Stereochemical Factors affecting Second-sphere Co-ordination of Ferrioxamine B with *cis-syn-cis* and *cis-anti-cis* Isomers of Dicyclohexano-18-crown-6 in Chloroform and a Comparison with Alkali-metal and Ammonium Cations

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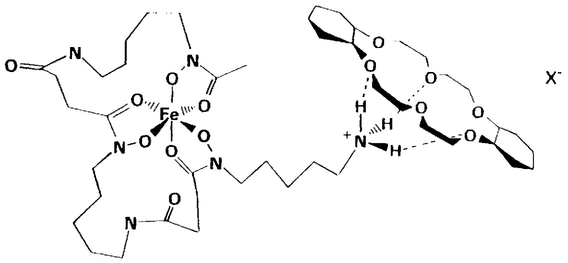
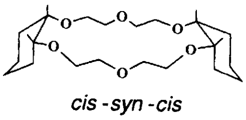
Second-sphere co-ordination of ferrioxamine B $[Fe(HL)]^+$ by dicyclohexano-18-crown-6 (eicosahydrodibenzo[*b,k*][1,4,7,10,13,16]hexaoxacyclooctadecine) occurs through host–guest complex formation with the protonated amine side chain $(CH_2)_5NH_3^+$. The influence of steric factors on the association constants (K_a) for both nitrate and perchlorate salts of ferrioxamine B with *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 (CE) in $CHCl_3$ has been investigated. For comparison purposes, association of the perchlorate salt of the indium(III) analogue of ferrioxamine B $[In(HL)]^+$ and the picrate salts of NH_4^+ and alkali-metal cations are included in this study (picrate = 2,4,6-trinitrophenolate). Although the absolute values of K_a for [M(HL)]X association with CE are strongly dependent on the anion identity, the selectivity ratio expressed for the *syn* crown ether isomer is 3:1 and is independent of anion variations. Comparison with alkali-metal and ammonium cations shows that the discrimination between *syn* and *anti* isomers of *cis*-dicyclohexano-18-crown-6 is dependent upon cation size and is the least for K^+ where the ionic radius best matches the cavity size. While *syn* isomer discrimination in $CHCl_3$ is closely related to the ionic radius, in water it is related to the hydrated radius. The *syn* over *anti* isomer preference exhibited by alkali-metal and ammonium cations is much more pronounced in water than in chloroform, which is likely due to the steric hindrance imposed by the large effective radius of the cations due to their hydration shell. Discrimination between the *syn* and *anti* isomers by $[M(HL)]^+$ in $CHCl_3$ is greater than expected based on comparison with the parent NH_4^+ ion. This is likely due to the significant steric requirements of the bulky metal complex molecule. The selectivity of the *syn* over the *anti* isomer is dominated by the preference of the bulky $[M(HL)]^+$ complex for the less hindered face of the *syn* isomer.

We have recently demonstrated that a crown ether can recognize the pendant protonated amine group of ferrioxamine B $[Fe(HL)]^+$ through second-sphere complex formation.[1] The resultant supramolecular assembly involving dicyclohexano-18-crown-6 (eicosahydrodibenzo[*b,k*][1,4,7,10,13,16]hexaoxacyclooctadecine) is illustrated in **I**. Our investigations of the ferrioxamine B–dicyclohexano-18-crown-6 interaction in chloroform[1,2] suggest that second-sphere association of a positively charged metal complex (and the resulting first-sphere co-ordination of a substituted ammonium cation) is influenced by the hydration shell of the cation and the counter anion. A partial hydration of the ion pair in wet chloroform results from a competition of the crown ether with water molecules associated with the first-co-ordination sphere of the substituted ammonium site and second co-ordination sphere of the iron(III) complex in **I**. We have suggested that partial hydration influences the steric requirements which the crown ether imposes on the supramolecular assembly and that they in turn play an important role in determining the stability of the host–guest complex.[2] Therefore, we have extended our investigations to include the association of ferrioxamine B with two different isomers of dicyclohexano-18-crown-6; the *cis-syn-cis* (**IIA**) and *cis-anti-cis* (**IIB**) isomers illustrated below.[3–6] The *syn* and *anti* isomers of the *cis*-dicyclohexano-18-crown-6 crown ether host provide different stereochemistries,[4,6] which influence host–guest complex formation.[7–12] As shown by crystal structures, the two cyclohexano rings of the *syn* isomer are on the same side and nearly perpendicular to the plane of the polyether ring.[4,13–15] We have included in our study the indium(III) analogue of ferrioxamine B, and both nitrate and perchlorate anions in order to establish the sensitivity of the *syn* and *anti* crown ether isomers to changes in the cation and anion of the ion pair which constitutes the supramolecular assembly in **I**.

