Crystal Structure and Conformational Flexibility of 2-(Acetylamino)prop-2-enoic Acid (*N*-Acetyldehydroalanine)

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The molecular structure of *N*-acetyldehydroalanine (2-acetylaminoprop-2-enoic acid) has been determined from three-dimensional *X*-ray data. $C_5H_7NO_3$ is monoclinic, space group $P2_1/n$, with $Z = 4$ in a cell of dimensions $a = 14.904(7)$, $b = 10.162(6)$, $c = 3.943(3)$ Å, $\beta = 91.7(1)°$. The structure was solved by direct methods and refined by full-matrix least-squares to R 0.060 for 1 350 observed reflections. The molecules exhibit a fully planar conformation and are linked by OH···O hydrogen bonds to form one-dimensional chains. The conformational flexibility is discussed on the basis of *ab initio* and empirical calculations.

MUCH effort has been devoted to theoretical and experimental investigations on the conformational behaviour of biological cyclopeptides.[1] Some of them contain α,β-unsaturated amino-acid residues, which may assume non-planar conformations (*e.g.* the family of tuberculostatic antibiotics [2]) though the presence of conjugative effects could suggest a preference for planar conformations. These considerations stimulated our interest in studies concerning the conformational flexibility of such unsaturated residues. Moreover, because of the lack of structural data in this field there is much scope for the use of diffraction methods.

The most common α,β-unsaturated amino-acid is dehydroalanine (2-aminoprop-2-enoic acid). We report here the *X*-ray structure of *N*-acetyldehydroalanine together with theoretical considerations on its conformational flexibility. The procedure adopted in the conformational analysis was similar to that used by us [3] for related molecules. In particular, the problem of torsional contributions was met by means of factorized (*i.e.* depending on single internal-rotation angles) potential functions which were derived from a comparison of quantum mechanical and empirical calculations.

EXPERIMENTAL

Single crystals of the title compound were grown as transparent needles by slow evaporation of an absolute ethanol solution of a commercial sample.

Crystal Data.—$C_5H_7NO_3$, $M = 129.12$, Monoclinic, $a = 14.904(7)$, $b = 10.162(6)$, $c = 3.943(3)$ Å, $\beta = 91.7(1)°$, $U = 596.9$ Å^3, $Z = 4$, $D_c = 1.44$ g cm^{-3}, $F(000) = 272$. Space group $P2_1/n$. Mo-K_α radiation, $\lambda = 0.710\,7$ Å; μ(Mo-K_α) = 0.78 cm^{-1}.

Intensity Measurements.—Intensities were collected on a Philips PW 1100 four-circle diffractometer operating in the θ—2θ scan mode (scanwidth 1°, scan speed 0.025° s^{-1}). Of 1 734 independent reflections measured up to θ 30°, 1 350 had intensities $I > 3\sigma(I)$, $\sigma(I)$ being calculated from the counting statistics of the measurements. In order to check the stability of the crystal and electronics during data collection two standard reflections were measured every 2 h. Intensities were corrected for Lorentz and polarization effects and were then put on an absolute scale by Wilson's method. Absorption and extinction corrections were ignored.

Structure Determination and Refinement.—Normalized structure factors were calculated and the 150 reflections with $|E(hkl)| \geqslant 2.17$ were used in the phasing program MULTAN.[4]

An E map was calculated according to ref. 4 and the structural solution was evident; R was then 0.22. The structure was refined by full-matrix least-squares methods and R reduced to 0.090. Hydrogen atoms, as derived from difference Fourier maps, were included in the scattering model with isotropic thermal parameters set equal to the isotropic-equivalent value of the attached non-hydrogen atom.[5] The final R factor was 0.060. The function minimized during refinement was $\Sigma w(|F_o| - |F_c|)^2$ where $w = 1$. All atomic scattering factors were taken from ref. 6. Calculations were carried out on the CYBER 76 computer of the Centro di Calcolo Interuniversitario dell'Italia Nord-Orientale with the SHELX 76 system of programs.[7] Observed and calculated structure factors and atom thermal parameters are listed in Supplementary Publication No. SUP 22431 (10 pp.).†

