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A Conformationally Restricted Aspartic Acid Analogue with a Norbornane Skeleton. II

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Abstract

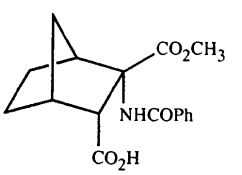
In (1*S*,2*R*,3*S*,4*R*)-3-benzamido-3-methoxycarbonylbicyclo[2.2.1]heptane-2-carboxylic acid, $C_{17}H_{19}NO_5$, the values determined for the torsion angles about the N—$C_\alpha(\varphi)$ and C_α—$CO(\psi)$ bonds correspond to a semi-extended conformation of the amino acid residue. The crystal structure is stabilized by two intermolecular hydrogen bonds (O—H···O and N—H···O) involving the benzamido, carboxylic acid and methyl ester groups.

Comment

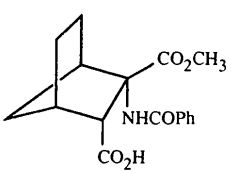
The introduction of non-natural amino acids into biologically active peptides has become one of the most powerful tools for studying the properties of such peptides (Gante, 1994; Liskamp, 1994). Specific structural, stereoelectronic, steric and conformational properties can be examined by proper design of such peptides. For some years, we have been focusing our attention on those amino acids that introduce specific conformational and topographical modifications to their side chains because of the significant changes in potency, receptor selectivity and biostability that can result when they are incorporated into bioactive peptides. Some chain-modification strategies have concentrated on conformational restrictions induced by (*a*) increased steric bulk and (*b*) cyclization of the side-chain atoms with the main-chain atoms.

Non-proteinogenic α,α-disubstituted α-amino acids bearing a second acidic functional group elsewhere in the molecule have received considerable attention as potential agonists or antagonists for excitatory amino acid neurotransmission (Johnson & Koerner, 1988; Watkins, Krogsgaard-Larsen & Honore, 1990). The synthesis of conformationally rigid analogues and homologues of the neurotransmitters glutamic and aspartic acids has aroused particular interest (Hashimoto, Ohfune & Shirahama, 1995; Tanaka, Iwabuchi & Sawanishi, 1995; Ornstein *et al.*, 1993). For these reasons, we have recently focused our attention on new cyclic aspartate analogues in which the functional groups are situated on a rigid molecular framework. In a recent paper, we reported that the easily accessible compound (*Z*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylidene]-2-phenyl-5(4*H*)-oxazolone readily gives, by reaction with cyclopentadiene, the corresponding '*exo*'/'*endo*' Diels–Alder adducts with high '*exo*' preference (Buñuel, Cativiela & Díaz-de-Villegas, 1994; Buñuel, Cativiela, Díaz-de-Villegas & Garcia, 1994). These compounds can be easily isolated in diastereomerically pure form and provide useful key intermediates in the synthesis of two new conformationally constrained aspartic acid analogues with a norbornane skeleton: *exo*-(I) and *endo*-(I) (Buñuel, Cativiela & Díaz-de-Villegas, 1996).

In a previous paper, we described the crystal and molecular structure of the major product *exo*-(I) (Buñuel, Cativiela, Díaz-de-Villegas & Gálvez, 1996); the results of the single-crystal X-ray analysis on the minor diastereomer *endo*-(I) are reported here.



exo-(I)



endo-(I)

Comparison of the bond distances and angles in compound *endo*-(I) with those determined for other norbornane structures, and in particular with the compound *exo*-(I), reveals no strikingly unusual features and these parameters lie within the expected ranges.

The norbornyl rings of compounds *endo*-(I) and *exo*-(I) show distortion from the C_{2v} symmetry of the parent hydrocarbon although this distortion is more important in the previously reported compound, *exo*-(I). Both diastereomers show a synchro twist *S*-(+,+) (Altona & Sundaralingam, 1970). The twisting in amino acid derivative *endo*-(I) can be seen from the C1—C2—C3—C4 and C4—C5—C6—C1 dihedral angles of 3.8 (6) and 0.2 (8)°, respectively.

