Lipophilic Bis(monoaza crown ether) Derivatives: Synthesis and Cation-Complexing Properties

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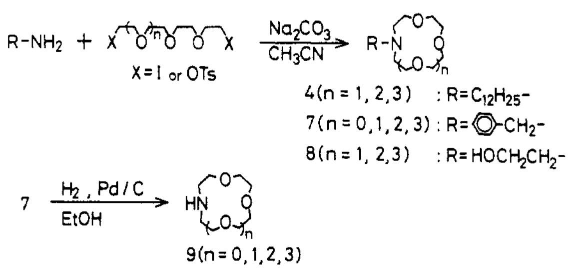
Eleven lipophilic bis(monoaza crown ether) derivatives [**1** and **2** (n = 0–3) and **3** (n = 1–3)] were synthesized, in which two monoaza crown ethers with 9-, 12-, 15-, or 18-membered rings are linked through the nitrogen atoms by an alkane-, diether-, or diester-type bridge chain bearing a dodecyl group. Sodium and potassium binding with the bis(monoaza crown ether) was determined potentiometrically and compared with those for previous bis(crown ethers) **5** (n = 1–3) and corresponding monocyclic analogues **4** and **6** (n = 1–3). Marked bis(crown ether) effect was observed only for the alkane-type bis(monoaza-12-crown-4) and bis(monoaza-15-crown-5) derivatives **1** (n = 1, 2) on complexing Na^+ and K^+, respectively. It was suggested that in some of the other bis(monoaza crown ethers) lariat–ether effect works instead. Bis(monoaza-9-crown-3) derivatives **1** and **2** (n = 0) possess very poor cation-complexing ability. Acidity constant values gave some hints about the bis(crown ether) effect.

Topology of macrocyclic polyethers is expected to contribute strongly to their cation complexation. Adoption of bicyclic structures is a most attractive strategy to enhance cation-complexing abilities and selectivities of monocyclic crown ethers. Macrobicyclic polyethers carrying two crown ether moieties at the end of a short-bridge chain, which are referred to as bis(crown ethers), possess different cation-complexing properties than corresponding monocyclic analogues.[1–4] Bis(crown ethers) are most likely to form intramolecular sandwich-type complexes with particular cations that are a little larger than the crown ring cavities by cooperative action of two adjacent crown rings. As a result of such complex formation, the bis(crown ethers) exhibit excellent selectivities toward the particular cations as compared to the corresponding monocyclic analogues. For instance, bis(15-crown-5)[2–4] and bis(12-crown-4)[5,6] derivatives can be highly selective for K^+ and Na^+, respectively, although the ion selectivities depend on their bridge chain length and configuration. A number of bis(crown ether) derivatives have, therefore, been designed and synthesized so far,[7–10] and various applications of bis(crown ethers) have been developed such as cation separations[2,11] and ion-selective electrodes.[12–18] Bis(crown ethers) with photoresponsive ion selectivities have been designed as well,[19,20] taking advantage of ion-selectivity difference between cis and trans bis(crown ethers).[3]

Scheme I



This bis(crown ether) principle can be extended to monoaza crown ether derivatives in which an oxygen atom in the crown ring is replaced by a nitrogen atom. Bis(monoaza crown ethers) may be easier to synthesize than "conventional" bis(crown ethers) containing only oxygen atoms as the ring heteroatom. Some bis(monoaza crown ethers) are accessible from N-unsubstituted monoaza crown ethers by simple linking of the two crown rings through the nitrogen atoms.[21] We have synthesized various lipophilic bis(monoaza crown ethers) with 9-, 12-, 15-, and 18-membered rings linked by three different bridge chains and evaluated stability constants for their complexes with Na^+ and K^+. We recently communicated excellent, pH-sensitive cation selectivities for some of the bis(monoaza crown ethers) in membrane cation transport.[22] Here we report the syntheses of the lipophilic bis(monoaza crown ether) derivatives and their cation-complexing abilities in a bulk phase. Comparison of the bis(monoaza crown ethers) with previous bis(crown ethers) and corresponding monocyclic analogues is also described.

Results and Discussion

Synthesis. Bis(monoaza crown ethers) **1** and **2** (n = 0–3) and **3** (n = 1–3), which have four different crown rings and three different bridge chains, were synthesized according to Scheme I. The crown rings are monoaza-9-crown-3, -12-crown-4, -15-crown-5, and -18-crown-6. As

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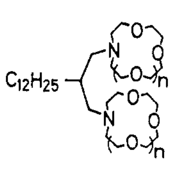
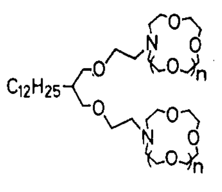


1 (n = 0, 1, 2, 3)



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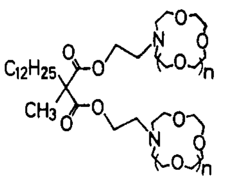
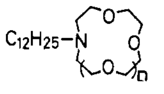
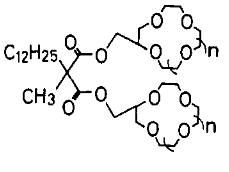


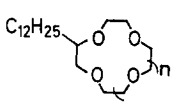
3 (n = 1, 2, 3)



4 (n = 1, 2, 3)



5 (n = 1, 2, 3)

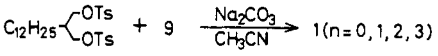


6 (n = 1, 2, 3)

the bridge chain, alkane-, diether-, and diester-type ones were chosen. We have also incorporated a lipophilic dodecyl group into the bridge chains, since high lipophilicity is required for applications of the resulting bis(monoaza crown ethers) as ionophores.

