Macrocyclic Ligands Examined by Fast Atom Bombardment Mass Spectrometry: Direct Observation of Metal Cation Selectivity in Complexation

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Complex formation between metal cations and macrocyclic ligands has been observed by fast atom bombardment (F.A.B.) mass spectrometry of their aqueous glycerol and other solutions, the abundances of gas-phase ions at *m/z* values corresponding to metal cation–ligand complexes reflecting closely the calculated concentrations of these complexes in solution at normal temperatures; the results suggest that metal cation–ligand complex formation in solution for wide ranges of metal cations and many different types of macrocyclic ligands can be assessed rapidly and semi-quantitatively by the F.A.B. technique.

Complex formation between metallic cations and macrocyclic ligands has been reviewed extensively.[1] Methods for determination of the stability constant (K_s) for a metal cation–macrocyclic ligand complex have been discussed.[2] Stability constants, along with enthalpies and entropies of formation, have provided insights into the reasons for variations in stability of such metal cation–macrocyclic ligand complexes. This thermochemical information can be used to aid the design of new macrocyclic ligands having increased binding strength or selectivity for particular cations.[3] However, a rapid method for examining the complexation of one or a range of metal cations with one or a range of macrocyclic ligands has not been available.[1,2] Recently, we described the use of fast atom bombardment (F.A.B.) mass spectrometry for investigation of the change in concentration of metal cation–crown ether complexes with variation in concentrations of cations.[4] We report here the direct observation of selectivity in metal cation–macrocyclic ligand complexation for Li^+, Na^+, K^+, Rb^+, and Cs^+. The method is illustrated for 15-crown-5 (15C5)† and results for other macrocyclic ligands are shown in Table 1.

A glycerol–water (2:1 v/v) solution was prepared containing the iodides of lithium, sodium, potassium, rubidium,

† Abbreviations for trivial names of common macrocyclic ligands are used. The abbreviations, followed by the trivial name and the full name in parentheses, are as follows: 12C4 (12-crown-4; 1,4,7,10-tetraoxacyclododecane); 15C5 (15-crown-5; 1,4,7,10,13-pentaoxacyclotridecane); 18C6 (18-crown-6; 1,4,7,10,13,16-hexaoxacyclo-octadecane); DCH18C6 (dicyclohexano-18-crown-6; 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane); DCH24C8 (dicyclohexano-24-crown-8; 2,5,8,11,18,21,24,27-octaoxatricyclo[26.4.0.0^{12,17}]dotriacontane); C222 (cryptand-2.2.2; 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8.]hexacosane).

Table 1. Abundances of [ligand + metal]$^+$ ions[a] relative to the tetra-n-butylammonium ion as internal standard.[b]

Macrocyclic ligand[c]	Na^+	K^+	Rb^+[d]	Cs^+
12C4[e]	—	—	—	—
15C5	21.1 (243)	10.0 (259)	5.3 (305, 307)	1.7 (353)
18C6	2.9 (287)	183.4 (303)	114.5 (349, 351)	23.3 (397)
DCH18C6	17.9 (395)	387.4 (411)	131.2 (457, 459)	19.2 (505)
DCH24C8	9.2 (483)	39.5 (499)	41.1 (545, 547)	27.8 (593)
C222	28.0 (399)	464.6 (415)	152.3 (461, 463)	— (509)

[a] Abundances are shown followed by m/z values for [ligand + metal]$^+$ in parentheses. No ions were observed for [ligand + Li]$^+$ in any of the spectra. [b] The tetra-n-butylammonium ion at m/z 242 from the internal standard was assigned arbitrarily a peak height of 10 units for each spectrum. [c] For abbreviations used for ligands, see footnote †. [d] Abundance after addition of peak heights corresponding to isotopes ^{85}Rb and ^{87}Rb. [e] For this ligand, all metal cations complexed preferentially to glycerol.

and caesium, each at a concentration of 0.005 M. As an internal standard, tetra-n-butylammonium chloride (which does not form complexes with the macrocyclic ligands used in this study) was incorporated at a concentration of 6×10^{-5} M. A glycerol–water (2:1) solution of 15C5 (0.005 M) was prepared also. For the mass spectrometric experiment, an analytical solution was prepared by mixing equal volumes of the two solutions so that all components, except for the internal standard, were present in equimolar ratios; accordingly, the metal cations were competing for a limited amount of the 15C5 ether.

