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Cyclohexanedione Bisaminals as Intermediates for Cyclen, Homocyclen, and Cyclam Synthesis

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Abstract: A new easy-to-run route to cyclen, homocyclen, and cyclam is proposed, based on the cyclization with dibromo- or ditosyloxy-derivatives of bisaminal intermediates obtained by condensation of the appropriate linear tetraamine with cyclohexanedione. In the cyclization step, the use of cesium carbonate instead of potassium carbonate as proton trapper caused a remarkable increase of yields.

Keywords: Bisaminal, cyclam, cyclen, cyclohexanedione, cyclization, homocyclen

INTRODUCTION

Macrocyclic tetraamines are interesting because of their remarkable complexing properties and find applications in many areas. Their derivatives are widely developed as extractants, as cation and anion sensors, and particularly as magnetic resonance imaging (MRI) contrast agents.[1,2] Thus, easy-to-run routes for the basic tetraazamacrocycles cyclen, cyclam, and analogues are still of substantial interest. The well-known and most usual method for different macrocyclic tetraamines synthesis is the Richman and Atkins condensation of N-tosyl derivatives of linear amines with a biselectrophile, namely a ditosylate.[3] However, this general method is not without certain

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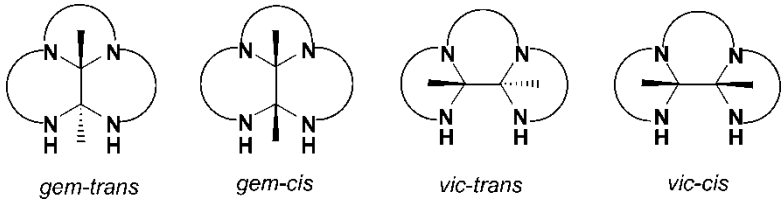
disadvantages: the last deprotection step necessitates a strong acidic medium and, above all, it is not "atom economic."

The idea of a "template effect" induced by the rigidification of a linear tetraamine obtained by condensation with a dicarbonyl compound and followed by cyclization of the resulted bisaminal with a biselectrophile is relatively recent.[4] We previously reported a successful procedure for the synthesis of tetraazamacrocycles as cyclen, homocyclen, and cyclam via cyclization of bisaminal derivatives obtained by condensation of an appropriate linear tetraamine with butanedione.[5] Other bisaminal intermediates issued from condensation of tetraamines with glyoxal,[6] pyruvic aldehyde,[7] or phenylglyoxal[8] were reported in the literature; however, to our knowledge, it seems that the use of these compounds as precursors of tetraazamacrocycles is sometimes more difficult for the following causes. First, macrocyclic bisaminals issued from glyoxal are very stable;[9] they resist acidic hydrolysis and necessitate more complicated deprotection reactions involving hydroxylamine, oxidation agent, or hydrazine hydrate to release the macrocycle.[4,6] Second, in some cases, linear tetraamine bisaminals are not stable and, during the cyclization reaction or deprotection step, lead to some complications: formation of amidinium salts or conversion to lactam and even to amino acid.[8] Moreover, the formation of linear tetraamine bisaminals often gives rise to a mixture of stereoisomers because of several possibilities for condensation.[10] That could yield multiple stereoisomers according to the *vic*- or *gem*-insertion of the dicarbonyl reagent and *cis*- or *trans*-configuration of the resulting bisaminal bridge (Scheme 1). In the case of asymmetrical dicarbonyl compounds, the situation could be still more complicated. Furthermore, it is not certain that all these isomers present the same reactivity toward a biselectrophile derivative to give a macrocyclic intermediate.

The formation of a bisaminal with a cyclic dicarbonyl compound should allow us to avoid a complex mixture of isomers and to make the bisaminal structure more rigid. As a matter of fact, bisaminals **1a, 2a**, and **3a** obtained from condensation of triethylenetetraamine **1**, N,N′-bis(2-aminoethyl)-1,3-propanediamine **2**, and N,N′-bis(3-aminopropyl)-1,2-ethylene-diamine **3** with cyclohexan-1,2-dione were, to our knowledge, never involved in cyclization processes.[11] So, it appeared interesting to study the possibility of their



Scheme 1. Theorical bisaminals of linear tetraamines.

