Tetrahedron Vol. 41, No. 10, pp. 2015 to 2018, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

MOLECULAR AND ELECTRONIC STRUCTURE OF THE DEHYDROALANINE DERIVATIVES

THE CYCLIC DIPEPTIDE

K. H. ONGANIA
Institut für Organische und Pharmazeutische Chemie der Universität Innsbruck,
Innrain 52a, A-6020 Innsbruck, Austria

G. GRANOZZI
Istituto di Chimica Generale ed Inorganica dell'Università, Via Loredan 4, 35100 Padova, Italy

V. BUSETTI
Istituto di Chimica Organica dell'Università, Via Marzolo 1, 35100 Padova, Italy

and

M. CASARIN and D. AJÒ*
Istituto di Chimica e Tecnologia dei Radioelementi del C.N.R:, Corso Stati Uniti 4, 35100 Padova, Italy

(*Received in UK 7 September* 1984)

Abstract—The molecular structure of the cyclic dipeptide of dehydroalanine (3,6-dimethylene-piperazine-2,5-dione) has been determined from three-dimensional X-ray data. $C_6H_6N_2O_2$ is monoclinic, space group $P2_1$, with $Z = 2$ in a cell of dimensions $a = 5.261(3)$, $b = 13.617(4)$, $c = 4.570(3)$ Å, $\beta = 104.58(5)°$. Molecules are planar and they are linked in ribbons by two hydrogen bonds through the amido-groups. The vapour-phase He(I) and He(II) photoelectron spectra are also presented. The assignments are proposed by comparison with simpler related molecules and supported by *ab initio* calculations. Analogies with respect to the photoelectron results of the corresponding acyclic compound N-acetyldehydroalanine are discussed.

In many natural biologically active peptides α,β-unsaturated amino acid derivatives (Fig. 1) are present.[1,2] They are particularly interesting because of their unusual conformational and electronic features.

In previous papers we reported upon the electronic structure [by photoelectron (PE) spectroscopy] of N-acetyldehydroalanine (*dehydro*-Ala-OH, Fig. 1a: $R_1 = R_2 = H$, $R_3 = OH$),[3] N-acetyldehydrophenylalanine (*dehydro*-Phe-OH, Fig. 1a: $R_1 = C_6H_5$, $R_2 = H$, $R_3 = OH$)[4] and several ethyl esters (Fig. 1a: $R_1 = H, CH_3, C_6H_5$; $R_2 = H, CH_3$; $R_3 = OC_2H_5$).[5] In particular, these studies evidentiated the significant interaction between "semilocalized" π_N and π_{CC} MOs, giving rise to $\pi^{\pm}_{NCC}$ combinations, which depends on both molecular conformation and nature of the β-substituent.

In order to distinguish between conformational[2–11] and electronic[3–5] effects on the electronic structure of dehydro amino acid derivatives, PE investigation of more rigid cyclic systems appear particularly suited.

Although an enormous amount of work has been carried out till now on the molecular[12] and electronic structure[13–14] of saturated cyclic dipeptides, little attention has been paid so far to the structure of the corresponding α,β-unsaturated systems. Moreover, several singly or doubly α,β-unsaturated cyclic dipeptides (in particular albonoursin[15] and roquefortine[16]) exhibit biologically and pharmacologically relevant properties, and some of them are very interesting in peptide asymmetric hydrogenation.[17]

In this paper we present a study of the molecular and the electronic structure of the cyclic dipeptide of dehydroalanine (cyclo(*dehydro*-Ala)$_2$, Fig. 1b: $R_1 = R_2 = R'_1 = R'_2 = H$).† The crystal structure of the title compound is the first reported of any α,β-unsaturated cyclic dipeptide. The electronic structure have been derived from the results of both He(I) and He(II) PE investigations and quantum mechanical *ab initio* calculations.

