

## The Molecular Conformation of Cyclodi- $\beta$ -alanyl

By David N. J. White\* and Michael H. P. Guy, Chemistry Department, The University, Glasgow G12 8QQ

Empirical force-field calculations have been used to predict the conformational preferences of the isolated (gas phase; 25°) molecule of cyclodi- $\beta$ -alanyl. The twist-boat conformer with  $\chi_1$ † torsion angles of  $-28^\circ$  is preferred to the extent of 1.4 kcal mol $^{-1}$  (steric energy) over the alternative twist-boat, with corresponding torsion angles of  $+35^\circ$ , and to the extent of 2.1 kcal mol $^{-1}$  relative to the centrosymmetric chair conformer.

THE eclipsed configuration around the  $C_i^\alpha-C_i^\beta$  † bonds of the rigid  $^1$  chair form of cyclodi- $\beta$ -alanyl (1a) results in appreciable Pitzer strain which can only be relieved at the expense of an increase in Baeyer strain (*i.e.* bond angle deformation). On the other hand, the flexible  $^1$  boat form (1b) can avoid eclipsing, without associated bond angle deformation, by twisting around the  $C_i^\alpha-C_i^\beta$  bonds; furthermore, the interaction of the electric dipoles associated with the peptide groups is energetically more favourable than the corresponding effect in the chair form. Leaving aside the obvious differences, this situation is similar to that prevailing in cyclo-octa-1,5-diene where the minimum energy conformation appears to be a twist-boat  $^{2,3}$  with  $C_{sp^2}-CH_2-CH_2-C_{sp^2}$  torsion angles of  $-27^\circ$ . ‡

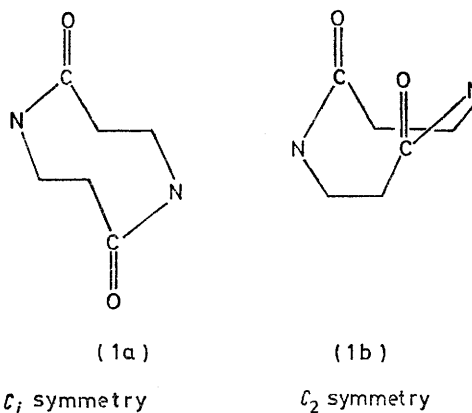
These factors, when taken in conjunction with the conformational similarities between cyclo-olefins and the corresponding cyclic peptides,<sup>4</sup> would seem to indicate a preference for the twist-boat conformation. Although the presence of a non-intersecting two-fold axis is a geo-

† See Appendix for definition of nomenclature.

‡ However Ermer (personal communication) calculates this torsion angle to be  $-55^\circ$  using the Lifson-Ermer consistent force-field and we have recently obtained a value of  $-51^\circ$  using the Allinger valence force-field.

<sup>1</sup> J. D. Dunitz and J. Waser, *J. Amer. Chem. Soc.*, 1972, **94**, 5645.

metrical prerequisite for flexibility of the molecule,<sup>1</sup> the extent to which this freedom is manifest, and the relative



energies of the boat and chair forms are a complex function of the various interatomic forces.

A recent X-ray analysis<sup>5</sup> has indicated that crystals of

<sup>2</sup> G. Favini, F. Zuccarello, and G. Buemi, *J. Mol. Struct.*, 1969, **3**, 385.

<sup>3</sup> K. Hedberg, unpublished work.

<sup>4</sup> O. Ermer and S. Lifson, *J. Amer. Chem. Soc.*, 1973, **95**, 4121.

