Acta Cryst. (1997). C**53**, 1659–1661

Two Cyclohexanespiro-5′-hydantoin Monohydrates

Ted J. Gauthier, T. Scott Yokum, Guillermo A. Morales, Mark L. McLaughlin, Yen-Hsiang Liu and Frank R. Fronczek

Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA. E-mail: fronz@chxray1.chem.lsu.edu

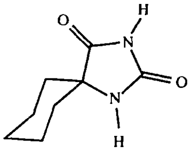
(*Received 9 April 1997; accepted 19 May 1997*)

Abstract

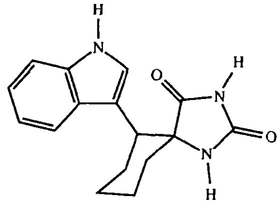
Cyclohexanespiro-5′-hydantoin monohydrate, $C_8H_{12}N_2O_2.H_2O$, has a chair-shaped cyclohexane ring with endocyclic torsion-angle magnitudes in the range 54.4 (2)–56.3 (2)°. All potential hydrogen-bond donors are involved in intermolecular hydrogen bonding, with lengths in the range 2.760 (2)–2.908 (2) Å. In its indolyl adduct, 2-(3-indolyl)cyclohexanespiro-5′-hydantoin monohydrate, $C_{16}H_{17}N_3O_2.H_2O$, the cyclohexane moiety adopts a chair conformation with the indolyl substituent in an equatorial position. The N—H portion of the hydantoin ring is *cis* to indolyl, while the C═O of the hydantoin is *trans*. Endocyclic torsion-angle magnitudes of the cyclohexane ring are in the range 54.2 (2)–56.7 (2)°. All potential hydrogen-bond donors are involved in intermolecular hydrogen bonds, with lengths 2.828 (2)–3.187 (2) Å.

Comment

Of the aromatic amino acids, tryptophan is easiest to selectively excite due to its red-shifted absorbance. Therefore, it would be useful to use tryptophan as a fluorescent probe to study protein conformations. All of the quenching mechanisms of tryptophan in a protein environment are not fully understood. In order to study these mechanisms, it would be beneficial to limit the flexibility of the molecule. As a result, a constrained derivative of tryptophan can be used to help define how orientation of the peptide bond affects quenching (Chen, Liu, Yu & Barkley, 1996). As part of a synthetic effort to prepare these compounds, we have synthesized cyclohexanespiro-5′-hydantoin, (1), and 2-(3-indolyl)cyclohexanespiro-5′-hydantoin, (2), and have determined the crystal structures of their crystalline monohydrates as part of the complete characterization of the reaction products. α,α-Disubstituted amino acids are of interest because of their ability to promote specific secondary structures when incorporated into peptides. Compound (1) was synthesized as a precursor to an α,α-disubstituted cyclohexane amino acid, *i.e.* 1-amino-1-cyclohexane carboxylic acid, and compound (2) as a precursor to a constrained tryptophan derivative.



(1)



(2)

The bond distances and angles within the hydantoin (2,4-imidazolidenedione) units of both molecules are normal, typical of those observed in 5,5-dimethylhydantoin (Cassady & Hawkinson, 1982) and in other spiro-5′-hydantoins (Vilches, Florencio, Smith-Verdier & Garcia-Blanco, 1981; Smith-Verdier, Florencio, & Garcia-Blanco, 1977, 1979; Florencio, Smith-Verdier & Garcia-Blanco, 1978, 1982). The hydantoin unit is very nearly planar in both molecules, with maximum deviations from planarity of 0.014 (2) Å (O1) in (1) and 0.031 (2) Å (O2 and N3′) in (2). The indole ring system of (2) exhibits a maximum deviation of 0.024 (2) Å (for C12) from planarity and this plane forms a dihedral angle of 58.83 (4)° with that of the hydantoin. The cyclohexane rings of both molecules are in chair conformations, with endocyclic torsion-angle magnitudes of 54.4 (2)–56.3 (2)° for (1) and 54.2 (2)–56.7 (2)° for (2).

In both structures, all available hydrogen-bond donors of the hydantoin, indole and water are involved in intermolecular hydrogen bonds; these are detailed in Tables 2 and 4. In both, the carbonyl O1 atom accepts a hydrogen bond from water. In (1), N1′—H donates to a carbonyl O atom and N3′—H donates to water, while in (2), these roles are reversed. In (1), the carbonyl O2 atom accepts from N—H, while in (2), it accepts from water. In (1), all hydrogen bonds are linear within experimental error, while in (2), they are less so, with angles about hydrogen varying from 115 (2) to 174 (2)°.

