] These values are given simply by the reciprocal of $k_{\mathrm{LiNa}}^{\mathrm{Pot}}$.

say, it is considered that the methyl group of **2b** functions as a steric barrier to prevent the access of two crown ether molecules to the sandwich complex formation. Moreover, conformational fixation of the dodecyl group by the introduction of the methyl group geminal to the quaternary carbon, such as observed in lariat ethers,[36] may be another factor of the steric hindrance. Similarly, incorporation of two methyl groups into **2a** on the opposite side of the crown ether ring improved the Li^+ selectivity slightly, but the further incorporation of two methyl groups into **2** did not (Figure 4). On the contrary, in the case of the trimethyl derivative **2d**, there is a pronounced drop in the Li^+ preference over the other cations except Na^+ compared to the monomethyl and dimethyl ones **2b** and **2c**. It is probably because the increased bulkiness on the periphery of **2d** interferes with the complex formation even with Li^+.[8]

The Li^+ selectivity relative to Na^+ is a most important factor for the application and practical use of the lipophilic crown-4 derivatives as Li^+ ionophores. The values of selectivity coefficients $k_{\mathrm{LiNa}}^{\mathrm{Pot}}$ and $k_{\mathrm{NaLi}}^{\mathrm{Pot}}$, the latter ones of which are given simply by the reciprocal of the former ones and represent actual selectivity ratios of Li^+ over Na^+, are summarized in Table I. It should be noted that the 14-member ring macrocycles **2** possess excellent Li^+ selectivity relative to Na^+. In particular, in the 14-crown-4 derivatives **2b** through **2d** the selectivity ratios of Li^+ over Na^+ amount to about 150. In the Li^+/Na^+ ratio of the potentiometric selectivity of the membranes, the lipophilic 14-crown-4 derivatives, to the best of our knowledge, surpass the previous Li^+ ionophores such as crown ether analogues[13,14] and acyclic neutral carriers.[1-4] In order to get some information about Li^+ selectivity over Na^+ of dodecyl-methyl-14-crown-4 **2b** in a bulk phase, attempts were made to evaluate conductometrically complex formation constants of the crown ether for perchlorates of Li^+ and Na^+ in acetonitrile. The formation constant for the 1:1 crown ether–Li^+ complex was successfully determined, being 1.0×10^6 mol^{-1} dm^3. Unfortunately, the conductivity changes were so small on stepwise addition of **2b** to a $NaClO_4$ acetonitrile solution that an accurate value for the Na^+ complex could not be obtained. Nevertheless, the formation constant of the 1:1 crown ether–Na^+ complex was roughly estimated as 1×10^3–5×10^3 mol^{-1} dm^3. Therefore, the Li^+/Na^+ selectivity ratio of **2b** on complex formation in the bulk phase can be estimated as a value ranging from 2×10^2 to 1×10^3. Thus, this result regarding complex formation in the bulk phase has again confirmed to us the excellent Li^+ selectivity of the 14-crown-4 derivative.

Wide applications are expected for the highly Li^+-selective 14-crown-4 derivatives, particularly **2b** which is rather easy to prepare. One of the most important applications is the Li^+-selective electrode based on them.[37] For example, the electrode is a promising candidate as a tool for monitoring Li^+ activity in blood which contains a small quantity of Li^+ compared to Na^+ during therapy for maniacal psychosis.[38-40] The Li^+ ionophore might also be used as a drug to promote Li^+ permeation into the nervous systems during therapy.[4] Other applications are in selective separation of Li^+ or its isotope by transport through a liquid membrane and by solvent extraction.

Experimental Section

Chemicals. Unless otherwise specified all reagents were the best grade and were used as received. Dioxane and THF were distilled over Na. Ethanol and *tert*-butyl alcohol were dried by distillation over their alkoxides of Na. Ethyl ether, pyridine, and acetonitrile were distilled over $CaCl_2$, KOH, and P_2O_5, respectively. Water was deionized and distilled through a Widmer column. Alkyl and alkanoyl halides were purified by vacuum distillation. Alkali and alkaline-earth metal chlorides were analytical grade. PVC (average polymerization degree of 1100, Wako) was purified by repeated precipitation from THF in methanol. NPOE was prepared with a modification to the previous procedure.[41] KTpClPB was produced according to the literature.[42]

