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Stoichiometry Determination of Cation-Macrocyclic Complexes Based on the ^{1}H NMR Chemical Shift of the Cation-Coordinated Water Molecules

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Synopsis. The stoichiometries of alkali and alkaline earth metal complexes with macrocyclic ligands were determined in a water-containing nitrobenzene solution by means of ^{1}H NMR. The chemical shift of the water protons was more sensitive to the complexation than that of the methylene protons of the ligands.

In early papers,[1–5] we showed that alkali and alkaline earth metal cations exist as hydrated state in a water-containing nitrobenzene solution and, when these cations undergo complexation with macrocyclic ligands, the water molecules attached to the cations are partially or almost fully released. These findings suggest that the equivalence point of the complexation may be detected by observing the chemical shift of the water protons as a function of the ligand concentration. The stoichiometries of unsubstituted 12- to 18-membered crown ether complexes with the alkali and alkaline earth metal cations have been determined by means of ^{1}H NMR.[6] In this paper, the usefulness of the method was confirmed with macrocyclic ligands, such as 21-crown-7 (21C7), 24-crown-8 (24C8), 4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (C22) and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (C222).

Experimental

Materials. 21C7 was synthesized according to the method of Dale and Kristiansen.[7] The crude product was adsorbed on a cation-exchange column (Amberlite CG 120) connected to an anion-exchange column (Amberlite IRA-400, Rohm & Haas) and then eluted by water. Colored impurities were also removed by the deionization process. Evaporation of the solvent under reduced pressure left a viscous residue. The substance was dissolved in a small quantity of acetonitrile and then cooled in a refrigerator. The resulting crystalline 21C7-acetonitrile complex was decomposed under vacuum for at least 12 h at room temperature. The 21C7 thus obtained was ^{1}H NMR spectroscopically pure. 24C8 was synthesized in the same way. C22 and C222 (Merck) were used without further purification.

The alkali and alkaline earth metal salts with 2,2′,4,4′,6,6′-hexanitrodiphenylamine (HND) were prepared as described previously.[6] The Li, Sr, and Ba salts contained 4 molecules of water of crystallization, the Ca salt 11, and the K, Rb, and Cs salts contained none.

For ^{1}H NMR measurements, solutions were prepared by dissolving weighed ligands and salts into deuterated nitrobenzene (99%, Merck), the water content being adjusted by adding a certain amount of water-saturated nitrobenzene. The K, Rb, and Cs salts were made $(2.5—4.0)\times10^{-2}$ mol dm^{-3} solutions and the others $(1.5—5.0)\times10^{-3}$ mol dm^{-3} solutions. The ligands were made about 0.8 or 0.04 mol dm^{-3} solutions; the concentrated solutions were used for the titration of the concentrated salt solution.

NMR Measurements. To an NMR tube, 400 μl of the salt solution was transferred and the chemical shift of the water proton was measured on a Hitachi FT-NMR R600 (60 MHz) spectrometer. A 5 μl-aliquot of a ligand solution was added to the solution and mixed well on a vibrator-type mixer. The chemical shifts of both the water proton and the ligand protons were measured. The measurements were repeated until the ligand/cation mole ratio increased to about 2 or 3. Tetramethylsilane was used as internal standard. The chemical shifts were reprodueced within 0.4 Hz. All the measurements were carried out at 25 °C.

Results and Discussion

^{1}H NMR Spectra. The chemical shift spectra for Ca^{2+}–C222 at different ligand/cation mole ratios are shown in Fig. 1. The spectrum of the free ligand (**0**) consisted of a triplet due to $-OCH_2-$ (about δ 3.6), a triplet for $-NCH_2-$ (about δ 2.6), and a singlet for $-OCH_2CH_2O-$ (δ 3.7). A peak at δ 2.5 may be due to residual water in the solvent. Resonance signals centered at about δ 8 are due to the aromatic protons of undeuterated nitrobenzene. The spectrum of a water-containing ligand-free Ca(HND)$_2$ solution (**1**) consisted of two singlets (water and aromatic protons of HND at δ 3.2 and 8.8, respectively). Addition of the ligand to this solution resulted in a strong upfield shift of the water protons (from δ 3.2 in **1** to 3.0 in **2**

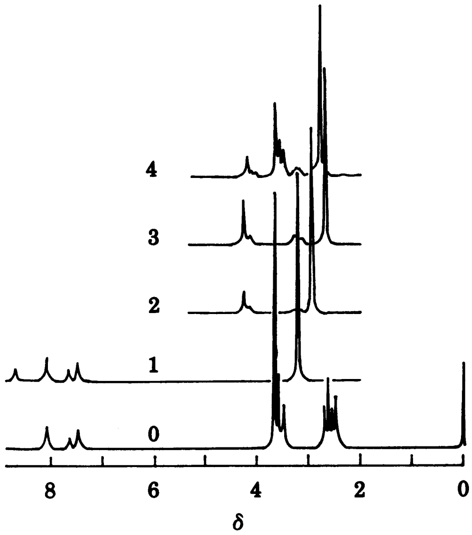

Fig. 1. ^{1}H NMR spectra of the water and ligand protons for Ca^{2+}–C222.
Initial concn of Ca^{2+}: 0.0048 M (1 M=1 mol dm^{-3}).
0: C222, **1**: [L]/[M]=0, **2**: [L]/[M]=0.5, **3**: [L]/[M]=1, **4**: [L]/[M]=2.0.