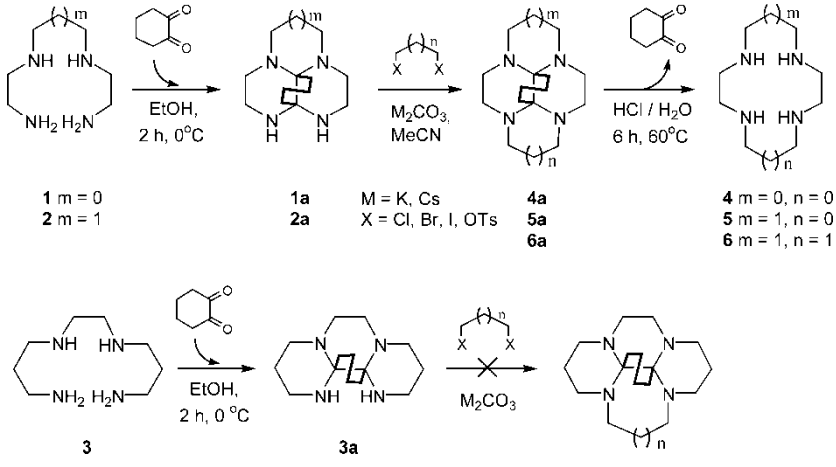
utilization to obtain cyclen, homocyclen, and cyclam through their subsequent condensation with biselectrophiles and deprotection. In this article, we report synthesis, properties, and particularities of cyclohexanedione bisaminals.

RESULTS AND DISCUSSION

As previously observed, the condensation of linear tetraamines **1, 2**, and **3** with cyclohexanedione in ethanol led to only a single condensation product, the most stable isomer containing the maximum of six-membered fused rings: the *gem-cis* isomer for bisaminals **1a** and **2a** and the *vic-cis* in the case of bisaminal **3a** (Scheme 2).[11] The resulting bisaminals, obtained in 80–90% yield, were characterized by ^{13}C NMR spectroscopy, and as expected for *cis*-configurations, exchange phenomena were observed for the three bisaminals.

X-ray analysis performed for compound **1a** showed asymmetrical geometry of this bisaminal in a crystal state, which corresponds to the most favorable thermodynamic form with all six-membered cycles in chair conformation. The ORTEP view with principal bond lengths is given in Fig. 1.

The macrocyclization of linear tetraamine bisaminals **1a, 2a**, and **3a** with a dielectrophilic substrate such as dichloro-, dibromo-, diiodo-, and ditosyloxyethane or propane was performed under standard conditions for such reactions (i.e., potassium carbonate as proton trapper in acetonitrile at mild temperature) (Scheme 2). Cyclization of bisaminals **1a** and **2a** with dibromo- and ditosyloxy- derivatives led to cyclen, homocyclen, and cyclam bisaminals **4a**, **5a**, and **6a**, respectively, in 20–50% yield. The reaction generated a significant quantity of oligomer products. In the case of reactions with



Scheme 2. General route to cyclen, homocyclen, and cyclam via cyclohexanedione bisaminals.

