66. Photo-Cleavable Cryptands: Synthesis and Structure

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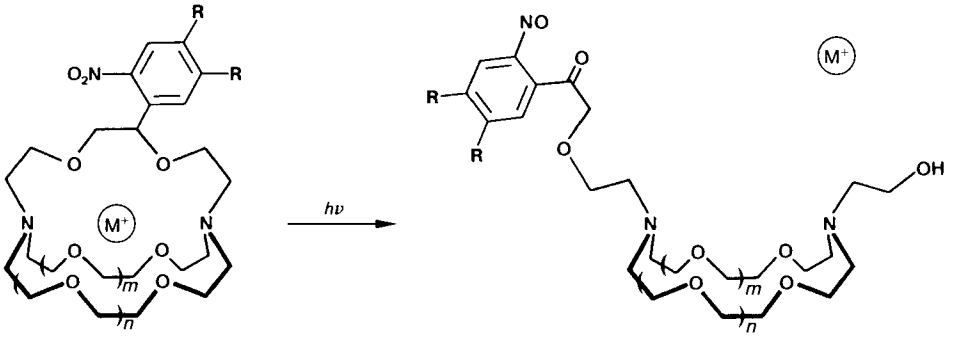
The four photo-cleavable ligands **1**–**4** of the macrobicyclic-cryptand type have been synthesized by introducing a photo-sensitive 2-nitrobenzyl- or 4,5-dimethoxy-2-nitrobenzyl-ether bond into one of the bridges. These compounds are expected to retain the selective binding features of the parent cryptands and to allow the photolytically induced release of alkali ions in aqueous solution. The crystal structures of the ligand 5-(2-nitrophenyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (**3**) and of its KSCN complex **13** have been determined. They are analogous to those of the corresponding parent species, confirming the macrobicyclic geometry and the cryptate nature of the complex. Spectroscopic properties are reported.

Introduction. – In order to perform fast kinetic studies or transport measurements across membranes involving alkali ions, in particular on systems of physiological interest, it would be desirable to create cation-concentration jumps or pulses without the application of special mixing techniques so as to avoid mechanical perturbance of the system. Especially, in view of physiological investigations, selective concentration jumps of alkali ions, *e.g.* of K^+ in the presence of Na^+ and Mg^{2+}, are of considerable interest. Light-induced cation-concentration changes represent a method of choice for introducing such processes. This may, in principle, be realized by introducing the cation into the particular reaction system in a protected form, namely bound to a suitable light-sensitive ligand. Upon a fast photochemical modification of the ligand, leading, *e.g.*, to the cleavage of a strategic bond, it may be possible to achieve a substantial affinity decrease, thus inducing a release of the cation into the solution.

Up to now, processes of this type have been realized only for alkaline-earth cations by means of photo-cleavable chelating ligands such as those of the 1,1-bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (= 2,2′,2″,2‴-[(ethane-1,2-diyl)bis(oxy)bis-(phen-2,1-ylenenitrilo)]tetrakis[acetic acid]; BAPTA) type (nitr-*n*; *n* = 1–7) [1] [2] or DM-nitrophen, derived from ethylenediaminetetraacetic acid (= 2,2′,2″,2‴-[(ethane-1,2-diyl)bis(nitrilo)]tetrakis[acetic acid]; EDTA) [3] [4].

As far as alkali ions are concerned, the molecular concept of the cryptands [5] offers promising features for designing light-sensitive ligands exhibiting the required characteristics mentioned above. These cage-like polyoxadiaza macrobicycles form strong alkali-ion complexes of high selectivity in aqueous solution, where the cation selectivity is determined by the prechosen cavity size of the particular ligand. Furthermore, because of their high water solubility, cryptand-type ligands may be expected to present no pronounced tendency to interact with biological or lipid membranes. This represents an important aspect from the point of view of physiological applications.

Scheme



R = H: $m = n = 0$ R = MeO: $m = n = 1$
$m = 1, n = 0$
$m = n = 1$

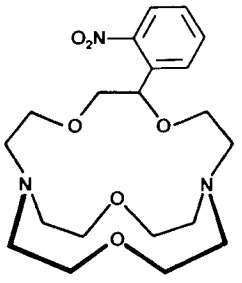
We have introduced the photo-cleavable 2-nitrobenzyl-ether bond into one of the bridges of the macrobicyclic structure of these ligands. Illumination by UV light is expected to lead to a splitting of this bridge and thus to the formation of a monocyclic photoproduct with a drastically reduced affinity for the complexed alkali ion, essentially due to the loss of the cryptate effect as indicated in the *Scheme*.

We describe here the synthesis of four new light-sensitive cryptands **1**–**4** and discuss some of their structural and spectral properties.

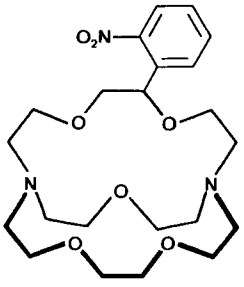
Synthesis of the Cryptands 1–4. – The light-sensitive cryptands **1**–**4** were synthesized by the general strategy of macrobicycle formation described in detail in earlier work [6]. Our synthetic scheme involved: *1*) the stepwise build-up of a photo-cleavable bridge **8** of triethylene-glycol type, bearing on each end an acyl-chloride function, *2*) its condensation with a diazapolyoxa monocycle, and *3*) reduction of the amide functions of the resulting bicyclic diamide to the final cryptand.

The diacyl dichlorides **8a** and **8b** were obtained in a five-step reaction sequence. The educts 2-nitrobenzaldehyde and 4,5-dimethoxy-2-nitrobenzaldehyde were transformed into the diols **5a** and **5b**, respectively, *via Wittig* olefination and *cis*-hydroxylation following literature procedures [3] [7]. Standard *Williamson* etherification of **5a** and **5b**, with *tert*-butyl bromoacetate and NaH as base, afforded the di(*tert*-butyl)esters **6a** and **6b** as yellow oils in 59 and 57% yield, respectively. Treatment of **6a** and **6b** with CF_3COOH gave the crystalline diacids **7a** (82% yield) and **7b** (78% yield), which were converted into the dichlorides **8a** and **8b**, respectively, with excess oxalyl chloride in toluene (90 and 95% yield, resp.).

Condensation of **8a** and **8b** with diazapolyoxa macrocycles of different ring sizes ([1.1] (= [12]-N_2O_2), [2.1] (= [15]-N_2O_3), and [2.2] (= [18]-N_2O_4)) [6] under conditions of high dilution afforded the macrobicyclic diamides **9**–**12** in 55–75% yield. The somewhat higher yields of these cyclization steps compared to those reported for the unsubstituted analogues [6] could be related to a slightly higher rigidity of the bridging unit due to the benzylic substituent as well as to a decreased reactivity of the acyl-chloride function, which causes less decomposition during the cyclization over 14 h.