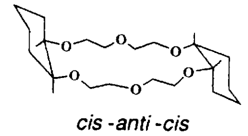


I



cis-syn-cis

IIA



cis-anti-cis

IIB

There are data in the literature for the stability constants of the *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-

crown-6 with different alkali- and alkaline-earth metal cation salts in water and in methanol,[7–11] and for potassium picrate in dichloromethane (picrate = 2,4,6-trinitrophenolate).[12] Host–guest association in organic media of low polarity imposes requirements different from those found for the association in polar solvents. For example, while the log stability constant (log K_a) for the association of K^+ with *cis*-dicyclohexano-18-crown-6 in $CHCl_3$ is 8.30,[8] log K_a for the association of K^+ with the *cis-syn-cis* isomer of dicyclohexano-18-crown-6 in methanol and in water is 6.01[9] and 2.18[9] (2.02[10]), respectively. In order better to understand the influence of stereochemistry on the association of ferrioxamine B with dicyclohexano-18-crown-6, we have also determined the association constants for both the *cis-syn-cis* and *cis-anti-cis* isomers with several alkali-metal picrates in wet chloroform. In addition to Na^+, K^+ and Cs^+, which differ in ionic radius and charge density, and therefore solvation shell composition, we also determined the stability constant for NH_4^+ complexation with the *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6.

In general, studies of assemblies such as described here are of importance due to their relationship to molecular recognition of biological metal-ion transport compounds, metal complex extractions and trace- and precious-metal recovery. The specific use of ferrioxamine B for our studies is of interest for several reasons: (*i*) studies of supramolecular assembly formation involving ferrioxamine B are of interest due to the role this complex plays in siderophore-mediated iron transport;[16,17] (*ii*) the use of ferrioxamine B allows us to investigate host–guest complexation between an alkyl amine and a crown ether host utilizing a chromophore attached to the alkylammonium ion guest; (*iii*) ferrioxamine B provides the opportunity to study the influence of steric factors on second-sphere co-ordination; and (*iv*) use of ferrioxamine B enables this study to contribute to an understanding of the structural aspects of crown-ether complexation with biologically important bulky molecules in organic solvent media, where a closer analogy to the natural environment may be made than in solid-state structures.

Experimental

Materials.—cis *Isomers of dicyclohexano*-18-*crown*-6. *cis*-Dicyclohexano-18-crown-6, a mixture of approximately equal parts of *cis-syn-cis* and *cis-anti-cis* isomers, was used as obtained from Aldrich. Pure *cis-syn-cis* and *cis-anti-cis* isomers were prepared by a reported procedure which relies upon the different solubility properties of the two isomers as lead and oxonium ion complexes.[18] Chloroform solutions were prepared by dissolving appropriate amounts of *cis-syn-cis* and/or *cis-anti-cis* isomers in a known volume of $CHCl_3$.

$[M(HL)]X$ (M = Fe^{III} *or* In^{III}, X = ClO_4 *or* NO_3). The ferrioxamine B complex $[Fe(HL)]^+$ and its indium(III) analogue $[In(HL)]^+$ were prepared as described previously.[1,2] A known amount of deferriferrioxamine B (H_4L^+; Sigma) was dissolved in a small volume of water, followed by the addition of indium(III) or iron(III) perchlorate or nitrate stock solution. The Fe^{III}, In^{III} and acid content of the stock solutions were determined as previously described.[1,2,19] The pH of the $[Fe(HL)]^+$ and $[In(HL)]^+$ perchlorate solutions was adjusted to 3.2 and 5.6, respectively, by the addition of solid $Mg(OH)_2$. Known stability constants[20] establish that the six-co-ordinate indium(III) complex is the predominant species at pH 5.6 when $[In^{III}]_{tot} = 0.02$ and $[H_4L^+]_{tot} = 0.022$ mol dm^{-3}. pH Measurements were performed using a Corning combination glass electrode. After the desired pH was reached, the solutions were filtered and used in the extraction and distribution equilibrium experiments. The ionic strength was maintained at $I = 0.1$ mol dm^{-3} with $Mg(ClO_4)_2$ or $Mg(NO_3)_2$, prepared by the neutralization of the corresponding acid with $Mg(OH)_2$.

M(pic) (M = Na, K, Cs *or* NH_4^+, *pic* = *picrate*). Picrate salt solutions for the determination of K_{ex} constants for M^+ were prepared such that $[M^+] = 5.00 \times 10^{-4}$ mol dm^{-3} (NH_4^+, K^+) or 8.93×10^{-3} mol dm^{-3} (Na^+, Cs^+), $[Mg(pic)_2] = 2.5 \times 10^{-4}$ mol dm^{-3}, and $[Mg(NO_3)_2] = 3.33 \times 10^{-2}$ mol dm^{-3}. Nitrate salts (Fisher Scientific) of sodium, potassium, ammonium and caesium chloride (Alfa) were used for the preparation of picrate salt solutions of the desired concentration of M^+. The concentrations of Na^+, K^+, Cs^+ and NH_4^+ were determined by passing an aliquot through a column containing Dowex 50W-X8 cation exchange resin, followed by titration with 0.1 mol dm^{-3} NaOH. Magnesium nitrate solution [$Mg(NO_3)_2$; Sigma, 99.995+ %] was added to maintain the ionic strength at $I = 0.1$ mol dm^{-3}. The magnesium picrate solution was prepared as previously described,[1] neutralizing either $(MgCO_3)_4 \cdot Mg(OH)_2 \cdot 5H_2O$ (Sigma) or $Mg(OH)_2$ (Aldrich) with a saturated aqueous solution of picric acid. Picric acid (Aldrich, >98%) was recrystallized from water. The picrate concentration was determined spectrophotometrically using the aqueous picrate molar absorptivity, $\varepsilon_{356} = 1.44 \times 10^4$ dm^3 mol^{-1} cm^{-1}.[21]

Doubly distilled water saturated with chloroform and chloroform saturated with water was used throughout the experiments.

