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(±)-5-(4-Methoxyphenylaminocarbonyl)-1-azabicyclo[3.3.0]octan-2-one benzene solvate

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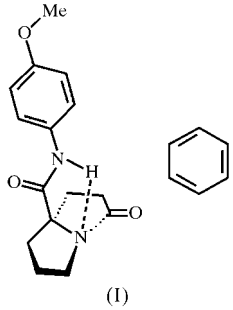
The title *trans* prolyl amide exists as a benzene solvate, $C_{15}H_{18}N_2O_3\cdot C_6H_6$, with positional disorder of the prolyl ring. The molecular structure is influenced by a close intramolecular N—H···N contact that provides structural support for the intramolecular catalysis of peptidyl–prolyl *cis–trans* isomerization.

Comment

The amide group is a fundamental structural feature that plays an important role in the construction of molecular conformations and associations. Through a resonance-assisted process, the local geometry of the amide moiety rarely deviates from planarity, even when influenced by sterically encumbered environments (Patai, 1992; Zabicky, 1970). This conformational preference is most clearly seen from a search of the Cambridge Structural Database (CSD, Version 5.24; Allen, 2002) for acyclic secondary amide structures, which yielded 2633 entries with 5567 –C—CO—NH—C– fragments. Of these entries, more than 95% adopt a planar geometry, with torsion angles of 180±10° (4935 fragments) or 0±10° (102 fragments). Because of this conformational boundary and the tendency of amides to form robust hydrogen-bond interactions (Bernstein *et al.*, 1994), the amide group is a powerful tool for decoding the structural preferences of molecular recognition.



(I)

Non-bonded contacts involving the amide fragment of peptidyl–prolyl residues are known to play a significant role in the function of biological systems, examples of this role being protein folding and catalysis (Fischer, 1994; Schmid *et al.*, 1993). Although the *cis–trans* isomerization of amide C—N bonds is significant in these processes, the intimate details of this isomerization remain relatively vague. From theoretical results, Fischer *et al.* (1993, 1994) proposed an intramolecular catalytic pathway for isomerization, which involves protonation of the prolyl amide N atom followed by free rotation about the C—N bond. The existence of intramolecular N—H···N interactions was later supported by kinetic and spectroscopic evidence of a model system composed of a family of proline compounds (Cox & Lectka, 1998, 2000); the title

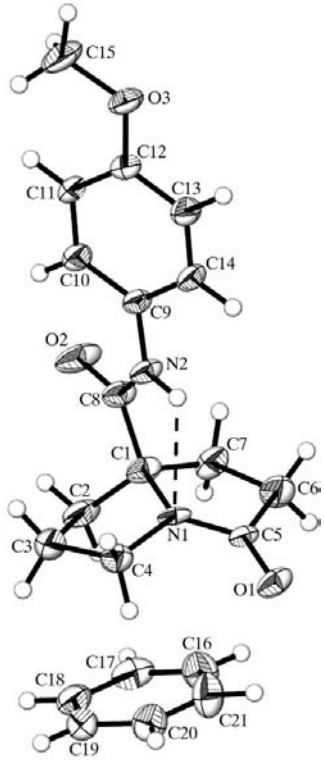


Figure 1
A view of the molecular structure of (I), showing the atom-labeling scheme and an intramolecular N—H···N contact (dashed line). Displacement ellipsoids are shown at the 50% probability level.

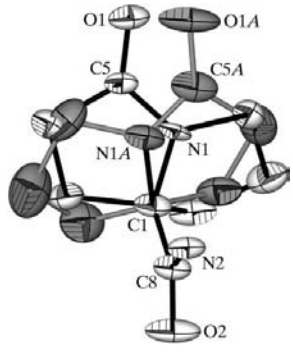


Figure 2
The positional disorder of the proline moiety. Displacement ellipsoids are shown at the 50% probability level.

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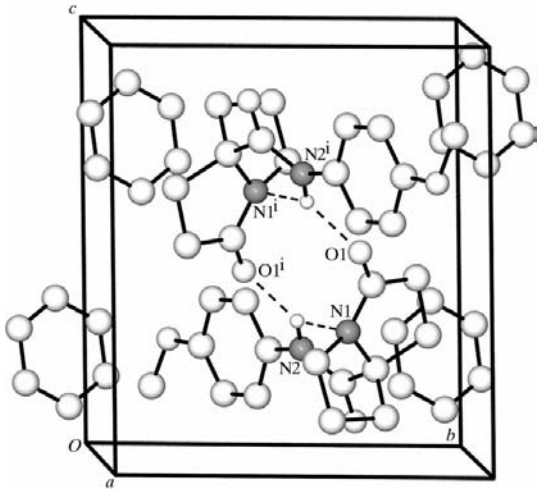

Figure 3
Part of the crystal structure of (I), showing bifurcated N—H···N/O hydrogen-bond interactions (dashed lines) that form cyclic motifs. [Symmetry code: (i) $2-x, 1-y, 1-z$.]

compound, (I), was one of several compounds employed in the study. Data gleaned from this investigation not only revealed an important N—H···N contact but also suggested this intramolecular interaction as a point of entry to *cis–trans* isomerization and a key source of catalytic behavior. The crystal structure of (I) provides additional evidence for intramolecular prolyl N—H···N interactions.