Conformational Calculations.—In the empirical calculations, performed by a modified version of the GEMO program,[8] the total conformational energy is defined as a summation of physically relevant contributions, *i.e.*

$$E_t = E_{vdW} + E_{ele} + \Sigma_n E_{tor}(\theta_n)$$

where E_{vdW} is the summation of pairwise van der Waals non-bonded interactions, calculated by '6-exp' potential calculations, and $E_{ele}(\theta_n)$ is the torsional potential hindering contributions, only monopolar terms being included, values for the fractional charges being obtained by *ab initio* calculations, and $E_{tor}(\theta_n)$ is the torsional potential hindering free rotation depending only on the θ_n torsion angle.

The method used to obtain torsional potentials from quantum mechanical calculations was described in ref. 3. The *ab initio* calculations were performed by the GAUSSIAN 70 program [10] using Pople's minimal STO 3G basis set.[11]

Conformational energy maps were calculated at 30° steps of ϕ[C(1)-C(2)-N-C(4)] and ψ[N-C(2)-C(1)-O(2)] torsion angles (see Figure 1). The 0° value of ϕ and ψ corresponds to a *cis*-conformation. The ω[H(N)-N-C(4)-O(3)] torsion angle was fixed in the *trans*-conformation.

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† See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

RESULTS AND DISCUSSION

X-*Ray Structure*.—A schematic view of the molecule showing the atom numbering system used in the crystallographic analysis, intramolecular bond distances and angles, and the definition of relevant torsion angles is presented in Figure 1. Final positional parameters of all atoms are reported in Table 1. The whole molecule is approximately planar and the best least-squares plane through it is given in Table 2, together with the atom deviations therefrom.

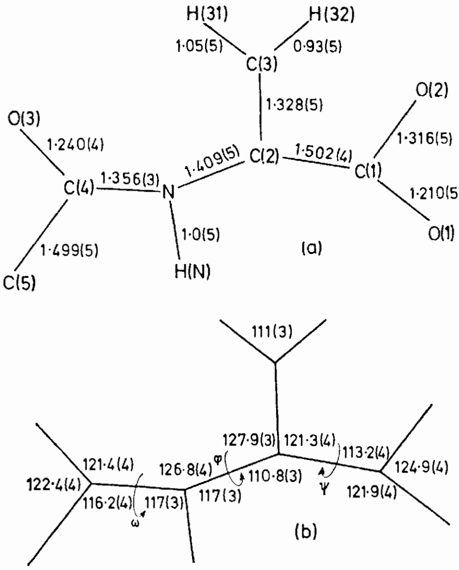


FIGURE 1 Schematic view of the molecule showing (a) intramolecular bond distances (Å), and (b) angles and relevant torsion angles (°); estimated standard deviations are in parentheses

The dimensions of the peptide group are to some extent different from those usually found in simple peptides.[12] In particular, the N–C(2) bond length is shorter while N–C(4) is longer. These findings are in excellent agreement with those reported for *N*-acetylbis(dehydrophenylalanyl)glycine [13] and seem to be peculiar to α,β-unsaturated peptide systems. This agreement is particularly significant since the last-mentioned tripeptide does not assume a planar arrangement for its ϕ and ψ torsion angles because of steric hindrance. Furthermore, the unusually high values for the C(4)–N–C(2) and N–C(2)–C(3) bond angles can be justified by steric repulsion between C(3) and O(3) as demonstrated by the short C(3) · · · O(3) distance (2.84 Å).