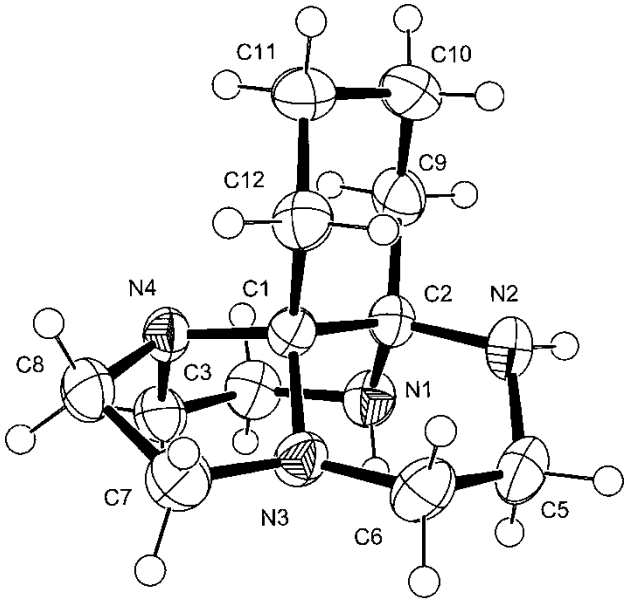


Figure 1. ORTEP view of **1a**. Selected bonds length, (Å): C(1)–C(2) 1.552(2), N(1)–C(2) 1.4748(19), N(2)–C(2) 1.457(2), C(1)–N(3) 1.4773(18), and C(1)–N(4) 1.4772(19).

dichloro- derivatives, no products were obtained, and the starting bisaminal was recovered: obviously, dichloroethane and dichloropropane are not reactive enough. On the contrary, diiodo-reagents are too reactive, and only oligomer products were formed in a short space of time, even under very mild conditions (20°C), except in the case of **2a** with diiodopropane, where cyclization occurs in 63% yield. The experimental conditions and results are given in Table 1. For bisaminal **3a,** no cyclization was observed in any case. The starting bisaminal was entirely recovered, and no trace of substitution products was observed. On the one hand, the configuration of the two nitrogen atoms is certainly not favorable for a nucleophilic substitution, which should lead either to cyclocondensation or to oligomerization, and on the other hand, because the starting biselectrophile was not recovered, certainly an elimination reaction occurred.

These very moderate yields of macrocyclic bisaminals **4a**–**6a** prompted us to look for more favorable conditions for the reaction. Changing of solvent, time, or temperature had no great influence on the yields. We also tried to use an alternative base. Replacement of potassium carbonate by triethylamine or diisopropylethylamine also kept yields at the same level. However, the use of cesium carbonate instead of potassium carbonate caused a remarkable increase of yields. Reaction of bisaminals **1a** and **2a** with dibromoethane or dibromopropane in the presence of a double excess of cesium carbonate in acetonitrile led to the formation of cyclic tetraamine

Table 1. Experimental conditions of the cyclization step

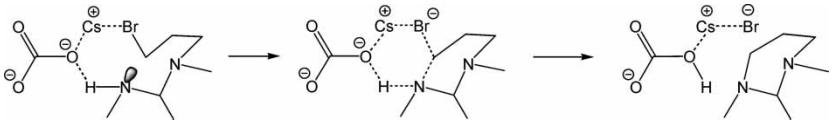
Starting bisaminal	Reagent		T (°C)	Time	Product	Yield (%)[b]	
	n	X				K_2CO_3	Cs_2CO_3
1a	0	Br	40	5 days	**4a**	31	90
1a	0	I	20	18 h	—[a]	—	—
1a	0	OTs	40	4 days	**4a**	20	50
1a	1	Br	40	3 days	**5a**	21	80
1a	1	I	20	18 h	—[a]	—	—
1a	1	OTs	40	2 days	**5a**	20	56
2a	0	Br	40	3 days	**5a**	23	85
2a	0	I	20	5 h	—[a]	—	—
2a	0	OTs	40	4 days	**5a**	51	55
2a	1	Br	40	3 days	**6a**	47	91
2a	1	I	20	18 h	**6a**	63	75
2a	1	OTs	40	2 days	**6a**	30	60

[a]Only oligomer products.
[b]Yields after recrystallization.

bisaminals **4a–6a** in about 80–90% yield. It appears that the nature of the cation in the intramolecular nucleophilic substitution process is of crucial importance. Such phenomenon, described in literature as the "cesium effect,"[12] has been known for a long time and consists in a strong promotion of cyclization reaction versus competitive oligomerization process. The influence of the cesium cation was observed for various ring-closure reactions as formation of macrocyclic lactones, crown-ethers, and others. An initial interpretation of the phenomenon considered that a fast intramolecular reaction would take place on the surface of the large, polarizable cesium ion.[13] It could be assumed that this effect is mainly due to the close carbonate–cesium ion pair. After the first nucleophilic substitution reaction, the second step of the cyclization implies the double activation of the remaining electrophilic moiety and simultaneously of the nucleophilic one. On the one hand, the cesium ion acts as a Lewis catalyst toward the leaving group while, on the other hand, the carbonate ion activates the nucleophilicity of the neighboring nitrogen atom through hydrogen bonding. The process takes place in the favorable shape of a six-membered ring. The best results were obtained with bromine as leaving group (Scheme 3).

