CHEMISTRY LETTERS, PP. 571-574, 1982.

CROWN COMPLEXANES.
CARBOXYMETHYL AND PHOSPHONOMETHYL DERIVATIVES OF AZA-CROWN ETHERS[1)]

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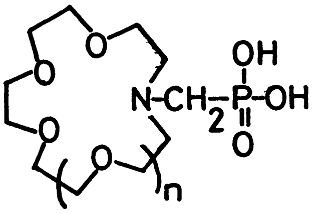
The complexane-type chelating agents were derived from aza-crown ethers either by N-carboxymethylation or N-phosphonomethylation. The macrocyclic complexanes obtained (crown complexanes) interacted in aqueous media with various metal ions with an uncommon selectivity. The metal ions are incorporated in the crown ether ring on complexation.

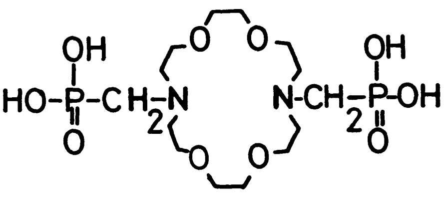
The importance of alkali and alkaline earth metal ions in the physiological process in the living organisms is widely recognized.[2)] The role of some trace transition metals in biological processes is also well known. Much efforts have been made for synthetic carriers or ionophores, which mediate a selective transport of metal ions through a lipophilic barrier.[3)] However, rather little has been explored for the compounds which selectively bind alkali or alkaline earth metals and remain essentially in aqueous media.[4)] The major family of traditional chelating agents has the metal selectivity which follows either Irving-Williams type stability order or a HSAB (hard and soft acids and bases) concept. The chelating agents which deviate from this classification are rare. Such uncommon complexing agents should be highly useful as reagents in studying the physiochemical processes in the living cells which take place under a subtle balance of metal ion concentration.[5)]

In the present communication, the synthesis and the properties of the macrocyclic complexanes **1** - **5** ("crown complexanes"[1)]) are described. These compounds show a much higher affinity to alkali and alkaline earth metals and some unique selectivity among transition metals as compared with the traditional chelating agents.

The crown complexanes were synthesized either by carboxymethylation or phosphonomethylation of the parent aza-crown ethers according to the ordinary synthetic procedures. The isolation and purification were achieved by an ion exchange column treatment followed by recrystallization. The details will be given in a separate communication.[6)] The compounds were readily soluble in water,



1 (n = 1) **2** (n = 2)



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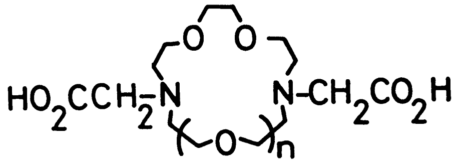
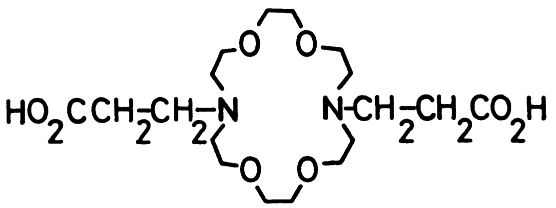


4 (n = 1) **5** (n = 2)



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appreciably soluble in methanol and insoluble in non-polar organic solvents.

The interaction of the complexanes (H_nL) with sodium ion was studied using a sodium ion-selective electrode at a high pH region (pH 11.8∿12.2, $(CH_3)_4NOH$), where all the dissociable protons of the ligands are liberated. The complex formation constants defined by Eq. 1 were calculated and are summarized in Table 1.[7)]

$$Na^+ + L^{n-} \rightleftarrows NaL^{1-n} \quad : \quad K_{NaL} = \frac{[NaL^{1-n}]}{[Na^+][L^{n-}]} \qquad (1)$$

Table 1 Formation constants of NaL^{1-n} [a)]

ligand	**1**	**2**	**3**	**4**	**5**	**6**
K_{NaL}	40	20	(20)[b)]	700	90	-[c)]

a) 25°C; μ=0.1, $(CH_3)_4NBr$

b) Intervention of Na_2L^{2-} complex

c) No complex formation

The sodium complex is more stable for the 15-crown-5 type complexanes (**1**,**4**) than for the 18-crown-6 type complexanes (**2**,**5**). This suggests that the metal selectivity of these crown complexanes is in line with an ordinary metal size selectivity of the parent crown ethers. The complexane with propionic acid pendent groups (**6**)[1b)] as well as the parent monoaza- and diaza-crown ethers in this study did not show any measurable affinity to sodium. The determination of the formation constants for potassium was unsuccessful, because a potassium-selective electrode failed to work under the relevant experimental conditions.

The formation constants of divalent metal complexes were measured potentiometrically for **4** and **5** in the same manner as reported previously.[1b)] The definitions of the equilibrium constants are given in Eqs. 2 and 3. Figure 1 shows some of the typical titration curves. The constants calculated are summarized in Table 2 along with other related constants. Since the complexanes interact with potassium rather strongly, the equilibrium constants obtained in the presence of 0.1 M potassium nitrate are to be regarded as conditional constants.

The formation constants increase as the ring size of the crown ether decreases and the ring size of the aminocarboxylate-chelate decreases, and, as such, the stability of the divalent metal complexes approaches that of EGTA, a linear version of the crown complexane. The slow rate of equilibration for some of the metal complexes with **4** excluded the accurate measurement of the formation constants. This abnormal behavior, which is currently being studied, is presumably associated with a structural change within the complex.

