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CONFORMATIONAL FLEXIBILITY OF THE DEHYDROALANINE DERIVATIVES: MOLECULAR AND ELECTRONIC STRUCTURE OF (Z)-N-ACETYLDEHYDROPHENYLALANINE

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Abstract—The molecular structure of (Z)-*N*-acetyldehydrophenylalanine (1-phenyl-2-acetylaminoprop-2-enoic acid) has been determined from three-dimensional X-ray data. $C_{11}H_{11}NO_3 \cdot 2H_2O$ is monoclinic, space group $P2_1/a$, with $Z = 4$ in a cell of dimensions $a = 18.260(5)$, $b = 6.050(2)$, $c = 11.411(4)$ Å, $\beta = 105.96(3)°$. The molecules exhibit a non-planar conformation as far as the φ torsion angle is concerned and they are linked by hydrogen bonds through two water molecules. Conformational flexibility is discussed on the basis of theoretical conformational analysis by taking into account the possibility of deviation from the planarity within the side chain. Theoretical results lead to exclusion any planar conformation for the title molecule. The vapour-phase He(I) photoelectron spectrum is also presented. The assignments are proposed by comparison with simpler related molecular systems and supported by INDO/S calculations. The effects of non-planarity on the electronic structure are discussed.

INTRODUCTION

α,β-Unsaturated amino acid residues play an important role in several natural peptides whose biological activities are well known.[1] A knowledge of the conformational behavior and the electronic peculiarities of such residues may be of importance in order to assess the structure-activity relationships of these compounds.

In previous papers[2,3] we reported on the conformational theoretical analysis of *dehydro*-Ala (N-acetyl-N'-methylamide of dehydroalanine; Fig. 1:R=R'=H; R"=$NHCH_3$) and *dehydro*-Phe (Nacetyl-N'-methylamide of dehydrophenylalanine; Fig. 1:R=C_6H_5; R'=H; R"=$NHCH_3$). The results indicated that the conformational behaviour of these molecules is very different from that of their saturated counterparts.

Besides theoretical investigations we also reported on the molecular (by diffraction methods)[4] and electronic structure (by photoelectron spectroscopy, PES)[5] of *dehydro*-Ala–OH (Fig. 1: R=R'=H; R"=OH). The molecules assume a fully extended conformation in the crystal state.[4] The hypothesis of a planar conformation also in the gas phase, at least as the φ torsion angle is concerned, was supported by the PES results, which evidentiated a remarkable π interaction between the acetamido- and vinyl-groups.[5]

In the present paper we report on the molecular and electronic structure of *dehydro*-Phe–OH (Fig. 1: R=C_6H_5; R'=H; R"=OH) in order to clarify the effects of the introduction of bulky side chains and for comparison with the behaviour of the corresponding amidic compound.[3]

Conformational studies of dehydrophenylalanine and its derivatives are of interest not only from a biological point of view but also in order to investigate the mechanism of their asymmetric hydrogenation catalysed by metal complexes.[6,7]

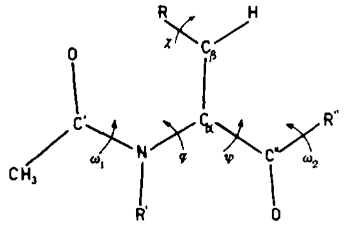

Fig. 1. General structural formula of dehydroalanine derivatives quoted in the present paper. Relevant torsion angles are shown.

RESULTS AND DISCUSSION

X-ray structure. The final positional parameters are reported in Table 1 and the mean plane equations with most relevant interplanar angles are listed in Table 2.

Bond distances and angles and the numbering scheme of the atoms are shown in Fig. 2 (respectively (a) and (b)). The dimensions of the peptide group are to some extend different both from those usually found in simple peptides[17] and those of *dehydro*-Ala–OH.[4] In particular, the N–C_α bond length (1.438 Å) is slightly shorter than the mean value reported for saturated peptides (1.449 Å),[17] but significantly longer than in *dehydro*-Ala–OH (1.409 Å), which assumes a planar arrangement.[4] The conformation of *dehydro*-Phe–OH is nearly planar as far as the cinnamic moiety is concerned ($\psi = 13.9°$; $\omega_1 = 0.5°$; $\chi = 4.8°$) while a marked deviation from planarity is found for the φ torsion angle ($\varphi = 71.7°$).

