

New Synthesis of *trans*-Disubstituted Cyclam Macrocycles – Elucidation of the Disubstitution Mechanism on the Basis of X-ray Data and Molecular Modeling

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A new way to synthesize *trans*-disubstituted cyclam tetraazamacrocycles **1** is reported. The synthesis proceeds in three steps via the tricyclic 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane system **2**, which can be selectively dialkylated and hydrolyzed under basic conditions to give the final product **1**. An understanding of the reactivity, based

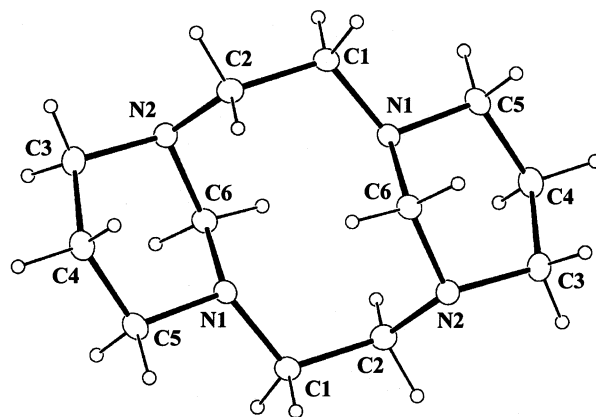
on the X-ray experimental electrostatic potential and molecular modeling of the 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane macrotricyclic system, has permitted the elucidation of a new reaction pathway leading to the *trans*-disubstituted cyclam.

The design and the synthesis of tetraazamacrocycloalkanes has been the subject of growing interest during past years due to their ability to coordinate different metal cations. Among the derivatives of this class of macrocycles, the cyclam (1,4,8,11-tetraazacyclotetradecane) has been extensively studied, either as a simple ligand or as an *N*-substituted ligand^{[1][2][3][4][5][6]}. Moreover, it is well known that the *N,N'*-functionalized cyclam can lead to hexacoordinated complexes. To date, numerous *N,N'*-functionalized cyclams have been described in the literature^{[7][8]}, and, recently, we reported the synthesis of the *cis*-4,8-*N*-disubstituted cyclam^[9]. As the classical synthetic scheme^{[7][8]} leading to *trans*-4,8-*N*-disubstituted cyclam involving 4,8-*N*-bis-(*para*-toluenesulfonyl)tetraazacyclotetradecane as intermediate gives low yields, here we propose an alternative synthesis.

The described synthetic route proceeds at room temp. to yield the *trans*-*N,N'*-disubstituted cyclam **1** at a high rate. As represented in Scheme 1, the first step leads to the 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane derivative **2**. This macrocyclic compound has already been prepared using formaldehyde and cyclam as starting reagents^{[10][11]}. We have obtained, quantitatively, the macrotricyclic **2** by refluxing cyclam in a 30% NaOH aqueous solution in the presence of dichloromethane^[12]. The pure product was easily isolated by concentration of the organic phase and

recrystallisation from a THF/water mixture. The presence of the methylenic bridges was confirmed by ¹H NMR (δ = 5.4) and ¹³C NMR (δ = 69). The crystallographic structure of **2** (Figure 1) shows a *trans* conformation for the two methylenic bridges.

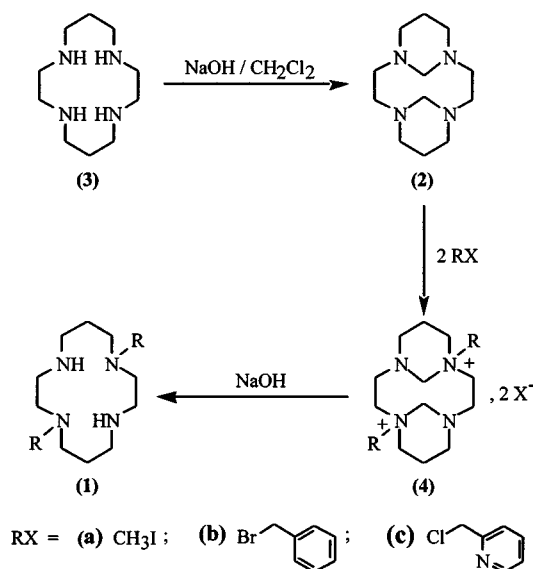
Figure 1. ORTEP view and numbering scheme of **2** with 50% probability thermal ellipsoids for non-H atoms



