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FUNCTION OF AMIDE GROUP IN SYNTHETIC MULTIDENTATES ON COMPLEXATION TOWARD ALKALI AND ALKALINE EARTH METAL CATIONS

Yohji NAKATSUJI, Hirofumi KOBAYASHI, and Mitsuo OKAHARA*
Department of Applied Chemistry, Faculty of Engineering, Osaka University,
Yamada-oka 2-1, Suita, Osaka 565

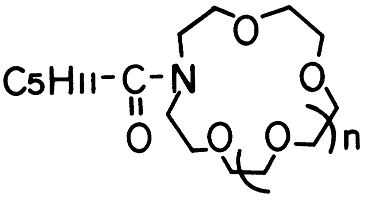
Kenji MATSUSHIMA
Department of Applied Chemistry, Faculty of Science and Technology,
Kinki University, Kowakae, Higashi-osaka, Osaka 577

Several macrocyclic multidentates having one amide group were newly prepared and their complexation property toward Na^+, K^+, Ca^{2+}, and Ba^{2+} was examined by the extraction method. The affinity toward Ca^{2+} was observed and the orientation of the amide group toward the cation was suggested to be important for the molecular design of ligands.

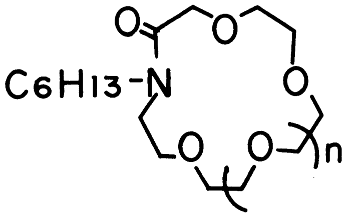
Recently a variety of synthetic multidentates such as crown ethers and cryptands have been noticed to be important model compounds for natural ionophores in relation to the complexation property toward specific cations, which are considered to participate in the maintenance of organisms *in vivo*. Ether and carbonyl oxygen atoms of ester and amide groups are well known as the effective coordination groups of such natural ionophores; the amide group has scarcely been used for synthetic macrocyclic multidentates,[1-4] in contrast to noncyclic mulitidentates[5] extensively studied by Simon *et al.* for the purpose of molecular design of the carrier for the ion-selective electrode, probably because of the necessity of considering the orientation of the amide group. We now describe the synthesis of some macrocyclic compounds having an amide group and their complexation property toward alkali and alkaline earth metal cations in order to obtain the fundamental data concerning the coordination of the amide group toward cations.

N-Caproyl-1-aza-18-crown-6(**1a**) was easily obtained from the acylation of the corresponding unsubstituted monoaza crown ether, which can be prepared according to the method recently developed,[6] by using caproyl chloride in 70% yield as a slightly yellow oil. bp 155°C/0.01 Torr(Kugelrohr); MS, *m/e*(relative intensity) 361(M^+, 10), 262(14), 86(48), 56(57), 45(60), 44(43), 43(100); IR(neat) 1640 cm^{-1}($\nu_{C=O}$); ^1H NMR($CDCl_3$) δ 0.89(t, 3H), 1.12-1.48(m, 4H), 1.48-1.80(m, 2H), 2.34(t, 2H), 3.40-3.82(m, 24H); Found: C, 59.86; H, 9.80; N, 3.85.

Calcd for $C_{18}H_{35}NO_6$: C, 59.81; H, 9.76; N, 3.87. 1b: Yield 73%; bp 125°C/0.02 Torr(Kugelrohr). N-Hexyl-1-aza-2-oxo-18-crown-6(2a) was prepared by the intramolecular cyclization reaction[7] of the corresponding oligoethylene glycol derivative having an amide group in the system of *t*-BuOK/*t*-BuOH in 12% yield as a slightly yellow oil. bp 170°C/0.01 Torr(Kugelrohr); MS, *m/e*(relative intensity) 361(M^+, 24), 262(27), 127(35), 72(43), 56(40), 45(100), 44(50), 43(71); IR(neat) 1640 cm^{-1}($\nu_{C=O}$); ^1H NMR($CDCl_3$) δ 0.90(t, 3H), 1.13-1.62(m, 8H), 3.20-3.80(m, 22H), 4.30+4.36(s+s, 2H); Found: C, 60.04; H, 9.71; N, 4.04. Calcd for $C_{18}H_{35}NO_6$: C, 59.81; H, 9.76; N, 3.87. 2b: Yield 10%; bp 160°C/0.01 Torr(Kugelrohr). The compound 3a having methylene chain spacers between the amide group and the oxyethylene part was also synthesized by the condensation reaction of the diol with an amide group and tetraethylene glycol di-*p*-toluenesulfonate in 7% yield as a slightly yellow oil. bp 220°C/0.01 Torr(Kugelrohr); MS, *m/e*(relative intensity) 417(M^+, 3), 170(75), 84(54), 57(69), 55(40), 45(100), 44(41), 43(77), 42(50), 41(40); IR(neat) 1640 cm^{-1}($\nu_{C=O}$); ^1H NMR($CDCl_3$) δ 0.92(t, 3H), 1.12-2.10(m, 14H), 2.10-2.60(m, 2H), 3.02-3.90(m, 24H); Found: C, 63.59; H, 10.57; N, 3.05. Calcd for $C_{22}H_{43}NO_7$: C, 63.28; H, 10.38; N, 3.35. 3b: Yield, 7%; bp 190°C/0.01 Torr(Kugelrohr). The open chain analog (4a) was prepared by aminolysis of the corresponding methyl ester[8] in 74% yield as a slightly yellow oil. bp 175°C/0.01 Torr(Kugelrohr); MS, *m/e*(relative intensity) 393(M^+, 3), 186(59), 103(43), 59(100), 58(43), 45(35), 44(13), 43(28); IR(neat) 1670 cm^{-1}($\nu_{C=O}$); ^1H NMR($CDCl_3$) δ 0.86(t, 3H), 1.08-1.68(m, 8H), 3.10-3.40(m, 5H), 3.40-3.74(m, 20H), 3.96(s, 2H), 6.94(bs, 1H); Found: C, 57.77; H, 10.15; N, 3.50. Calcd for $C_{19}H_{39}NO_7$: C, 57.99; H, 9.99; N, 3.56. 4b: Yield, 73%; bp 165°C/0.01 Torr(Kugelrohr). All new compounds were purified by silica gel column chromatography after distillation(Kugelrohr).



