Second-Sphere Coordination of Ferrioxamine B and Association of Deferriferrioxamine B, $CH_3(CH_2)_4NH_3^+$, NH_4^+, K^+, and Mg^{2+} with Synthetic Crown Ethers and the Natural Ionophores Valinomycin and Nonactin in Chloroform

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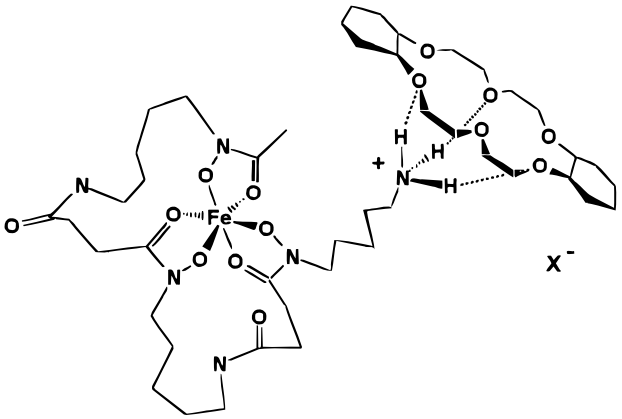
The interaction of ferrioxamine B, $FeHDFB^+$, through a protonated amine side chain, with various host ionophore structures to form a host−guest complex in the second coordination shell has been investigated. Host−guest association constants (K_a) in water saturated chloroform are reported for synthetic crown ethers with different cavity size and substituents (18-crown-6 and its dicyclohexano, benzo, and dibenzo derivatives; dibenzo and dicyclohexano derivatives of 24-crown-8; and dibenzo-30-crown-10). The natural ionophores valinomycin and nonactin were also found to form stable second-sphere complexes with ferrioxamine B in wet chloroform. Results are reported for both picrate and perchlorate salts of $FeHDFB^+$. Since the protonated amine side chain of ferrioxamine B may be viewed as a substituted amine, the host−guest association constants for $FeHDFB^+$ are compared to the interaction of Mg^{2+}, K^+, NH_4^+, $CH_3(CH_2)_4NH_3^+$, and H_4DFB^+ with the same ionophores. This is the first report of nonactin complexation of this series of cations in an organic medium of low polarity and one of the few reports of valinomycin complexation. To the best of our knowledge these are the first reported stability constants for the association of (Mg^{2+},2pic$^-$) with natural and synthetic ionophores in chloroform. K_a values for ferrioxamine B complexation by the synthetic crown ethers are influenced by ring size and substituent. Despite significant preorganization capabilities, the large cavities of valinomycin, nonactin and benzo-30-crown-10 do not form as stable host−guest assemblies with bulky substituted amine cations such as ferrioxamine B as does *cis*-dicyclohexano-18-crown-6.

Introduction

The highly specific molecular recognition of iron(III) siderophores by host molecules generated by living organisms, followed by transport across the lipid membrane, has been suggested as a step involved in the siderophore mediated acquisition of iron by some microbes.[1,2] An understanding of the principles of molecular recognition may aid in determining the probability of such processes being involved in microbial siderophore uptake mechanisms. It has been established that an iron(III) complex of the linear trihydroxamic acid deferriferrioxamine B (ferrioxamine B, $FeHDFB^+$) is recognized by the crown ether *cis*-dicyclohexano-18-crown-6 (DC-18-C-6), giving rise to a stable supramolecular assembly, **I**, in chloroform.[3] The recognition is accomplished by complexation of the protonated amine side chain of ferrioxamine B by the crown ether. In addition to being considered as an interaction between an alkyl substituted ammonium ion guest and crown ether host, the supramolecular assembly may also be viewed in the context of the second-sphere coordination of an iron siderophore complex with an ionophore. We have established that the anion influences the stability of the assembly (**I**) in wet chloroform through the size of its hydration shell.[4] The sensitivity to anion hydration shell is equivalent to changes in the $MHDFB^+$ hydration shell brought about by changing M (M(III) = Al, Fe, Ga, and In).[3,4] Stereochemical effects, as expressed through the preference of $FeHDFB^+$ for second-sphere coordination by *cis-syn-cis*-DC-18-C-6 over *cis-anti-cis*-DC-18-C-6, make a significant contribution to the overall stability of the assembly (**I**).[5] Due to the distinct steric requirements of the bulky $FeHDFB^+$ structure, the stability of the supramolecular assembly is expected to be strongly influenced by the structure and flexibility of the macrocyclic host.[6]



I

The current study considers the influence of the host crown ether substituent and ring size (**II**−**V**) on ferrioxamine B host−

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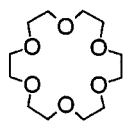
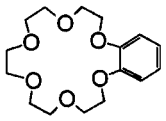


II

18-crown-6

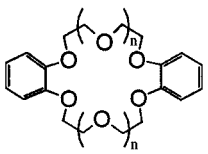
(18-C-6)



III

benzo-18-crown-6

(B-18-C-6)



IV

a) n = 1, dibenzo-18-crown-6

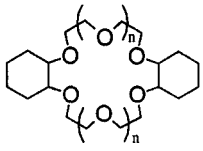
(DB-18-C-6)

b) n = 2, dibenzo-24-crown-8

(DB-24-C-8)

c) n = 3, dibenzo-30-crown-10

(DB-30-C-10)



V

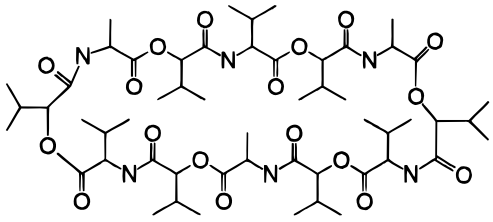
a) n = 1, *cis*-dicyclohexano-18-crown-6

(*cis*-DC-18-C-6)

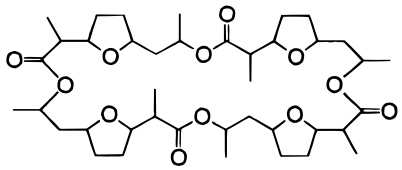
b) n = 2, dicyclohexano-24-crown-8

(DC-24-C-8)

guest complex stability. In addition to these synthetic ionophores, our study includes the natural cyclic ionophores valinomycin, **VI**, and nonactin, **VII**. This allows us to



VI



VII

investigate whether the transport patterns that are employed in nature for the metabolism of cationic species[7−12] may prove to be efficient in the second-sphere complexation of ferrioxamine B. In addition to their three-dimensional array of donor groups, these natural ionophores have favorable binding dynamics in the form of rapid guest complexation/decomplexation kinetics as an advantage over the synthetic crown ethers.[13] It is also of interest to consider whether these large ionophores can associate with ferrioxamine B or with the metal-free ligand through polar interactions with the amide functionalities of the hydroxamic acid backbone in addition to the protonated amine side chain. In this way $FeHDFB^+$ may be in more intimate contact with the ionophore.