<sup>5</sup> D. N. J. White and J. D. Dunitz, *Israel J. Chem.*, 1972, **10**, 249.

cyclodi- $\beta$ -alanyl are composed of molecules in a  $C_2$  conformation with  $\chi_i$  torsion angles of  $-27^\circ$ , and further, that the atomic vibration tensors are inconsistent with significant torsional oscillations around the  $C_i^\alpha-C_i^\beta$  bonds. However, it does not necessarily follow that the minimum energy conformation and molecular vibrations of the isolated molecule correspond to those of the molecule constrained by an intermolecular force field, as in the crystalline state.<sup>6</sup>

The situation concerning the isolated molecule has been investigated *via* molecular mechanics calculations \* of the potential energy of the  $C_i$  chair conformer and the variation of potential energy as a function of  $\chi_i$  for the  $C_2$  boat forms.

#### METHODS

Energy minimisation is accomplished by means of an iterative Newton-Raphson procedure, whereby the cartesian co-ordinates of the atoms corresponding to the trial conformation ( $x^b$ ) are adjusted to converge upon the equilibrium values for the minimum energy conformation ( $x^m$ ).

Initially, when the partial derivatives of the potential energy with respect to the trial co-ordinates ( $\partial V/\partial x^b$ ) are large, iterative application of equation (1)<sup>7</sup> to each of the

$$\frac{\partial V}{\partial x_i^b} = -\sum_{j=1}^3 \frac{\partial^2 V}{\partial x_i^b \partial x_j^b} \sigma x_j \begin{cases} i = 1, 3 \\ \sigma x_j = x_j^m - x_j^b \end{cases} \quad (1)$$

atoms in turn results in rapid convergence on the vicinity of the minimum. However, convergence of these equations is poor when  $\partial V/\partial x^b$  are small (*i.e.* when the co-ordinates are approaching their equilibrium values) and it becomes necessary to solve equation (2) for co-operative movements of

$$x_i^m = x_i^b - F_{ij}^{-1} \Delta V(x_j) \begin{cases} i = 1, 3n \\ j = 1, 3n \end{cases} \quad (2)$$

the atoms in order to obtain satisfactory convergence. The matrix of second derivatives ( $F_{ij}$ ) has order  $3n$ , where  $n$  is the number of atoms, and rank  $3n - 6$  corresponding to the number of degrees of freedom of the molecule. The six null eigenvalues correspond to rotations and translations of the molecule which must be eliminated before  $F_{ij}$  can be inverted. In practice this can be accomplished by means of the generalised inverse<sup>8</sup> which also facilitates calculation of the vibrational frequencies.

The derivatives are evaluated numerically from the expression for  $V$  as a function of the internal co-ordinates, non-bonded distances and coulombic interactions [equation (3) with  $\alpha = r/(r_1^* + r_2^*)$ ], *via* the appropriate transform-

$$V = \sum_b \frac{1}{2} k_b (b - b_0)^2 + \sum_\tau \frac{1}{2} k_\tau (\tau - \tau_0)^2 + \sum_\theta \frac{1}{2} k_\theta (1 \pm \cos n\theta) + \sum_\delta \frac{1}{2} k_\delta (\pi - \delta)^2 + \sum_r \epsilon \{-2.25\alpha^6 + 8.28 \times 10^5 \exp(-\alpha/0.0736)\} + \sum_q q_i q_j / r \quad (3)$$

ations from cartesian to internal co-ordinates. The variables  $b$ ,  $\tau$ ,  $r$ , and  $\theta$  are bond lengths, bond angles, 1,4 and

\* For an up-to-date bibliography of molecular mechanics calculations and their applications to peptides see E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, 1973, **95**, 8005 and H. A. Scheraga, *Chem. Rev.*, 1971, **71**, 195, respectively.

<sup>6</sup> M. Bixson and S. Lifson, *Tetrahedron*, 1967, **23**, 769.

