Tetrahedron Vol. 38, No. 22, pp. 3329 to 3334, 1982
Printed in Great Britain.

0040-4020/82/223329-06$03.00/0
Pergamon Press Ltd.

CONFORMATIONAL FLEXIBILITY OF DEHYDROALANINE DERIVATIVES. CRYSTAL AND MOLECULAR STRUCTURE OF 2-N-ACETYLDEHYDROPHENYLALANYL-L-PROLINE

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(*Received in the UK* 28 *January* 1982)

Abstract—The molecular structure of the title compound has been determined from three-dimensional X-ray data. $C_{16}H_{18}N_2O_4\cdot\frac{1}{2}H_2O$ is monoclinic, space group C2, with $Z = 4$ in a cell of dimensions: $a = 18.508(3)$, $b = 9.517(4)$, $c = 10.538(4)$ Å, $\beta = 120.00(3)°$. One water molecule coordinates four molecules in a tetrahedral arrangement. The conformation of this molecular system is discussed also on the basis of the known structure of related compounds and previously reported theoretical results.

Many biologically relevant peptides contain α,β-unsaturated amino-acid residues which are particularly interesting because of their unusual conformational[1-5] and electronic[3,4] features.

In previous papers we reported on the molecular structure of N-acetyldehydroalanine (*dehydro*-Ala–OH) which assumes an extended conformation in the crystal state[5] and, at least as the φ torsion angle is concerned, also in the gas phase.[3] On the contrary, we have shown that (Z)-N-acetyldehydrophenylalanine (*dehydro*-Phe–OH) is non planar both in the solid state and in the vapour phase.[4]

Conformational studies of dehydrophenylalanine and its derivatives are of interest not only from a biological point of view[1,6] but also in order to investigate the mechanism of their asymmetric hydrogenation, which is related to the conformational behaviour of the substrate.[7-12]

A systematic study is in progress in our laboratories on a series of dehydrophenylalanyl peptides (*dehydro*-Phe–X–OH, with various X residues in the L-configuration). In the present paper we report the crystal and molecular structure when X = L-Pro. It is noteworthy that this peptide exhibits a peculiar behaviour under hydrogenation, i.e. low optical efficiency leading predominantly to the D-Phe product.[9]

EXPERIMENTAL

Crystal data. $C_{16}H_{18}N_2O_4\cdot\frac{1}{2}H_2O$, M = 311.3. Crystals of the title compound (prepared according Ref. 13) obtained from methanol solution, are monoclinic, space group C2, $a = 18.508(3)$, $b = 9.517(4)$, $c = 10.538(4)$ Å, $\beta = 120.00(3)°$, $U = 1607.49$ Å^3, $Z = 4$, $D_m = 1.29$, $D_C = 1.287$ g·cm^{-3}, F(000) = 660, MoKα radiation, $\lambda = 0.7107$ A, μ(MoKα) = 1.24 cm^{-1}.

Solution and refinement of the structure. Intensity data were measured on a Philips PW1100 four circle diffractometer (graphite monochromatized MoKα radiation, $\vartheta - 2\vartheta$ scan mode). For data collection a crystal of approx. 0.2 × 0.2 × 0.1 mm was used. Data were not corrected for absorption. A total of 1459 reflections was measured for $\vartheta \leq 25°$; 1078 of them had $I > 2.5\sigma(I)$. The structure was solved by multiple solution procedure with the MULTAN program[14] and refined by full-matrix least-squares methods, unitary weights. Hydrogen atoms were derived from difference Fourier maps and refined, with isotropic thermal parameters, by one cycle of full-matrix least squares. Final R index is 4.8%. Calculations were performed on a Cyber '76 computer by the SHELX-76 program[15] for crystal structure determination. All atomic scattering factors were taken from Ref. 16. Observed and calculated structure factors are listed in Supplementary Publication No. 000 (PPpp).

