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Synthesis and Crystal Structure of a Macrotricyclic Chelating Agent

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The reaction between *N*-benzyl-2,2′-iminobis[*N*-(chloroethanoyl)ethylamine] and 1,4-diazacycloheptane in acetonitrile furnished as the main product the 7/15-membered macrobicycle 7-benzyl-3,11-dioxo-1,4,7,10,13-pentaazabicyclo[11.3.2]-octadecane, and a 7,7,30-macrotricyclic compound as a minor product. The structure of the minor 2:2 cyclization product, 7,23-dibenzyl-3,11,19,27-tetraoxo-1,4,7,10,13,17,20,23,26,29-decaazatricyclo[27.3.2.2^{13,17}]hexatriacontane, was established by X-ray diffraction analysis. The macrotricyclic compound crystallizes in the triclinic space group *P*-1, cell dimensions $a = 8.352(2)$, $b = 10.195(2)$, $c = 12.064(3)$ Å, $\alpha = 94.44(2)$, $\beta = 100.84(2)$, $\gamma = 94.26(2)$ and $Z = 1$ ($D_x = 1.34$ g cm^{-3}).

There is an increasing interest in the use of metal chelates in medicine; this includes both therapeutic and diagnostic applications.[1] Contrast agents for magnetic resonance imaging (MRI) constitute a new class of diagnostic drugs based on paramagnetic chelates or superparamagnetic particles.[2,3] The most interesting paramagnetic element for these chelates is gadolinium(III). Four chelating agents are today widely used for chelation of Gd in clinically useful chelates: the acyclic compounds DTPA and DTPA-BMA, and the 12-membered macrocycles DOTA **1a** and HP-DO3A **1b**.[4,5]

As part of our on-going program on the synthesis of new contrast agents for medical imaging we are focussing on bicyclic macrocycles with 7/15-membered rings and their corresponding dimers.[6,7]

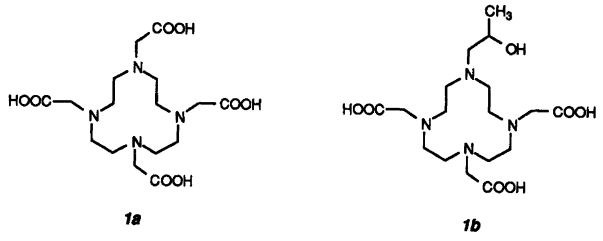


Fig. 1. The 12-membered macrocycles DOTA (**1a**) and HP-DO3A (**1b**).

