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N-(2-Carboxybenzoyl)-L-leucine methyl ester

Alvaro B. Onofrio,[a] Eliezer Jäger,[a] Tiago A. S. Brandão,[b] Adailton J. Bortoluzzi[b] and Faruk Nome[b]*

[a]Departamento Química, PUC, 90619-000 Porto Alegre, RS, Brazil, and [b]Departamento Química, UFSC, 88040-900 Florianópolis, SC, Brazil
Correspondence e-mail: faruk@qmc.ufsc.br

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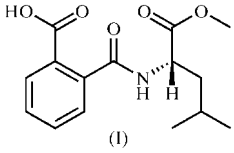
The title compound (with the systematic name 2-{[(1*S*)-1-(methoxycarbonyl)-3-methylbutyl]aminocarbonyl}benzoic acid), $C_{15}H_{19}NO_5$, crystallizes in the monoclinic space group $P2_1$, with two independent molecules per asymmetric unit. The most notable difference between the two molecules is in the dihedral angles between the planes of the carboxyl group and the benzene ring, which are 3.5 (3) and 25.7 (1)°. This difference may account for the fact that two competing reactions are observed in aqueous solution, namely cyclization to form the imide *N*-phthaloylleucine and hydrolysis of *N*-(2-carboxybenzoyl)-L-leucine methyl ester to phthalic acid and leucine.

Comment

In a previous paper (Onofrio *et al.*, 2001) we studied the intramolecular acid catalysis of *N*-(2-carboxybenzoyl)-L-leucine methyl ester, (I), a simple model of aspartic proteinases which has been extensively investigated as a theoretical model (Wu *et al.*, 2003*a*,*b*). The intramolecular reactions of (I) in aqueous solution result in both cyclization to form the imide *N*-phthaloylleucine, and hydrolysis of (I) to phthalic acid and leucine. Imide formation predominates under high acid concentrations ([HCl] > 3 *M*) and hydrolysis in the range [HCl] < 3 *M* to pH 5. In this paper, we present the newly solved crystal structure of (I).



(I)

N-(2-Carboxybenzoyl)-L-leucine methyl ester crystallizes with two independent molecules per asymmetric unit, (I) and (I′). These derived molecular structures, showing the atom-numbering scheme, are displayed in Fig. 1.

Bond lengths (Table 1) in both cases agree with the presence of withdrawing groups in the ring, where the carboxyl group has the strongest influence. The dihedral angle between the planes of the carboxyl group and the benzene ring is only 3.5 (3)° in (I) and 25.7 (1)° in (I′). The most significant differences in the bond lengths of the ring are that the C2—C3 bond is shorter by 0.013 Å and the C4—C5 bond is longer by 0.015 Å in structure (I), which reflects the resonance of the substituents with the benzene ring. Relevant bond-length correlations are discussed below. Bond lengths in the carboxyl and amide groups of both structures are very similar to those found in the Cambridge Structural Database (CSD, Version 5.27 of November 2005; Allen, 2002) [12 crystal structures of *o*-carboxybenzamides, where C1—C16 = 1.483 (7) Å, C16—O4 = 1.202 (11) Å, C6—C7 = 1.509 (11) Å, C7—N8 = 1.346 (11) Å and C7—O1 = 1.228 (10) Å], with the exception of the C1′—C16′ bond length of 1.456 (7) Å, which is significantly shorter than the values in its counterpart and in the other *o*-carboxybenzamides, namely CPPHAM (Mornon, 1970), BOLFIR (Kennard *et al.*, 1982), CIBPEI and CIBPIM (Smith *et al.*, 1983), CIBPIM01, VECCAH and VECCEL (Bocelli *et al.*, 1989), CIHFAA (Shin *et al.*, 1984), INODIY, INODUK and INODUK01 (Glidewell *et al.*, 2004), and JINBAJ (Hegde *et al.*, 1991).

The two benzene rings are virtually planar, with no H atom deviating from the six-atom plane by more than 0.037 Å in (I) or by more than 0.012 Å in (I′). Primary substituents are also virtually planar in (I), with no atom more than 0.062 Å out of the plane. However, in structure (I′), atoms C7′ and C16′ are 0.154 and 0.136 Å out of the plane, respectively, and they occupy opposite sides in relation to the ring plane, no doubt for steric reasons. This must be because of the requirements of the O4′—C16′—C1′—C6′ torsion angle, at 22.5 (9)°, which pushes the amide group to the opposite side. Obviously, this irregular conformation is possible because the carboxyl group is stabilized by hydrogen bonding between atom O4′ and the H atom on atom O5 of its counterpart (Fig. 2).