Methods.—*Ferrioxamine B and the indium*(III) *analogue cations.* The distribution of ferrioxamine B perchlorate, and its extraction into chloroform solution by the *syn* and *anti* isomers of dicyclohexano-18-crown-6 was performed as described previously for the isomer mixture.[1] The distribution and the extraction of $[In(HL)]ClO_4$ were accomplished similarly. In the distribution experiment chloroform (40 cm^3) was shaken vigorously with an aqueous solution (40 cm^3) of $[In(HL)]ClO_4$. After equilibration, the layers were separated and the chloroform layer evaporated to dryness. The residue was dissolved in water (1 cm^3) followed by the addition of iron(III) stock solution (0.02 cm^3) to exchange the In^{III} with Fe^{III}.[22,23] The concentration of the resulting $[Fe(HL)]^+$ was determined by UV/VIS spectroscopy at 425 nm ($\varepsilon_{425} = 2600$ dm^3 mol^{-1} cm^{-1}).[24] In the extraction experiment, a solution of $[In(HL)]ClO_4$ (2.00 cm^3) was mixed with a chloroform solution (2.00 cm^3) of crown ether. After equilibration the layers were separated and $[In(HL)]^+$ was re-extracted from the organic layer into the aqueous phase by 0.1 mol dm^{-3} KNO_3. The Fe^{III} stock solution was added in excess to an aliquot of the aqueous phase to allow the formation of $[Fe(HL)]^+$. The concentration of $[Fe(HL)]^+$ was determined as stated above. In all experiments the initial concentrations of $[Fe(HL)]^+$ and $[In(HL)]^+$ were ≈ 0.02 mol dm^{-3}, while crown ether concentrations ranged between 0.01 and 0.10 mol dm^{-3}.

Alkali-metal and ammonium cations. Distribution data for all four alkali-metal and ammonium picrates were taken from the literature.[25] Extraction from aqueous to chloroform phase was accomplished as follows. An aqueous picrate solution of a particular cation (2.00 cm^3) was mixed with a chloroform solution (2.00 cm^3) of crown ether. After equilibration, the concentration of picrate was determined in both the aqueous and chloroform layer using its aqueous molar absorptivity, $\varepsilon_{356} = 1.44 \times 10^4$ dm^3 mol^{-1} cm^{-1} and organic molar absorptivities for each cation picrate assembly with the crown ether (CE). The molar absorptivities for $[Na^+, CE, pic^-]$ (org), $[NH_4^+, CE, pic^-]$ (org) and $[K^+, CE, pic^-]$ (org) were previously determined,[1,2] and that for $[Cs^+, CE, pic^-]$ (org) was determined in a similar manner. After equilibration of caesium picrate between the chloroform and aqueous phase, the organic phase caesium picrate concentration was calculated as the difference between the initial and aqueous phase Cs^+ concentrations. Since the initial Cs^+ and picrate concentrations were not equal, after equilibration of the phases $[Cs^+]_{aq} = [Cs^+]_0 - [pic^-]_{org}$ and $[pic^-]_{org} = [pic^-]_0 - [pic^-]_{aq}$. The molar absorptivity for $[Cs^+, CE, pic^-]$ (org) ($A_{org}/[pic]_{org}$) was determined to be $\varepsilon_{366} = 1.65 \times 10^4$ dm^3 mol^{-1} cm^{-1}. The molar absorptivities for $[M^+, CE, pic^-]$ (org) correspond to a

Table 1 Extraction (K_{ex}), and host–guest association (K_a) equilibrium constants for ferrioxamine B [Fe(HL)$^+$, X$^-$] and its indium(III) analogue [In(HL)$^+$, X$^-$] (X = ClO_4 or NO_3) with *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 and their mixture in chloroform at 25 °C

[M(HL)$^+$, CE, X$^-$] [a]	K_{ex} [b]/dm^6 mol^{-2}	K_a [c]/dm^3 mol^{-1}	K_a(*syn*)/K_a(*anti*) [d]
[Fe(HL)$^+$, CE*, ClO_4^-] [e]	5.50	1.77×10^4	
[Fe(HL)$^+$, *syn*-CE, ClO_4^-]	10.51	3.39×10^4	
[Fe(HL)$^+$, *anti*-CE, ClO_4^-]	3.30	1.06×10^4	3.2
[Fe(HL)$^+$, CE*, NO_3^-] [e]	4.78×10^{-2}	1.64×10^2	
[Fe(HL)$^+$, *syn*-CE, NO_3^-]	7.09×10^{-2}	2.44×10^2	
[Fe(HL)$^+$, *anti*-CE, NO_3^-]	2.39×10^{-2}	0.82×10^2	3.0
[In(HL)$^+$, CE*, ClO_4^-]	12.26	2.67×10^4	
[In(HL)$^+$, *syn*-CE, ClO_4^-]	20.54	4.47×10^4	
[In(HL)$^+$, *anti*-CE, ClO_4^-]	6.27	1.36×10^4	3.3