The crystal packing is given in Fig. 3. Two water molecules are linked to *dehydro*-Phe–OH hydrogen bonds, the first one to the carboxyl group and the second one to the amidic oxygen. Another hydrogen bond is present between each pair of adjacent water molecules (see Table 3).

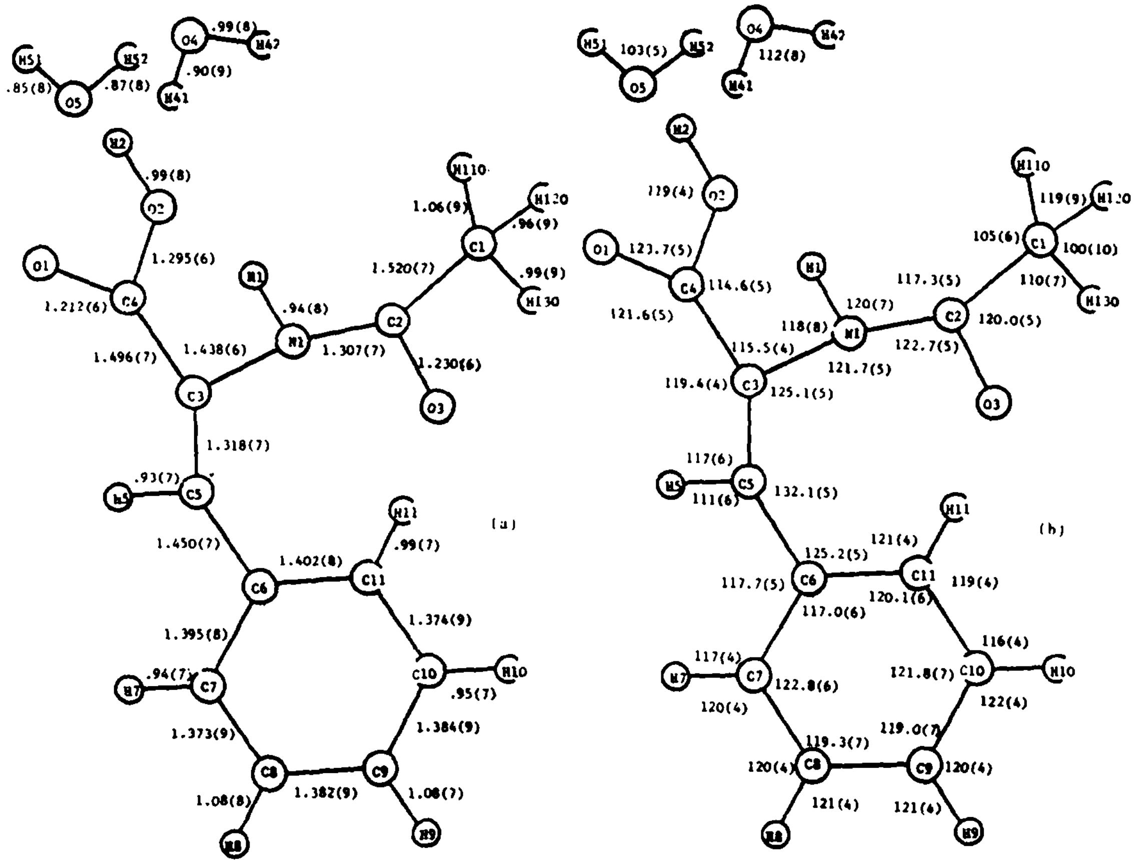

Fig. 2. Schematic view of the title molecule showing (a) bond distances (Å) and (b) angles (°). e.s.d.'s are in parentheses.

