Synthesis and Conformation Studies of a Dodecaazanonacyclotetratetracontane

M. Rachel Suissa,*[a,b] Christian Rømming,[b] and Johannes Dale[b]

Abstract: Compound **3** was prepared by self-assembly of 1,3,5-pentanetriamine and aqueous formaldehyde in quantitative yield (Figure 1). This molecule can exist in four well-defined diamond-lattice conformations of symmetries D_{2d}, S_4, C_{2v} and D_{2d}. Low-temperature ^{13}C NMR spectroscopy indicates the existence of three main conformers; their relative populations depend on the solvent used. An extra set of low-intensity lines is also observed. A conformation interconversion scheme is proposed; it involves two additional less populated quasi-diamond-lattice intermediates derived from a helix compressed along its axis. One of these is trapped as a 1:2 clathrate with 1,4-dioxane; its crystal structure is reported.

Keywords: azaalkanes · conformation analysis · NMR spectroscopy · polycycles · self-assembly

Introduction

Hexamethylenetetramine **1** (HMTA, Figure 1), first prepared in 1860 by Butlerow[1] in a reaction of gaseous ammonia with paraformaldehyde, is probably the earliest known example of the formation of multicyclic compounds by self-assembly.[2] This symmetric adamantane-like structure is readily made in quantitative yield because of the unique ability of saturated six-membered rings to adopt a perfect diamond-lattice conformation. In 1955, Krässig observed that 1,3-propanediamine and formaldehyde form a pentacyclooctaaza compound (**2**; Figure 1) with remarkable ease.[3] Its conformation in a 1:1 clathrate[+] with benzene was determined in 1974 by Murray-Rust, who pointed out that the observed conformation was the less symmetric (S_4) of the two possible diamond-lattice conformations (D_{2d} and S_4).[4] Low-temperature NMR spectroscopy of a toluene solution of compound **2**, done in our laboratory, revealed a mixture of the two conformers, while a CD_2Cl_2 solution contained practically only the D_{2d} form.[5] Crystals grown from CH_2Cl_2 were then shown by Rømming to be a stable complex of the D_{2d} conformer with two solvent molecules.[5]

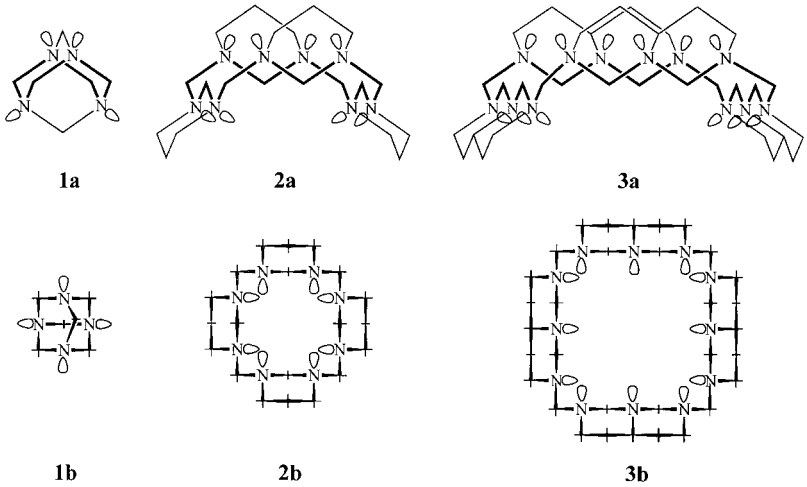

Figure 1. A homologous series of 8-, 16-, and 24-membered rings, prepared by condensation of ammonia or amines with formaldehyde.

From these structural data, it was predicted that the product obtained from 2,2-dimethyl-1,3-propanediamine (Table 1, **4**) should be stable only in the D_{2d} conformation, as was indeed observed.[6] This in turn led us to the conclusion that a bridging pentamethylene chain would be long enough to span

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[+] By clathrates we mean enclosure compounds in which guest molecules interact by weak van der Waals forces with their host molecules, while in complexes there is a defined coordination between the macrocycle and its guest.

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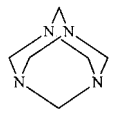
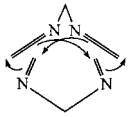
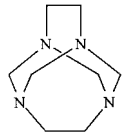
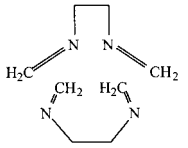
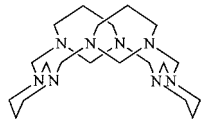
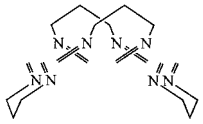
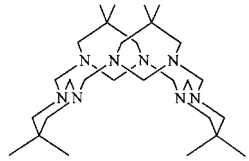
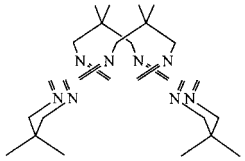
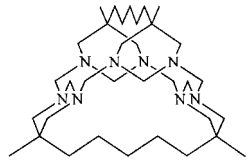
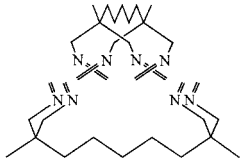
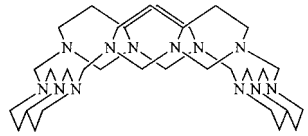
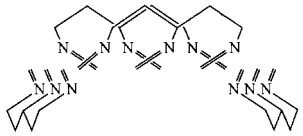
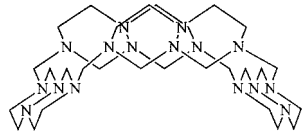
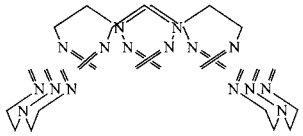
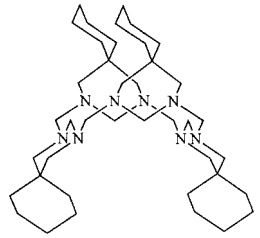
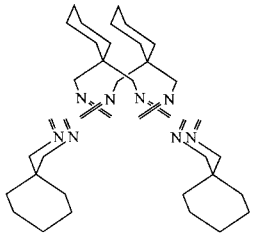
Table 1. The mass spectra (EI) of the multicyclic amines correspond mainly to those of di- or oligo-imines.

	Macrocycle	Imine	Mass Spectrum [%][a]	Ref.
1			140 (70), 112 (11), 85 (9), **71** (5), 42 (100)	[1]
8			168 (80), 139 (17), 126 (21), 111 (12), 99 (31), **85** (74), 56 (25), 49 (16), 42 (100), 18 (39)	[3]
2			259 (28), 197 (34), **99** (82), 70 (53), 56 (59), 42 (100)	[3, 5]
4			379 (14), 253 (31), **127** (100), 84 (51), 42 (52)	[6]
5			584 (80), 583 (100), **293** (22)	[7]
3			**152** (100), 125 (7), 98 (35), 82 (16), 70 (22), 56 (32).	[8]
6			**154** (57), 112 (55), 98 (23), 85 (36), 70 (62), 56 (100), 42 (98), 28 (80)	[9]
7			664 (0.5), 499 (3), 333 (11), **167** (33), 137 (45), 124 (76), 109 (17), 95 (44), 81 (26), 67 (44), 42 (100)	[21]

[a] The mass spectra have been done by us.

Abstract in Norwegian: *Forbindelse **3** ble syntetisert i kvantitativt utbytte ved selvkondensasjon av 1,3,5-pentantriamin og vandig formaldehyd. Molekylet kan opptre i tre veldefinerte diamantgitter-konformasjoner med henholdsvis D_{2d}, S_4 og C_{2v} symmetri, samt i en mindre stabil D_{2d}-form. Lavtemperatur ^{13}C NMR-spektroskopi bekrefter at de tre hovedkonformerene er tilstede i mengdeforhold som avhenger av det anvendte løsningsmiddel, og at den fjerde konformer gir svakere NMR signaler. Mekanismen for utveksling av konformasjoner er illustrert i et skjema som også må innbefatte to mellomprodukter av "kvasi-karakter", dannet ved at en diamantgitterhelix komprimeres langs helixaksen. En av disse danner et 1:2 klatrat med 1,4-dioksan, og krystall-strukturen av dette rapporteres.*

across the 16-membered ring, one above and one below, to produce a cagelike septicyclic molecule with a compact "tetrahedral" van der Waals surface of D_{2d} symmetry (Table 1, **5**). The required 2,2,8,8-tetrakis(aminomethyl)nonane was synthesized and condensed with formaldehyde to give compound **5** in 81% yield.[7] Recently, we reported the synthesis of a 24-membered ring **3** (1,3,7,9,11,15,17,19,23,25,27,34-dodecaazanonacyclo[25.5.3.$2^{6,9}$.$2^{14,17}$.$2^{22,25}$.$1^{3,7}$.$1^{11,15}$.$1^{19,23}$.$0^{30,34}$]-tetratetracontane) from 1,3,5-pentanetriamine and formaldehyde.[8] A full discussion of its properties is the subject of this paper.