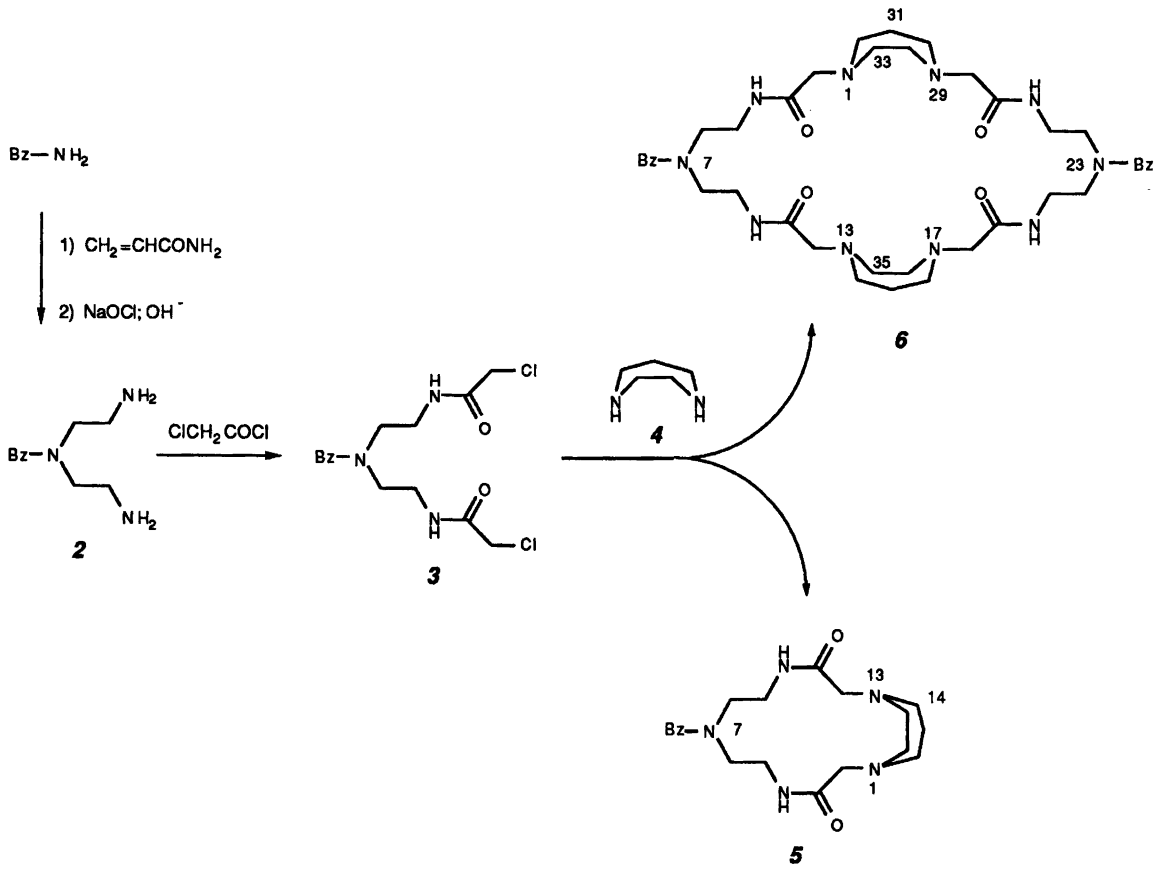
Results and discussion

Synthesis. The 7/15-membered macrobicycle **5** was prepared in 75% yield from the condensation of the chloramide **3** and 1,4-diazacycloheptane **4**.

Ring-closing reactions between dichlorides and diamines are a general synthetic method for the preparation of aza-crown macrocycles.[8–10] During the synthesis of the 7/15-membered macrobicycle **5** we obtained a minor crystalline product which on the basis of ^{1}H and ^{13}C NMR and mass spectroscopy, and elemental analysis, was assumed to possess a dimeric structure **6** resulting from a 2:2 cyclization process. A single crystal structure analysis verified the structure as **6**.

Formation of dimers and larger products are well described side-reactions in the 1:1 cyclization synthesis of macrocycles.[8] However, we have not encountered these large molecules in previous work when condensing bisanhydrides and acyclic diamines.[7]

In a high concentration experiment (ca. 0.1 M) the 1:1- and 2:2-addition products were isolated in *lower* yields compared with those obtained when a lower concentration (ca. 0.01 M) was employed. The ratio between the two products was somewhat reduced as well. The reduced overall yield of both products can be explained from polycyclizations (3:3, 4:4, etc.) and polymerization. According to Ziegler *et al.*[11] polymerization can be prevented when the cyclization is carried out in concentrations not exceeding 0.001 M.



Scheme 1. Synthesis of 7-benzyl-3,11-dioxo-1,4,7,10,13-pentaazabicyclo[11.3.2]octadecane (**5**) and 7,23-dibenzyl-3,11,19,27-tetraoxo-1,4,7,10,13,17,20,23,26,29-decaazatricyclo[27.3.2.2^{13,17}]hexatriacontane (**6**).

High concentration favoured to some extent the 2:2 cyclization process. The ratios between the 1:1 and the 2:2 processes were found to be approximately 1:1/2:2 = 6.2 and 1:1/2:2 = 6.8 when employing high (ca. 0.1 M) and low concentration (ca. 0.01 M), respectively.