[a] CE* corresponds to a mixture of *cis-syn-cis* (*syn*-CE) and *cis-anti-cis* (*anti*-CE) isomers of dicyclohexano-18-crown-6. [b] Defined by equations (2) and (3) and determined from plots of equation (7). [c] Defined in equation (11) and calculated from equation (12) where K_d values for [Fe(HL)$^+$, Cl$^-$], [Fe(HL)$^+$, NO_3^-] and [In(HL)$^+$, ClO_4^-] are 3.10×10^{-4}, 2.91×10^{-4} and 4.60×10^{-4} dm^3 mol^{-1} respectively. [d] Selectivity ratio for host–guest complex formation (K_a) with *cis-syn-cis*- and *cis-anti-cis*-dicyclohexano-18-crown-6 in $CHCl_3$ solvent. [e] Data from ref. 2.

mixture of *syn* and *anti* isomers. It has been assumed that molar absorptivities for the assemblies involving either of the two isomers are equal for the following reasons: (*i*) no shift in λ_{max} occurs for [M$^+$, CE, pic$^-$] (org) when changing from the *syn* to the *anti* isomer; and (*ii*) calculations made based on aqueous and organic phase data gave the same K_{ex} value. In all picrate determinations, corrections were applied for magnesium extraction by measuring the extractibility of a blank solution containing 5.00×10^{-4} mol dm^{-3} picrate (magnesium salt) in 3.33×10^{-2} mol dm^{-3} $Mg(NO_3)_2$. The crown ether concentrations ranged from 3×10^{-3} to 2×10^{-2} mol dm^{-3}.

cis-*Dicyclohexano*-18-*crown*-6. The distribution of the mixture of *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 between an aqueous and organic phase has been previously determined by its re-extraction with potassium picrate into the organic phase.[1]

All spectrophotometric determinations were performed using a Hewlett-Packard 8451A Diode Array spectrophotometer. All reported values are based on 3 to 5 independent determinations and the errors are within 10%, except for distribution data which are within 25%.

Results

Overall Extraction Equilibria.—The overall experimental approach to determining host–guest association constants in chloroform in the presence of various cations, anions and crown ether isomers involves determining extraction and distribution equilibria. An overall extraction equilibrium for the systems reported here is shown in equation (1), where

$$[M(HL)]^+ (aq) + Mg^{2+} (aq) + 3X^- (aq) + 2CE (org) \xrightleftharpoons{K_{overall}} [M(HL)^+, CE, X^-] (org) + [Mg^{2+}, CE, 2X^-] (org) \quad (1)$$

$[M(HL)]^+$ is ferrioxamine B (M = Fe) or its indium(III) analogue (M = In), CE is the *cis-syn-cis* or *cis-anti-cis* isomer of dicyclohexano-18-crown-6 or their mixture, and X$^-$ is ClO_4^- or NO_3^-. The function of the magnesium salt is to permit all experiments to be carried out at a constant ionic strength (I = 0.1 mol dm^{-3}). As elaborated on below, the Mg^{2+} cation provides negligible competition for the crown ether cavity.

The overall extraction experiment may be broken down conceptually into two extraction equilibria, one involving $[M(HL)]^+$ [equations (2) and (3)] and one involving Mg^{2+} [equations (4) and (5)]. The overall extraction constant ($K_{overall}$)

$$[M(HL)]^+ (aq) + X^- (aq) + CE (org) \xrightleftharpoons{K_{ex}^{M(HL)^+, CE, X^-}} [M(HL)^+, CE, X^-] (org) \quad (2)$$

$$K_{ex}^{M(HL)^+, CE, X^-} = [M(HL)^+, CE, X^-]_{org}/[M(HL)^+]_{aq}[X^-]_{aq}[CE]_{org} \quad (3)$$

$$Mg^{2+} (aq) + 2X^- (aq) + CE (org) \xrightleftharpoons{K_{ex}^{Mg^{2+}, CE, 2X^-}} [Mg^{2+}, CE, 2X^-] (org) \quad (4)$$

$$K_{ex}^{Mg^{2+}, CE, 2X^-} = [Mg^{2+}, CE, 2X^-]_{org}/[Mg^{2+}]_{aq}[X^-]_{aq}^2[CE]_{org} \quad (5)$$

may then be expressed as the product of the extraction constants for the individual equilibria of interest as shown in equation (6).

$$K_{overall} = K_{ex}^{M(HL)^+, CE, X^-} \cdot K_{ex}^{Mg^{2+}, CE, 2X^-} \quad (6)$$

