The Preparation and Conformational Studies of 5,5,11,11,17,17,23,23-Octamethyl-1,3,7,9,13,15,19,21-octaaza-quinquecyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane

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The title compound was obtained by condensation of 2,2-dimethyl-1,3-propanedi-amine with formaldehyde. The predicted D_{2d} conformation was confirmed both by NMR spectroscopy in toluene solution and by X-ray crystal structure analysis.

Condensation of 1,3-propanediamine with aqueous formaldehyde is known to yield a quinquecyclic tetrameric product 1 (R=H) with remarkable ease.[1,2] After short reaction times a bicyclic oxadiaza compound 2 (R=H) is also reversibly formed,[2] and in a slow irreversible rearrangement reaction a Z,E-isomeric mixture of 1-formyl-3-methylhexa-hydropyrimidine 3 (R=H) is produced[2,3] (Scheme 1).

The tetramer 1 (R=H) can exist in two well defined conformations of symmetry D_{2d} and S_4, respectively. In each of these, the central 16-membered ring as well as the four laterally fused 6-membered rings strictly follow the diamond lattice. The S_4 conformer was first found in a crystalline 1:1 clathrate with benzene,[4] but recently we found the D_{2d} conformer in a crystalline 1:2 complex with dichloromethane.[5] In toluene solution, NMR spectroscopy revealed a roughly 1:1 mixture of both conformers, whereas in dichloromethane the D_{2d} conformer was practically the sole component.[5]

Molecular models indicate that if the 2-carbon of 1,3-propanediamine were to carry two methyl substituents, the S_4 conformation of the expected tetrameric condensation product 1 (R=CH$_3$) with formaldehyde would have four unfavourable 1,3-diaxial interactions, each between one CH$_3$ substituent of a 6-membered ring and one CH$_2$ group of the central macrocycle, as visualized in the perspective drawing of Fig. 1(b). Fig. 1(a) shows that the D_{2d} conformation would have no such steric problem and should therefore be the one adopted exclusively. This conformational homogeneity, together with the lack of vicinal spin-couplings, should lead to a significant simplification of the ¹H NMR spectra, which were extremely complex for the unsubstituted compound 1 (R=H). It was also predicted that the four 'inner' methyl substituents would prevent access to the nitrogen atoms and thus make complex formation, for example with dichloromethane, impossible.

Synthesis. The reaction between formaldehyde and 2,2-dimethyl-1,3-propanediamine proceeded in much the same way as with 1,3-propanediamine,[2] the main difference being that the temporary occurrence of the bicyclic byproduct 2 was not observed. This can be simply understood as being due to steric hindrance to the adoption of the strainless chair conformation in both 6-membered rings (Fig. 2) when the R-group is methyl instead of hydrogen. The rearrangement product 3 (R=CH$_3$) was, as before, the final irreversible product after prolonged reaction times. A short reaction time was therefore needed to optimize the yield of the quinquecyclic tetramer 1 (R=CH$_3$). As expected, it crystallized without occlusion of solvent molecules.

NMR spectroscopy. As the D_{2d} conformation possesses the constitutional symmetry of the ring skeleton, no dynamic process that involves the ring carbons can be observed in the ¹³C NMR spectrum. Only the ¹³C line for the geminal methyl substituents split into two below about 50 °C. This provides one value for the activation free energy for the only possible site-exchange process, namely that which can be simply classified as ring inversion. Strictly, however, it must involve a multistep sequence of six-membered ring inversions, nitrogen inversions and bond rotations. This same process could also be observed in the ¹H NMR spec-
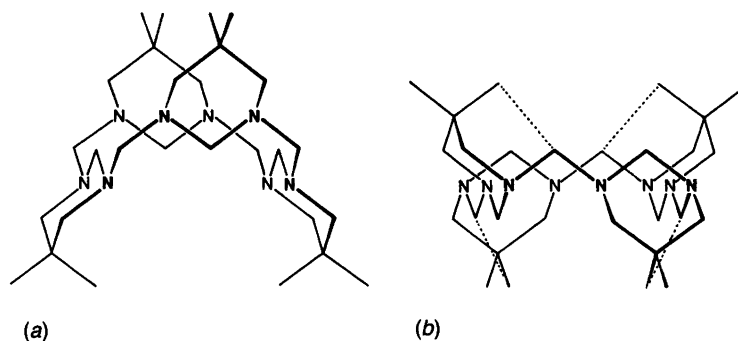