RESULTS AND DISCUSSION

A schematic view of the title molecule (showing its conformation) is shown in Fig. 1, the corresponding ORTEP drawing (together with atom numbering scheme) in Fig. 2, and the final positional parameters in Table 1. Bond distance and angles are shown in Fig. 3. The crystal packing is given in Fig. 4: one water molecule, having its oxygen atom on the binary axis links four *dehydro*-Phe–Pro–OH molecules (Fig. 5); the water oxygen atom O(5) is 2.762 Å apart from the carboxylic oxygen atoms O(2) belonging to the molecules at (x, y, z) and ($\bar{x}$, y, $\bar{z}$) and the carboxylic hydrogen atom lies approx. (10° deviation) along the O(2)–O(5) direction. O(5) is also 2.709 Å apart from the acetamido oxygen atoms O(3) of the molecules at $(\frac{1}{2} - x, -\frac{1}{2} + y, \bar{z})$ and $(-\frac{1}{2} + x, -\frac{1}{2} + y, z)$ and the water hydrogen atom lies approximately (3° deviation) along the O(5)–O(3) direction. Finally, O(5) is −0.44 Å out of the carboxyl plane at (x, y, z) and 0.84 Å out of the acetamido plane at $(-\frac{1}{2} + x, -\frac{1}{2} + y, z)$.

The dimensions of the *dehydro*-Phe unit are different from those found in saturated peptides;[17] in particular, the amide bond N(1)–C(2) is significantly longer (1.344 Å) than the mean value (1.32_5 Å) reported for saturated

Table 1. Fractional atomic coordinates and anisotropic thermal parameters for non-hydrogen atoms, × 10⁴. Fractional atomic coordinates, × 10³, for hydrogen atoms, B values are those of the attached C atoms. E.s.d.'s are in parentheses

Atom	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{23}	β_{13}	β_{12}
O(1)	2157(3)	-418(8)	1064(6)	561(31)	486(35)	674(35)	146(32)	313(27)	44(28)
O(2)	1278(3)	1317(8)	-173(7)	379(30)	554(34)	710(39)	135(30)	222(29)	74(27)
O(3)	4954(4)	3255(9)	1991(6)	830(42)	776(42)	527(36)	254(33)	230(32)	-136(36)
O(4)	3598(3)	1893(9)	2824(5)	372(23)	602(35)	450(29)	-35(27)	223(22)	54(25)
O(5)	0	0	0	570(41)	472(45)	490(42)	0	309(34)	0
N(1)	5351(3)	1820(9)	3895(8)	297(29)	467(35)	457(41)	36(34)	150(30)	-18(28)
N(2)	3425(3)	868(9)	748(6)	335(30)	561(40)	346(33)	-28(30)	176(27)	49(27)
C(1)	5797(6)	4241(13)	4378(12)	590(54)	533(60)	825(66)	20(50)	381(51)	-31(46)
C(2)	5339(5)	3079(10)	3307(9)	447(42)	474(49)	602(50)	117(41)	255(38)	32(36)
C(3)	4790(4)	744(10)	3007(7)	425(38)	519(48)	369(38)	37(35)	230(32)	25(35)
C(4)	3886(4)	1221(9)	2160(8)	356(35)	328(34)	505(45)	7(34)	201(33)	-51(30)
C(5)	4985(4)	-582(10)	2941(8)	430(40)	452(43)	475(41)	-53(41)	206(35)	-25(37)
C(6)	5809(5)	-1262(9)	3646(9)	498(42)	358(38)	527(48)	15(36)	333(38)	12(32)
C(7)	6465(5)	-936(10)	5018(9)	478(44)	516(49)	410(43)	-4(38)	203(36)	73(37)
C(8)	7219(5)	-1577(11)	5557(9)	456(46)	500(50)	474(46)	-41(42)	123(39)	13(41)
C(9)	7355(5)	-2536(11)	4735(10)	483(46)	535(52)	688(67)	76(46)	325(49)	108(40)
C(10)	6717(5)	-2883(11)	3352(10)	761(54)	536(55)	573(48)	-3(41)	419(44)	149(44)
C(11)	5952(6)	-2254(11)	2824(10)	645(53)	485(46)	427(53)	9(40)	210(43)	56(40)
C(12)	3740(6)	348(13)	-197(10)	718(5)	822(77)	534(53)	-24(54)	366(48)	72(53)
C(13)	3149(6)	968(15)	-1658(10)	824(62)	1053(83)	409(51)	44(54)	326(47)	229(57)
C(14)	2311(6)	937(15)	-1685(10)	601(52)	958(78)	327(46)	77(53)	172(40)	28(55)
C(15)	2564(4)	1333(10)	-104(8)	449(38)	392(40)	375(37)	57(34)	187(29)	60(34)
C(16)	2000(4)	636(10)	352(8)	460(43)	436(43)	317(36)	1(35)	108(33)	6(37)
H-O(2)	98(8)	84(14)	-10(14)		H(10)	678(4)	-363(10)	271(9)	
H-O(5)	1(7)	-62(15)	78(12)		H(11)	559(7)	-237(12)	191(12)	
H-N(1)	566(6)	173(11)	487(11)		H(12.1)	370(4)	-75(8)	-21(7)	
H(1.1)	608(5)	397(9)	549(11)		H(12.2)	435(6)	65(10)	18(10)	
H(1.2)	620(7)	448(13)	415(12)		H(13.1)	307(5)	36(9)	-248(9)	
H(1.3)	543(7)	500(12)	412(11)		H(13.2)	336(6)	214(11)	-166(11)	
H(5)	453(3)	-124(5)	232(5)		H(14.1)	196(6)	164(12)	-225(10)	
H(7)	640(4)	-27(8)	555(7)		H(14.2)	212(7)	-27(12)	-184(11)	
H(8)	766(4)	-132(7)	646(7)		H(15)	250(6)	223(10)	-9(11)	
H(9)	789(4)	-296(8)	522(8)						