Apparatus. Infrared spectra were recorded on a Hitachi 215 grating spectrophotometer. Melting points were determined on a MP melting point apparatus and were uncorrected. Mass spectra were measured at 70 eV with a Hitachi RMU-6E instrument. ^1H NMR spectra were recorded on a JOEL JMN-PS-100 spectrometer as CCl_4 solutions of 0.5–10 wt % concentrations unless otherwise stated. Gas chromatographic analyses were performed on a Shimadzu GC-3BT gas chromatograph equipped with a thermal conductivity detector and a 3 mm × 1.7 m 5% Silicone OV-1 column on 60/80 mesh Chromosorb W/AW. Preparative reversed-phase liquid chromatography was conducted on a Kyowaseimitsu K-880 liquid chromatograph, a Waters R-40 differential diffractometer, and a 20 mm × 250 mm column packed with 15-μm irregular-type ODS silica. The eluent was methanol, and the flow rates ranged from 8.8 to 12.5 mL/min. Elemental analyses were achieved on a YANACO MT-2 CHN Corder. EMF measurements were conducted by using pH/mV meters of TOKO Model TP-1000 and Corning Model 130. Conductivity measurements were performed on a conductivity apparatus of YANACO Model MY-7.

Syntheses. General Procedure for Preparation of Lipophilic Crown-4 Derivatives via Reaction I. In a dry dioxane solution (400 mL) of the lipophilic propanediol derivative (10 mmol) NaH (60% in oil, 25 mmol) was suspended and the mixture refluxed with mechanically stirring for $^1/_2$ h. To the refluxing suspension was added $LiClO_4$ (ca. 50 mmol) and subsequently a dry dioxane solution (50 mL) of the appropriate polyoxyalkanediol ditosylate (11 mmol) dropwise. After the addition was complete, the mixture was refluxed for an additional 12 h. After the reaction the mixture was concentrated to a volume of about 50 mL, 200 mL of water was added slowly. The solution was then neutralized with dilute HCl and extracted with $CHCl_3$ (50 mL × 3). The combined extracts were washed with water and dried over $MgSO_4$. The solvent was then removed by rotary evaporation. The residue was dissolved in hot hexane, and then the solution was cooled. After the resulting solid of unreacted propanediol was filtered off, the solvent was evaporated under vacuum. Silica gel chromatography using a gradient elution technique with 0–5% methanol in benzene afford a crude product of the corresponding crown-4 derivative, which was further purified by the preparative reversed-phase liquid chromatography.

Dodecyl-13-crown-4 or 12-Dodecyl-1,4,7,10-tetraoxacyclotridecane (1a). 2-Dodecylpropane-1,3-diol (**7**(R = H)) was produced by conventional $LiAlH_4$ (2 equiv) reduction of the corresponding ethyl malonate in ethyl ether overnight at ambient temperature. Compound **1a** was prepared by Reaction I of 2-dodecylpropane-1,3-diol (**7**(R = H)) and triethylene glycol ditosylate, obtained in turn in a previous procedure.[43] The product was isolated as an analytically pure oil that converted to a white solid while standing (3%): mp 48.5–49.5 °C; IR (KBr) 2900, 2840, 1460, 1350, 1120 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H, CH_3), 1.15–1.40 (m, 22 H, $(CH_2)_{11}$), 1.50–1.75 (m, 1 H, CH), 3.32–3.65 (m, 16 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 358 (M^+, 3), 45 (100).

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Anal. Calcd for $C_{21}H_{42}O_4$: C, 70.34; H, 11.81. Found: C, 70.11; H, 11.85.

Dodecyl-14-crown-4 or 6-Dodecyl-1,4,8,11-tetraoxacyclotetradecane (2a). Compound **2a** was prepared as described in the procedure for Reaction I from the propanediol **7**(R = H) and 3,7-dioxanonane-1,9-diol ditosylate (**8**(*m* = 0, *n* = 1)), which was in turn obtained according to the procedure reported previously.[12] The product was isolated as a pure oil that converted to a white solid while standing (3%): mp 46.5–47.0 °C; IR (KBr) 2900, 2840, 1460, 1355, 1120 cm^{-1}; ^1H NMR δ 0.87 (t, 3 H, CH_3), 1.18–1.40 (m, 2 H, $(CH_2)_{11}$), 1.49–1.75 (m, 3 H, CH and $OCH_2CH_2CH_2O$), 3.37–3.64 (m, 16 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 372 (M^+, 6), 45 (100). Anal. Calcd for $C_{22}H_{44}O_4$: C, 70.92; H, 11.90. Found: C, 70.92; H, 11.87.

