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SYNTHESIS OF LARIAT DIAZACROWN ETHERS WITH TERMINAL AMINO GROUPS IN THE SIDE CHAINS

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Treatment of diazacrown ethers with N-(haloalkyl)- and N-(haloethoxy)phthalimides gives the corresponding N,N'- substituted diazacrown ether. Hydrazinolysis of the latter then gives diazacrown ethers with terminal primary amino groups in the side chain. Their reductive methylation using formaldehyde in formic acid gives the dimethylamino derivatives. The presence of a lariat effect was demonstrated by treating the compounds obtained with picrates of alkali and alkaline-earth metals.

Keywords: diazacrown ethers, N,N'-substituted, terminal amino groups, lariat effect.

Crown ethers with functional donor groups in the side chain (lariat crown ethers) form, in many cases, stronger complexes with metal cations than their unsubstituted analogs and show highly selective complex formation [1-3]. As a rule this is due to the participation of a donor group side chain in the complex formation with the cation. For specific structural compliances this can react with the cation found in the crown ether cavity involving axial positions (the lariat effect) and establish a three dimensional ligand environment around it [4-6]. One of the factors deciding the complex forming properties of the lariat crown ethers is the nature of the side chain donor groups. Among the large group of synthesized lariat azacrown ethers the least studied are compounds having a terminal amino group in the side chain [4]. Such compounds form stable complexes both with hard alkali and alkaline-earth ions and also with weak transition and certain other metal ions [7-10]. In this connection we have synthesized novel substituted diazacrown ethers with terminal amino groups in the side chain and qualitatively assessed the existence of the lariat effect in their reaction with alkali and alkaline-earth metal picrates.

Lariat azacrown ethers with amino groups in the side chain are usually prepared by the acylation of azacrown ethers with activated derivatives of α-amino acids, by alkylation with α-halo acid N,N-dialkylamides and subsequent reduction of the obtained compounds with lithium aluminium hydride or diborane [7, 8], by alkylation of primary amine or secondary diamines with the corresponding dihalides or ditosylates [11, 12], and also by the addition of azacrown ethers to acrylonitrile and reduction of the nitrile group [10]. An interesting method for the preparation of lariat aza- and diazacrown ethers based on compounds with a benzotriazole group in the side chain has been presented [6]. All of the listed methods are not comprehensive since they do not allow the introduction of side chains with varying bond length and nature of functional group.

We propose a synthetic route which, in our view, is the most rational and general method for the preparation of substituted azacrown ethers with terminal amino groups in the side chain.

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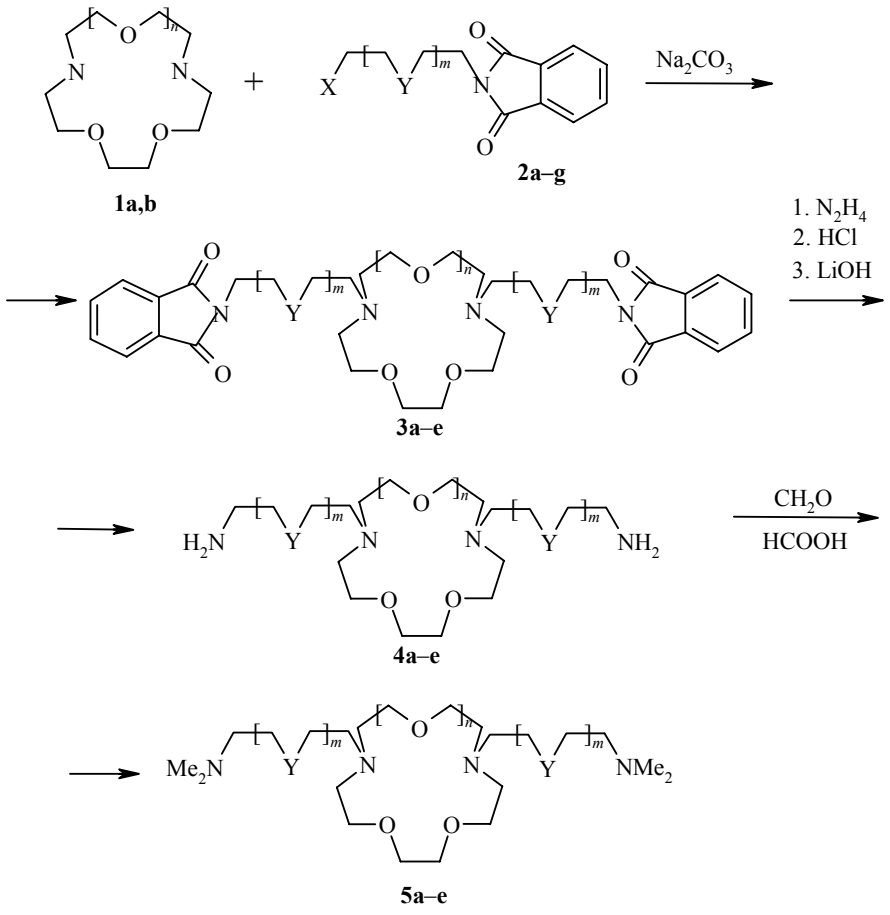

