Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

10-Deacetyl baccatin III dimethyl sulfoxide disolvate

James K. Harper,[a] N. Kent Dalley,[b] Anna E. Mulgrew,[a] F. G. West[a] and David M. Grant[a]*

[a]Department of Chemistry, University of Utah, 315 S. 1400 E. Rm. 1320, Salt Lake City, UT 84112, USA, and [b]Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602, USA
Correspondence e-mail: grant@chemistry.utah.edu

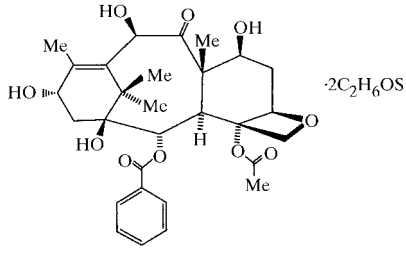
Received 1 June 2000
Accepted 29 August 2000

The title compound, $C_{29}H_{36}O_{10}\cdot 2C_2H_6OS$, forms a monoclinic crystal containing two hydrogen-bonded dimethyl sulfoxide molecules per 10-deacetyl baccatin III. The lattice is further stabilized by two additional hydrogen bonds and a dipole–dipole interaction. A comparison of 10-deacetyl baccatin III with the structurally similar docetaxel reveals differences primarily in the benzoyl moiety, while comparisons to baccatin III identify relative differences principally in the cyclooctane- and cyclohexane-ring conformations.

Comment

The success of paclitaxel and docetaxel (also known as taxol and taxotere, respectively) as anticancer drugs has prompted the study of the crystal structures of these and related taxanes. These studies have revealed the structures of both paclitaxel (Mastropaolo *et al.*, 1995) and docetaxel (Gueritte-Voegelein *et al.*, 1990), as well as 2-carbamate taxol (Gao & Golik, 1995), baccatin V (Castellano & Hodder, 1973), 7-mesylpaclitaxel (Gao & Chen, 1996), baccatin III (Gabetta *et al.*, 1995) and 10-deacetyl-7-epitaxol (Gao & Parker, 1996), which share a common tetracyclic ring structure and substitution pattern with paclitaxcel and docetaxel. However, no studies have yet appeared describing the crystal structure of 10-deacetyl baccatin III used in the semi-synthetic production of both paclitaxel and docetaxel. In addition, baccatin III derivatives display unusual reactivity as a result of a congested tertiary structure. A description of the structure of 10-deacetyl baccatin III, (I), is therefore of interest.

A crystal of (I) serendipitously appeared upon evaporation of a dimethyl sulfoxide (DMSO) solution under vacuum. The crystal was of sufficient quality to be subjected to X-ray analysis. The solid obtained contains two DMSO molecules acting as hydrogen-bond acceptors to the hydroxy H atoms at O1 and O7 (Fig. 1). Hydrogen-bonding data are given in Table 2. Disorder is observed in the DMSO molecule which is hydrogen bonded to O1 and consists primarily of inversion about the S atom. Refinement of this DMSO molecule found an approximate 2:1 occupancy of the *B* and *C* forms, respectively. This disorder is expected to cause a corresponding change in the H1—O1—C1—C2 dihedral angle due to H1 following the oxygen of DMSO from one form to another.



(I)

This subtle change is not discernible in the position of the O1 atom and is not expected for the H1 atom as the present study would be insensitive to the motion of an H atom. However, previous work (Harper & Grant, 2000) suggests that the difference may be important in solid-state NMR analyses currently being pursued in our laboratory. The OH at position C13 serves as a hydrogen-bond donor to the C9 carbonyl of a neighboring molecule. The C9 carbonyl additionally forms a weak intramolecular hydrogen bond with the OH at C10. The carbonyl of the benzoyl moiety in an adjacent molecule and the S1*A* sulfur of the DMSO appear to interact *via* an intermolecular electrostatic dipole–dipole interaction [S1*A*···O21 = 3.265 (5) Å ($2-x, \frac{1}{2}+y, 1-z$) and O1*A*—S1*A*···O21 = 170.3 (4)°]. This type of electrostatic interaction suggests an additional possible role for the benzoyl group in the bioactivity of taxanes.