For purposes of comparison with ferrioxamine B, we have also investigated other cation guest interactions with this group of host molecules. NH_4^+ was investigated since it may be considered as the parent ion for the protonated amine side chain of ferrioxamine B. K^+ was included in our study because it may be used as a standard for literature comparisons of host−guest complex formation involving substituted amines. Pentylamine was included as it represents the amine side chain of ferrioxamine B. Its inclusion along with the metal-free ligand deferriferrioxamine B permits us to consider more fully the steric influence of the ferrioxamine B iron(III) coordination shell on host−guest complex stability. Ionophore complex formation with Mg^{2+} was also investigated as this cation was used to maintain constant ionic strength in our experiments. Mg^{2+} is optimum for this purpose as the distribution of its salts from the aqueous to the chloroform phase is low, resulting in a low extraction constant (K_{ex}) and therefore negligible interference with measurements of the host−guest complexation constants for the cations of interest.

Experimental Section

Materials. *cis*-Dicyclohexano-18-crown-6 (**Va**), a mixture of equal parts of *syn* and *anti* isomers, 18-crown-6 (**II**), benzo-18-crown-6 (**III**), dibenzo-18-crown-6 (**IVa**), dibenzo-24-crown-8 (**IVb**), dibenzo-30-crown-10 (**IVc**) and dicyclohexano-24-crown-8 (**Vb**) were used as obtained from Aldrich. The UV−visible spectra of benzo-crown ethers exhibit an absorption band in chloroform at either 278 or 276 nm. Molar absorptivities are related to the number of benzo substituents and were determined from absorbance *vs* concentration data. Results are in agreement with the literature.[14] Crown ether, λ_{max} (ϵ): **III**, 278 nm (2200 M^{-1} cm^{-1}); **IVa**, 278 nm (5300 M^{-1} cm^{-1}); **IVb**, 278 nm (5100 M^{-1} cm^{-1}); **IVc**, 276 nm (4800 M^{-1} cm^{-1}). The decreasing trend in molar absorptivities for **IVa**, **IVb**, and **IVc** parallels the increase in the spatial separation of benzo groups as the size of the ether ring increases. Nonactin (from *Streptomyces griseus*), **VI**, and valinomycin, **VII**, were used as obtained from Sigma. Sources and criteria for purity of all cation guests, including ferrioxamine B, are as described previously.[3]

Twice distilled water and chloroform saturated with water were used in the extraction and distribution equilibrium experiments.

Aqueous Solutions. The aqueous solutions of the cations were prepared to satisfy two criteria: (1) the extractability of the picrate or perchlorate salts from the aqueous into the chloroform phase must be sufficient to be observable; and (2) the ionic strength of the solutions must be maintained at 0.1 M. The aqueous solutions of ferrioxamine B picrate (3.00×10^{-3} M) and ferrioxamine B perchlorate (1.50×10^{-2} M) were prepared as previously described,[3,4] and their concentrations determined spectrophotometrically from absorbance readings at 425 nm (ϵ = 2600 M^{-1} cm^{-1}).[15] The concentrations of supporting electrolytes $Mg(pic)_2$ and $Mg(ClO_4)_2$ were kept at 3.33×10^{-2} M and 3.00×10^{-2} M, respectively to maintain ionic strength at 0.1. The pH of the solution was 3.2.

Magnesium nitrate and picrate solutions used to maintain a constant ionic strength were obtained and prepared as described previously.[3] *Extreme care should be taken while working with both picric acid and picrate salts.* A magnesium picrate solution was prepared by neutral-

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Table 1. Absorption Maxima and Molar Absorptivities of Assemblies of Ionophores with Picrate Salts in Chloroform at 25 ± 0.5 °C[a]

	cation							
	Mg^{2+}		K^+		NH_4^+		$CH_3(CH_2)_4NH_3^+$	
ionophore	ϵ[b]	λ_{max}[c]	ϵ[b]	λ_{max}[c]	ϵ[b]	λ_{max}[c]	ϵ[b]	λ_{max}[c]
none	26 600[d]	332[d]						
cis-DC-18-C-6	39 800[e]	370[e]	15 900[f]	366[f]	16 100[e]	364[e]	19 900[e]	375[e]
B-18-C-6			16 100	366				
DB-18-C-6			15 700	364				
DB-30-C-10	28 800[g]	358	17 700	378			14 100	374
valinomycin	38 800[g]	374	19 200	378	18 900	378	17 600	378
nonactin	38 800[g]	374	20 000	378	19 600	378	20 000	378

[a] Values given correspond to the molar absorptivities of (cation,L,pic) assemblies and are an average of three to five independent determinations with an average error <2%, except in the case of Mg^{2+},L,2pic$^-$ where the estimated error is <20%. [b] M^{-1} cm^{-1}. [c] nm. [d] Value given corresponds to the molar absorptivity of the ion pair (cation,pic) in chloroform. The ϵ of aqueous picrate anion is 14 400 M^{-1} cm^{-1} at 356 nm.[16] [e] Reference 3. [f] Reference 4. [g] Estimated values; see text.

ization of $Mg(OH)_2$ (Aldrich) with picric acid. Picric acid (Aldrich) was twice recrystallized from water. Picrate concentration was determined spectrophotometrically at 356 nm ($\epsilon = 1.44 \times 10^4$ M^{-1} cm^{-1}).[16]

Aqueous solutions of NH_4^+ and K^+ cations were prepared by mixing solutions of their nitrate salts with magnesium picrate solution. The concentrations in the resulting solutions were 0.1 M NH_4NO_3, 0.1 M KNO_3, and 7.50×10^{-5} M $Mg(pic)_2$. The concentrations of KNO_3 and NH_4NO_3 in their aqueous solutions were determined using a cation exchange resin, followed by titration with 0.1 M NaOH.[3] An aqueous solution of H_4DFB^+ was prepared by dissolving the mesylate salt (Sigma) to give a concentration of 0.1 M in a 2.50×10^{-4} M $Mg(pic)_2$ solution.