In a second step, the 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane ligand was dissolved in CH₃CN and two equiv. of an alkyl halide (methyl iodide, benzyl bromide, or picolyl chloride) were rapidly added to yield the new disubstituted macrotricyclic **4** having two non-adjacent quaternary nitrogen atoms. Due to their ionic character, compounds **4a–c** are insoluble in CH₃CN and so were isolated by filtration. High yields were obtained and no *cis*-

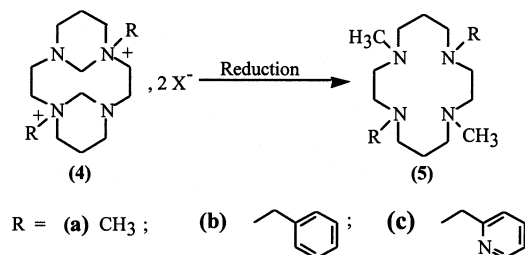
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Scheme 1



disubstituted macrocycle was detected. This indicates a strong selectivity for the *trans* disubstitution. ^1H -NMR spectra of **4a–c** are not unambiguous due to the inequivalence of the geminal protons, indicating a rigid structure for these compounds. Nevertheless, the presence of the methylenic bridge (N–CH₂–N) was confirmed by a ^1H -NMR signal at $\delta = 5$ and a ^{13}C -NMR resonance at $\delta = 79$. It has to be noted that **4c** is relatively unstable at high concentration in water. This property was confirmed on the basis of a NMR study angles in the spectra with time indicating the decomposition of **4c** to **1c**. Such specific behavior can be explained by the presence of the pyridine group acting as a basic reagent. Such a hypothesis is also confirmed by the last reaction step, since the expected *trans*-disubstituted cyclam **1** is easily formed after basic hydrolysis of **4** in NaOH (3 mol l^{−1}) at room temp. NMR spectra of **1a–c** show clearly the disappearance of the methylenic bridges. Moreover, the tetra-substituted cyclam **5** can be isolated by reduction of **4** with NaBH₄ (Scheme 2). Reduction of **4a** releases the tetramethylcyclam, which was previously described by Barefield and Wagner^[13]. ^1H - and ^{13}C -NMR spectra for **5b** and **5c** are similar to those observed for **4a** and **4b**, except for the methylenic resonance.

Scheme 2



A significant improvement in the synthesis of **1** is due to the fact that in each step reagents and products have very different solubilities and are easy to separate.

In the present paper we also focus on understanding the factors that control the reactivity of **2** towards electrophilic and nucleophilic reactants. The Molecular Electrostatic Potential (MEP)^{[14][15][16][17][18][19]} of a molecule is a real physical property which can be either determined experimentally, by X-ray and electron diffraction methods^{[20][21][22][23][24]}, or from the calculated electronic wave functions. One of the first applications of the MEP was to determine reactivity maps in order to explain and predict the sites of electrophilic attack on a molecule. We have thus used the MEP to localize the more electronegative sites of the 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane ligand which may undergo an electrophilic attack.

In this study we show that the calculated Molecular Electrostatic Potential (MEP) reproduces quantitatively the experimental X-ray potential. It has been used to rationalize the disubstitution of **2**.