(1)



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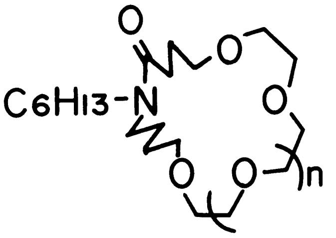

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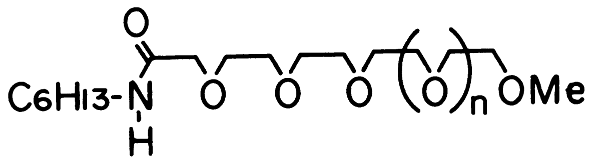

(4)

1a - 4a : n = 2
1b - 4b : n = 1

The complexing ability of crown ethers having an amide group out of the crown ring(1) toward cations was relatively low as shown by the extraction data(Table). These findings would be interpreted by the idea that the nitrogen of amide group bearing a cationic character hinders the access of the cation and the carbonyl oxygen can not coordinate the cation captured in the crown ring. On the other hand, monoamide-type crown ethers having an amide group as the constituent of the crown ring(2) have the possibility of turning the carbonyl oxygen toward the inside of the ring to some extent as suggested by the C.P.K. model examination and so 2a shows the stronger affinity toward cations in comparison with 1a.

The ease of extraction with dibenzo-24-crown-8 had been recognized by Takeda[9] to be Ba^{2+}(ionic radius: 1.35 Å) > K^+(1.33 Å); Na^+(0.95 Å) > Ca^{2+}(0.99 Å) when the cations having similar ionic radii were compared. In addition, the stability constants estimated by the solubility of the complexes in H_2O for dibenzo-18-crown-6[10] and by titration calorimetry in MeOH for both 18-crown-6 and 21-crown-7[11] had been known to display the similar trend. However, 2a showed the following order of complexation(Ba^{2+} > K^+; Ca^{2+} > Na^+), somewhat different from normal crown ethers. The addition effect of $Ca(SCN)_2$ or NaSCN on the ^1H NMR spectral pattern was examined for 1a and 2a in CD_3OD. The combination of 2a and $Ca(SCN)_2$ showed the downfield shift of methylene protons adjacent to the amide group and the distinct splitting of the protons of oligooxyethylene chain, while other combinations(2a and NaSCN; 1a and $Ca(SCN)_2$; 1a and NaSCN) scarcely changed the spectral pattern in the absence of the salt.[12] The stronger affinity toward Ca^{2+} than Na^+ and the cooperation of carbonyl oxygen and oxyethylene chain in 2a were supported by ^1H NMR as well as the extraction experiments. The lower complexing property of 2b in comparison with 2a is ascribed to the decreased binding sites. The affinity toward Ca^{2+} of these compounds seems to agree very closely with that obtained in N-bridged benzimidazolinones.[13,14] It is interesting that the negatively polarized oxygen atom used as the coordination site is common to all these ligands.

Table Extractability(%) of Synthetic Multidentates(1 - 4)[a]

Cation	Ligand 1a	2a	3a	4a	1b	2b	3b	4b
Na^+	5	20	15	9	3	12	12	9
K^+	6	19	16	12	4	14	17	9
Ca^{2+}	5	37	25	4	3	20	26	4
Ba^{2+}	5	43	70	24	5	18	22	14

a. extraction conditions[9]: 25°C; aqueous phase (10 ml): $[M^{n+}(NO_3)n]=1.0 \times 10^{-2}$ M; [Picric acid]=7.0×10^{-3} M. organic phase (CH_2Cl_2, 10 ml): [Ligand]=1.4×10^{-2} M.

In order to clarify the orientation effect of carbonyl oxygen in more detail, we designed the new macrocycles 3 having one amide group which can freely coordinate the cation captured in the ring by using flexible methylene chain spacers according to the C.P.K. model examination. The complexation property of these ligands is rather similar to the corresponding 2; the increased affinity of 3a toward Ba^{2+} and 3b toward Ca^{2+} by introducing spacers seems to display the importance of the orientation of the amide group.

Macrocyclic multidentates are generally recognized to be superior to the corresponding noncyclic analogs in their properties such as the strength of complexation and the selectivity for a variety of cations. However, it is naturally expected that such general trend is not necessarily observed when the orientation of the coordination group becomes one of the most important factors dominating the complexation property. As for noncyclic analogous multidentates, 4 displayed lower complexing ability toward cations in comparison with the corresponding 2 and these trends strongly show the importance of the macrocyclic effect. The extraction of Ca^{2+} was more difficult than that of Na^+ in these open chain analogs(4a and 4b) in accordance with dibenzo-24-crown-8.[9] So, it is noteworthy that the preference of Ca^{2+} to Na^+ is specific for macrocyclic compounds such as 2 and 3.

In conclusion, these findings obtained in this study suggest that introduction of the amide group into the synthetic macrocycles gives the possibility of molecular design of ligands having a novel cation selectivity.

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