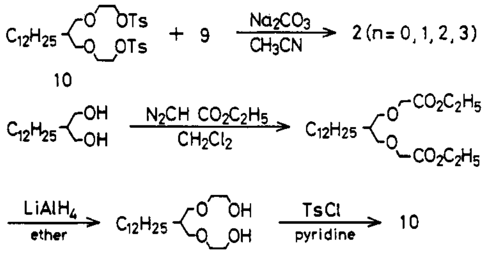
As the starting material for the syntheses of the bis(monoaza crown ethers), unsubstituted and *N*-hydroxyethyl monoaza crown ether derivatives, **9** (*n* = 0–3) and **8** (*n* = 1–3), are needed. Several synthetic approaches for monoaza crown ethers have been described.[23-28] We have adopted the synthetic method for monoaza-12-crown-4 derivatives by Calverley and Dale.[23] The monoaza-12-crown-4 derivatives **8** and **9** (*n* = 1) were obtained according to the previous method.[23] We extended this method to the syntheses of monoaza-9-crown-3, -15-crown-5, and -18-crown-6 derivatives **8** (*n* = 2, 3) and **9** (*n* = 0, 2, 3). Note that in the cyclization reaction to **7** (*n* = 0) an excess of $LiClO_4$ is required for suppressing yield of a byproduct (7,16-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane). Similar reactions using dodecylamine as the amine source afforded *N*-dodecyl monoaza crown ethers **4** (*n* = 1–3), which were employed for comparison with the lipophilic bis(monoaza crown ethers) in the cation-complexing property. All of the monocyclic monoaza crown ethers employed here were isolated and purified by conventional vacuum distillation or Kugelrohr distillation. Another starting material for the syntheses of the bis(monoaza crown ethers) is the bridge chains carrying a dodecyl group, which were prepared in the usual manner.

The alkane-type bis(monoaza crown ethers) **1** (*n* = 0–3) were synthesized by diamination of 2-dodecylpropane-1,3-diol ditosylate with the respective unsubstituted monoaza crown ethers in refluxing acetonitrile in the presence of Na_2CO_3 (reaction 1). This reaction is similar to that



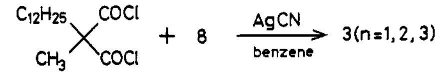
(1)

for previously reported bis(monoaza-12-crown-4) derivatives,[21] which do not carry the long aliphatic chain. In our case, monosubstituted products in which only one end of the bridge chain is aminated were obtained in comparably large quantity, even by 5-day reaction. This might be because the dodecyl group, together with the already incorporated crown ring, interferes sterically with the second amination. Preparative gel permeation chromatography (GPC) yielded oily products of the lipophilic bis(monoaza crown ethers), which were further purified by alumina chromatography. The analogous reactions of 5-dodecyl-3,7-dioxanonane-1,9-diol ditosylate with **9** (*n* = 0–3) afforded the diether-type bis(monoaza crown ethers) **2** (*n* = 0–3) (reaction 2). Reaction 2 generally proceeded a little



(2)

faster than reaction 1, probably due to alleviation of the steric hindrance by the use of the longer and more flexible bridge chain. Bis(monoaza crown ethers) **3** (*n* = 1–3) can be synthesized by reaction of 2-dodecyl-2-methylmalonyl chloride with **8** (*n* = 1–3) in refluxing benzene in the presence of AgCN[29] (reaction 3). The reflux had to be



(3)

continued for 1 week since this reaction is again a sluggish one. We also attempted to use tertiary amines like triethylamine instead of AgCN, but AgCN gave the better result. The crude products of **3** (*n* = 1–3) were also subject to preparative GPC and alumina chromatography. The yields on the final reactions for the bis(monoaza crown ethers) and the corresponding monocyclic analogues are listed in Table I.

Cation-Complexing Abilities. Stability constants (K_s) for Na^+ and K^+ complexation with the lipophilic bis(monoaza crown ethers) and the macrocyclic analogues **1** and **2** (*n* = 0–3) and **3** and **4** (*n* = 1–3) were determined in methanol ($MeOH/H_2O = 95/5$) containing 1.1×10^{-2} mol dm^{-3} tetramethylammonium hydroxide at 25 °C, using the ion-selective electrode method developed by Frensdorff.[30] Previous bis(crown ethers) and their monocyclic analogues containing no nitrogen atom in the crown ring, **5**[6,16] and **6** (*n* = 1–3),[37] were also employed for comparison, but the K_s determination was effected without tetramethylammonium hydroxide. The log K_s values, obtained assuming 1/1 stoichiometry of the crown ether and the cation, are summarized in Table I, together with the selectivity ratios of Na^+/K^+ and K^+/Na^+.

The alkane-type bis(monoaza-12-crown-4) derivative **1** (*n* = 1) showed remarkable bis(crown ether) effect, that is, enhancement in the cation-complexing ability and the ion selectivity for cations that are a little larger than the crown ring cavities by formation of intramolecular sandwich-type complexes. The corresponding monocyclic analogue **4** (*n* = 1) possesses poor cation-complexing abilities for Na^+ and K^+. Specifically, the Na^+ complexation by **1** (*n* = 1) was enhanced by a log K_s value of 2.5 as compared to the corresponding monocyclic analogue. The high Na^+ selectivity against K^+ is noteworthy, exceeding greatly that for **5** (*n* = 1), which is a prominent neutral carrier for Na^+-selective PVC membrane electrodes.[5] Such powerful Na^+ complexation by similar