A pentylamine solution was prepared by titrating pentylamine (Aldrich) with picric acid up to pH ~5.6 to assure the protonation of the amine site. To maintain the ionic strength at 0.1 M, $Mg(NO_3)_2$ solution was added to the pentylamine solution to a concentration of 3.33×10^{-2} M. The final solution was 8.64×10^{-4} M pentylamine picrate and 3.33×10^{-2} M $Mg(NO_3)_2$.

Chloroform Solutions. Chloroform solutions of crown ethers, nonactin, and valinomycin were made by dissolving appropriate amounts of material in a known volume of $CHC1_3$. The concentration of ionophores varied between 6.00×10^{-5} to 5.00×10^{-1} M, depending on the extractabilities of the cations investigated.

Methods. Distribution Equilibrium—$Mg(pic)_2$. The picrate concentrations of the aqueous magnesium solutions were varied from 2.50×10^{-3} to 1.01×10^{-1} M. The distribution of magnesium picrate was obtained by vigorously shaking 300 mL of aqueous picrate solution with 300 mL of chloroform. The mixture was left overnight to equilibrate and the layers were separated. The chloroform layer was evaporated on a rotary evaporator under vacuum. The residue was dissolved in 2.5 mL of chloroform, followed by an absorbance reading. Water (2 mL) was added to 2 mL of chloroform solution and practically all of the organic phase picrate was redistributed to the aqueous layer where its concentration was determined from the aqueous picrate molar absorptivity ($\epsilon_{345} = 1.44 \times 10^4$ M^{-1} cm^{-1}).[16] The molar absorptivity of the ion pair $(Mg^{2+},2pic^-)_{org}$ was then calculated as $\epsilon(Mg^{2+},2pic^-)_{org\,332} = 26\,600 \pm 800$ M^{-1} cm^{-1} (Table 1). Atomic absorption spectrophotometry was used in order to verify the accuracy of this result. An aqueous solution of magnesium picrate, obtained either after the redistribution of organic picrate or by direct dissolution of the organic phase (Mg^{2+},2pic$^-$) residue in water, was passed through an anion exchange resin (AG 1-X8, Bio-Rad; nitrate form) to eliminate picrate anion. The concentration of Mg^{2+} was determined using a Model 3100 Perkin-Elmer atomic absorption spectrophotometer at 285.2 nm. The two methods were in excellent agreement.

Distribution Equilibria—Crown Ethers, Valinomycin, and Nonactin. We have utilized the high molar absorptivity of the picrate anion whenever possible in determining the distribution constants of ionophores. In cases of low association of an ionophore with the picrate salt, the absorptivity of the benzo group(s) on the ionophore was used.

The distribution of ionophores between chloroform and water was determined in the same way as described for *cis*-DC-18-C-6,[3,17] by the reextraction of the ionophore (L) from the aqueous phase with potassium picrate into chloroform, followed by the spectrophotometric determination of $[K^+,L,pic^-]_{org}$. In separate experiments the molar absorptivities of the corresponding (K^+,L, pic$^-$) assemblies in chloroform were determined as previously described,[3-5] and are given in Table 1. If the extractability of K^+ with the ionophore into the organic phase was sufficiently high, essentially all of the ionophore that had been distributed into the aqueous phase was redistributed back into the chloroform phase in the reextraction step. Since NH_4^+ forms a more stable complex with nonactin than K^+,[12] ammonium picrate was used for nonactin redistribution. A gravimetric method[18] was used in the case of 18-C-6. Namely, after the equilibration of the aqueous and chloroform layers, the chloroform layer was left to evaporate and the residue weighed. The stability constants for the association of K^+,pic$^-$ with DB-24-C-8 and with DB-30-C-10 were not sufficiently high, as found here and elsewhere,[19] to allow the majority of aqueous phase crown ether to be redistributed into the chloroform phase in the form of its potassium picrate complex. Therefore, given that both DB-24-C-8 and DB-30-C-10 favor the organic over the aqueous phase, and taking advantage of the presence of the benzo groups, the aqueous crown ether concentration was determined after its redistribution into the organic phase, using previously determined molar absorptivities (see above). The distribution constant of B-18-C-6 was determined in two ways, by the redistribution of the aqueous crown ether alone and as its K^+ complex. The two methods are in excellent agreement.

Extraction Equilibria. The extraction of ferrioxamine B and other cations was performed as previously described.[3,4] A competition between K^+ and $FeHDFB^+$ or H_4DFB^+ was used to determine the concentration of ferrioxamine B and deferriferrioxamine B in the organic phase, by means of their reextraction into the aqueous phase through displacement by 0.1 M KNO_3. When the association of ($FeHDFB^+$,pic$^-$) with an ionophore was investigated, after the reextraction an aliquot of the aqueous layer was passed through an anion exchange resin to eliminate picrate, followed by the spectral determination of $FeHDFB^+$.[3] The same procedure was applied to the determination of (H_4DFB^+,pic$^-$) in the organic layer, followed by an additional step once the picrate was eliminated. Namely, the concentration of H_4DFB^+ was determined as its Fe(III) complex, $FeHDFB^+$, formed by reaction with aqueous acidic iron(III) stock solution.[15,20]

In the extraction of other cations the concentration of the cation in the organic phase was determined either using the molar absorptivity of the corresponding $(cation^+,L,pic^-)_{org}$ assembly in chloroform determined in a separate experiment,[3] or was calculated as the difference between the initial and aqueous concentrations.[3-5] Whenever experimental conditions permitted, both layers were examined. The molar

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Table 2. Extraction Equilibrium Constants (log K_{ex}; eq 3) for Picrate and Perchlorate Salts with Different Ionophores in Chloroform[a]

	log K_{ex}						
ionophore	Mg^{2+}	K^+	NH_4^+	$CH_3(CH_2)_4NH_3^+$	H_4DFB^+	$FeHDFB^+$	$FeHDFB^{+}$ [b]
18-C-6		>8.40[c]	6.98[c]			3.18	0.87
B-18-C-6		5.06				2.19	−0.30
		4.61[d]					
DB-18-C-6		4.87[c]	3.83[c]			1.57	−1.18
DB-24-C-8		2.81	2.57			0.96	−1.83
DB-30-C-10	1.57	4.01	2.99	2.31		0.90	−2.01
cis-DC-18-C-6[e]	1.09	5.64[f]	5.29[f]	5.53[f]	2.90[f]	3.05[f]	0.74[g]
cis-syn-cis isomer DC-18-C-6		5.68[h]	5.35[h]				1.02[h]
cis-anti-cis isomer DC-18-C-6		5.59[h]	5.24[h]				0.52[h]
DC-24-C-8							−1.18
valinomycin	1.27	6.40	4.75	3.57	0.80	1.22	
nonactin	1.96	4.59	5.26	4.56	1.56	1.65	