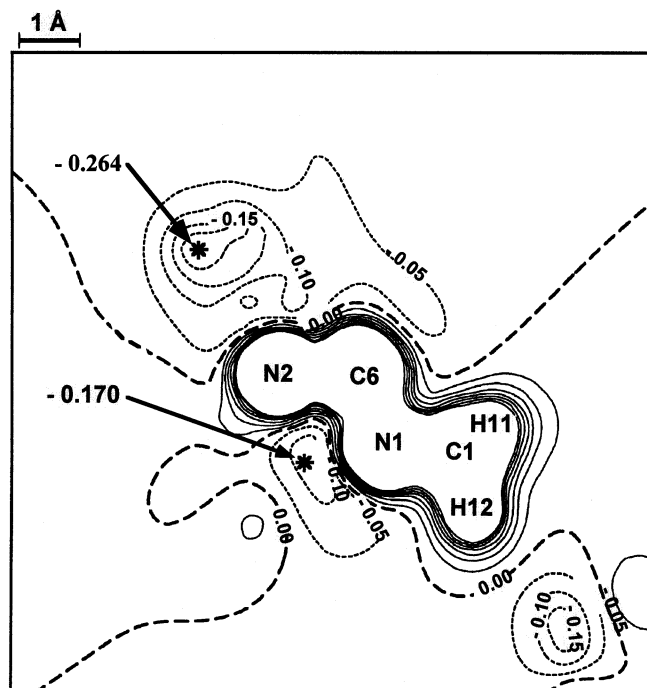
As the MEP depends strongly on the conformation and configuration of the molecule, it was important to correctly define the molecular geometry (global and local minimum conformations) before starting the calculation of electronic properties^[25]. The crystallographic data^[26] have been used to benchmark these calculations: the X-ray structure must be among the low-energy conformers obtained from the calculations, and experimental structural features such as bond lengths and angles (Table 1)^{[26][27]} must be retrieved by the calculation. These calculated results for the global minimum structure are given as supporting information. They show a rather good agreement between calculated and experimental geometric parameters, which validates the construction-search strategy and the force field used to perform the MM calculations. The MM global-minimum structure has also been reoptimized with the PM3 semi-empirical method (SPARTAN Molecular Modeling Package)^[28]. The calculated vibrational spectrum was then used to clearly determine whether it was a real minimum or a transition state, and finally the MEP was calculated. The PM3 results seem to be in better agreement with the experiment than the MM results, especially for the valence angles (see Supporting Information). It is, however, important to note that the calculations have been carried out on isolated molecules in vacuum; therefore, the comparison with crystal structure parameters is not straightforward. The experimental electrostatic potential^[21] was calculated from a multipolar refinement^[29] using the good-quality medium-resolution X-ray diffraction data ($\sin\theta/\lambda = 0.70 \text{ \AA}^{-1}$) obtained. Figure 2 gives the experimental MEP of the ligand in the (C6–N1–C1) plane. The PM3 MEP were also calculated. As expected, negative potential regions appear in the vicinity of the N1 and N2 atoms. The deepest negative potential corresponds to the N2 atom in both the experimental and PM3 theoretical maps ($-0.26 \text{ e/\AA}$ and $-0.30 \text{ e/\AA}$, respectively), whereas the negative region around N1 peaks at -0.17 and $-0.20 \text{ e/\AA}$, respectively. Thus the experimental and PM3-calculated ratios $V_{\text{N}_2}(\vec{r})/V_{\text{N}_1}(\vec{r})$ (1.53 and 1.50 respectively) unambiguously indicate that electrophilic attack takes place on both *trans*-N2 nitrogen atoms, giving rise to the new disubstituted macrotricyclic. Moreover the

N1 nitrogen atom, which is more sterically hindered than N2, favors this *trans*-disubstitution reaction.