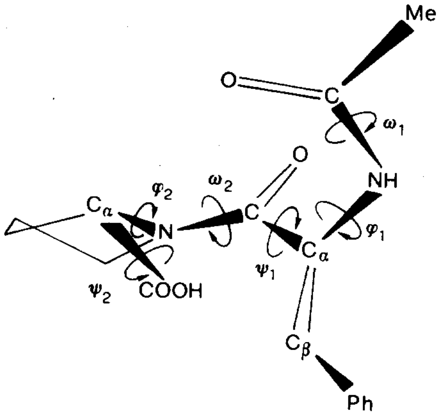

Fig. 1. Schematic view of the title molecule.

peptides, while the C_α–N N(1)–C(3) one is shorter (1.425 Å) than the mean one for saturated peptides (1.45 Å). This is in keeping with previous observations on unsaturated peptides[13] and *dehydro*-Ala–OH,[5] but in contrast with the reported values for *dehydro*-Phe–OH,[4] where the amide bond is even shorter than the mean one for saturated peptides. Bond angles around C_α exhibit intermediate values between those reported for *dehydro*-Ala–OH and *dehydro*-Phe–OH.

The conformation of the *dehydro*-Phe residue is described (see also Fig. 1) by the following values of the torsion angles: ω_1(C(1)–C(2)–N(1)–C(3)) = 165.9°, φ_1(C(2)–N(1)–C(3)–C(4)) = −51.5°, ψ_1(N(1)–C(3)–C(4)–N(2)) = 135.2°. Theoretical conformational analysis predicted for the *dehydro*-Phe residue the existence of six energy minima, none of which corresponds to a planar conformation (Fig. 6). The conformation of the title compound in the crystal state, as concerns the *dehydro*-Phe moiety, is ascribed to the minimum energy region V.

Analogous conformation was previously found for the second residue of the tripeptide (*dehydro*-Phe)$_2$–Gly,[13] at variance with the corresponding residue of (*dehydro*-Phe)$_2$–Ala.[18] This point to a relevant influence of the nature of the saturated residue on the conformation of the preceding unsaturated one.