This situation, a base ion paired with a metal ion engaged in a cyclic transition state is very similar to the classical one invoked rationalized *syn* elimination in the E2 reaction of neutral substances.[14] The higher solubility of cesium salts in aprotic solvent undoubtedly constitutes the other determining factor.[12]

Bisaminals **4a–6a** were characterized by ^{13}C NMR spectroscopy, and temperature-dependent changes were observed as well. For example, the



Scheme 3. Illustration of the "cesium effect."

spectrum of the compound **4a** recorded at 203 K (Fig. 2; spectrum a) consists of seven signals: one corresponds to the two aminal carbons, four are assigned to the eight α-carbon atoms, and two correspond to the bisaminal bridge cycle carbons. This observation is consistent with conformationally labile enantiomeric forms with axial symmetry. At 253 K, a coalescence phenomenon is observed (spectrum b), and at room temperature, fast exchange between the two enantiomeric forms occurs (spectrum c). Then, the spectrum consists of five signals; only two of them are assigned to the eight α-carbon atoms: it corresponds to the mean spectrum in which carbon atoms exchange two by two their situation (Scheme 4). The same observations are done between 298 K and 343 K for bisaminal **5a** and between 363 K and 403 K for bisaminal **6a**.

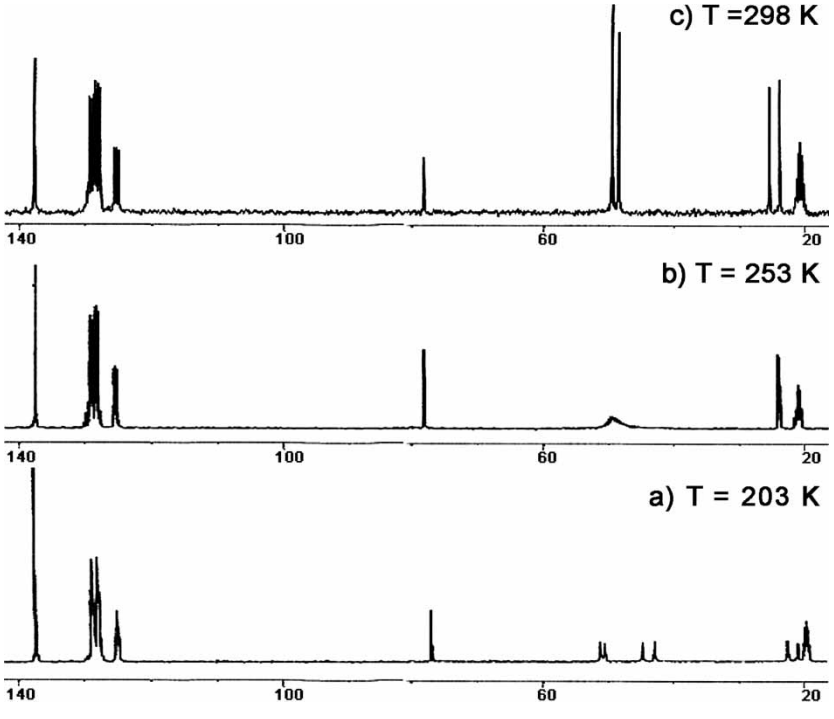
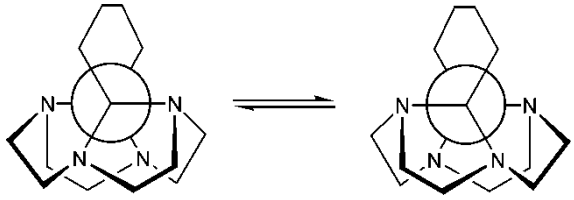


Figure 2. ^{13}C NMR spectra of bisaminal **4a** in toluene-d^8.