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Table I. Stability Constants for Na^+ and K^+ Complexation by Bis(monoaza crown ether) Derivatives and Their Analogues[a]

compd	ring size	presence of ring N	yield, %	log K_s		selectivity ratio	
				Na^+	K^+	Na^+/K^+	K^+/Na^+
1 (n = 0)	9	yes	12	1.11	<0.7		
2 (n = 0)	9	yes	31	<0.1	0.80		
1 (n = 1)	12	yes	28	4.24	2.37	75	0.013
2 (n = 1)	12	yes	36	2.63	2.97	0.46	2.2
3 (n = 1)	12	yes	20	1.99	1.95	1.2	0.83
4 (n = 1)	12	yes	50	1.79	1.25	3.4	0.29
5 (n = 1)	12	no	*b*	2.99[e]	2.06[e]	8.3	0.12
6 (n = 1)	12	no	*c*	1.25	2.08	0.15	6.8
1 (n = 2)	15	yes	22	2.72	4.37	0.022	44
2 (n = 2)	15	yes	30	3.89	3.66	1.7	0.60
3 (n = 2)	15	yes	21	3.95	3.73	1.7	0.60
4 (n = 2)	15	yes	54	2.97	2.65	2.1	0.48
5 (n = 2)	15	no	*d*	2.96	5.06	0.0078	130
6 (n = 2)	15	no	*c*	3.13	3.29	0.70	1.4
1 (n = 3)	18	yes	19	3.20	4.83	0.024	42
2 (n = 3)	18	yes	23	4.20	5.80	0.025	40
3 (n = 3)	18	yes	18	4.02	5.52	0.032	32
4 (n = 3)	18	yes	35	3.37	4.79	0.038	26
5 (n = 3)	18	no	*d*	4.00	5.83	0.015	67
6 (n = 3)	18	no	*c*	3.32	4.18	0.14	7.4

[a] Measured in MeOH/H_2O (95/5) and calculated as 1/1 crown ether/metal complexes. [b] Reference 6. [c] Reference 37. [d] Reference 16. [e] 3.26 for Na^+ and 1.73 for K^+ in MeOH.[6]

bis(monoaza-12-crown-4) derivatives without a long aliphatic chain in the bridge chain has also been confirmed by ^{13}C NMR spectroscopy.[21] On the other hand, no remarkable increase in the stability constant for Na^+ was observed for the diether- and diester-type bis(monoaza-12-crown-4) derivatives **2** and **3** (n = 1). An examination of CPK molecular models suggested that the bridge chains for **2** and **3** (n = 1) are a little too long for the formation of their intramolecular sandwich-type complexes with Na^+. As a result, despite of the bis(crown ether) structure, **2** and **3** (n = 1) exhibit only poor Na^+ selectivities over K^+, which are distinct from that for **1** (n = 1). The ion selectivity of Na^+ over K^+ in the **3** (n = 1) system resembles that for the monocyclic analogue **4** (n = 1) and is even reversed in the **2** (n = 1) system. Thus, the kind (or the length) of the bridge chain in the bis(monoaza crown ethers) affects appreciably their bis(crown ether) effect. There seems to be some lariat-ether effect[31] on the cation complexation by the diether- and the diester-type bis(monoaza-12-crown-4) derivatives **2** and **3** (n = 1). The ethereal[25,32] and carbonyl[33] oxygen atoms in the bridge chains may participate in the cation complexation as additional binding sites, thus resulting in the increased stability constants for Na^+ and K^+, especially in the **2** (n = 1) system.

The similar cation-complexing tendency was found in the bis(monoaza-15-crown-5) derivatives, but the bis(crown ether) effect brought about promotion in the complexation of K^+, which exceeds slightly the crown ring cavity in size, instead of Na^+. Excellent K^+ selectivity against Na^+, which is also seen in the previous bis(15-crown-5) derivative **5** (n = 2), was attained only in the alkane-type bis(monoaza-15-crown-5) derivative **1** (n = 2). It seems likely that lariat-ether effect based on the oxygen-containing bridge chains functions in the diether- and diester-type bis(monoaza-15-crown-5) **2** and **3** (n = 2), taking into account their greater stability constants for Na^+ and K^+ than the monocyclic analogues **4** (n = 2). Such lariat-ether effect has also been reported in asymmetrical bis(crown ethers) containing a monoaza-15-crown-5 and a benzo crown ether moieties at the end of an oligooxyethylene chain, in which the benzo crown ether moiety hardly participates in the cation complexation.[34] Due to the concurrent enhancement of Na^+ and K^+ complexation, the K^+ selectivities in **2** and **3** (n = 2) remained poor, the selectivity ratios being quite similar to that for **4** (n = 2). Thus, the selectivity difference between **1** (n = 2) and a group of **2**/**3** (n = 2) is remarkable, reflecting the bridge chain structures of the bis(monoaza-15-crown-5) derivatives.

There seems to be no significant bis(crown ether) effect on Na^+ and K^+ complexation by the bis(monoaza-18-crown-6) derivatives unlike in the 12- and 15-membered ring systems. This is partly because the monocyclic monoaza-18-crown-6 itself possesses high cation-complexing abilities, especially for K^+. It is interesting to note that the alkane-type bis(monoaza-18-crown-6) **1** (n = 3) and the monocyclic analogue **4** (n = 3) have comparable stability constants for Na^+ and K^+. This may suggest that one of the two adjacent crown rings in **1** (n = 3) hardly cooperates with the other one in the cation complexation. The concurrent enhancement of Na^+ and K^+ complexation by **2**, **3**, and **5** (n = 3) might be again attributed to the lariat-ether effect. Also, a possibility about formation of 1/2 bis(crown ether)/cation complexes, in which two cations are complexed independently by the two adjacent crown rings, cannot be denied in the bis(crown ethers) with the 18-membered rings.

The stability constants for the bis(monoaza-9-crown-3) derivatives are very small, probably due to poor cation-complexing ability of the 9-crown-3 cycle itself. One might expect the bis(crown ethers) to show some affinity for Li^+ because of the small crown cavity. In a separate experiment for cation membrane transport through a membrane, however, **1** and **2** (n = 0) proved inactive as ionophores for Li^+ as well as the other alkali metal ions.