Scheme 1.
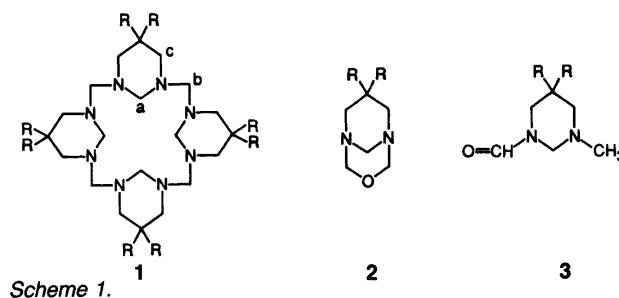
Fig. 1. Possible diamond-lattice conformations for **1**, (a) of D_{2d} and (b) of S_4 symmetry.

trum for the CH$_3$ groups, as well as for the CCH$_2$N and NCH$_2$N signals of the six-membered rings, but of course not for the NCH$_2$N signals of the 'corner' positions of the 16-membered ring, since these hydrogens are geminally identical, the carbon atom being on a twofold axis of symmetry. All these details prove unequivocally the D_{2d} symmetry and the conformational homogeneity of the tetramer. The ^{1}H NMR spectra of a toluene-d_8 solution at two temperatures are shown in Fig. 3 to demonstrate the simplicity at slow exchange (0 °C) and the incipient broadening at 40 °C for the two CH$_2$ quartets and the CH$_3$ doublet.

Since the four observed coalescence temperatures for one and the same process are spread over a wide temperature range, they provide a unique opportunity to plot the activation free energies $\Delta G^{\neq}$, each determined at the coalescence temperature, where error sources are at a minimum,[6] against the temperature to split it reliably into $\Delta H^{\neq}$ and $\Delta S^{\neq}$ parameters for the exchange process. The four independent values for the calculated barrier height are given in Table 1. These $\Delta G^{\neq}$ values are all a little higher than those found for the corresponding compound with R=H (ca. 66 kJ mol^{-1} instead of ca. 61 kJ mol^{-1}), presumably because of steric effects. A plot of $\Delta G^{\neq}$ against T, or the equivalent[6] Eyring plot, gave a rather low activation enthalpy (ca. 45 kJ mol^{-1}) and a large and negative activation entropy (ca. -63 J K^{-1} mol^{-1}). Although the error limits are wide (Table 1), the large numerical value and the negative sign for $\Delta S^{\neq}$ seem real and are surprising for a conformational process. However, other examples are known.[6]

Crystal structure. An ORTEP plot of the molecule is presented in Fig. 4. The projection corresponds to that of the upper figure of Fig. 5 of Ref. 5 which shows the structure of
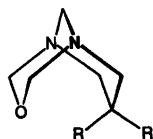

Fig. 2. The chair–chair conformation of **2**, possible when R=H, but not when R=CH$_3$.

the dichloromethane complex of the parent non-methylated compound.

The bond lengths are normal, the average bridge C–N bond length is 1.453(1) Å and the average ring C–H bond is 1.461(3) Å, the figures in parentheses being sample standard deviations. The average C–C bond length is 1.531(2) Å. Bond angles deviate less than 2.3° from tetrahedral.

The molecules have the expected D_{2h} symmetry. The exterior shape is approximately tetrahedral and they pack together in the crystals in sheets in the (100) plane sharing faces through a number of H–H van der Waal's contacts. Along the a axis only edges are left for comparatively few contacts explaining the extreme tendency for cleavage parallel to the (100) planes.

Experimental

Condensation reaction between 2,2-dimethyl-1,3-propane-diamine and formaldehyde. To a stirred solution of 2,2-dimethyl-1,3-propanediamine (Tokyo-Kasei) (5.1 g, 0.05 mol) and NaOH (0.2 g, 0.005 mol) in water (5 ml), kept below 40 °C by ice cooling, was added dropwise a 37 % formalin solution (12.1 g, 0.15 mol CH$_2$O). The mixture was stirred overnight at room temperature during which time a white, tough solid mass precipitated which was filtered off. Recrystallization from dioxane gave
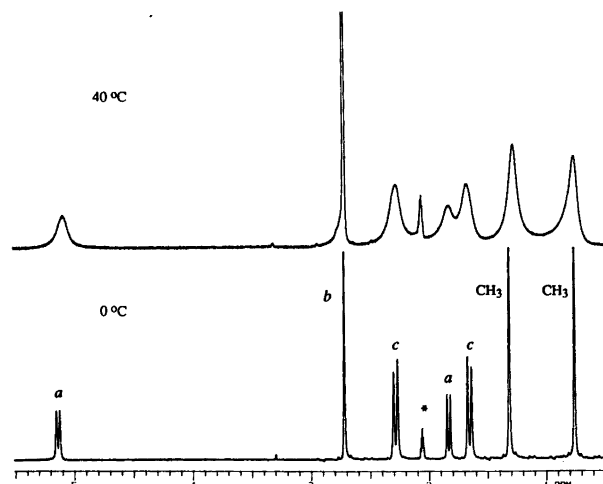

Fig. 3. ^{1}H NMR spectra of **1** in toluene-d_8 at 0 and 40 °C.