Dodecyl-methyl-14-crown-4 or 6-Dodecyl-6-methyl-1,4,8,11-tetraoxacyclotetradecane (2b). The synthetic procedure for 2-dodecyl-2-methylpropane-1,3-diol (**7**(R = CH_3)) is the same as that for **7**(*R* = *H*). Compound **2b** was prepared from the propanediol and the diol ditosylate **8**(*m* = 0, *n* = 1) via Reaction I and isolated as a colorless oil (22%): IR (neat) 2900, 2830, 1450, 1350, 1290, 1130, 1110 cm^{-1}; ^1H NMR δ 0.75 (s, 3 H, CH_3C), 0.87 (t, 3H, CH_3CH_2), 1.10–1.35 (m, 22 H, $(CH_2)_{11}$), 1.50–1.75 (m, 2 H, $OCH_2CH_2CH_2O$), 3.20 (s, 4 H, OCH_2C), 3.44–3.64 (m, 12 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 386 (M^+, 6), 103 (100). Anal. Calcd for $C_{23}H_{46}O_4$: C, 71.45; H, 11.99. Found: C, 71.00; H, 12.31.

Dodecyl-dimethyl-14-crown-4 or 6-Dodecyl-13,13-dimethyl-1,4,8,11-tetraoxatetradecane (2c). 5,5-Dimethyl-3,7-dioxanonane-1,9-diol ditosylate (**9**) was obtained in the following way. Reaction of 2,2-dimethylpropane-1,3-diol (1 equiv) with chloroacetic acid (2.5 equiv) in refluxing *tert*-butyl alcohol in the presence of *t*-BuOK (5 equiv) gave 5,5-dimethyl-3,7-dioxa-1,9-dioic acid, which was esterified by refluxing in ethanol in the presence of TsOH. The diethyl ester (1 equiv) was then reduced by $LiAlH_4$ (4 equiv) in THF to yield 5,5-dimethyl-3,7-dioxanonane-1,9-doil, which was in turn converted to the tosylate **9** in a conventional manner.[43] Compound **2c**, prepared from the propanediol **7**(R = H) and the above ditosylate **9** as described in the procedure for Reaction I, was isolated as an analytically pure oil after chromatography, which gradually converted to a white solid (3%): mp 44.5–45.0 °C; IR (KBr) 2910, 2850, 1470, 1130, 1110 cm^{-1}; ^1H NMR δ 0.80 (s, 6 H, CH_3CCH_3), 0.87 (t, 3 H, CH_3CH_2), 1.10–1.36 (m, 22 H, $(CH_2)_{11}$), 1.40–1.70 (m, 1 H, CH), 3.19 (s, 6 H, OCH_2C), 3.36–3.60 (m, 12 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 400 (M^+, 3), 69 (100). Anal. Calcd for $C_{24}H_{48}O_4$: C, 71.95; H, 12.08. Found: C, 71.68; H, 12.17.

Dodecyl-trimethyl-14-crown-4 or 6-Dodecyl-6,13,13-trimethyl-1,4,8,11-tetraoxacyclotetradecane (2d). Reaction I of the propanediol **7**(R = CH_3) with the ditosylate **9** afford compound **2d** as a colorless oil (4%): IR (neat) 2910, 2840, 1460, 1350, 1130 cm^{-1}; ^1H NMR δ 0.76 (s, 3 H, 6-CH_3), 0.82 (s, 6 H, 13-CH_3), 0.88 (t, 3 H, CH_3CH_2), 1.05–1.35 (m, 22 H, $(CH_2)_{11}$), 3.19 (s, 8 H, OCH_2C), 3.48 (s, 8 H, OCH_2CH_2O); MS, *m/e* (% relative intensity) 414 (M^+, 2), 69 (100). Anal. Calcd for $C_{25}H_{50}O_4$: C, 72.41; H, 12.15. Found: C, 72.67; H, 12.31.