Structures (I) and (I′) were optimized in the gas phase (*GAUSSIAN98*; Frisch *et al.*, 1998), and at the B3LYP/6-31-G(d,p) level they both converge to the same conformation, which is very similar to the structure of (I′). The most signif-

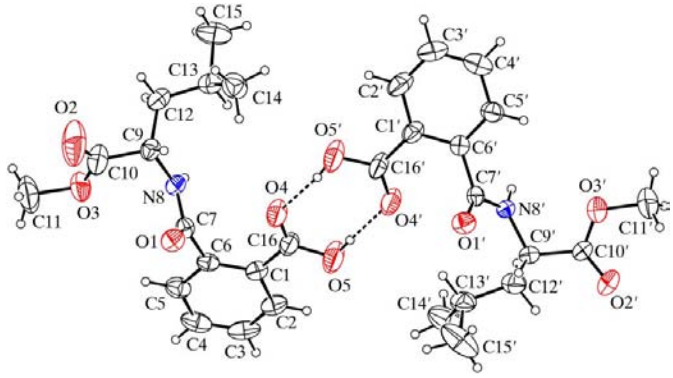


Figure 1
The molecular structures of molecules (I) and (I′), showing the atom-labelling schemes. Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii.

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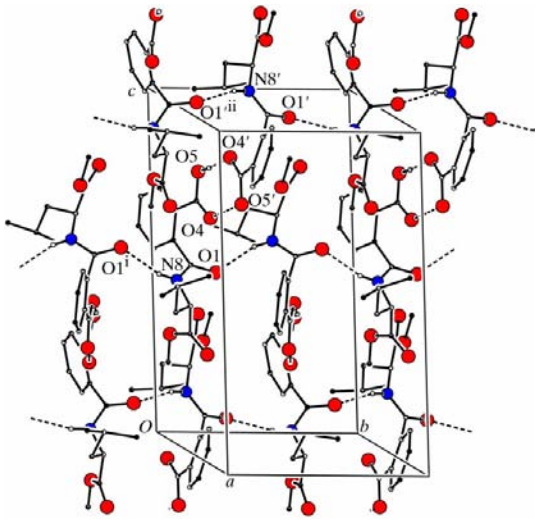

Figure 2
A view of the packing of the title compound, showing the intermolecular hydrogen bonds (dashed lines). [Symmetry codes: (i) $-x+1$, $y-\frac{1}{2}$, $-z+1$; (ii) $-x$, $y+\frac{1}{2}$, $-z+1$.]

icant observation in relation to this is that the carboxyl group of (I) is twisted in relation to the benzene ring of the optimized structure by 25.8°, which suggests that (I) is stabilized by an extensive hydrogen-bond network in the crystal structure.

The O4—C7 distances [2.690 (5) and 2.781 (5) Å in (I) and (I′), respectively] can be used to show the intramolecular attack path to the formation of phthalic anhydride and L-leucine methyl ester through a tetrahedral intermediate mechanism. Indeed, it can be observed that, in the structure of (I′), the torsion of the carboxyl group in relation to the benzene ring will probably promote the attack of atom O4 on the carbonyl atom C7, which is consistent with the attainment of the transition state. A similar mechanistic pattern has been observed in the formation of 1,8-naphthalic anhydride from 1,8-naphthalic acid (Yunes *et al.*, 1997). Structure–structure relationships between O4—C7 distances and selected bond lengths of compounds (I) and (I′) or other *o*-carboxybenzoamides show that other bond lengths, *e.g.* C7—O1 and C7—N8, are effectively constant with a decrease in the O4—C7 distance. Furthermore, C16—N8 distances [3.625 (5) and 3.775 (5) Å in (I) and (I′), respectively], which are important in the intramolecular cyclization to form the imides, are considerably longer than the O4—C7 distance (see above), which is consistent with the preferential hydrolysis reaction normally observed in aqueous solutions.

Experimental

The title compound was prepared according to the previously published procedure of Onofrio *et al.* (1999). Colourless crystals of (I) were grown from a pale-yellow oil at room temperature and analytical data were consistent with previous melting point and ^{1}H NMR analyses. Configuration of the product undoubtedly corresponds to the *S* enantiomer, since the synthetic procedure does not involve the asymmetric C atom of the starting material, L-(+)-leucine.