[a] Data are collected at 25 ± 0.5 °C, I = 0.1 M (maintained by the salts of different cations present in the solution; see Experimental Section). Values given are an average of 3−5 independent determinations with an average error for K_{ex} < 5% except for the extraction of Mg^{2+} where the error is <20%. [b] Perchlorate salt; all other data are for picrate salts. [c] Reference 19. [d] Reference 19; value obtained at 22−23 °C. [e] Mixture of equal parts of *cis-syn-cis* and *cis-anti-cis* isomers. [f] Reference 3. [g] Reference 4. [h] Reference 5.

absorptivities of the cation assemblies with crown ethers obtained here, together with those previously determined,[3,4] are listed in Table 1. On the basis of the experimentally determined molar absorptivities and the corresponding λ_{max} of a tight ion pair in chloroform, solvent separated ion pair in water, and crown ether separated ion pair in chloroform, an estimation of the molar absorptivities was made for the association of (Mg^{2+},2pic$^-$) with DB-30-C-10, valinomycin, and nonactin (Table 1).

Results

Overall Extraction Equilibria. The experimental approach to determining host−guest association constants in chloroform in the presence of various cations, anions and ionophores involves the determination of extraction and distribution equilibria. An overall equilibrium for the systems reported here is shown in eq 1, where the cation is either a substituted

$$RNH_3^+{}_{aq}\ (\text{or } K^+{}_{aq}) + Mg^{2+}{}_{aq} + 3X^-{}_{aq} + 2L_{org} \overset{K_{overall}}{\rightleftharpoons} (RNH_3^+,L,X^-)_{org} + (Mg^{2+},L,2X^-)_{org} \quad (1)$$

ammonium ion ($RNH_3^+ = NH_4^+$, $CH_3(CH_2)_4NH_3^+$, H_4DFB^+ or $FeHDFB^+$) or K^+. The anion X^- is either picrate or perchlorate. L denotes any of the ionophores **II**−**VII**. The function of the magnesium salt is to provide a constant ionic strength (I = 0.1) and/or to introduce the desired anion. When the counterion was picrate, independent extraction experiments for Mg^{2+} in the absence of RNH_3^+ or K^+ were used to determine the extraction equilibrium constant for $Mg(pic)_2$ and/or to correct the overall extraction data for Mg^{2+} complexation with the ionophore. The extraction of magnesium perchlorate by a crown ether into the organic phase is negligible relative to the extraction of the perchlorate salt of the cation of interest and therefore may be neglected.[4,5]

The overall extraction constant ($K_{overall}$) may be expressed as the product of the extraction constants for the individual equilibria of interest as shown in eq 2.[3] The extraction constant

$$K_{overall} = (K_{ex}{}^{RNH_3^+,L,X^-})(K_{ex}{}^{Mg^{2+},L,2X^-}) \quad (2)$$

of interest, $K_{ex}{}^{RNH_3^+,L,X^-}$, is given by eqs 3 and 4. The values

$$K_{ex}{}^{RNH_3^+,L,X^-} = D_{RNH_3^+}/\{[X^-]_{aq}[L]_{org}\} \quad (3)$$

$$D_{RNH_3^+} = [RNH_3^+,L,X^-]_{org}/[RNH_3^+]_{aq} = [K_{overall}/K_{ex}{}^{Mg^{2+},L,2X^-}][X^-]_{aq}[L]_{org} = [K_{ex}{}^{RNH_3^+,L,X^-}][[X^-]_{aq}[L]_{org} \quad (4)$$

of $K_{ex}{}^{RNH_3^+,L,X^-}$ were obtained from the slopes of linear plots of $D_{RNH_3^+}$ *vs* $\{[X^-]_{aq}[L]_{org}\}$. $[X^-]_{aq}$ was calculated as the difference between the total and organic phase concentrations of X^-, and $[L]_{org}$ was calculated as the difference between the total organic phase concentration of L and $[RNH_3^+,L,X^-]_{org}$. The linearity of these plots also serves to confirm the 1:1 stoichiometry of the host−guest complex as shown in eq 1. Values for $K_{ex}{}^{RNH_3^+,L,X^-}$, $K_{ex}{}^{Mg^{2+},L,2X^-}$, and $K_{ex}{}^{K^+,L,X^-}$ are listed in Table 2.

Distribution Equilibria—Picrate and Perchlorate Salts. In order to use the extraction equilibrium data to calculate host−guest association constants in chloroform, $K_{ex}{}^{RNH_3^+,L,X^-}$ and $K_{ex}{}^{K^+,L,pic^-}$ must be corrected for the distribution of the ion pair (RNH_3^+,pic$^-$ and K^+,pic$^-$) between the aqueous and chloroform phases in the absence of the ionophore host, L. Distribution equilibria (K_d) of the picrate salts of $CH_3(CH_2)_4NH_3^+$, H_4DFB^+, and $FeHDFB^+$ between the aqueous and chloroform phases were determined previously.[3] The K_d values given in the literature[21] were used for the distribution of NH_4(pic) and K(pic). All K_d values are compiled in Table 3.

The distribution of magnesium picrate may be described in the same way as the distribution of other cations using eqs 5 and 6. We find that in the region of Mg^{2+} concentration from

$$Mg^{2+}{}_{aq} + 2pic^-{}_{aq} \overset{K_d}{\rightleftharpoons} (Mg^{2+},2pic^-)_{org} \quad (5)$$

$$K_d = [Mg^{2+},2pic^-]_{org}/\{[Mg^{2+}]_{aq}[pic^-]_{aq}{}^2\} \quad (6)$$

2.50×10^{-3} M to 1.01×10^{-1} M the ratio of $[Mg^{2+},2pic^-]_{org}/[Mg^{2+}]_{aq}$ does not satisify eq 6. Namely, when varying the initial Mg^{2+} concentration in this range the equilibrium organic phase Mg^{2+} concentration remained essentially constant, presumably due to saturation conditions. Saturation appears even

