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APPLICATION OF DNMR, GROUP THEORY AND MOLECULAR MECHANICS IN THE ELUCIDATION OF THE INVERSION PROCESS IN THE FLEXIBLE MOLECULE PERHYDROTETRA-AZAPYRENE

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Abstract—The inversion process in *cis*-10b,10c-perhydro-1H,6H-3a,5a,8a,10a-tetraazapyrene (1) has been investigated by ^1H and ^{13}C NMR. The free energy of activation is found to be 14.95 ± 0.2 kcal mole^{-1} at 45°. Application of group theoretical techniques led to a graph representing the essential symmetry properties of the potential energy surface for conformational change. The energies of intermediates on this graph were then estimated using molecular mechanics calculations. This combined approach suggests that the total inversion proceeds via a conformation of C_{2v} symmetry with two non-chair piperazine rings, calculated to be 6.8 kcal mole^{-1} less stable than the ground state conformation (C_2 symmetry).

Cis-10b, 10c-perhydro-1H, 6H-3a, 5a, 8a, 10a-tetra-azapyrene (PTAP) (1) is a stereochemically intriguing molecule displaying temperature dependent ^1H and ^{13}C NMR spectra.[1] Two reports have appeared of crystal structure determinations for derivatives of this ring system.[3,4] Both of these reports show the molecules to possess folded conformations with all of the component 6-membered rings having chair conformations. The observed conformations of the component hexahydropyrimidine and piperazine rings are in accord with our knowledge of the conformational analysis of these systems[5] since each of the hexhydropyrimidine rings carries one axial and one equatorial N-substituent. It therefore seems reasonable that the conformation of PTAP corresponding to the global energy minimum is 2.

The sole symmetry element possessed by the conformation 2 is a twofold axis (C_2) and the molecule therefore has an enantiomer (2*). Inspection of models reveals that 2 interconverts with 2* by a process that must involve finally the inversion of all four N atoms and of both piperazine rings but not inversion of the hexahydropyrimidine rings.† This paper is concerned with the energetics of the inversion process and with delineating possible pathways by which this inversion process may occur. The problem of ring and N inversion in 1,4,5,8 - tetra - azadecalins, which form the central part of PTAP is being investigated by Fuchs *et al.*[6]

NMR results

The $^{13}C[^1H]$ spectrum of PTAP at 100° in toluene d_8 solution (firmly stoppered tube) shows four lines (Table 1), consistent with the molecule having time averaged C_{2v} symmetry. This symmetry is also consistent with the ^1H NMR data at 100° in toluene-d_8 solution, although the ^1H spectra are far from as simple as the ^{13}C spectra. On cooling, the lines in both ^1H and ^{13}C spectra broaden and then resharpen at lower temperatures. This is seen most clearly in the ^{13}C spectra, where six lines have become visible and sharp by 0°. This six line spectrum would be consistent with molecules possessing either a plane of symmetry (σ_{yz}) which cuts both piperazine rings in half, or with a C_2 axis of symmetry. The plane of symmetry is not only inconsistent with the ^1H NMR spectra at slow exchange, for which an AA'BB' spectrum would be required for the piperazine hydrogens, but also would require some non-chair 6-membered rings in the molecule which seems most unlikely. In fact the piperazine hydrogen resonances are much more consistent with the ABCD spectrum demanded by the C_2 all-chair conformation.

The NMR spectral data are therefore completely in accord with the conformation anticipated from the crystallographic results, and moreover agree with the expected interconversion between the two enantiomeric C_2 folded all-chair conformations 2 and 2* becoming slow on the NMR time scale in the temperature range studied. Coalescence temperatures for the ^{13}C spectra are at $47.5 \pm 5°$ and $61.5 \pm 5°$ giving $\Delta G_c^{\ddagger}$ values of 15.55 ± 0.3 and 15.57 ± 0.3 kcal mole^{-1} (Table 1).