Acidity constants (K_a) of the bis(monoaza crown ether) derivatives were determined by pH-metric titration with tetramethylammonium hydroxide methanol/water (90/10)

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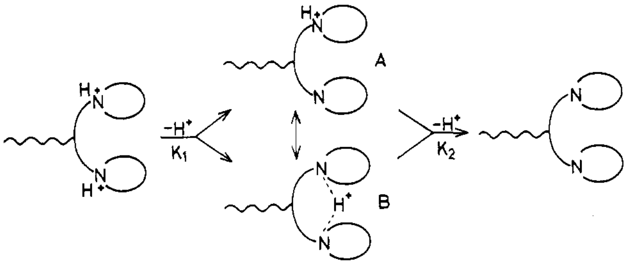
Table II. Acidity Constants of Monoaza Crown Ether Derivatives[a]

compd	pK_a	12-membered ring, (n = 1)	15-membered ring, (n = 2)	18-membered ring, (n = 3)
1	pK_1	5.4	4.1	5.3
	pK_2	9.8	9.7	10.0
2	pK_1	8.3	7.5	8.2
	pK_2	8.6	8.4	8.8
3	pK_1	6.8	6.3	6.8
	pK_2	7.5	7.1	7.8
4	pK	9.0	8.7	9.0

[a] Measured by pH-metric titration in $MeOH/H_2O$ (90/10).

Scheme II



to get some information about the cooperative action of the two adjacent crown rings [bis(crown ether) effect]. Table II shows that any of the bis(monoaza crown ethers) has two K_a values, that is, the first and second acidity constants (K_1, K_2) as observed in the usual α,ω-diaminoalkanes. Very interestingly, the alkane-type bis(monoaza crown ethers) (1 series) are distinct from the diether- and the diester-type ones (2 and 3 series) in that the former ones exhibit great differences between the K_1 and K_2 values. The pK_1 values for 1 are much lower and the pK_2 ones are higher than the pK_a values for the corresponding monocyclic analogues 4. In 2 and 3, which contain the longer bridge chains, the pK_1 values are increased and the differences between pK_1 and pK_2 are decreased as compared to those for 1. This finding suggests that on the monoprotonation of 1 the cyclic species **B**, as illustrated in Scheme II, is preferable to **A** and highly stable on account of the favorable proximity of the two bridgehead nitrogens on the crown rings. The easy cooperation of the crown ring nitrogens on the monoprotonation of 1 may explain partly the marked bis(crown ether) effect on the formation of intramolecular sandwich-type complexes of Na^+ with 1 (n = 1) and K^+ with 1 (n = 2).

Experimental Section

Chemicals. All reagents were the best grade and were used as received unless otherwise specified. Benzene, diethyl ether, pyridine, methanol, and ethanol were distilled over Na, KOH, $Mg(OMe)_2$, and NaOEt, respectively. Acetonitrile and dichloroethane were dried by distillation over P_2O_5. Water was deionized and distilled. Dodecylamine, benzylamine, ethanolamine, and triethanolamine were purified by vacuum distillation. Alkali-metal perchlorates were analytical grade.

Apparatus. Infrared spectra were recorded on a Hitachi 215 grating spectrophotometer. Mass spectra were measured at 70 eV with a Hitachi RMU-6E instrument. ^1H NMR spectra were recorded on a JEOL JMN-PS-100 spectrometer as $CDCl_3$ solutions of 5–10 wt % concentrations. Gel permeation chromatography was conducted on a JAI LC-07 liquid chromatograph with a polystyrene gel column (20 mm × 600 mm, 200/300 mesh, JAI-GEL-2H). The eluent was chloroform, and the flow rate was 3.3 mL min^{-1}. Elemental analyses were achieved on a YANACO MT-2 CHN Corder.

Syntheses. General Procedure for the Preparation of Bis(monoaza crown ether) Derivatives via Reactions 1 and 2. In a dry acetonitrile solution (100 mL) of the unsubstituted monoaza crown ethers (6 mmol) was suspended Na_2CO_3 (25 mmol), and then the mixture was refluxed while stirring mechanically in a nitrogen atmosphere. To the refluxing suspension was added dropwise a dry acetonitrile solution (30 mL) of the dodecylpropanediol or dodecyldioxanonanediol ditosylate (2.7 mmol). After the addition was complete, the mixture was refluxed for 7 days. After the reaction, the mixture was concentrated and then water (100 mL) was added. The solution was extracted with chloroform (50 mL × 3), and the combined extract was dried over Na_2SO_4. The solvent was then removed by rotary evaporation. Gel permeation chromatography affords an oily product of bis(monoaza crown ether) derivative, which was further purified by alumina chromatography with diethyl ether/methanol (98/2).

***N,N'*-(2-Dodecylpropane-1,3-diyl)bis(monoaza-12-crown-4) or *N,N'*-(2-Dodecylpropane-1,3-diyl)bis(1-aza-4,7,10-trioxacyclododecane) (1, *n* = 1).** 2-Dodecylpropane-1,3-diol ditosylate[35] was prepared by $LiAlH_4$ (2 equiv) reduction of diethyl dodecylmalonate in diethyl ether (77%), followed by the conventional tosylation in pyridine (82%). Monoaza-12-crown-4 9 (n = 1)[23] was obtained by Pd/C hydrogenolysis (89%) of the N-benzyl derivative, which in turn was prepared by the cyclization reaction of benzylamine (1 equiv) with 1,11-diiodo-3,6,9-trioxaundecane (1 equiv) in refluxing acetonitrile in the presence of Na_2CO_3 (3 equiv) for 24 h (40%). Compound 1 (n = 1) was prepared by reaction 1 of 2-dodecylpropane-1,3-diol ditosylate and 9 (n = 1). The product was isolated as a colorless oil: 28%; IR (neat) 2900, 2830, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3), 1.08–1.40 [m, 22 H, $(CH_2)_{11}$], 1.48–1.64 (m, 1 H, CH), 2.15–2.48 (m, 4 H, $CHCH_2N$), 2.66 (t, 8 H, $OCH_2CH_2NCH_2CH_2$), 3.50–3.89 (m, 24 H, CH_2OCH_2); MS, m/e (% relative intensity) 558 (M^+, 0.4), 214 (100). Anal. Calcd for $C_{31}H_{62}O_6N_2$: C, 66.63; H, 11.18; N, 5.01. Found: C, 66.27; H, 11.20; N, 5.10.