1



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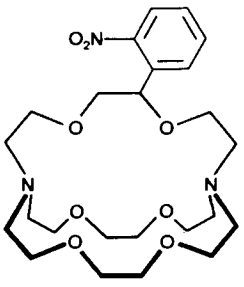

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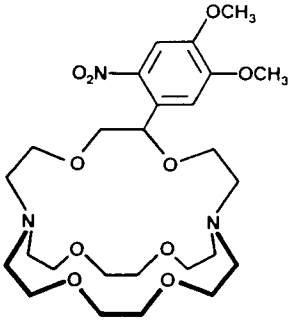

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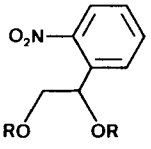
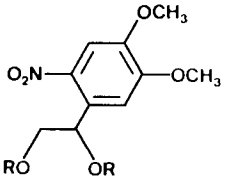
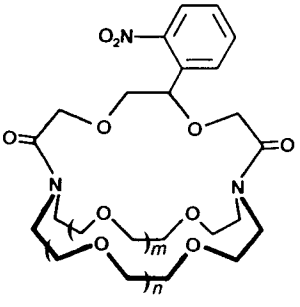


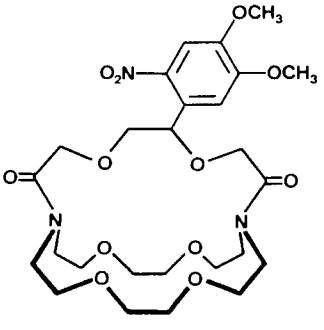
5a R = H
6a R = $CH_2COOC(CH_3)_3$
7a R = CH_2COOH
8a R = CH_2COCl



5b R = H
6b R = $CH_2COOC(CH_3)_3$
7b R = CH_2COOH
8b R = CH_2COCl



9 $m = n = 0$
10 $m = 1, n = 0$
11 $m = n = 1$



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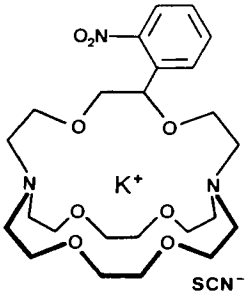

13

Selective reduction of the diamide functions of **9–12** with the $BH_3 \cdot THF$ complex under conditions where the aromatic NO_2 group remains unchanged [8], followed by hydrolysis of the resulting boron-nitrogen compounds with CF_3COOH gave the protonated ligands **1–4** (**1–3**, quantitative; **4**, 65% yield). Neutralization by passage over a column of *Dowex 1 × 8* (OH^- form) led to the free cryptands. The lower yield of **4** compared to **1–3** may be attributed to a partial hydrolytic cleavage of the acid-sensitive benzyl-ether bond during CF_3COOH treatment. Only in case of **4**, a final purification of the product by hexane extraction was required.

The macrobicyclic ligands **1**, **2**, and **4** are slightly yellow oils, whereas **3** could be crystallized from MeOH as colorless needles. All cryptands exhibit fairly high solubility in H_2O as well as in organic solvents of high and medium polarity.

The potassium cryptate **13** of the macrobicycle **3** was obtained in a manner similar to that used for formation of the K^+ cryptate of the parent ligand [2.2.2] [9]. Incubation of **3** with excess KSCN in $CHCl_3$ yielded **13** quantitatively and in crystalline form, after crystallization from AcOEt.

Crystal Structures of Cryptand 3 and of Its Potassium Complex 13. – In general, cryptands show a high tendency to form strong alkali-ion complexes in solution [5]. The selected alkali ion is coordinated in the centre of the cavity in its desolvated form. Binding of the cation is stabilized *via* ion-dipole interactions with all ether O-atoms and both bridgehead N-atoms.

A detailed insight into the nature of cation binding and the related changes of the ligand geometry in the solid state has been obtained by solving the crystal structures of both the light-sensitive cryptand **3** (*Fig. 1a*) and its corresponding KSCN cryptate **13** (*Fig. 1b*).

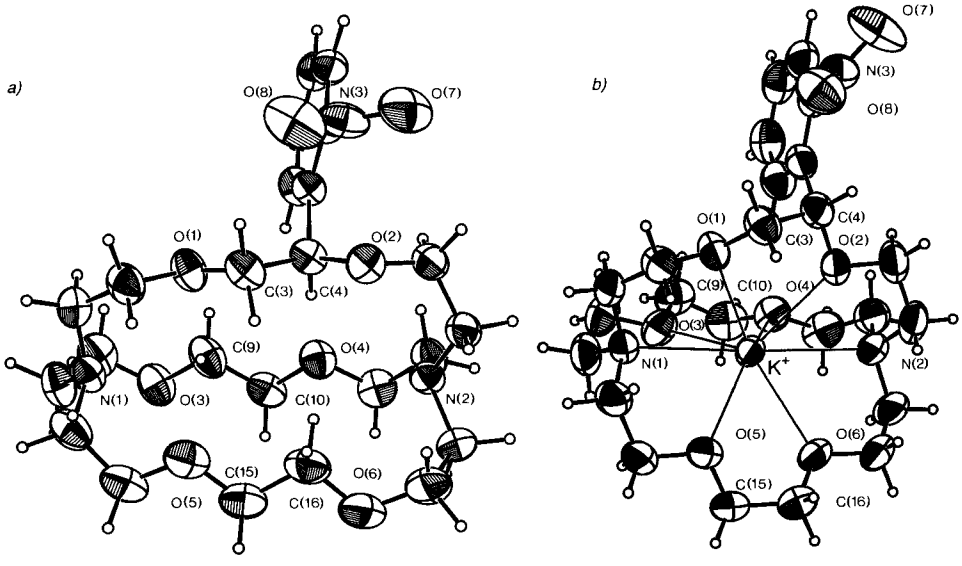

Fig. 1. *ORTEP representations of the crystal structures of* a) *the photo-cleavable cryptand* **3** *and* b) *its KSCN cryptate* **13**

The cavity of the free ligand **3** shows an elongated shape with an intramolecular N···N distance of 6.802(3) Å[1]). The central O–C–C–O segment of each chain has an all-*trans* conformation and is parallel to the N···N axis. The geometry of the cavity is only slightly affected by the 2-nitrophenyl substituent and agrees well with the structure of the free unsubstituted cryptand [2.2.2] [10].

After complex formation, a significantly different structure is obtained. The ligand cavity of the cryptate **13** reveals a more spherical shape which is typical for cryptates [11] [12]. The central CH_2CH_2 groups point away from the centre of the complex and the intramolecular N···N distance of 5.932(3) Å is much smaller than that in the free cryptand **3**. The cryptate **13** exhibits approximately three-fold symmetry about the N···N axis with the exception of the 2-nitrophenyl substituent. All C–C bonds have synclinal and all C–O bonds antiperiplanar conformation.