†These latter rings start and finish the overall inversion process in the same state of inversion. As will be seen below, inversion of these rings may be involved as part of the overall process, but at some stage they must revert to their original configuration. In other words the total number of inversions of a piperazine ring or a nitrogen atom must be odd whilst that for a hexahydropyrimidine ring must be even. This is essentially a topological property of the $2 \rightleftharpoons 2^*$ process and does not rely on knowing the structure of the intermediate conformations.

Table 1. ^{13}C NMR Data for PTAP (recorded at 20.13 MHz). Chemical Shifts in ppm to high frequency of TMS for a *ca* 20% solution in toluene d_8

Atom Number	Temperature	
	0°	+100°
1	53.1 56.5 (Tc 47.5±5°)	55.2
2	20.5	20.9
3	45.4 54.9 (Tc 61.5±5°)	50.4
4	77.5	78.0

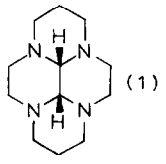
Analysis of inversion pathways

Whilst the coalescence phenomena are in accord with the **2** → **2*** exchange becoming slow on the NMR timescale it is by no means apparent how the molecules accomplish this exchange. In attempting to unravel this problem a large number of possible intermediates and their interconversions have to be considered. It is clearly most unlikely that the interconversion takes place in one step with synchronous inversion of four N atoms and two rings, and so the route(s) followed by the molecules as they invert must involve several discrete intermediates. For the interconversion of the two enantiomers it is clear that at some crucial point the process must involve either:

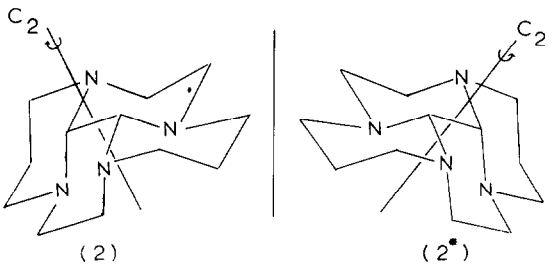
(i) one or more conformations with at least one mirror plane (a centre of symmetry is not possible), or

(ii) two enantiomeric conformations that interconvert rapidly. Inspection of models shows that several conformations with the required mirror planes are possible, and therefore that the problem is not trivial.

To describe the inversion process it would be desirable to compute the potential energy surface of 1 and to find the pathway(s) of lowest energy connecting configurations **2** and **2***. This can only be achieved in practice by limiting the dimensionality of the problem (i.e. projecting the energy surface onto the most important conformational coordinates) and carrying out calculations for a few important intermediates. Since we have determined an activation energy, intermediates which have energies above the ground state by much more than this amount can be eliminated.



(1)



(2) (2*)

Symmetry considerations

Symmetrical configurations are particularly important. They correspond to points on the potential energy surface where some or all of $(\partial V/\partial p_i) = 0$ (V being the potential energy of the molecular configuration, and p_i being the parameters describing conformational change). Since both local minima and transition states must have all $(\partial V/\partial p_i) = 0$, some of them may be discovered by examining (highly) symmetrical configurations.

The activation energy of the interconversion process should correspond to the height above the ground state (2) of the highest transition state along the reaction pathway (minimum energy pathway). If one of our symmetrical configurations corresponds to this transition state then calculation of its energy will give the activation energy. If (as will be seen to be the case) all the symmetrical configurations are local minima then calculation of their energies sets a lower bound for the activation energy. Knowledge of the experimental activation energy may well limit the allowed intermediates to a small number and, as will be seen, these constraints may allow most of the pathway to be described qualitatively.

We shall therefore assume (a) symmetrical intermediate(s) and concentrate our attention on the ways in which the molecules might reach this state. It was reasonable at this stage to investigate possible intermediates and interconversion pathways by using molecular models. We found that all of the chemically acceptable intermediates with planes of symmetry have two rings in non-chair conformations (N) and have two of the four nitrogen atoms inverted. However when the all-chair structure **2** is destroyed the molecule appears to gain considerable flexibility and many different interconversion pathways seemed possible.