<sup>7</sup> D. N. J. White and G. A. Sim, *Tetrahedron*, 1973, **29**, 3933.

higher interatomic distances, and torsion angles, respectively. The improper torsion angle  $\delta$  accounts for out-of-plane bending at the trigonal atoms. As none of the currently available and well proven valence force-fields (VFF)<sup>4,10</sup> has been extended to include the additional force-constants

Valence force-field constants <sup>a</sup>					
Stretch			Bend		
Bond	$b_0$	$\frac{1}{2}k_b$	Angle	$\tau_0$	$\frac{1}{2}k_\tau$
CO	1.24	632	CNC <sub>i</sub> $\beta$	124	0.017
			CNH <sub>i</sub>	119	0.008
CN	1.32	441	C <sub>i</sub> $\beta$ NH <sub>i</sub>	117	0.010
			OCN	123	0.015
NC <sub>i</sub> $\beta$	1.47	379	OCC <sub>i</sub> $\alpha$	120	0.013
NH <sub>i</sub>	1.00	430	NCC <sub>i</sub> $\alpha$	117	0.010
CC <sub>i</sub> $\alpha$	1.51	372	NC <sub>i</sub> $\beta$ C <sub>i</sub> $\alpha$	113	0.010
			NC <sub>i</sub> $\beta$ H <sub>i</sub> $\beta$	110	0.010
C <sub>i</sub> $\alpha$ C <sub>i</sub> $\beta$	1.54	326	CC <sub>i</sub> $\alpha$ C <sub>i</sub> $\beta$	113	0.007
C <sub>i</sub> $\alpha$ H <sub>i</sub> $\alpha$ , C <sub>i</sub> $\beta$ H <sub>i</sub> $\beta$	1.09	331	CC <sub>i</sub> $\alpha$ H <sub>i</sub> $\alpha$	110	0.008
			C <sub>i</sub> $\beta$ C <sub>i</sub> $\alpha$ H <sub>i</sub> $\alpha$	110	0.008
			H <sub>i</sub> $\alpha$ C <sub>i</sub> $\alpha$ H <sub>i</sub> $\alpha$ , H <sub>i</sub> $\beta$ C <sub>i</sub> $\beta$ H <sub>i</sub> $\beta$	109	0.012
van der Waals <sup>b</sup>			Torsion <sup>c</sup>		
Contact	$r^*$	$\epsilon$	Bond	Fold	$\frac{1}{2}k_\theta$
O...O	1.54	0.070	CN	2	12.00
N...N	1.60	0.066	NC <sub>i</sub> $\beta$	3	0.50
C...C	1.85	0.033	CC <sub>i</sub> $\alpha$	3	0.38
C <sub>i</sub> $\alpha$ ...C <sub>i</sub> $\beta$	1.55	0.116	C <sub>i</sub> $\alpha$ C <sub>i</sub> $\beta$	3	1.42
Out-of-plane bending			Charges <sup>12</sup>		
Deformation angle	$\frac{1}{2}k_\delta$		Atom	Charge	
C <sub>i</sub> $\alpha$ OCN	0.0012		O	-0.416	
C <sub>i</sub> $\beta$ H <sub>i</sub> NC	0.0002		N	-0.305	
			C	0.449	
			H	0.272	

<sup>a</sup> Energy in kcal mol<sup>-1</sup>, lengths in Å, angles in degrees, charges in units of e. <sup>b</sup> For cross terms  $\epsilon$  is taken as the geometric mean of  $\epsilon$  for each contributor. <sup>c</sup> This value is partitioned between each of the individual torsion angles around each bond.

necessary for facilitating molecular mechanics calculations on peptides, it seemed preferable to construct such a VFF rather than use an already available Urey-Bradley FF<sup>9</sup> which would entail some lack of consistency with our previous work<sup>7</sup> and the aforementioned VFFs. The various force constants are listed in the Table and whilst the force-field could be further refined it proved possible to reproduce the geometry and vibrational frequencies of 2-pyrrolidone and caprolactam with sufficient precision for some degree of confidence to be placed in the results for cyclodi- $\beta$ -alanyl.

The variation of steric energy as a function of  $\chi_i$  was determined by means of Wiberg and Boyd's technique<sup>11</sup> and, using their notation, values of  $c_1$  of up to 75 were necessary to cover the range  $-60$  to  $+70^\circ$  in  $10^\circ$  steps.