Table 1. Experimental parameters for 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane (**2**): bond lengths and angles

Bonds	Experimental bond lengths [Å]	Angles	Experimental angles [°]
N1–C1	1.464 (2)	C1–N1–C5	112.82 (9)
N1–C5	1.463 (2)	C1–N1–C6	115.2 (1)
N1–C6	1.460 (2)	C5–N1–C6	108.80 (9)
N2–C2	1.479 (2)	C2–N2–C6	114.05 (9)
N2–C3	1.488 (2)	C2–N2–C3	110.6 (1)
N2–C6	1.466 (2)	C3–N2–C6	107.80 (9)
C1–C2	1.526 (2)	N1–C1–C2	115.6 (1)
C3–C4	1.534 (2)	N2–C2–C1	115.8 (1)
C4–C5	1.522 (2)	N2–C3–C4	113.0 (1)
		C3–C4–C5	111.3 (1)
		N1–C5–C4	109.7 (1)
		N1–C6–N2	110.7 (1)

Figure 2. Experimental molecular electrostatic potential [eÅ⁻¹] of 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane in the (C6–N1–C1) plane



In conclusion, we have reported and discussed a new and simple way to synthesise *trans*-disubstituted and tetrasubstituted cyclams. As proven by using three alkylating reagents in this work, this new method of synthesis can be, without any doubt, extended to other substituents, allowing the synthesis of numerous disubstituted macrocycles.

The support of the CNRS is gratefully acknowledged.

Experimental Section

General: 1,4,8,11-tetraazacyclotetradecane (cyclam) was prepared using the procedure detailed by Barefield and Wagner^[30]. All other reagents were commercial grade and used without further

purification. – NMR: Bruker AC200 spectrometer (200 MHz), CDCl₃ or D₂O solutions with Me₄Si as reference. – MS (EI or LSIMS): Kratos concept 32 S (*m*-nitrobenzyl alcohol as matrix for LSIMS). – Microanalyses: EA 1108 CHNS Fisons instrument.

Synthesis of 1,4,8,11-Tetraazatricyclo[9.3.1.1^{4,8}]hexadecane (2**).** – **Method A:** A solution of cyclam in dichloromethane (1 g, 5 mmol in 100 ml) was added to an aqueous solution of sodium hydroxide (30 g in 100 ml). After refluxing the mixture for 36 h, the two phases were separated and the aqueous phase extracted with dichloromethane. The organic phases were dried with MgSO₄ and concentrated to give a yellowish product which was recrystallised from THF/water to give colourless crystals. Yield 0.89 g (88%).

Method B: Two equiv. of formaldehyde (0.90 ml, 37% in water) were rapidly added to an aqueous solution of cyclam (1 g, 1.07 mmol in 60 ml) at 0°C. The mixture was stirred for 2 h and the white precipitate formed was then filtered, washed with water and dried under reduced pressure. The white powder obtained was used without further purification and crystallised in a THF/water mixture. Yield 96%. – ¹H NMR (CDCl₃): δ = 1.05–1.20 (m, 2 H, β-CH₂), 2.1–2.5 (m, 2 H, β-CH₂), 2.34 (d, 4 H, α-CH₂), 2.66 (td, 4 H, α-CH₂), 2.86 (d, 2 H, N–CH₂–N), 2.70–2.90 (m, 4 H, α-CH₂), 3.10 (d, 4 H, α-CH₂), 5.41 (dt, 2 H, N–CH₂–N). – ¹³C NMR (CDCl₃): δ = 20.42 (β-CH₂), 49.57 (α-CH₂), 53.90 (α-CH₂), 69.08 (N–CH₂–N). – C₁₂H₂₄N₄ (224.2): calcd. C 64.24, H 10.78, N 24.97; found C 64.12, H 10.63, N 24.92.

Synthesis of 1,8-Dimethyl-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane Diiodide (4a**):** 1 g (4.45 mmol) of **2** was dissolved in acetonitrile (ca. 30 ml) and two equiv. of methyl iodide (1.3 g, 9.15 mmol) were rapidly added. The solution was stirred at room temp. for 2 h and the white precipitate formed was then filtered, washed with a small quantity of CH₃CN and dried under vacuum. This crude compound was recrystallised in water to give white crystals. Yield 2.04 g (90%). – ¹H NMR (D₂O): δ = 1.83 (m, 2 H, β-CH₂), 2.3–2.6 (m, 4 H), 2.88 (t, 6 H, α-CH₂), 3.11 (s, 6 H, N–CH₃), 3.2–3.6 (m, 8 H), 4.44 (m, 2 H, α-CH₂), 5.3 (dt, 2 H, N–CH₂–N). – ¹³C NMR (D₂O): δ = 22.53 (β-CH₂), 49.75 (N–CH₃), 50.52 (α-CH₂), 53.33 (2 C, α-CH₂), 66.36 (α-CH₂), 79.36 (N–CH₂–N). – C₁₄H₃₀I₂N₄ (508.1): calcd. C 33.09, H 5.95, N 11.08; found C 33.12, H 5.97, N 10.79.