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Table 3. Distribution Equilibrium Constants between Water and Chloroform for Picrate Salts (K_d; eq 6) and Ionophores (K_d'; eq 7)[a]

picrate salts	K_d[b]	picrate salts	K_d[b]
Mg^{2+}	2.54×10^{-3} [c]	$CH_3(CH_2)_4NH_3^+$	2.37×10^{-1} [e]
K^+	2.55×10^{-3} [d]	H_4DFB^+	2.17×10^{-2} [e]
NH_4^+	4.02×10^{-3} [d]	$FeHDFB^+$	2.40×10^{-1} [e]

ionophores	K_d'	$[L]_{org}$, %
18-crown-6	2.20×10^{-1}	81.97
cis-DC-18-C-6	6.30×10^{-4}[e]	99.94
DC-24-C-8	9.50×10^{-4}[f]	99.91
B-18-C-6	3.03×10^{-3}	99.70
DB-18-C-6	1.15×10^{-4}	99.99
DB-24-C-8	1.74×10^{-4}	99.98
DB-30-C-10	2.94×10^{-4}	99.97
valinomycin	$<10^{-6}$	>99.99
nonactin	$<10^{-6}$	>99.99

[a] Data are collected at 25 ± 0.5 °C. Values given are an average of three to five independent determinations. The average error limits are as follows: $Mg(pic)_2$ (<20%); B-18-C-6 and DB-18-C-6 (<11%); DB-24-C-8 and DB-30-C-10 (<20%); valinomycin and nonactin (<20%). [b] M^{-1}. [c] M^{-2}. The value represents a conditional distribution constant D′ valid for the initial Mg^{2+} concentration of 3.33×10^{-2} M as discussed in the text. [d] Reference 21. [e] Reference 3. [f] Estimated value based on the assumption that the observed influence of the increase in cavity size of the dibenzo crown ethers from 18 to 24 atoms on its distribution is also operative in the case of dicyclohexano derivatives. On the basis of known stability constants for K^+,pic^- with crown ethers of different cavity sizes and different substituents on the ether ring, it has been shown that the increase in the ring size from DB-18-C-6 to DB-24-C-8 decreases $K_a \sim 2$ log units. Therefore, the expected log K_a for the interaction of K^+ with DC-24-C-8 should be ~6.2. This constant is too low to allow the accurate determination of the K_d' for DC-24-C-8 on the basis of the re-extraction of aqueous crown ether as its K^+ complex back into the chloroform. The lack of a benzo group on the DC-24-C-8 ether ring does not allow the determination of the crown ether concentration using its molar absorptivity.

at a fairly low initial Mg^{2+} concentration of 2.5×10^{-3} M. This concentration is equal to the concentration of alkali picrate salts used by Koenig *et al.*[24] in the determination of their distribution constants between chloroform and water. The saturation effect is a consequence of the limitations imposed by the high charge density of the 2+ cation. Therefore a conditional distribution constant D' is applicable when the initial concentration of $Mg(pic)_2$ is 3.33×10^{-2} M. This particular concentration was maintained constant in all Mg^{2+} extraction experiments, whereas the ionophore concentration was varied.

The distribution of the perchlorate salt of $FeHDFB^+$ between chloroform and water ($K_d = 3.10 \times 10^{-4}$ M^{-1}) was determined previously[4] and used here in all calculations related to the association of ($FeHDFB^+$,ClO_4^-) with an ionophore host.

Distribution Equilibria—Crown Ethers, Valinomycin, and Nonactin. If a significant amount of ionophore (L) is distributed into the aqueous phase in the course of an extraction experiment, its concentration in the organic phase must be corrected using its distribution constant, K_d', as shown in eq 7. K_d' (= $[L]_{aq}/[L]_{org}$) values are listed in Table 3.

$$L_{org} \overset{K_d'}{\rightleftharpoons} L_{aq} \qquad (7)$$

The distribution of a crown ether is strongly influenced by the number of oxyethylene ($-OCH_2CH_2-$) units,[22,23] by the effect of the substituents on lipophilicity[23] and by conformational mobility.[9] We observe (Table 3) a linear correlation with a slope of 0.1 ± 0.01 between log K_d' and the number of oxyethylene units for the three dibenzo crown ethers investigated. The slope, referred to as an oxyethylene fragment,[23] correlates with the hydrophobicity of the crown ethers. An identical trend was also observed for the same crown ethers in 1-octanol.[23]

The distribution of the natural ionophores valinomycin and nonactin into the aqueous phase is so low that despite the high stability constants for their association with K(pic) and NH_4(pic), and the high molar absorptivities of the corresponding ionophore assemblies in chloroform, there was no detectable level of these ionophores in the aqueous phase.

A separate experiment was performed to confirm that the high affinity of the hydrophilic $FeHDFB^+$ for the aqueous phase does not affect the distribution of an ionophore through an interaction with $FeHDFB^+_{aq}$. Experiments were carried out using 18-C-6 (the ionophore with the highest distribution into the aqueous phase) and nonactin (lowest distribution into the aqueous phase). After the extraction equilibrium of $FeHDFB^+$ was achieved, the ionophore was reextracted from the aqueous layer by K(pic) or NH_4(pic), which have significantly higher stabilities with 18-C-6 and nonactin, respectively, than FeHDFB(pic). It was observed that the distribution of the ionophore was not affected significantly by association with the hydrophilic $FeHDFB^+$. Data available in the literature[19] for the interactions of different cations with different crown ethers in polar and apolar media suggest that association of an ionophore with a $FeHDFB^+$ cation in the aqueous phase, if any, is expected to be several orders of magnitude less than the interaction in the organic phase. Therefore, aqueous phase host−guest association is not expected to affect the aqueous $FeHDFB^+$ and ionophore concentrations. Consequently, K_{ex} data, corrected for distribution of the cation (K_d) and ionophore (K_d'), can be used to calculate host−guest complex formation constants (K_a) in chloroform.

Host−Guest Equilibria. The host−guest association equilibrium of interest in chloroform solution is described in eq 8.

$$(RNH_3^+,X^-)_{org} + L_{org} \overset{K_a}{\rightleftharpoons} (RNH_3^+,L,X^-)_{org} \qquad (8)$$

Host−guest association constants, K_a, for RNH_3^+ may be calculated from $K_{ex}^{RNH_3^+,L,X^-}$ and K_d according to eq 9, provided

$$K_a = (K_{ex}^{RNH_3^+,L,X^-})/K_d \qquad (9)$$

that either the macrocycle is present only in the chloroform phase, or that any association with crown ether in the aqueous phase leads to formation of a complex that is several orders of magnitude lower in stability than the corresponding complex in the organic phase. These criteria were established in separate experiments as described above. Equation 9 is also used for quantifying the interaction of K^+ and Mg^{2+} with the ionophores studied, using $K_{ex}^{K^+,L,X^-}$ and $K_{ex}^{Mg^{2+},L,2X^-}$, respectively.