TABLE 1

Final atom positional parameters, with estimated standard deviations in parentheses *

	x/a	y/b	z/c
N	3 980(1)	6 384(2)	1 532(7)
O(1)	5 675(1)	6 086(2)	3 688(7)
O(2)	6 088(1)	8 048(2)	1 675(7)
O(3)	2 723(1)	7 220(2)	−1 016(7)
C(1)	5 508(2)	7 096(3)	2 177(8)
C(2)	4 591(2)	7 379(3)	669(7)
C(3)	4 437(2)	8 435(3)	−1 245(9)
C(4)	3 095(2)	6 327(3)	643(8)
C(5)	7 397(2)	4 881(3)	−1 729(9)
H(31)	390(3)	868(4)	774(9)
H(32)	494(2)	914(3)	828(9)
H(N)	423(3)	560(4)	273(9)
H(51)	720(5)	530(6)	−358(11)
H(52)	793(5)	460(6)	−251(11)
H(53)	744(5)	551(6)	28(11)
H(2)	665	780	261

* For non-hydrogen atoms $\times 10^4$, for hydrogen atoms $\times 10^3$; hydrogen atoms are numbered according to the atom to which they are bonded.

TABLE 2

Deviations (Å) of atoms from the best least-squares plane through the molecule. The equation of the plane is $-0.252\,2X + 0.478\,4Y + 0.841\,1Z = 2.103\,6$ in orthogonal Å space with X parallel to a, Z perpendicular to a in the ac plane, and Y perpendicular to the ac plane

N	0.02	O(3)	0.04	C(3)	−0.09
O(1)	−0.04	C(1)	0.01	C(4)	0.02
O(2)	0.08	C(2)	−0.02	C(5)	−0.02

The dimensions of the carboxy-group are all within the range usually found in carboxylic acids.[14]

The molecule assumes a fully extended conformation ($\phi \approx \psi \approx \omega \approx 180°$). The arrangement for the ω torsion angle is very close to the standard one.[12] The conformation around ψ is in agreement with that of fumaric acid [15] in which the *trans*-arrangement of C_β–C_α–C=O occurs. However it is noteworthy that acrylic, crotonic, and sorbic acids [16] have the *cis*-conformation.

The crystal packing is presented in Figure 2: the molecules are linked in one-dimensional chains approximately parallel to a by an intermolecular hydrogen-bonding system between the carboxylic oxygen of one molecule and the amide carbonyl group of the adjacent one [O(2)–H · · · O(3); O(2) · · · O(3) 2.59 Å]. This value is within the range usually observed.[17] None of the remaining intermolecular contact distances are shorter than the sum of the van der Waals radii.

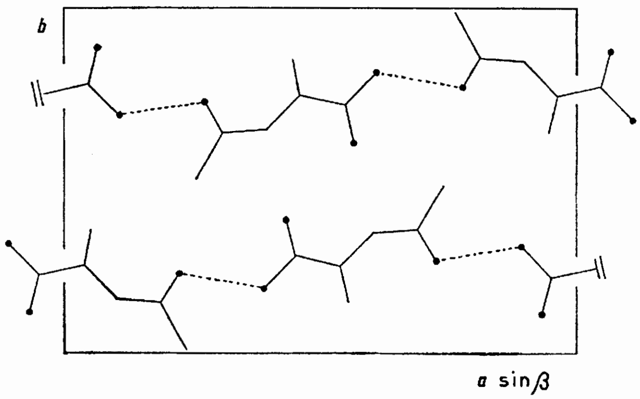
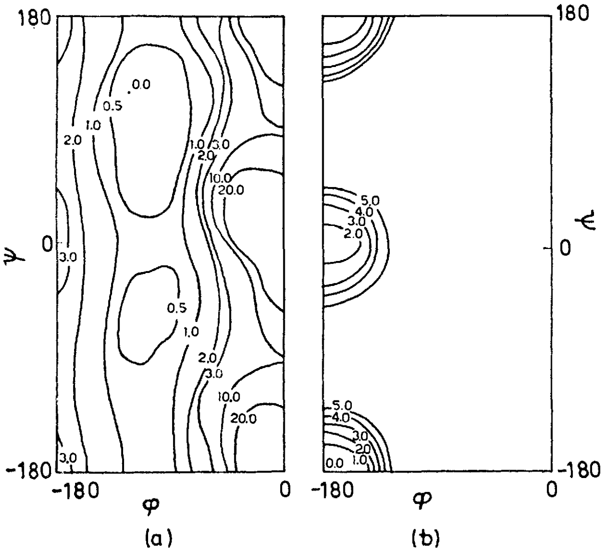


FIGURE 2 The crystal structure projected down c, showing the hydrogen bonding system

Conformational Analysis.—In order to save computational efforts the analysis was performed on *N*-formyldehydroalanine. For the conformational investigation of a free molecule it is not appropriate to use structural parameters which could be influenced by strong intermolecular interactions, *e.g.* hydrogen bonds. The geometry of the carboxy- and formylamino-groups was therefore derived from gas-phase results for related molecules [3,18] while the remaining structural parameters were taken from those of Figure 1.