Dodecyl-15-crown-4 or 10-Dodecyl-1,4,8,12-tetraoxacyclopentadecane (3a). The preparation of 4,7-dioxadecane-1,10-diol ditosylate (**8**(*m* = 1, *n* = 0)) is as follows: The Michael reaction of ethylene glycol (1 equiv) with acrylonitrile (2.2 equiv) in the presence of a catalytic amount of Na metal yielded 1,8-dicyano-3,6-dioxaoctane, which was then converted to 4,7-dioxadecane-1,10-dioic dimethyl ester by methanolysis in the presence of TsOH (2.2 equiv) in refluxing methanol. $LiAlH_4$ (4 equiv) reduction of the dimethyl ester (1 equiv) in refluxing THF gave 4,7-dioxadecane-1,10-diol, which was then tosylated in the usual manner. Compound **3a** was prepared from the propanediol **7**(R = H) and the above ditosylate **8**(*m* = 1, *n* = 0) according to the procedure for Reaction I and isolated as a white solid (7%): mp 54.5–55.5 °C; IR (KBr) 2900, 2840, 1470, 1350, 1140, 1120 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H, CH_3CH_2), 1.18–1.38 (m, 22 H, $(CH_2)_{11}$), 1.52–1.75 (m, 5 H, CH and $OCH_2CH_2CH_2O$), 3.20–3.60 (m, 16 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 386 (M^+, 4), 59 (100). Anal. Calcd for $C_{23}H_{46}O_4$: C, 71.45; H, 11.99. Found: C, 71.19; H, 11.95.

Dodecyl-methyl-15-crown-4 or 10-Dodecyl-10-methyl-1,4,8,12-tetraoxacyclopentadecane (3b). Compound **3b**, prepared from the propanediol **7**(R = CH_3) and the diol ditosylate **8**(*m* = 1, *n* = 0) as described in the general procedure for Reaction I, was obtained as a colorless oil (15 %): IR (neat) 2900, 2840, 1455, 1340, 1120 cm^{-1}; ^1H NMR δ 0.75 (s, 3 H, CH_3C), 0.87 (t, 3 H, CH_3CH_2), 1.10–1.35 (m, 22 H, $(CH_2)_{11}$), 1.52–1.74 (m, 4 H, $OCH_2CH_2CH_2O$), 3.09 (s, 4 H, OCH_2C), 3.32–3.60 (m, 12 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 400 (M^+, 4), 86 (100). Anal. Calcd for $C_{24}H_{48}O_4$: C, 71.95; H, 12.08. Found: C, 72.19; H, 12.37.

Dodecyl-16-crown-4 or 3-Dodecyl-1,5,9,13-tetraoxacyclohexadecane (4a). One of the components for the cyclization reaction, 4,8-dioxaundecane-1,11-diol ditosylate (**8**(*m* = 1, *n* = 1)) was prepared by the reaction of 1,3-dibromopropane (1 equiv) with an excess of 1,3-propanediol (5 equiv) in the presence of KOH (2.2 equiv), followed by the conventional tosylation. The cyclization (Reaction I) of the propanediol **7**(R = H) and the above ditosylate **8**(*m* = 1, *n* = 1) yielded a white solid of **4a** (1%): mp 42.5–43.0 °C; IR(KBr) 2910, 2845, 1470, 1345, 1130 cm^{-1}; ^1H NMR δ 0.87 (t, 3 H, CH_3C), 1.18–1.28 (m, 22 H, $(CH_2)_{11}$), 1.55–1.76 (m, 7 H, CH and $OCH_2CH_2CH_2O$), 3.20–3.58 (m, 16 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 400 (M^+, 5), 58 (100). Anal. Calcd for $C_{24}H_{48}O_4$: C, 71.95; H, 12.08. Found: C, 71.71; H, 11.99.

Dodecyl-methyl-16-crown-4 or 3-Dodecyl-3-methyl-1,5,9,13-tetraoxacyclohexadecane (4b). Compound **4b**, prepared from the propanediol **7**(R = CH_3) and the diol ditosylate **8**(*m* = 1, *n* = 1) as described in the general procedure for Reaction I, was obtained as a colorless oil (4%): IR (neat) 2910, 2850, 1460, 1360, 1125 cm^{-1}; ^1H NMR δ 0.76 (s, 3 H, CH_3C), 0.88 (t, 3 H, CH_3CH_2), 1.12–1.35 (m, 22 H, $(CH_2)_{11}$), 1.56–1.80 (m, 6 H, $OCH_2CH_2CH_2O$), 3.11 (s, 4 H, OCH_2C), 3.32–3.54 (m, 12 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 414 (M^+, 3), 100 (100). Anal. Calcd for $C_{25}H_{50}O_4$: C, 72.41; H, 12.15. Found: C, 72.45; H, 12.34.