It is worth noting that **5** forms complexes of approximately the same stability with all the

Table 2 Conditional equilibrium constants, 25°C, μ = 0.1 (KNO_3)

ligand	pK_{a,H_nL}				$\log K_{ML}$							
	H_4L^{2+}	H_3L^+	H_2L	HL^-	Mg	Ca	Sr	Ba	Co	Ni	Cu	Zn
4	<2	2.3	8.35	8.63	(6.7)[a]	8.06	7.20	6.74	(12)[a]	-[a]	>14	(12)[a]
5	<2	2.0	7.89	8.02	<2	7.67	7.69	7.66	7.00	7.46	>14	8.03
6[b]	2.61	3.67	8.26	8.92	<2	4.04	4.38	3.79	-	-	-	-
EGTA[c]					5.1	10.89	7.97	8.00	12.33	13.50	17.72	14.37

a) Slow equilibrium

b) Ref. 1b; small interactions with Co(II), Ni(II), and Zn(II); moderate, not so strong as **4** or **5**, interactions with Cu(II)

c) [(Ethylenedioxy)diethylenedinitrilo]tetraacetic acid; K_{ML} calculated from ΔH° and ΔS° values (Ref. 8)

$$H_nL^{n-2} \rightleftharpoons H_{n-1}L^{n-3} + H^+ \quad :$$

$$K_{a,H_nL} = \frac{[H_{n-1}L^{n-3}][H^+]}{[H_nL^{n-2}]} \qquad (2)$$

$$M^{2+} + L^{2-} \rightleftharpoons ML \quad :$$

$$K_{ML} = \frac{[ML]}{[M^{2+}][L^{2-}]} \qquad (3)$$

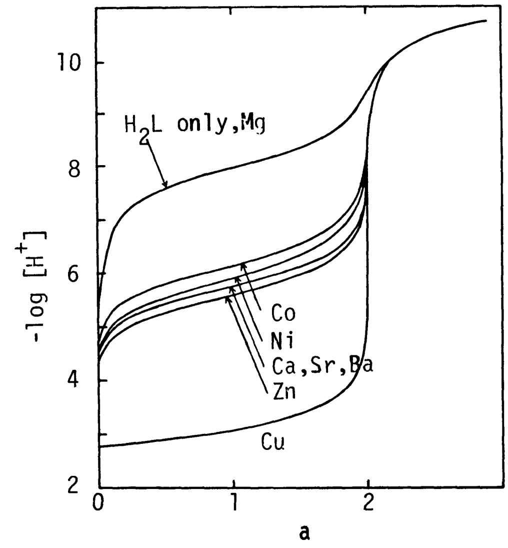

Fig. 1. Titration curves for **5** - M^{2+}
a: mol of KOH added per mol of H_2L

divalent metals studied except for magnesium and copper. The pH-dependent conditional formation constant ($\log K_{CaL}$) estimated at pH 7 is 5.7 for **5**[9] and 6.4 for EGTA. Thus, under the physiological pH conditions, **5** is as effective as EGTA in complexing calcium, while it does not seriously affect the transition metal concentrations as EGTA possibly does.

The unique complexing property of **5** is most certainly associated with the binding of metals into the crown ether cavity. The X-ray crystal structure analysis of the copper(II) complex of **5** exemplified this.[10] The complex assumed a square planar structure with respect to the coordination of the α-aminoacid functional groups. The crown ether ring extended toward the axial directions, and the one each of the two ethereal oxygens barely approached from the top and the bottom, completing the distorted octahedral coordination around the copper. This structure explains the extraordinary stability of the copper complex of **5** (Table 2). The other transition metal complexes would not be stabilized under this structural restriction of the ligand.

The crown complexane is not simply multidentate but multifunctional; the spacially confined desposition of the coordinating groups not only fulfills the coordination sites of the metal, but also restricts the preferable size and the stereochemistry of the metal to be encapsulated. In this sense, a molecular framework for the "multifunctional" chelating agent is not necessarily limited to crown ethers. The present work constitutes just a starting point for such a line of study.

Acknowledgement. The present work was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture.

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6) The preparation of **2** is given below to provide an idea of the synthetic procedures. A mixture of monoaza-18-crown-6 (2.0 g, 8.0×10^{-3} mol), phosphorous acid (1.3 g), concentrated hydrochloric acid (0.8 g), 37 % aqueous formaldehyde (4.0 g), and water (1.6 g) was heated to reflux for 3 h. The reaction mixture was concentrated under reduced pressure, redissolved in water and applied to a column containing an anion exchange resin AG-MP-1 (Bio-Rad Laboratories; 800 ml in wet volume, OH^- form, *ca* 1 mol). After the column was washed with water (200 ml), the compound was eluted from the column with 10 % acetic acid (100-200 ml). The eluate was concentrated under reduced pressure to give a crystalline solid (2.5 g), which was dissolved in methanol containing a small amount of water and then recrystallized by adding acetone and ether. Yield 2.1 g (74 %), mp 76-78°C. The ^1H NMR and elemental analysis data supported the proposed structure.
7) The ligand solutions (0.015 M, 1 M = 1 mol dm^{-3}; pH 12.2) were titrated with a 1 M standard sodium chloride solution. The variation of sodium ion concentration was measured with a Horiba 1512A pNa electrode. The complexation equilibria were analyzed according to the conventional procedure.
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(Received February 16, 1982)