The three compounds mentioned above (**1**–**3**) have cyclic structures formed by a chain of alternating carbon and nitrogen atoms, on to which four "carbon atom handles" are fused and which have an overall diamond-lattice structure. Figure 1 shows an oblique view (a) and a vertical projection

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(b) of the D_{2d} conformation of the eight-membered ring **1**, the 16-membered ring **2**, and of the 24-membered-ring **3**. One may consider HMTA as a lower homologue of this series, since each of the four 8-membered rings that can be defined follow the diamond-lattice structure (Figure 1, **1b**). However, the pairs of nitrogen atoms are too close, and two transannular CH_2 bridges are needed to fill the interior space. Higher homologues should have fewer restrictions, and hence several conformations become possible, depending on the size of the molecule. As mentioned, the 16-membered ring system can exist in two conformations, the most symmetrical of which is shown in Figure 1 (**2a**, **2b**). The next member of this series has a 24-membered ring (Figure 1, **3a**, **3b**), which consists of four rigid *trans*-decalin-like units connected by four CH_2 groups. It can exist in four well-defined conformations of symmetries D_{2d}, S_4, C_{2v} and D_{2d}.

The "square" conformation of these molecules is made of four identical parts joined together by four CH_2 "corners" that have adjacent *gauche* bonds of identical sign. These four CH_2 "corners" are located in the same plane and carry geminally identical hydrogen atoms.

We have already reported briefly on the synthesis and crystal structure of a tetrahydrate of compound **3**.[8] In the present paper, we describe in detail the synthesis of the starting material 1,3,5-pentanetriamine and we include the spectroscopic data. A conformation analysis is given to help the assignment of the NMR signals. Detailed conformation interconversion paths are proposed, supported by the crystal structure of one of the less populated conformers trapped as a 2:1 clathrate with 1,4-dioxane. A general mechanism for the self-assembly reaction of amines with formaldehyde is also proposed. A second full paper will follow that will also deal with a 24-membered ring (Table 1, **6**) prepared by the condensation of 1,1-bis(2-aminoethyl)hydrazine with formaldehyde.[9, 10]

Results and Discussion

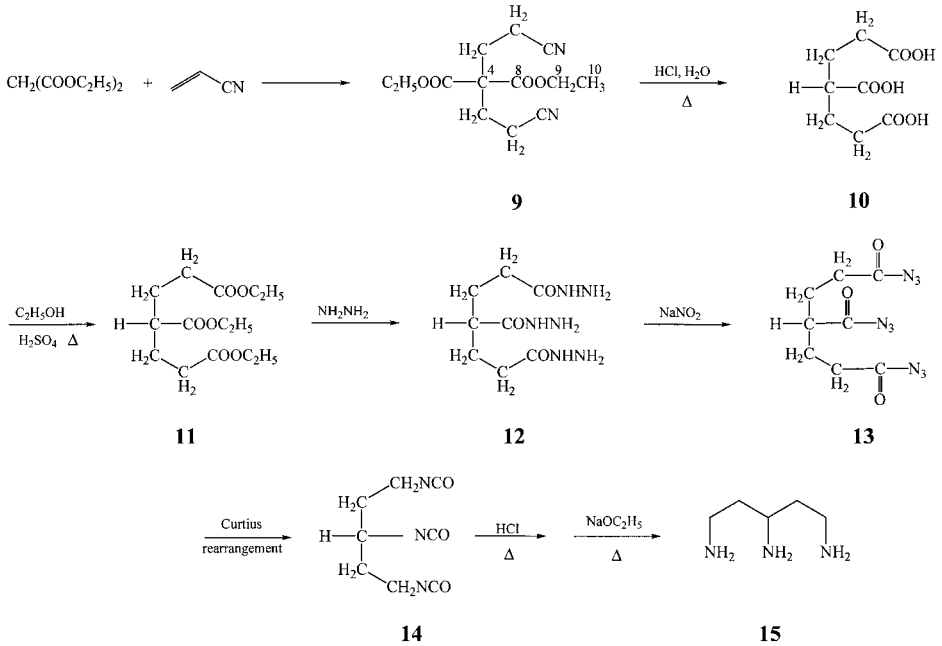
Synthesis: 1,3,5-Pentanetriamine (Scheme 1, **15**) was prepared by the method of Rüssel.[11] Since Rüssel gave no spectroscopic data, and a very high purity of the triamine is essential, we describe the synthesis in detail. The compound 3,3-di(carboethoxy)-1,7-heptanedinitrile **9** was prepared from diethyl malonate and acrylonitrile in 91% yield. Long reaction times were needed to hydrolyse the dinitrile **9** to the corresponding tricarboxylic acid **10**. Esterification of the tricarboxylic acid gave the best yield when catalysed by sulfuric acid. Triamine **15** was obtained after conversion of trihydrazine **12** to the corresponding triazide **13**. Curtius rearrangement, followed by hydrolysis, gave the corresponding tris-ammonium-trichloride. The free amine had to be distilled carefully. Condensation of the triamine with formaldehyde at 10 °C (molar ratio 1:3) gave, after approximately 30 minutes, compound **3** in quantitative yield.

The mechanism of the condensation reaction: Condensation of amines with formaldehyde gives in most cases a polymer, which can be isomerized, usually in an organic solvent like 1,4-dioxane, to the corresponding multicyclic compound in high yields. This condensation reaction meets the criteria of strict covalent self-assembly.[2] A fundamental feature of this process is its reversibility. Dynamic disassembly and reassembly enable recovery from initial mismatching and lead ultimately to stable structures at thermodynamic equilibrium. Clearly, cyclic products formed from polymers are expected to be thermodynamically favoured both by enthalpy (less conformational strain) and by entropy (larger number of molecules). Normally the monomer is strained, whereas the chosen oligomer would have a strain-free conformation.

The reaction between ammonia and formaldehyde to give HMTA is perhaps the most extreme case: a perfect diamond lattice of the highest possible symmetry [Eq. (1)].

$$6\,CH_2O + 4\,NH_3 \rightleftharpoons H_2C{=}N{-}CH_2{-}N{=}CH_2 + 6\,H_2O \rightleftharpoons C_6H_{12}N_4 + 6\,H_2O \quad (1)$$

The literature about this condensation is quite confusing, and a careful review is needed, but is beyond the scope of this paper. However, a few examples may illustrate the confusion: Evans proposed 1,3,5-triazacyclohexane as the intermediate in the condensation of ammonia with formaldehyde.[12] Nielsen et al. claim to have proved the formation of this precursor and of 1,3,5,7-tetraazabicyclo[3.3.1]nonane by NMR spectroscopy,[13] but we have not been able to reproduce their NMR results. The mechanism they propose for this



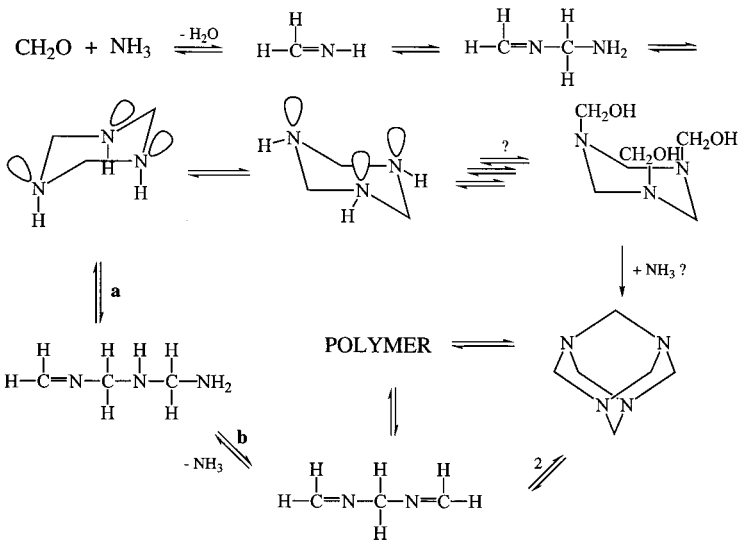
Scheme 1. The synthesis of 1,3,5-pentanetriamine.[11]

condensation seems too complicated for such a simple, fast and very clean reaction.