A problem as complex as this can only be tackled if simplifying assumptions are made, and rules as to the nature of permissible changes are required. We shall describe the possible conformations of PTAP by the following eight parameters: The configuration at each nitrogen atom (lone pair "up" (represented as ●) or "down") and the conformation of each 6-membered ring (chair (C), inverted chair (C*) or non-chair (N)). This would, in theory, require an eight-dimensional potential energy surface and allow $2^4 \times 3^4 = 1296$ possible conformations, but most of these would involve huge amounts of strain and are therefore not possible.

In our simplification of the problem we can use the symmetry properties of the system. In this we parallel the approach of Pickett and Strauss in their description of the interconversion of cyclohexane[7] and related molecules. We wish to project the energy surface onto just those coordinates describing the most important conformational processes of the system. In the case of molecules as small as cyclohexane and cycloheptane there are few enough conformational degrees of freedom (3 and 4) to include them all, but for PTAP the dimensionality of the problem is larger (perhaps as large as 8) and it is very difficult to formalise the very complex geometrical constraints imposed by the fusion of the four rings. We therefore adopt a modified approach in which the symmetry (**H**) of the projected energy surface is computed first. Intermediates are then represented as points in a space of the appropriate symmetry. In the present case we shall not be concerned with the metric properties of this space, and shall use only its symmetry properties to produce a graph of the intermediates (ver-

tices) and their interconversion pathways (edges). An earlier example of such a graph for a flexible molecule has already been published by two of us.[8]

In our approach we regard all molecular configurations as distortions of a symmetrical reference structure (which need not be of low energy). This reference structure (with symmetry G) corresponds to the origin of our projected potential energy surface (in n-dimensional space). Any other structure can be represented by a distortion vector in this space. The basis of this approach and its formalism was developed in the context of distorted tetrahedra[9] but has been generalised to molecules distorted from any symmetry.[10] Certain types of distortion have particular significance, where one or more symmetry elements of the reference point group G have been retained. The corresponding point on the projected potential energy surface (which has symmetry H) must then lie at a special position (in the crystallographic sense) of the n-dimensional point group H.

Pickett and Strauss's description of the conformation of cyclohexane illustrates the approach.[7] The reference point group (G) is taken as D_{6h}, i.e. a planar regular hexagon. This configuration corresponds to the origin of the projected potential energy (PE) surface which is 3-dimensional. The symmetry (H) of the PE surface in this case is also D_{6h}. (To avoid confusion between the symmetry of molecules and the symmetry of the PE surface we shall use Hermann–Manguin symbols for the PE surface in keeping with our earlier practice.[10]) Since out-of-plane distortions of a planar regular hexagon transform as

$$B_{2g} + E_{2u}$$

we write

$$\mathbf{H}(D_{6h}(B_{2g}, E_{2u})) = \bar{6}2m.$$

Since H and G are isomorphic an arbitrary out-of-plane distortion for cyclohexane has the kernel symmetry C_1 but certain configurations have special (cokernel) symmetries. Particular examples are the boat (C_{2v}), twist (D_2) and chair (D_{3d}) configurations which correspond to special positions on the potential energy surface (respectively x,0,0 (on $mm2$ symmetry element), 0,y,0 (on $m'm2$ symmetry element) and 0,0,z (on $6mm$ symmetry element). Any other configurations can be described by combinations of these distortions. (It is important to realise that this description in symmetry terms does not depend on the distortions being small. Although large distortions mean that other symmetry coordinates may be non-zero (for example, bond length distortions may occur) the conformation can still be represented by a point in a 3-space of $\bar{6}m2$ symmetry).