RESULTS AND DISCUSSION

X-ray structure: Final positional parameters are reported in Table 1. Molecules are planar (maximum

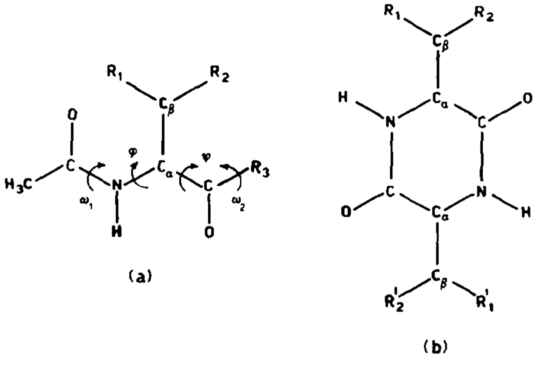

Fig. 1. General structural formula of acyclic (a) and cyclic (b) dehydroalanine derivatives quoted in the present paper. Relevant torsion angles are shown.

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† 3,6-Dimethylene-piperazine-2,5-dione.

Table 1. Fractional atomic coordinates, e.s.d.'s in parentheses

	x/a	y/b	z/c
O(1)	0.493(3)	0.095	−0.014(3)
O(2)	0.996(3)	−0.093(1)	0.986(3)
N(1)	0.986(3)	0.027(2)	0.672(3)
N(2)	0.505(2)	−0.028(1)	0.342(3)
C(1)	0.876(2)	0.083(1)	0.410(3)
C(2)	0.882(3)	−0.050(1)	0.773(3)
C(3)	0.631(4)	−0.083(2)	0.594(3)
C(4)	0.600(3)	0.052(2)	0.237(4)
C(5)	1.000(3)	0.157(2)	0.300(4)
C(6)	0.520(3)	−0.162(2)	0.651(4)

The non-centrosymmetric structure has not only a pseudo-centre of symmetry, but also atoms O(1) and O(2), N(1) and N(2), C(5) and C(6), are related by a pseudo-binary screw axis, along x, thus the difficulty of refinement.

deviation 0.05 Å for ring atoms, 0.14 Å for methylene carbon atoms). Rather surprisingly however, molecules are not centrosymmetric; this is to be ascribed to intermolecular interactions, in particular to hydrogen bonds.

Crystal packing is given in Fig. 2. The origin molecule is linked in planar ribbons by two hydrogen bonds ($N_1 \cdots O_1^I$: 2.84(2) Å, N_1–$H(N_1) \cdots O_1^I$: 174(1)°; $O_2 \cdots N_2^I$: 2.90(2) Å; $O_2 \cdots H(N_2)^I$–N_2^I: 176(1)°) to the molecule (I) at $x+1, y, z+1$. The ring N_1–C_2–O_2–N_2^I–C_4^I–O_1^I is planar also (average deviation 0.03 Å).

Photoelectron spectra and quantum mechanical calculations: He(I) and He(II) PE spectra are shown in Figs. 3a and b, respectively. In the first spectral region (9–13 eV *ca*) four bands (labeled A, B, C and D) are present. Bands A and B have approximately twice the intensity of bands C and D. In this region we expected six ionizations: four from the two amido groups and two from the vinyl bonding MOs. The spectrum is better resolved than that of the saturated corresponding systems,[13–14] where ionizations from MOs mainly localized on the nitrogen atoms ($\pi_N^\pm$) and in-plane oxygen lone pairs ($n_O^\pm$) are in general superimposed; this is evidence for a significant conjugation extent in the α,β-unsaturated systems, while in the saturated cyclic dipeptides the two amidic groups behave independently. Moreover, the sp^2 character of all non-hydrogen atoms simplifies the spectrum markedly, as expected.

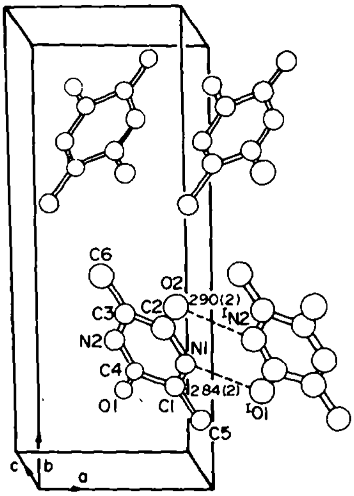

Fig. 2. Crystal packing of cyclo(*dehydro*-Ala)$_2$.