The extraction of Mg^{2+} by the crown ether into the organic phase was found to be negligible relative to $[M(HL)]^+$.[1] There are no reports in the literature for Mg^{2+} extraction unless accompanied by the highly hydrophobic picrate anion.[7,8,26–28] Thus the concentration of the [Mg^{2+}, CE, 2X$^-$] (org) was neglected in the overall extraction equilibrium given by equation (1). The extraction constant $K_{ex}^{M(HL)^+, CE, X^-}$ may then be expressed by equation (7), where $D_{[M(HL)]^+}$ is expressed by equation (8).

$$K_{ex}^{M(HL)^+, CE, X^-} = D_{[M(HL)]^+}/[X^-]_{aq}[CE]_{org} \quad (7)$$

$$D_{[M(HL)]^+} = [M(HL)^+, CE, X^-]_{org}/[M(HL)^+]_{aq} = (K_{overall}/K_{ex}^{Mg^{2+}, CE, 2X^-})[X^-]_{aq}[CE]_{org} = K_{ex}^{M(HL)^+, CE, X^-}[X^-]_{aq}[CE]_{org} \quad (8)$$

The values of $K_{ex}^{M(HL)^+, CE, X^-}$ were obtained from the slopes of linear plots of $D_{[M(HL)]^+}$ *vs.* $[X]_{aq}[CE]_{org}$, where $[X^-]_{aq}$ and $[CE]_{org}$ were taken as their initial concentrations in the aqueous and chloroform phases, respectively, due to being present in excess and the lack of competition for CE from Mg^{2+}. The linearity of these plots also serve to confirm the 1:1 stoichiometry of the host–guest complex as shown in equation (2). Values for $K_{ex}^{M(HL)^+, CE, X^-}$ are listed in Table 1.

Distribution Equilibria.—In order to use extraction equilibrium data to calculate host–guest association constants in chloroform, $K_{ex}^{M(HL)^+, CE, X^-}$ must be corrected for the distribution of the ion pair $[M(HL)]^+$, X$^-$ between the aqueous and chloroform phases in the absence of crown ether at constant ionic strength. Distribution equilibria (K_d) for

Table 2 Extraction (K_{ex}) and host–guest association (K_a) equilibrium constants for alkali and ammonium picrate salts with *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6, and their mixture in chloroform at 25 °C

			$K_a(syn)/K_a(anti)$				
$[M^+$, CE, $pic^-]$[a]	K_{ex}[b]/dm^6 mol^{-2}	K_a[c]/dm^3 mol^{-1}	$CHCl_3$[d]	Water[e]	r_i[f]/Å	r_h[g]/Å	ΔH_h[h]/kJ mol^{-1}
$[Na^+$, CE*, $pic^-]$	1.71×10^3	9.83×10^5			1.02	3.58	−407
$[Na^+$, *syn*-CE, $pic^-]$	2.32×10^3	13.30×10^6					
$[Na^+$, *anti*-CE, $pic^-]$	1.22×10^3	8.71×10^5	1.9	3.3			
$[K^+$, CE*, $pic^-]$	4.07×10^5	1.60×10^8			1.38	3.31	−324
$[K^+$, *syn*-CE, $pic^-]$	4.72×10^5	1.85×10^8					
$[K^+$, *anti*-CE, $pic^-]$	3.87×10^5	1.52×10^8	1.2	2.5			
$[Cs^+$, CE*, $pic^-]$	1.80×10^4	3.33×10^6			1.67	3.29	−274
$[Cs^+$, *syn*-CE, $pic^-]$	2.40×10^4	4.43×10^6					
$[Cs^+$, *anti*-CE, $pic^-]$	1.11×10^4	2.04×10^6	2.2	2.2			
$[NH_4^+$, CE*, $pic^-]$	1.98×10^5	4.93×10^7			1.46	3.31	−320
$[NH_4^+$, *syn*-CE, $pic^-]$	2.28×10^5	5.66×10^7					
$[NH_4^+$, *anti*-CE, $pic^-]$	1.75×10^5	4.36×10^7	1.3	3.4			

[a] CE* Corresponds to a mixture of *cis-syn-cis* (*syn*-CE) and *cis-anti-cis* (*anti*-CE) isomers of dicyclohexano-18-crown-6. [b] Defined as shown in equations (2) and (3) and determined from plots of equation (7). [c] K_a Values are calculated using equation (12), where K_d values are taken from ref. 25 and are as follows: 1.74×10^{-3} (Na^+), 2.55×10^{-3} (K^+), 5.4×10^{-3} (Cs^+), 4.02×10^{-3} (NH_4^+) dm^3 mol^{-1}. [d] Selectivity ratio for host–guest complex formation (K_a) with *cis-syn-cis* and *cis-anti-cis* dicyclohexano-18-crown-6 in $CHCl_3$ solvent. [e] Selectivity ratio in water; data from ref. 10 and ref. 11. [f] M^+ ionic radius; ref. 29. [g] M^+(aq) hydrated radius; ref. 30. [h] M^+(g) hydration enthalpy; ref. 31.