In **13**, O(2)–C(4) and O(2)–C(5) ether bonds next to the aromatic substituent have lengths of 1.431(3) and 1.430(4) Å, respectively, and are slightly longer than the remaining ten ether bonds, which show an average length of 1.418 Å. The same effect is observed in the K^+-free compound **3**, where the O(2)–C(4) and O(2)–C(5) bonds exhibit lenghts of 1.432(3) and 1.426(3) Å, respectively, and are 0.016 Å longer than the remaining C–O bonds. A similar elongation is found for the C(3)–C(4) bonds of **3** and **13**, being *ca.* 0.014 and 0.020 Å, respectively, longer than the corresponding C(9)–C(10) and C(15)–C(16) bonds in the other bridges. Since no steric interactions are observed between the ligand cage and the 2-nitrophenyl substituent, these bond-length elongations are likely to result from the electronic effect caused by the C(4)-substituent.

The K^+ ion is coordinated to the six O-atoms and both N-atoms of the cryptand, forming a coordination polyhedron which is described best as a trigonal prism. The K–O(1) and K–O(2) distances of 2.931(2) and 2.856(2) Å, respectively, are considerably longer than the K–O(3), K–O(4), K–O(5), and K–O(6) distances, which range from 2.762(2) to 2.799(2) Å. This may again be caused by an electronic effect of the 2-nitrophenyl group, as already mentioned above. The K^+ complex of the unsubstituted cryptand is characterized by a higher symmetry and almost equal K–O distances [12].

The angle between the planes of the NO_2 group and the aryl ring is 73.6(1)° for **3** and 38.7(2)° for **13**.

Spectroscopic Properties. – *NMR Properties.* To achieve maximum free binding energy, marked conformational changes of the cryptand upon complex formation occur also in solution, which can be investigated employing ^{1}H-NMR spectroscopy. As an example, the 200-MHz ^{1}H-NMR spectra of cryptand **3** and of the KSCN cryptate **13** in $CDCl_3$ are shown in *Fig. 2*. As a consequence of complex formation, the broad *m* at 2.7 ppm, assigned to the CH_2N protons, is split into two groups (2.5 and 2.7 ppm), accompanied by a 0.1 ppm down-field shift of the *m* centre. A similar down-field shift is observed for the CH_2O resonances of **3** and **13** at 3.7 and 3.65 ppm, respectively, as well as for the methine *q* (5.20 and 5.15 ppm, resp.). These observations are consistent with the ^{1}H-NMR-shift changes found upon cryptate formation between the unsubstituted cryptands [6] and various alkali ions, as reported earlier [9], and indicate that similar conformational transitions occur during the coordination of the alkali ion by these light-cleavable analogues.

[1]) Errors specified in parentheses.

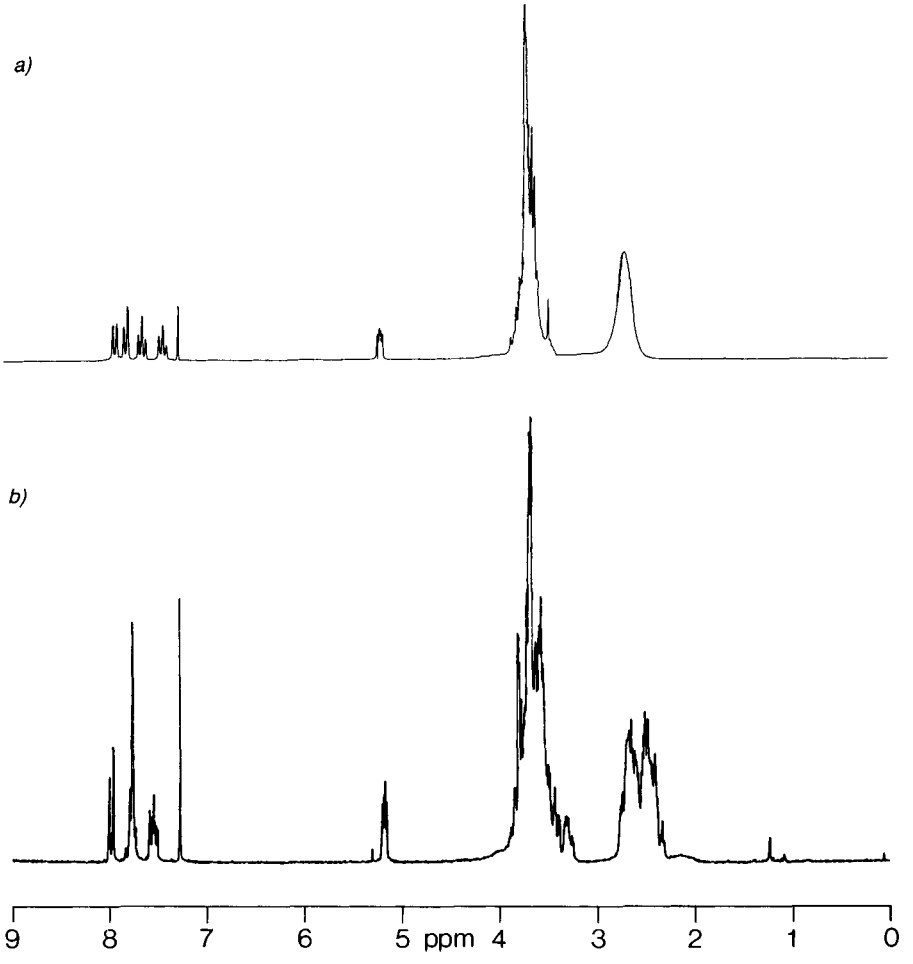

Fig. 2. *200-MHz ^{1}H-NMR spectra* ($CDCl_3$) *of* a) *cryptand* **3** *and* b) *of its KSCN cryptate* **13**

UV-Absorption Properties. The UV-absorption spectra of the photo-cleavable cryptands were measured in alkaline aqueous solution (examples shown in *Fig. 3*). The spectra exhibit the expected features characteristic of the 2-nitrophenyl ($\lambda_{max} = 265$ nm, $\varepsilon = 5400$ M^{-1} cm^{-1} [13]) and the 4,5-dimethoxy-2-nitrophenyl group ($\lambda_{max} = 350$ nm, $\varepsilon = 4300$ M^{-1} cm^{-1} [4]), which have been reported earlier.

Addition of sufficiently high concentrations of alkali-ion salts to form the corresponding cryptates (described elsewhere) does only lead to small intensity changes in the UV-absorption spectra. This indicates that neither the absorption of the nitrophenyl chromophore nor that of the unsubstituted cryptand bridges are altered markedly as a consequence of alkali-ion coordination. The latter result is consistent with earlier findings [14].