***N,N'*-(2-Dodecylpropane-1,3-diyl)bis(monoaza-15-crown-5) or *N,N'*-(2-Dodecylpropane-1,3-diyl)bis(1-aza-4,7,10,13-tetraoxacyclopentadecane) (1, *n* = 2).** Monoaza-15-crown-5 9 (n = 2) was obtained in a similar way to 9 (n = 1), using 1,14-diiodo-3,6,9,12-tetraoxatetradecane as the α,ω-diiodooligooxyethylene (88%). Compound 1 (n = 2) was prepared from 9 (n = 2) and 2-dodecylpropane-1,3-diol ditosylate as described in the procedure for reaction 1 and isolated as a colorless oil: 22%; IR(neat) 2920, 2850, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.12–1.44 [m, 22 H, $(CH_2)_{11}$], 1.48–1.62 (m, 1 H, CH), 2.24–2.44 (m, 4 H, $CHCH_2N$), 2.72 (t, 8 H, $OCH_2CH_2NCH_2CH_2O$), 3.52–3.84 (m, 32 H, CH_2OCH_2); MS, m/e (% relative intensity) 646 (M^+, 0.9), 258 (100). Anal. Calcd for $C_{35}H_{70}O_8N_2$: C, 64.98; H, 10.91; N, 4.33. Found: C, 64.94; H, 11.11; N, 4.18.

***N,N'*-(2-Dodecylpropane-1,3-diyl)bis(monoaza-18-crown-6) or *N,N'*-(2-Dodecylpropane-1,3-diyl)bis(1-aza-4,7,10,13,16-pentaoxacyclooctadecane) (1, *n* = 3).** Monoaza-18-crown-6 9 (n = 3) was accessible from 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane in a similar way to 9 (n = 1) (47%). Compound 1 (n = 3), prepared from 9 (n = 3) and 2-dodecylpropane-1,3-diol ditosylate as described in the general procedure for reaction 1, was obtained as a colorless oil: 19%; IR (neat) 2900, 2830, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3), 1.12–1.44 [m, 22 H, $(CH_2)_{11}$], 1.48–1.62 (m, 1 H, CH), 2.16–2.52 (m, 4 H, $CHCH_2N$), 2.70 (t, 8 H, $OCH_2CH_2NCH_2CH_2O$), 3.47–3.88 (m, 40 H, CH_2OCH_2); MS, m/e (% relative intensity) 734 (M^+, 0.6), 302 (100). Anal. Calcd for $C_{39}H_{78}O_{10}N_2$: C, 63.73; H, 10.70; N, 3.81. Found: C, 63.45; H, 10.87; N, 3.87.

***N,N'*-(2-Dodecylpropane-1,3-diyl)bis(monoaza-9-crown-3) or *N,N'*-(2-Dodecylpropane-1,3-diyl)bis(1-aza-4,7-dioxacyclononane) (1, *n* = 0).** Monoaza-9-crown-3 9 (n = 0) was synthesized with a modification to the procedure for 1 (n = 1), using 3,6-dioxaoctane-1,8-diol ditosylate (31%). On the cyclization reaction for 7 (n = 0), $LiClO_4$ (6 equiv) was added to the reaction system to raise the yield. Compound 1 (n = 0), prepared as described in the general procedure for reaction 1, was isolated as a colorless oil: 12%; IR (neat) 2900, 2820, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.16–1.52 [m, 22 H, $(CH_2)_{11}$], 1.56–1.66 (m, 1 H, CH), 2.47 (t, 4 H, $CHCH_2N$), 2.77 (t, 8 H, $OCH_2CH_2NCH_2CH_2$), 3.68–3.87 (m, 16 H, CH_2OCH_2); MS, m/e (% relative intensity) 470 (M^+, 0.7), 170 (100). Anal. Calcd for

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[35] Skarżewski, J.; Młochowski, J. *Tetrahedron* **1983**, *39*, 309–312.

$C_{27}H_{54}O_4N_2$: C, 68.94; H, 11.49; N, 5.96. Found: C, 69.16; H, 11.50; N, 6.05.

(5-Dodecyl-3,7-dioxanonane-1,9-diyl)bis(monoaza-12-crown-4) or (5-Dodecyl-3,7-dioxanonane-1,9-diyl)bis(1-aza-4,7,10-trioxacyclododecane) (2, *n* = 1). 5-Dodecyl-3,7-dioxanonane-1,9-diol ditosylate (**10**) was obtained in the following way. Reaction of 2-dodecylpropane-1,3-diol (1 equiv) with ethyl diazoacetate (2.2 equiv) in dry 1,2-dichloroethane in the presence of BF_3OEt_2 for 1 h at room temperature and then for 2 h at the refluxing temperature gave diethyl 5-dodecyl-3,7-dioxanonane-1,9-dioate (51%).[36] The diacid ester (1 equiv) was then reduced by $LiAlH_4$ (2 equiv) in ethyl ether to yield 5-dodecyl-3,7-dioxanonane-1,9-diol (80%), which was converted to the corresponding ditosylate **10** in the usual fashion (80%). Compound **2** (*n* = 1) was prepared from **9** (*n* = 1) and **10** as described in the general procedure for reaction 2 and was isolated as a colorless oil: 36%; IR (neat) 2920, 2850, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.14–1.48 [m, 22 H, $(CH_2)_{11}$], 1.66–1.88 (m, 1 H, CH), 2.64–2.84 (m, 12 H, CH_2N), 3.37 (t, 4 H, $CHCH_2OCH_2$), 3.54 (d, 4 H, $CHCH_2O$), 3.60–3.82 (m, 24 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 646 (M^+, 4), 188 (100). Anal. Calcd for $C_{35}H_{70}O_8N_2$: C, 64.98; H, 10.91; N, 4.33. Found: C, 64.56; H, 11.05; N, 4.45.