$[In(HL)]ClO_4$ were determined in the same way as described for $[Fe(HL)]ClO_4$ and $[Fe(HL)]NO_3$.[2] The distribution of MgX_2 into the chloroform phase was negligibly small so that K_d values for $[M(HL)]^+$ were readily determined from measurements of $[M(HL)^+, X^-]_{org}/[M(HL)^+]_{aq}$ at a fixed $[X^-]_{aq}$ as shown in equations (9) and (10).

$$[M(HL)]^+ (aq) + X^- (aq) \overset{K_d}{\rightleftharpoons} [M(HL)^+,X^-] (org) \qquad (9)$$

$$K_d = [M(HL)^+, X^-]_{org}/\{[M(HL)^+]_{aq}[X^-]_{aq}\} \qquad (10)$$

The K_d values for $[Fe(HL)^+, ClO_4^-]$, $[Fe(HL)^+, NO_3^-]$ and $[In(HL)^+, ClO_4^-]$ are 3.10×10^{-4}, 2.91×10^{-4} and 4.60×10^{-4} dm^3 mol^{-1} respectively.

Host–Guest Equilibria.—The host–guest association equilibrium of interest in chloroform solution is described in equation (11). Values for host–guest association constants, K_a, may be

$$[M(HL)^+, X^-] (org) + CE (org) \overset{K_a}{\rightleftharpoons} [M(HL)^+, CE, X^-] (org) \qquad (11)$$

calculated from $K_{ex}^{M(HL)^+, CE, X^-}$ and K_d according to equation (12), provided that the crown ether is present only in the

$$K_a = K_{ex}^{M(HL)^+, CE, X^-}/K_d \qquad (12)$$

chloroform phase. This was established experimentally by determining the distribution equilibrium of *cis*-dicyclohexano-18-crown-6 between chloroform and water [CE (org) $\rightleftharpoons$ CE (aq)], $K_d' = 6.3 \times 10^{-4}$.[1] The distribution of each isomer in CH_2Cl_2 is reported to be nearly identical.[12] It is reasonable to assume that the same is valid for the distribution of both isomers into $CHCl_3$, ensuring the crown ether association in the aqueous phase to be negligible. Host–guest association constants (K_a) for $[M(HL)^+$, CE, $X^-]$ (org) are listed in Table 1.

Alkali-metal and ammonium salts. The same equilibria were considered for alkali-metal and ammonium picrates as described above for $[M(HL)]^+$ in order to obtain values for the association constants, K_a, for $[M^+$, CE, $X^-]$ in chloroform ($M^+ = Na^+, K^+, Cs^+$ or NH_4^+, X^- = picrate). The K_d values for these salts were obtained from the literature.[25] The association constants (K_a) of these picrate salts with *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6, as well as with their mixture, obtained in chloroform are reported in Table 2. Data related to the mixture of isomers are in excellent agreement with values reported in the literature.[25] For the purpose of comparison, there are also data listed in Table 2 for the selectivity ratio $K_a(syn)/K_a(anti)$ for the association of these cations with *cis-syn-cis* and *cis-anti-cis* dicyclohexano-18-crown-6 and chloride anion in water.[10,11]

Discussion

Second-sphere co-ordination of $[M(HL)]^+$ by *cis*-CE occurs through host–guest complex formation with the protonated amine side chain as shown in **I**.[1] The association constant (K_a) for host–guest complex formation [equation (11)] is higher for the *cis-syn-cis* isomer than for the *cis-anti-cis* isomer (Table 1). The origin of the *syn*/*anti* preference expressed by $[M(HL)]^+$ must be due to the fact that the *syn* isomer **IIA** has two different faces, one which is open and one which is sterically hindered, while the *anti* isomer **IIB** provides two equivalent faces. Although the absolute values of K_a are dependent on M^{III} (Fe^{III} or In^{III}) and the counter ion (ClO_4^- and NO_3^-), the selectivity ratio $K_a(syn)/K_a(anti)$ remains relatively constant at 3 (Table 1). Our discussion will focus on two interconnected key points that are of interest regarding this observed selectivity ratio. One is the origin of the selectivity and the other is the relative orientation in solution of the components that comprise the supramolecular assembly **I**.

We may assume that the bulky guest, $[M(HL)]^+$, approaches the less crowded face of the *cis-syn-cis* isomer host **IIa**. Consequently, the steric hindrance associated with this orientation should be similar to the approach of the cation to the unsubstituted crown ether, 18-crown-6. This assumption is supported by the almost equivalent association constants for $[Fe(HL)]^+$ with 18-crown-6 (log K_a = 4.40[32] and 4.38[33] obtained by extraction and by liquid-membrane transport, respectively) and with *cis-syn-cis*-dicyclohexano-18-crown-6 (log K_a = 4.53, Table 1), while K_a is significantly lower for the association with *cis-anti-cis* isomer (log K_a = 4.03, Table 1).