#### RESULTS AND DISCUSSION

The form of the torsional potential for  $\phi$  in peptides has not been conclusively established<sup>12,13</sup> although recent

<sup>8</sup> A. Warshel and S. Lifson, *J. Chem. Phys.*, 1970, **53**, 582.

<sup>9</sup> A. Warshel, M. Levitt, and S. Lifson, *J. Mol. Spectroscopy*, 1970, **33**, 84.

<sup>10</sup> N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, 1971, **93**, 1637.

<sup>11</sup> K. B. Wiberg and R. H. Boyd, *J. Amer. Chem. Soc.*, 1972, **94**, 8426.

<sup>12</sup> R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, 1966, **45**, 2091.

<sup>13</sup> D. A. Brant and P. J. Flory, *J. Amer. Chem. Soc.*, 1965, **87**, 2791.

*ab initio*<sup>14</sup> and semi-empirical<sup>15</sup> molecular orbital calculations indicate that for model compounds such as *N*-methyl-formamide and -acetamide the C $\alpha$ -H bond eclipses the peptide (C-N) bond in the minimum energy

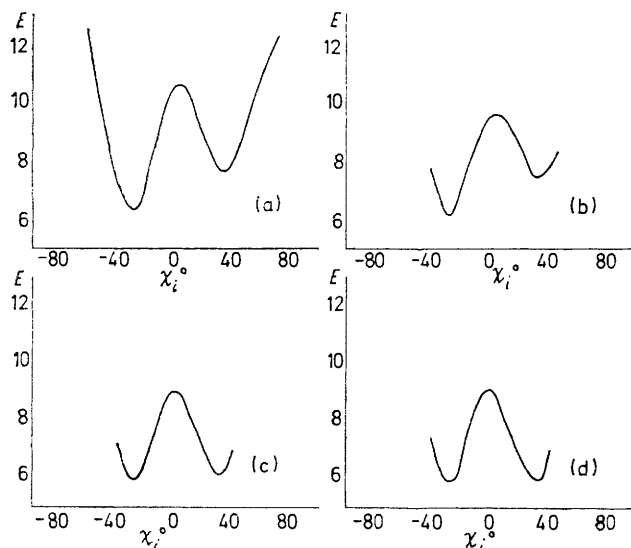


FIGURE 1 Variation of steric energy ( $C_2$  boat conformers) with  $\chi_i$  for various combinations of the magnitude and phase of the barrier to free  $\phi$  rotation: (a)  $\frac{1}{2}k\phi = 0.50$   $\frac{1}{2}k\psi = 0.38$   $V(\phi) = \frac{1}{2}k\phi \times \frac{1}{2}\sum_x [1 - \cos 3\theta(\text{CNC}_i\beta X) + 1 + \cos 3\theta(\text{HNC}_i\beta X)]$ ; (b)  $\frac{1}{2}k\phi = 0.38$   $\frac{1}{2}k\psi = 0.50$   $V(\phi) = \frac{1}{2}k\phi \times \frac{1}{2}\sum_x [1 - \cos 3\theta(\text{CNC}_i\beta X) + 1 + \cos 3\theta(\text{HNC}_i\beta X)]$ ; (c)  $\frac{1}{2}k\phi = 0.50$   $\frac{1}{2}k\psi = 0.38$   $V(\phi) = \frac{1}{2}k\phi \times \frac{1}{2}\sum_x [1 + \cos 3\theta(\text{CNC}_i\beta X) + 1 - \cos 3\theta(\text{HNC}_i\beta X)]$ ; (d)  $\frac{1}{2}k\phi = 0.38$   $\frac{1}{2}k\psi = 0.50$   $V(\phi) = \frac{1}{2}k\phi \times \frac{1}{2}\sum_x [1 + \cos 3\theta(\text{CNC}_i\beta X) + 1 - \cos 3\theta(\text{HNC}_i\beta X)]$

conformation. The calculated values of the barrier to free  $\phi$  rotation are somewhat variable<sup>14-16</sup> and although there is general agreement that the barrier is small (*ca.* 1 kcal mol<sup>-1</sup>) this has not been verified experimentally.