Synthesis of 1,8-Dibenzyl-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane Dibromide (4b**):** This compound was prepared by the same procedure as for **4a** except that the mixture was stirred for 24 h after the addition of benzyl bromide (2 equiv.). Yield 2.27 g (90%). – ¹H NMR (D₂O): δ = 1.85 (m, 2 H, β-CH₂), 2.20–2.70 (m, 4 H), 2.90 (d, 4 H), 3.20–3.50 (m, 10 H), 4.40 (t, 2 H), 4.65 (d, 4 H, N–CH₂–Ph), 5.50 (d, 2 H, N–CH₂–N), 7.51 (m, 10 H, aromatic H). – ¹³C NMR (D₂O): δ = 22.11 (β-CH₂), 50.10 (α-CH₂), 50.28 (α-CH₂), 53.88 (α-CH₂), 62.25 (N–CH₂–Ph), 65.63 (α-CH₂), 79.34 (N–CH₂–N), 128.59, 131.90, 133.51, 135.56 (6 C, aromatic C). – C₂₆H₃₈Br₂N₄ (564.1): calcd. C 55.13, H 6.76, N 9.89; found C 55.26, H 6.96, N 10.05.

Synthesis of 1,8-Dipyridyl-4,11-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane Dichloride (4c**):** This compound can be prepared by the same procedure as described for **4a**. However, the reaction time is very long (3 weeks) and the yield is low (15%). Therefore, it is preferable to use an excess (4 equiv.) of picolyl chloride. 5 g (30 mmol) of picolyl chloride hydrochloride was first deprotonated in aqueous NaOH solution (pH = 12). After extraction with CH₂Cl₂, the organic phases were dried with MgSO₄ and concentrated to give a red liquid which was added to the cyclam solution (1.68 g, 7.5 mmol in 50 ml of CH₃CN). After 3 d, the precipitate was fil-

tered off, washed with CH₃CN and dried under vacuum. Yield 2.24 g (56%). – ¹H NMR (D₂O): δ = 1.87 (m, 2 H, β-CH₂), 2.3–2.7 (m, 4 H), 2.8–3.8 (m, 14 H), 4.39 (t, 2 H), 4.76 (d, 4 H, N–CH₂–pyr.), 5.55 (d, 2 H, N–CH₂–N), 7.53 (t, 2 H, pyr.), 7.68 (d, 2 H, pyr.), 8.00 (t, 2 H, pyr.), 8.61 (d, 2 H, pyr.). – ¹³C NMR (CDCl₃): δ = 22.11(β-CH₂), 50.30 (α-CH₂), 50.65 (α-CH₂), 53.77 (α-CH₂), 63.00 (N–CH₂–pyr.), 66.09 (α-CH₂), 79.74 (N–CH₂–N), 128.44, 131.29, 141.32, 149.11, 152.73 (5 C, pyr.). – C₂₄H₃₆Cl₂N₆·3 H₂O (532.3): calcd. C 54.03, H 7.93, N 15.75; found C 53.56, H 7.92, N 15.77.

Synthesis of 1,8-Disubstituted 1,4,8,11-Tetraazacyclotetradecane (1): Compounds **1a**, **1b**, or **1c** were prepared by dissolving 0.5 g of **4a** (0.58 mmol), **4b** (0.88 mmol), or **4c** (0.93 mmol) in 100 ml of an aqueous NaOH solution (3 mol l^{−1}). After stirring for 3 h, the solution was extracted with CHCl₃ (5 × 30 ml). The organic phases were collected, dried with MgSO₄, and concentrated under vacuum to give the expected compound with a quantitative yield.