The approach in the present example is similar. As reference symmetry we take C_{2v}, corresponding to conformations such as F and $H^{\dagger}$; this is the highest symmetry needed to explain the equivalence of protons in the dynamic NMR processes. We shall consider other configurations with all possible subgroup symmetries of C_{2v}, viz. C_1 (e.g. C†), C_2 (e.g. A†), σ_{xz} (e.g. I†) and σ_{yz} (e.g. G†). Distortions leading to these symmetries transform as

$$A_1 + A_2 + B_1 + B_2.$$

We can thus write

$$\mathbf{H}(C_{2v}(A_1, A_2, B_1, B_2)) = \mathbf{J}$$

where J (of order 4) is a 4-dimensional point group with general positions

$$\zeta\eta\xi\chi, \quad \zeta\bar{\eta}\xi\bar{\chi}, \quad \zeta\eta\bar{\xi}\bar{\chi}, \quad \zeta\eta\bar{\xi}\bar{\chi}.‡$$

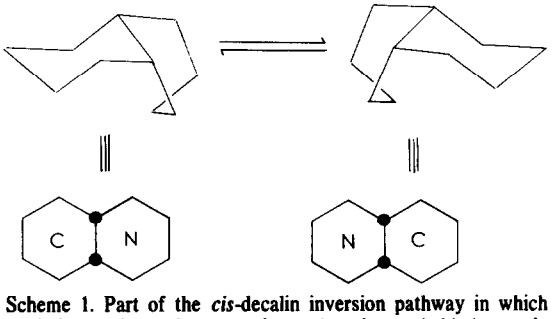
The coordinates η, ξ and χ correspond to orthogonal distortions with cokernel symmetries, C_2, σ_{xz} and σ_{yz}, and their origins are defined at their intersection. Coordinate ζ corresponds to distortions preserving C_{2v} symmetry and has a floating origin in J. We can use this fact to project J down the ζ coordinate into its 3-dimensional sub-group 222 (= D_2) with the understanding that there will be an orthogonal ζ axis whose metric properties are not represented. (In fact, since only two C_{2v} geometries are considered their projection into the new origin is not a serious loss.) Regardless of the true dimensionality of the problem (we might require subsidiary orthogonal axes η', η'', etc.) it is possible to construct a graph embedded in 4-space which indicates not only the intermediates and their interconversions but also the symmetry properties of the molecule. Anticipating our results slightly, the graph of the intermediates and their interconnections is shown in Fig. 1.

Geometrical constraints

To simplify the analysis of the interconversion pathways we have assumed the following plausible axioms:

(i) Nitrogen inversion can never occur without a simultaneous change in the conformation of one of the rings containing the nitrogen atom (either C → N or N → C).

(ii) If two rings are *cis* fused, one having a chair (C) and the other a non-chair (N) conformation, the ring conformations can be interchanged by a process of relatively low energy. This corresponds to part of the inversion pathway for *cis*-decalin (Scheme 1). This process can be accomplished by a simultaneous exchange of conformations in both rings coupled with a rotation about the central bond of *ca* 120°. No nitrogen inversion occurs during this process. In effect it consists of transferring the strain in one ring to its neighbour by a process



Scheme 1. Part of the *cis*-decalin inversion pathway in which strain is transferred from one ring to the other probably by a twin twist intermediate.

†Letters refer to intermediates (Scheme 3).

‡This result is stated without proof but can be shown using the general method described in Ref. 10.