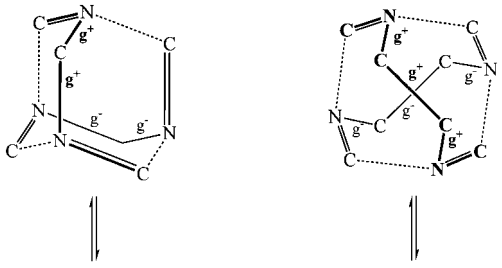
Methanimine has been obtained by gas-phase elimination of HCl from *N*-chloromethanamine or by flash vacuum thermolysis of 2-azabicyclo[2.2.n]alkenes.[14] The NMR spectrum of methanimine was recorded at $-95\,^{\circ}C$, as the compound decomposes to HMTA and to polymeric materials above $-80\,^{\circ}C$.[14] The authors proposed that this decomposition occurs via 1,3,5-triazacyclohexane as reported by Nielsen et al.[13] We have no reason to believe that methanimine decomposes to HMTA via 1,3,5-triazacyclohexane and we think instead that the di-imine $CH_2{=}N{-}CH_2{-}N{=}CH_2$ is formed and that it dimerizes rapidly to HMTA.

As shown in Scheme 2, if HMTA is to be formed via 1,3,5-triazacyclohexane, three formaldehyde molecules have to be oriented in axial positions; this will cause unfavourable 1,3-diaxial interactions. The product cannot then equilibrate further with its corresponding imine (by loosing water) and then react with the last ammonia molecule to finish the building of the HMTA structure. Hydrated hemi-aminal adducts can hardly be involved as important intermediates in this reaction, since aldehyde-ammonia adducts are not stable (depending on pH) and readily undergo dehydration and polymerization. The simplest imaginable way to form HMTA is to let two di-imine units of opposite conformations (g^+g^+ and g^-g^-) come together like in the folding of hands (Scheme 3). The fit is perfect for the formation the four bonds needed.

Condensation of 1,2-ethanediamine with formaldehyde gives 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane,[3, 4, 15, 16] which is an analogue of HMTA (Table 1, **8**). It can be described as a tetraazacyclooctane with two transannular ethylene bridges, while HMTA is a tetraazacyclohexane with two transannular methylene bridges. Krässig proposed a wrong structure for this molecule, assuming that tetrahydroimidazole was the direct precursor in this reaction.[3] Tetrahydroimidazole can be excluded, since its five-ring structure is not retained in the tricyclo-structure of **8**. Furthermore, the mass spectrum of **8** contains mainly the molecular ion and the



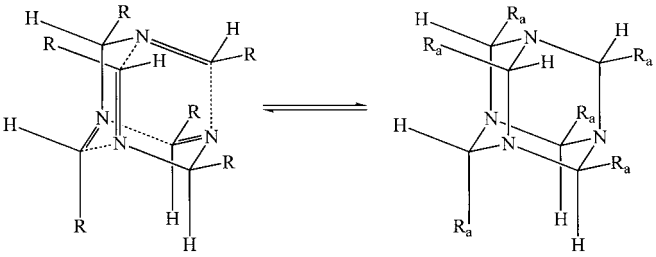
Scheme 2. The simplest way to form HMTA is from two di-imine units (b) and not from 1,3,5-triazacyclohexane (a).[12]



1 **8**

Scheme 3. Formation of four bonds gives the corresponding tetracyclic compound directly. The two dimeric units have opposite configurations in both cases.

mass of the corresponding di-imine with its fragments (Table 1, **8**), but there is no peak corresponding to tetrahydroimidazole. Repeating this reaction, we isolated a jelly-like



Scheme 4. Does condensation of aromatic aldehydes with ammonia form HMTA derivatives?

polymer by distilling water from the reaction mixture. This polymer isomerized quickly in boiling 1,4-dioxane to **8**. Again, the simplest way to form this multicyclic product is to assume that two di-imine units react together as shown in Scheme 3.

The fact that condensation of aromatic aldehydes with ammonia gives stable di-imine products supports the general mechanism we propose.[17–19] Ahmad et al. claim to have synthesized various HMTA derivatives (and their corresponding di-imines) by replacing formaldehyde with aromatic aldehydes, but they have not proven their structures.[17] Because of severe steric problems, as shown in Scheme 4, six molecules of the aldehydic substituent R can not be accommodated on the surface of HMTA, which can be considered equivalent to four cyclohexane surfaces. In each ring, one can define three axially related 1,3,5-positions, of which only one can accommodate an aromatic R group to avoid the forbidden 1,3-interaction. The other two R groups must be in equatorial positions if this is to be sterically tolerated (equatorial R group of one ring becoming an axial R group in the

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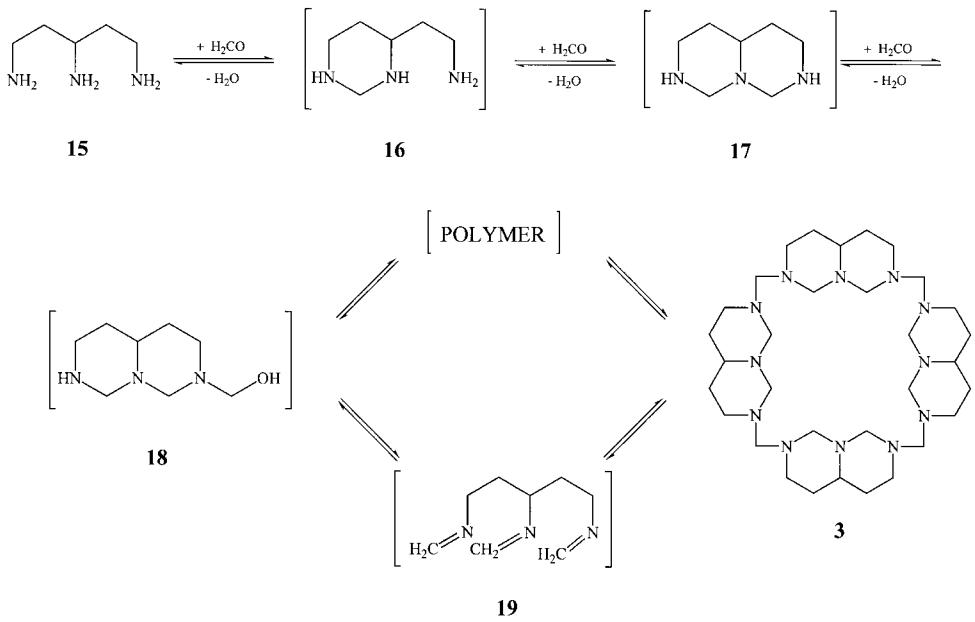
other ring). This is possible only for two of the four cyclohexane rings. The other two rings must then carry two axial R groups in 1,3-positions and a third in an equatorial position, which creates two forbidden 1,3-diaxial interactions. Thus, only four of these six aromatic substituents can be accommodated on the surface of HMTA.

The reaction between 1,3-propanediamine and formaldehyde was first believed to lead directly to the favoured 16-membered ring **2**.[16] It is now clear that rapid condensation to a polymer occurs. The polymer then dissolves in refluxing 1,4-dioxane to give the multicyclic product in high yield, with small amounts of 1-formyl-3-methyl-1,3-diazacyclohexane and 3-oxa-1,5-diazabicyclo[3.3.1]nonane, and trace amounts of 1,3-diazacyclohexane. Evans proposed a mechanism for this reaction involving 1,3-diazacyclohexane as the intermediate.[12] This molecule cannot be the final precursor in this reaction, but rather an intermediate to the corresponding di-imine. The stable conformation of 1,3-diazacyclohexane is the one with diaxial N–H, which has repulsive interactions between the two lone-pair orbitals. After this has reacted with one formaldehyde molecule, it must react further to the di-imine, which can in turn either polymerize or dimerize to molecule **2**.