Crystal data

$C_{15}H_{19}NO_5$
$M_r = 293.31$
Monoclinic, $P2_1$
$a = 11.735$ (3) Å
$b = 9.263$ (3) Å
$c = 15.340$ (2) Å
$\beta = 106.18$ (3)°
$V = 1601.4$ (7) Å^3
$Z = 4$
$D_x = 1.217$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 5.8$–12.1°
$\mu = 0.09$ mm^{-1}
$T = 293$ (2) K
Irregular block, colourless
0.50 × 0.46 × 0.33 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
4649 measured reflections
4496 independent reflections
2272 reflections with $I > 2\sigma(I)$
$R_{int} = 0.032$
$\theta_{max} = 29.0°$
$h = -15 \rightarrow 15$
$k = -12 \rightarrow 0$
$l = -20 \rightarrow 0$
3 standard reflections
every 200 reflections
intensity decay: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.060$
$wR(F^2) = 0.192$
$S = 0.99$
4496 reflections
387 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1093P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C7—O1	1.234 (5)	C7′—O1′	1.231 (5)
C7—N8	1.325 (5)	C7′—N8′	1.334 (5)
N8—C9	1.454 (5)	N8′—C9′	1.454 (5)
C10—O2	1.208 (7)	C10′—O2′	1.160 (5)
C10—O3	1.276 (8)	C10′—O3′	1.289 (6)
O3—C11	1.479 (7)	O3′—C11′	1.453 (7)
C16—O4	1.199 (5)	C16′—O4′	1.224 (5)
C16—O5	1.300 (5)	C16′—O5′	1.307 (6)
O2—C10—O3	123.1 (6)	O2′—C10′—O3′	120.4 (5)
O2—C10—C9	121.9 (6)	O2′—C10′—C9′	124.2 (5)
O3—C10—C9	115.0 (5)	O3′—C10′—C9′	114.5 (4)
C10—O3—C11	115.6 (6)	C10′—O3′—C11′	118.1 (5)
C13—C12—C9	115.5 (3)	C13′—C12′—C9′	113.8 (4)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N8—H8···O1^{i}	0.86	2.11	2.946 (5)	164
N8′—H8′···O1′^{ii}	0.86	2.12	2.962 (5)	165
O5—H5O···O4′	0.82	1.82	2.639 (5)	174
O5′—H5O′···O4	0.82	1.84	2.641 (5)	166

Symmetry codes: (i) $-x, y-\frac{1}{2}, -z+1$; (ii) $-x+1, y-\frac{1}{2}, 2-z$.

The H atoms of the amine and carboxylic acid groups were found in a difference Fourier map. These H atoms were treated using a riding model (N—H = 0.86 Å and O—H = 0.82 Å), with U_{iso}(H) = 1.2U_{eq}(parent). H atoms bonded to C atoms were added in their calculated positions and included in the structure-factor calculations, with C—H distances in the range 0.93–0.98 Å and with U_{iso}(H) = 1.2U_{eq}(C), or 1.5U_{eq}(methyl C).

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *SET4* in *CAD-4 EXPRESS*; data reduction: *HELENA* (Spek, 1996); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Shel-

drick, 1997); molecular graphics: *ZORTEP* (Zsolnai *et al.*, 1996); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1242). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Altomare, A., Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Guagliardi, A., Moliterni, A. G. G., Polidori, G. & Spagna, R. (1999). *J. Appl. Cryst.* **32**, 115–119.

Bocelli, G., Rizzoli, C. & Ori, O. (1989). *Z. Kristallogr.* **189**, 301–316.

Enraf–Nonius (1994). *CAD-4 EXPRESS*. Version 5.1/1.2. Enraf–Nonius, Delft, The Netherlands. for methyl H.

Frisch, M. J. *et al.* (1998). *GAUSSIAN98*. Gaussian Inc., Pittsburgh, PA, USA.

Glidewell, C., Low, J. N., Skakle, J. M. S. & Wardell, J. L. (2004). *Acta Cryst.* C**60**, o120–o124.

Hegde, R. S., Mehanna, A. & Abraham, D. J. (1991). *Acta Cryst.* C**47**, 1293–1296.

Kennard, C. H. L., Smith, G. & Katekar, G. F. (1982). *Aust. J. Chem.* **35**, 1933–1937.

Mornon, J. P. (1970). *Acta Cryst.* B**26**, 1985–1999.

Onofrio, A. B., Guesser, J. C., Joussef, A. C. & Nome, F. (2001). *J. Chem. Soc. Perkin Trans. 2*, pp. 1863–1868.

Onofrio, A. B., Joussef, A. C. & Nome, F. (1999). *Synth. Commun.* **29**, 3039–3049.

Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.

Shin, W., Kim, Y. C. & Koo, C. H. (1984). *Bull. Korean Chem. Soc.* **5**, 23–26.

Smith, G., Kennard, C. H. L. & Katekar, G. F. (1983). *Aust. J. Chem.* **36**, 2455–2463.

Spek, A. L. (1996). *HELENA*. University of Utrecht, The Netherlands.

Wu, Z., Ban, F. & Boyd, R. J. (2003*a*). *J. Am. Chem. Soc.* **125**, 3642–3648.

Wu, Z., Ban, F. & Boyd, R. J. (2003*b*). *J. Am. Chem. Soc.* **125**, 6994–6994.

Yunes, S. F., Gesser, J. C., Chaimovich, H. & Nome, F. (1997). *J. Phys. Org. Chem.* **10**, 461–465.

Zsolnai, L., Pritzkow, H. & Hutter, G. (1996). *ZORTEP*. University of Heidelberg, Germany.