***N,N'*-(5-Dodecyl-3,7-dioxanonane-1,9-diyl)bis(monoaza-15-crown-5) or *N,N'*-(5-Dodecyl-3,7-dioxanonane-1,9-diyl)-bis(1-aza-4,7,10,13-tetraoxacyclopentadecane) (2, *n* = 2).** Reaction 2 of **9** (*n* = 2) with **10** afforded compound **2** (*n* = 2) as a colorless oil: 30%; IR (neat) 2900, 2840, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.14–1.44 [m, 22 H, $(CH_2)_{11}$], 1.64–1.87 (m, 1 H, CH), 2.64–2.86 (m, 12 H, CH_2N), 3.36 (t, 4 H, $CHCH_2OCH_2$), 3.53 (d, 4 H, $CHCH_2O$), 3.59–3.82 (m, 32 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 735 (M^+, 3), 232 (100). Anal. Calcd for $C_{39}H_{78}O_{10}N_2$: C, 63.73; H, 10.70; N, 3.81. Found: C, 63.82; H, 10.78; N, 3.84.

***N,N'*-(5-Dodecyl-3,7-dioxanonane-1,9-diyl)bis(monoaza-18-crown-6) or *N,N'*-(5-Dodecyl-3,7-dioxanonane-1,9-diyl)-bis(1-aza-4,7,10,13,16-pentaoxacyclooctadecane) (2, *n* = 3).** Reaction 2 of **9** (*n* = 3) with **10** afforded compound **2** (*n* = 3) as a colorless oil: 23%; IR (neat) 2900, 2830, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.12–1.45 [m, 22 H, $(CH_2)_{11}$], 1.66–1.86 (m, 1 H, CH), 2.66–2.92 (m, 12 H, CH_2N), 3.38 (t, 4 H, $CHCH_2OCH_2$), 3.53 (d, 4 H, $CHCH_2O$), 3.58–3.82 (m, 40 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 823 (M^+, 3), 276 (100). Anal. Calcd for $C_{43}H_{86}O_{12}N_2$: C, 62.74; H, 10.53; N, 3.40. Found: C, 62.46; H, 10.56; N, 3.47.

***N,N'*-(5-Dodecyl-3,7-dioxanonane-1,9-diyl)bis(monoaza-9-crown-3) or *N,N'*-(5-Dodecyl-3,7-dioxanonane-1,9-diyl)-bis(1-aza-4,7-dioxanonane) (2, *n* = 0).** Reaction 2 of **9** (*n* = 0) with **10** afforded compound **2** (*n* = 0) as a colorless oil: 31%; IR (neat) 2900, 2840, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3), 1.16–1.48 [m, 22 H, $(CH_2)_{11}$], 1.70–1.89 (m, 1 H, CH), 2.82 (t, 4 H, $CHCH_2OCH_2CH_2N$), 2.91 (t, 8 H, CH_2N), 3.42 (t, 4 H, $CHCH_2OCH_2$), 3.53 (t, 4 H, $CHCH_2O$), 3.68–3.88 (m, 16 H, CH_2OCH_2); MS, *m/e* (% relative intensity) 558 (M^+, 1.1), 144 (100). Anal. Calcd for $C_{31}H_{62}O_6N_2$: C, 66.67; H, 11.11; N, 5.02. Found: C, 66.30; H, 11.33; N, 5.16.

General Procedure for the Preparation of Bis(monoaza crown ether) via Reaction 3.[16] In a dry benzene solution (200 mL) of the *N*-hydroxyethyl monoaza crown ethers (7 mmol) was placed AgCN[29] (10 mmol), and the mixture was stirred mechanically at room temperature for 1 h. To the suspension was added dropwise a dry benzene solution (30 mL) of 2-dodecyl-2-methylmalonyl chloride (3 mmol). The mixture was then refluxed in the dark for 7 days. After the reaction the mixture was filtered, the filtrate was passed through a short Celite column. The solution obtained was concentrated, and then water (100 mL) was added. The solution was extracted with chloroform (50 mL × 3), and the combined extract was dried over Na_2SO_4. The solvent was then evaporated off. The similar workup of the crude product by the chromatography to that for reactions 1 and 2 yielded an analytically pure product.

***N,N'*-(5-Dodecyl-5-methyl-4,6-dioxo-3,7-dioxanonane-1,9-diyl)bis(monoaza-12-crown-4) or 2,2-Bis[[2-(1-aza-4,7,10-trioxacyclododecyl)ethoxy]carbonyl]tetradecane (3, *n* = 1).** 2-Dodecyl-2-methylmalonyl chloride[16] was obtained by treating the corresponding malonic acid with thionyl chloride in benzene. *N*-Hydroxyethyl monoaza 12-crown-4 **8** (*n* = 1) was prepared by the cyclization reaction of ethanolamine (1 equiv) with 1,11-diiodo-3,6,9-trioxaundecane (1 equiv) in refluxing acetonitrile in the presence of Na_2CO_3 (3.8 equiv) for 24 h (32%). Compound **3** (*n* = 1) was prepared from the malonyl chloride and **8** (*n* = 1) as described in the general procedure for reaction 3 and was isolated as a colorless oil: 20%; IR (neat) 2910, 2840, 1720, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, CH_3CH_2), 1.04–1.32 [m, 20 H, $(CH_2)_{10}$], 1.38 (s, 3 H, CH_3C), 1.70–1.92 (m, 2 H, CH_2C), 2.69–2.90 (m, 12 H, CH_2N), 3.55–3.80 (m, 24 H, CH_2OCH_2), 4.22 (t, 4 H, $COOCH_2$); MS, *m/e* (% relative intensity) 688 (M^+, 0.3), 188 (100). Anal. Calcd for $C_{36}H_{68}O_{10}N_2$: C, 62.76; H, 9.95; N, 4.07. Found: C, 62.66; H, 9.99; N, 4.23.