1, **3–5 a** n = 1, **b** n = 2; **2a**,**b–5a**,**b m** = 0; **2c–5c** m = 1, Y = $(CH_2)_2$;
2d–5d m = 1, Y = 0; **2e–5e** m = 2, Y = 0; **2a** X = Br, **b–d** X = Cl, **e–g** X = I

The synthesis of the N,N'-substituted diazacrown ethers **3a-e** was carried out by treating diaza-15-crown-5 (**1a**) or diaza-18-crown-6 (**1b**) with N-(2-bromoethyl)- (**2a**), N-(6-iodohexyl)- (**2e**), N-[2-(2-iodoethoxy)ethyl]- (**2f**), and N-{2-[2-(iodoethoxy)ethoxy]ethyl}phthalimides (**2g**). Reaction of diazacrown ethers **1a,b** with phthalimide **2a** in acetonitrile in the presence of sodium carbonate gives the N,N'-[(2-phthalimido)ethyl]diaza-15-crown-5 (**3a**) and N,N'-[(2-phthalimido)ethyl]diaza-18-crown-6 (**3b**) in low yield. Carrying out the same reaction without solvent at 100°C gives a markedly higher yield of compounds **3a,b**. By contrast, this alkylation of the diazacrown ethers **1a,b** by the iodides **2f-g** under similar conditions did not give satisfactory results. Good yields were obtained when this reaction was carried out in refluxing acetonitrile over 18 h in the presence of sodium carbonate. The increased heating time lowers the yield of the target products, evidently as a result of the partial quaternization of the alkylation product.

The starting iodides **2e-g** were synthesized from N-(6-chlorohexyl)- (**2b**), N-[2-(2-chloroethoxy)ethyl]- (**2c**), and N-{2-[2-(chloroethoxy)ethoxy]ethyl}phthalimides (**2d**) by refluxing them with sodium iodide in acetonitrile. The bromide **2a** and chlorides **2b-d** were prepared by treating potassium phthalimide with dibromoethane, 1,6-dichlorohexane, 1-chloro-2-(2-chloroethoxy)ethane, and 1-chloro-2-[2-(chloroethoxy)-ethoxy]ethane respectively.

Treatment of hydrazine hydrate with the diazacrown ethers **3a-e** gave 70-85% yields of the lariat diazacrown ethers **4a-e** which contain terminal primary amino groups in the side chains. The diazacrown ethers with terminal dimethylamino groups **5a-e** were prepared by reductive methylation of compounds **4a-e** *via* reaction with formaldehyde in formic acid.