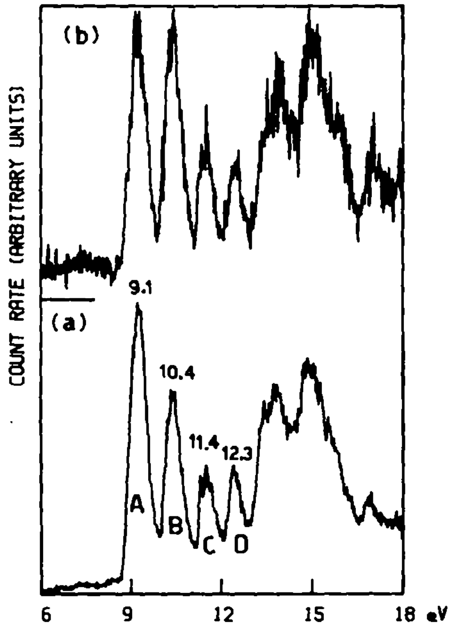

Fig. 3. He(I) and He(II) (b) photoelectron spectra of cyclo-(*dehydro*-Ala)$_2$.

The discussion may benefit from an experimental correlation diagram (Fig. 4). As a matter of fact, the title

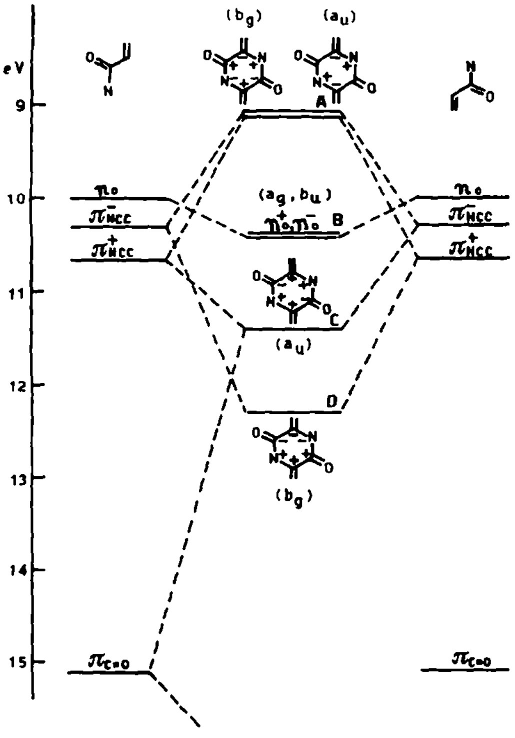

Fig. 4. Experimental correlation diagram between cyclo-(*dehydro*-Ala)$_2$ and acrylamide.

compound (whose symmetry is reasonably assumed to be C_{2h} in the vapour phase) may be described (Fig. 4) as being formed by two acrylamide units (see ref. 18 for the photoelectron study of the latter compound). By assuming, in this planar cyclic system, an interaction between adjacent π_N and π_{CC} MOs (or better their symmetry combination $\pi_N^\pm$, $\pi_{CC}^\pm$) approximately equivalent to that previously reported for acyclic *dehydro*-Ala-OH, the assignments are straightforward. Band A is assigned to two out of four combinations of MOs of π symmetry mainly localized on the nitrogen atoms and vinyl groups, namely $(\pi_{NCC}^-)^+$ (a_u) and $(\pi_{NCC}^-)^-$ (b_g) (see Fig. 4). Band B is related to ionizations from n_o^+ (a_g) and n_o^- (b_u) combinations of in-plane oxygen lone-pairs: actually, ionization energy difference (ΔIE) in γ-dicarbonyl is generally rather small.[19] Bands C and D should be associated to the two remaining symmetry combinations $(\pi_{NCC}^+)^\pm$ of the enamidic MOs. Their degeneracy is lifted by different interactions with inner π MOs of the same symmetry, mainly localized on the carbonyl oxygen atoms.

The analysis of the He(II) spectrum (Fig. 3b) corroborates the above assignments since band B clearly increases its relative intensity under He(II) radiation, as expected for MOs ($n_o^\pm$) highly localized on the oxygen atoms.[20] Moreover, the relative intensity of band C with respect to D also increases under He(II) radiation thus reflecting a greater contribution from the oxygen atoms to the MO related to band C.