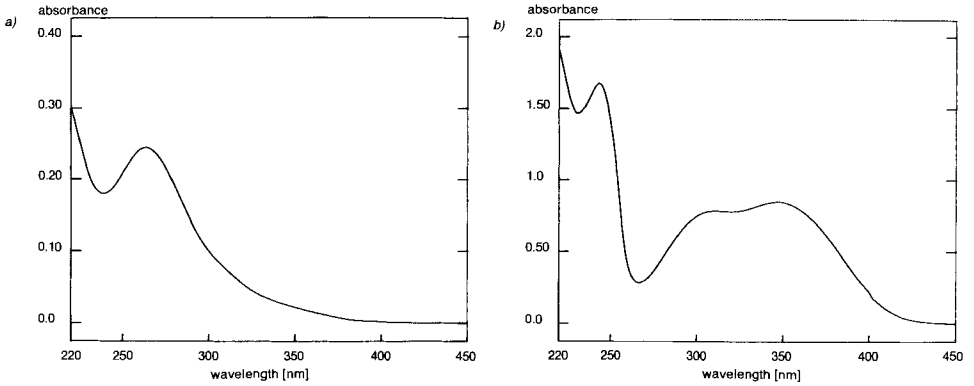

Fig. 3. *UV-absorption spectra of* a) *0.05* mM *cryptand* **2** *in 100* mM *and* b) *of 0.16* mM *cryptand* **4** *in 10* mM *tetramethylammonium hydroxide*

Conclusion. – Procedures have been worked out to synthesize different light-cleavable cryptands. In view of their cavity size and on the basis of the results obtained for the parent compounds [5] [9], ligands **1** and **2** are expected to bind preferentially the Li^+ and Na^+ cations, respectively, and **3** as well as **4** preferentially the K^+ cation. The macrobicyclic structure of cryptands **1–4** results from the synthetic pathway and agrees with the spectral properties expected on the basis of those presented by the parent compounds [6]. In addition, the structure has been confirmed for cryptand **3** in its crystalline state. The nature of its alkali-ion binding site has also been characterized by X-ray crystal-structure determination in case of the KSCN cryptate **13**.

Upon binding of the K^+ ion, a conformational rearrangement occurs from a narrow, elongated to a more spherical cavity, similar to the results obtained for the unsubstituted cryptands and cryptates [10] [12]. All solvate molecules of the cation are substituted by the coordinating N- and O-atoms of the ligand. Evidence that conformational changes due to alkali-ion binding occur also in solution have been found by ^{1}H-NMR studies. The absorption spectra of the light-cleavable cryptands remain essentially unchanged upon binding of alkali ions.

The photo-sensitive groups are well suited for inducing an efficient photolytic reaction [1–4] [15] that leads to the cleavage of the strategic C(4)–O(2) bond and the opening of the cryptand cavity. This should result in the release of the bound cation (see *Scheme*). These expectations have been confirmed by photolysis studies which will be described elsewhere. To predict quantitatively the selectivity and magnitude of the photolytically induced concentration jumps, thermodynamic and kinetic studies will be required.

The authors are grateful to Dr. *B. Dietrich* and Mr. *E. Lewitzki* for stimulating discussions and helpful advice. We thank Mrs. *A. Rigault-Marquis* for providing a sample of 1,7-dioxa-4,10-diazacyclododecane and Mr. *P. Maltèse* for his help in performing the NMR measurements.

Experimental Part

General. Materials: 4,5-Dimethoxy-2-nitrobenzylaldehyde, *tert*-butyl bromoacetate, CF_3COOH, $BH_3 \cdot THF$ (*Aldrich*); 2-nitrobenzaldehyde, NaH, oxalyl chloride (*Fluka*); KSCN, Et_3N (*Prolabo*); 1,4,10-trioxa-7,13-diazacyclopentadecane (= *Kryptofix 21*), 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (= *Kryptofix 22*; *Merck*). Be-

cause of the UV-light sensitivity of the compounds, all synthetic work was carried out under red light. M.p.: uncorrected. UV spectra: *Hewlett-Packard-8450A* UV/VIS spectrometer; at 25° in a 1-cm quartz cuvette. NMR spectra: at r.t. on a *Bruker-SY-200* spectrometer at 200 MHz (^{1}H) and 50.3 MHz (^{13}C) or on a *Bruker-AX-300* spectrometer at 250 MHz (^{1}H) and 63 MHz (^{13}C); δ(H) in ppm relative to residual protiated solvent in $CDCl_3$ (7.26) or CD_3OD (3.30); δ(C) in ppm relative to solvent $CDCl_3$ (77.0) or CD_3OD (49.0); coupling constants J in Hz. Fast-atom-bombardement mass spectroscopy (FAB-MS): positive mode, *FAB-HF-VG-Analytical* apparatus in a 4-nitrobenzyl alcohol (NBA) matrix, unless otherwise specified. Elemental analysis were performed by the Institut de Chimie, Strasbourg, analytical service, or by the Institut für organische Chemie, J. W. Goethe-Universität Frankfurt.

*Di(*tert*-butyl) 4-(2-Nitrophenyl)-3,6-dioxaoctanedioate* (= *Di(*tert*-butyl) 2,2'-{[1-(2-Nitrophenyl)ethane-1,2-diyl]bis(oxy)}bis[acetate]*; **6a**). A soln. of 1-(2-nitrophenyl)ethane-1,2-diol [3] [7] (**5a**; 1.83 g, 10 mmol) and *tert*-butyl bromoacetate (11.3 g, 59 mmol) in dry THF (8 ml) was added dropwise to an ice-cold, stirred suspension of NaH (0.75 g, 30 mmol) in dry THF (35 ml) under N_2. The resulting mixture was stirred at r.t. for 12 h. After the addition of H_2O (40 ml), the mixture was extracted with AcOEt (3 × 50 ml). Evaporation of the collected org. layers and purification of the remaining crude residue by column chromatography (CC; silica gel (70–230 mesh), CH_2Cl_2/AcOEt 4:1) gave **6a** as a yellow oil (2.44 g, 59%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.35, 1.38 (2*s*, 6 CH_3); 3.70–3.85 (*AB* of *ABX*, $CHCH_2O$); 3.90, 3.97 (*AB*, J = 24.5, $CHOCH_2COO$); 4.03 (*s*, CH_2OCH_2COO); 5.30 (*X* of *ABX*, $CHCH_2O$); 7.40 (*dt*, J = 1.5, 7.8, 1 arom. H); 7.60 (*dt*, J = 1.2, 7.6, 1 arom. H); 7.78 (*dd*, J = 1.3, 7.8, 1 arom. H); 7.88 (*dd*, J = 1.2, 8.1, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 27.77, 27.82 (CH_3); 67.5, 68.9 (OCH_2COO); 74.6 ($CHCH_2O$); 76.4 ($CHCH_2O$); 81.2, 81.5 ($(CH_3)_3C$); 124.2, 128.6, 129.0, 133.3, 133.8, 148.4 (arom. C); 168.7, 169.2 (C=O). FAB-MS: 412 (5, $[M + H]^+$), 300 (93, $[M - CH_2C(CH_3)_2 - CH_2C(CH_3)_2 + H]^+$), 224 (100, $[M - CH_2C(CH_3)_2 - OCH_2CO_2(CH_3)_3]^+$). Anal. calc. for $C_{20}H_{29}NO_8$ (411.5): C 58.38, H 7.10, N 3.40; found: C 58.57, H 7.16, N 3.41.