The host−guest association constants, K_a, for ($FeHDFB^+$, L,pic^-), (RNH_3^+,L,pic^-), (K^+,L,pic^-), (Mg^{2+},L,2pic^-), and ($FeHDFB^+$,L,ClO_4^-) are listed in Table 4.

Discussion

When the parent NH_4^+ cation is substituted with an iron(III) complex, the resulting substituted amine cation $FeHDFB^+$ has distinct steric requirements for association with a host ionophore.[3,5] The stability of the host−guest complex is also affected by the nature of the counterion[4] and by the conformational characteristics of the ionophore, as evidenced by the interaction of $FeHDFB^+$ with *cis-syn-cis* and *cis-anti-cis* isomers of DC-18-C-6 (**Va**).[5] The molecular recognition observed and

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Table 4. Host−Guest Association Equilibrium Constants (log K_a; eqs 8 and 9) for Picrate and Perchlorate Salts with Different Ionophores in Chloroform[a]

	log K_a						
ionophore	Mg^{2+}	K^+	NH_4^+	$CH_3(CH_2)_4NH_3^+$	H_4DFB^+	$FeHDFB^+$	$FeHDFB^{+}$ [b]
18-C-6		>11[c]	9.38[c]			3.80	4.38
B-18-C-6		7.65				2.81	3.21
		7.20[d]					
DB-18-C-6		7.46[c]	6.23[c]			2.19	2.33
DB-24-C-8		5.40	4.97			1.58	1.68
DB-30-C-10	4.17	6.60	5.39	2.94		1.52	1.50
cis-DC-18-C-6[e]	3.69	8.23[f]	7.69[f]	6.16[f]	4.56[f]	3.67[f]	4.25[g]
cis-syn-cis isomer DC-18-C-6		8.27[h]	7.75[h]				4.53[h]
cis-anti-cis isomer DC-18-C-6		8.18[h]	7.64[h]				4.03[h]
DC-24-C-8							2.33
valinomycin	3.87	8.99	7.15	4.20	2.46	1.84	
nonactin	4.56	7.18	7.66	5.19	3.22	2.27	

[a] Data are collected at 25 ± 0.5 °C, I = 0.1 M (maintained by the salts of different cations present in the solution; see Experimental Section). Values given are an average of three to five independent determinations with an average error for K_{ex} < 5% except for the extraction of Mg^{2+} where error is <20%. [b] Perchlorate salt; all other data are for picrate salts. The distribution of the perchlorate salt of $FeHDFB^+$ between the chloroform and water, given by $K_d = 3.1 \times 10^{-4}$ M^{-1} (error <25%), was determined previously[4] and used in all K_a calculations. [c] Reference 19. [d] Reference 19, value is obtained at 22−23 °C. [e] Mixture of equal parts of *cis-syn-cis* and *cis-anti-cis* isomers. [f] Reference 3. [g] Reference 4. [h] Reference 5.

quantified for the interaction of $FeHDFB^+$ with *cis*-DC-18-C-6 and with its *syn* and *anti* isomers[3−5] has been extended in this report to other crown ethers and to the natural cyclic systems valinomycin and nonactin as well.

Our investigation was designed to establish the following: (1) the influence of crown ether substituent and ring size on the stability of the complex formed in the second coordination shell of ferrioxamine B, $FeHDFB^+$; (2) the effect of the $FeHDFB^+$ counter anion (picrate and perchlorate) on host−guest complex stability when structural features of the crown ethers are varied; and (3) any special characteristics associated with the natural cyclic ionophores valinomycin and nonactin when compared to synthetic crown ethers. Since it may be viewed as a substituted amine, the association of $FeHDFB^+$ with different ionophores is compared with the corresponding host−guest complexes of Mg^{2+}, K^+, NH_4^+, pentylamine, and deferriferrioxamine, H_4DFB^+. This enables us to determine the influence of the ferrioxamine B iron(III) coordination sphere on the stability of host−guest complex formation.

As can be seen from the data in Table 4, host−guest complex formation for ferrioxamine B with the synthetic crown ethers investigated decreases in stability with increasing cavity size, from 18 to 30 atoms. This is true for both cyclohexano and benzo substituents, and picrate and perchlorate counterions. These data are consistent with the known affinity of the 18-C-6 cavity for a NH_4^+ guest. Addition of a cyclohexano substituent to the 18-C-6 cavity has a negligible effect on K_a for $FeHDFB^+$. Addition of a benzo substituent to the 18-C-6 ring decreases K_a for $FeHDFB^+$ by about 1 log unit per benzo group. The benzo substituent makes the crown ether ring more rigid and also acts as an electron withdrawing group, decreasing the ability of the ether oxygen atoms to engage in H-bonding with the protonated amine side chain of $FeHDFB^+$.

Figure 1 illustrates the change in host−guest association constant (K_a) with change in crown ether ring size and substituent for ferrioxamine B, and also compares these data with the corresponding association constants for K^+ and NH_4^+ guests. Figure 1 demonstrates the insensitivity of $FeHDFB^+$ to changing crown ether structure from 18-C-6 (**II**) to *cis*-DC-18-C-6 (**Va**), while at the same time there is a significant drop in K_a for K^+ and NH_4^+. The oxygen atoms in 18-C-6 are located alternatively above and below the mean crown ether plane.[24] However, the cavity structure of the dicyclohexano

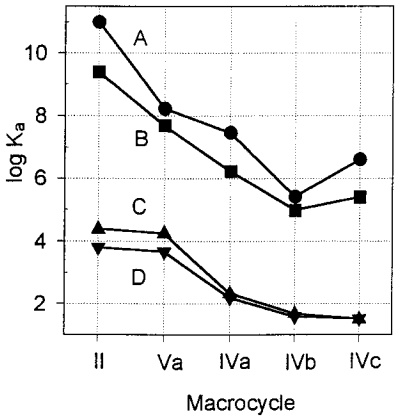

Figure 1. Plots of log K_a as a function of crown ether substituent and ring size for A (K^+,pic^-), B (NH_4^+,pic^-), and ferrioxamine B (C ($FeHDFB^+$,ClO_4^-) and D ($FeHDFB^+$,pic^-)). Roman numerals on the *x*-axis define macrocyclic structures as illustrated in the text.

derivative *cis*-DC-18-C-6 is less regular due to the sp^3 hybridized carbon atoms connecting the hexane rings to the crown ether ring. This influences the ability of DC-18-C-6 to adjust to the size of the guest and thus lowers the stability of the K^+ (and NH_4^+) crown ether assembly relative to 18-C-6. K^+ is an optimum match for the 18-C-6 cavity[8,25] and is located in the center of the mean oxygen plane.[24,26−28] NH_4^+ is, however, displaced out of the plane,[24] and by comparison with other substituted amine cations[19,21,29,30] we predict an even greater displacement for $FeHDFB^+$. Consequently, we ascribe the relative sensitivities of the cation guests to changing the crown ether host from 18-C-6 to DC-18-C-6 as being due to their different distances from the mean oxygen plane of the crown ether cavity. Being located within the cavity, K^+ is expected

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to be very sensitive to any changes in this "ideal" cavity conformation. This is in contrast to the bulky $FeHDFB^+$, which from a position above the crown ether plane "sees" the crown ether ring as an averaged negative dipole in space.