1a: ¹H NMR (CDCl₃): δ = 1.37 (q, 4 H, β-CH₂), 1.82 (s, 6 H, N–CH₃), 2.0–2.15 (m, 8 H, α-CH₂), 2.21–2.38 (m, 8 H, α-CH₂), 2.70 (bs, 2 H, NH). – ¹³C NMR (CDCl₃): δ = 26.64 (β-CH₂), 42.11 (N–CH₃), 47.86 (α-CH₂), 50.47 (α-CH₂), 57.29 (α-CH₂), 58.65 (α-CH₂). – MS (LSIMS); *m/z* (%): 229 [M + H]⁺. – C₁₂H₂₈N₄ (282.2): calcd. C 63.11, H 12.36, N 24.53; found C 63.33, H 12.49, N 24.34.

1b: ¹H NMR (CDCl₃): δ = 1.82 (q, 4 H, β-CH₂), 2.45–2.90 (m, 18 H, α-CH₂ and NH), 3.71 (s, 4 H, N–CH₂–Ph), 7.15–7.35 (m, 10 H, aromatic H). – ¹³C NMR (CDCl₃): δ = 26.67 (β-CH₂), 48.45 (α-CH₂), 50.91 (α-CH₂), 52.33 (α-CH₂), 54.83 (α-CH₂), 58.47 (N–CH₂–Ph), 127.65, 128.79, 130.25, 138.00 (6 C, aromatic C). – MS (EI); *m/z* (%): 380 [M]⁺. – C₂₄H₃₆N₄ (380.3): calcd. C 75.73, H 9.54, N 14.73; found C 75.17, H 9.61, N 14.22.

1c: ¹H NMR (CDCl₃): δ = 1.74 (q, 4 H, β-CH₂), 2.50–2.80 (m, 16 H), 3.67 (s, 4 H, N–CH₂–pyr.), 3.80 (br. s, 2 H, NH), 7.08 (t, 2 H, pyr.), 7.39 (d, 2 H, pyr.), 7.56 (t, 2 H, pyr.), 8.47 (d, 2 H, pyr.). – ¹³C NMR (CDCl₃): δ = 26.54 (β-CH₂), 48.10 (α-CH₂), 50.01 (α-CH₂), 52.49 (α-CH₂), 54.86 (α-CH₂), 60.05 (N–CH₂–pyr.), 122.47, 123.87, 136.73, 149.61, 159.23 (5 C, pyr.). – MS (LSIMS); *m/z* (%): 383 [M + H]⁺. – C₂₂H₃₄N₆ (382.3): calcd. C 69.07, H 8.96, N 21.97; found C 68.96, H 9.05, N 21.74.

Synthesis of 1,4,8,11-Tetramethyl-1,4,8,11-tetraazacyclotetradecane (5a), 1,8-Dimethyl-4,11-dibenzyl-1,4,8,11-tetraazacyclotetradecane (5b), and 1,8-Dimethyl-4,11-dipyridyl-1,4,8,11-tetraazacyclotetradecane (5c): Compounds **5a**, **5b**, and **5c** were obtained by dissolution of 1 mmol of **4a**, **4b**, or **4c** in an EtOH/H₂O (95:5) mixture. 10 equiv. of NaBH₄ were then added and the mixture was refluxed during 3 h. After return to room temp., 10 ml of HCl (3 M in water) was added. The mixture was concentrated to dryness and the residue was then dissolved in 100 ml of water and concentrated KOH was added (pH = 12). After extraction with CHCl₃ (5 × 30 ml), the organic phases were collected, dried with MgSO₄ and concentrated to give the expected tetrasubstituted tetraazamacrocyclic. Yields ca. 90%.