Dodecyl-methyl-13-crown-4 or 12-Dodecyl-12-methyl-1,4,7,10-tetraoxacyclotridecane (1b). Reaction II. Li wire (0.1 mol) was dissolved in dry *t*-BuOH with refluxing. To the refluxing mixture were added successively 2-dodecyl-2-methylpropane-1,3-diol (0.033 mol), triethylene glycol dichloride (0.033 mol), and LiBr (0.033 mol). Refluxing was continued for 20 days. After the reaction mixture was concentrated to a volume of 50 mL, 100 mL of water was added. The solution was extracted with $CHCl_3$ (50 mL × 5). The combined extracts were washed with water and dried over $MgSO_4$. The solvent was then evaporated off. Similar workup of the crude product by chromatography to that in Reaction I yielded a pure product of **1b** as a colorless oil (10%): IR (neat) 2910, 2845, 1460, 1350, 1120 cm^{-1}; ^1H NMR δ 0.76 (s, 3 H, CH_3C), 0.87 (t, 3 H, CH_3CH_2), 1.08–1.40 (m, 22 H, $(CH_2)_{11}$), 3.19 (s, 4 H, OCH_2C), 3.40–3.68 (m, 12 H, OCH_2CH_2O); MS, *m/e* (% relative intensity) 372 (M^+, 2.5), 45 (100). Anal. Calcd for $C_{22}H_{44}O_4$: C, 70.92; H, 11.90. Found: C, 70.69; H, 12.07.

2-(Octadecyloxymethyl)-12-crown-4 or 2-(Octadecyloxymethyl)-1,4,7,10-tetraoxacyclododecane (5a). A suspension of NaH (5.5 mmol) and 2-(hydroxymethyl)-12-crown-4 (5 mmol)[18] in THF (100 mL) was refluxed for about $^1/_2$ h. To the refluxing mixture was added dropwise octadecyl bromide (5.5 mmol) dissolved in THF (20 mL). The mixture was refluxed for 2 days, and then the solvent was removed and the residue extracted with benzene (50 mL). The insoluble materials (inorganic salts) were filtered off and washed with benzene. The combined benzene solution was evaporated under vacuum. Silica gel chromatography (ethyl acetate) and subsequent recrystallization from methanol yielded a white solid of **5a** (40%): mp 48.5–49.5 °C; IR (KBr) 2900, 2840, 1460, 1350, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3), 1.20–1.70 (m, 32 H, $CH_3(CH_2)_{16}$), 3.35–3.88 (m, 19 H, OCH_2 and CH); MS, *m/e* (% relative intensity) 458 (M^+, 4), 175 (100). Anal. Calcd for $C_{27}H_{54}O_5$: C, 70.70; H, 11.87. Found: C, 70.52% H, 11.88.

2-(Octadecanoyloxymethyl)-12-crown-4 or 2-(Octadecanoyloxymethyl)-1,4,7,10-tetraoxacyclododecane (5b). Compound **5b** was prepared in a similar procedure to that for the 15-crown-5 derivatives reported elsewhere.[44] **5b** (50%): white solid; mp 39.3–39.8 °C; IR (KBr) 2900, 2845, 1730, 1470, 1390, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3), 1.20–1.37 (m, 28 H, $CH_3(CH_2)_{14}$), 1.50–1.70 (m, 2 H, CH_2CH_2CO), 2.30 (t, 2 H, CH_2CO), 3.55–3.90 (m, 15 H, CH_2OCH_2 and CH), 4.10 (d, 2 H, $COOCH_2$); MS, *m/e* (% relative intensity) 472 (M^+, 6), 45 (100). Anal. Calcd for $C_{27}H_{52}O_6$: C, 68.31; H, 11.47. Found: C, 68.55; H, 11.08.

