Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(+)-Gibberellin C: hydrogen-bonding pattern of the monohydrate of a non-racemic pentacyclic diterpenoid

Hugh W. Thompson, Andrew P. J. Brunskill and Roger A. Lalancette*

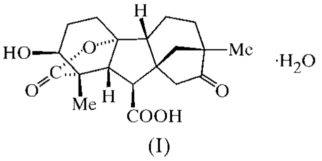
Carl A. Olson Memorial Laboratories, Department of Chemistry, Rutgers University, Newark, NJ 07102, USA
Correspondence e-mail: rogerlal@andromeda.rutgers.edu

Received 28 July 2000
Accepted 25 September 2000

In the monohydrate of the title compound, (+)-2β,4aα-dihydroxy-1,7-dimethyl-8-oxo-4bβ,7α-gibbane-1α,10β-dicarboxylic acid-1,4a-lactone, $C_{19}H_{24}O_6 \cdot H_2O$, intermolecular hydrogen bonding progresses helically along **b** from carboxyl to ketone [$O\cdots O$ = 2.694 (5) Å]. The carboxyl and lactone carbonyl groups in translationally related molecules within a helix both accept hydrogen bonds from the same water of hydration. The oxygen of this water in turn accepts a hydrogen bond from the hydroxyl group of a third screw-related molecule in an adjacent counterdirectionally oriented helix, yielding a complex three-dimensional hydrogen-bonding array. Intermolecular $O\cdots H-C$ close contacts were found to the carboxyl and lactone carbonyls, the hydroxyl, and the water.

Comment

In our pursuit of X-ray crystal structures of keto carboxylic acids (Lalancette *et al.*, 1999), acidic degradation was carried out on commercial gibberellic acid (gibberellin A_3). In addition to the desired gibberic acid, this gave a minute yield of a by-product we have identified as gibberellin C, whose monohydrate, (I), yielded the X-ray structure and solid-state hydrogen-bonding pattern we now report.



(I)

The gibberellins are an important family of diterpenoid plant-growth factors first isolated from cultures of the fungus *Gibberella fujikuroi* in the late 1930s. However, (I) is almost certainly not a 'primary' gibberellin, isolable directly from such sources without synthetic transformation, despite one suggestion of such a source (Connolly & Hill, 1991). Gibberellin C is known to arise from gibberellin A_1 by acid-catalyzed rearrangement of the bridged *C*/*D* ring juncture (Mander, 1992; Stork *et al.*, 1965). Since commercial gibberellin A_3 is offered in a purity of only *ca* 90%, isolation of (I), in our case, undoubtedly resulted from transformation of gibberellin A_1 present as an impurity. Both the structure (Cross *et al.*, 1961) and stereochemistry (Hartsuck & Lipscomb, 1963; McCapra *et al.*, 1966) of gibberellin C have long been firmly established, but the stereochemistry at C4b shown in the reference cited above (Connolly & Hill, 1991) is incorrect. The early structure-elucidation literature on gibberellins is both voluminous and replete with provisional structural (Takahashi *et al.*, 1959) and stereochemical (Cross *et al.*, 1961) assignments subsequently superseded. An excellent and exhaustive more recent review of the chemistry of the gibberellins is available (Mander, 1992).

Fig. 1 shows the asymmetric unit for (I) with its Chemical Abstracts 'gibbane' numbering, which differs from the alternative 'gibberellin' numbering often encountered (Mander, 1992; Budavari, 1989). The H atoms at C4b and C10a, as well as the methyl at C1, the hydroxyl at C2, the methano (C11) bridge and the carboxyl, all lie on the 'upper' β face of the molecule. Only the lactone and ketone bridges have α stereochemistry. The molecule has very little conformational flexibility and the only available skeletal rotation of significance involves the carboxyl, which is turned so that its C=O group is toward the β face. The H atom of the axial hydroxyl group is aimed away from the ring system toward a water of hydration, which in turn donates hydrogen bonds to two different C=O groups in separate molecules (see below). Fig. 1 shows this water, arbitrarily, in its hydrogen-bonding relationship to the lactone carbonyl (O4).