TABLE 1. Characteristics of the N,N'- Substituted Diazacrown Ethers **3-5**

Compound	Empirical formula	Found, % / Calculated, %			Mass spectrum, *m/z*	^{1}H NMR spectrum($CDCl_3$), δ, ppm, spin-spin coupling (*J*, Hz)	Yield, %
		C	H	N			
3a	$C_{30}H_{36}N_4O_7$	63.82 / 63.74	6.43 / 6.52	9.92 / 9.86	564	2.6 (8H, m, NCH_2); 2.9 (4H, t, *J* = 6.9, NCH_2); 3.4 (8H, m, OCH_2); 3.5 (4H, s, OCH_2); 3.6 (4H, t, *J* = 6.9, CH_2N); 7.7 (8H, m, C_6H_4)	61
3b	$C_{32}H_{40}N_4O_8$	63.14 / 63.13	6.62 / 6.69	9.20 / 9.17	608	2.7 (8H, t, *J* = 6.1, NCH_2); 2.9 (4H, t, *J* = 7.0, NCH_2); 3.4 (8H, m, OCH_2); 3.5 (8H, s, OCH_2); 3.7 (4H, t, *J* = 7.0, CH_2N); 7.7 (8H, m, C_6H_4)	87
3c	$C_{40}H_{56}N_4O_8$	66.64 / 66.70	7.83 / 7.85	7.77 / 7.72	720	1.4 (16H, m, CH_2); 2.6 (12H, m, NCH_2); 3.5 (16H, m, OCH_2); 3.8 (4H, t, *J* = 7.2, CH_2N); 7.7 (8H, m, C_6H_4)	40
3d	$C_{36}H_{48}N_4O_{10}$	62.06 / 62.11	6.94 / 6.93	8.04 / 8.02	696	2.7 (12H, m, NCH_2); 3.5 (24H, m, OCH_2); 3.8 (4H, t, *J* = 5.8, CH_2N); 7.7 (8H, m, C_6H_4)	65
3e	$C_{40}H_{56}N_4O_{12}$	61.21 / 61.27	7.19 / 7.13	7.14 / 7.16	784	2.7 (12H, m, NCH_2); 3.5 (32H, m, OCH_2); 3.8 (4H, t, *J* = 5.8, CH_2N); 7.7 (8H, m, C_6H_4)	48
4a	$C_{14}H_{32}N_4O_3$	55.24 / 55.16	10.59 / 10.62	18.40 / 18.50	304	1.5 (4H, br. s , NH); 2.5 (12H, m, NCH_2); 2.8 (4H, m, $\underline{CH_2}NH_2$); 3.4 (8H, m, OCH_2); 3.6 (4H, s, OCH_2)	84
4b	$C_{16}H_{36}N_4O_4$	55.15 / 55.20	10.41 / 10.37	16.08 / 16.13	348	1.6 (4H, br. s , NH); 2.6 (12H, m, NCH_2); 2.8 (4H, m, $\underline{CH_2}NH_2$); 3.4 (8H, t, *J* = 6.2, OCH_2); 3.5 (8H, s, OCH_2)	75
4c	$C_{24}H_{52}N_4O_4$	62.57 / 62.63	11.38 / 11.43	12.16 / 12.11	460	1.1 (4H, br. s , NH); 1.3 (16H, m, CH_2); 2.4 (12H, m, NCH_2); 2.6 (4H, m, $\underline{CH_2}NH_2$); 3.5 (16H, m, OCH_2)	85
4d	$C_{20}H_{44}N_4O_6$	55.02 / 55.05	10.16 / 10.12	12.83 / 12.75	436	1.5 (4H, br. s , NH); 2.5 (8H, t, *J* = 6.2, NCH_2); 2.6 (4H, t, *J* = 5.8, NCH_2); 2.8 (4H, t, *J* = 5.8, $\underline{CH_2}NH_2$); 3.3 (8H, t, *J* = 6.2, OCH_2); 3.5 (16H, m, OCH_2)	70
4e	$C_{24}H_{52}N_4O_8$	54.94 / 54.93	9.99 / 9.95	10.68 / 10.59	524	1.9 (4H, br. s , NH); 2.5 (8H, t, *J* = 6.2, NCH_2); 2.6 (4H, t, *J* = 5.8, NCH_2); 2.8 (4H, t, *J* = 5.8, $\underline{CH_2}NH_2$); 3.3 (8H, t, *J* = 6.2, OCH_2); 3.5 (24H, m, OCH_2)	79
5a	$C_{18}H_{40}N_4O_3$	59.97 / 59.91	11.18 / 11.25	15.54 / 15.48	360	2.2 (12H, s, CH_3); 2.5 (16H, m, NCH_2); 3.4 (8H, m, OCH_2); 3.5 (4H, s, OCH_2)	85
5b	$C_{20}H_{44}N_4O_4$	59.37 / 59.44	10.96 / 10.89	13.85 / 13.87	404	2.2 (12H, s, CH_3); 2.5 (16H, m, NCH_2); 3.4 (8H, t, *J* = 6.2, OCH_2); 3.5 (8H, s, OCH_2)	63
5c	$C_{28}H_{60}N_4O_4$	65.07 / 65.11	11.70 / 11.76	10.84 / 10.77	516	1.3 (16H, m, CH_2); 2.1 (12H, s, CH_3); 2.4 (16H, m, NCH_2); 3.4 (8H, t, *J* = 6.2, OCH_2); 3.5 (8H, s, OCH_2)	77
5d	$C_{24}H_{52}N_4O_6$	58.51 / 58.47	10.64 / 10.71	11.37 / 11.32	492	2.2 (12H, s, CH_3); 2.5 (12H, m, NCH_2); 2.7(4H, t, *J* = 5.8, NCH_2); 3.4 (8H, t, *J* = 6.2, OCH_2); 3.5 (16H, m, OCH_2)	75
5e	$C_{28}H_{60}N_4O_8$	57.90 / 57.85	10.41 / 10.43	9.65 / 9.62	580	2.2 (12H, s, CH_3); 2.5 (8H, t, *J* = 6.2, NCH_2); 2.6 (4H, t, *J* = 5.8, NCH_2); 2.8 (4H, m, NCH_2); 3.4 (8H, t, *J* = 6.2, OCH_2); 3.5 (24H, m, OCH_2)	63