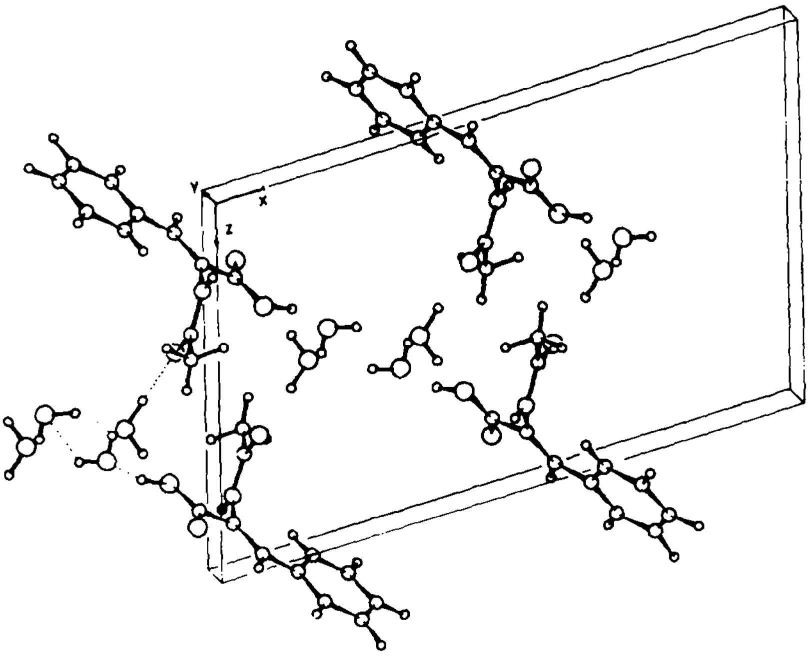

Fig. 3. Molecular packing in the unit cell viewed down the *b* axis. Hydrogen bonds are shown by dotted lines.

Table 1. Fractional atomic coordinates and anisotropic thermal parameters for non-hydrogen atoms, $\times 10^4$. Fractional atomic coordinates, $\times 10^3$, and isotropic thermal parameters for hydrogen atoms. e.s.d.'s are in parentheses

Atom	X	Y	Z	β11	β22	β33	β23	β13	β12	B(Å²)
O(1)	-343(3)	4814(6)	8276(4)	623(34)	156(21)	478(30)	-77(20)	69(25)	30(21)	
O(2)	-879(3)	2248(8)	6934(5)	523(34)	273(26)	473(32)	-68(25)	-41(27)	28(25)	
O(3)	735(3)	877(8)	6480(5)	740(38)	333(28)	492(33)	-82(25)	275(29)	-146(27)	
O(4)	-1554(4)	-1020(11)	5136(7)	601(40)	416(34)	559(40)	-164(32)	163(35)	-112(29)	
O(5)	-1886(5)	4901(12)	5799(10)	685(49)	508(43)	1148(59)	380(45)	-79(45)	58(39)	
N(1)	212(4)	-749(9)	7805(6)	590(41)	177(27)	356(36)	-55(24)	172(31)	-55(27)	
C(1)	459(6)	-2973(14)	6196(9)	615(61)	335(42)	497(53)	-226(40)	84(52)	-22(44)	
C(2)	474(4)	-776(11)	6848(6)	425(42)	267(36)	343(36)	-70(31)	59(33)	-29(33)	
C(3)	207(4)	1240(9)	8493(6)	389(36)	171(27)	355(36)	-59(27)	137(32)	-27(29)	
C(4)	-362(4)	2949(10)	7880(6)	479(43)	221(32)	344(38)	-7(28)	141(35)	-53(30)	
C(5)	674(4)	1664(10)	9575(7)	457(44)	211(32)	388(41)	-58(28)	119(36)	-9(30)	
C(6)	1296(4)	414(11)	10358(6)	427(40)	244(36)	465(42)	16(32)	203(35)	11(32)	
C(7)	1722(5)	1421(14)	11428(7)	496(48)	411(51)	574(48)	57(40)	125(42)	48(42)	
C(8)	2359(5)	467(16)	12190(8)	539(55)	743(64)	532(54)	46(48)	18(44)	124(49)	
C(9)	2589(6)	-1594(15)	11906(9)	645(61)	639(59)	665(62)	234(41)	186(53)	194(48)	
C(10)	2166(5)	-2650(14)	10863(9)	749(64)	399(47)	763(61)	167(45)	326(53)	179(47)	
C(11)	1531(5)	-1692(12)	10097(8)	585(53)	288(42)	537(52)	46(52)	161(44)	48(39)	
H(1)	4(6)	-206(14)	807(8)							3.8
H(2)	-132(4)	323(11)	656(9)							4.3
H(5)	61(4)	301(14)	993(7)							4.8
H(7)	155(4)	280(12)	1163(6)							4.5
H(8)	265(4)	129(12)	1303(7)							7.0
H(9)	310(5)	-235(14)	1247(7)							6.5
H(10)	229(5)	-410(17)	1064(8)							7.1
H(11)	123(5)	-255(16)	939(9)							5.9
H(110)	-7(7)	-370(18)	620(10)							8.0
H(120)	58(7)	-283(19)	543(11)							8.0
H(130)	88(7)	-394(19)	665(11)							8.0
H(41)	-130(6)	-60(18)	590(10)							2.1
H(42)	-124(5)	-97(15)	457(8)							6.6
H(51)	-237(5)	474(15)	556(7)							4.4
H(52)	-178(7)	555(20)	519(12)							6.6