5a: ¹H NMR (CDCl₃): δ = 1.54 (q, 4 H, β-CH₂), 2.09 (s, 12 H, N–CH₃), 2.32 (t, 16 H, α-CH₂). – ¹³C NMR (CDCl₃): δ = 25.19 (β-CH₂), 44.20 (N–CH₃), 54.62 (α-CH₂), 54.86 (α-CH₂). – MS (EI); *m/z* (%): 256 [M]⁺. – C₁₄H₃₂N₄ (256.3): calcd. C 65.57, H 12.58, N 21.85; found C 65.73, H 12.88, N 21.76.

5b: ¹H NMR (CDCl₃): δ = 1.59 (q, 4 H, β-CH₂), 2.10 (s, 6 H, N–CH₃), 2.40–2.70 (m, 16 H, α-CH₂), 3.55 (s, 4 H, N–CH₂–Ph), 7.15–7.40 (m, 10 H, aromatic H). – ¹³C NMR (CDCl₃): δ = 24.84 (β-CH₂), 43.97 (N–CH₃), 51.76 (α-CH₂), 51.89 (α-CH₂), 54.83 (α-

CH₂), 55.64 (α-CH₂), 60.21 (N–CH₂–Ph), 127.36, 128.74, 129.60, 140.62 (6 C, aromatic C). – MS (LSIMS); *m/z* (%): 409 [M + H]⁺. – C₂₆H₄₀N₄ (408.3): calcd. C 76.42, H 9.87, N 13.71; found C 76.38, H 9.83, N 13.76.

5c: ¹H NMR (CDCl₃): δ = 1.60 (q, 4 H, β-CH₂), 2.03 (s, 6 H, N–CH₃), 2.30–2.70 (m, 16 H, α-CH₂), 3.66 (s, 4 H, N–CH₂–pyr.), 7.02 (t, 2 H, pyr.), 7.50 (m, 4 H, pyr.), 8.40 (d, 2 H, pyr.). – ¹³C NMR (CDCl₃): δ = 24.85 (β-CH₂), 43.84 (N–CH₃), 52.03 (α-CH₂), 52.33 (α-CH₂), 54.88 (α-CH₂), 55.52 (α-CH₂), 61.90 (N–CH₂–pyr.), 122.38, 123.68, 136.80, 149.41, 161.17 (5 C, pyr.). – MS (LSIMS); *m/z* (%): 411 [M + H]⁺. – C₂₄H₃₈N₆ (410.3): calcd. C 70.19, H 9.33, N 20.48; found C 70.15, H 9.30, N 20.13.

Supporting Information (Available on the WWW under <http://www.wiley-vch.de/home/eurjoc> or from the Author): Table S1: calculated semiempirical PM3 and molecular mechanics parameters for 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane (bond lengths and angles); Figure S1: PM3-calculated molecular electrostatic potential of 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexadecane in the (C6–N1–C1) plane.

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scent method has been used for the final minimization of the global minimum.

- [26] Crystal data for **2**: C₁₂N₄H₂₄·6H₂O, *M* = 332.45, triclinic, *P* $\bar{1}$, *a* = 6.358(1), *b* = 6.724(1), *c* = 10.801(2) Å, α = 94.26(1), β = 94.77(1), γ = 99.76(1)°, *V* = 451.7(1) Å³, *Z* = 1, data collection with a CAD4F (Enraf-Nonius) with Mo-*K* α radiation (λ = 0.7107 Å), *T* = 110(3) K, $(\sin\theta/\lambda)_{\max}$ = 0.70 Å⁻¹, 1771 data [*I* = 3 σ (*I*)] for 184 parameters, *R* = 3.6%, *wR* = 3.6%, G.O.F. = 1.75 for the spherical atom refinement^[27]; *R* = 2.96%, *wR* = 3.10%, G.O.F. = 1.54 for the constrained multipole refinement^[29]. Data collection details, positional and equivalent isotropic thermal parameters, and anisotropic thermal motion parameters for non-H atoms obtained after the spherical atom refinement of **2** have been deposited with the Cambridge Cryst-

tallographic Data Centre as supplementary publication no. CCDC-101492. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

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