RING AND NITROGEN INVERSION IN A FLEXIBLE HIGHLY SYMMETRICAL MOLECULE

THE CONFORMATIONS OF
1,3,7,9,13,15,19,21-OCTAAZAPENTACYCLO[19,3,1,1^{3,7},1^{9,13},1^{15,19}]

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Abstract—The possible conformations of the title compound and their modes of interconversion via ring and nitrogen inversion processes are delineated. At high temperatures ($> +80°$) the ^{1}H NMR spectra are consistent with time averaged D_{4h} symmetry and rapid ring and nitrogen inversion. At lower temperatures (*ca.* $-10°$) the time-averaged symmetry is D_{2d} and inversion of the 6-membered rings is frozen out, nitrogen inversion remaining rapid. The free energy of activation for the total inversion of all four 6-membered rings is 13·5 kcal mole^{-1}, higher than in similar monocyclic systems. This higher energy is a reflection of the multiple ring inversion pathway required for total inversion of all the 6-membered rings.
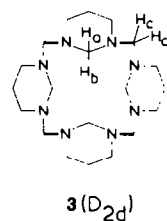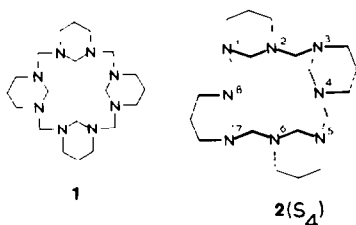
INTRODUCTION

Condensation of 1,3-diaminopropane with formaldehyde yields an ususual macrocyclic molecule in which four hexahydropyrimidine rings are linked into a 16-membered ring (1). Because of our continuing interest in the conformations and conformational processes in hexahydropyrimidines,[2-4] and in the structures of amine-formaldehyde condensation products[5-8] we have investigated 1 by X-ray crystallography and by variable temperature NMR spectroscopy.

The most stable conformation of the central 16-membered ring of 1 is likely to have D_{2d} symmetry with all atoms lying on or near points of the diamond lattice.[9] In this arrangement eight of the ring bonds will have staggered arrangements whilst the remaining eight will have gauche arrangements, producing a molecule with the minimum of torsional strain and *trans*-annular interactions. Although the title compound 1 contains additional 6-membered rings, the most stable conformation is still likely to be based on this diamond lattice geometry.

1

2(S$_4$)

The crystal structure of the benzene solvate of 1[8] showed a conformation (depicted schematically as 2, in which the molecule has exact S$_4$ symmetry, and all 28 atoms are close to diamond lattice points. Intermolecular contacts were shown to be unimportant in affecting the geometry of the molecule, and it is probable that this represents the most stable conformation of the system. At first sight this may seem surprising since each 6-membered ring has one axial substituent and an equally strain-free, and more symmetrical (D_{2d}), conformation 3

can be produced, in which all the N atoms are equatorially substituted. However, dipolar interactions favour N,N' disubstituted hexahydropyrimidines with one equatorial and one axial substituent and 3 may consequently be less stable than 2,[4,10,11] although our studies suggest that this energy difference is small.

Solutions of 1 at normal temperatures are likely to consist of many other conformations besides 2 and 3 interconverting at various rates. There are many more less symmetrical conformations formed by inversion of one or more 6-membered rings and by inversion at any of the N atoms. Since both of these processes destroy the D_{2d} symmetry of the 16-membered ring, these species are almost certainly of higher energy than 2 or 3 but will be of importance in determining the pathways for their interconversions. It is known that in hexahydropyrimidines inversion at nitrogen is a much faster process than ring inversion,[2,4,10,11] and if this holds in the present case it becomes possible to analyse the pathways for interconversion and the geometries of the intermediates. Before discussing our experimental results we shall therefore derive the interrelation of these intermediates.