Table 2. Equations of least-squares planes in the form $(lX + mY + nZ) \times 10^3 = d$ in orthogonal Å space and some interplanar angles (mean e.s.d.'s are 0.5°)

	plane	l	m	n	d	maximum displacement
1	N(1),C(1),C(2)	783	-210	585	3486	
2	N(1),C(2),C(3)	782	-220	583	3484	
3	N(1),C(3),C(4)	819	-407	-405	-5340	
4	O(2),C(3),C(4)	772	252	-584	-7018	
5	N(1),C(3),C(5)	796	422	-435	-5557	
6	C(3),C(5),C(6)	789	434	-435	-5530	
7	C(5),C(6),C(7)	788	372	-490	-6171	
8	O(3),C(1),C(2)	774	-217	595	3582	
9	C(3),C(4),C(5),C(6)	805	393	-444	-5671	.02(1)
10	O(1),O(2),O(4),O(5)	771	287	-568	-6820	.02(1)
11	C(6),C(7),C(8), C(9),C(10),C(11)	742	426	-517	-6436	.01(1)

1-2	.5°	3-4	13.9	5-6	.8	9-10	9.6	1-11	79.1	8-11	80.0
2-3	71.7	4-5	13.0	6-7	4.8	1-10	77.8	3-11	7.9	9-11	5.9

Table 3. Hydrogen bonding structural parameters

Hydrogen bond	Coordinates of acceptor	O...O	O - H	O...H	<O - H...O
O(5) - H(52)...O(4)	$x, 1+y, z$	2.699(5)Å	.87(8)Å	2.12(8)Å	124(5)°
O(4) - H(42)...O(3)	$\bar{x}, \bar{y}, 1-z$	2.676(5)	.99(8)	1.69(7)	177(5)
O(5) - H(51)...O(4)	$-\frac{1}{2}-x, \frac{1}{2}+y, 1-z$	2.809(4)	.85(8)	1.97(7)	172(5)
O(2) - H(2)....O(5)	x, y, z	2.515(4)	.99(8)	1.54(8)	167(5)

Conformational analysis. In Fig. 4 the conformational energy map of *dehydro*-Phe–OH is reported where the χ value is the optimum one for each point of the φ, ψ map. Within 7 kcal mol^{-1} four energy minima are present, i.e. I($\varphi = -130°$, $\psi = 0°$), II($\varphi = -50°$, $\psi = 0°$), III($\varphi = -130°$, $\psi = 180°$), IV($\varphi = -50°$, $\psi = 180°$). The relative energy values are E(I) = 1.0 kcal mol^{-1}, E(II) = 2.9 kcal mol^{-1}, E(III) = 0.0 kcal mol^{-1}, E(IV) = 2.6 kcal mol^{-1}. Common features to all these minima are the planarity as far as ψ torsion angle is concerned and a 50° deviation from planarity for φ torsion angle.