In the case of compound **3**, we did not observe any polymer formation, and the macrocycle was formed in water after a very short reaction time. When we condensed 1,2-bis(2-aminoethyl)hydrazine with formaldehyde,[9] we obtained a soluble polymer that isomerized in boiling 1,4-dioxane to give the corresponding tetramer (Table 1, **6**; see also Ref. [10]). A highly insoluble polymer was formed in the case of the cage-like septicyclic molecule **5**[7] (Table 1), and it isomerized to give the corresponding macrocycle within a few hours in boiling 1,4-dioxane. Condensation of 1,1-bis(aminomethyl)cyclohexane with formaldehyde resulted in soluble polymers that isomerized in a few minutes to give macrocycle **7** in boiling dichloromethane (Table 1).[20]

The mass spectra of these molecules are summarized in Table 1. Mass spectra of compounds **1**, **5** and **8** show mainly the molecular ions, while the mass spectra of the other molecules display mainly the masses of the corresponding imine and its fragments. The mass spectra of these three compounds can be explained by the fact that the fragmentation of these noncage molecules into two halves requires four C–N bonds to be simultaneously broken in the case of molecules **1** and **8**, resulting in two bis-imine units. In the case of molecule **5**, eight C–N bonds need to be broken. The other five molecules produce four imines each. The predominance of the oligo-imine units in the mass spectra of these molecules supports our conclusion that the imine structure is retained in the macrocyclic system and, hence, is the final precursor for its formation.

Summing up, all of these compounds are formed in high yields by condensation of amines with formaldehyde. As the geometry of the oligo-imines is preserved in the multicyclic structures, we propose them as the ultimate precursors in this condensation. All the stages in the process are reversible; a polymer and its parent oligo-imine are in equilibrium with the corresponding multicycle. Reversible and irreversible by-products are possible when the geometry of the intermediates allows it, provided that the polymer formed is soluble enough to participate in equilibrium processes. Scheme 5 shows the self-assembly mechanism of 1,3,5-pentanetriamine with formaldehyde as an example. The intermediates in this case exclude the possibility of the formation of irreversible and reversible by-products that are favoured by entropy over time, as was the case in the condensation of 1,3-propanediamine with formaldehyde.[16]



Scheme 5. A proposed mechanism for the self-assembly of 1,3,5-pentanetriamine with formaldehyde.

The best solvent we found for the isomerization is 1,4-dioxane. The less soluble the polymer, the higher the temperature and the longer the reaction time needed to complete the isomerization reaction. When no polymer formation is observed, we believe that the reason for this may be high solubility of the polymer, relatively high stability of the oligo-imine, high thermodynamic stability of the macrocycle or a combination of these factors.

Conformational analysis: Adopting the standard approach to the conformation analysis of macrocyclic alkanes,[21] we considered the possible diamond-lattice conformations for the central 24-membered ring, assuming that each of the four laterally fused *trans*-decalin-like moieties is already rigidly fixed in a diamond-lattice pattern. We further assume that

each of the four methylene groups linking the *trans*-decalin moieties can be attached either equatorially or axially to the nitrogen atoms. This results in four possible conformations [Figure 2 and Figure 5 (see later)]: conformer **A** with all eight bonds of the four CH_2 groups attached equatorially (e) to the nitrogens, **B** in which each CH_2 group is attached equatorially to one nitrogen and axially (a) to the other in the sequence e,a,e,a,e,a,e,a, **C** with one CH_2 group attached equatorially to one nitrogen and axially to the other, while the second CH_2 group is attached axially to one nitrogen and equatorially to the other, and so on alternately in the sequence a,e,e,a,a,e,e,a, and **D** with eight axial attachments. Any other combination will be incompatible with the diamond lattice and will therefore introduce strain. The relative stabilities of these conformers on an enthalpy basis must be directly dependent on the relative stabilities of equatorial and axial *N*-alkyl substituents in azacyclohexanes. Assuming equatorial preference, we can conclude that the stability order would be: $\mathbf{A} > \mathbf{B} = \mathbf{C} > \mathbf{D}$. The stability order on an entropy basis can roughly be estimated from the molecular rotational symmetry, all four conformers being achiral. Conformers **A** and **D** have D_{2d} symmetry ($\sigma = 4$), **B** has S_4 symmetry ($\sigma = 2$) and **C** has C_{2v} symmetry ($\sigma = 2$). By increasing the temperature, the entropy will favour the four conformers in the order: $\mathbf{B} = \mathbf{C} > \mathbf{A} = \mathbf{D}$. If the enthalpy differences are neglected, a statistical mixture of 17 % **A**, 33 % **B**, 33 % **C** and 17 % **D** is expected. In practice, the choice of conformation is dominated by interaction with the solvent, either by external solvation or by internal clathrate or complex formation.

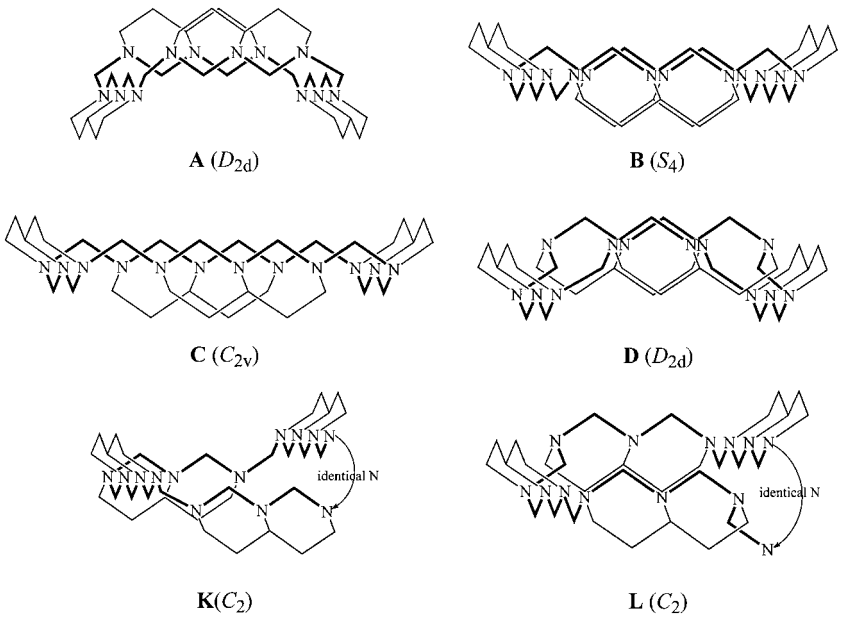


Figure 2. The four conformers and two intermediates derived from the diamond lattice: the helical symmetry of the intermediates **K** and **L** is seen clearly here.

Conformational interconversion paths: Interconversion between **B** and **A**, between **C** and **A** or between **C** and **B** requires four nitrogen inversion steps of relatively high energy, while interconversion between **A** and **D** requires eight nitrogen inversion steps. Each nitrogen inversion is accompanied by appropriate adjustments of the torsion angles in the eight C–N bonds that connect the four unchanged *trans*-decalin-like units. These adjustments occur over lower barriers.

The simplest and most direct interconversion paths connecting any pair of these conformers is through three intermediate non-diamond-lattice conformers, as shown in Scheme 6 and Scheme 7. The four conformers **A**, **B**, **C** and **D** are of perfect diamond-lattice type and are expected to be the most stable in solution. Their interconversion requires other less stable conformers as intermediates. Two of these, **K** and **L**, are of special interest, since both of them are common intermediates of the three direct interconversion paths between the conformers. The "vertical" projections of **K** and **L** shown in Scheme 6 might suggest that these are also strain-free and of the diamond-lattice types. However, they have been derived from one turn of a strain-free helix by vertical compression along the helix axis. Hence, they are chiral like the parent helix (C_2 symmetry) and somewhat strained (Figure 2). The term "quasi-diamond-lattice type" is proposed for them. Finally, six even more highly strained intermediates lacking symmetry are needed to complete the scheme shown in Scheme 6, with one intermediate (not drawn) between each pair of "arrows". Each of the six pairs of "arrows" implies that changes have been made successively at two diametrically[+] opposed "corners" (Scheme 7). The population of these intermediates is assumed to be negligible at any instant.