The variation of steric energy ( $C_2$  boat conformers) with  $\chi_i$  for various combinations of the magnitude and phase of the barrier to free  $\phi$  rotation is illustrated in a series of graphs (Figure 1a-d). Comparison of the first (Figure 1a, b) and second (Figure 1c, d) pair of graphs demonstrates the comparative insensitivity of the result to modest changes in the barrier height for  $\phi$  rotation. On the other hand, the phase of the barrier has a profound effect on the relative energies of the two non-equivalent twist-boat conformers with  $\chi_i$  *ca.* +30° and *ca.* -30°. If the calculations are based on a phase for the  $\phi$  barrier consistent with the MO predictions (Figure 1a) then the free energy difference between the two forms amounts to 1.4 kcal mol<sup>-1</sup> in favour of the latter (if the potential energy difference is equated to  $\Delta G$ , as seems appropriate in this case). This conclusion is supported by preliminary n.m.r. results<sup>17</sup> which suggest that cyclodi- $\beta$ -alanyl

<sup>14</sup> L. L. Shipman and R. E. Christofferson, *J. Amer. Chem. Soc.*, 1973, **95**, 1408.

<sup>15</sup> J. F. Yan, F. A. Momany, R. Hoffmann, and H. A. Scheraga, *J. Phys. Chem.*, 1970, **74**, 420.

<sup>16</sup> B. Maigret, B. Pullman, and M. Dreyfus, *J. Theor. Biol.*, 1970, **26**, 321.

exists in solution as an equilibrium mixture of unequally populated conformations, and to a certain extent by the occurrence of the  $\chi_i$  *ca.* -30° conformer in the crystalline state. On the other hand, calculations based on the alternative phase (Figure 1c) predict that the two conformers are energetically equivalent. This situation is at variance with the evidence discussed previously and also, to a lesser extent, with the absence of disorder in the crystal structure (*cf.* the observed molecular structure of 4,4,8,8-tetramethylcyclodecanecarboxylic acid<sup>18</sup> which corresponds to a space, time, and lattice average over two nearly isoenergetic and closely related conformations). The rather tenuous experimental evidence therefore seems to support the MO calculations and further discussion is based on the assumption that the MO forecast is correct.

The calculated geometry of the minimum energy twist-boat conformer of the dipeptide (Figure 2b) is very similar to the geometry of the molecule observed in the crystalline state (Figure 2a). Any discrepancies are probably due to deficiencies in the force field and the effects of intermolecular forces, particularly hydrogen bonding. In the latter context it is worth noting that the most significant difference between the two conformations occurred in the parameters  $\delta_N$  describing the out-of-plane bending at the