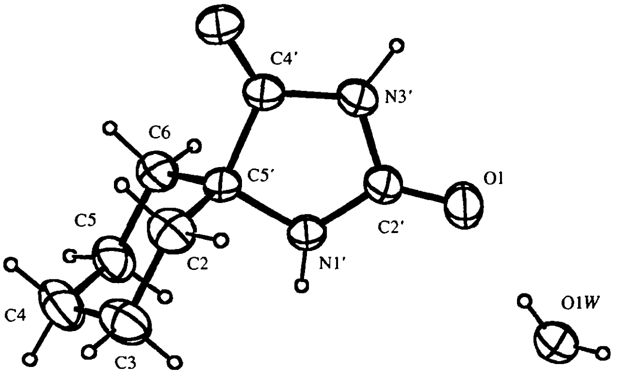


Fig. 1. The molecular structure of (1).H_2O, with 40% probability ellipsoids. H atoms are shown as circles of arbitrary radii.

Acta Crystallographica Section C
ISSN 0108-2701 © 1997

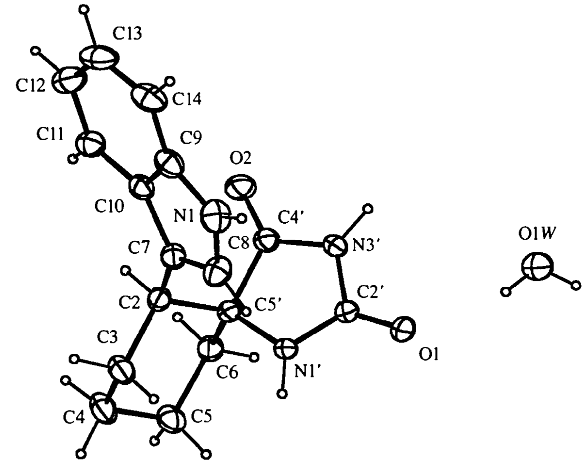


Fig. 2. The molecular structure of (2).H_2O, with 30% probability ellipsoids. H atoms are shown as circles of arbitrary radii.

Experimental

Compound (1) was prepared by reacting cyclohexanone with KCN and ammonium carbonate, according to a procedure reported by Tsang, Schmied, Nyfeler & Goodman (1984). Crystals of the monohydrate were grown by refrigeration of a solution in methanol–water. Compound (2) was prepared *via* a Bücherer–Bergs synthesis on 2-(3-indolyl)cyclohexanone under an inert atmosphere with heating. The crude product was dissolved in basic water and the pH was adjusted to 7. Crystals of the monohydrate formed within 48 h.

Compound (1).H_2O

Crystal data

$C_8H_{12}N_2O_2.H_2O$
$M_r = 186.21$
Orthorhombic
$Pna2_1$
$a = 16.889\ (1)$ Å
$b = 9.2407\ (5)$ Å
$c = 6.2644\ (6)$ Å
$V = 977.6\ (2)$ Å^3
$Z = 4$
$D_x = 1.265$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 25 reflections
$\theta = 14$–$30°$
$\mu = 0.78$ mm^{-1}
$T = 296$ K
Fragment
0.33 × 0.10 × 0.10 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scans (North, Phillips & Mathews, 1968)
$T_{\min} = 0.84$, $T_{\max} = 0.93$
3174 measured reflections
2002 independent reflections

1722 reflections with $I > \sigma(I)$
$R_{\rm int} = 0.034$
$\theta_{\max} = 75.0°$
$h = 0 \rightarrow 21$
$k = -11 \rightarrow 11$
$l = -7 \rightarrow 7$
3 standard reflections
frequency: 120 min
intensity decay: 0.4%

Refinement

Refinement on F^2
$R(F) = 0.038$
$wR(F^2) = 0.039$
$S = 1.466$
1722 reflections
174 parameters
All H atoms refined
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0004F_o^4]$
$(\Delta/\sigma)_{\max} = 0.005$
$\Delta\rho_{\max} = 0.23$ e Å^{-3}
$\Delta\rho_{\min} = -0.30$ e Å^{-3}
Extinction correction: isotropic (Zachariasen, 1963)
Extinction coefficient: $8.5\ (2) \times 10^{-6}$

Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
Absolute configuration: refinement of the antipodal structure was inconclusive; for the reported absolute structure, $R = 0.03803$, $wR = 0.03908$, $S = 1.466$, while the alternate structure yielded $R = 0.03801$, $wR = 0.03910$, $S = 1.467$.