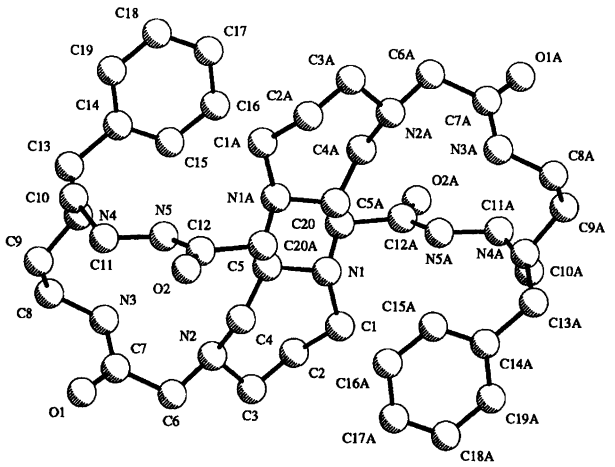


Fig. 2. Perspective drawing of 7,23-dibenzyl-3,11,19,27-tetraoxo-1,4,7,10,13,17,20,23,26,29-decaazatricyclo [27.3.2.2^{13,17}]hexatriacontane (**6**) showing the numbering of atoms.

This is in accordance with the general literature on macrocycle cyclization reactions.[12]

Other factors which might slow down the 1:1 cyclization process are the rigidity of the cyclic diamine **4** and the *cis–trans* isomerism of the amide bonds. Compounds like catechols are typical rigid difunctional molecules which have been found to behave more sluggishly in 1:1 cyclizations.[13]

Crystal structure. The crystals of the more polar product, $C_{40}H_{62}N_{10}O_4$, are triclinic with space group *P*-1, cell dimensions $a = 8.352(2)$, $b = 10.195(2)$, $c = 12.064(3)$ Å, $\alpha = 94.44(2)$, $\beta = 100.84(2)$, $\gamma = 94.26(2)$ and $Z = 1$ ($D_x = 1.34$ g cm^{-3}). Using $2\theta_{(max)} = 55°$ and Mo K_α radiation, and choosing an observed–unobserved cut-off at $2.5\sigma(I)$, a total of 3588 observed reflections were recorded on an automatic diffractometer at low temperature. No corrections for secondary extinction or absorption were applied. The structure was solved by direct methods[14] and refined by full-matrix least-squares techniques.[15] Weights in least-squares were calculated from the standard deviations in intensities, $\sigma(I)$, taken as $\sigma(I) = [C_1 + (0.02C_2)^2]^{1/2}$, where C_1 is the total number of counts and C_2 the net count. Anisotropic temperature factors were used for non-hydrogen atoms. Hydrogen atom positions were calculated. The final *R*-value was

4.27% (R_w = 4.72%) for 3588 observed reflections. RMS amplitudes of thermal motion range from 0.16 to 0.28 Å. Final fractional coordinates with estimated standard deviations are listed in Table 1. Bond distances and angles with estimated standard deviations are given in Table 2. Fig. 2 is a perspective drawing of the molecule showing

Table 1. Final fractional coordinates and equivalent temperature factors with estimated standard deviations for all atoms in **6**.