Scheme 4. Equilibrium between two enantiomeric forms of bisaminal **4a**.

X-ray analysis for **4a** was performed and represents in solid state one of the possible conformers characterized by chair conformation for all six-membered rings as well (Fig. 3).

Bisaminal **6a** was also prepared by direct reaction of cyclohexanedione with the corresponding macrocycle; it corresponds also to the most stable isomer containing the maximum of six-membered fused rings and therefore is identical to the one obtained by cyclization. Concerning compounds **4a** and **5a**, cyclohexanedione did not react with cyclen and homocyclen, consequently, cyclization appeared to be the only way to obtain these bisaminals.

Bisaminals **4a**–**6a** were easily deprotected to form tetraazamacrocycles. Contrary to bisaminals of glyoxal derivatives, which require hard conditions for the deprotection (treating by hydrazine hydrate at high temperature), cyclohexanedione ones lose bisaminal bridges in 1 M hydrochloric acid solution, at 60°C, during a few hours. Resulting tetraamine hydrochlorides

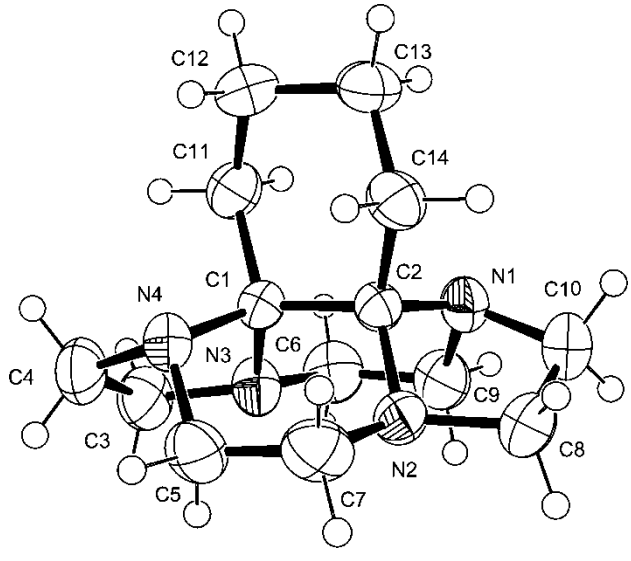


Figure 3. ORTEP of **4a**. Selected bonds length, (Å): C(1)–C(2) 1.518, N(1)–C(2) 1.454, N(2)–C(2) 1.472, C(1)–N(3) 1.462, and C(1)–N(4) 1.474.

gave their free form after 3 h in refluxing acetonitrile in the presence of potassium carbonate or, alternatively, using a strong anionic exchange resin (Amberlyst® A-26). Moreover, relatively expensive cyclohexanedione could be successfully recovered after deprotection and used again.

In conclusion, compared to previous methods proposed for the synthesis of cyclen, homocyclen, and cyclam based on the bisaminal chemistry, the association of cyclohexanedione and cesium carbonate undoubtedly constitutes an improvement: starting from the linear tetraamine, after three protection–cyclization–deprotection steps, the desired macrocycles are obtained in 75–80% yields. Removal and recovery of the protective group is cleanly and quantitatively carried out under mild acidic conditions. This procedure could certainly be successfully applied to synthesize more complicated structures containing a functionalized pendant arm brought by the biselectrophilic moiety. Further work concerning this aspect is currently in progress.

EXPERIMENTAL

General

All reagents were of commercial quality, and solvents were dried according to standard procedures. NMR spectra were acquired on a Bruker AC 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 74.47 MHz). The chemical shifts are in δ values relative to the internal standard TMS. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Mass spectra were measured using a ZabSpec TOF Micromass spectrometer. Elemental analyses were carried out by the Service de Microanalyse, CNRS, 91198 Gif sur Yvette, France.