Table 1. *Selected geometric parameters (Å, °) for (1).H_2O*

O1—C2′	1.218 (2)	N3′—C2′	1.397 (2)
O2—C4′	1.220 (2)	N3′—C4′	1.345 (2)
N1′—C2′	1.326 (2)	C4′—C5′	1.518 (2)
N1′—C5′	1.461 (2)		
C2′—N1′—C5′	113.4 (1)	O2—C4′—N3′	126.6 (2)
C2′—N3′—C4′	111.4 (1)	O2—C4′—C5′	125.3 (1)
O1—C2′—N1′	129.4 (2)	N3′—C4′—C5′	108.1 (1)
O1—C2′—N3′	123.3 (1)	N1′—C5′—C4′	99.9 (1)
N1′—C2′—N3′	107.3 (1)		

Table 2. *Hydrogen-bonding geometry (Å, °) for (1).H_2O*

D—H···A	D—H	H···A	D···A	D—H···A
N1′—H1′···O2$^{\rm i}$	0.82 (2)	2.09 (2)	2.908 (2)	176 (2)
N3′—H3′···O1$W^{\rm ii}$	0.95 (2)	1.82 (2)	2.760 (2)	175 (2)
O1W—H2W···O1	0.96 (2)	1.83 (2)	2.788 (2)	177 (2)
O1W—H1W···O1$^{\rm iii}$	0.88 (2)	1.98 (2)	2.852 (2)	178 (3)

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

Compound (2).H_2O

Crystal data

$C_{16}H_{17}N_3O_2.H_2O$
$M_r = 301.35$
Monoclinic
$P2_1/c$
$a = 11.991\ (1)$ Å
$b = 8.3535\ (7)$ Å
$c = 15.159\ (1)$ Å
$\beta = 94.731\ (8)°$
$V = 1513.3\ (4)$ Å^3
$Z = 4$
$D_x = 1.323$ Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 25 reflections
$\theta = 6$–$17°$
$\mu = 0.72$ mm^{-1}
$T = 296$ K
Prism
0.20 × 0.14 × 0.13 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3469 measured reflections
3113 independent reflections
2560 reflections with $I > \sigma(I)$

$R_{\rm int} = 0.032$
$\theta_{\max} = 75.0°$
$h = 0 \rightarrow 15$
$k = 0 \rightarrow 10$
$l = -18 \rightarrow 17$
3 standard reflections
frequency: 120 min
intensity decay: 0.3%

Refinement

Refinement on F^2
$R(F) = 0.054$
$wR(F^2) = 0.088$
$S = 1.533$
2560 reflections
276 parameters
All H atoms refined
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0004F_o^4]$
$(\Delta/\sigma)_{\max} = 0.049$
$\Delta\rho_{\max} = 0.20$ e Å^{-3}
$\Delta\rho_{\min} = -0.11$ e Å^{-3}
Extinction correction: isotropic (Zachariasen, 1963)
Extinction coefficient: 2.3 (1) × 10^{-6}
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 3. *Selected geometric parameters (Å, °) for (2).H$_2$O*

O1—C2′	1.224 (2)	N1—C9	1.372 (2)
O2—C4′	1.208 (2)	N3′—C2′	1.386 (2)
N1′—C2′	1.336 (2)	N3′—C4′	1.368 (2)
N1′—C5′	1.458 (2)	C4′—C5′	1.525 (2)
N1—C8	1.374 (2)		
C2′—N1′—C5′	112.9 (1)	O2—C4′—C5′	126.8 (1)
C8—N1—C9	109.0 (1)	N3′—C4′—C5′	106.7 (1)
C2′—N3′—C4′	111.8 (1)	N1′—C5′—C4′	100.9 (1)
O2—C4′—N3′	126.4 (2)		

Table 4. *Hydrogen-bonding geometry (Å, °) for (2).H$_2$O*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1N···O1*W*^{i}	0.88 (2)	2.17 (2)	3.056 (2)	174 (2)
N1′—H1N′···O1*W*^{ii}	0.88 (2)	2.10 (2)	2.972 (2)	172 (2)
N3′—H3N′···O1^{iii}	0.91 (2)	1.97 (2)	2.828 (2)	157 (2)
O1*W*—H2*W*···O1	0.90 (3)	2.04 (3)	2.856 (2)	151 (3)
O1*W*—H1*W*···O2^{ii}	0.80 (3)	2.76 (3)	3.187 (2)	115 (2)