The molecular conformation of (I), as observed in the crystal structure, is shown in Fig. 1. The amide group exists as the *trans* isomer [C9—N2—C8—C1 = 174.2 (2)° and C9—N2—C8—O2 = −4.9 (4)°], with the prolyl fragment disordered equally over two positions (Fig. 2). As anticipated, the amide HN2 atom is directed towards the prolyl group and forms roughly equidistant intramolecular contacts with the disorderd prolyl N atoms. Inspection of the structural parameters of this N2—HN2···N1 interaction (Table 1) provides evidence for the existence of an intramolecular hydrogen bond. These data parallel previously reported results for the 4-bromo derivative [CSD refcode RINGAW; N···N = 2.790 (6) Å, H···N = 2.35 (5) Å and N—H···N = 120 (4)°; Cox *et al.*, 1997], thus supplying additional evidence that the N—H···N contact is a viable electrostatic interaction rather than a conformational artifact.

Inspection of the crystal structure reveals pairs of molecules linked by N—H···O hydrogen bonds to form centrosymmetric motifs (Fig. 3 and Table 1). These molecular assemblies [described by graph sets $N_1 = S(5)R_2^2(14)$ and $N_2 = R_2^4(8)$; Bernstein *et al.*, 1995] result from association of the amide H atom with a proline O atom of a neighboring molecule. This intermolecular N2—HN2···O1 interaction occurs in both proline conformers and displays reasonable hydrogen-bond geometry. Atom HN2 is involved in both intra- and intermolecular hydrogen bonding and forms a nearly planar three-center motif, as evidenced from the sum of the angles around HN2 for the N2—HN2···N1/O1 [344 (2)°] and N2—HN2···N1*A*/O1*A* [359 (2)°] bifurcated contacts.

Experimental

Crystalline samples of (I) were obtained from T. Leckta (Department of Chemistry, Johns Hopkins University). Sample quality was assessed by polarized microscopy, and a single crystal was adhered with cyanoacrylate glue to a glass fiber for subsequent crystallographic investigation.

Crystal data

$C_{15}H_{18}N_2O_3\cdot C_6H_6$
$M_r = 352.42$
Triclinic, $P\overline{1}$
$a = 9.7611$ (14) Å
$b = 10.1229$ (15) Å
$c = 10.7545$ (13) Å
$\alpha = 88.349$ (9)°
$\beta = 87.715$ (9)°
$\gamma = 62.925$ (9)°
$V = 945.4$ (2) Å^3
$Z = 2$
$D_x = 1.238$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 16 reflections
$\theta = 20.2$–23.9°
$\mu = 0.08$ mm^{-1}
$T = 298$ (2) K
Transparent plate, colorless
0.81 × 0.43 × 0.12 mm

Data collection

Siemens *P*4 diffractometer
$\theta/2\theta$ scans
5059 measured reflections
4295 independent reflections
2607 reflections with $I > 2\sigma(I)$
$R_{int} = 0.021$
$\theta_{max} = 27.5$°
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 13$
$l = -13 \rightarrow 13$
3 standard reflections every 97 reflections
intensity decay: <3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.054$
$wR(F^2) = 0.134$
$S = 1.02$
4295 reflections
312 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0438P)^2 + 0.282P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—HN2···N1	0.84 (2)	2.39 (2)	2.767 (8)	108 (2)
N2—HN2···N1*A*	0.84 (2)	2.30 (2)	2.690 (9)	109 (2)
N2—HN2···O1^{i}	0.84 (2)	2.13 (2)	2.883 (2)	148 (2)
N2—HN2···O1*A*^{i}	0.84 (2)	2.13 (2)	2.950 (4)	162 (2)

Symmetry code: (i) $2-x, 1-y, 1-z$.

The proline moiety of (I) exhibits positional disorder over two sites that are related by a rotation of 8.8° about the C1—C8 bond. Since the site-occupancy factors for these two sites refined to being nearly equal, 50% occupancy factors were applied to each of the two positions. Atom HN2 was located in a difference density map, and the remaining H-atom positions were treated as riding, with C—H distances of 0.95 (aromatic), 0.98 (CH_3) and 0.99 Å (CH_2). Riding methyl H atoms were allowed to rotate freely during refinement using the AFIX 137 command of *SHELXTL* (Bruker, 1998).

Data collection: *XSCANS* (Bruker, 1999); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXTL* and *SHELXL*97 (Sheldrick, 1997); molecular graphics: *X-SEED* (Barbour, 2001); software used to prepare material for publication: *X-SEED*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1247). Services for accessing these data are described at the back of the journal.

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