TABLE 2. Maximum Positions (λ_{max}) and Relative Shifts ($\Delta\lambda_{max}$)* of the Metal Picrate Absorption Bands in the Presence of One Hundred Fold Excess of Compounds **1b**, **4**, **5b-e** and **6** in THF.

Compound	LiPi		NaPi		KPi		MgPi		CaPi	
	λ_{max}	$\Delta\lambda_{max}$	λ_{max}	$\Delta\lambda_{max}$	λ_{max}	$\Delta\lambda_{max}$	λ_{max}	$\Delta\lambda_{max}$	λ_{max}	$\Delta\lambda_{max}$
1b	357	10	—	—	364	5	359	32	358	23
4b	379	32	380	27	380	21	376	49	378	43
4c	—	—	—	—	—	—	380	53	390	45
4d	380	33	380	27	380	20	380	53	380	45
4e	378	31	376	23	379	19	377	50	379	44
5b	378	31	380	27	378	18	375	47	378	43
5c	—	—	—	—	—	—	358	31	—	—
5d	370	17	368	20	370	11	370	43	373	38
5e	378	32	379	26	379	21	376	48	374	39
6	349	3	358	5	—	—	356	30	352	17

* $\Delta\lambda_{max}$ is the difference in position of the metal picrate absorption band in the presence and absence of the ligand.

The value of the induced shift of the absorption maximum of picrate anion ($\Delta\lambda_{Pi}$) in low polarity media [13] can serve as a test for the presence of the lariat effect. The method is based on the known dependence of the $\Delta\lambda_{Pi}$ on the degree of separation of the ion pair of the studied metal picrate. Evidently, the greater the shielding of the metal cation by the lipophilic envelope of the ligand the greater will be the degree of separation of the ion pair of the picrate and, in turn, this will lead to an increase in the bathochromic shift of the picrate anion band. In fact, the crown ether gives rise to a two dimensional ligand around the cation and this leads to a markedly smaller value of $\Delta\lambda_{Pi}$ than for cryptands which have a three dimensional intramolecular cavity. With the creation of the lariat effect the value of $\Delta\lambda_{Pi}$ markedly exceeds the shift observed for the unsubstituted compounds and approaches that observed for cryptands and this is quite understandable since, in this case, a three dimensional environment is created around the cation.