Extended basis set *ab initio* calculations fully support the above assignments. The a_u and b_g combinations of the π_{NCC}^- units are predicted to be quasi-degenerate (-9.66, -9.71 eV) and to lie at higher energy values than the π_{NCC}^+ ones. The a_u combination of the π_{NCC}^+ MOs $(\pi_{NCC}^+)^+$ (-12.52 eV) involves oxygen atoms to a greater extent than the b_g one $(\pi_{NCC}^+)^-$ (-14.29 eV). This is in agreement with the relative increase of band C with respect to band D under He(II) radiation. The two oxygen "lone-pair" MOs are quasi-degenerate also (-12.22, -12.30 eV).

The difference between the computed (according to the Koopmans theorem)[21] and experimental IEs may be ascribed to differential relaxation energy contributions not taken into account at this stage. When the values of relaxation terms R_i previously calculated for analogous molecular systems[22] are used, the agreement is quite good (within 0.3 eV).

CONCLUSIONS

The above reported X-ray data are the first ones concerning an α,β-unsaturated cyclic dipeptide.

A direct comparison of the PE results with those of the corresponding acyclic compound *dehydro*-Ala-OH shows an interesting analogy: the ΔIE value between the two lower ionizations of π symmetry (π_N and π_{CC} or better π_{NCC}^- and π_{NCC}^+) is 2.34 eV in *dehydro*-Ala-OH,[3] while the corresponding value in cyclo(*dehydro*-Ala)$_2$ [measured as the ΔIE between the quasi-degenerate $(\pi_{NCC}^-)^\pm$ ionizations (band A) and the $(\pi_{NCC}^+)^\pm$ (bands C, D) average IE value] is 2.75 eV.

This indicates that the interaction extent is very similar in cyclo(*dehydro*-Ala)$_2$ and *dehydro*-Ala-OH, and supports a planar conformation for *dehydro*-Ala-OH in the vapour phase, which is in agreement with the results of theoretical conformational analysis.[6]

Analogous investigations of α,β-unsaturated cyclic dipeptides bearing different side chains ($R_1 = R_1' \neq H$) are in progress.[29]

EXPERIMENTAL

Crystal data. $C_6H_6N_2O_2$, M = 138.1. Crystals of the title compound, prepared according to ref. 23, obtained from H_2O/CH_3COCH_3 1:1 soln, are monoclinic, space group $P2_1$, $a = 5.261(3)$, $b = 13.617(4)$, $c = 4.570(3)$ Å, $\beta = 104.58(5)°$, $U = 316.9(3)$, $Z = 2$, $D_m = 1.44$, $D_c = 1.448$ g cm^{-3}, F(000) = 144, MoK_α radiation (monochromatized by a graphite plate), $\lambda = 0.71069$ Å, μ(MoK_α) = 1.04 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). For data collection a crystal 0.16 × 0.20 × 0.28 mm was used. θ–2θ scan mode, scan width 1.40°, scan speed 0.020° s^{-1}, background measured for 10 s at each extremity, θ 2° to 33°, three standard intensity reflections (-1 4 1), (2 2 0), (-1 2 1) measured at 3 hr intervals: no significant variation. Unit cell: least square refinement of 28θ values, $38° < \theta < 45°$; Lorentz polarization correction, no adsorption correction.

Of 1320 collected reflections, 385 had $I > 2.5\ \sigma(I)$. The structure was solved by direct methods; E map revealed all non-hydrogen atoms. Full matrix least-squares refinement (on F), unit weights. Hydrogen atoms in calculated positions. Final difference map revealed no peak > 0.25 e Å^{-3}. The refinement converged to R = 0.071. Calculations were performed on a Cyber 76 computer by the *SHELX*[24] and *MULTAN78*[25] programs for crystal structure determination. All atomic scattering factors were taken from ref. 26. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 45,267.

Quantum mechanical calculations. Quantum mechanical calculations were performed by the *ab initio* method using the *GAUSSIAN70* package.[27] The 6-31G extended basis set[28] was adopted. Geometrical parameters were obtained from the crystal internal coordinates by symmetrization to the C_{2h} point group.

Photoelectron spectra. He(I) and He(II) excited PE spectra were recorded on a Perkin–Elmer PS-18 spectrometer modified by inclusion of a hollow-cathode discharge lamp giving high photon flux at the He(II) wavelengths (Helectros Developments). The spectrometer was connected on line with a MINC 23 computer (DEC). Data acquisition was carried out by several sweeps over 500 distinct channels. Typical sweep time amounts to 5–10 min. The spectra were calibrated by reference to the peaks of inert gases admitted into the target chamber and to 1 s^{-1} He self ionization.