The precise mechanism of each interconversion step is thought to involve a slow local nitrogen inversion followed by a fast adjustment of the torsion angles, primarily in the adjustment of macrocyclic C–N bonds. This unit process is repeated in successive steps so that all values for the energy barriers are expected to have much the same height.

NMR spectroscopy: The high-temperature ^1H NMR spectrum in CD_2Cl_2 of compound **3** is given in Figure 3 and consists of nine resonances corresponding to the constitutional symmetry. The absorptions are generally broad as this is an averaged spectrum of all the conformers present. The molecule contains a pair of protons *b* (A_2). The equality of the chemical shifts of these two protons is a result of the existence of a C_2 symmetry operator interconverting the two nuclei. Two absorptions (AX) belong to protons *a* with $^2J_{a1,a2} = |9|$. This value is due to the neighboring nitrogens and reflects the conformational rigidity of the *trans*-decalin units of the molecule. These two

[+] Choosing two adjacent "corners" results in intermediates lacking any degree of symmetry.

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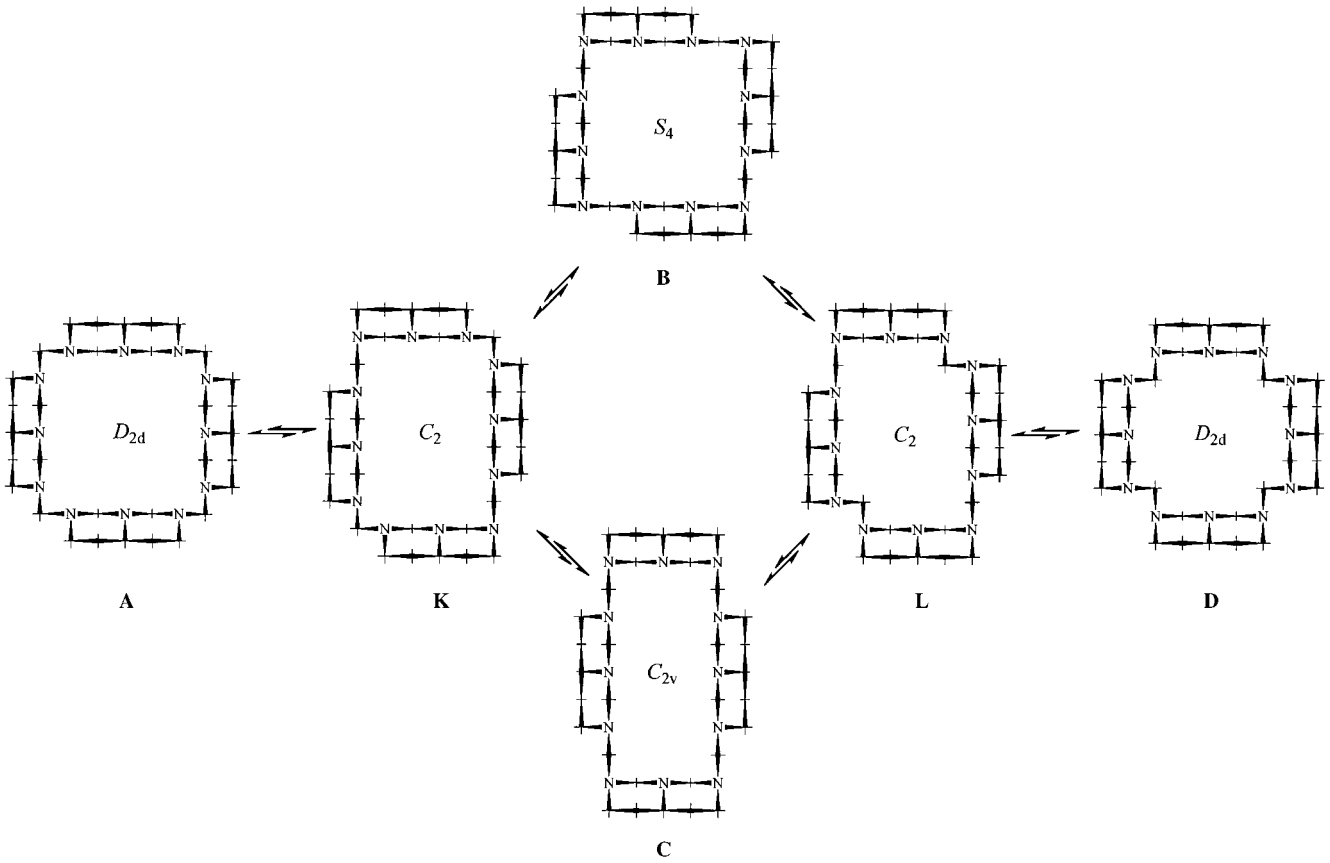
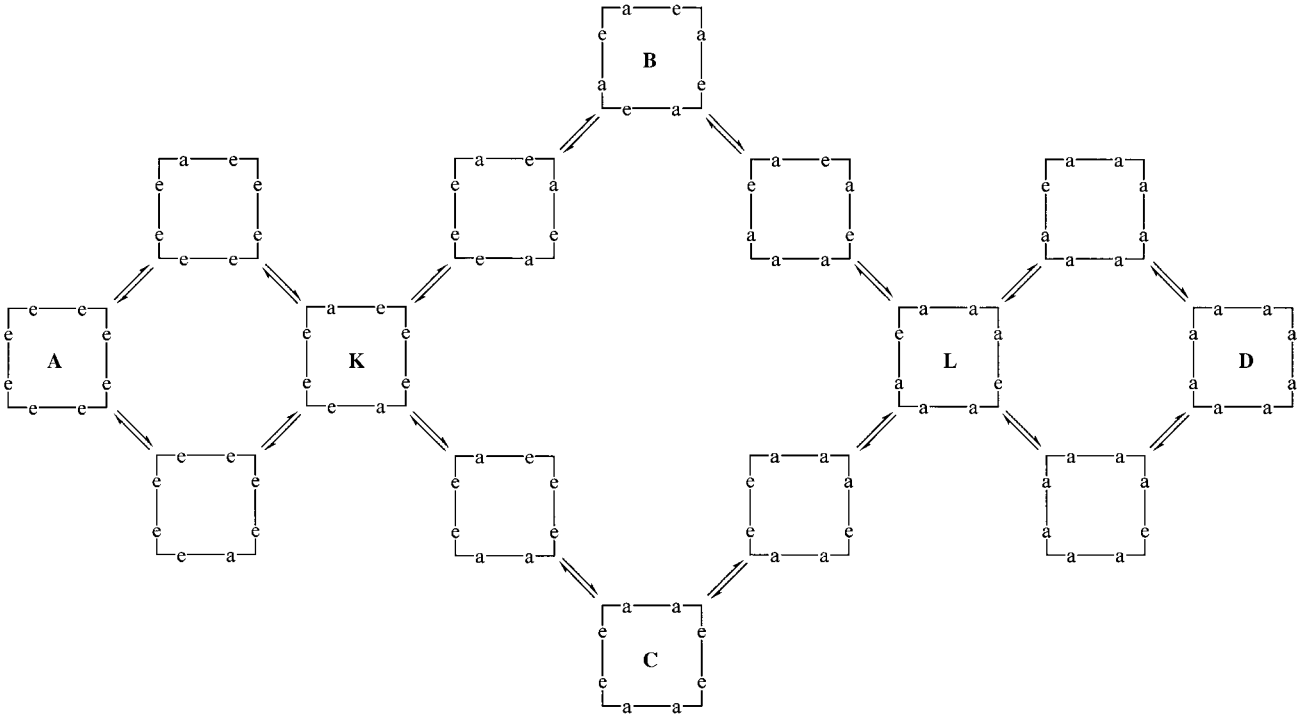


Scheme 6. Interconversion among the four low energy conformers.



Scheme 7. Detailed interconversion among the four possible conformers. **A**, **B**, **C** and **D** are strain-free diamond-lattice rings. **K** and **L** are chiral diamond-lattice helices compressed along the helical axis. The others are unpopulated chiral intermediates. Because this 24-membered macrocycle consists of four conformationally rigid bicyclic units, the total conformation may be described by a sequence of letters a and e, giving the mode of attachment of the corner atom (equatorial or axial attachment) to the rigid bicyclic units.