The present analysis also identifies differences in (I) relative to the related compounds docetaxel and baccatin III. Docetaxel differs most significantly from (I) in the relative orientation of the carboxyl and benzene groups of benzoyl. Deviations from coplanarity, as found in docetaxel, are likely to be costly in terms of π-electron delocalization. This study, in

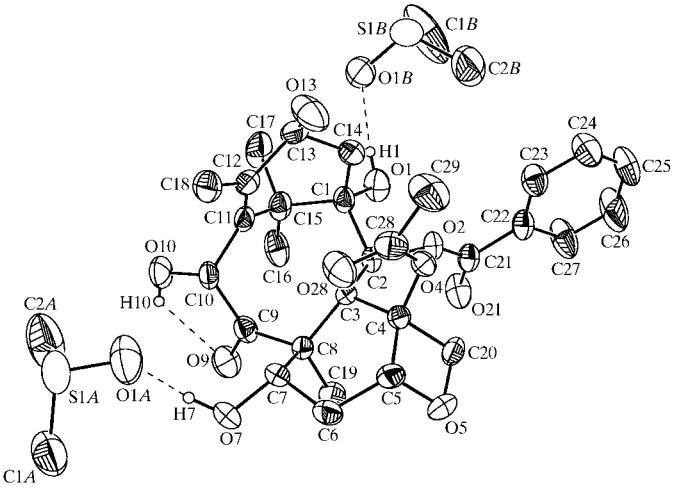


Figure 1
The asymmetric unit of the title compound showing the atom-numbering scheme and 40% probability displacement ellipsoids. The disordered DMSO molecule with lower occupancy is not shown.

 © 2001 International Union of Crystallography • Printed in Great Britain – all rights reserved

conjunction with the earlier studies on related derivatives, establishes that the benzoyl group exhibits an unexpected conformational flexibility that may be relevant to the bioactivity of taxanes.

The structure of (I) also differs from the most closely related analog, baccatin III, primarily in the cyclooctane and cyclohexane rings. Most significantly, eight corresponding dihedral angles differ by more than 7° [with three of these (C3—C2—C1—O1, C5—C6—C7—C8, and C7—C6—C5—O5) differing by nearly 10°]. Accompanying these differences are significantly shorter bond lengths at C6—C7 and C9—C10 of (I). The observation of a shorter C9—C10 bond length in (I) (1.523 Å *versus* 1.580 Å in baccatin III) supports Gabetta's contention (Gabetta *et al.*, 1995) that '... linear strain in baccatin III derivatives is affected by acylation ...'.

Experimental

Crystals of (I) were obtained by vacuum evaporation (200 mm Hg; 1 mm Hg = 133.322 Pa) of a dimethyl sulfoxide solution.

Crystal data

$C_{29}H_{36}O_{10}\cdot 2C_2H_6OS$
$M_r = 700.83$
Monoclinic, $P2_1$
$a = 9.3677\ (10)$ Å
$b = 21.991\ (4)$ Å
$c = 9.4564\ (11)$ Å
$\beta = 115.827\ (9)°$
$V = 1753.5\ (4)$ Å^3
$Z = 2$
$D_x = 1.327$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 35 reflections
$\theta = 7$–$17°$
$\mu = 0.213$ mm^{-1}
$T = 293\ (2)$ K
Block, colorless
0.5 × 0.4 × 0.3 mm

Data collection

Bruker $P4$ diffractometer
θ–2θ scans
4342 measured reflections
4103 independent reflections
3005 reflections with $I > 2\sigma(I)$
$R_{int} = 0.025$
$\theta_{max} = 27.49°$
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 28$
$l = -11 \rightarrow 11$
3 standard reflections
every 97 reflections
intensity decay: <2.0%

Refinement

Refinement on F^2
$R(F) = 0.056$
$wR(F^2) = 0.136$
4100 reflections
436 parameters
H-atom refinement: see text
$w = 1/[\sigma^2(F_o^2) + (0.0775P)^2 + 0.4816P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.34$ e Å^{-3}
$\Delta\rho_{min} = -0.26$ e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter: 0.08 (15)

All non-H atoms were refined anisotropically except for S1*C*, O1*C* and C2*C*. These disordered atoms were assigned to the disordered DMSO of lower occupancy. Hydroxy H atoms were located in a difference map and their isotropic displacement parameters were refined. All other H atoms were refined using a riding model and equivalent isotropic displacement parameters selected to correspond with their adjacent C atoms ($1.5U_{eq}$ for methyl H atoms and $1.2U_{eq}$ for the remaining H atoms). H atoms of the disordered DMSO molecule were not included in the refinement.