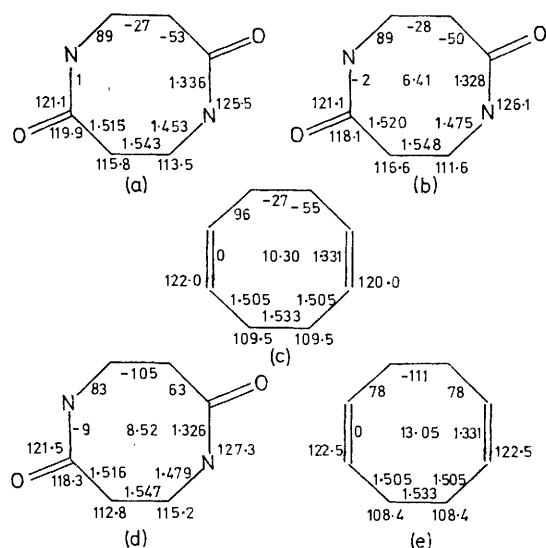


FIGURE 2 (a) Geometry of cyclodi- $\beta$ -alanyl from the crystal structure analysis; (b) calculated geometry for the twist-boat,  $C_2$  symmetry; (c) cyclo-octa-1,5-diene, calculated geometry for twist-boat,  $C_2$  symmetry;<sup>2</sup> (d) cyclodi- $\beta$ -alanyl geometry of  $C_4$  chair; (e) cyclo-octa-1,5-diene, calculated geometry for  $C_{2h}$  chair conformer.<sup>2</sup> Internal values: upper, torsion angles; lower, bond lengths. Peripheral values, bond angles. Central, steric energies in kcal mol<sup>-1</sup>

nitrogen atoms, which were of similar magnitude but opposite sign in each case. Winkler and Dunitz<sup>19</sup> have discussed the possibility of a shallow double minimum in

<sup>17</sup> J. D. Dunitz, personal communication.

<sup>18</sup> M. Bixson, H. Decker, J. D. Dunitz, H. Eser, S. Lifson, C. Mosselman, J. Slicher, and M. Svoboda, *Chem. Comm.*, 1967, 360.

<sup>19</sup> F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169.

the potential curve for  $\delta_N$  and it would appear that the forces acting on the amide hydrogen atoms as a result of intermolecular hydrogen bonding are of sufficient magnitude to determine which side of the  $CNC_i^\beta$  plane is preferred (see packing diagram <sup>5</sup>).

The centrosymmetric chair form of cyclodi- $\beta$ -alanyl (Figure 2d) is destabilised to the extent of 2.1 kcal mol<sup>-1</sup> relative to the  $C_2$  twist-boat conformer where the Pitzer strain is reduced by twisting around the  $C_i^\alpha-C_i^\beta$  bonds. Since the question of the equilibrium and transformation kinetics of the boat-chair interconversion has been raised <sup>5</sup> it would be useful to obtain an estimate of the free energy difference between the two conformers. The higher entropy of the twist-boat form arises almost entirely from its greater conformational flexibility (the contributions to the entropy of the  $C_2$  form, from chirality and symmetry, cancel whereas neither factor contributes to the entropy of the  $C_i$  form) so that  $\Delta G$  is probably at least 3 kcal mol<sup>-1</sup> if  $\Delta H$  is equated with the difference in steric energy. This would result in a 99:1 equilibrium mixture of twist-boat and chair forms in the gas phase at room temperature.

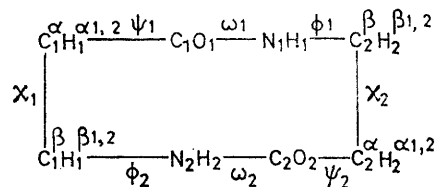
The calculated geometries of the twist-boat (Figure 2c) and chair (Figure 2e) forms of cyclo-octa-1,5-diene provide a further illustration of the conformational similarities between cyclic amides and the corresponding olefins. This is not too surprising when the partial double bond character of the amide bonds and the similarities in torsional potential functions are taken into account.

The root-mean-square amplitude of  $\chi_i$  libration for the

minimum energy twist-boat conformer of cyclodi- $\beta$ -alanyl can be estimated from the half-width of the potential curve at a height of 0.6 kcal mol<sup>-1</sup> ( $RT$  at 25°) above the minimum. This leads to a value of *ca.* 5° which, taken in conjunction with the rigid-body analysis of the atomic vibration tensors in the crystalline state, leads to the conclusion that the twist-boat conformer is not, in reality, particularly flexible.

#### APPENDIX

It is not possible to adhere rigidly to the IUPAC-IUB recommendations <sup>20</sup> for biochemical nomenclature when dealing with certain synthetic peptides, although it is advisable to do so insofar as is possible. A non-standard description (A) of cyclodi- $\beta$ -alanyl is therefore appended.



(A)

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<sup>20</sup> *Biochemistry*, 1970, **9**, 3471.