Turning attention to the proline residue, all bond distances and angles are within the usual range. The pirrolidine ring is *exo*[19]

$$\chi_1(C(13)\text{–}C(14)\text{–}C(15)\text{–}N(2)) = -27.2°,$$
$$\chi_2(C(12)\text{–}C(13)\text{–}C(14)\text{–}C(15)) = 39.0°,$$
$$\chi_3(N(2)\text{–}C(12)\text{–}C(13)\text{–}C(14)) = -35.5°,$$
$$\chi_4(C(15)\text{–}N(2)\text{–}C(12)\text{–}C(13)) = 19.2°.$$

The main chain conformation is described by the following values of the torsion angles:

$$\omega_2(C(3)\text{–}C(4)\text{–}N(2)\text{–}C(15)) = -178.6°,$$
$$\varphi_2(C(4)\text{–}N(2)\text{–}C(15)\text{–}C(16)) = -69.2°,$$
$$\psi_2(N(2)\text{–}C(15)\text{–}C(16)\text{–}O(2)) = 164.4°,$$

this conformation is different from that reported for the analogous fragment in model compounds of dehydrochlamydocin, where the proline amide group is *cis*.[11] The possibility of *cis–trans* conformational isomerism, peculiar to N-substituted residues (such as proline), can be related to the low optical efficiency of the title compound under hydrogenation.[9]

CONCLUSIONS

The conformation of *dehydro*-Phe-Pro-OH corresponds to one of the energy minima predicted by theoretical conformational analysis. This gives further support to the validity of the reported[1,2,4,5] theoretical investigations on this class of compounds.

The influence of the nature of the saturated residue on the conformation of the unsaturated one supports our idea that conformational flexibility of unsaturated residues is similar to, if not greater than that of saturated analogues.

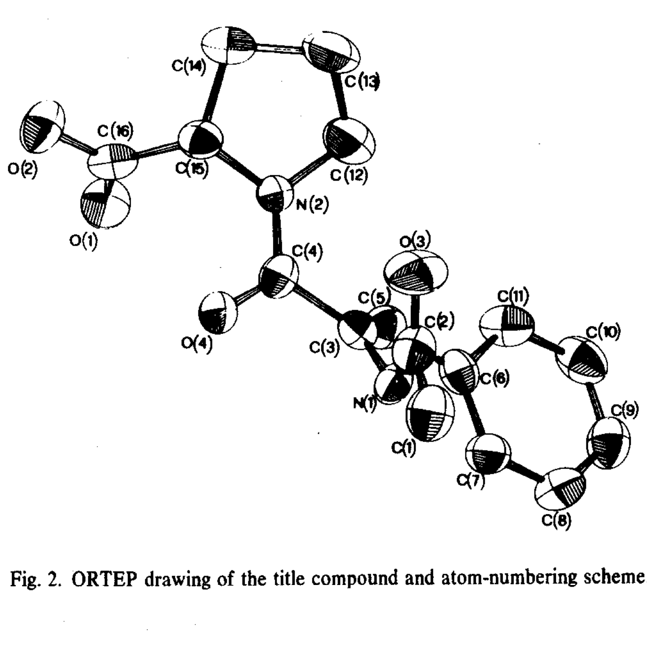

Fig. 2. ORTEP drawing of the title compound and atom-numbering scheme.

