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N-[4-(Morpholinocarbonylmethoxy)phenyl]acetamide monohydrate: a potential antiamnesic agent

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In the title compound, $C_{14}H_{18}N_2O_4 \cdot H_2O$, a potential anti-amnesic agent, the morpholine ring adopts a symmetric chair conformation. The conformation of the molecule in the crystal structure and that of the energy-minimized free molecule do not differ significantly. In the crystalline state, the molecules are stabilized by intermolecular $N-H \cdots O$, $O-H \cdots O$ and weak $C-H \cdots O$ interactions.

Comment

The crystal structures of several examples of a new class of antiamnesic agent have been reported from our laboratory (Thamotharan, Parthasarathi, Gupta *et al.*, 2003*a*,*b*,*c*,*d*; Thamotharan, Parthasarathi, Malik *et al.*, 2003*a*,*b*; Sundar *et al.*, 2005, 2006). The X-ray crystal and molecular structure determination of the title compound, (I), was undertaken in order to confirm the connectivity of the compound and determine its stereochemistry.


(I)
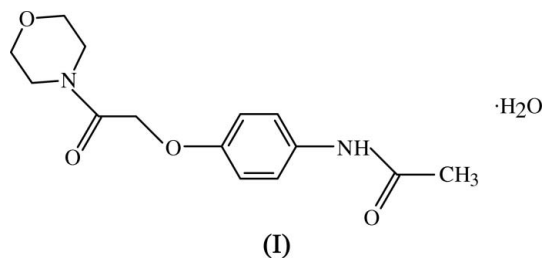
In the molecule of (I) (Fig. 1), the C1—N1—C13 angle [127.93 (13)°] is comparable with the corresponding angle in five related structures, viz. *N*-[4-(pyrrolidin-1-ylcarbonyl-methoxy)phenyl]acetamide, (II) [130.06 (18)°; Sundar *et al.*,2005], 2-[4-(acetamido)phenoxy]-*N*,*N*-dimethylacetamide, (III) [129.72 (18)°; Sundar *et al.*, 2006], *N*-[4-(4-methyl-piperazin-1-ylsulfonyl)phenyl]acetamide, (IV) [128.43 (19)°; Guo, 2004], *N*-(4-amino-2-methoxyphenyl)acetamide, (V) [129.78 (17)°; Robin *et al.*, 2002] and *N*-[4-(acetyloxy)-phenyl]acetamide, (VI) [128.8 (2)°; Caira *et al.*, 1999]. A possible reason for the large value of this angle, when compared with the normal value of 120°, may be the short intramolecular contact between the atoms O3···H2 (2.38 Å), which is less than the sum of their van der Waals radii (2.72 Å; Bondi, 1964; Rowland & Taylor, 1996), leading to an intra-molecular C—H···O interaction (Table 1) (Desiraju, 1997). Similar short contacts (2.37 Å) are observed between the corresponding atoms in (II) (2.37 Å), (III), (2.30 Å), (IV) (2.30 Å), (V) (2.36 Å) and (VI) (2.26 Å).
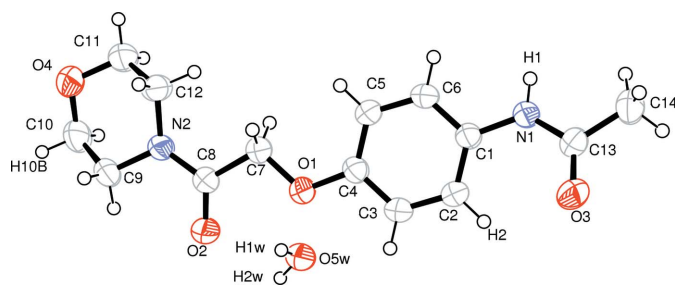
Figure 1
A view of the molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as circles of arbitrary radii. H atoms involved in the hydrogen-bonding interactions are labelled for clarity.
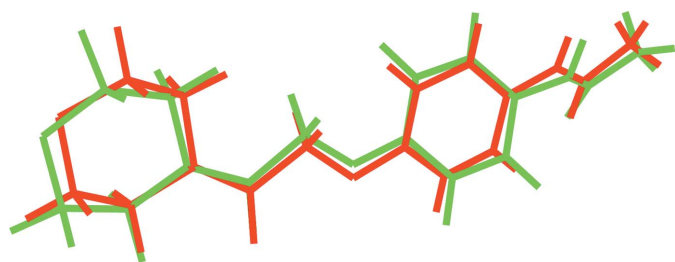
Figure 2
A superimposed fit of the molecule of (I) in the crystal structure (red) and its energy-minimized counterpart (green).