A spectrophotometric study of the reaction of the substituted azacrown ethers **4b-e** and **5b-e** with lithium, sodium, potassium, magnesium, and calcium picrates was carried out in tetrahydrofuran. In most cases the addition to the picrate solution of one hundred fold excesses of the ligand gave a maximal possible shift of the picrate absorption (λ_{Pi} 376-380 nm) and this points to the formation of separated ion pairs. It probably indicates a high stability for the complex since the value of $\Delta\lambda_{Pi}$ is only slightly sensitive to the ratio of the picrate-ligand concentration to the extent of 1/(2-5) (Table 2).

In contrast to this, the unsubstituted diaza-18-crown-6 (**1b**) and N,N'-dibenzyldiaza-18-crown-6 (**6**), which cannot show the lariat effect, show a much smaller shift in the absorption maximum of the picrate anion (λ_{Pi} 349-364 nm) (Table 2). This points to the presence of a lariat effect in compounds **4b-a**–**5b-e**. Since the side chains of these diazacrown ethers differ in length, number, and nature of the donor atoms evidently, in each specific example, the participation of particular heteroatoms in complex formation will be determined by the possibility of achieving a structural and electronic maximization for the cation and crown ether side chain respectively.

The side chains in compound **4c** contain six methylene groups and the lariat effect can be achieved only with the participation of the side amino groups in complex formation. The appearance of *gem*-dimethyl substituents on the nitrogen atoms in compound **5c** evidently hinders their participation in interaction with a cation and as a result, in this case, the shift observed (λ_{Pi} 358 nm) is similar to that of the unsubstituted diazacrown ether (see Table 2). A markedly smaller shift in the absorption maximum of the picrate anion is observed for the crown ether **5d** (λ_{Pi} 368-373 nm) when compared with its unsubstituted analog **4d** (λ_{Pi} 380 nm). In compounds with a short (**4b**) or longer (**4e**) side chain the introduction of methyl substituents at the amino groups does not influence the shift values. Evidently, the observed differences in the spectroscopic behavior of the studied crown ether complexes is due to the possible coordination of the ion with both the nitrogen and the oxygen atoms of the side chain and also the possibility of realizing complexes of different structure. Unfortunately, the data for the values of the induced shifts of picrate anion point only to the participation of the heteroatoms of the side chains in complex formation but do not allow one to make more specific conclusions about the structure of the complexes formed.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AM-250 (250 MHz) instrument using $CDCl_3$ and HMDS internal standard. Mass spectra were obtained on a Varian MAT 112 instrument with an electron impact ionization of 40 and 70 eV. UV spectra were taken on a Specord M40 UV-vis spectrophotometer. The purity of all of the compounds obtained was monitored chromatographically. Thin-layer chromatography was carried out on glass plates with an applied layer of basic aluminium oxide (L 5/40, Chemapol) and using Silufol UV-254 bound layer silica gel plates. GLC was performed on a Chrom-5 apparatus, 3 × 1500 mm column, 5% SP 2100 on Chromaton N-Super. 1,2-Dibromoethane, 1,6-dichlorohexane, 1,5-dichloro-3-oxapentane, and 1,8-dichloro-

3,6-dioxaoctane were used as commercial products. The diazacrown ethers **1a,b** were obtained according to the method in [14]. N,N'-Dibenzyldiaza-18-crown-6 (**6**) was prepared by the method in [5].

N-(2-Bromoethyl)phthalimide (2a). A suspension of potassium phthalimide (43 g, 0.23 mol) in 1,2-dibromoethane (284 g, 1.5 mol) was refluxed for 20 h with vigorous stirring. The excess dibromoethane was distilled off under reduced pressure. The residue was dissolved in benzene (200 ml) and the unreacted potassium phthalimide and 1,2-diphthalimidoethane were filtered off. The benzene was distilled off and the residue was recrystallized from ethanol (55 ml). Yield 43.8 g (75%); mp 82-83°C which agrees with that reported [15].