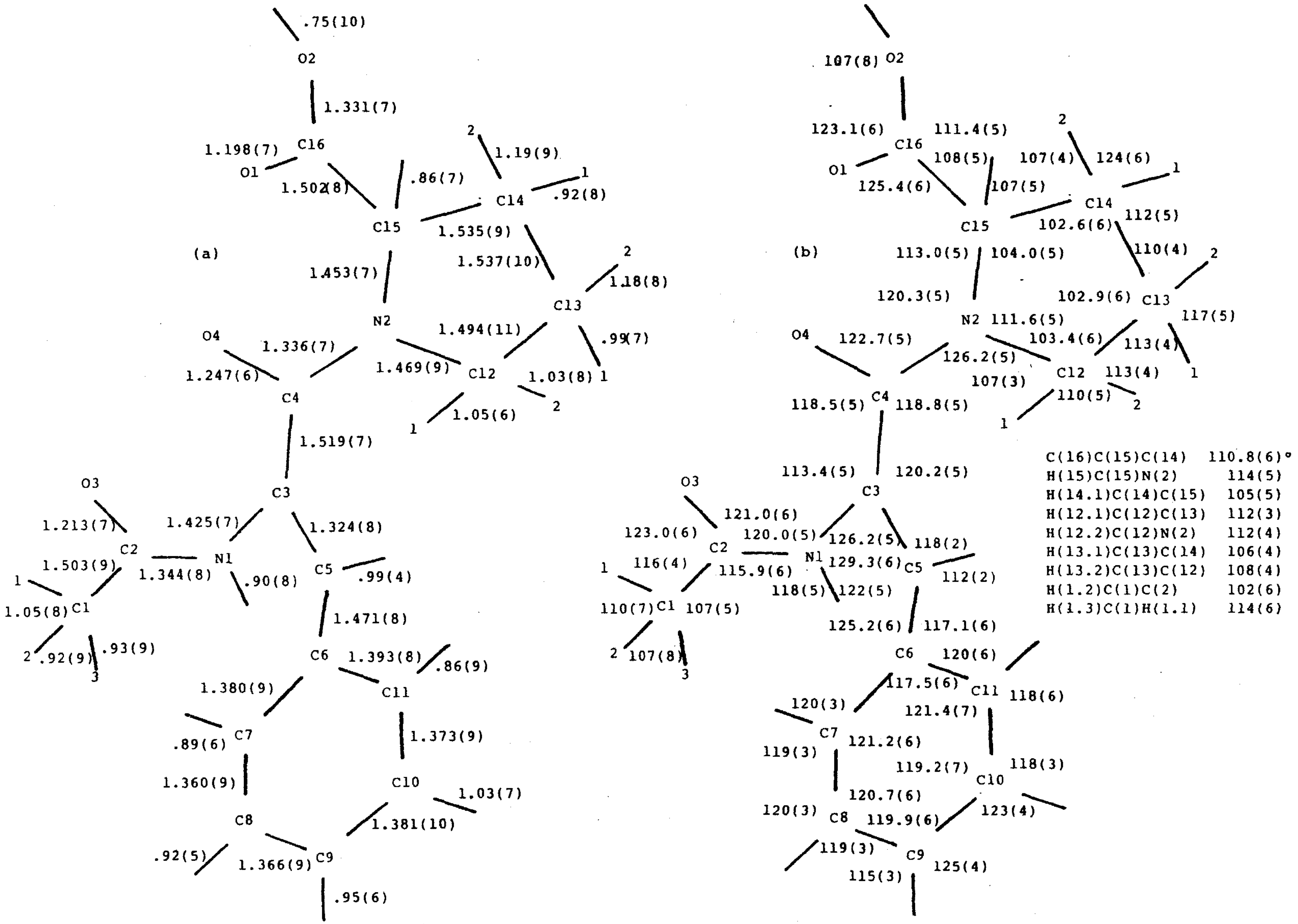

Fig. 3. Schematic view of the title molecule showing (a) bond distances (Å) and (b) angles (°), e.s.d.'s in parentheses.

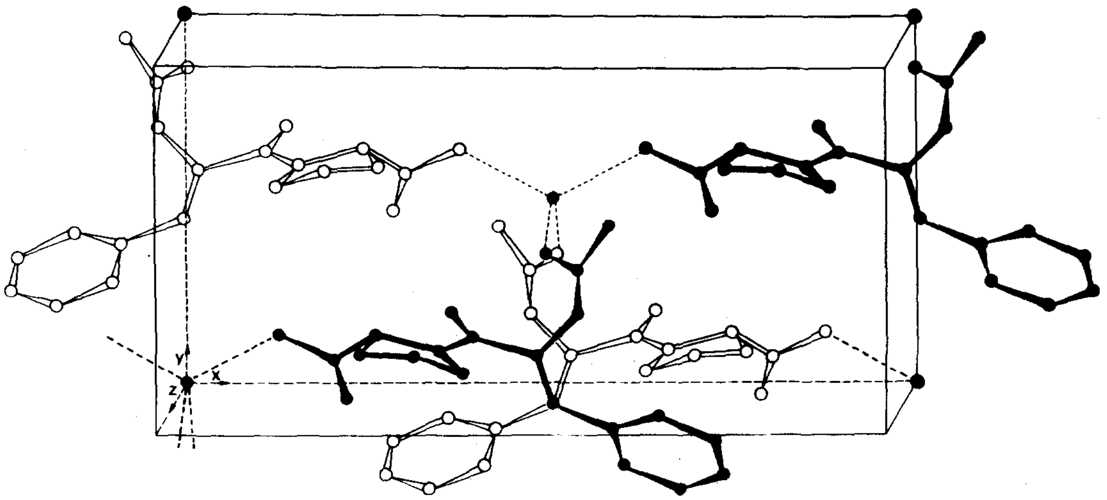

Fig. 4. Molecular packing in the unit cell projected onto the ab plane.