General Procedure for the Synthesis of Linear Tetraamine Bisaminals 1a–3a

These three bisaminals were previously described;[11] here, their synthesis was performed as following: a solution of cyclohexanedione (560 mg, 5 mmol) in ethanol (30 mL) was added dropwise to a solution of the tetraamine (730 mg, 5 mmol for tetraamine **1**; 800 mg, 5 mmol for tetraamine **2**; or 870 mg, 5 mmol for tetraamine **3**) in ethanol (30 mL) at 0°C with intensive stirring, and the mixture was kept at the same temperature for 3 h. The solvent was removed under reduced pressure, and the residue was treated by diethyl ether (50 mL). A small quantity of insoluble polymer product was filtered off, and the solvent was removed to yield the corresponding bisaminal. The bisaminal can be used as such in the next step or better, recrystallized in hexane.

Bisaminal 1a: White solid, mp 110°C, yield 90%.

Bisaminal 2a: White solid, mp 124°C, yield 90%.
Bisaminal 3a: White solid, mp 133°C, yield 80%.

General Procedure for the Synthesis of Cyclic Tetraamine Bisaminals 4a–6a

The biselectrophile compound (1.1 mmol) was added to an acetonitrile (10 mL) mixture of the corresponding linear tetraamine bisaminal (1 mmol) and potassium or cesium carbonate (4 mmol). The resulting mixture was stirred at the temperature and for the time indicated in Table 1. Then, the solid was filtered off, and the solvent was removed under reduced pressure. Resulting white powder was recrystallized from hexane. Yields and conditions are indicated in Table 1.

Data

Bisaminal 4a. White solid, mp 76°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.53-1.57$ (m, 4H, $C\underline{H}_2CH_2C_{aminal}$), 1.65 (m, 4H, $CH_2C\underline{H}_2C_{aminal}$), 2.81–2.94 (m, 16H, $C\underline{H}_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 22.3$ ($\underline{C}H_2CH_2C_{aminal}$), 22.6 ($CH_2\underline{C}H_2C_{aminal}$), 47.5, 48.4 ($\underline{C}H_2N$), 77.4 ($\underline{C}_{aminal}$). IR (KBr): $\bar{\nu}(cm^{-1}) = 2950$, 2919, 2896, 2803, 2854, 1214, 1180, 1125, 1041, 961. Anal. calcd. for $C_{14}H_{24}N_4$: C, 67.70; H, 9.74; N, 22.56; found: C, 67.98; H, 10.02; N, 22.26.

Bisaminal 5a. White solid, mp 97°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.07-1.17$ (m, 1H, $C\underline{H}_2CH_2N$), 1.40–1.55 (m, 4H, $CH_2C\underline{H}_2C_{aminal}$), 2.20–3.35 (m, 1H, $C\underline{H}_2CH_2N + 4H$, $C\underline{H}_2CH_2C_{aminal} + 15H$, $C\underline{H}_2N$), 3.70–3.85 (m, 1H, CH_2N). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 17.9$, 18.3, 19.5, 21.3, 22.4 ($\underline{C}H_2CH_2N + \underline{C}H_2\underline{C}H_2C_{aminal}$), 43.9, 44.3, 45.7, 45.8, 46.8, 48.8, 50.3, 51.3 ($\underline{C}H_2N$), 72.5, 78.9 ($\underline{C}_{aminal}$). IR (KBr): $\bar{\nu}(cm^{-1}) = 2939$, 2889, 2857, 2810, 1256, 1211, 1190, 1142, 1046, 1001, 946, 878. Anal. calcd. for $C_{15}H_{26}N_4$: C, 68.66; H, 9.99; N, 21.35; found: C, 68.79; H, 9.74; N, 21.25. HRMS (ESI): calcd. for $C_{15}H_{27}N_4$: 263.2236 $[M+H]^+$; found: 263.2235.