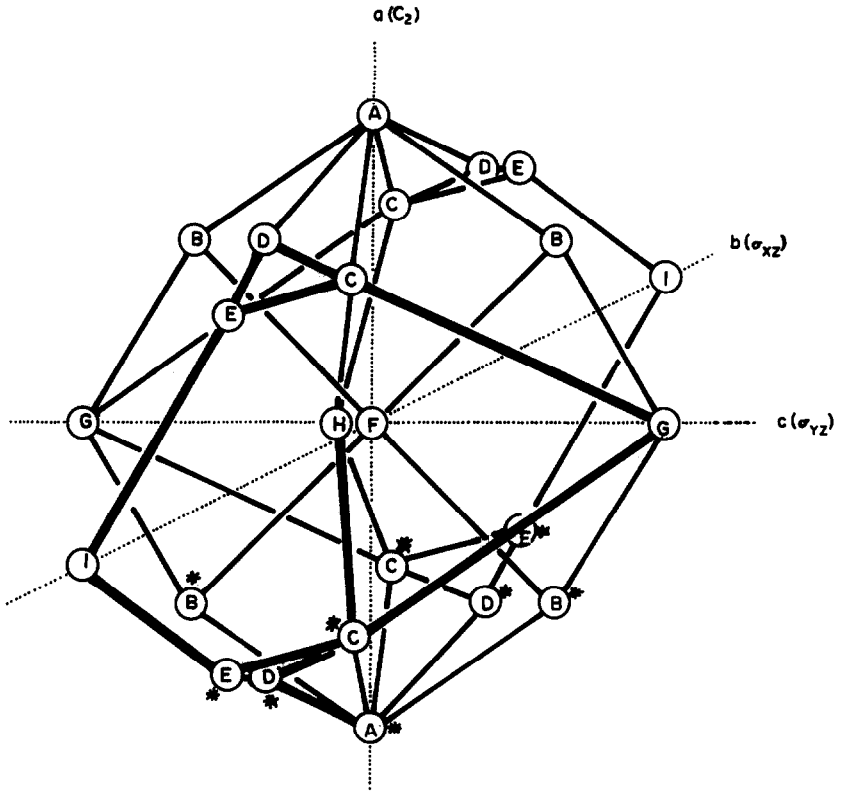
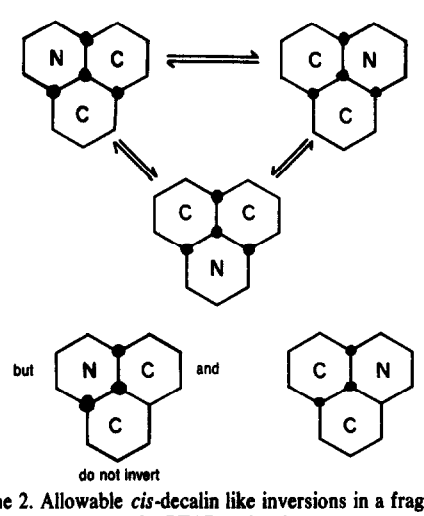


Fig. 1. Graph of the interconversions of nine possible conformers of PTAP. The diagram represents a three dimensional figure with D_2 (= 222) symmetry. Asterisks denote opposite chirality. Points (H) and (F) are distinct but in three dimensions coincide at the intersection of a, b & c; they are slightly displaced for clarity.

of low energy. Since the overall barrier to ring inversion in *cis*-decalin, of which this forms a part, is *ca* 12.5 kcal mole^{-1} [11] the energy required for this process is almost certainly less than this and therefore smaller than our overall observed barrier. Since the *cis*-decalin analogues in our compound always have further rings fused to them an additional rule is necessary.

(iii) Molecular models show that in the tricyclic fragment (3) transfer of strain from one ring to another as in (ii) is only of low energy if all rings are *cis* fused (Scheme 2).