3 (D$_{2d}$)

(a) *Slow ring inversion with fast nitrogen inversion.* As the molecules possess 8 N atoms 256 conformations due to nitrogen inversion are possible, but some of these are identical because of molecular connectivity. These conformations are listed in Table 1 (where only one example of each multiple set of equivalent conformations is given). Inversion of all the N atoms gives 2*, the mirror image of 2, although there is no enantiomerism because of the S$_4$ axis. This inversion process can be imagined as proceeding probably, though not necessarily, through 3 which it appears is of sufficiently low energy (*vide infra*) to be involved. The intermediates in the 2⇄3⇄2*

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Table 1. Conformers of the macrocycle produced by nitrogen inversion alone

One inversion (8 conformers)			
1	2		
Two inversions (28 conformers)			
12	13*	14	15*(2)
23	24	25	26(2)
Three inversions (56 conformers)			
123	124	125	126
127	128	135*	136
138	145	146	148
168	246		
Four inversions (70 conformers)			
1234	1235	1236	1237
1238	1245	1246	1247
1248	1256(2)	1257	1258
1267	1268	1357*(1)	1358
1368	1458(2)	1468	2468(1)

The 256 conformers are distributed as $1 + 8 + 28 + 56 + 70 + 56 + 28 + 8 + 1$.

The nitrogen atoms are labelled as in 2, where the odd numbers correspond to atoms with axial substituents in the ground state. The conformer is defined by the numbers of the N atoms which have a different type of substituent from that in the ground state (i.e. have inverted once). When the number of inversions (n) is greater than 4 the conformer is the enantiomer of one with $8-n$ inversions and the numbers then denote the atoms which have *not* inverted. The multiplicity of each conformer is 4 except where a number appears in parentheses. If the D_{2d} intermediate is the only molecule with four inversions of low enough energy to form part of the reaction pathway then only asterisked species can lie on this.

process are indicated by asterisks in Table 1 and the conformational network for these interconversions is represented in Fig. 1 (where only half is shown as the diagram is antisymmetric). The portion shown is isomorphous with the graph for ring inversion (Fig. 2) but posseses a lower symmetry (C_{4v}). If any other species with four inverted nitrogen centres are of comparable energy to 3 the network will be extremely complicated involving a much larger number of the 256 conceivable conformations. Provided that these nitrogen inversion processes are rapid on the NMR time scale, the molecules will have time averaged D_{2d} symmetry, where the bridging
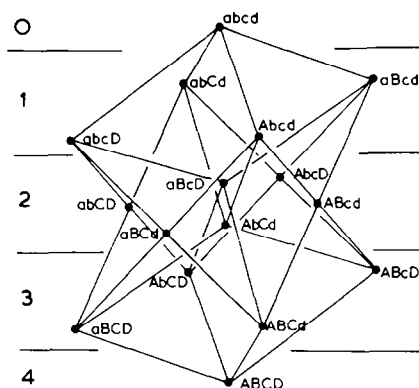

Fig. 2. Interrelation of conformers produced by ring inversion. A change from upper to lower case (or *vice versa*) represents inversion of the corresponding ring. The regions 0–4 represent the number of ring inversions relative to abcd.

methylenes lie on the twofold axes and the σ_d planes bisect the 6-membered rings.

(b) *Fast inversion both in the 6-membered ring and at nitrogen.* The sets of conformations with time-averaged D_{2d} symmetry due to rapid nitrogen inversion may interconvert by successive inversions of the 6-membered rings. For simplicity we shall describe this interconversion by looking at the inversion of 3 to its mirror image 3*. Figure 2 shows the 4-dimensional hypercube required to specify this process projected into its 3-dimensional subgroup D_{4h}. The conformations of lowest energy, ABCD and abcd, correspond to 3 and 3* respectively and changing the case of one of the ring letters corresponds to ring inversion. ABCd and related species have C_s symmetry, ABcd, etc, correspond to C_{2h} symmetry and AbCd/aBcD represent conformations with C_{4v} symmetry. Whether the inversion proceeds via the C_{2h} or C_{4v} intermediates will depend upon the relative energy of these species, which is not easily estimated from models. If we make the assumption that all the species in Fig. 2 are of equal energy and that all inversion processes are of the same probability, the transmission coefficient for the process ABCD → abcd can be estimated. The probability of a molecule reaching stage 2 from stage 1 is 3/4 and as
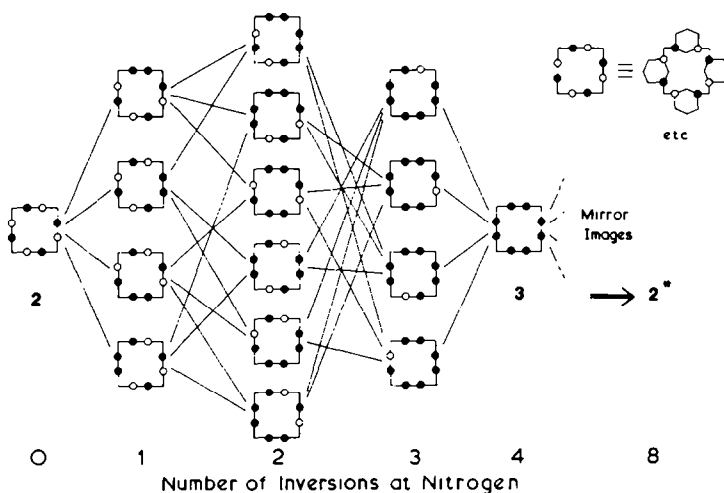

