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X-ray Structure Analysis Online

Structure of Etoposide

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The title compound, $C_{29}H_{32}O_{13}$, is a potent antitumor drug. Its crystal belongs to space group $P2_1$ with cell dimensions a = 11.527(4), b = 6.215(2), c = 21.670(7)Å, and β = 100.60(3)°. The final R value is 0.099. The characteristic four-ring system of the aglycone moiety takes a slightly curved structure with the dihedral angle between the two five-membered rings at both ends being 12(1)°. Both the pyranose and 1,3-dioxane rings take chair conformations.

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The chemical structure of etoposide [(9-[(4,6-*O*-ethylidene-*β*-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one)] is shown in Fig. 1. Etoposide forms a ternary complex with topoisomerase II and DNA, leading to an accumulation of DNA breaks, and finally cell death.[1] Etoposide is used primarily for treating testicular tumors and small cell carcinoma of the lung. Although the structure of the aglycone moiety was reported,[2] the structure of the glycoside has not been determined so far. Since etoposide is a potential anticancer drug that is clinically used now, it is important to disclose its inherent three-dimensional structure.

Etoposide was purchased from Sigma Co. Colorless platelet single crystals of the molecule were grown from a methanol solution. It was very difficult to obtain large crystals of good quality. In addition, the obtained crystals were very fragile. The crystal (0.3 × 0.1 × 0.07 mm) was mounted on a glass fiber and used for data collection. The crystal was the biggest ever obtained. The structure was solved by direct methods and refined by a full-matrix least-squares method. Three water molecules of crystallization were found during the X-ray analysis. All of them were disordered and the occupancy factors were less than 1.0 (0.25, 0.35, 0.40, respectively). Due to the disordered water molecule and the small and poorly diffracting crystal, the number of significant reflections observed was fairly small. Although oxygen atoms were refined anisotropically, carbon atoms were refined isotropically to fulfill the requirement of the crystallographic refinement. The hydrogen atoms of the hydroxyl groups and water molecules could not be located. The positions of other H-atoms were geometrically calculated, and not refined. The absolute configuration of the molecule was suggested by referring to that of D-glucose. The crystal and experimental data are given in Table 1.

The molecular structure with the ring labeling system drawn by ORTEP-III[5] is shown in Fig. 2. Selected bond lengths and bond angles are given in Table 2. Both the pyranose and 1, 3-dioxane rings take chair conformations. Binding of the sugar moiety brings about a significant conformational difference in the aglycone moiety. The torsion angles in rings A, C and D are given in Table 3 together with the corresponding values in the aglycone crystal.[2] Rings C in both structures take half-chair conformations. However, the torsion angles around C6, C9 and

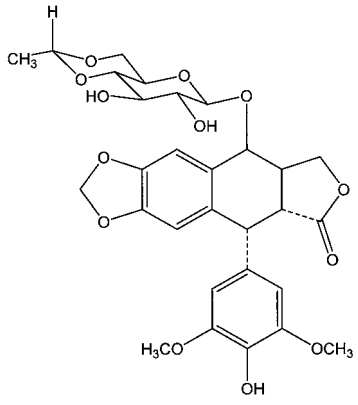

Fig. 1 Chemical structure of Etoposide.

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Table 1 Crystal and experimental data

Formula: $C_{29}H_{32}O_{13}\cdot H_2O$	
Formula weight = 606.58	
Crystal system: monoclinic	
Space group: $P2_1$	Z = 2
a = 11.527(4)Å	
b = 6.215(2)Å	β = 100.60(3)°
c = 21.670(7)Å	
V = 1526.0(9)Å^3	
D_x = 1.320 g/cm^3	
No. of observations (I>3.00σ(I)) = 1150	
θ_{max} = 68.22° with Cu K_a	
R(I>3.00σ(I)) = 0.099	
$(\Delta\sigma)_{max}$ = 0.000	
$(\Delta\rho)_{max}$ = 0.40 eÅ^3	
$(\Delta\rho)_{min}$ = – 0.30 eÅ^3	
Measurement: Rigaku RAXIS-RAPID	
Program system: CrystalStructure 3.6.0[3]	
Structure determination: SIR92[4]	
Refinement: full-matrix	
CCDC No.630746	

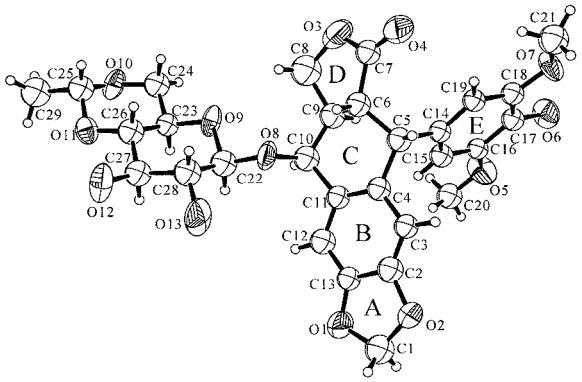

Fig. 2 Molecular structure of Etoposide along with the labeling atoms. Thermal ellipsoids of non-H atoms are drawn at the 40% probability level.