An energy-minimization calculation was carried out on the isolated molecule of (I), using the program *WINMOPAC* (Shchepin & Litvinov, 1998). A least-squares fit of the energy-minimized molecule of (I) with its X-ray counterpart gives an r.m.s. deviation of 0.393 Å (Fig. 2). In the energy-minimized molecule, rotation about the C1—N1, N1—C13 and C4—O2 single bonds is possible and might have reduced the strain observed in the molecules of the crystal structure. This can be seen in the lengthening of the short intramolecular O3···H2 contact distance from 2.38 Å in the crystal structure of (I) to 3.07 Å in the energy-minimized free molecule, thereby relieving the strain.

The morpholine ring in (I) adopts a symmetric chair conformation (Swenson *et al.*, 1980). The dihedral angle between the least-squares planes of the phenoxy and acet-amide units is 22.3 (3)°. This value is significantly large when compared with the values observed in (II) [4.4 (2)°] and (III) [11.4 (2)°]. This indicates that the conformation of (I) is altered compared with that observed in (II) and (III), because of the different substituents at C8 in these structures. This is also evident from the values of the r.m.s. deviations calculated by superposition of the phenyl acetamide units of (I) and (II) (2.597 Å), (I) and (III) (2.490 Å) and (II) and (III) (1.658 Å).

In the crystalline state, the molecules of (I) are stabilized by intermolecular N—H···O, C—H···O and O—H···O hydrogen bonds (Table 1). These hydrogen bonds link the molecules into a double-layered structure parallel to the $(10\bar{1})$ plane.

Experimental

Methyl-2-(4-acetamidophenoxy)acetate (1.0 g, 4.48 mmol) was added to morpholine (0.5 ml, 5.73 mmol) and the mixture was stirred with a magnetic stirrer at 373 K for 10 h. Crushed ice was added and the residue obtained by extraction with dichloromethane was crystallized from petroleum ether and acetone (90:10) (yield 0.846 g, 67.89%; m.p. 418–420 K).

Crystal data

$C_{14}H_{18}N_2O_4 \cdot H_2O$	$Z = 4$
$M_r = 296.32$	$D_x = 1.336$ Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation
$a = 7.6438$ (18) Å	$\mu = 0.10$ mm^{-1}
$b = 17.170$ (5) Å	$T = 298$ (2) K
$c = 11.597$ (3) Å	Block, brown
$\beta = 104.520$ (7)°	$0.4 \times 0.4 \times 0.3$ mm
$V = 1473.4$ (7) Å^3	

Data collection

Bruker SMART CCD 1K area-detector diffractometer	17319 measured reflections
ω scans	3024 independent reflections
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)	2354 reflections with $I > 2\sigma(I)$
$T_{min} = 0.927$, $T_{max} = 1.000$	$R_{int} = 0.036$
	$\theta_{max} = 26.4°$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0588P)^2 + 0.2971P]$
$R[F^2 > 2\sigma(F^2)] = 0.042$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.120$	$(\Delta/\sigma)_{max} = 0.001$
$S = 1.02$	$\Delta\rho_{max} = 0.21$ e Å^{-3}
3024 reflections	$\Delta\rho_{min} = -0.16$ e Å^{-3}
204 parameters	Extinction correction: *SHELXL97* (Sheldrick, 1997)
H atoms treated by a mixture of independent and constrained refinement	Extinction coefficient: 0.022 (2)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···O3	0.93	2.38	2.910 (2)	116
O5W—H1W···O2	0.84 (3)	2.17 (3)	2.9617 (19)	157 (3)
O5W—H2W···O3^i	0.89 (3)	1.85 (3)	2.7348 (19)	174 (2)
N1—H1···O5W^{ii}	0.87 (2)	2.00 (2)	2.8566 (18)	169 (2)
C10—H10B···O5W^i	0.97	2.55	3.473 (2)	159

Symmetry codes: (i) $-x + \frac{3}{2}, y + \frac{1}{2}, -z + \frac{1}{2}$; (ii) $-x + 2, -y, -z + 1$.

Atoms H1, H1W and H2W were located in a difference Fourier map and refined freely. All other H atoms were placed in geometrically idealized positions, with C–H distances in the range 0.93–0.97 Å, and constrained to ride on their parent atoms, with U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) for others.

Data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997), *PLATON* (Spek, 2003) and *QMOL* (Gans & Shalloway, 2001); software used to prepare material for publication: *SHELXL97* and *PARST* (Nardelli, 1995).

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