Because the carboxyl is not dimerized but hydrogen bonded to other species, it shows no disorder. Averaging of C—O bond lengths and C—C—O angles by disorder is common in carboxyl dimers (Leiserowitz, 1976), but is not seen in catemers and other hydrogen-bonding arrangements whose geometry cannot support the mechanisms responsible for such averaging. In (I), these C—O bond lengths are 1.191 (5) and

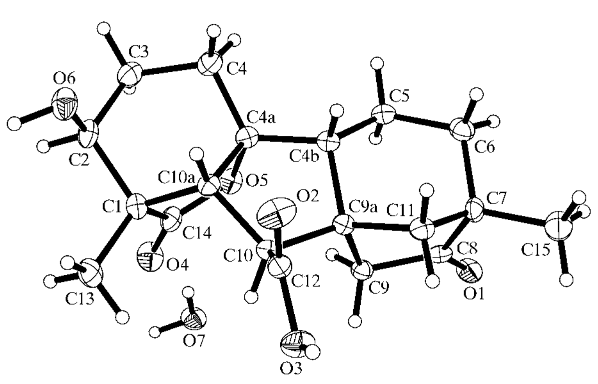


Figure 1
A view of the asymmetric unit of (I), with the atom-numbering scheme. The water of hydration is shown, arbitrarily, in its hydrogen-bonding relationship to the lactone carbonyl group. Displacement ellipsoids are drawn at the 20% probability level.

1.320 (6) Å, with angles of 123.7 (5) and 112.3 (5)°. Our own survey of 56 keto acid structures which are not acid dimers gives average values of 1.20 (1) and 1.32 (2) Å, and 124.5 (14) and 112.7 (17)° for these lengths and angles, in accord with typical values of 1.21 and 1.31 Å, and 123 and 112° cited for highly ordered dimeric carboxyls (Borthwick, 1980). No discernable disorder was observed for either methyl group.

Fig. 2 illustrates the packing arrangement with its complex hydrogen bonding. Compound (I) was not intended as part of our study of keto-acid hydrogen bonding, which avoids hydroxyl groups as complicating factors. Nevertheless, (I) adheres to a standard keto-acid hydrogen-bonding motif in forming acid-to-ketone catemers [O$\cdots$O distance = 2.694 (5) Å; O—H$\cdots$O angle = 168°], whose components are screw-related in **b** (Brunskill *et al.*, 1999). Two counter-directional screw-related sets of helices exist, and the carboxyl and lactone carbonyl groups in translationally related molecules within a given helix both act as acceptors for hydrogen bonds from a single water of hydration [O$\cdots$O distances = 2.819 (6) and 2.749 (5) Å; O—H$\cdots$O angles = 155 (6) and 160 (6)°], whose oxygen, in turn, accepts a hydrogen bond from the hydroxyl group of a third screw-related molecule in an adjacent counterdirectionally oriented helix [O$\cdots$O distance = 2.732 (6) Å; O—H$\cdots$O angle = 167 (6)°]. Thus, molecules of water act both to brace each helix and to bridge it, alternately, to two different screw-related neighboring chains in a complex three-dimensional array. While each water participates in hydrogen bonds to three separate gibberellin molecules, each gibberellin receives a hydrogen bond to each of its three carbonyls and donates hydrogen bonds from both its OH and COOH groups. Only the 'ether O' of the lactone is not involved in the hydrogen bonding.

We have characterized the geometry of hydrogen bonding to carbonyls using a combination of the H$\cdots$O=C angle and the H$\cdots$O=C—C torsion angle. These describe the approach of the H atom to the O atom in terms of its deviation from, respectively, C=O axiality (ideal = 120°) and planarity with the carbonyl (ideal = 0°). In (I), these criteria are applicable to three of the four hydrogen bonds present. Approach angles for the acid-to-ketone hydrogen bond are H$\cdots$O=C 123.8° and H$\cdots$O=C—C −6.2°. The analogous angles for the water-to-acid hydrogen bond are 129.8 and 50.2°, and for the water-to-lactone hydrogen bond, 134.8 and 18.9°.