Atom	x	y	z	U_{eq} [a]
O1	0.70388(15)	0.61644(11)	0.63690(10)	0.042
O2	0.13319(14)	0.28298(12)	0.69296(10)	0.039
N1	0.67620(14)	0.00234(11)	0.38794(10)	0.021
N2	0.76378(15)	0.32799(12)	0.45755(10)	0.024
N3	0.85949(15)	0.44679(11)	0.67383(10)	0.023
N4	0.73467(14)	0.33216(11)	0.86797(10)	0.022
N5	0.39850(15)	0.24638(12)	0.73941(11)	0.027
C1	0.71747(19)	0.06602(15)	0.28986(12)	0.026
C2	0.8566(2)	0.1761(2)	0.3146(1)	0.031
C3	0.8039(2)	0.3115(2)	0.3445(1)	0.032
C4	0.63272(18)	0.22987(14)	0.47375(12)	0.025
C5	0.69229(17)	0.09411(14)	0.49164(12)	0.023
C6	0.7213(2)	0.4627(2)	0.4803(1)	0.031
C7	0.75908(18)	0.51478(14)	0.60458(13)	0.028
C8	0.91886(18)	0.49430(14)	0.79234(12)	0.024
C9	0.79389(18)	0.47087(14)	0.86734(12)	0.024
C10	0.58675(19)	0.32362(14)	0.91659(13)	0.026
C11	0.43614(19)	0.34985(14)	0.83291(13)	0.028
C12	0.24743(18)	0.21935(14)	0.67751(13)	0.026
C13	0.86134(19)	0.25733(15)	0.92991(13)	0.028
C14	0.81713(17)	0.11033(14)	0.90730(12)	0.023
C15	0.80770(19)	0.04878(15)	0.79923(13)	0.029
C16	0.7650(2)	−0.0855(2)	0.7763(1)	0.035
C17	0.7323(2)	−0.1607(2)	0.8615(2)	0.037
C18	0.7428(3)	−0.1008(2)	0.9694(2)	0.046
C19	0.7848(2)	0.0343(2)	0.9918(1)	0.039
C20	0.22307(18)	0.10627(15)	0.58479(13)	0.028
HN3	0.906(6)	0.385(4)	0.646(4)	0.06(1)
HN5	0.480(6)	0.198(4)	0.722(4)	0.07(1)
H11	0.627(6)	0.100(4)	0.251(4)	0.00(1)
H12	0.749(6)	−0.007(5)	0.240(4)	0.01(1)
H21	0.909(6)	0.180(4)	0.243(4)	0.05(1)
H22	0.943(6)	0.154(5)	0.365(4)	0.03(1)
H31	0.897(6)	0.386(5)	0.341(4)	0.04(1)
H32	0.711(6)	0.329(4)	0.293(4)	0.04(1)
H41	0.540(6)	0.230(4)	0.414(4)	0.03(1)
H42	0.607(6)	0.260(4)	0.547(4)	0.02(1)
H51	0.809(6)	0.108(4)	0.534(4)	0.02(1)
H52	0.632(6)	0.046(4)	0.537(4)	0.03(1)
H61	0.608(6)	0.475(4)	0.455(4)	0.04(1)
H62	0.788(6)	0.516(5)	0.451(4)	0.04(1)
H81	0.942(6)	0.593(5)	0.798(4)	0.02(1)
H82	1.015(6)	0.456(4)	0.818(4)	0.03(1)
H91	0.841(6)	0.513(4)	0.948(4)	0.02(1)
H92	0.706(6)	0.516(5)	0.838(4)	0.02(1)
H101	0.594(6)	0.385(4)	0.988(4)	0.03(1)
H102	0.573(6)	0.241(5)	0.941(4)	0.02(1)
H111	0.342(6)	0.353(4)	0.868(4)	0.03(1)
H112	0.445(5)	0.431(5)	0.803(4)	0.04(1)
H131	0.876(6)	0.287(4)	1.014(4)	0.03(1)
H132	0.955(6)	0.273(4)	0.902(4)	0.04(1)
H15	0.834(6)	0.107(4)	0.740(4)	0.04(1)
H16	0.758(5)	−0.127(4)	0.696(4)	0.06(1)
H17	0.694(6)	−0.264(5)	0.843(4)	0.07(1)
H18	0.723(5)	−0.160(4)	1.037(4)	0.09(1)
H19	0.793(5)	0.082(4)	1.069(4)	0.06(1)
H201	0.111(6)	0.078(4)	0.573(4)	0.04(1)
H202	0.253(6)	0.141(4)	0.523(4)	0.04(1)

[a] $U_{eq} = (U11 + U22 + U33)/3$ for anisotropic atoms.