The stainless steel tip of an F.A.B. probe was coated with a thin layer (1—2 μl) of the analytical solution. Positive ion F.A.B. mass spectrometry was performed using a primary atom beam of Xe (8 keV) on a VG 7070F mass spectrometer coupled to a Finnigan Incos Data System. At an accelerating voltage of 3 kV, the mass range m/z 35—850 was scanned in 15 s (scan cycle time, 18 s). Twenty successive spectra of each analytical solution were acquired and scans 5—15 inclusive were summed to afford the final spectrum. The abundance of ions at each m/z value corresponding to metal cation–15C5 complex was measured relative to the abundance of the internal standard tetra-n-butylammonium ion at m/z 242. Results are shown in Table 1.

The experiment was repeated for 12C4, 18C6, DCH18C6, DCH24C8, and C222. Comparative results are shown in Table 1. Corrections have not been made for differences in sensitivity of the mass spectrometer at various m/z values, *i.e.*, transfer coefficients were not measured.[3] For any one macrocyclic ligand with a series of metal cations, these corrections lead to small changes in relative abundances and are unlikely to invalidate the general conclusions drawn here. For comparative purposes, using published values of stability constants in aqueous solution, concentrations of metal cation–macrocyclic ligand complexes have been calculated for solutions containing all three ions, K^+, Rb^+, and Cs^+; these concentrations are compared in Table 2.

At the chosen concentrations, no ions were observed corresponding to complex formation between 12C4 and alkali metal cations. Instead, abundant ions were observed at m/z values corresponding to $[G_n + Met]^+$ or $[G_n + H]^+$ where G is glycerol, Met is the alkali metal, and n varies from one upwards. Thus, glycerol must co-ordinate more effectively to alkali metal cations than does 12C4. Although in these experiments glycerol is used in large excess (solvent) compared with the concentration of macrocyclic ligand, it was found to compete effectively in complex formation with alkali metal cations only for 12C4. In methanol, the stability constant (log K_S) for complexation of Na^+ to the 12-crown-4 ethers, 2,5,8,11-tetramethyl-1,4,7,10-tetraoxacyclododecane, and 2,5,12,15-tetraoxatricyclo[14.4.0.0^{6,11}]icosane is 1.4[5a] and 2.18[5b] respectively; in an aqueous medium, these log K_S values

Table 2. Calculated[a] concentrations[b] of [ligand + metal]$^+$ complexes in aqueous solutions containing all three ions, K^+, Rb^+, and Cs^+.

Macrocyclic ligand[c]	K^+	Rb^+	Cs^+
15C5	12.4	9.6	14.2
18C6	123	50.8	14.8
DCH18C6	124	47.1	13.9
DB24C8[d]	115	144	128
C222	385	113	0.6

[a] Calculated by an iterative procedure (ref. 3) from stability constants determined in aqueous solution: 15C5 (ref. 9); 18C6 (refs. 9, 10); DCH18C6 (refs. 9, 11); DB24C8 (refs. 10, 11); C222 (ref. 12). [b] Concentrations ($\times 10^5$) in mol l^{-1}. For the calculations, 0.005 M concentrations of K^+, Rb^+, Cs^+ and macrocyclic ligand were assumed. [c] For abbreviations used for ligands, see footnote †. [d] Stability constant for DCH28C8 and K^+, Rb^+, do not appear to be available and data for dibenzo-24-crown-8 (DB24C8) were substituted.

can be expected to fall to nearly zero.‡ Observation of ions at m/z values corresponding only to $[G_n + Met]^+$ or $[G_n + H]^+$ and not to metal cation–12C4 complexes is in keeping with very small K_S values. For the other macrocyclic ligands (Table 1), ions at m/z values corresponding to $[G_n + Met]^+$ or $[G_n + H]^+$ were either absent or present in very low abundance. For all macrocyclic ligands, no ions corresponding to Li^+–ligand complex were observed, again in keeping with the very small log K_S values in aqueous solution for Li^+ complexes with the ligands used here in comparison[2] with the values of log K_S for Na^+, K^+, Rb^+, and Cs^+.