Table 2 Selected bond lengths (Å), bond angles (°) and torsion angles (°)

O(1)—C(1)	1.44(2)	O(1)—C(13)	1.36(2)
O(2)—C(1)	1.45(2)	O(2)—C(2)	1.44(2)
O(3)—C(7)	1.34(2)	O(3)—C(8)	1.49(2)
O(4)—C(7)	1.21(2)	O(6)—C(17)	1.36(2)
O(7)—C(21)	1.41(2)	O(8)—C(10)	1.47(2)
O(8)—C(22)	1.39(2)	O(9)—C(22)	1.52(2)
O(9)—C(23)	1.43(2)	O(10)—C(24)	1.38(2)
O(10)—C(25)	1.35(2)	O(11)—C(25)	1.45(2)
O(11)—C(26)	1.41(2)	O(12)—C(27)	1.41(2)
O(13)—C(28)	1.47(2)		
O(1)—C(1)—O(2)	109(2)	C(13)—O(1)—C(1)	106(1)
O(1)—C(13)—C(2)	113(1)	O(1)—C(13)—C(12)	128(2)
C(2)—O(2)—C(1)	105(1)	O(2)—C(2)—C(3)	129(2)
O(2)—C(2)—C(13)	107(1)	O(3)—C(7)—O(4)	123(2)
O(3)—C(7)—C(6)	108(2)	C(8)—O(3)—C(7)	110(2)
O(3)—C(8)—C(9)	105(2)	O(4)—C(7)—C(6)	130(2)
O(8)—C(10)—C(9)	113(1)	O(8)—C(10)—C(11)	106(1)
C(22)—O(8)—C(10)	116(1)	O(8)—C(22)—O(9)	107(1)
O(8)—C(22)—C(28)	111(2)	C(23)—O(9)—C(22)	111(1)
O(9)—C(22)—C(28)	110(2)	O(9)—C(23)—C(24)	110(1)
O(9)—C(23)—C(26)	112(1)	O(10)—C(24)—C(23)	114(1)
C(25)—O(10)—C(24)	112(1)	O(10)—C(25)—O(11)	111(1)
O(10)—C(25)—C(29)	111(2)	C(26)—O(11)—C(25)	110(1)
O(11)—C(25)—C(29)	106(1)	O(11)—C(26)—C(23)	113(2)
O(11)—C(26)—C(27)	113(1)	O(12)—C(27)—C(28)	113(1)
O(12)—C(27)—C(26)	116(1)	O(13)—C(28)—C(22)	110(1)
O(13)—C(28)—C(27)	110(1)		

C10 are significantly different and the half-chair structure in the aglycone crystal is flatter than that in the glycoside. Ring D in both crystals takes a very similar conformation, being an envelope on C9. Ring A in the glycoside is almost planar. In the aglycone crystal, however, it takes an envelope conformation on C1. Despite these conformational differences, the four-ring systems composed of rings A, B, C and D in both structures are similarly curved with the dihedral angles between the least-squares planes of the A and D rings being 12(1) and 17.9(3)° in the glycoside and aglycone crystals, respectively.

Table 3 Torsion angles(°) in rings A, C and D

	glycoside	aglycone[2]
Ring A		
O1-C1-O2-C2	-6(2)	17.8(6)
C1-O2-C2-C13	5(2)	-11.0(6)
O2-C2-C13-O1	-2(2)	0.3(6)
C2-C13-O1-C1	-2(2)	10.8(6)
C13-O1-C1-O2	5(2)	-17.6(6)
Ring C		
C4-C5-C6-C9	-50(2)	-53.1(4)
C5-C6-C9-C10	69(2)	68.0(5)
C6-C9-C10-C11	-50(2)	-46.1(5)
C9-C10-C11-C4	20(2)	18.2(6)
C10-C11-C4-C5	-5(2)	-7.5(6)
C11-C4-C5-C6	20(2)	24.1(5)
Ring D		
O3-C8-C9-C6	33(2)	32.6(4)
C8-C9-C6-C7	-33(1)	-31.0(4)
C9-C6-C7-O3	21(2)	19.3(5)
C6-C7-O3-C8	2(2)	1.9(5)
C7-O3-C8-C9	-23(2)	-22.4(4)

The dihedral angles between rings B and E are 83(1) and 88.5(2)° in the glycoside and aglycone crystals, respectively. The exocyclic bond angles around the C10 atom are significantly influenced by binding of the sugar moiety. All of the bond lengths and angles in the molecule are within the expected ranges.

Because the hydrogen atoms of the hydroxyl groups could not be located, it is not possible to describe the hydrogen bonds in which the hydroxyl groups are involved. The intermolecular O···O distances, however, indicate that all of the hydroxyl groups are involved in the intermolecular hydrogen bonds.

Acknowledgements

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