N-(6-Chlorohexyl)phthalimide (2b). A suspension of potassium phthalimide (21 g, 0.11 mol) and 1,6-dichlorohexane (177.7 g, 1.14 mol) has stirred at 130°C for 20 h. The cooled product was filtered and the excess 1,6-dichlorohexane was distilled off under reduced pressure. The residue was crystallized from pentane (200 ml). Yield 23.7 g (78%); mp 38-39°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.5 (8H, m, CH_2); 3.4 (2H, t, *J* = 6.2, CH_2Cl); 3.6 (2H, t, *J* = 7.2, CH_2N); 7.8 (4H, m, C_6H_4). Found, %: C 63.17; H 6.11; N 5.19. $C_{14}H_{16}ClNO_2$. Calculated, %: C 63.28; H 6.07; N 5.27.

N-[2-(2-Chloroethoxy)ethyl]phthalimide (2c) was prepared similarly from potassium phthalimide (200 g, 1.08 mol) and 1,5-dichloro-3-oxapentane (1522 g, 10.6 mol). After distillation of solvent the residue was crystallized by the addition of pentane (100 ml). The precipitate was filtered off and the product was purified by extraction with pentane in a Soxhlet apparatus for 50 h. Yield 250 g (91.5%); mp 71-72°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.6 (4H, m, CH_2O); 3.8 (2H, t, *J* = 6.6, CH_2Cl); 3.9 (2H, t, *J* = 5.8, CH_2N); 7.6 (4H, m, C_6H_4). Found, %: C 56.87; H 4.83; N 5.44. $C_{12}H_{12}ClNO_3$. Calculated, %: C 56.82; H 4.77; N 5.52.

N-{2-[2-(Chloroethoxy)ethoxy]ethyl}phthalimide (2d) was prepared similarly from potassium phthalimide (185 g, 1.0 mol) and 1,8-dichloro-3,6-dioxaoctane (1870 g, 10 mol). Yield 89% as an oil. ^{1}H NMR spectrum, δ, ppm: 3.5 (8H, m, CH_2O); 3.8 (4H, m, CH_2Cl, CH_2N); 7.5 (4H, m, C_6H_4). Found, %: C 56.41; H 5.50; N 4.65. $C_{14}H_{16}ClNO_4$. Calculated, %: C 56.48; H 5.42; N 4.70.

N-(6-Iodohexyl)phthalimide (2e). A mixture of N-(6-chlorohexyl)phthalimide **2b** (23.7 g, 0.09 mol) and freshly ignited sodium iodide (30 g, 0.2 mol) in dry acetonitrile (200 ml) was refluxed for 10 h with vigorous stirring. The precipitated NaCl was filtered off and washed with acetonitrile. The filtrate was evaporated under reduced pressure, the residue was dissolved in chloroform (100 ml), and the solution was washed with a 5% solution of sodium thiosulfate and dried over calcium chloride. Chloroform was distilled off and the residue was recrystallized from pentane (300 ml). The precipitated crystals were filtered off and dried in air. Yield 28.6 g (89.7%); mp 75-76°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.5 (8H, m, CH_2); 3.1 (2H, t, *J* = 6.5, CH_2I); 3.6 (2H, t, *J* = 7.2, CH_2N); 7.7 (4H, m, C_6H_4). Found, %: C 47.12; H 4.48; N 3.88. $C_{14}H_{16}INO_2$. Calculated, %: C 47.08; H 4.51; N 3.92.

N-[2-(2-Iodoethoxy)ethyl]phthalimide (2f) was prepared similarly from the phthalimide **2c** (91 g, 0.36 mol) and NaI (120 g, 0.8 mol) in acetonitrile (500 ml). After distillation of chloroform the product was crystallized from a mixture of hexane (1250 ml) and benzene (375 ml). Yield 120 g (97%); mp 84-86°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.2 (2H, t, *J* = 7.0, CH_2I); 3.6 (2H, t, *J* = 6.0, $\underline{CH_2}CH_2N$); 3.7 (2H, t, *J* = 7.0, $\underline{CH_2}CH_2I$); 3.9 (2H, t, *J* = 6.0, CH_2N); 7.6 (4H, m, C_6H_4). Found, %: C 41.82; H 3.56; N 4.02. $C_{12}H_{12}INO_3$. Calculated, %: C 41.76; H 3.50; N 4.06.