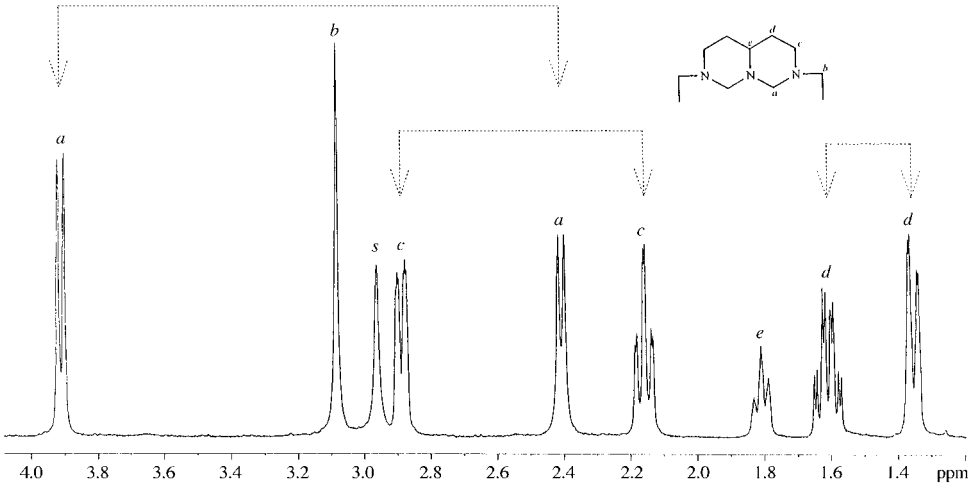


Figure 3. ^{1}H NMR spectrum of compound **3** (500 MHz) in CD_2Cl_2 at 298 K (s = solvent).

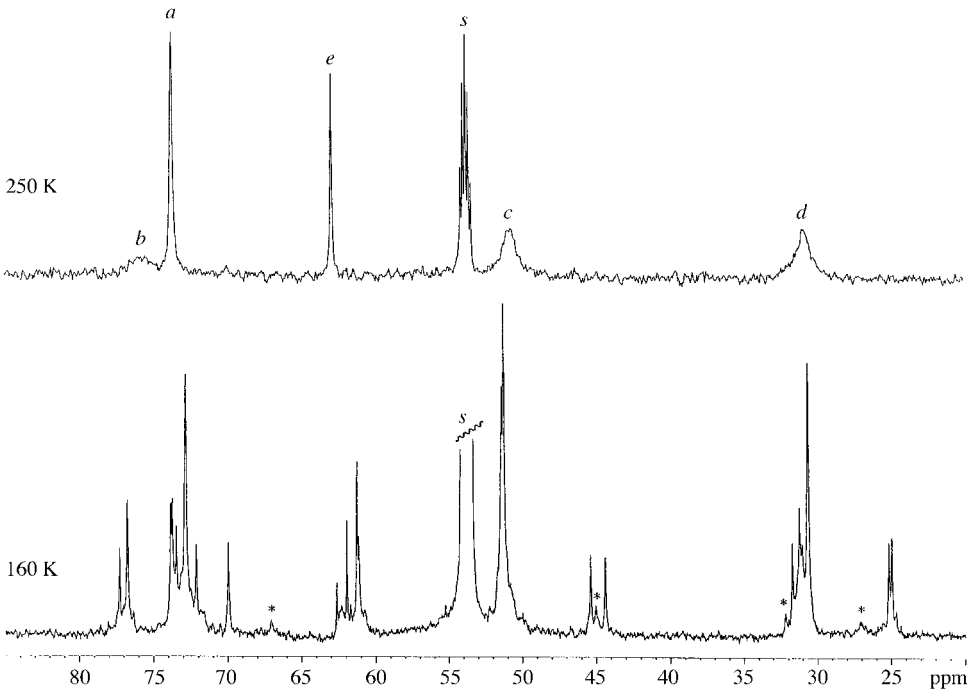


Figure 4. ^{13}C NMR spectrum of compound **3** (600 MHz) in CD_2Cl_2 at 250 K and in CD_2Cl_2:CCl_3F (1:1) at 160 K (s = solvent).

signals at $\delta = 2.8$ and 3.8 represent the inner and outer *a* protons, or equatorial and axial protons, respectively. The value of ^{2}J for the *c* protons is lower than that for the *d* protons as expected; the values are $^{2}J_{c1,c2} = |11.9|$ and $^{2}J_{d1,d2} = |12.7|$, respectively.

The interconversion of the four possible conformers is more easily studied by ^{13}C NMR spectroscopy, since the spectra are simple because of the high symmetries of these conformers. The low-temperature ^{13}C NMR spectrum for a mixture of the four conformers **A**, **B**, **C** and **D** should consist of 27 lines: five lines for each of the conformers **A** and **D**, $C_b(1)$ $C_a(1)$ $C_e(1)$ $C_c(1)$ $C_d(1)$ in the ratio of 1:2:1:2:2 respectively; eight lines for conformer **B**, $C_b(1)$ $C_a(2)$ $C_e(1)$ $C_c(2)$ $C_d(2)$, (ratio of 1:1:1:1:1:1:1:1, respectively); and nine lines for conformer **C**, $C_b(1)$ $C_a(2)$ $C_e(2)$ $C_c(2)$ $C_d(2)$, (ratio of 2:2:2:1:1:2:2:2:2, respectively). On heating they should merge to give five lines that correspond to the chemical symmetry. If only conformer **A** is present, its ^{13}C NMR spectrum should consist of five lines and it should remain unaffected at variable temperatures, as **A** already has constitutional symmetry. No low-energy processes should be observed in this case. If **A** and **D** are present, the high-temperature ^{13}C NMR spectrum should consist of five lines (averaged spectrum) that on cooling should split into 10 lines. The same is true for the other possible combinations.

[D_2]Dichloromethane or a mixture of freons and [D_2]dichloromethane was used for these low-temperature experiments. The higher-temperature ^{13}C NMR spectrum in CD_2Cl_2 consists of five lines as shown in Figure 4. On cooling, the lines broaden, followed by splitting and then sharpening of the new lines, to give the final slow-exchange spectrum. In the solvent mixture CD_2Cl_2:CCl_3F (1:1) at 160 K, the spectrum consists of 22 lines: five lines for **A**, eight for **B** and nine for **C** in a ratio of 3:2:2 respectively. In addition to these 22 lines, the spectrum includes an extra set of low intensity lines; some of them are marked with an asterisk. This set of lines could be ascribed to the fourth conformer **D**, but the species **K** and **L** of low population are also possible candidates, even though we do not see as many lines as expected. The possibility of complex formation between the different conformers and solvent molecules seems to be excluded, since the complexes should cause large shifts, and we did not observe such shifts. We also expect that some of these complexes would lose their symmetry and give rise to additional resonances.

Geminal site exchange of CH_2 protons in compound **3** is rendered impossible by the presence of one CH group in each "decalin" unit. If these were all replaced by N, thus allowing inversion, geminal exchange would become possible.[10]

Complexation: Molecule **3** is built of four *trans*-decalin-like units, each containing three pairs of nonbonding electrons from the nitrogens. Because all of its stable conformers can be derived from the diamond lattice, the four decalin units in

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each of them are divided into two pairs, one pointing above and one pointing below the central 24-membered ring, to produce a "double sandwich" (Figure 2).

The orientation of the electron pairs is dependent on the symmetry of the different conformers, as shown in Figure 5. Conformer **A** has two parallel rows of electron pairs (3 and 3) above, and two below the central 24-membered ring. These electrons lie on the edge of the cleft on either side, and each of these two rows can form complexes with molecules that fit into the cleft. In conformer **B**, the rows of electrons consist of only two pairs each. Four pairs of electrons are oriented out from the central ring and are available for interaction with solvent molecules. The size of the central ring is, however, identical to the one in **A** conformer. The central ring is particularly long and narrow in conformer **C**, with six electron pairs on the edges of one cleft (3 and 3) and two pairs on the edges of the other cleft (1 and 1). As with conformer **B**, four electron pairs are oriented away from the central ring.