We have included benzo crown ether derivatives in our study in order to investigate the impact of electronic effects on the stability of the cation-crown ether interaction. The expected decrease in K_a occurs for DB-18-C-6 (**IVa**) compared to *cis*-DC-18-C-6 (**Va**), but in this case $FeHDFB^+$ is more sensitive to the change than K^+ (Figure 1). The structures of DC-18-C-6 and DB-18-C-6 were calculated using a MM2 force field.[31] From these calculations it is evident that the cavity of DB-18-C-6 in all of the conformations (represented by different minima) appears to be much better defined (*i.e.*, more regularly shaped) than the cavity of DC-18-C-6. For K^+ this feature may diminish the unfavorable electronic effect of the benzo substituent. However, the electronic effect is fully expressed in the case of $FeHDFB^+$, where the electron-withdrawing benzo groups lower the negative charge density in the crown ether ring and diminish the ability of the oxygen atoms to H-bond to the protonated amine side chain. When one or two benzo groups are attached to the ether ring, there is a corresponding 1 and 2 log unit drop in the association constant with $FeHDFB^+$ relative to the 18-C-6 parent structure (Table 4 and Figure 1).

The greater sensitivity of K^+, relative to $FeHDFB^+$, to the "size" of the ionophore cavity (discussed above for 18-C-6 and DC-18-C-6) is further illustrated by increasing the cavity size from DB-18-C-6 (**IVa**) to DB-24-C-8 (**IVb**) (Figure 1). However, an additional increase in cavity size from DB-24-C-8 (**IVb**) to DB-30-C-10 (**IVc**) results in an increase in the stability of the K^+ and NH_4^+ assemblies. A reasonable explanation for this stability increase is that the crown ether ring is now much less constrained in a planar configuration and has enough flexibility and size to wrap around a spherical cation.[24,26,32,33] The substituted amine guest in $FeHDFB^+$ is not spherical and has considerable bulk. However, one might speculate that partial ionophore "wrapping" is responsible for making $FeHDFB^+$ less sensitive to the increase in crown ether ring size going from DB-24-C-8 (**IVb**) to DB-30-C-10 (**IVc**), relative to the increase in ring size from DB-18-C-6 (**IVa**) to DB-24-C-8 (**IVb**).

The sensitivity of the NH_4^+ guest to different crown ether host structures (Figure 1) is intermediate to that of K^+ and $FeHDFB^+$. This is expected, as the ammonium cation has some of the guest characteristics of both K^+ (*e.g.* "size") and $FeHDFB^+$ (*e.g.* H-bonding).

We observe from the solution behavior of (K^+,pic^-) in chloroform that a 1:1 complex is formed with DB-24-C-8. This is consistent with the reported interaction of (K^+,pic^-) with B-24-C-8 in chloroform,[34] and is in contrast with the crystal structure of (K^+,SCN^-)/DB-24-C-8 obtained from ethanol solution,[35,36] which showed that the crown ether can accommodate two K^+ ions in its cavity.

Both picrate and perchlorate counterions were used for the $FeHDFB^+$ extraction experiments. Previous results from our laboratory have shown that the stability of the ($FeHDFB^+$, DC-18-C-6,X^-) assembly in chloroform is sensitive to the identity of the counterion X^-.[4,5] This has been attributed to the difference in hydration enthalpies of the anions investigated.[4] Similar relative stability behavior for perchlorate and picrate anions is observed in this work. The more stable assemblies are formed with perchlorate anion and both anions exhibit the same relative trend in changes of K_a with crown ether structure (Figure 1). However, when the stability of the assembly drops significantly from DB-18-C-6 (**IVa**) to DB-24-C-8 (**IVb**) and to DB-30-C-10 (**IVc**), the sensitivity of the ligand to the counterion diminishes (Figure 1). This suggests that as K_a decreases, indicative of a more "loose" association of $FeHDFB^+$ with the crown ether, the influence of the anion hydration shell is diminished.

In addition to the synthetic crown ethers, we also investigated the ability of the natural product ionophores nonactin and valinomycin to recognize the protonated amine side chain of ferrioxamine B, the parent ammonium and substituted amine cations, and Mg^{2+} and K^+. K_{ex} and K_a values are given in Tables 2 and 4. No data have been reported in the literature for the association of nonactin with these cations in apolar organic solvents, while only a few data are available for valinomycin.[19] With the exception of K^+, our data show that in chloroform solution nonactin exhibits a higher affinity for the cations investigated than valinomycin. In addition to our data in $CHCl_3$, nonactin is also reported to favor complexation of NH_4^+ over K^+ in methanol,[37,38] due to the favorable arrangement of the carbonyl groups.

In addition to K^+, NH_4^+, and RNH_3^+, we also report here the association constants of (Mg^{2+},$2pic^-$) with different ionophores (Table 4). To the best of our knowledge these are the first stability constants (K_a) reported for the association of (Mg^{2+},$2pic^-$) with natural and synthetic ionophores in chloroform. Only extractabilities (K_{ex}) of $Mg(pic)_2$ with crown ethers from water into an organic solvent have been reported previously.[3,39−41] It has been assumed previously that Mg^{2+} association with ionophores in apolar organic solvents is negligible. However, our data in Table 4 illustrate that there is a significant degree of interaction between (Mg^{2+},$2pic^-$) and DB-30-C-10, *cis*-DC-18-C-6, valinomycin, and nonactin. These results are important for understanding the principles of stereoelectronic complementarity between host and guest, and solvent effects in supramolecular chemistry.[30]

Although the radius of Mg^{2+} (0.72 Å[25]) is less than the optimum for the ionophores investigated, complexes of reasonable stability are observed (Table 4). This is likely due to the high charge density of the cation and considerable preorganization of the ionophore. The effect of the unfavorable cation size appears to be of the same magnitude as the effect of the substitution of one hydrogen atom of a NH_4^+ cation by a bulky metal complex. The host−guest assemblies (Mg^{2+},*cis*-DC-18-C-6,$2pic^-$) and ($FeHDFB^+$,*cis*-DC-18-C-6,pic^-) have essentially the same stability in chloroform (Table 4). K_a values for complexation of Mg^{2+} by DB-30-C-10, valinomycin, and nonactin are greater than for ferrioxamine B.