***N,N'*-(5-Dodecyl-5-methyl-4,6-dioxo-3,7-dioxanonane-1,9-diyl)bis(monoaza-15-crown-5) or 2,2-Bis[[2-(1-aza-4,7,10,13-tetraoxacyclopentadecyl)ethoxy]carbonyl]tetradecane (3, *n* = 2).** *N*-Hydroxyethyl monoaza 15-crown-5 **8** (*n* = 2) was obtained in a similar way to **8** (*n* = 1) (19%). Compound **3** (*n* = 2), prepared from the malonyl chloride and **8** (*n* = 2) as described in the procedure for reaction 3, was isolated as a colorless oil: 21%; IR (neat) 2915, 2850, 1725, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3CH_2), 1.12–1.32 [m, 20 H, $(CH_2)_{10}$], 1.37 (s, 3 H, CH_3C), 1.68–1.92 (m, 2 H, CH_2C), 2.76 (t, 12 H, CH_2N), 3.52–3.82 (m, 32 H, CH_2OCH_2), 4.15 (t, 4 H, $COOCH_2$); MS, *m/e* (% relative intensity) 776 (M^+, 0.7), 232 (100). Anal. Calcd for $C_{40}H_{76}O_{12}N_2$: C, 61.83; H, 9.86; N, 3.61. Found: C, 61.64; H, 9.95; N, 3.69.

***N,N'*-(5-Dodecyl-5-methyl-4,6-dioxo-3,7-dioxanonane-1,9-diyl)bis(monoaza-18-crown-6) or 2,2-Bis[[2-(1-aza-4,7,10,13,16-pentaoxacyclooctadecyl)ethoxy]carbonyl]tetradecane (3, *n* = 3).** *N*-Hydroxyethyl monoaza 18-crown-6 **8** (*n* = 3) was obtained in a similar way to **8** (*n* = 1) (14%). Reaction 3 of **8** (*n* = 3) with the malonyl chloride afforded compound **3** (*n* = 3) as a colorless oil: 18%; IR (neat) 2920, 2850, 1730, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, CH_3CH_2), 1.08–1.32 [m, 20 H, $(CH_2)_{10}$], 1.38 (s, 3 H, CH_3C), 1.66–1.92 (m, 2 H, CH_2C), 2.82 (t, 12 H, CH_2N), 3.47–3.81 (m, 40 H, CH_2OCH_2), 4.19 (t, 4 H, $COOCH_2$); MS, *m/e* (% relative intensity) 864 (M^+, 0.5), 276 (100). Anal. Calcd for $C_{44}H_{84}O_{14}N_2$: C, 61.09; H, 9.79; N, 3.24. Found: C, 60.71; H, 9.99; N, 3.46.

Preparation of *N*-Dodecyl Monoaza Crown Ethers 4 (*n* = 1–3). *N*-Dodecyl-monoaza-12-crown-4 [**4** (*n* = 1), 50%], -monoaza-15-crown-5 [**4** (*n* = 2), 54%], and -monoaza-18-crown-6 [**4** (*n* = 3), 35%] were prepared by the cyclization reaction of dodecylamine with the appropriate α,ω-diiodooligooxyethylene in refluxing acetonitrile in the presence of Na_2CO_3 for 30 h, according to the procedure in the literature.[23]

Preparation of Lipophilic Bis(crown ethers) 5 (*n* = 1–3) and Their Monocyclic Analogues 6 (*n* = 1–3). The syntheses for compounds **5** (*n* = 1–3) have been already reported elsewhere.[6,16] Compounds **6** (*n* = 1–3) were prepared by the cyclization reaction of tetradecane-1,2-diol with an appropriate oligo(ethylene glycol) ditosylate in refluxing dioxane in the presence of LiH or NaH, with a modification to the procedure in the literature.[37]

Stability Constants. The procedure for the stability constant measurements with ion-selective electrodes is the same as the Frensdorff's,[30] except for that the ideal Nernstian slope (59.16 mV per 10-time activity change) was not necessarily adopted for the calculation. Before each set of emf measurements, calibration of ion-selective electrodes was made against known concentrations of metal perchlorates to obtain a corrected slope (varying from 50 to 60 mV) for Nernst equation. In that case, the straight lines in the calibration plots possess correlation coefficient of at least 0.9999. The emf measurements were conducted at 25 °C by using a Corning Model 130 pH/mV meter. The electrodes employed were a Na^+-selective glass electrode (TOKO 1100 Na^+), a K^+-selective glass electrode (TOKO 1200 K^+), and a Ag/AgCl reference electrode (TOKO CR-501C) containing 1.0 mol dm^{-3} NH_4Cl as the internal solution. The measuring solvent was methanol/water (95/5). For the monoaza crown ether (**1**–**4**) systems,

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[36] Ammann, D.; Bissig, R.; Güggi, M.; Pretsch, E.; Simon, W. *Helv. Chim. Acta* **1975**, *58*, 1535–1548.

[37] Bowsher, B. R.; Rest, A. J.; Main, B. G. *J. Chem. Soc., Dalton Trans.* **1984**, 1421–1425.

J. Org. Chem. **1986**, *51*, 4979–4983

tetramethylammonium hydroxide of 1.1 × 10^{-2} mol dm^{-3} was contained in the measuring solvent to exclude the protonation of the nitrogen bridgehead. To 15 mL of 1 × 10^{-3} mol dm^{-3} alkali-metal perchlorate solution was added 0.3 mL of 5 × 10^{-3} mol dm^{-3} crown ether solution. Thereafter, 0.3 mL of the crown ether solution was added at each time until the total added volume was 6 mL. The emf readings were made after 4-min stirring of the solution at each addition. The microcomputer for the data processing was NEC PC-8801 mK II.