*Di(*tert*-butyl) 4-(4,5-Dimethoxy-2-nitrophenyl)-3,6-dioxaoctanedioate* (= *Di(*tert*-butyl) 2,2'-{[1-(4,5-Dimethoxy-2-nitrophenyl)ethane-1,2-diyl]bis(oxy)}bis[acetate]*; **6b**). As described for **6a** using 1-(4,5-dimethoxy-2-nitrophenyl)ethane-1,2-diol (**5b**) [3]. Purification by CC (silica gel (70–230 mesh), CH_2Cl_2/AcOEt 3:1). Yellow oil (57%). ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.40, 1.44 (2*s*, 6 CH_3); 3.77–3.85 (*AB* of *ABX*, $CHCH_2O$); 3.92, 3.98 (2*s*, 2 CH_3O); 3.94 (*AB*, $CHOCH_2COO$); 4.03 (*s*, CH_2OCH_2COO); 5.46 (*X* of *ABX*, $CHCH_2O$); 7.35 (*s*, 1 arom. H); 7.60 (*s*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 28.0 (CH_3); 56.3, 56.3 (CH_3O); 67.7, 69.2 (OCH_2COO); 74.7 ($CHCH_2O$); 81.5, 81.7 ($(CH_3)_3C$); 107.1, 110.2, 129.4, 140.6, 148.2, 153.7 (arom. C); 168.9, 169.4 (C=O). FAB-MS: 494 (3, $[M + Na]^+$), 472 (8, $[M + H]^+$), 360 (22, $[M - CH_2C(CH_3)_2 - CH_2C(CH_3)_2 + H]^+$), 284 (100, $[M - CH_2C(CH_3)_2 - OCH_2CO_2C(CH_3)_3]^+$). Anal. calc. for $C_{22}H_{33}NO_{11}$ (471.5): C 56.04, H 7.05, N 2.97; found: C 55.89, H 7.20, N 2.91.

4-(2-Nitrophenyl)-3,6-dioxaoctanedioic Acid (= *2,2'-{[1-(2-Nitrophenyl)ethane-1,2-diyl]bis(oxy)}bis[acetic Acid]*; **7a**). A soln. of **6a** in ice-cold CF_3COOH was left for 30 min at r.t., the solvent evaporated, and the crude solid redissolved in the minimum volume of CH_2Cl_2. After the addition of hexane and cooling to −10°, **7a** crystallized as colorless needles (1.39 g, 82%). M.p. 92–93°. ^{1}H-NMR (CD_3OD, 200 MHz): 3.75–3.90 (*AB* of *ABX*, $CHCH_2O$); 4.06 (*s*, $CHOCH_2COO$); 4.22 (*s*, CH_2OCH_2COO); 5.33 (*X* of *ABX*, $CHCH_2O$); 7.54 (*dt*, J = 1.6, 7.7, 1 arom. H); 7.72 (*dt*, J = 1.2, 7.7, 1 arom. H); 7.83 (*dd*, J = 1.6, 7.9, 1 arom. H); 7.98 (*dd*, J = 1.2, 8.1, 1 arom. H). ^{13}C-NMR (CD_3OD, 50.3 MHz): 67.6, 69.3 (OCH_2COO); 75.8 ($CHCH_2O$); 78.3 ($CHCH_2O$); 125.5, 130.1, 130.3, 134.6, 150.3, (arom. C); 173.4, 174.0 (C=O). Anal. calc. for $C_{12}H_{13}NO_8 \cdot H_2O$ (317.3): C 45.43, H 4.77, N 4.42; found: C 45.47, H 4.98, N 4.57.

4-(4,5-Dimethoxy-2-nitrophenyl)-3,6-dioxaoctanedioic Acid (= *2,2'-{[1-(4,5-Dimethoxy-2-nitrophenyl)-ethane-1,2-diyl]bis(oxy)}bis[acetic Acid]*; **7b**). As described for **7a**. Crystallization from $CHCl_3$/hexane 1:1 gave **7b** as a yellow solid (77%). M.p. 102–103°. ^{1}H-NMR (CD_3OD, 200 MHz): 3.70–3.90 (*AB* of *ABX*, $CHCH_2O$); 3.88, 3.94 (2*s*, 2 CH_3O); 4.05, 4.11 (*AB*, J = 16.4, $CHOCH_2COO$); 4.24 (*s*, CH_2OCH_2COO); 5.43 (*X* of *ABX*, $CHCH_2O$); 7.37 (*s*, 1 arom. H); 7.63 (*s*, 1 arom. H). ^{13}C-NMR (CD_3OD, 50.3 MHz): 56.8, 56.9 (CH_3O); 67.7, 69.3 (OCH_2COO); 75.8 ($CHCH_2O$); 78.7 ($CHCH_2O$); 109.1, 111.3, 129.3, 142.3, 149.9, 155.2 (arom. C); 173.5, 174.0 (C=O). Anal. calc. for $C_{14}H_{17}NO_{10} \cdot \frac{1}{2}H_2O$ (368.3): C 45.66, H 4.93, N 3.80; found: C 45.45, H 4.99, N 3.74.