We used perchlorate and nitrate salts of $[Fe(HL)]^+$ in order to consider the influence of the anion on the conformational preference in the supramolecular assembly **I**. There is an ≈100 fold difference in the association constant (K_a) for $[Fe(HL)]ClO_4$ and $[Fe(HL)]NO_3$ with dicyclohexano-18-crown-6, which is discussed elsewhere[2] in terms of differences in anion hydration. That difference remains essentially the same in the association of [Fe(HL)]ClO_4 and [Fe(HL)]NO_3 with *syn* (2.14 log units) and *anti* (2.12 log units) isomers of *cis*-cyclohexano-18-crown-6 (Table 1). We conclude therefore that it is the cation that determines the direction and the magnitude of the conformational discrimination. The ratio $K_a(syn)/K_a(anti)$ is independent of the anion.

If cation influence is important, then we should observe a variation in isomer discrimination by changing the cation. The K_a for the association of $[In(HL)]^+$ and $[Fe(HL)]^+$ with *cis-syn-cis*-dicyclohexano-18-crown-6 differs by only 0.12 log units (Table 1). This is attributed to the anticipated small difference in $[M(HL)]^+$ (M = Fe^{III} or In^{III}) hydration shells, based on the known small difference in hydration enthalpy for $[In(H_2O)_6]^{3+}(g)$ and $[Fe(H_2O)_6]^{3+}(g)$.[1] Consequently there was no significant change in *syn*/*anti* discrimination between $[Fe(HL)]^+$ and $[In(HL)]^+$. Therefore, we investigated significantly different cations such as the parent ammonium ion and alkali-metal ions. The data for the association of the picrate salts of the alkali metals and ammonium with the *syn* and *anti* isomers of *cis*-dicyclohexano-18-crown-6 in $CHCl_3$ may be compared with $K_a(syn)/K_a(anti)$ ratios for perchlorate and nitrate salts of $[M(HL)]^+$, since no anion effect on the stereoselectivity ratio for the $[Fe(HL)]^+$-*cis*-dicyclohexano-18-crown-6 interaction was observed.

In addition to data in apolar chloroform where solvent effects occur to a lesser degree, we considered data reported for the complexation of the same alkali-metal and ammonium cations in water,[9-11] where solvent effects are expected to be dominant and therefore more easily recognized and understood. This provides a useful data base for the comparison needed for elucidation of the conformational preferences and molecular recognition in solution.[1,2,31,34-38]

Fig. 1 illustrates the discrimination ratio $[K_a(syn)/K_a(anti)]$ for the alkali-metal and NH_4^+ cations in chloroform and water[10,11] plotted as a function of the ionic radius. A significant variation in the *syn*/*anti* preference is observed when the cation is changed. Although there is a preference for the *syn* over the *anti* isomer for all of these cations in both solvents, these data illustrate that the discrimination is significantly greater in water than in chloroform. This is likely due to the different degree of solvation competition between the crown ether and water, and crown ether and chloroform, for a given cation which results in a different degree of steric hindrance. This also results in lower absolute values of the crown ether association constants for these different cations in water than in $CHCl_3$.[7-11]

In apolar chloroform, where solvent effects are fairly weak, the preference of the cation for the *syn* isomer should be most closely influenced by the cation ionic radius, and therefore should resemble host–guest complex formation in the gas phase.[39,40] Data in Table 2 and Fig. 1 illustrate that discrimination between the *syn* and *anti* isomers is the least for K^+, where the ionic radius (r = 1.38 Å[29]) is the best match for the 18-crown-6 cavity size (r = 1.3–1.7 Å[41]). Once the solvation shell is largely stripped away[26,38,42] the approach of the small potassium cation to the cavity will not be significantly affected by the differences in the topology of the *syn* and *anti* isomers of *cis*-dicyclohexano-18-crown-6. This is evident in the $K_a(syn)/K_a(anti)$ ratio of 1.2 for K^+ in $CHCl_3$ in contrast to 2.5 in water (Table 2). The value of K_a for the interaction of K^+ with 18-crown-6 (> 10^{11} dm^3 mol^{-1})[7] is significantly higher than with *cis-syn-cis*-dicyclohexano-18-crown-6 (1.85 × 10^8 dm^3 mol^{-1}, Table 2). This suggests that the different topology and limited flexibility of *cis-syn-cis*-dicyclohexano-18-crown-6 may not allow K^+ to sit exactly in the centre of the cavity as is the case for 18-crown-6.[43-45] The cations NH_4^+ and K^+ in $CHCl_3$ show similar preferences towards the *syn* isomer, which we attribute to their similar ionic radii. For the smaller Na^+ and larger Cs^+ ions we observed an increase in the ratio $K_a(syn)/K_a(anti)$ relative to K^+ and NH_4^+ (Fig. 1). This may be rationalized by the existence of additional conformational requirements for complexation of these ions, as shown in X-ray structural analyses where Na^+ requires a folding of the 18-crown-6 structure,[43,44,46] while the large Cs^+ ion is out of the mean oxygen plane.[44,47] It may be assumed that a large Cs^+ ion will favour the open side of *cis-syn-cis*-dicycohexano-18-crown-6. Although there is no direct evidence, the opposite may be operative for the association of Na^+, whereby an approach from the hindered side affords a favourable three-dimensional effect.