Data collection: *XSCANS* (Bruker, 1997); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL/PC* (Sheldrick, 1994); program(s) used to refine structure: *SHELXTL/PC*; molecular graphics: *SHELXTL/PC*; software used to prepare material for publication: *SHELXTL/PC*.

Table 1
Selected geometric parameters (Å, °).

C1—C14	1.539 (7)	C6—C7	1.515 (7)
C1—C15	1.561 (6)	C7—C8	1.567 (7)
C1—C2	1.566 (6)	C8—C9	1.551 (6)
C2—C3	1.561 (6)	C9—C10	1.522 (7)
C3—C4	1.551 (5)	C10—C11	1.509 (6)
C3—C8	1.579 (5)	C11—C12	1.343 (7)
C4—C20	1.529 (6)	C11—C15	1.530 (7)
C5—O5	1.456 (6)	C12—C13	1.524 (7)
C5—C6	1.523 (7)	C13—C14	1.548 (7)
O5—C20	1.444 (6)		
C14—C1—C15	111.1 (4)	C6—C7—C8	111.4 (4)
C14—C1—C2	111.6 (4)	C9—C8—C7	102.2 (3)
C15—C1—C2	111.3 (4)	C19—C8—C3	113.8 (3)
C3—C2—C1	118.8 (3)	C9—C8—C3	115.8 (3)
C4—C3—C2	111.7 (3)	C7—C8—C3	105.4 (3)
C4—C3—C8	110.3 (3)	C10—C9—C8	122.9 (4)
C2—C3—C8	116.0 (3)	C11—C10—C9	113.2 (3)
C20—C4—C5	85.8 (3)	C12—C11—C10	120.5 (4)
C20—C4—C3	120.4 (3)	C12—C11—C15	120.0 (4)
C5—C4—C3	120.8 (3)	C10—C11—C15	119.2 (4)
O5—C5—C6	113.7 (4)	C11—C12—C13	119.5 (4)
O5—C5—C4	90.8 (4)	C12—C13—C14	111.5 (4)
C6—C5—C4	119.2 (4)	C1—C14—C13	118.1 (4)
C20—O5—C5	91.8 (3)	C11—C15—C1	106.2 (4)
C7—C6—C5	113.5 (4)	O5—C20—C4	91.4 (3)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···O1*B*	0.90	1.98	2.865 (10)	166
O1—H1···O1*C*	0.90	1.75	2.631 (16)	165
O7—H7···O1*A*	0.96	1.73	2.678 (8)	169
O13—H13···O9^{i}	0.99	2.19	3.128 (7)	156
O10—H10···O9	0.76	2.10	2.581 (5)	122

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

The National Institutes of Health of the Department of Health and Human Services supported this work under grant GM08521–38. Bristol–Myers Squibb provided the 10-deacetyl baccatin III used in this study as a gift to FGW.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1143). Services for accessing these data are described at the back of the journal.

References

Bruker (1997). *XSCANS*. Version 2.21. Bruker AXS Inc., Madison, Wisconsin, USA.
Castellano, E. E. & Hodder, O. J. R. (1973). *Acta Cryst.* B**29**, 2566–2570.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Gabetta, B., Bellis, P. D. & Pace, R. (1995). *J. Nat. Prod.* **58**, 1508–1514.
Gao, Q. & Chen, S.-H. (1996). *Tetrahedron Lett.* **37**, 3425–3428.
Gao, Q. & Golik, J. (1995). *Acta Cryst.* C**51**, 295–298.
Gao, Q. & Parker, W. L. (1996). *Tetrahedron*, **52**, 2291–2300.
Gueritte-Voegelein, F., Guenard, D., Mangatal, L., Potier, P., Guilhem, J., Cesario, M. & Pascard, C. (1990). *Acta Cryst.* C**46**, 781–784.
Harper, J. K. & Grant, D. M. (2000). *J. Am. Chem. Soc.* **122**, 3708–3714.
Mastropaolo, D., Camerman, A., Luo, Y., Brayer, G. D. & Camerman, N. (1995). *Proc. Natl Acad. Sci. USA*, **92**, 6920–6924.
Sheldrick, G. M. (1994). *SHELXTL/PC*. Version 5.03. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.