4-(2-Nitrophenyl)-3,6-dioxaoctanedioyl Chloride (= *2,2'-{[1-(2-Nitrophenyl)ethane-1,2-diyl]bis(oxy)}bis-[acetyl Chloride]*; **8a**). The crystal water from **7a** (0.74 g, 2.34 mmol) was removed by azeotropic distillation with toluene. The residual solid was resuspended in 6 ml of oxalyl chloride/toluene 2:1 and stirred for 20 h at r.t. After evaporation, the residue was redissolved in Et_2O/hexane 1:2 and cooled to −30°: **8a** crystallized as colorless needles (0.708 g, 90%). M.p. 78°. ^{1}H-NMR ($CDCl_3$, 200 MHz): 3.80–3.99 (*AB* of *ABX*, $CHCH_2O$); 4.40, 4.58 (*AB*, J = 18.3, $CHOCH_2COO$); 4.56 (*s*, CH_2OCH_2COO); 5.37 (*X* of *ABX*, $CHCH_2O$); 7.53 (*dt*, J = 1.8, 7.6, 1 arom. H);

7.70 (*dt*, J = 1.2, 7.8, 1 arom. H); 7.77 (*dd*, J = 1.8, 7.8, 1 arom. H); 8.02 (*dd*, J = 1.1, 8.1, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 74.9, 75.1 (OCH_2COO); 76.3 ($CHCH_2O$); 77.7 ($CHCH_2O$); 124.9, 128.8, 129.5, 132.3, 134.0, 148.1 (arom. C); 171.3, 171.8 (C=O). FAB-MS: 570 (8, $[M + 2\ NBA - 2\ HCl + H]^+$); 592 (4, $[M + 2\ NBA - 2\ HCl + Na]^+$); 453, 455 (7, 3, $[M + NBA - HCl + H]^+$); 242, 244, (38, 15, $[M - OCH_2COCl]^+$); 224, 226 (26, 11, $[M - CH_2OCH_2COCl]^+$). Anal. calc. for $C_{12}H_{11}Cl_2NO_6$ (336.1): C 42.88, H 3.30, N 4.17; found: C 43.04, H 3.04, N 3.99.

4-(4,5-Dimethoxy-2-nitrophenyl)-3,6-dioxaoctanedioyl Chloride (*= 2,2'-{[1-(4,5-Dimethoxy-2-nitrophenyl)-ethane-1,2-diyl]bis(oxy)}bis[acetyl Chloride]*; **8b**). As described for **8a**. Yellow needles (95%). M.p. 67–68°. ^{1}H-NMR ($CDCl_3$, 200 MHz): 3.77–3.99 (*AB* of *ABX*, $CHCH_2O$); 3.95, 3.99 (2*s*, 2 CH_3O); 4.51 (*s*, OCH_2COO); 4.57 (*s*, OCH_2COO); 5.49 (*X* of *ABX*, $CHCH_2O$); 7.21 (*s*, 1 arom. H); 7.64 (*s*, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 50.3 MHz): 56.4, 56.6 (CH_3O); 75.1, 75.2 (OCH_2COO); 76.4 ($CHCH_2O$); 78.1 ($CHCH_2O$); 108.0, 109.6, 127.4, 140.4, 148.8, 153.9 (arom. C); 171.3, 171.8 (C=O). FAB-MS: 302, 304 (100, 35, $[M - OCH_2COCl]^+$); 288, 290 (41, 16, $[M - CH_2OCH_2COCl]^+$). Anal. calc. for $C_{14}H_{15}Cl_2NO_8$ (396.2): C 42.44, H 3.82, N 3.54; found: C 42.71, H 4.01, N 3.44.

5-(2-Nitrophenyl)-4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]icosane-2,9-dione (**9**). Within 14 h, a soln. of **8a** (259 mg, 0.76 mmol) and a soln. of 1,7-dioxa-4,10-diazacyclododecane (125 mg, 0.72 mmol), both in 30 ml of dry toluene, were added simultaneously dropwise to an efficiently, magnetically stirred soln. of Et_3N (0.22 ml, 1.58 mmol) in dry toluene (150 ml) at r.t. The insoluble solid was filtered off and the filtrate evaporated. After redissolving in $CHCl_3$, the oily residue was separated by CC (silica gel (70–230 mesh), $CHCl_3$ containing 2–5% MeOH). Evaporation and drying the product for 24 h at 50°/ < 0.1 Torr gave **9** as a white solid (173 mg, 55%). M.p. 127–129°. ^{1}H-NMR ($CDCl_3$, 200 MHz; superposition of spectra of four slowly exchanging isomers): 2.75–4.75 (*m*, 22 H, CH_2O, OCH_2CO, CH_2N); 5.15–5.55 (*m*, 1 H, $CHCH_2O$); 7.33–7.48 (*m*, 1 arom. H); 7.53–7.63 (*m*, 1 arom. H); 7.72–7.82 (*m*, 1 arom. H); 7.92 (*dd*, J = 1.2, 7.9, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 46.0–51.7, 66.3–80.5 (complex signal groups, CH_2N, OCH_2CO, CH_2O, $CHCH_2O$); 123.7, 124.1, 124.7, 128.3, 128.4, 128.6, 128.7, 129.0, 129.1, 129.7, 132.6, 133.0, 133.4, 133.6, 133.8, 134.6, 148.6 (arom. C); 169.7, 169.8, 169.9 (C=O). FAB-MS: 460 (5, $[M + Na]^+$), 438 (100, $[M + H]^+$). Anal. calc. for $C_{20}H_{27}N_3O_8$ (437.5): C 54.91, H 6.22, N 9.61; found: C 54.80, H 6.19, N 9.65.

5-(2-Nitrophenyl)-4,7,13,16,21-pentaoxa-1,10-diazabicyclo[8.8.5]tricosane-2,9-dione (**10**). As described for **9**, but using *Kryptofix 21* instead of 1,7-dioxa-4,10-diazacyclododecane. White solid (70%). M.p. 80–84°. ^{1}H-NMR ($CDCl_3$, 200 MHz; superposition of spectra of slowly exchanging isomers): 2.55–5.05 (complex *m*, 26 H, CH_2O, OCH_2CO, CH_2N); 5.25–6.0 (*m*, 1 H, $CHCH_2O$); 7.33–8.13 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 46.1–50.7, 60.4–78.5 (complex signal groups, CH_2N, OCH_2CO, CH_2O, $CHCH_2O$); 124.4, 124.7, 125.0, 128.6, 128.9, 129.1, 129.5, 133.8, 134.5, 148.6 (arom. C); 170.2, 170.8, 171.1 (C=O). FAB-MS: 482 (100, $[M + H]^+$). Anal. calc. for $C_{22}H_{31}N_3O_9$ (481.5): C 54.88, H 6.49, N 8.73; found: C 54.94, H 6.58, N 8.46.