N-{2-[2-(Iodoethoxy)ethoxy]ethyl}phthalimide (2g) was prepared similarly from the phthalimide **2d** (89.1 g, 0.3 mol) and NaI (105 g, 0.7 mol). After distillation of chloroform the product was extracted from the residue with refluxing heptane (1.0 l). The heptane was evaporated to give compound **2g** as a light-yellow oil. Yield 113 g (96%). ^{1}H NMR spectrum, δ, ppm (J, Hz); 2.9 (2H, t, *J* = 6.9, CH_2I); 3.5 (4H, m, CH_2O); 3.6 (2H, t, *J* = 5.8, $\underline{CH_2}CH_2N$); 3.7 (2H, t, *J* = 7.0, $\underline{CH_2}CH_2I$); 3.9 (2H, t, *J* = 5.8, CH_2N); 7.6 (4H, m, C_6H_4). Found, %: C 43.15; H 4.21; N 3.67. $C_{14}H_{16}INO_4$. Calculated, %: 43.21; H 4.14; N 3.60.

2-(2-{13-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,4,10-trioxa-7,13-diazacyclopentadecan-7-yl}ethyl)-1H-isoindole-1,3(2H)-dione (3a). A mixture of the diaza-15-crown-5 **1a** (2.18 g, 10 mmol), phthalimide **2a** (12.7 g, 50 mmol), and freshly ignited sodium carbonate (5.3 g, 50 mmol) was stirred for 10 h at 100°C. Chloroform (30 ml) was added dropwise to the hot solution which was then cooled and the precipitate formed was filtered off and the chloroform evaporated under reduced pressure. The residue was dissolved in a 1:1 mixture of benzene and HCl (1 N). The benzene layer was separated and the aqueous extracted with benzene (50 ml). The aqueous solution was treated with sodium carbonate to pH 9-10 and extracted with benzene (2 × 50 ml). After distillation of benzene **3a** was obtained as a light-yellow oil. Yield 4.0 g.

2-(2-{16-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl}ethyl)-1H-isoindole-1,3(2H)-dione (3b) was prepared similarly from diaza-18-crown-6 **1b** (2.62 g, 10 mmol) and phthalimide **2a** (12.7 g, 50 mmol). After distillation of benzene the residue was recrystallized from a 1:1 mixture of heptane and benzene (70 ml). Yield 5.0 g; mp 116-117°C.

2-(6-{16-[6-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)hexyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl}hexyl)-1H-isoindole-1,3(2H)-dione (3c). A mixture of diaza-18-crown-6 **1b** (7.86 g, 30 mmol), phthalimide (28.6 g, 0.08 mol), and freshly ignited sodium carbonate (32 g, 0.3 mol) in dry acetonitrile (150 ml) was refluxed with stirring for 18 h. After cooling, the precipitate was filtered and the acetonitrile was distilled from the filtrate under reduced pressure. Benzene (100 ml) and 1N HCl (100 ml) were added to the residue. The oily lower layer separated in this way crystallized over 10-12 h. The crystals were filtered off, washed with benzene, and treated with a saturated solution of sodium carbonate (100 ml) at 60°C. The product was removed using benzene and the extract was dried over anhydrous sodium sulfate and the solvent distilled off. The residue was crystallized from heptane (400 ml). Yield 9.2 g; mp 41-42°C.

2-{2-[2-(16-{2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethoxy]ethyl}-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl}ethyl)-1H-isoindole-1,3(2H)-dione (3d) was prepared similarly by refluxing diaza-18-crown-6 **1b** (1.05 g, 4 mmol) and the phthalimide **2f** (3.45 g, 10 mmol) in the presence of lithium carbonate (3.0 g, 40 mmol) in acetonitrile (20 ml) for 30 h. After distillation of benzene the residue was crystallized from an 18:11 mixture of heptane and benzene. Yield 1.8 g; mp 96-97°C.