The main differences between aspartic acid analogues *exo*-(I) and *endo*-(I) involve the spatial arrangement of the methyl ester, benzamido and carboxylic acid groups

relative to the norbornane ring, the peptide backbone torsion angles and the crystal packing. In the compound *endo*-(I), the methyl ester group attached to atom C2 adopts a nearly eclipsed conformation with respect to the C2—C3 bond of the norbornane ring [C3—C2—C8—O2 −5.5 (8)°]. The amide linkage is found in the usual *trans* conformation [C2—N—C10—C11 173.7 (6)°] and adopts an antiperiplanar conformation with respect to the C1—C2 bond of the norbornane ring [C10—N—C2—C1 168.2 (6)°]. The carboxylic acid adopts a conformation that avoids eclipsing of the C2—C3 and C3—C4 bonds of the norbornane ring [C2—C3—C17—O5 and C4—C3—C17—O5 are −65.7 (8) and 52.5 (8)°, respectively].

The amino acid residue exhibits a semi-extended conformation; the values of the backbone torsion angles C10—N—C2—C8 [φ = 49.0 (7)°] and N—C2—C8—O2 [ψ = −130.8 (6)°] (IUPAC–IUB Commission on Biochemical Nomenclature, 1970) fall in the F^* region of the conformational map (Zimmerman, Pottle, Nemethy & Scheraga, 1977).

In the crystal, the molecules form an infinite layer perpendicular to the crystallographic *a* axis, characterized by two different intermolecular hydrogen bonds: one (acid)O—H···O=C(amide) and one (amide)N—H···O=C(methyl ester) [O5···O3^{i} 2.589 (9), H0···O3^{i} 1.67 Å and O5—H0···O3^{i} 175.8 (7)°; N···O1^{ii} 2.874 (7), H···O1^{ii} 1.92 Å and N—H···O1^{ii} 176.4 (6)°, symmetry codes: (i) $\frac{3}{2}-x$, $\frac{1}{2}+y$, $-z$, (ii) $\frac{3}{2}-x$, $\frac{1}{2}+y$, $1-z$]. The layers are held together by van der Waals interactions between the phenyl and norbornane groups.

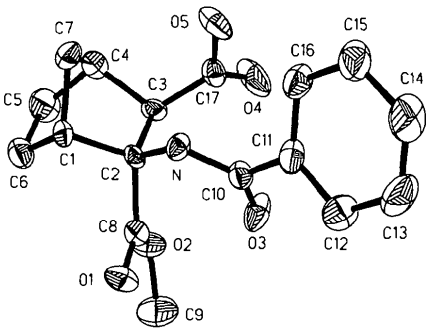


Fig. 1. The molecular structure of *endo*-(I). Displacement ellipsoids are drawn at the 50% probability level. H atoms have been omitted for clarity.

Experimental

The compound *endo*-(I) was prepared according to a procedure described by Buñuel, Cativiela & Díaz-de-Villegas (1996). Crystals were obtained by slow evaporation from hexane solution.

Crystal data

$C_{17}H_{19}NO_5$
M_r = 317.34
Monoclinic
*C*2
a = 21.329 (5) Å
b = 9.268 (5) Å
c = 8.262 (5) Å
β = 106.160 (5)°
V = 1568.7 (13) Å^3
Z = 4
D_x = 1.344 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 42 reflections
θ = 5.20–11.76°
μ = 0.099 mm^{-1}
T = 293 (2) K
Prism
0.44 × 0.3 × 0.12 mm
Colourless

Data collection

Siemens *P*4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
1799 measured reflections
1657 independent reflections
1369 reflections with $I > 2\sigma(I)$
R_{int} = 0.0277
θ_{max} = 25°
$h = -1 \rightarrow 25$
$k = -1 \rightarrow 11$
$l = -9 \rightarrow 9$
3 standard reflections every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0688
$wR(F^2)$ = 0.2488
S = 1.117
1653 reflections
210 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0994P)^2 + 5.5765P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.02
$\Delta\rho_{max}$ = 0.52 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.006 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)

H atoms were refined with a riding model, with a common U_{iso} of 0.046 (5) Å^2. The H atoms on C9 were introduced at geometrically calculated positions; all others were found from ΔF synthesis. No unusual bond lengths or angles were found and uncertainties in C—C bonds ranged from 0.008 to 0.014 Å.