5-(2-Nitrophenyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane-2,9-dione (**11**). As described for **9**, but using *Kryptofix 22* instead of 1,7-dioxa-4,10-diazacyclododecane. White solid (75%). M.p. 74–78°. ^{1}H-NMR ($CDCl_3$, 200 MHz; superposition of spectra of 4 slowly exchanging isomers): 2.6–3.1 (*m*, 2 H, CH_2N); 3.4–4.7 (*m*, 28 H, CH_2O, OCH_2CO, CH_2N); 5.08, 5.27, 5.37, 5.64 (*X*'s of *ABX*'s, 1 H (1:7:10:3), $CHCH_2O$); 7.4–8.02 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 47.3–49.6, 67.7–72.0, 73.5–80.7 (complex signal groups, CH_2N, OCH_2CO, CH_2O, $CHCH_2O$); 124.6, 124.7, 128.8, 128.9, 129.1, 129.2, 133.3, 133.6, 133.9, 134.0, 148.4, 148.5 (arom. C); 168.1, 168.6, 169.2, 169.4, 169.7 (C=O). FAB-MS: 548 (46, $[M + Na]^+$), 526 (100, $[M + H]^+$). Anal. calc. for $C_{24}H_{35}N_3O_{10} \cdot H_2O$ (543.6): C 53.03, H 6.86, N 7.73; found: C 53.08, H 6.74, N 7.51.

5-(4,5-Dimethoxy-2-nitrophenyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane-2,9-dione (**12**). As described for **9**, but using **8b** and *Kryptofix 22* instead of **8a** and 1,7-dioxa-4,10-diazacyclododecane, respectively. Slightly yellow powder (70%). M.p. 84–88°. ^{1}H-NMR ($CDCl_3$, 200 MHz; superposition of spectra of 4 slowly exchanging isomers): 2.6–3.1 (*m*, 2 H, CH_2N); 3.35–4.7 (*m*, 31 H, CH_2O, OCH_2CO, CH_2N, CH_3O); 4.94, 5.39, 5.45, 5.72 (*X*'s of *ABX*'s, 1 H, $CHCH_2O$); 7.18, 7.25, 7.33, 7.41 (*s*, 1 H (1:9:3:7), 1 arom. H); 7.57, 7.58, 7.61, 7.73 (*s*, 1 H (1:9:3:7), 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 46.0–49.5, 56.4–56.8, 68.0–81.0 (complex signal groups, CH_3O, CH_2N, OCH_2CO, CH_2O, $CHCH_2O$); 107.8, 108.0, 109.5, 109.8, 109.9, 128.6, 129.4, 140.5, 148.2, 148.3, 153.7, 153.9, 154.1 (arom. C); 168.0, 168.5, 169.2, 169.4 (C=O). FAB-MS: 608 (17, $[M + Na]^+$), 586 (100, $[M + H]^+$). Anal. calc. for $C_{26}H_{39}N_3O_{12}$ (585.6): C 53.33, H 6.71, N 7.18; found: C 52.83, H 6.77, N 7.10.

5-(2-Nitrophenyl)-4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]icosane (**1**). A 1M soln. of $BH_3 \cdot THF$ (2.5 ml, 2.5 mmol) in THF was added quickly to an ice-cold, stirred soln. of **9** (130 mg, 0.29 mmol) in dry THF (4 ml) under N_2. The ice-bath was removed and the soln. stirred at r.t. for 30 min, afterwards refluxed for 2 h. After cooling to r.t., H_2O (6 ml) was added with great caution. The mixture was evaporated and the residual, white solid redissolved in MeOH and evaporated again, which was repeated 3 times. After the addition of 4 ml of CF_3COOH/THF 1:1 and

stirring at r.t. for 1 week, the soln. was thoroughly evaporated. The crude product was redissolved in H_2O (2 ml) and passed through an anion-exchange column (2 g *Dowex 1* × *8*, OH^- form, 200–400 mesh) with H_2O. Evaporation and drying the product at < 0.1 Torr gave **1** as a slightly yellow oil (119 mg, 100%). UV/VIS (0.01M 2-amino-2-(hydroxymethyl)propane-1,3-diol hydrochloride (*Tris*-HCl) pH 8.0): 265 (4500). ^{1}H-NMR ($CDCl_3$, 250 MHz): 2.55–2.92 (*m*, 12 H, CH_2N); 3.35–3.9 (*m*, 14 H, CH_2O); 5.12 (*X* of *ABX*, 1 H, $CHCH_2O$); 7.40 (*dt*, $J = 1.3, 7.7$, 1 arom. H); 7.60 (*dt*, $J = 1.3, 7.9$, 1 arom. H); 7.74 (*dd*, $J = 1.2, 7.9$, 1 arom. H); 7.87 (*dd*, $J = 1.3, 8.1$, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 63 MHz): 54.7, 54.9, 55.3, 55.7, 57.1, 57.2 (CH_2N); 69.1, 69.2, 69.4, 70.0, 70.2, 70.5 (CH_2O); 74.9 ($CHCH_2O$); 77.5 ($CHCH_2O$); 124.2, 128.2, 128.7, 133.1, 135.7, 148.9 (arom. C). FAB-MS: 432 (7, $[M + Na]^+$), 410 (100, $[M + H]^+$). Anal. calc. for $C_{20}H_{31}N_3O_6$ (409.5): C 58.66, H 7.63, N 10.26; found: C 58.87, H 7.52, N 10.23.

5-(2-Nitrophenyl)-4,7,13,16,21-pentaoxa-1,10-diazabicyclo[8.8.5]tricosane (**2**). As described for **1** from **10**. Slightly yellow oil, mixture of 2 diastereoisomeric pairs. UV/VIS (0.1M Me_4NOH): 263 (4900). ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.44–2.86 (*m*, 12 H, CH_2N); 3.33–3.9 (*m*, 18 H, CH_2O); 5.14, 5.23 (*X*'s of *ABX*'s, 1 H, $CHCH_2O$); 7.39 (*t*, $J = 7.6$, 1 arom. H); 7.60 (*t*, $J = 7.5$, 1 arom. H); 7.76 (*d*, $J = 8.0$, ½ H, arom. H); 7.80 (*d*, $J = 8.1$, ½ H, arom. H); 7.84 (*d*, $J = 7.6$, ½ H, arom. H); 7.88 (*d*, $J = 8.0$, ½ H, arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 55.4, 55.9, 56.2, 56.75, 56.8, 56.98, 57.05 (CH_2N); 68.1, 69.5, 69.6, 69.7, 69.9, 70.2, 70.3, 70.5, 70.6 (CH_2O); 74.67, 74.71 ($CHCH_2O$); 76.7, 77.2 ($CHCH_2O$); 124.2, 128.2, 129.1, 129.2, 133.1, 133.3, 135.6, 135.7, 148.8, 149.0 (arom. C). FAB-MS: 476 (13, $[M + Na]^+$), 454 (100, $[M + H]^+$). Anal. calc. for $C_{22}H_{35}N_3O_7$ (453.5): C 58.26, H 7.78, N 9.27; found: C 58.11, H 7.50, N 8.99.