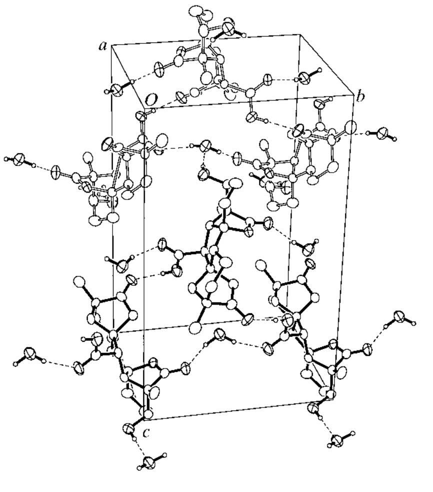


Figure 2
A partial packing diagram for (I), illustrating the complex hydrogen-bonding arrangement. All carbon-bound H atoms have been removed for clarity, but several peripheral waters are shown. The two counter-directional screw-related acid-to-ketone helices shown are differentiated by their bond shading. Displacement ellipsoids are drawn at the 40% probability level.

In addition to the hydrogen bonds, a variety of O$\cdots$H—C close contacts lie within the 2.7 Å limit we have often used for such non-bonded packing interactions (Steiner, 1997). Steiner & Desiraju (1998) have compiled data for a large number of C—H$\cdots$O contacts and found significant statistical directionality even at cutoff distances as great as 3.0 Å, leading to the conclusion that these may be legitimately viewed as 'weak hydrogen bonds', presumably contributing significantly more to packing forces than simple van der Waals attractions. In (I), these include contacts to neighbors screw-related in **c** for O2 (2.70 Å to H5*A*), for O5 (2.69 Å to H13*C*), and for O6 (2.56 Å to H11*B*), plus one for the water (O7) (2.65 Å) involving H9*A* of a molecule screw-related in **a**.

Experimental

Commercial gibberellic acid, obtained from Acros Organics/Fisher Scientific, Springfield, NJ, USA, and sold as '90%+ pure', was treated with refluxing 1.75 *M* HCl as described by Cross (1954). Compound (I), m.p. 538 K, was slowly deposited from the decanted aqueous layer in extremely low yield, and was recrystallized from ethyl acetate, yielding the crystal used for this study.

Crystal data

$C_{19}H_{24}O_6 \cdot H_2O$
$M_r = 366.40$
Orthorhombic, $P2_12_12_1$
$a = 9.7300$ (10) Å
$b = 10.661$ (2) Å
$c = 17.898$ (3) Å
$V = 1856.6$ (5) Å^3
$Z = 4$
$D_x = 1.311$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 39 reflections
$\theta = 4.17$–13.95°
$\mu = 0.100$ mm^{-1}
$T = 293$ (2) K
Rhombohedron, colorless
0.40 × 0.30 × 0.20 mm

Data collection

Siemens *P*4 diffractometer
$2\theta/\theta$ scans
3758 measured reflections
1879 independent reflections
1054 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.063$
$\theta_{\rm max} = 24.99°$

$h = -11 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -21 \rightarrow 21$
3 standard reflections every 97 reflections intensity variation: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.053$
$wR(F^2) = 0.108$
$S = 1.02$
1879 reflections
247 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0359P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.31$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.17$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0034 (10)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O1^{i}	0.82	1.89	2.694 (5)	168
O7—H7*A*···O4	0.98 (7)	1.81 (7)	2.749 (5)	160 (6)
O7—H7*B*···O2^{ii}	0.92 (7)	1.96 (7)	2.819 (6)	155 (6)
O6—H6···O7^{iii}	0.92 (7)	1.82 (7)	2.732 (6)	167 (6)
C13—H13*C*···O5^{iii}	0.96	2.69	3.638 (7)	168
C11—H11*B*···O6^{iv}	0.97	2.56	3.468 (6)	155
C9—H9*A*···O7^{i}	0.97	2.65	3.307 (7)	125
C5—H5*A*···O2^{iv}	0.97	2.70	3.537 (7)	145

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

All non-carboxyl H atoms were found in electron-density difference maps but were placed in calculated positions and allowed to refine as riding models with displacement parameters set at 120% of their respective C atoms. The hydroxyl H6 atom and the water H7*A*/*B* atoms were also found in electron-density difference maps and their positional parameters were allowed to refine; their isotropic displacement parameters were set at 150% of the O atom. The carboxyl H atom was found in difference maps and was allowed to ride on its O atom at a distance of 0.82 Å. The absolute configuration was chosen to match the known configuration of other gibberellins (Mander, 1992).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXL*97; software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1300). Services for accessing these data are described at the back of the journal.

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