The position and the relative energy of the minima are significantly different from those found for *dehydro*-Ala–OH:[4] in particular, in the title compound the region of the conformational space corresponding to planar arrangement around the φ torsion angle is forbidden due to the presence of the phenyl group.

Moreover, the conformational behaviour is somewhat

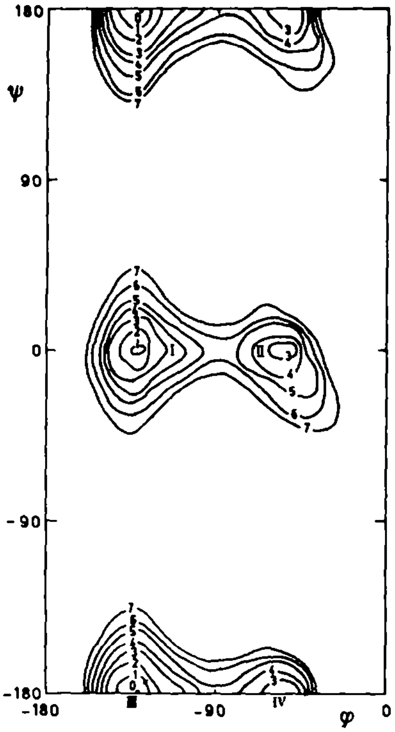

Fig. 4. Conformational energy map. Energy values are in kcal mol^{-1} from the absolute minimum. Only the region $-180° \leq \varphi \leq 0°$ is reported because of molecular symmetry.

different from *dehydro*-Phe[3] also, where the presence of the methylamido-group prevents *trans* conformations around the ψ torsion angle.

The crystal state conformation of *dehydro*-Phe–OH described in the previous paragraph ($\varphi = 71.7°$, $\psi = 13.9°$) is very close to minimum II, which is an excited one; however, packing energy should account for this little amount of energy.

The few experimental X-ray data of related compounds can be of value in checking the reliability of our theoretical prediction, in particular as regards the existence of several energy minima. The conformation of *dehydro*-Phe–OCH_3 in a transition metal complex[7] can be located in the energy minimum region III, whereas the conformation of N-Boc-*dehydro*-Leu–OH[18] can be assigned to the energy minimum IV. Finally, the conformation of *N*-benzyldehydrophenylalanine[19] can be related either to II or IV energy minimum regions. Discrimination between these two possibilities is prevented by the lack of detailed information on the structure of the carboxyl group.

The body of the X-ray results lends support to our theoretical predictions, since all the experimental conformations lie near the calculated energy minima and the multiplicity of populated conformational regions corroborates the small energy differences among the calculated minima.

Photoelectron spectrum. Due to the existence of four allowed conformational regions *dehydro*-Phe–OH could assume in the vapour phase a conformation different from that in the crystal state. However, according to our theoretical results, all four types of conformation imply a significant deviation from the planarity around the φ torsion angle.

In principle PE spectroscopy can be of value[20] in checking this theoretical model since it allows detecting the effects of a steric inhibition of resonance between π systems.

In Fig. 5 the He(I) excited spectrum of *dehydro*-Phe–OH is reported. Bands are labelled in alphabetic order.

Only the first region, including bands A, B, C, D and E, is of interest for the purpose of our investigations. In this spectral region (8–13 eV), by making reference to the spectra of *dehydro*-Ala–OH[5] and styrene,[21] nine ionization events are expected. Five of them correspond to MOs of the styryl moiety: we indicate (Fig. 6) as π_1 and π_3 the MOs arising from the interaction between a component of the benzene MO e_{1g} and the vinyl π system, while π_2 represents the second non-interacting component of the benzene $\pi\, e_{1g}$ *MO* whereas the pair that we label σ_1, σ_2 is related to the $\sigma\, e_{2g}$ MO of benzene. Two MOs pertain to acetamido-fragment (n_O oxygen lone pair and π_N mainly localized on the nitrogen atom) and two MOs to the carboxyl group (n'_O oxygen lone pair and non-bonding π_{COOH}).