(4-Octadecanoylbenzo)-13-crown-4 or (4-Octadecanoyl-2,3-benzo)-1,4,7,11-tetraoxacyclotridecane-2-ene (6b). Compound **6b** was prepared by the reaction of benzo-13-crown-4 (**6a**) (0.1 mol)[12] and octadecanoic acid (0.125 mol) using a Eaton's reagent (CH_3SO_3H/P_2O_5 = 25 g/2.5 g)[45] with a modification of the procedure in the literature.[46] The crude product was purified by Kugelrohr distillation, followed by recrystallization from ethanol. **6b** (8%): white solid; mp 67.5–68.5 °C; IR (KBr) 2900, 2835, 1670, 1590, 1275, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3), 1.20–1.45 (m, 28 H, $CH_3(CH_2)_{14}$), 1.50–2.02 (m, 4 H, $OCH_2CH_2CH_2O$ and CH_2CH_2CO), 2.88 (t, 2 H, CH_2CO), 3.65–3.90

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(m, 8 H, CH_2OCH_2), 4.05–4.30 (m, 4 H, $ArOCH_2$), 7.48–7.70 and 6.80–7.00 (m, 3 H, aromatic H); MS, *m/e* (% relative intensity) 504 (M^+, 89), 280 (100). Anal. Calcd for $C_{31}H_{52}O_5$: C, 73.77; H, 10.38. Found: C, 73.51; H, 10.41.

Evaluation of Lithium Selectivity as a Potentiometric Selectivity Coefficient. Membrane Electrode. The typical procedure for membrane preparation is as follows: PVC (100 mg), NPOE (250 mg), crown ether (3.6 mg, 1 wt %), and KTpClPB (about 2.4 mg, 50 mol % to the crown ether) were dissolved in 3–4 mL of THF. This solution was then poured into a flat Petri dish of 34-mm inner diameter. Gradual evaporation of the solvent at room temperature gave a transparent, flexible membrane of about 0.15 mm in thickness. A disk of 7 mm in diameter was cut from the PVC membrane using a cork borer and incorporated into an electrode body of Orion Model 92. The diameter of the exposed membrane was about 2 mm. After injection of 1 M LiCl aqueous solution as the internal solution, the electrode was conditioned by soaking into 1 M LiCl aqueous solution overnight. The external reference electrode is a double junction type Ag/AgCl glass electrode. The composition of electrochemical cell is given as Ag·AgCl|1 M LiCl|PVC membrane|sample solution|0.1 M NH_4NO_3|4 M KCl|AgCl·Ag.

EMF Measurements. All EMF measurements were made at 25 °C, using a pH/mV meter of high input impedance in combination with a recorder. Sample solutions were magnetically stirred and kept in a double-wall glass container connected with a circulating bath. The electrode systems and the mV meter were contained in a Faraday cage to cut off any electrical noise. The EMF values were corrected by subtracting a liquid-junction potential between the external rederence electrode and the sample solution in the high Li^+ concentrations. The liquid-junction potentials were computed according to Henderson's equation.[47]

Selectivity Coefficients. The potentiometric selectivity coefficients k_{LiM}^{Pot} determined here are defined in the Nicolsky–Eisenman equation:[48]

$$E = \text{constant} + \frac{2.303RT}{F} \log \left[a_{Li} + k_{LiM}^{Pot}(a_M)^{1/z_M}\right]$$

where E = the experimentally observed potential, R = the gas constant, T = the thermodynamic temperature, F = the Faraday constant, a_{Li} = the Li^+ activity, a_M = the activity of the foreign cation, and z_M = the charge of the foreign cation. The selectivity coefficients were determined by a mixed solution method (fixed interference method) according to IUPAC recommendations.[20] The EMF of the electrochemical cell was measured with solutions of a constant level of foreign cation and varying Li^+ activity. The constant concentrations for the foreign cations were 5×10^{-2} M for alkali metal ions and H^+, and 5×10^{-1} M for alkaline-earth metal ions and NH_4^+ in the case of **2** through **4**. In the case of the other crown ethers, they were 5×10^{-5} M for alkali metal ions, 5×10^{-2} M for Mg^{2+} and H^+, and 5×10^{-3} M for the other foreign cations. When the EMF values obtained are plotted against the Li^+ activity, the intersection of the extrapolation of the linear portions of this plots gives the values of a which are to be used to compute k_{LiM}^{Pot} from the equation

$$k_{LiM}^{Pot} = a/(a_M)^{1/z_M}$$

In the Li^+ concentrations of less than 0.1 M the activity coefficients γ were calculated by using the following equation based on the Debye–Hückel theory:

$$\log \gamma = -0.509(I)^{1/2}/(1 + I^{1/2})$$

where I denotes the ionic strength. Some of the experimental values of activity coefficients in the literature[49] were also employed in the higher Li^+ concentrations.