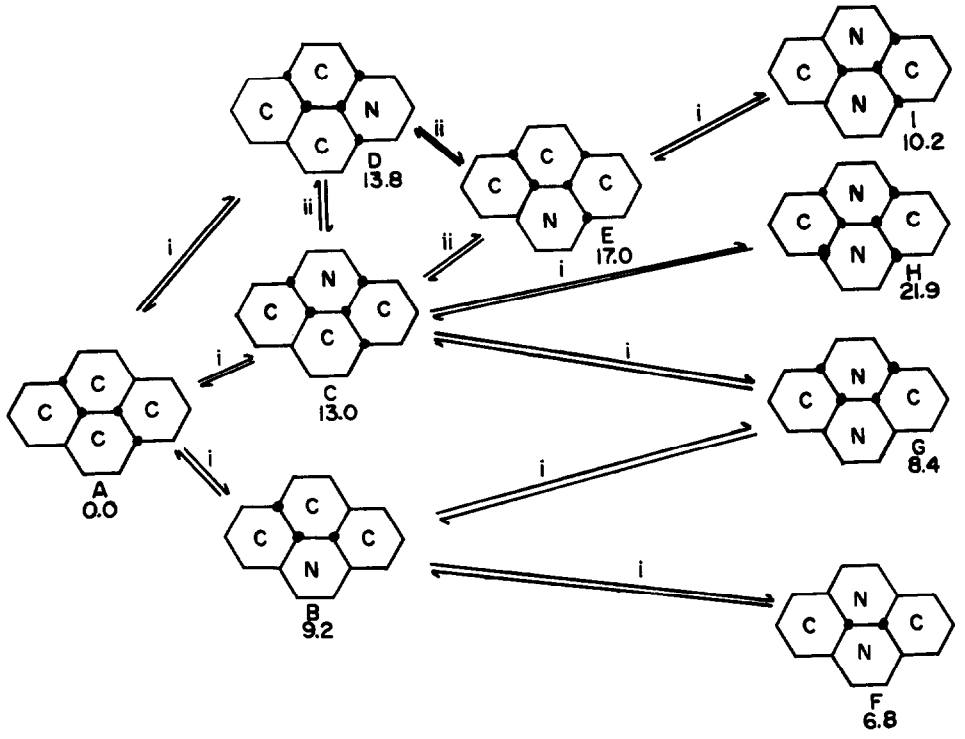


Scheme 2. Allowable *cis*-decalin like inversions in a fragment of the PTAP molecule.

The interconversion graph

Using the notation described above we may write the conformation of PTAP as A where central methine hydrogens and the pairs of electrons on two of the neighbouring N atoms are above the plane of the paper and designated filled in circle ●. A study of molecular models shows that only eight configurations (B–I, Scheme 3) are of low enough energy to be considered as possible intermediates (i.e. local energy minima) in the A → A* inversion. Fortuitously it happens that there is only one stereochemically reasonable configuration possible for each cokernel symmetry (*A*, *G* and *I*) and this simplifies the final interconversion graph. Scheme 3 shows all the interconversions allowed under assumptions (i)–(iii) but because of symmetry only one quarter of the information is included (i.e. this is the asymmetric unit of Fig. 1). Each interconversion is represented by a line and assuming that *A–I* are all local minima each line must involve at least one transition state. There may be other additional high-energy local minima but these are unlikely to change the general picture.

The full interconversion graph is given in Fig. 1. There are three orthogonal axes (a, b, c); each is a twofold axis of symmetry and maps to a set of molecular configurations with cokernel symmetry. (The symmetry of the diagram in three dimensions is 222.) A molecule with no symmetry (e.g. *B*) gives rise to four points (each labelled *B*) which correspond to isometric but not identical configurations, i.e. they are of identical energy, but have arisen from A by inversion of different symmetry related atoms and rings. Where points are related by twofold rotation about axes b or c in the diagram they are



Scheme 3. One quarter of the total inversion pathway for PTAP giving the energies of the species A–I relative to A.

enantiomers; where they are related by rotation about a, the chirality is retained.

Where a configuration has C_2 symmetry, e.g. *A*, it lies on a, where it has $C_{s(xy)}$ symmetry corresponds to a point lying at the intersection of a, b and c. Conformations *F* and *H* fulfil this condition and give rise to points (F) and (H). In four or more dimensions these points would be distinct but in our three dimensional projection they coincide and are shown displaced for clarity.

Molecular mechanics calculations

Which path or paths the molecules take for the interconversion of *A* with its enantiomer *A** will depend on the energies of the intermediates *B–I* and the activation energies for the processes shown in Fig. 1. The above graph theoretical delineation of possible inversion pathways has enabled us to simplify the problem enough to make some further headway by performing molecular mechanics calculations on the conformations *A–I*.