Table 2. Bond distances and bond angles with estimated standard deviations for non-hydrogen atoms.

Distances		Distances	
O1–C7	1.231(2)	O2–C12	1.227(2)
N1–C1	1.476(2)	N1–C5	1.481(2)
N1–C20	1.461(2)	N2–C3	1.464(2)
N2–C4	1.478(2)	N2–C6	1.463(2)
N3–C7	1.340(2)	N3–C8	1.454(2)
N4–C9	1.464(2)	N4–C10	1.463(2)
N4–C13	1.474(2)	N5–C11	1.455(2)
N5–C12	1.336(2)	C1–C2	1.524(3)
C2–C3	1.518(3)	C4–C5	1.523(3)
C6–C7	1.517(3)	C8–C9	1.522(3)
C10–C11	1.512(3)	C12–C20	1.517(3)
C13–C14	1.508(3)	C14–C15	1.388(3)
C14–C19	1.382(3)	C15–C16	1.382(3)
C16–C17	1.383(3)	C17–C18	1.379(3)
Angle		**Angle**	
C1–N1–C5	113.8(2)	C1–N1–C20	111.3(2)
C5–N1–C20	108.4(2)	C3–N2–C4	113.1(2)
C3–N2–C6	109.7(2)	C4–N2–C6	111.1(2)
C7–N3–C8	121.3(2)	C9–N4–C10	109.8(2)
C9–N4–C13	111.7(2)	C10–N4–C13	110.9(2)
C11–N5–C12	121.8(2)	N1–C1–C2	116.9(2)
C1–C2–C3	114.1(2)	N2–C3–C2	113.8(2)
N2–C4–C5	112.8(2)	N1–C5–C4	115.8(2)
N2–C6–C7	114.5(2)	O1–C7–N3	123.3(2)
O1–C7–C6	120.7(2)	N3–C7–C6	116.0(2)
N3–C8–C9	113.9(2)	N4–C9–C8	114.6(2)
N4–C10–C11	112.3(2)	N5–C11–C10	110.5(2)
O2–C12–N5	122.4(2)	O2–C12–C20	120.9(2)
N5–C12–C20	116.7(2)	N4–C13–C14	111.8(2)
C13–C14–C15	119.8(2)	C13–C14–C19	121.6(2)
C15–C14–C19	118.6(2)	C14–C15–C16	120.7(2)
C15–C16–C17	120.3(2)	C16–C17–C18	119.5(2)
C17–C18–C19	120.0(2)	C14–C19–C18	120.9(2)

the numbering of atoms. Lists of thermal parameters and observed and calculated structure factors are available from P. Groth on request.

Experimental

General methods. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian XL-200 instrument using Me_4Si or the central solvent peaks (^{13}C) of $CDCl_3$ (77 ppm) or CD_3OD (49 ppm) as internal references. Melting points were determined on a Reichert melting point apparatus and are uncorrected. Mass spectra were recorded on a Micromass 7070F instrument. Elemental analyses were performed by Ilse Beetz, Mikroanalytisches Laboratorium, D-96301 Kronach, Germany.