Conformers **B** and **C** were always present in a ratio of 1:1 in all the solvent mixtures that we used for the DNMR experiments, while the relative population of **A** to (**B** + **C**) was solvent dependent. The fourth conformer, **D**, has only four electron pairs on the edges of the clefts, two above (1 and 1) and two below (1 and 1) the central ring. The remaining eight electron pairs are oriented in the corners out from the central ring and are divided into four groups. Each group, together with the NCH_2N corner unit to which it is connected, creates a small helix of C_2 symmetry, and the electron pairs are located one above the other. The central ring is much smaller in this conformer than in **A** and **B**.

Although we have tried to crystallize all these four conformers by forming complexes or clathrates with other molecules, nearly all of the crystals we have obtained contained only the **A** conformer. Crystallization of molecule **3** from ethyl acetate gave in one case the **A** conformer as tetrahydrate.[8] In another case, the **A** conformer crystallized with a disordered ethyl acetate molecule in the cleft of compound **3**. Surprisingly, a crystalline 1,4-dioxane clathrate of the **K** conformer (C_2 intermediate) was formed (Figure 6).

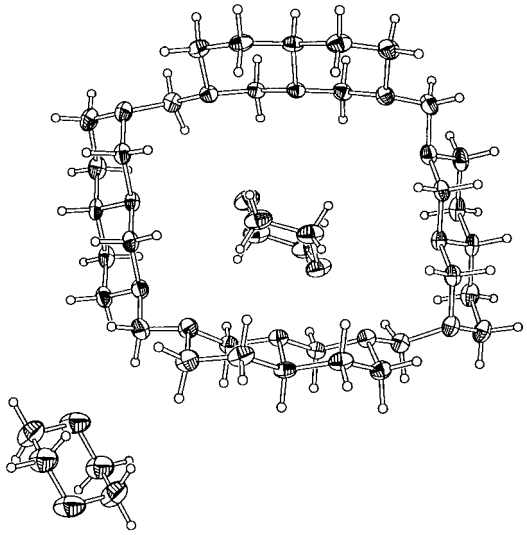

Figure 6. ORTEP plot of the C_2 intermediate.

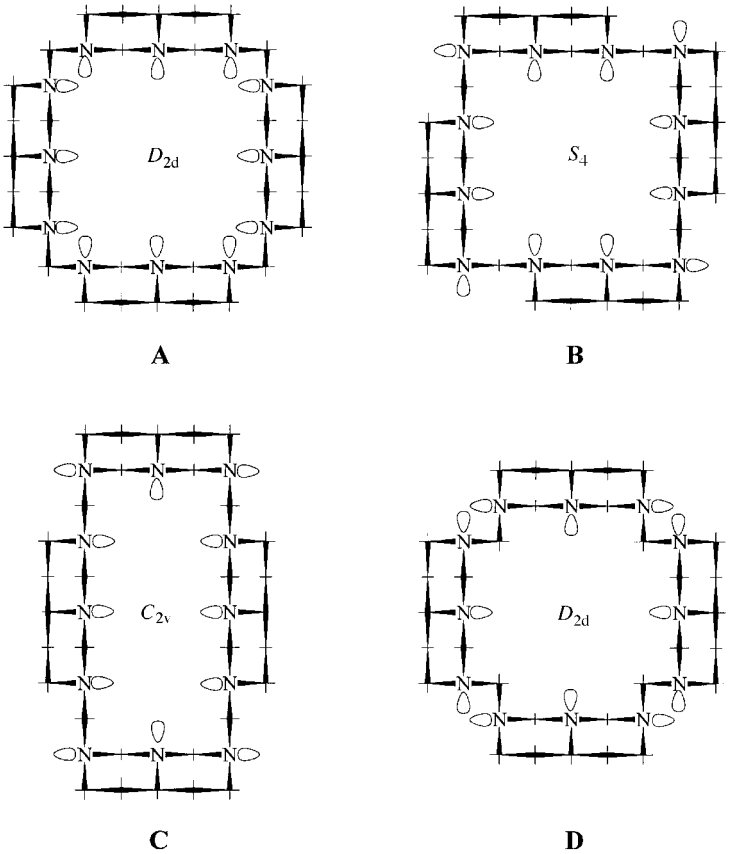

Figure 5. The four stable conformers with their nonbonding electrons.

This intermediate is stabilized in the crystal structure by van der Waals interactions between dioxane molecules located in the center of the 24-membered ring and dioxane molecules located between the macrocycles. This crystal structure supports the interconversion pathway we propose (Scheme 5 and 6) for this molecule.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded with Bruker DPX300, Bruker DRX500, and DRX600 instruments. The temperatures were calibrated with CD_3OD. Temperatures below the freezing point of methanol were determined by extrapolating with a calibration graph. Standard 2D experiments were used to confirm the assignments of H and C resonances. The mass spectra under impact conditions (EI) were usually recorded at 70 eV ionization potential, and methane or ammonia was used for chemical ionization (CI). Melting points are uncorrected.

Preparation of 3,3-di(carbethoxy)-1,7-heptanedinitrile (9): A stirred solution of diethyl malonate (160 g, 1.0 mol) and tetraethylammonium hydroxide pentahydrate (10 g, 0.06 mol) in 1,4-dioxane (400 mL) was cooled to 10 °C. A solution of acrylonitrile (199 mL, 3.0 mol) in 1,4-dioxane (50 mL) was added dropwise over 2 h, and the temperature was kept under 20 °C. The reaction was left overnight at room temperature. The mixture was acidified with HCl (3 M), was poured into cold water (1 L), and was stirred well. After a short time, the compound crystallized and was pure enough to continue to the next stage (243 g, 91 % yield). It could be further recrystallized from benzene. M.p. 63 °C; MS (CI, NH_3): *m*/*z* (%): 284 (100 %) $[M+NH_4]^+$; MS (CI): *m*/*z* (%): 266 (1), 221 (14), 154 (34), 108 (100), 69 (41), 53 (19), 41 (20), 29 (50); ^1H NMR (500 MHz, $CDCl_3$): δ = 4.22 (q, J = 7.1 Hz, 4H; CH_2CH_3), 2.42 (dt, J = 7.7 Hz, 4H; H3,5), 2.21 (dt,

$J = 7.7$ Hz, 4H, H2,6), 1.25 (t, $J = 7.1$ Hz, 4H; CH_2CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 169.0$ (C=O), 118.5(CN), 62.4 (CH_2CH_3), 55.5 (C4), 29.5 (C2,6), 13.8 (CH_2CH_3), 13.0 (C3,5).

1,3,5-Pentanetricarboxylic acid (10): 3,3-Di(carbethoxy)-1,7-heptanedinitrile (210 g, 0.80 mol) dissolved in HCl (6 M, 500 mL) was refluxed and stirred continuously for 3 days. The acid crystallized at low temperature (≈5 °C) as the monohydrate. Concentration of the mother liquor and cooling resulted in a second crop of acid (140 g, 87% yield). M.p. 208 °C (dehydrates at 114 °C); MS (CI): *m*/*z* (%): 186 (2), 140 (13), 114 (95), 86 (71), 55 (100), 42 (59); ^{1}H NMR (500 MHz, D_2O): $\delta = 2.31$ (m, 1H; H3), 2.24 (m, 2H; H1,5), 1.70 (m, 2H; H2,4); ^{13}C NMR (500 MHz, D_2O + CD_3OD): $\delta = 180.4$ (C3 *C*=O), 178.5 (C1,5 *C*=O), 44.7 (C3), 32.3 (C2,4), 27.4 (C1,5).