Table 1. Barrier to geminal site exchange of methylene and *gem*-dimethyl groups determined by DNMR spectroscopy.[a]

Signal used	$T_c/°C$	$\Delta v/Hz$	k/s^{-1}	$\Delta G^*/kJ\ mol^{-1}$
$^1H\ CH_2$-a	103	991	2201	68.7
$^1H\ CH_2$-c	62	189	421	65.5
$^1H\ CH_3$	59	167	370	65.3
$^{13}C\ CH_3$	50	68	151	65.8

[a]Eyring rate plot: $\Delta H^* = 45\pm6\ kJ\ mol^{-1}$, $\Delta S^* = -63\pm18\ J\ mol^{-1}\ K^{-1}$.

5,5,11,11,17,17,23,23-octamethyl-1,3,7,9,13,15,19,21-octa-azaquinquecyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosane **1** (R=CH₃). Yield 5.57 g (88 %), m.p. 209–215 °C. ¹H NMR (300 MHz, toluene-d_8, 0 °C): δ 0.78 (12 H, s), 1.33 (12 H, s), 1.67 (8 H, d, *J* 10 Hz), 1.85 (4 H, d, *J* 10 Hz), 2.30 (8 H, d, *J* 10 Hz), 2.74 (8 H, s), 5.16 (4 H, d, *J* 10 Hz). ¹³C NMR (75 MHz, toluene-d_8, −20 °C): δ 25.6 (CH₃), 26.5 (CH₃), 31.4 (quat. C), 64.4 (CCH₂N), 73.3 (NCH₂N), 76.6 (NCH₂N).

In a second experiment run under the same conditions, the mixture was left at room temperature for 3 days. The resulting precipitate was filtered off and washed with hot water. The combined aqueous phase and washings were extracted with chloroform (5×25 ml) and the organic phase was dried (Na₂SO₄), and the solvent evaporated off. Distillation at reduced pressure gave *3,5,5-trimethyl-1,3-diaza-cyclohexane-1-carbaldehyde* **3** (R=CH₃). Yield 3.2 g (56 %), b.p. 110 °C/10 mmHg. The NMR spectra revealed the presence of two isomers, *Z* and *E*, in a ratio of ca. 2:3. ¹H NMR (300 MHz, CDCl₃): δ 0.77 (6 H, CCH₃, *Z*+*E*), 2.0 (3 H, NCH₃, *Z*+*E*), 2.0 (2 H, 4-CH₂, *Z*+*E*), 2.76+3.0 (2 H, 6-CH₂, *Z*+*E*), 3.7+3.5 (2 H, 2-CH₂, *Z*+*E*), 7.7+8.0 (1 H, CH=O, *Z*+*E*). ¹³C NMR (75 MHz, CDCl₃): δ 24.3 (CCH₃, *Z*), 24.5 (CCH₃, *E*), 30.9 (C-5, *E*), 31.0 (C-5, *Z*), 42.3 (NCH₃, *E*), 42.5 (NCH₃, *Z*), 49.6 (C-6, *E*), 55.8 (C-6,
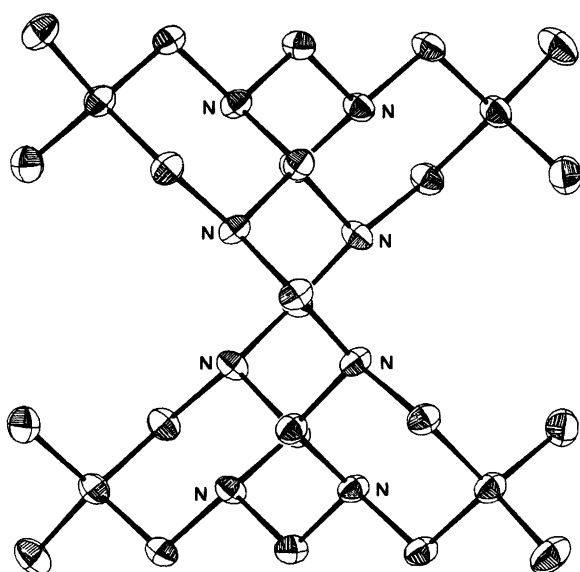
Table 2. Crystal and experimental data.