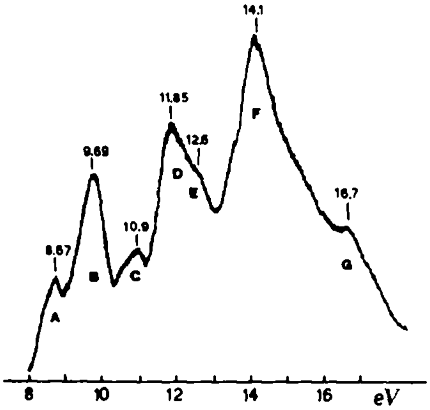

Fig. 5. He(I) excited PE spectrum of the title molecule.

The comparison of the IE's of the title compound with those of styrene[21] and *dehydro*-Ala–OH[5] and relative intensity arguments point to the assignment of band A to the ionization from the π_1 MO, while the ionization from π_2 is likely to be included in the band B, together with the π_N and n_O MOs. Consistently, n'_O is to be assigned to band C and the remaining ionizations (from π_{COOH}, π_3, σ_1 and σ_2) to band D and E. This picture is strongly substantiated by the quantum mechanical results reported in Fig. 6, where a theoretical correlation diagram between the eigenvalues of *dehydro*-Phe–OH and those of the related molecules acetamide and cinnamic acid is shown.

The IE value corresponding to π_N MO should be the most reliable probe of the hypothetical deviation from planarity around the φ torsion angle. This because the interaction between π_N and π_3 MOs is strongly dependent upon the actual value of φ. Unfortunately the π_N ionization is not directly detectable within the broad band B. Nevertheless an approximate gauge of IE(π_N) can be obtained; in fact, by comparison between the IE(π_1) values of styrene and the title compound, a 0.25 eV shift toward higher IE is observed. A corresponding effect on π_2 (which represents a pure benzene MO[21]), if any, should be smaller. Therefore the uppermost limit for IE(π_2) is *ca*. 9.4 eV, so that within

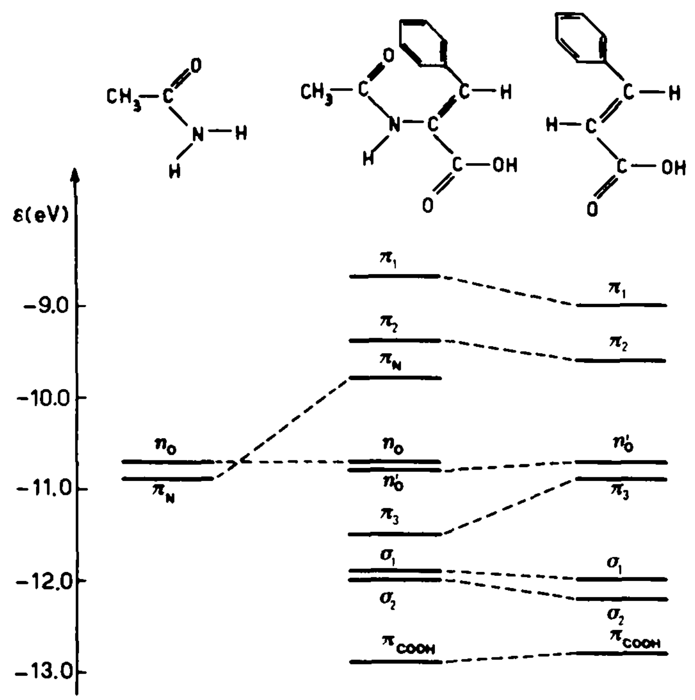

Fig. 6. Correclation diagram of INDO/S eigenvalues (eV) between acetamide, the title compound and cinnamic acid.

the symmetrical band B the lower IE component is to be assigned to π_2 and the IE(π_N) cannot be less than *ca.* 9.7 eV (the center of the band B). This value is significantly greater than the corresponding one in the planar *dehydro*-Ala-OH (*ca.* 9.2 eV). This is a proof of a smaller extent of the conjugation through N–C_α bond in *dehydro*-Phe-OH than in *dehydro*-Ala-OH, in agreement with the proposed conformational behaviour in vapour phase.