Triethyl-1,3,5-pentanetricarboxylate (11): 1,3,5-Pentanetricarboxylic acid (70 g, 0.34 mol) in absolute ethanol (700 mL) and concentrated sulfuric acid (50 mL) was refluxed and stirred continuously for 3–4 days (the acid dissolved gradually). The solvent was carefully distilled off, and cold water was added to the residue. The ester was extracted with diethyl ether several times. The ether phase was washed with sodium carbonate solution and water, and then dried. Purification by vacuum distillation (b.p. 182–186 °C/12 mm Hg) gave 65 g (83% yield) of the ester. MS (CI, CH_4): *m*/*z* (%): 289 (7), 243 (100), 214 (23), 185 (8), 169 (20), 155 (8), 141 (14), 123 (1), 114 (15), 99 (6), 71 (6), 55 (8); MS (EI): *m*/*z* (%): 288 (0.3), 243 (7), 214 (33), 185 (15), 169 (28), 155 (14), 141 (24), 123 (20), 114 (30), 99 (12), 71 (13), 55 (21), 41 (11), 29 (28), 28 (41), 18 (100); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.04$ (q, $J =$ 7.1 Hz, 4H; CH_2CH_3), 4.02 (q, $J = 7.1$ Hz, 2H; CH_2CH_3), 2.33 (m, 1H; H3), 2.22 (m, 4H; H1,5) 1.82 (m, 2H; H2,4), 1.73 (m, 2H; H2,4), 1.14 (q, $J =$ 7.2 Hz, 9H, CH_2CH_3); ^{13}C NMR (500 MHz, CD_2Cl_2): $\delta = 174.6$ (C3 *C*=O), 172.6 (C5 *C*=O), 60.3 (CH_2CH_3), 60.2 (CH_2CH_3), 43.7 (C3), 31.6 (C1,5), 26.9 (C2,4), 14.1 (CH_2CH_3), 14.0 (CH_2CH_3).

1,3,5-Triaminopentane (15): Triethyl-1,3,5-pentanetricarboxylate (115.2 g, 0.40 mol) dissolved in absolute ethanol (400 mL) was stirred under N_2 atmosphere at room temperature. Anhydrous hydrazine (51.6 g, 1.6 mol), carefully dissolved in absolute ethanol (100 mL), was added dropwise to the triester solution. The mixture was refluxed for 24 h and then cooled. The product was filtered off, dissolved in HCl solution (6 M, 250 mL), and cooled to −10 °C, before diethyl ether (250 mL) was added. The temperature of the mixture was stabilized at 0 °C, and sodium nitrite (81.8 g, 1.2 mol) dissolved in water (150 mL) was added dropwise. After stirring for 3 h, the mixture was separated, and the water phase was extracted with diethyl ether (3 × 100 mL). $CaCl_2$ was added to the combined ether phases, and the mixture was left in the refrigerator (≈5 °C) overnight. The ether phase was decanted, and the same volume of absolute ethanol was added to it. This mixture was refluxed and stirred continuously for 48 h until no more nitrogen evolved. The solvents were carefully evaporated, and the residue (≈76 g) was dissolved in HCl solution (3 M, 500 mL) and refluxed and stirred continuously for 12 hours. Water was carefully evaporated (in small portions in a one-liter flask), and the crude triammonium chloride (62 g) was dissolved in absolute ethanol (200 mL) with an equivalent amount of sodium ethoxide [Na (19.3 g, 0.84 mol) in ethanol] and was refluxed for 2 hours. NaCl was filtered off, and the ethanol was evaporated carefully in small portions. The crude triamine (30 g, 64% yield) was further purified by vacuum distillation (0.01 mm Hg) at 84–100 °C (bath temperature was 205 °C).

Trihydrazide **(12)**: MS (CI, CH_4): *m*/*z* (%): 246 (0.5), 215 (9), 198 (6), 183 (100), 166 (6), 155 (20), 141 (6), 55 (11); MS (EI): *m*/*z* (%): 215 (12), 183 (100), 155 (47), 141 (10), 113 (7), 69 (8), 55 (30), 41 (12), 32 (24), 31 (14); ^{1}H NMR (500 MHz, CF_3CO_2D, $\delta = 11.50$): $\delta = 4.59$ (m, $J = 4.6$ Hz, 1H; H3), 4.42 (t, $J = 7.4$ Hz, 4H), 3.97 (m, $J = 7.4$ Hz, 2H; H2,4), 3.87 (m, $J =$ 7.42 Hz; H2,4); ^{13}C NMR (500 MHz, CF_3CO_2D, $\delta = 164.2$): $\delta = 178.2$ (C3 *C*=O), 176.6 (C1,5 *C*=O), 45.5 (C3), 32.9, (C1,5), 29.3 (C2,4).

Triamine 15: MS (CI, CH_4): *m*/*z* (%): 118 (100), 83 (6), 71 (11); MS (EI): *m*/*z* (%): 83 (22), 71 (40), 70 (13), 56 (14), 44 (100), 42 (12), 30 (97); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.64$ (h, $J = 8.3$, 4.6 Hz, 1H, H3), 2.51 (m, 4H; H1,5), 1.28 (m, 2H, H2,4), 1.12 (m, 2H; H2,4), 0.89 (br s, 6NH_2); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 47.1$ (C3), 41.6 (C1,5), 38.9 (C2,4).

Molecule 3: Aqueous formalin (8.80 mL, 0.102 mol, 37%) diluted with water (10 mL) was added dropwise to a stirred ice-cold solution of 1,3,5-triaminopentane (4.00 g, 0.034 mol) in water (25 mL). After 30 min, a white precipitate formed. The mixture was heated slightly (≈70 °C) and filtered while warm. Compound **3** was obtained as a white solid on cooling (5.2 g, 100%). M.p. 221 °C; MS (EI): *m*/*z* (%): 153 (31), 152 (100), 125 (7), 98 (35), 97 (20), 83 (16), 82 (16), 70 (22), 57 (27), 56 (32), 55 (27); ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 3.91$ (d, $J = 9.2$ Hz, 1H; Ha1), 3.09 (s, 2H; Hb), 2.29 (ddd, $J = 11.8$, 4.3, 2.9 Hz, 1H; Hc1), 2.41 (d, $J = 9.2$ Hz, 1H; Ha1), 2.16 (dt, $J = 12.1$, 12.1, 2.9, 1H; Hc2), 1.80 (ddt, $J = 11.0$, 2.7 Hz, 1H; He), 1.61 (dddd, $J = 12.6$, 12.6, 11.0, 4.4 Hz, 1H; Hd1), 1.36 (dddd, $J = 12.8$, 2.6 Hz, 1H; Hd2); ^{13}C NMR (500 MHz, CD_2Cl_2, 298 K): $\delta = 74.9$ (Cb), 73.1 (Ca), 62.3 (Ce), 50.0 (Cc), 30.1 (Cd); ^{13}C NMR (600 MHz, CCl_3F:CD_2Cl_2 (≈1:1), 160 K): $\delta = 77.3$, 76.8 (D_{2d}), 73.9, 73.7, 73.5, 72.9 (D_{2d}), 72.1, 70.0 (Cb and Ca 8 lines); 62.6, 62.0, 61.3 (D_{2d}), 61.2 (*C*e 8 lines); 51.4, 51.3 (D_{2d}), 45.4, 44.4 (C_c 5 lines); 31.8, 31.3, 30.7 (D_{2d}), 25.0, 24.7 (Cd 5 lines).

X-ray crystallography: X-ray data were collected on a Siemens SMART CCD diffractometer,[22] with graphite monochromated $Mo_{K\alpha}$ radiation. Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm; further information is given in Table 2. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[22] Absorption corrections were applied by the use of the SADABS program.[23] The structure was determined and refined using the SHELXTL program package.[24] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen positions were calculated from geometrical criteria and refined with isotropic thermal parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102850. Copies of the data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)

Table 2. Crystal data for compound **3**.

empirical formula	$C_{40}H_{76}N_{12}O_4$
M_w	394.56
T [K]	150 (2)
λ [Å]	0.71073
crystal system	orthorhombic
space group	*C*2/*c*
a [Å]	24.415(1)
b [Å]	6.461(1)
c [Å]	27.360(2)
V [Å^3]	4301.2(2)
Z, ρ_{calcd} [Mg m^{-3}]	4, 1.219
$\mu(Mo_{K\alpha})$ [mm^{-1}]	0.081
$F(000)$	1728
crystal size [mm]	0.45 × 0.2 × 0.12
θ range for data collection [°]	1.49 to 30.51
limiting indices	$-34 \le h \le 34$, $-8 \le k \le 9$, $-39 \le l \le 37$
reflections collected	unique 22640 / 6505 [R(int) = 0.045]
refinement method	full-matrix least-squares on F^2
data / restraints / parameters	5330 / 0 / 405
goodness-of-fit on F^2	1.204
final R indices [$I > 2\sigma(I)$]	$R1 = 0.063$, w$R2 = 0.128$
R indices (all data)	$R1 = 0.095$, w$R2 = 0.173$
largest $\Delta\rho$ [e Å^{-3}]	0.367 / −0.190

Acknowledgments

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