Fig. 1. Part of the reaction pathway for species produced by nitrogen inversion alone. Only those corresponding to asterisked species in Table 1 are shown. Open circles represent axial substituents and filled ones equatorial.

one half of the molecules in stage 2 must continue through to complete the ring inversion, the likelihood of an initial inversion in ABCD leading to abcd is 3/8. Since the initial process is four times more likely than in a monocyclic system, the transmission coefficient is 3/2 compared to hexahydropyrimidine itself. When both ring and nitrogen inversions occur rapidly the average symmetry of the whole system is D_{4h}.

To examine the ground state conformation of **1** in solution and to determine whether the above schemes derived on the basis of our previous crystallographic work and NMR results hold for this tetrameric compound, we have recorded and analysed the ^{1}H NMR spectrum of **1** over a large range of temperature.

EXPERIMENTAL

The title compound **1** was prepared as described by Krassig[1] and purified by recrystallisation from benzene. Its identity was confirmed by a single crystal X-ray analysis of the benzene solvate.[8] The pure compound was obtained simply by exposure to the atmosphere at room temperature when all the benzene was lost.

^{1}*H NMR spectra* were obtained from dilute (*ca.* 5% w/v) solutions of **1** in CFCl$_3$ ($-60°$ to $+20°$) and pyridine-d$_5$ ($-10°$ to $+90°$). A Perkin–Elmer R32 spectrometer operating at 90 MHz equipped with standard variable temp. and spin decoupling accessories was employed. Representative spectra are shown in Fig. 3.

DISCUSSION

A relatively sharp spectrum is observed at $-10°$ in both CFCl$_3$ and pyridine-d$_5$. This spectrum broadens with both increase and decrease of temperature. The $-10°$ spectrum is entirely consistent with our time-averaged D_{2d} model having rapid nitrogen and slow ring inversion. The methylene groups H$_c$ give a sharp singlet at τ 6·99 consistent with the time-averaged diad and absence of abnormal shielding effects. The methylene hydrogens H$_a$ and H$_b$ which lie in a σ_d plane but are not related by any symmetry element of the model form an AX system with the low field portion at τ 5·70 and the high field portion (from the axial hydrogens) at a more normal value of τ 7·54. The unprecedentedly low chemical shift for the equatorial hydrogen[2-4] is undoubtly due to its proximity to the lone pair on nitrogen in a neighbouring ring in conformation **2**. Such deshielding has been observed in similar molecules where hydrogens are forced into pairs of electrons on heteroatoms. An interesting example is the 3-heterosubstituted bicyclo (3,3,1) nonane system (**4**) where the hydrogen forced into the hetero-atom is strongly deshielded.[12] Spin decoupling confirmed that these four lines do indeed form an AX system and the coupling constant was measured to be $9·5 \pm 0·5$ Hz. The large uncertainty is due to broadened lines caused by long range couplings, residual kinetic broadening and the onset of kinetic broadening due to other process. The model compounds (**5** and **6**) have geminal coupling constants of 7·9 and 11·0 Hz respectively.[4] The intermediate value we observe suggests that **1** has appreciable amounts of both
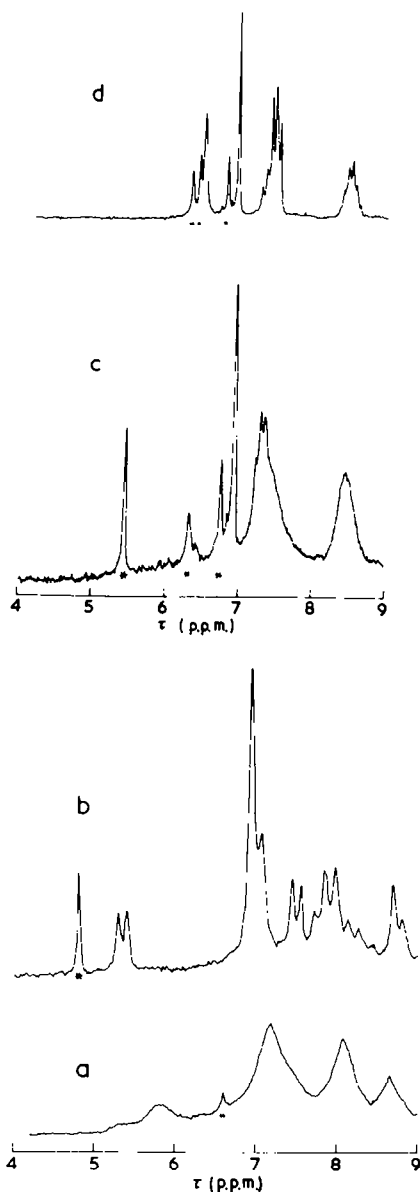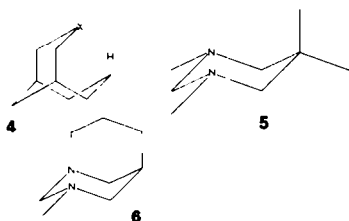