Data collection: *XSCANS* (Siemens, 1993). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL-Plus* (Sheldrick, 1989). Software used to prepare material for publication: *SHELXL*93 and *PARST* (Nardelli, 1983).

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Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: BM1118). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Molecular Tiling in the 1:1 Adduct of 1,4-Diazabicyclo[2.2.2]octane and 1,3,5-Benzenetricarboxylic Acid

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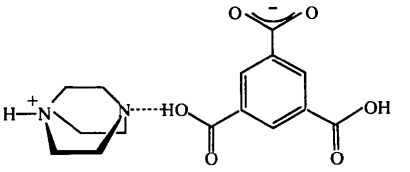
Abstract

The 1:1 adduct formed between 1,4-diazabicyclo-[2.2.2]octane and 1,3,5-benzenetricarboxylic acid is a salt, $C_6H_{13}N_2^+.C_9H_5O_6^-$. The components both lie on a mirror plane and are linked by O—H···O, O—H···N and N—H···O hydrogen bonds into planar two-dimensional sheets; these sheets are formed by repetition of a single $R_6^6(38)$ ring which thus generates a tiling pattern with plane group *pg*.

Comment

In the structure of 1,1,1-tris(4-hydroxyphenyl)ethane, $CH_3C(C_6H_4OH)_3$, the molecules are linked by O—H···O hydrogen bonds into square nets, pairs of which are interwoven and further interconnected to give a multiply interwoven three-dimensional architecture (Ferguson, Bell, Coupar & Glidewell, 1997). Fragmentation of this structure by the interpolation of 1,4-diazabicyclo[2.2.2]octane (DABCO) or piperazine molecules, which act as acceptors of hydrogen bonds, to form the adducts 1,1,1-tris(4-hydroxyphenyl)ethane–1,4-diazabicyclo[2.2.2]octane–water (1/1/1) and 1,1,1-tris(4-hydroxyphenyl)ethane–piperazine (4/3), does not change the three-dimensional character of the hydrogen bonding, but merely increases its complexity (Ferguson, Bell, Coupar & Glidewell, 1997). An even more elaborate interwoven network is formed by 1,3,5-benzenetricarboxylic acid, $C_6H_3(COOH)_3$ (trimesic acid, TMA) (Duchamp & Marsh, 1969); although interpolation of hydrogen-bond acceptors into this material generally leads to a simplification of the crystal architectures, three-dimensional hydrogen bonding often still persists (Herbstein & Kapon, 1978; Herbstein, Kapon & Wasserman, 1978; Herbstein, Kapon, Maor & Reisner, 1981). We have now prepared a 1:1 adduct from TMA and DABCO, which proves to be the salt $C_6H_{13}N_2^+.C_9H_5O_6^-$, (1), in which a single but complete proton transfer has occurred; there are three types of hydrogen bond, O—H···O, O—H···N and N—H···O, but the main structural motif is a simple strictly planar two-dimensional sheet with no interweaving.



(1)

Compound (1) crystallizes in the space group *Pnma* with a Z' of 0.5, as usually found for this space group (Brock & Dunitz, 1994). All the atoms of the TMA monoanion lie on the mirror plane, while the protonated DABCO lies across this plane with atoms N2, N3, C21 and C31 on the mirror plane. It has been pointed out (Brock & Dunitz, 1994) that mirror planes are always occupied since unoccupied ones require the occurrence of like–like interactions between adjacent molecules. Within the asymmetric unit (Fig. 1), atom O31 acts