The calculations were performed in Warsaw using Allinger's MM1 program.[12,13] The final energy results are presented in Table 2 and the final calculated geometries are available as supplementary material. Energy minimisations were carried out in two stages differing in their treatment of intermediate Van der Waals interactions. The first stage of minimisation generally started from crude atomic coordinates. The second stage used the geometries resulting from the first stage calculations.

The energy minimisation for intermediates containing symmetry elements was initially performed keeping the symmetry elements intact. Thus *F* and *I* were minimised with C_{2v} symmetry. When these minimisations were allowed to proceed further with either partial removal of symmetry restrictions to C_2 or total removal to give C_1 there was no significant change of either geometry or energy. It seems therefore as if these intermediates really do possess C_{2v} symmetry.

The suggested interconversion process

The results of the energy minimisation support our assumption that the intermediates in Scheme 3 are local energy minima, in particular those of C_{2v} symmetry about which we initially had some doubts. If we make one further assumption, namely that all processes of type (i) are of roughly equal activation energy, we can now use the calculated energies of the intermediates to rule out some of the pathways.

Any route from A to A* must involve exactly four steps to type (i) and therefore to a first approximation the pathway taken is not dependent on the activation energy for processes of type (i). Two alternatives now need to be considered. If processes of type (ii) are of higher energy than (i) then *D*, *E* and *I* cannot be involved in $A \rightarrow A^*$. If, as we consider more likely, processes (ii) have activation energies similar to or less than (i) then the pathway taken will depend primarily on the energies of intermediates *B–I*. The overall barrier for any pathway can then be approximated as

$$\Delta E^{\ddagger} \sim E(X) - E(A) + \Delta E^{\ddagger}(i)$$

where X is the highest energy imtermediate on that pathway. Thus our calculations lead us to the conclusion that the route $A \rightarrow B \rightarrow F \rightarrow B^* \rightarrow A^*$ is the most probable method by which the molecules of this compound perform this remarkable inversion.

EXPERIMENTAL

The sample of **1** used was prepared in Warsaw using established literature methods.[2,14]

Table 2. Steric Energy (kcal/mole) for Different Conformations of PTAP from Energy Minimization Calculation[a]

Deformation or Interaction	Conformation energy terms, kcal/mole								
	A	B	C	D	E	F	G	H	I
Bond stretching	5.84	6.53	6.27	6.66	7.53	6.75	6.54	6.07	6.03
Bond bending	5.95	9.69	12.63	11.93	13.59	4.95	6.35	16.90	9.46
Bond stretch.-bend	0.96	1.04	1.50	1.51	1.76	0.76	1.07	2.03	1.33
Vad der Waals									
1,4-	23.79	25.50	26.06	26.32	26.39	26.21	26.66	27.36	26.55
other	-2.63	-2.44	-2.57	-2.05	-1.22	-2.22	-1.68	-1.59	-2.46
Torsional	0.48	2.60	3.24	3.86	3.15	2.79	3.21	4.15	3.08
Torsion.-bend	-0.01	-0.14	-0.27	-0.27	-0.35	-0.00	-0.02	-0.16	-0.04
Dipole-dipole	-0.11	0.71	0.43	0.10	0.39	1.83	0.56	1.43	0.47
Total steric energy	34.27	43.49	47.29	48.06	51.24	41.07	42.69	56.19	44.42
Excess steric energy[b]	0.00	9.22	13.02	13.79	16.97	6.80	8.42	21.92	10.15
Dipole moment, D	0.052	1.230	1.053	1.219	1.578	2.255	1.097	1.533	1.741

[a]All calculations were done on CDC CYBER 73 computer using MM1 program (N. L. Allinger, University of Georgia, Athens, Georgia, U.S.A., 1975 version).
[b]In relation to conformation A.

NMR spectra were obtained on a Perkin–Elmer R32 spectrometer (^{1}H) or on Bruker WP80 spectrometer (^{13}C) in Stirling.

Molecular mechanics calculations performed on a computer in Warsaw using Allinger's MM1 program parameterised for amine N atoms.[12,13]

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