2-[2-(2-{2-[16-(2-{2-[2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)ethoxy]ethoxy}ethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]ethoxy}ethoxy)ethyl]-1H-isoindole-1,3(2H)-dione (3e) was prepared similarly from diaza-18-crown-6 **1b** (1.05 g, 4 mmol) and phthalimide **2g** (3.9 g, 10 mmol) in the presence of lithium carbonate (3.0 g, 40 mmol). Distillation of benzene gave **3e** as a light-yellow oil. Yield 1.5 g.

2-[13-(2-Aminoethyl)-1,4,10-trioxa-7,13-diazacyclopentadecan-7-yl]ethylamine (4a), 2-[16-(2-Aminoethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]ethylamine (4b), 6-[16-(6-Aminohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclopentadecan-7-yl]hexylamine (4c), 2-(2-{16-[2-Aminoethoxy)ethyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]ethoxy)ethylamine (4d), and 2-{2-[2-(16-{2-[2-(2-Aminoethoxy)ethoxy]ethyl}-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)ethoxy]ethoxy}ethylamine (4e). (General Method). Hydrazine hydrate (67 mmol) was added dropwise with vigorous stirring to a refluxing solution of the diazacrown ether **3** (33 mmol) in ethanol (100 ml). The mixture was refluxed for 7 h and diluted with HCl (6 N, 22 ml). The precipitate was filtered off and ethanol was removed at reduced pressure. Water (120 ml) was added to the residue and the precipitate was filtered off. A saturated aqueous solution of LiOH was added to the filtrate to pH 10-11. The product was extracted with chloroform over 10 h. Distillation of the chloroform gave the diazacrown ether **4** as a light-yellow oil.

N-(2-{13-[2-(Dimethylamino)ethyl]-1,4,10-trioxa-7,13-diazacyclopentadecan-7-yl}ethyl)-N,N-dimethylamine (5a), N-(2-{16-[2-(Dimethylamino)ethyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl}ethyl)-N,N-dimethylamine (5b), N-6-{16-[6-(Dimethylamino)hexyl]-1,4,10,13-tetraoxa-7,16-diazacyclopentadecan-7-yl}hexyl)-N,N-dimethylamine (5c), N-{2-[2-(16-{2-[2-dimethylamino)ethoxy]ethyl}-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)ethoxy]ethyl}-N,N-dimethylamine (5d), and N-[2-(2-{2-[16-(2-{2-[2-(dimethylamino)ethoxy]ethoxy}ethyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]ethoxy}ethoxy)-ethyl]-N,N-dimethylamine (5e). (General Method). An aqueous solution of formaldehyde (40%, 5 ml) was

added to a solution of the diazacrown ether **4** (1.5 mmol) in formic acid (5 ml). The mixture was refluxed for 10 h, diluted with conc. HCl (10 ml), and evaporated to dryness under reduced pressure. This operation was repeated once more. The residue was dissolved in water (10 ml), diluted with a saturated solution of LiOH to pH 10-11, and extracted with chloroform (5 × 5 ml). After distillation of chloroform, the product was removed from the residue using refluxing hexane (3 × 10 ml). The hexane was evaporated to give the diazacrown ether **5** as a light-yellow oil.

Method for Determining the Value of the Induced Shift (Δλ) of the Absorption Band of Metal Picrates in the Presence of Diazacrown Ethers. A sample of the diazacrown ether (5 mmol) was dissolved in a solution of the appropriate metal picrate (5 ml, 0.05 M) in THF. Subsequent dilution with the metal picrate solution then gave solutions with the diazacrown ether:picrate ratios of 50, 10, 2, 1, 0.75, 0.5, and 0.2. Measurements were carried out over 12 h in order to reach system equilibrium. The value of Δλ was calculated as the difference between the λ_{max} of the picrate with a one hundred fold excess of the diazacrown ether and the picrate λ_{max} in its absence. The results are given in Table 2.

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