N-Benzyl-2,2'-iminobis[N-(chloroethanoyl)ethylamine] (**3**). Separate solutions of chloroethanoyl chloride (46.2 g, 0.805 mol) in $CHCl_3$ (400 ml) and K_2CO_3 (102.6 g, 0.742 mol) in H_2O (300 ml) were added dropwise over a 2 h period to a stirred solution of *N*-benzyl-2,2'-iminobis(ethylamine)[16] (**2**; 46.2 g, 0.239 mol) in $CHCl_3$ (300 ml). The stirring was continued for 24 h at ambient temperature. The mixture was then transferred to a separatory funnel and the pH adjusted to 10 with 2 M NaOH. The $CHCl_3$ layer was collected and the aqueous phase extracted with $CHCl_3$ (150 ml). The combined $CHCl_3$ extracts were washed with saturated, aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated to dryness *in vacuo* furnishing a white, solid material (74.85 g; 90%) which was not further purified. R_f [SiO_2; 5% CH_3OH in $CHCl_3$]: 0.4. MS [*m/z*; CI/isobutane; ions with relative intensity ≥ 5%]: 350 (12), 349 (12), 348 (67), 347 (19), 346 [M^+ ($2 \times {}^{35}Cl$) 100], 312 (6), 239 (7), 220 (8). ^1H NMR ($CDCl_3$): δ 2.58 (4 H, t, *J* 5.5 Hz), 3.30 (4 H, q, *J* 5.8 Hz), 3.51 (2 H, s), 3.95 (4 H, s), 7.0–7.2 (2 H, m), 7.2–7.4 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 37.7, 42.9, 53.0, 58.5, 126.5, 127.5, 128.0, 137.7, 164.9.

7-Benzyl-3,11-dioxo-1,4,7,10,13-pentaazabicyclo[11.3.2]octadecane (**5**). A solution of 1,4-diazacycloheptane (**4**; 6.64 g, 36.34 mmol) in acetonitrile (150 ml) was added in one portion to a mixture of *N*-benzyl-2,2'-iminobis[*N*-(chloroethanoyl)ethylamine] (**3**; 11.44 g, 33.04 mmol) and K_2CO_3 (15.08 g, 109.13 mmol) in acetonitrile (250 ml). The mixture was stirred at ambient temperature for 63 h. An additional portion of 1,4-diazacycloheptane (0.330 g, 3.29 mmol) was added. The mixture was then refluxed for

8 h followed by stirring at room temperature for 15 h. Most of the solvent was removed *in vacuo*. 2 M NaOH (25 ml) and saturated aqueous NaCl (25 ml) were added to the residue which was extracted with $CHCl_3$ (250, 125 and 125 ml). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residue (16.41 g) was chromatographed on an SiO_2 column (92 g) furnishing two fractions on elution with 5% MeOH in $CHCl_3$. The less polar fraction (5.52 g; oil; 45%) was identified as 7-benzyl-3,11-dioxo-1,4,7,10,13-pentaazabicyclo[11.3.2] octadecane (**5**). R_f [SiO_2; 10% CH_3OH in $CHCl_3$]: 0.8. MS [*m/z* (EI; ions ≥ 70 with relative intensity ≥ 15%]: 374 ($[M+1]^+$, 27), 373 (M^+, 95), 282 [$(M-C_6H_5CH_2)^+$, 16], 225 [$(M-148)^+$, 23], 182 (16), 170 (18), 134 (18), 127 (41), 125 (27), 113 (28), 112 (16), 111 (20), 97 (16), 91 (100), 82 (16), 70 (29). ^{1}H NMR ($CDCl_3$): δ 1.6–2.1 (2 H, m), 2.3–2.9 (13 H, m), 3.0–3.7 (7 H, m), 3.48 (2 H, s), 7.1–7.4 (5 H, m), 7.9 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 33.2, 35.5, 53.0, 56.1, 56.6, 57.1, 64.2, 126.6, 127.5, 128.0, 137.0, 169.2. The more polar fraction was identified as below.