Fig. 3. Representative ^{1}H NMR spectra (90 MHz) of **1** at various temperatures. (a) $-60°$C, 5% w/v in CFCl$_3$, (b), (c), (d) 5% w/v in pyridine-d$_5$. (b) $-10°$C; (c) $+35°$C; (d) $+90°$C. The asterisked peaks are due to small amounts of impurities

equatorial-axial **2** and diequatorial **3** conformations. This means that there is probably little energy difference between **2** and **3** and is well in line with previous observations on related systems.[4] The remainder of the spectrum is more difficult to interpret, but decoupling experiments lead us to assign resonances at τ 7·05 and τ 7·90 to equatorial and axial C(4,6) hydrogens. The resonance at *ca.* τ 8·2 corresponds to the axial C(5) hydrogen whilst its equatorial partner is at *ca.* τ 8·70. This reversal of the normal relative positions of axial and equatorial H atoms has been observed in this series before.[13]

The changes in the spectrum as the temperature is increased are consistent with a raising of the average symmetry from D_{2d} to D_{4h}. All signals except the methylene singlet broaden at first, but then sharpen, until at about $+80°$ the spectrum consists of the expected
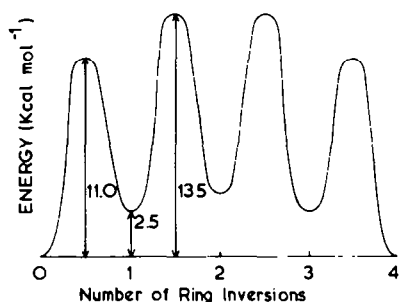
Fig. 4. Approximate reaction profile corresponding to the processes of Fig. 2.

singlets for both types of methylene between nitrogen and the approximmately first order triplet-quintet pattern for the propylene bridges. Coalescence for the $H_a H_b$ system occurs at $+35 \pm 5°$ giving a value for $\Delta G_c^{\ddagger}$ of $13 \cdot 5 \pm 0 \cdot 5 \, \text{kcal mole}^{-1}$ (transmission coefficient taken as 1). The nearest comparable figure is that for N,N'-diethylhexahydropyrimidine of $11 \cdot 2 \, \text{kcal mole}^{-1}$ (transmission coefficient = 1).[2] Since our present system is *more* likely to invert than the N,N'-diethyl compound, the barrier increase must be sought in enthalpy and not entropy of activation. We believe that the higher barrier in the present case arises from the multiple ring inversions needed for conversion of ABCD to abcd as shown in Fig. 2, and that the reaction profile can be approximately represented by Fig. 4. This suggests that those sets of conformations with one ring inverted are (very approximately) $2 \cdot 5 \, \text{kcal mole}^{-1}$ less stable than those sets of D_{2d} symmetry.

The changes that occur on cooling the system below $-10°$ are less easily interpretable. All resonances broaden due to the slowing down of further inversion processes. These could be either of the nitrogen inversion or single ring inversion (ABCD $\rightarrow$ ABCd) type. Although our model requires the τ $6 \cdot 99$ singlet to split into an AB quartet if the S_4 conformation is the most stable at low temperatures, we were not able to observe this due to the general broadening of all lines.

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