REFERENCES

[1] D. H. Rich and P. K. Bhatnagar, *J. Am. Chem. Soc.* **100**, 2218 (1978) and refs therein.

[2] D. Ajò, G. Granozzi, E. Tondello and A. Del Pra, *Biopolymers* **19**, 469 (1980) and refs therein.

[3] D. Ajò, G. Granozzi, E. Ciliberto and I. Fragalà, *J. Chem. Soc. Perkin Trans. II* 483 (1980).

[4] D. Ajò, M. Casarin, G. Granozzi and V. Busetti, *Tetrahedron* **37**, 3507 (1981).

[5] D. Ajò, M. Casarin, G. Granozzi, H. C. J. Ottenheijm and R. Plate, *Recl Trav. Chim. Pays-Bas* **103**, 365 (1984).

[6] D. Ajò, G. Granozzi, E. Tondello, A. Del Pra and G. Zanotti, *J. Chem. Soc. Perkin Trans. II* 927 (1979).

[7] D. Ajò, M. Casarin, G. Granozzi, *J. Mol. Struct.* **86**, 297 (1982).

[8] D. Ajò, V. Busetti and G. Granozzi, *Tetrahedron* **38**, 3329 (1982).

[9] V. Busetti, D. Ajò and M. Casarin, *Acta Cryst.* **C40**, 1245 (1984).

[10] D. Ajò, V. Busetti, G. Granozzi and M. Liakopoulou-Kyriakides, *Acta Cryst.* **C40**, 327 (1984).

[11] D. Ajò, V. Busetti, H. C. J. Ottenheijm and R. Plate, *Acta Cryst.* **C40**, 324 (1984).
[12] Y. Kanaoka and E. Sato, *Kagaku, Kioto* **36**, 79 (1981).
[13] S. D. Worley, S. H. Gerson, N. Bodor and J. J. Kaminski, *Chem. Phys. Lett.* **60**, 104 (1978).
[14] D. Ajò, G. Granozzi, V. Guantieri and A. M. Tamburro, *J. Mol. Struct.* **96**, 369 (1983).
[15] C. Shin, M. Hayakawa, H. Kato, K. Mikami and J. Yoshimura, *J. Chem. Soc. Perkin Trans. I* 419 (1980) and refs therein.
[16] K. D. Barrow, P. W. Colley and D. E. Tribe, *J. Chem. Soc. Chem. Commun.* 225 (1979).
[17] Y. Hashimoto, H. Aoyagi, M. Waki, T. Kato and N. Izumiya, *Int. J. Peptide Protein Res.* **21**, 11 (1983).
[18] H. Van Dam and A. Oskam, *J. Electron Spectrosc. Relat. Phenom.* **13**, 273 (1978).
[19] D. Dougherty, P. Brint and S. P. McGlynn, *J. Am. Chem. Soc.* **100**, 5597 (1978).
[20] J. W. Rabalais, *Principles of Ultraviolet Photoelectron Spectroscopy*. Wiley, New York (1977).
[21] T. Koopmans, *Physica* **1**, 104 (1934).
[22] G. Granozzi, D. Ajò and I. Fragalà, *J. Electron Spectrosc. Relat. Phenom.* **18**, 267 (1980).
[23] J. L. Miller, F. C. Neuhaus, F. O. Lassen and C. H. Stammer, *J. Org. Chem.* **33**, 3908 (1968).
[24] G. M. Sheldrick, "*SHELX*". *Program for Crystal Structure Determination*, University of Cambridge (1976).
[25] P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M. M. Woolfson, "*MULTAN78*". *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*, University of York (England) and Louvain (Belgium).
[26] *International Tables for X-ray Crystallography*, 2nd Edn. Kynoch Press, Birmingham (1974).
[27] W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton and J. A. Pople, "*GAUSSIAN70*". Program 263, QCPE (University of Indiana, Bloomington, Indiana) (1974).
[28] W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.* **56**, 2257 (1971).
[29] D. Ajò, V. Busetti, G. Granozzi, H. C. J. Ottenheijm and R. Plate, manuscript in preparation.