7,23-Dibenzyl-3,11,19,27-tetraoxo-1,4,7,10,13,17,20,23,26,29-decaazatricyclo[27.3.2.2^{13,17}]hexatriacontane (**6**). Weight after crystallization (large prisms on standing at ambient temperature) from C_2H_5OH: 1.06 g (9%). M.p. 162 °C. R_f [SiO_2; 10% CH_3OH in $CHCl_3$]: 0.3. MS [*m/z*; EI; 80 < ions ≤ 446 with relative intensity ≥ 10%; 598 ≤ ions ≤ 747 with relative intensity ≥ 2%]: 747 ($[M+1]^+$, 4), 746 (M^+, 9), 655 ($[M-C_6H_5CH_2]^+$, 8), 598 ($[M-148]^+$, 2), 446 (15), 207 (19), 169 (12), 167 (12), 149 (30), 127 (12), 125 (12), 113 (12), 112 (11), 111 (10), 105 (15), 104 (17), 92 (18), 91 (100), 85 (10), 84 (19), 83 (20), 82 (15), 81 (10). ^{1}H NMR ($CDCl_3$): δ 1.6–1.8 (4 H, m), 2.4–2.8 (24 H, m), 3.08 (8 H, s), 3.2–3.35 (8 H, m), 3.64 (4 H, s), 7.08–7.25 (10 H, m), 7.35–7.5 (4 H, m). ^{13}C NMR (CD_3OD): δ 29.2, 38.0, 54.1, 56.1, 56.5, 59.0, 62.5, 127.3, 128.5, 129.2, 139.5, 171.8; ($CDCl_3$): δ 27.7, 36.7, 53.2, 54.9 (2 × ^{13}C), 57.9, 61.2, 126.6, 127.6, 128.1, 138.1, 169.7. Anal. calcd. for $C_{40}H_{62}N_{10}O_4$: C 64.32; H 8.37; N 18.75; O 8.57. Found: C 64.33; H 8.38; N 18.71.

Low concentration experiment. A solution of 1,4-diazacycloheptane (**4**; 0.360 g, 3.59 mmol) in acetonitrile (50 ml) was added in one portion to a mixture of *N*-benzyl-2,2′-iminobis[*N*-(chloroethanoyl)ethylamine] (**3**; 1.141 g, 3.30 mmol) and K_2CO_3 (1.546 g, 11.19 mmol) in acetonitrile (200 ml). The mixture was stirred at ambient temperature for a total of 165 h. A small amount of 1,4-diazacycloheptane (**4**; 52 mg, 0.52 mmol) had in the meantime been added to the reaction mixture. The solvent was removed *in vacuo*. Saturated aqueous NaCl (15 ml) was added to the residue which was extracted with CH_2Cl_2 (4 × 60 ml). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residue (1.30 g) was chromatographed on an SiO_2 column (15 g) furnishing two fractions on elution with 2, 5 and 10% MeOH in $CHCl_3$. The less polar fraction (968 mg) consisted of 7-benzyl-3,11-dioxo-1,4,7,10,13-pentaazabicyclo[11.3.2]-octadecane (**5**) and starting material **3** in the ratio 95: 5 as judged from TLC and ^{1}H and ^{13}C NMR spectroscopy. Estimated yield of compound **5** (920 mg): 75%. The weight of the more polar fraction, 7,23-dibenzyl-3,11,19,27-tetraoxo-1,4,7,10,13,17,20,23,26,29-decaazatricyclo[27.3.2.2^{13,17}]hexatriacontane (**6**), was found to be 135 mg corresponding to a yield of 11%.

High concentration experiment. An experiment using concentrations about ten times higher than in the experiment described above was carried out. A total of 25 ml acetonitrile was used for a mixture consisting of *N*-benzyl-2,2′-iminobis[*N*-(chloroethanoyl)ethylamine] (**3**; 1.142 g, 3.30 mmol), K_2CO_3 (1.514 g, 10.95 mmol) and 1,4-diazacycloheptane (**4**; 400 mg, 3.63 mmol). 7-Benzyl-3,11-dioxo-1,4,7,10,13-pentaazabicyclo[11.3.2]octadecane (**5**; 387 mg) and 7,23-dibenzyl-3,11,19,27-tetraoxo-1,4,7,10,13,17,20,23,26,29-decaazatricyclo[27.3.2.2^{13,17}]hexatriacontane (**6**; 59 mg) were obtained in yields of 31% and 5%, respectively.

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