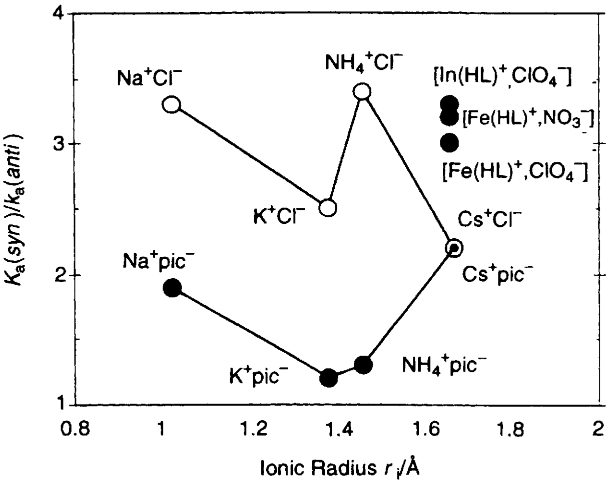


Fig. 1 Plot of the ratio of the host–guest association constant for *cis-syn-cis* and *cis-anti-cis*-dicyclohexano-18-crown-6 with various cations $[K_a(syn)/K_a(anti)]$ as a function of ionic radius.[29] Data obtained in $CHCl_3$ are from Tables 1 and 2 and are represented by closed circles, while data obtained in water[10,11] are represented by open circles. An estimated ionic radius for the alkylammonium side chain was used for [M(HL)]X (M = Fe^{III} or In^{III}, X = ClO_4 or NO_3); see text

In water, the size of the hydration shell of the cations, measured by their hydrated rather than by their ionic radii, is responsible for variations in their interactions with crown ethers. The crown ether encapsulated cation is not completely shielded and still interacts with water molecules,[34] which affects the conformation and the stability of the resulting complex. As the effective (hydrated) radii of the cations in water are significantly higher than their radii in apolar solvents, the steric requirements in water are more severe and are reflected in their $K_a(syn)/K_a(anti)$ ratios[10,11] given in Table 2. Hydrated radii, obtained from limiting ionic equivalent conductivity, are given in Table 2 for Na^+, K^+, Cs^+ and NH_4^+.[30,31] With its large hydration shell, the cation of highest charge density, Na^+, has the largest *syn* preference in the alkali-metal cation series (Table 2). The ions K^+ and Cs^+ differ in their ionic radii, but have almost identical hydrated radii and thus an almost identical $K_a(syn)/K_a(anti)$ ratio in water. As seen in Fig. 1, the *syn* preference for Cs^+ is the same in water and in $CHCl_3$. This suggests that the crown ether may feel a similar effective Cs^+ radius in both water and $CHCl_3$. It furthermore implies that due to the low charge density (and thus low ΔH_{hydr}) of Cs^+, the crown ether more readily competes with weakly bound water molecules of its hydration shell.

The complexation of NH_4^+ in water and its high *syn*/*anti* preference does not fit into the behaviour observed for the other cations investigated,[10,11] in the sense that it can not be rationalized on the basis of hydrated radii only. This pattern may be attributed to its four tetrahedrally arranged hydrogen atoms available for hydrogen bonding with both crown ether and water molecules, a property not shared with Na^+, K^+ and Cs^+. In addition, the arrangement of hydrogens could lead to distinct stereochemical requirements as evidenced through its interactions with natural ionophores valinomycin and nonactin.[32,39,48,49]

On the basis of our data in chloroform and literature data in water,[10,11] we conclude that the cation is responsible for the degree of *syn*/*anti* discrimination in either solvent. The *syn* discrimination exhibited by the $[M(HL)]^+$ cation in $CHCl_3$ is greater than expected, based on the data for the alkali metals and NH_4^+ in $CHCl_3$, and on an estimated ionic radius for the alkylammonium side chain of $[M(HL)]^+$ (see Fig. 1). A rough estimate for the effective ionic radius of the substituted alkylammonium side chain (1.66 Å) was obtained from the ratio of partial molar volumes at infinite dilution for ammonium chloride and methylammonium chloride.[50] The reason for the high $K_a(syn)/K_a(anti)$ ratio for $[M(HL)]^+$ relative to NH_4^+ (illustrated in Fig. 1) most probably lies in the fact that the ammonium cation, once substituted by an alkyl chain bearing a metal complex, imposes a highly specific steric demand upon the crown ether to accommodate it, presumably out of the ether oxygen plane. This is likely due to the steric bulk of the metal complex which may include the siderophore second-coordination or hydration shell, and ammonium cation first-coordination/hydration shell.

The fact that the cation determines the *syn* over *anti* preference is consistent with a dynamic solution structure for the supramolecular assembly **I** in $CHCl_3$ whereby complexation of the protonated amine side chain, *i.e.* the bulkier part of the $[M(HL)^+, X^-]$ ion pair, occurs on the least sterically hindered face of the crown ether (top in **IIA**). Available data and the dynamic nature of the ion pair in solution do not permit us to speculate on the relative position of the anion, which does not influence the *syn*/*anti* discrimination process.

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