For macrocyclic ligands other than 12C4, the variation in abundances of ions corresponding to metal cation–ligand complexes was closely parallel to that expected from published stability constant data (Table 2). For example, with the cryptand, C222, complexation was greatest for K^+ and ion abundances of cation–ligand complexes decreased in the order $K^+ > Rb^+ > Na^+$; this order would be expected for the relative concentrations of these complexes in aqueous solution (Table 2). In keeping with the very small stability constant for the Cs^+–cryptand complex, and, therefore, its extremely low concentration in a solution containing also Na^+, K^+, and Rb^+, no ions corresponding to it were observed. For DCH24C8, observed ion abundances for complexes decreased in the order $Rb^+ > K^+ > Cs^+$, again the order expected for the concentrations of these alkali metal–crown ether complexes (Table 2).

‡ For comparison of log K values in different solvents, see ref. 3, pp. 162—165; ref. 1(c), pp. 26—30; ref. 1(d), pp. 66—72; ref. 1(b), pp. 180—183.

For the purposes of F.A.B. mass spectrometry, the solvent was aqueous glycerol and no stability constants have been measured in this medium. The close relative similarity of F.A.B. ion abundances to concentrations of cation–ligand complexes calculated from stability data for water suggests that the magnitudes of stability constants are similar for both water and aqueous glycerol.

It has been pointed out that complexation of many metal cations with macrocyclic ligands has not been investigated or has received little attention.[6] To some extent, this has been due to the time-consuming nature of examining each potential cation–macrocyclic ligand complex individually. The method described here allows simultaneous investigation of many metal cations for complexation with any potential macrocycle, or other ligand.

As an example of this approach, trifluoromethylsulphonates of Zn^{2+}, Ag^{+}, Fe^{2+}, Mg^{2+}, Hg^{2+}, Pb^{2+}, Ba^{2+}, Ca^{2+}, and Cu^{2+} were mixed separately with the macrocyclic sulphide, 1,4,8,11-tetrathiacyclotetradecane in poly(ethylene glycol)200 as solvent. Ions corresponding to complex formation were observed for [Ag^{+} + sulphide] at m/z 375, 377, [Hg^{2+} + sulphide] at m/z 619 (centre of isotopes), and [Cu^{+} + sulphide] at m/z 331. No ions corresponding to complexes between the sulphide and the other metal cations were observed. This sulphide has been reported to form complexes with Ag^{+}, Hg^{2+}, Cu^{+}, Cu^{2+}, Ni^{2+}, Co^{3+}, and Nb^{5+}.[7]

Our approach is not restricted to polyether ligands. Cation selectivity of macrocyclic lactones can be examined in the same way. For example, the macrotetralide antibiotic, nonactin, affords ions at m/z values corresponding to [N + Met]$^{+}$, where N is nonactin and Met can be sodium or potassium. With molecular equivalents of nonactin and Na^{+} and K^{+} in a solvent of glycerol–ethanol (2:1 v/v), the ratio of ion abundances, [N + Na]$^{+}$ to [N + K]$^{+}$, was 1:17. This selectivity should be compared with published[8] ratios of affinity constants of 1:19 at 30 °C and 1:60 at 25 °C (in methanol) and 1:23 at 30 °C and 1:95 at 25 °C (in ethanol) in favour of K^{+}.

We suggest that F.A.B. mass spectroscopy can be used routinely to examine complex formation between metal cations and macrocyclic ligands in solution.

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