Acidity Constants. The pH-metric titration was carried out at 25 °C in methanol/water (90/10) under a nitrogen atmosphere, using a mV/pH meter (TOKO TP1000), a pH electrode (HORIBA 1026A), and a Ag/AgCl reference electrode (IWAKI IW 067). The ion strength was kept at 0.1 during the titration. The starting solutions contained 5 × 10^{-3} mol dm^{-3} crown ether, 7.75 × 10^{-2} mol dm^{-3} tetramethylammonium chloride, and 2.25 × 10^{-2} mol dm^{-3} HCl. To 10 mL of the solution was added the titrant containing 5.5 × 10^{-2} mol dm^{-3} tetramethylammonium hydroxide by 0.1-mL portions. The acidity constants, defined by the following equations, were calculated by using the microcomputer:

$$K_1 = [\mathrm{CrH}^+][\mathrm{H}^+]/[\mathrm{CrH_2}^{2+}] \qquad K_2 = [\mathrm{Cr}][\mathrm{H}^+]/[\mathrm{CrH}^+]$$

CrH_2^{2+}, CrH^+, and Cr stand for diprotonated, monoprotonated, deprotonated crown ethers, respectively.

Registry No. **1** ($n = 0$), 105040-36-6; **1** ($n = 1$), 102069-55-6; **1** ($n = 2$), 102069-56-7; **1** ($n = 3$), 102069-57-8; **2** ($n = 0$), 105040-37-7; **2** ($n = 1$), 105064-10-6; **2** ($n = 2$), 105040-38-8; **2** ($n = 3$), 105040-39-9; **3** ($n = 1$), 105040-40-2; **3** ($n = 2$), 105040-41-3; **3** ($n = 3$), 105040-42-4; **4** ($n = 1$), 102069-58-9; **4** ($n = 2$), 75006-56-3; **4** ($n = 3$), 75006-60-9; **5** ($n = 1$), 80403-59-4; **5** ($n = 2$), 87505-87-1; **5** ($n = 3$), 91787-47-2; **6** ($n = 1$), 102725-12-2; **6** ($n = 2$), 74649-89-1; **6** ($n = 3$), 83255-15-6; **7** ($n = 0$), 84761-08-0; **7** ($n = 1$), 84227-47-4; **7** ($n = 2$), 71089-11-7; **7** ($n = 3$), 63281-62-9; **8** ($n = 1$), 84227-48-5; **8** ($n = 2$), 81331-60-4; **8** ($n = 3$), 81331-61-5; **9** ($n = 0$), 7234-71-1; **9** ($n = 1$), 41775-76-2; **9** ($n = 2$), 66943-05-3; **9** ($n = 3$), 33941-15-0; **10**, 105040-45-7; Na, 7440-23-5; K, 7440-09-7; diethyl dodecylmalonate, 7252-87-1; 2-dodecylpropane-1,3-diol ditosylate, 71366-37-5; benzylamine, 100-46-9; dodecylamine, 124-22-1; ethanolamine, 141-43-5; 3,6-dioxaoctane-1,8-diol ditosylate, 36839-55-1; 1,11-diiodo-3,6,9-trioxaundecane, 37860-51-8; 1,14-diiodo-3,6,9,12-tetraoxatetradecane, 41024-91-3; 1,17-diiodo-3,6,9,12,15-pentaoxaheptadecane, 42749-27-9; 2-dodecylpropane-1,3-diol, 10395-09-2; ethyl diazoacetate, 623-73-4; diethyl 5-dodecyl-3,7-dioxanonan-1,9-oate, 105040-46-8; 5-dodecyl-3,7-dioxanonane-1,9-diol, 105040-47-9; tosyl chloride, 98-59-9; 2-dodecyl-2-methylmalonyl chloride, 87505-86-0.

Selective 1,4-Reduction of Chalcone with Anthracene Hydride via Base-Induced Fragmentation of Their Michael Adduct[1]

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Chalcone (**1**) and "anthracene hydride" (AH^-) form rapidly the anionic Michael adduct **2** in high yield along with the known dimerization product **5** of **1**. Prolonged reaction in the presence of an excess of AH^- converts **2** into anthracene A and the enolate **7** of the saturated ketone **8**. Reactions with other substrates show that the partial structure ArCCCO is necessary for this disproportionative fragmentation. This points to the intermediacy in the fragmentation of the enone dianion (e.g., 1^{2-}), with the β-aryl group stabilizing the second negative charge. The analogously formed Michael adduct of xanthene XH and **1** does not undergo fragmentation, indicating that a removable hydrogen in the proper position is necessary for the formation of the saturated carbonyl compound from its Michael adduct. Reduction of the carbonyl function could not be detected in any one of the reactions.

Anthracene hydride (AH^-; anion of 9,10-dihydroanthacene) is a conveniently prepared member of the so-called arene hydrides, formal adducts of an arene and a hydride ion.[2] It has been shown to be a strong reducing agent.[2] We report now on the selective reduction of the C=C double bond of chalcone (**1**) by AH^-. The mechanism involved may be considered to exclude any carbonyl reduction. This mechanism may perhaps also have some bearing on the mechanism of the reduction of carbonyl-conjugated C=C bonds by formate ion.[3] Selective reduction of the C=C double bond of chalcone and similar α,β-unsaturated monocarbonyl compounds has been described for special techniques[4] while the more familiar methods give usually product mixtures from competing reduction of C=C and C=O bonds.

Our experimental results are shown in Table I and Scheme I. AH^- and the other carbanionic reagents were generated in THF from 9,10-dihydroanthracene (AH_2) or from the respective precursors and butyllithium.[2] An excess of AH^- reduced **1** to 82% saturated ketone **8** and 17% **5** (entry 1). The formation of **8** is obviously coupled with an oxidation of AH^- to anthracene A that was found in more than 74% yield. **5** (mixture of two stereoisomers) is certainly formed by single-electron transfer from AH^- to **1**, followed by dimerization of the so-generated radical anion $1^{\bullet-}$. The dimer **4** undergoes cyclization to **5** that could be quantitatively dehydrated to **6** by dissolving in trifluoroacetic acid. A one-electron-reduction pathway[6] and the structures of **5**[6] and **6**[7] have been confirmed previously. Furthermore, we obtained 97% of **5** from **1** and the radical anion $A^{\bullet-}$ of anthracene in THF, probably the best method to prepare **5**.

When the reaction of **1** with an excess of AH^- was quenched with glacial acetic acid after 5 min (entry 2), roughly the same amount of **5** was isolated along with 78%

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