The conformational energy obtained by the summation of the electrostatic and van der Waals contributions is plotted in Figure 3(a) as a function of ϕ and ψ torsion angles. Only two regions around *cis,cis*- ($\phi = 0°$, $\psi = 0°$) and *cis,trans*- ($\phi = 0°$, $\psi = 180°$) conformations are energetically forbidden owing to repulsions between O(3) and, alternatively, O(2) or O(1). The remaining part of the conformational space is sterically accessible so that the role of conjugative effects is enhanced. Figure 3(b) shows the conformational map obtained by adding the torsional (see Figure 4) to the electrostatic and van der Waals contributions. Only two energy minima, corresponding to the *trans,trans*- and *trans,cis*-conformations are present. Assuming the *trans,trans* as being of zero energy, the *trans,cis* is at 0.7 kcal mol^{-1}. The absolute minimum corresponds to the crystal-state conformation we have established.* However the small energy difference between the two minima suggests that the intermolecular hydrogen-bonding could be the driving factor in determining the crystal-state conformation.

In principle, the reported results could be influenced to some extent by the assumed structural parameters; a critical parameter could be the N–C(2)–C(3) bond angle whose unusual value is connected to the *trans*-conformation around the ϕ torsion angle. However, calculations performed for different values of the N–C(2)–C(3) bond angle did not show relevant modifications, either in the low-energy regions or in the forbidden ones.



(a) (b)

FIGURE 3 Conformational energy map. Energy values are in kcal mol^{-1} from the absolute minimum. Only the region $-180° \leqslant \phi \leqslant 0°$ is reported because of molecular symmetry. (a) van der Waals and electrostatic contributions only, (b) torsional contributions included

Finally some considerations can be inferred about the conformational behaviour of the related dipeptide *N*-acetyl-*N'*-methyldehydroalanylamide: the torsion barrier around ψ should be larger than in the title compound as suggested by a comparison between our calculations on acrylic acid and acrylamide (barrier height 5.9 and 7.9 kcal mol^{-1} respectively), but the steric hindrance produced by replacement of the hydroxy-group by methylamino should prevent any fully planar conformation.

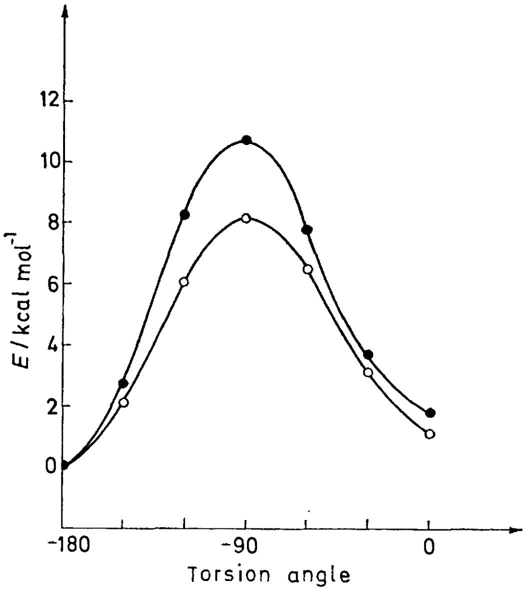


FIGURE 4 Torsional potentials adopted in the calculations: closed circles, around ϕ; and open circles, around ψ

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* Our calculations for acrylic acid, which predicted the *cis*-conformation to be 0.6 kcal mol^{-1} lower than the *trans*, were also in agreement with experimental results.[14,18]

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