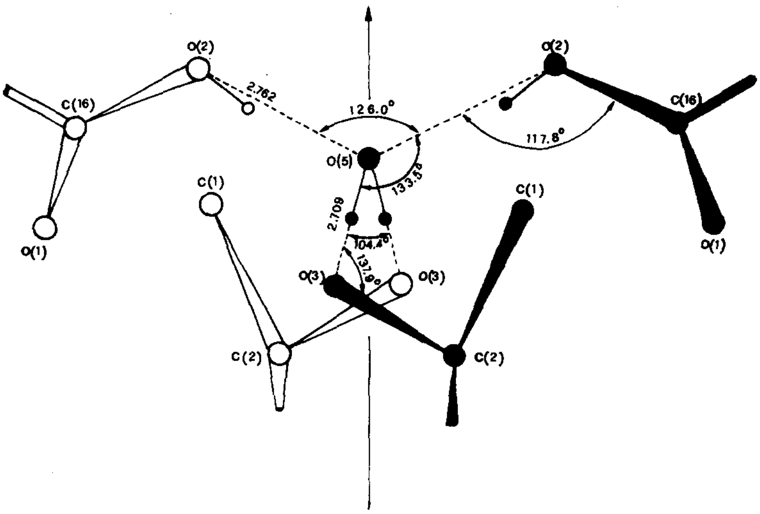

Fig. 5. Hydrogen bond network around the water molecule.

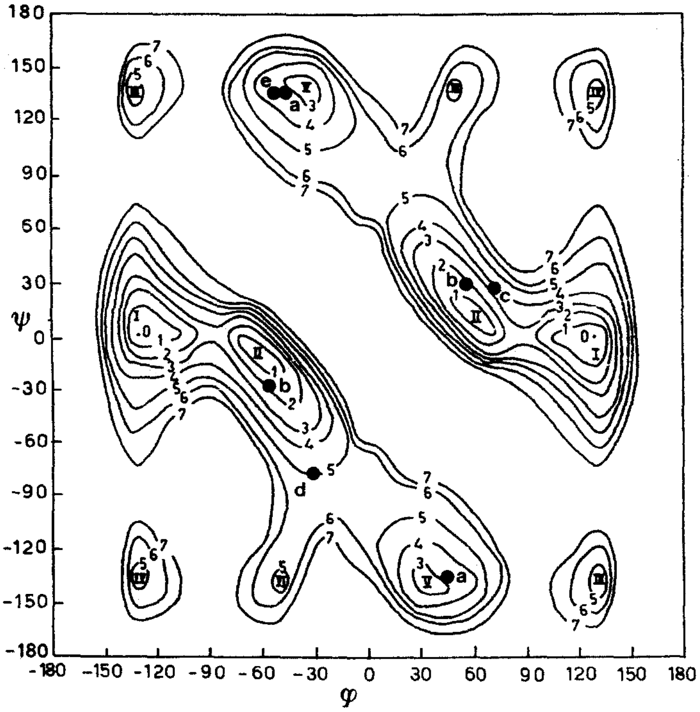

Fig. 6. Conformational energy map of *dehydro*-Phe residue. Energy values are in kcal mol^{-1} from the absolute minimum. Experimental conformations are shown by dots: a and b from Ref. 13; c and d from Ref. 18; e from the present paper. Due to the lack of chiral carbon atoms in (*dehydro*-Phe)$_2$–Gly molecule, dots a and b are reported twice.

Acknowledgement—We thank Prof. Osvaldo Pieroni and his colleagues for the gift of *dehydro*-Phe-Pro-OH and for helpful discussions.

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