Bisaminal 6a. White solid, mp 145°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.11-1.15$ (m, 2H, $C\underline{H}_2CH_2N$), 1.44–1.50 (m, 4H, $CH_2C\underline{H}_2C_{aminal}$), 2.16–2.25 (m, 4H, $C\underline{H}_2CH_2C_{aminal}$), 2.30–2.59 (m, 2H, $C\underline{H}_2CH_2N + 8H$, $C\underline{H}_2N$), 2.72–2.78 (m, 4H, $C\underline{H}_2N$), 3.25–3.32 (m, 2H, $C\underline{H}_2N$), 3.89–3.95 (m, 2H, $C\underline{H}_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 16.9$, 17.7, 21.5 ($\underline{C}H_2CH_2N + \underline{C}H_2\underline{C}H_2C_{aminal}$), 45.0, 45.6, 48.2, 49.5 ($\underline{C}H_2N$), 72.8 ($\underline{C}_{aminal}$). IR (KBr): $\bar{\nu}(cm^{-1}) = 2943$, 2883, 2809, 2777, 2752, 1355, 1345, 1305, 1195, 1158, 1026, 943, 880. Anal. calcd. for $C_{16}H_{28}N_4$: C, 69.52; H,

10.21; N, 20.27; found: C, 69.27; H, 10.17; N, 20.02. HRMS (ESI): calcd. for $C_{16}H_{29}N_4$: 277.2392 $[M + H]^+$; found: 277.2395.

General Procedure for the Deprotection of Bisaminals

The cyclic tetraamine bisaminal (1 mmol) was dissolved in 20 mL of 1 M hydrochloric acid, and the solution was stirred at 60°C for 6 h. Then, the solution was extracted by 3 × 20 mL of chloroform. Evaporation of chloroform solution yields pure cyclohexanedione. The water phase was evaporated as well to yield a brown solid, which was treated by ethanol (20 mL), and the mixture was stirred at room temperature for 1 h. Then, the resulting solid was filtered off and suspended in 20 mL of acetonitrile with potassium carbonate (4 mmol). The mixture was stirred overnight under reflux. Then the solid was filtered off, and the solvent was removed to yield quantitatively the corresponding macrocycle. Physical and spectroscopic properties correspond to literature data.

Data

Cyclen (4). White solid, mp 110°C. ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 2.02$ (br.s, 4H, NH), 2.59 (s, 16H, CH_2N). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 45.1$.

Homocyclen (5). White solid, mp 143°C. ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 2.14$ (m, 2H, CH_2CH_2N), 3.12 (m, 4H, CH_2N), 3.28 (m, 8H, CH_2N), 3.37 (m, 4H, CH_2N), 3.55 (br.s, 4H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 27.5$ (CH_2CH_2N), 45.9, 46.1, 47.4, 48.4 (CH_2N).

Cyclam (6). White solid, mp 187°C. ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.72$ (m, 4H, CH_2CH_2N), 2.55 (br.s, 4H, NH), 2.67 (s, 8H, CH_2N), 2.75 (m, 8H, CH_2N). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 28.4$ (CH_2CH_2N), 48.5, 50.0 (CH_2N).

Crystal structure determination of 1a. $C_{12}H_{22}N_4$, $M = 222.34$, $a = 11.7087(9)$, $b = 8.0299(5)$, $c = 12.4228(9)$ Å, $\alpha = 90.00°$, $\beta = 99.41°$, $\gamma = 90.00°$, $V = 1152.28(14)$ Å^3, $\mu = 0.080$ cm^{-1}, $Z = 4$, monoclinic, space group $P21/c$, $\lambda = 0.71073$ Å, $T = 293$ K, 2352 reflections collected, 1885 independent ($R_{int} = 0.0468$), 151 refined parameters, $R = 0.0545$, $wR_2 = 0.1208$.

Crystal structure determination of 4a. $C_{14}H_{24}N_4$, $M = 248.37$, $a = 24.228(8)$, $b = 8.1728(19)$, $c = 14.381(4)$ Å, $\alpha = 90.00°$, $\beta = 112.80(4)°$, $\gamma = 90.00°$, $V = 2625.0(13)$ Å^3, $\mu = 0.078$ cm^{-1}, $Z = 8$,

monoclinic, space group $C2/c$, $\lambda = 0.71073$ Å, $T = 295$ K, 3863 reflections collected, 1560 independent ($R_{int} = 0.088$), 163 refined parameters, $R = 0.0488$, $wR_2 = 0.0975$.

CCDC 291336 (**1a**) and CCDC 291337 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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