Conductivity Measurements. The conductivity measurements were carried out at 25 ± 0.1 °C with use of a conductivity cell with a cell constant of 0.479 cm^{-1}. The procedure is as follows: An acetonitrile solutions of the alkali metal perchlorate (5×10^{-4} M, 10 mL) was placed in the cell and the resistance of the solution measured. A stepwise increase in the crown ether concentration was effected by addition of a crown ether solution (2×10^{-2} M) to the cell with use of microsyringe. In order to keep the salt concentration constant during the titration, the crown ether solution contained the same concentration of salt as the initial salt solution. The resistance of the crown ether–salt solution was measured on each addition and corrected by the conductivity of pure acetonitrile. The molar conductivity of each addition of the crown ether solution was computed from the corrected value of the resistance. According to the procedure in the literature,[50,51] the complex formation constants for the 1:1 complex were calculated by least-square methods using a microcomputer.

Registry No. 1a, 92144-64-4; **1b**, 92144-65-5; **2a**, 91539-73-0; **2b**, 91539-72-9; **2c**, 92144-66-6; **2d**, 92144-67-7; **3a**, 92144-68-8; **3b**, 92144-69-9; **4a**, 92144-70-2; **4b**, 92144-71-3; **5a**, 92144-72-4; **5b**, 92144-73-5; **6a**, 62150-58-7; **6b**, 92144-74-6; **7** (R = H), 10395-09-2; **7** (R = CH_3), 13064-31-8; **8** (m = 0; n = 1), 92144-75-7; **8** (m = 1; n = 0), 92144-76-8; **8** (m = 1; n = 1), 92144-77-9; **9**, 92144-78-0; diethyl dodecylmalonate, 7252-87-1; 5,5-dimethyl-3,7-dioxa-1,9-nonandioic acid, 65115-11-9; diethyl 5,5-dimethyl-3,7-dioxa-1,9-nonandioate, 65115-08-4; 5,5-dimethyl-3,7-dioxanonane-1,9-diol, 92144-79-1; 1,8-dicyano-3,6-dioxaoctane, 3386-87-6; dimethyl 4,7-dioxadecane-1,10-dioate, 19364-66-0; 4,7-dioxadecane-1,10-diol, 92144-80-4; 2-(hydroxymethyl)-12-crown-4, 75507-26-5; triethylene glycol ditosylate, 19249-03-7; 2,2-dimethyl-1,3-propanediol, 126-30-7; chloroacetic acid, 79-11-8; ethylene glycol, 107-21-1; acrylonitrile, 107-13-1; 1,3-dibromopropane, 109-64-8; 1,3-propanediol, 504-63-2; 1,2-bis(2-chloroethoxy)ethane, 112-26-5; octadecyl bromide, 112-89-0; octadecanoic acid, 57-11-4; Li^+, 17341-24-1; PVC, 9002-86-2.

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Siderophore Iron-Release Mechanisms

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Abstract: The structures of the iron complexes of catechol, enterobactin, and the synthetic siderophore *N,N′,N″*-tris(2,3-dihydroxybenzoyl)-1,3,5-tris(aminoethyl)benzene (MECAM) are discussed. The recent proposal for a "tris(salicylate)" mode of coordination involving the ortho carbonyl of the 2,3-dihydroxybenzoyl rings for the triprotonated complex $[Fe(H_3MECAM)]^0$ (Pecoraro et al. *J. Am. Chem. Soc.* **1983**, *105*, 4617) is questioned, since this complex would require considerable compression for each of the three carbonyl oxygens. We propose an alternative structure involving catecholato coordination and support this suggestion with cyclic voltammetry data. $[Fe(MECAM)]^{3-}$ is capable of donating iron to *Escherichia coli* yet cannot be hydrolyzed by enterobactin esterase. These observations are critical to the development of theories for the intracellular iron-release mechanism of catecholato siderophores.

Iron is essential for virtually all life forms, having a critical role in the action of many enzymes and redox proteins. Animals obtain iron in their diet, but for plants and unicellular organisms iron is relatively inaccessible since it forms insoluble hydroxides. Many microorganisms have developed the ability to synthesize low molecular weight polydentate ligands that possess a high affinity

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