5-(2-Nitrophenyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (**3**). As described for **1** from **11**. Colorless needles (100%). M.p. 98–98.5°. UV/VIS (0.01M *Tris*-HCl pH 8.0): 265 (4500). ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.5–2.9 (*m*, 12 H, CH_2N); 3.3–3.9 (*m*, 22 H, CH_2O); 5.20 (*X* of *ABX*, 1 H, $CHCH_2O$); 7.42 (*dt*, $J = 1.4, 7.7$, 1 arom. H); 7.63 (*dt*, $J = 1.6, 7.6$, 1 arom. H); 7.79 (*dd*, $J = 1.4, 7.8$, 1 arom. H); 7.90 (*dd*, $J = 1.0, 8.1$, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 55.6, 55.7, 56.0, 56.1 (CH_2N); 68.5, 69.6, 70.2, 70.7, 70.8, 70.9 (CH_2O); 74.8 ($CHCH_2O$); 77.2 ($CHCH_2O$); 124.2, 128.2, 129.0, 133.1, 135.5, 148.7 (arom. C). FAB-MS: 520 (7, $[M + Na]^+$), 498 (100, $[M + H]^+$). Anal. calc. for $C_{24}H_{39}N_3O_8$ (497.6): C 57.93, H 7.90, N 8.44; found: C 57.88, H 7.84, N 8.36.

Monocrystals of **3** were obtained by slow evaporation of a MeOH soln. at r.t.

5-(4,5-Dimethoxy-2-nitrophenyl)-4,7,13,16,21,14-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (**4**). As described for **1** from **12**. After anion-exchange chromatography, the product was purified by hexane extraction. The soln. was evaporated to give **4** as a yellow oil (65%). UV/VIS (0.01M Me_4NOH): 347 (5100), 310 (4700), 243 (10100). ^{1}H-NMR ($CDCl_3$): 2.5–2.9 (*m*, 12 H, CH_2N); 3.4–3.8 (*m*, 22 H, CH_2O); 3.92, 3.96 (2*s*, 6 H, CH_3O); 5.34 (*X* of *ABX*, 1 H, $CHCH_2O$); 7.22 (*s*, 1 arom. H); 7.57 (*s*, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 55.5, 55.7, 55.9, 56.0, 56.2, 56.3, 56.5 (CH_3O, CH_2N); 69.1, 69.8, 70.0, 70.3, 70.6, 70.8, 71.0 (CH_2O); 75.0 ($CHCH_2O$); 77.3 ($CHCH_2O$); 107.7, 109.7, 131.2, 140.6, 147.9, 153.5 (arom. C). FAB-MS: 580 (8, $[M + Na]^+$), 558 (100, $[M + H]^+$). Anal. calc. for $C_{26}H_{43}N_3O_{10}$ (557.6): C 56.00, H 7.77, N 7.54; found: C 55.77, H 7.77, N 7.38.

Crystalline KSCN Cryptate of [5-(2-nitrophenyl)-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane-K^8,N^1,N^{10},O^4,O^7,O^{13},O^{16},O^{21},O^{24}*]potassium* (**13**). A mixture of **3** (21 mg, 42 µmol) and KSCN (32 mg, 220 µmol) in $CHCl_3$ (1.5 ml) was incubated under Ar at 60° for 5 min. After cooling to r.t., the mixture was stirred for 14 h. The residual salt was filtered off and washed with $CHCl_3$ (1 ml). The filtrate was evaporated. To obtain uniform crystals, the remaining yellow, oily cryptate was redissolved in hot AcOEt (10 ml). After cooling to r.t., **13** crystallized within 24 h as colorless, transparent prisms. M.p. 149–151°. ^{1}H-NMR ($CDCl_3$, 200 MHz): 2.3–2.8 (*m*, 12 H, CH_2N); 3.4–3.8 (*m*, 22 H, CH_2O); 5.15 (*X* of *ABX*, 1 H, $CHCH_2O$); 7.52 (*dt*, $J = 1.4, 7.8$, 1 arom. H); 7.68–7.81 (*m*, 2 arom. H); 7.95 (*dd*, $J = 1.0, 8.0$, 1 arom. H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 53.4, 53.5, 53.9, 54.2, 54.7 (CH_2N); 65.8, 67.3, 67.5, 67.7, 67.8, 70.35, 70.4, 70.6 (CH_2O); 74.2 ($CHCH_2O$); 77.2 ($CHCH_2O$); 124.9, 129.0, 129.4, 132.9, 134.0, 149.0 (arom. C).

X-Ray Structure Determination of **3** *and* **13**. Measurements were performed on an *Enraf-Nonius-CAD4* diffractometer using CuK_α radiation (graphite monochromator) at r.t. Data concerning the measurements and structure determinations are summarized in the *Table*. Empirical absorption corrections were based on psi scans. The calculations were performed with the SDP program system.

The structure of **3** was determined by direct methods using program *MULTAN 80*. All H-atoms were taken from a difference *Fourier* synthesis and included in the structure refinement with fixed isotropic thermal parameters. The final difference density was less than 0.28 e/Å^3.

The structure of **13** was determined by direct methods using program *SHELXS-86*. The H-atoms were placed at idealized calculated positions and were not refined. The SCN^- group was found to be disordered and was refined with a split-atom model. The final difference *Fourier* synthesis showed residual density up to 0.50 e/Å^3 near the disordered SCN^- group, but was otherwise less than 0.26 e/Å^3.

Table. *Crystal Data of* **3** *and* **13**

	3	**13**
Formula	$C_{24}H_{39}N_3O_8$	$C_{24}H_{39}N_3O_8 \cdot KSCN$
Mol. wt.	497.59	594.78
Crystal shape	needles	prismatic
Crystal color	colorless	colorless
Crystal dimensions [mm]	0.19 × 0.27 × 0.98	0.16 × 0.18 × 0.20
Crystal system	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a [Å]	7.968(3)	10.125(2)
b [Å]	11.0012(7)	11.726(2)
c [Å]	15.400(1)	14.084(2)
α [°]	74.396(5)	72.34(1)
β [°]	85.77(2)	72.56(2)
γ [°]	84.39(2)	77.43(2)
V [Å^3]	1292.3(5)	1505.3(5)
Z	2	2
ρ_{calc} [g/cm^3]	1.279	1.312
$\mu(CuK_\alpha)$ [cm^{-1}]	7.6	26.2
Absorption correction	0.95–1.00	0.92–1.00
Scan mode	ω	ω
Scan range	hemisphere	hemisphere
$(2\Theta)_{max}$ [°]	130	120
Number of reflections measured	4723	4773
Independent reflections	4367	4479
Reflections used with $I > O$	4265	4317
Number of variables	434	355
$R(F)$	0.055	0.048
$wR(F)$	0.048	0.043

Full data concerning the crystal-structure determinations have been deposited and are available from *Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH*, D–7514 Eggenstein-Leopoldshafen 2, on quoting the depository number *CSD*-55267, the names of the authors, and the journal citation.

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