Compound	$C_{28}H_{56}N_8$
Diffractometer	NICOLET *P3/F*
Radiation	Mo K_α (λ = 0.7107 Å)
Crystal system	Monoclinic
$a/Å$	21.728(3)
$b/Å$	14.320(3)
$c/Å$	10.454(4)
$\beta/°$	106.23(2)
$V/Å^3$	2123.1(1.5)
T/K	123
Space group	*C2/c* (No. 15)
M	504.80
$F(000)$	1120
Z	4
$D_x/g\ cm^{-3}$	1.074
Scan mode	ω
Scan speed (ω)/° min^{-1}	2.0–4.0
Scan range (ω)/°	1.6
Maximum sinθ/λ/$Å^{-1}$	0.70
Stability monitoring	3 Test refl./135 observ.
No. of indep. meas.	4565
No. with $I>3.0\ \sigma(I)$	2836
Weighting scheme	$w = [\sigma^2(F)]^{-1}$
No. of parameters refined	247
$R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$	0.046
$R_w = [\Sigma w(F_o-F_c)^2/\Sigma wF_o^2]^{1/2}$	0.048
$S = [\Sigma w(F_o-F_c)^2/(n-m)]^{1/2}$	2.47

Z), 62.7 (C-2, *Z*), 67.2 (C-4, *Z*), 67.7 (C-4, *E*), 69.2 (C-2, *E*), 160.5 (CH=O, *Z*), 160.9 (CH=O, *E*).

NMR spectroscopy. The NMR spectra were recorded on a Varian XL-300 instrument operating at 300 MHz for ¹H and 75.4 MHz for ¹³C. Temperatures were calibrated using an ethylene glycol 'thermometer'. Free energies of activation were estimated from rate constants at T_c using the relation $k = \pi \cdot \Delta v/\sqrt{2}$.

Table 3. Fractional coordinates. E.s.d.s in parentheses.

Atom	x	y	z	U_{eq}[a]$/Å^2$
N(1)	0.87604(5)	0.19404(8)	0.25959(11)	0.017
N(2)	0.95570(5)	0.19432(8)	0.46955(11)	0.017
N(3)	1.04096(5)	0.30763(8)	0.52151(11)	0.017
N(4)	1.12298(5)	0.30750(8)	0.40932(11)	0.017
C(1)	0.83742(6)	0.25020(12)	0.15066(13)	0.019
C(2)	0.91324(7)	0.25241(12)	0.36796(14)	0.019
C(3)	0.91792(7)	0.13043(11)	0.52678(15)	0.020
C(4)	0.87579(7)	0.06714(10)	0.41929(14)	0.020
C(5)	0.83548(7)	0.12999(11)	0.30857(15)	0.019
C(6)	0.91761(9)	0.00120(11)	0.36394(18)	0.026
C(7)	0.83123(9)	0.00995(13)	0.47890(18)	0.030
C(8)	0.99807(7)	0.25081(13)	0.57333(13)	0.019
C(9)	1.08402(7)	0.24922(12)	0.47061(14)	0.020
C(10)	1.16296(7)	0.37028(11)	0.50886(15)	0.019
C(11)	1.12187(7)	0.43355(10)	0.56968(14)	0.019
C(12)	1.07844(7)	0.37043(11)	0.62470(14)	0.019
C(13)	1.16567(9)	0.48988(12)	0.68359(17)	0.026
C(14)	1.08179(9)	0.50028(11)	0.46464(17)	0.024

[a]$U_{eq} = \Sigma U_{ij}/3$.

Fig. 4. ORTEP plot of compound **1**.

X-Ray diffraction. It proved difficult to obtain crystals of convenient size and shape. The best solvent was chloroform, from which hexagonal plates were formed. Cutting large crystals invariably resulted in disintegration, like a pack of cards. A single crystal without optimum geometry had to be used. Crystal data and conditions for the data collection are given in Table 2. Lattice parameters were determined from the accurate setting angles for 25 general reflections.

The intensity data were corrected for Lorentz and polarization effects but not for absorption and extinction. The standard deviation for the intensities were based on counting statistics with an addition of 2 % of the net intensity.

Atomic coordinates of all non-hydrogen atoms were determined by direct methods (MITHRIL).[7] Refinements were performed by least-squares calculations.[8] Hydrogen positions were calculated and included in the refinements. The non-hydrogen atoms were refined with anisotropic thermal parameters, the hydrogen atoms were refined with a common U of 0.025 Å.[2]

Final figures of merit are included in Table 2. Positional parameters for carbon and nitrogen atoms are listed in Table 3 together with their equivalent isotropic thermal parameters. Lists of structure factors, anisotropic thermal parameters and hydrogen parameters may be obtained from C.R. upon request.

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