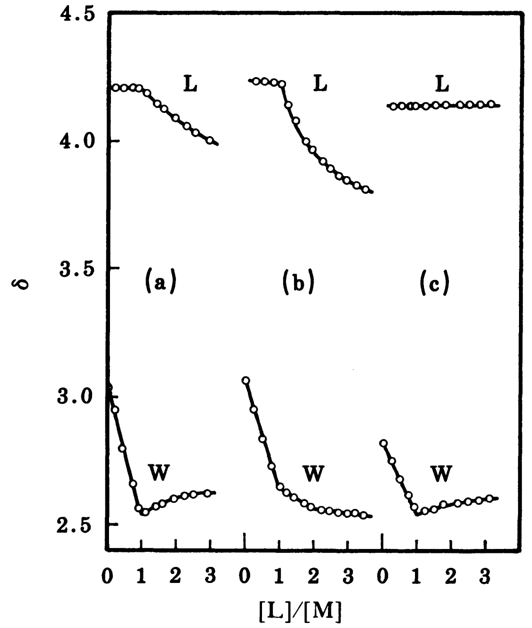

Fig. 2. Signal shifts of the ligand and water protons as a function of [L]/[M].
W: water signal, L: ligand signal.
(a): Ca^{2+}(0.0048 M)-C222, (b): Ca^{2+}(0.0024 M)-21C7, (c): Ca^{2+}(0.0022 M)-C22.

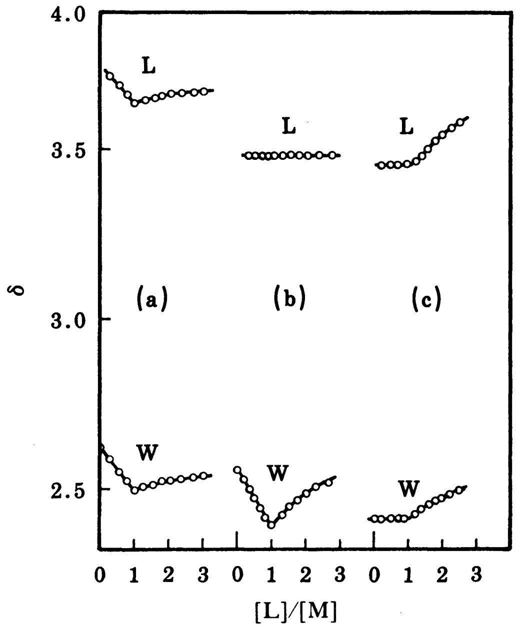

Fig. 3. Signal shifts of the ligand and water protons as a function of [L]/[M].
W: water signal, L: ligand signal.
(a): Li^+(0.034 M)-C222, (b): K^+(0.034 M)-C222, (c): Cs^+(0.031 M)-C222.

([C222]/[Ca^{2+}]=0.5)) and a strong downfield shift of the methylene signals due to complexation (from δ 2.6 and 3.6 in **0** to δ 3.2 (weak) and 4.2 in **2**, respectively). As the titration proceeded, the water signal continued to shift upfield until the equivalence point (**3**, [C222]/[Ca^{2+}]=1) was reached, but the signals of the complexed ligand showed virtually no shift. The further addition of the ligand caused a downfield shift of the water signal and a slight upfield shift of the signals of the complexed ligand (**4**, [C222]/[Ca^{2+}]=2). It was noted that, in spectrum **4**, the free ligand signals reappeared at δ 2.6 (not clear) and 3.6; the reappearance of the free ligand signals in the presence of excess ligand, however, was observed only with Sr^{2+}- and Ba^{2+}-15C5.

The spectral changes for C22 complexes were quite similar to those of C222. Uncomplexed 21C7 and 24C8 each gave a sharp singlet at δ 3.7 and their signal-shift patterns due to complexation were almost identical with those of 12- to 18-membered crown ethers.[6] Concerning the shift patterns, we found no fundamental difference between the 12- to 24-membered crown ethers and the nitrogen-containing macrocycles.

The magnitude and direction of the signal shifts for Ca^{2+}-C222 can clearly be seen from Fig. 2a, where curve W denotes the shift of the water signal and curve L, that of the ligand signal ($-OCH_2CH_2O-$). Hereafter, the signal shift measurements for C22 and C222 were made on this signal because of the ease of the measurements. Some typical shift patterns are shown in Figs. 2 (b,c) and 3 (a,b,c).