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

For (1).H$_2$O, C—H distances are 0.94 (2)–1.07 (3), N—H 0.82 (2)–0.95 (2) and O—H 0.88 (2)–0.96 (2) Å, while $U_{\rm iso}$ values for H atoms are in the range 0.054 (5)–0.119 (9) Å^2. For (2).H$_2$O, a series of ψ scans revealed no measurable change in intensity with rotation angle, thus, no absorption correction was carried out. C—H distances are 0.93 (2)–1.03 (2), N—H 0.88 (2)–0.91 (2) and O—H 0.80 (2)–0.90 (2) Å, while $U_{\rm iso}$ values for H atoms are in the range 0.031 (4)–0.19 (1) Å^2.

For both compounds, data collection: *CAD*-4 *Operations Manual* (Enraf–Nonius, 1977); cell refinement: *CAD*-4 *Operations Manual*; data reduction: *PROCESS MolEN* (Fair, 1990). Program(s) used to solve structures: direct methods *SHELXS*86 (Sheldrick, 1990) for (1).H$_2$O; direct methods *MULTAN*80 (Main *et al.*, 1980) for (2).H$_2$O. For both compounds, program(s) used to refine structures: *LSFM MolEN*; molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *CIF IN MolEN*.

The purchase of the diffractometer was made possible by a National Science Foundation chemical instrumentation grant, which we gratefully acknowledge. We thank the National Institutes of Health for support for this research *via* grant #GM42101.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1332). Services for accessing these data are described at the back of the journal.

References

Cassady, R. E. & Hawkinson, S. W. (1982). *Acta Cryst.* B**38**, 1646–1647.
Chen, Y., Liu, B., Yu, H.-T. & Barkley, M. D. (1996). *J. Am. Chem. Soc.* **118**, 9271–9278.
Enraf–Nonius (1977). *CAD-4 Operations Manual.* Enraf–Nonius, Delft, The Netherlands.
Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis.* Enraf–Nonius, Delft, The Netherlands.
Florencio, F., Smith-Verdier, P. & Garcia-Blanco, S. (1978). *Acta Cryst.* B**34**, 1317–1321.
Florencio, F., Smith-Verdier, P. & Garcia-Blanco, S. (1982). *Acta Cryst.* B**38**, 2089–2091.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN*80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Universities of York, England, and Louvain, Belgium.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Smith-Verdier, P., Florencio, F. & Garcia-Blanco, S. (1977). *Acta Cryst.* B**33**, 3381–3385.
Smith-Verdier, P., Florencio, F. & Garcia-Blanco, S. (1979). *Acta Cryst.* B**35**, 216–217.
Tsang, J. W., Schmied, B., Nyfeler, R. & Goodman, M. (1984). *J. Med. Chem.* **27**, 1663–1668.
Vilches, J., Florencio, F., Smith-Verdier, P. & Garcia-Blanco, S. (1981). *Acta Cryst.* B**37**, 201–204.
Zachariasen, W. H. (1963). *Acta Cryst.* **16**, 1139–1144.

Acta Cryst. (1997). C**53**, 1661–1665

Deux Composés Trisubstitués de la 4-Méthylènecyclooctanone

DARIA GINDEROW,[a] LOUIS FENSTERBANK,[b] CATHERINE JORAND-LEBRUN[b] ET MAX MALACRIA[b]

[a] *Laboratoire de Minéralogie et Cristallographie, URA 09 CNRS, Université Pierre et Marie Curie, T16, 4 place Jussieu, 75252 Paris CEDEX 05, France, et* [b] *Laboratoire de Chimie Organique de Synthèse, URA 408 CNRS, Université Pierre et Marie Curie, T44, 4 place Jussieu, 75252 Paris CEDEX 05, France. E-mail: ginderow@lmcp.jussieu.fr*

(*Reçu le 29 octobre 1996, accepté le 4 juin 1997*)

Abstract

The structures of two trisubstituted 4-methylenecyclooctanones are reported, namely, di-*tert*-butyl 2-methoxycarbonyl-4-methylene-1-oxocyclooctane-6,6-dicarboxylate (IUPAC numbering: di-*tert*-butyl 5-methoxycarbonyl-3-methylene-6-oxocyclooctane-1,1-dicarboxylate), $C_{21}H_{32}O_7$, (1), and di-*tert*-butyl 2-phenylsulfonyl-4-methylene-1-oxocyclooctane-6,6-dicarboxylate,