CONCLUSION

The conformation of *dehydro*-Phe-OH is non-planar both in the crystal state and in the vapour phase. The different conformational behaviour with respect to *dehydro*-Ala-OH affects the electronic structure, in particular as regards the enamic moiety; in general, the introduction of a bulky side chain in a dehydroalanyl system produces not only conformational effects, but also significant perturbations in the electronic structure and, as a consequence, in the chemical reactivity of these compounds. Both features are to be taken into account when the structure-activity relationships of related biological molecules are investigated.

EXPERIMENTAL

Crystal data. $C_{11}H_{11}NO_3 \cdot 2H_2O$, $M = 241.2$. Crystals of the commercial title compound, obtained from ethanol solution, are monoclinic, space group $P2_1/a$, $a = 18.260(5)$, $b = 6.050(2)$, $c = 11.41(4)$ Å, $\beta = 105.96(3)°$, $U = 1212.02$ Å^3, $Z = 4$, $D_m = 1.33$, $D_c = 1.322$ g cm^{-3}, F(OOO) = 512, MoK_α radiation, $\lambda = 0.7107$ Å, μ(MoK_α) = 1.24 cm^{-1}.

Solution and refinement of the structure. Intensity data were measured on a Philips PW 1100 four circles diffractometer (graphite-monochromatized MoK_α radiation, θ–2θ scan mode). For data collection a crystal of approximate dimensions 0.2 × 0.4 × 0.9 mm was used.

Data were not corrected for absorption. A total of 2227 reflections was measured for $\theta < 25°$; 1153 of them had $I > 2.5\sigma(I)$. The structure was solved by multiple solution procedure with the MULTAN program[8] and refined by full-matrix least-squares methods, unitary weights. R was reduced from 0.35 to 0.13. Hydrogen atoms were derived from difference Fourier maps, included in scattering factor calculations with isotropic thermal parameters, and refined by one cycle of full-matrix least-squares. Other non-hydrogen atoms were anisotropically refined. The refinement converged to R = 0.071.

Calculations were performed on a Cyber 76 computer by the SHELX-76 program for crystal structure determination.[9] All atomic scattering factors were taken from ref. 10.

Observed and calculated structure factors are listed in Supplementary Publication No. SUP 000 (PP pp).

Conformational calculations. Calculations were performed in 10° steps of the variable torsion angles (see Fig. 1) φ(C′–N–C_α–C″), ψ(N–C_α–C″–R″) and χ. The ω_1(CH_3–C′–N–C_α) and ω_2(C_α–C″–OH) torsion angles were fixed in the *trans* conformation and the *Z* configuration was assumed for the C_α–C_β double bond. The 0° value of the torsion angles corresponds to a *cis* conformation.

The total conformational energy is defined as the summation of physically relevant contribution, i.e.

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

where E_{vdW} is the summation of pairwise van der Waals nonbonded interactions, calculated by "6-exp" potential functions, E_{ele} is the summation of pairwise electrostatic contributions (only monopolar terms being included, values for fractional charges being obtained by *ab initio* calculations), and $E_{tor}(\theta_n)$ is the free rotation hindering torsional potential depending only on the θ_n torsion angle. The method used to obtain torsional potentials from quantum mechanical calculations was described in Ref. 11.

The *ab initio* calculations were performed by the Gaussian 70 program[12] using Pople's minimal STO 3G basis set.[13]

The geometry of the carboxy- and acetamido-groups was derived from gas-phase results for related molecules, while the remaining structural parameters were taken from those of Fig. 2.

Photoelectron spectroscopy. (*Z*)-N-acetyldehydrophenylalanine was sublimed *in vacuo* prior to use. He(I) excited PE spectrum was recorded on a Perkin-Elmer PS-18 spectrometer using a heated probe inlet system in the range 130°–145°. The spectrum was calibrated by reference to the peaks of the Xe and Ar gases simultaneously admitted into the target chamber.

Quantum mechanical calculations were performed within the INDO/S scheme[14,15] and the computed eigenvalues were related to the measured ionization energies (IEs) through Koopmans' approximation.[16]

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