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The encapsulation of the Mg^{2+} cation in the preorganized cavities of DC-18-C-6, DB-30-C-10, valinomycin, and nonactin is indicated by the shift in λ_{max} for (Mg^{2+},L,2pic$^-$) relative to the picrate ion pair (Mg^{2+},2pic$^-$) in chloroform and water (Table 1). (Mg^{2+},2pic$^-$)$_{CHCl_3}$ (λ_{max} = 332 nm) may be viewed as a tight ion pair and (Mg^{2+},2pic$^-$)$_{H_2O}$ (λ_{max} = 356 nm)[16] as a loose or solvent separated ion pair. Consequently, a λ_{max} shift to longer wavelength for the picrate anion may be interpreted as indicative of more effective shielding of the picrate anion from the Mg^{2+} cation. Encapsulation of Mg^{2+} by DB-30-C-10 in $CHCl_3$ shifts the λ_{max} from 332 to 358 nm. A further bathochromic shift is observed on complex formation with DC-18-C-6 (370 nm), valinomycin (374 nm) and nonactin (374 nm) (Table 1), which is also indicative of more efficient shielding of Mg^{2+} from the picrate anion.[42−49]

The picrate anion λ_{max} observed for the assemblies of picrate salts of K^+, NH_4^+, and $CH_3(CH_2)_4NH_3^+$ with valinomycin and nonactin is shifted to longer wavelength than the corresponding λ_{max} for the assemblies with *cis*-DC-18-C-6 (Table 1). This suggests more efficient shielding of the cation from its counterion by the natural ionophores than by the crown ether. This statement is further supported by the higher molar absorptivities obtained for both K^+ and NH_4^+ assemblies with valinomycin and nonactin than for their association with *cis*-DC-18-C-6. The same is true for K^+ association with DB-30-C-10, supporting its resemblance to the natural ionophores.[24,26,27] The failure of DB-30-C-10 to encapsulate the substituted ammonium cation in pentyl amine (as well as FeHDFB$^+$, *vide supra*) as efficiently as K^+, due to its steric bulk, is evidenced both through lower λ_{max} and lower ϵ values (Table 1).

Figure 2 compares the behavior of the two natural ionophores, nonactin and valinomycin, with the synthetic ionophores *cis*-DC-18-C-6 and DB-30-C-10 when complexing cations of different charge densities and steric requirements. Although *cis*-DC-18-C-6 and DB-30-C-10 are significantly different structures when compared to both valinomycin and nonactin, the overall pattern in the association of all four ionophores with the cations investigated is similar. The increase in the stability of assemblies going from Mg^{2+} to K^+ and/or NH_4^+ is a consequence of achieving a match between cation and ionophore cavity size. The decrease in the stability constants (K_a) when going from NH_4^+, to $CH_3(CH_2)_4NH_3^+$, to H_4DFB^+, to FeHDFB$^+$ occurs as a consequence of the decrease in the number of hydrogen atoms available for interaction with ether oxygen atoms, and steric hindrance.[3] NH_4^+, $CH_3(CH_2)_4NH_3^+$, H_4DFB^+, and FeHDFB$^+$ exhibit a similar relative pattern of stability constants (Figure 2) with *cis*-DC-18-C-6, valinomycin, nonactin, and DB-30-C-10. This pattern, in addition to the relatively lower stabilities of the complexes of FeHDFB$^+$,pic$^-$ with valinomycin and nonactin, suggests that the large macrocyclic cavities (*e.g.,* valinomycin, nonactin, and DB-30-C-10) do not provide any additional stabilizing interactions with the amide functionalities of the ferrioxamine B complex backbone.

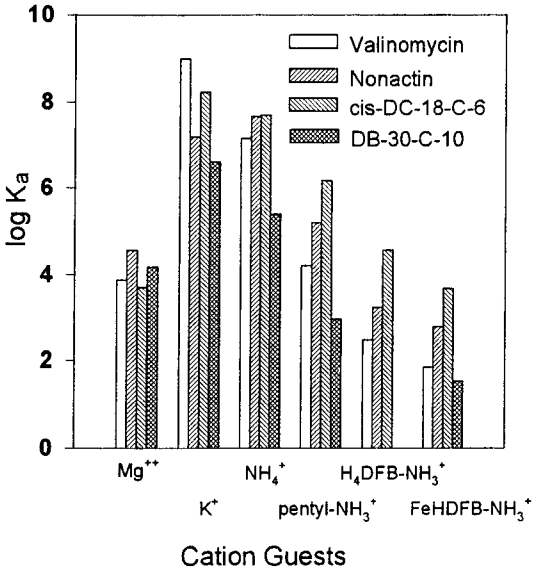

Figure 2. Multiple bar chart presenting log K_a for the association of picrate salts of different cation guests with *cis*-dicyclohexano-18-crown-6 (**Va**), dibenzo-30-crown-10 (**IVc**), valinomycin (**VI**), and nonactin (**VII**) hosts. The cations are placed in order of increasing ionic radius. A rough estimate for the effective ionic radius of the substituted alkyl ammonium side chain (1.66 Å) was obtained from the ratio of partial molar volumes at infinite dilution for ammonium chloride and methyl ammonium chloride.[50] A reasonable assumption can be made that similar ionic radius should be operative for all three cations bearing the alkylammonium chain. Deferriferrioxamine B ($H_4DFB-NH_3^+$) and ferrioxamine B (FeHDFB$-NH_3^+$) are represented with notations that emphasize their structures as NH_4^+ derivates.

We conclude that several synthetic and naturally occurring macrocycle ionophores are capable of recognizing ferrioxamine B through host−guest complexation of the protonated amine side chain. Results presented here demonstrate that both the electronic and structural characteristics of the host molecule, as well as cavity size, influence second coordination shell complexation of ferrioxamine B. The sensitivities of the host−guest association constants (K_a) to structural changes in the host differ between ferrioxamine B and the other guests investigated. This is largely due to the different steric requirements dictated by the bulky hexadentate Fe(III) complex attached to the protonated amine group of ferrioxamine B. These variations in host−guest stability with macrocycle host structure are of importance in interpreting the relative efficiencies of various ionophores in the bulk liquid membrane transport of ferrioxamine B.[6]

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