Curves W always exhibited a single break point at [L]/[M]=1, indicating the formation of 1:1 (M:L) complexes in the solution. There were, however, a few cases in which curves L lacked a break point. The curve W for Ca^{2+}-21C7 exhibited two break points at [L]/[M]=1 and 2 (Fig. 2b); the curve L, however, showed no break point at [L]/[M]=2. The curve L for Rb^+-C22 (Fig. 2c) lacked a break point. The same observation was true for K^+-C222 (Fig. 3b). The C222 signal (Fig. 3a) shifted upfield as the titration proceeded. The upfield shift was characteristic of all the complexes formed between small cations and ligands having a relatively large cavity. The water signal in Fig. 3c exhibited no shift until the equivalence point was reached; this was the case with Cs^+-C222 alone.

Chemical Shift of Water Protons. The complexation between hydrated cations and macrocyclic ligands can simply be represented as follows:

$$M(H_2O)_i + L \rightleftharpoons M(H_2O)_jL + (i-j)H_2O \qquad (1)$$

$$kH_2O + L \rightleftharpoons L(H_2O)_k \qquad (2)$$

where $i>j$. Two types of water molecules, i.e., cation- or ligand-bound and free, are present during the course of the titration. Based on the fast proton exchange between the bound and free water molecules, the water signal gave only one population-averaged peak. The population of the free water increases with the ligand concentration (Eq. 1). The characteristic upfield shift of water protons before the equivalence point can be explained by taking into account that the free water resonates at a higher field than the bound water. The downfield shift beyond the equivalence point can likewise be accounted for by a decrease in the free water (Eq. 2).

Table 1. [L]/[M] Values at the Break Points for the Alkali Metal Complexes

Ligand	Signal	Li^+	Na^+		K^+	Rb^+	Cs^+
12C4[a]	L[b]	1.00	0.88	2.02	0.96	0.97	1.03
	W[c]	0.98	0.99	1.99	0.97	0.99	1.00
15C5[a]	L	1.04	1.02		0.99	0.96	1.00
	W	0.98	1.00		0.99	0.98	0.96
18C6[a]	L	0.97	1.00		—	—	—
	W	1.05	0.95		1.00	0.98	1.01
21C7	L	1.00	—[d]		1.03	0.97	1.00
	W	1.00	1.02		1.00	1.00	1.00
24C8	L	1.00	1.00		1.00	0.96	1.02
	W	1.00	0.98		0.99	0.99	0.95
C22	L	0.99	1.00		1.06	1.02	1.00
	W	0.99	1.00		1.01	1.00	0.99
C222	L	1.03	—		—	—	0.99
	W	0.96	0.99		1.00	1.00	0.99

a) Revised from the data in Ref. 7; a few were redetermined. b) Ligand signal. c) Water signal. d) The symbol "—" indicates the lack of a break point.

It follows from the above discussion that the [L]/[M] ratio at the break point represents the stoichiometry of the complex in solution.

Usefulness of the Water Signal. The curves W were always V-shaped, exhibiting at least one break point; this has enabled sensitive and accurate stoichiometry determination. On the other hand, the curves L were mostly less sensitive and, for some complexes, completely insensitive to the complexation. It can, therefore, be concluded that the water signal is used to advantage in determining the stoichiometries of macrocyclic complexes.

Stoichiometries of the Complexes. The [L]/[M] ratios at the break points are summarized in Tables 1 and 2, together with the revised ones for 12C4, 15C5, and 18C6. The data obtained were all consistent with those reported by others.[8] As regards the present experiments, 1:1 complexes were found for all complexation systems. 1:2 complex was found only for Ca^{2+}–21C7.

Table 2. [L]/[M] Values at the Break Points for the Alkaline Earth Metal Complexes

Ligand	Signal	Ca^{2+}		Sr^{2+}		Ba^{2+}	
12C4[a]	L[b]	—[d]	2.00	—	2.00	1.00	2.00
	W[c]	—	1.96	0.94	1.97	1.02	2.00
15C5[a]	L	0.99	2.00	1.02		—	—
	W	0.98	2.07	0.98	1.92	1.00	1.96
18C6[a]	L	1.04		0.99		1.00	
	W	0.98		1.01		1.04	
21C7	L	1.01		1.02		0.98	
	W	1.00	2.00	0.97		0.98	
24C8	L	1.05		1.00		0.97	
	W	0.98		0.99		0.96	
C22	L	—		1.09		0.97	
	W	0.99		0.99		0.98	
C222	L	1.02		0.99		1.05	
	W	1.00		1.00		0.99	

a) Revised from the data in Ref. 7; a few were redetermined. b) Ligand signal. c) Water signal. d) The symbol "—" indicates the lack of a break point.

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