Crystal and Molecular Structure of 18α-Glycyrrhetinic Acid

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The crystal structure of 18α-glycyrrhetinic acid (*trans* junction of the D/E rings) has been determined in order to compare its stereochemical features with those of the known 18β form (*cis* junction of the D/E rings). The two stereoisomers exhibit different physiological actions. A comparison of their common moieties shows significant differences between the conformations of the unsaturated C ring, with some torsion angles differing by more than ten degrees. Further differences involve the convexity of the ABCD region, which in the α form is smaller than that observed in the β isomer, and smaller than that reported for the mean steroid configuration.

Glycyrrhizin, one of the main components of the root of *Glycyrrhiza glabra* L., has antiinflammatory, antiallergenic,[1] antiulcerous,[2] antihepatotoxic[3] activity, and shows steroid-like action.[4,5] The antiinflammatory activity is mainly attributable to the action of its aglycone, glycyrrhetinic acid (GA). GA exists as two stereoisomers, 18α-GA (3β-hydroxy-11-oxo-18α-olean-12-en-30-oic acid) with a *trans* D/E ring junction, and 18β-GA with a *cis* D/E ring junction. Recent studies have reported that 18α-GA and 18β-GA both exhibit physiological actions but following different mechanisms. Amagaya *et al.* reported that the antiinflammatory activity of 18α-GA is significantly stronger than that of 18β-GA,[6] whereas its antihepatotoxic activity was found to be significantly less.[3] The crystal structure determination of 18α-GA was carried out in order to compare its stereochemical features with those of the known 18β form, the structure of which has been determined as a water and acetone solvate in a 1 : 1 : 1 ratio.[7]

Table 1 Bond distances (Å) and bond angles (°)

C(1)–C(2)	1.530(9)	C(1)–C(10)	1.576(9)
C(2)–C(3)	1.52(1)	C(3)–C(4)	1.55(1)
C(3)–O(1)	1.432(8)	C(4)–C(5)	1.568(8)
C(4)–C(23)	1.54(1)	C(4)–C(24)	1.54(1)
C(5)–C(6)	1.52(1)	C(5)–C(10)	1.548(9)
C(6)–C(7)	1.530(9)	C(7)–C(8)	1.541(9)
C(8)–C(9)	1.558(9)	C(8)–C(14)	1.597(9)
C(8)–C(25)	1.550(9)	C(9)–C(10)	1.577(8)
C(9)–C(11)	1.519(9)	C(10)–C(26)	1.543(9)
C(11)–C(12)	1.452(9)	C(11)–O(2)	1.228(8)
C(12)–C(13)	1.330(9)	C(13)–C(14)	1.531(9)
C(13)–C(18)	1.529(9)	C(14)–C(15)	1.560(9)
C(14)–C(27)	1.564(9)	C(15)–C(16)	1.532(9)
C(16)–C(17)	1.53(1)	C(17)–C(18)	1.533(9)
C(17)–C(22)	1.54(1)	C(17)–C(28)	1.52(1)
C(18)–C(19)	1.535(9)	C(19)–C(20)	1.533(9)
C(20)–C(21)	1.53(1)	C(20)–C(29)	1.53(1)
C(20)–C(30)	1.53(1)	C(21)–C(22)	1.53(1)
C(30)–O(3)	1.321(8)	C(30)–O(4)	1.196(9)
C(2)–C(1)–C(10)	113.1(5)	C(1)–C(2)–C(3)	110.4(6)
C(2)–C(3)–C(4)	112.9(6)	C(2)–C(3)–O(1)	107.5(5)
C(4)–C(3)–O(1)	112.6(5)	C(3)–C(4)–C(5)	107.2(5)
C(3)–C(4)–C(23)	107.3(5)	C(3)–C(4)–C(24)	111.8(5)
C(5)–C(4)–C(23)	108.2(5)	C(5)–C(4)–C(24)	113.8(5)
C(23)–C(4)–C(24)	108.2(6)	C(4)–C(5)–C(6)	116.1(5)
C(4)–C(5)–C(10)	115.7(5)	C(6)–C(5)–C(10)	109.4(5)
C(5)–C(6)–C(7)	110.9(6)	C(6)–C(7)–C(8)	112.4(5)
C(7)–C(8)–C(9)	109.4(5)	C(7)–C(8)–C(14)	109.6(5)
C(7)–C(8)–C(25)	109.1(5)	C(9)–C(8)–C(14)	109.2(5)
C(9)–C(8)–C(25)	110.7(5)	C(14)–C(8)–C(25)	108.8(5)
C(8)–C(9)–C(10)	117.0(5)	C(8)–C(9)–C(11)	108.3(5)
C(10)–C(9)–C(11)	115.1(5)	C(1)–C(10)–C(5)	107.3(5)
C(1)–C(10)–C(9)	106.5(5)	C(1)–C(10)–C(26)	108.4(5)
C(5)–C(10)–C(9)	106.8(5)	C(5)–C(10)–C(26)	114.4(5)
C(9)–C(10)–C(26)	113.0(5)	C(9)–C(11)–C(12)	116.6(5)
C(9)–C(11)–O(2)	124.9(6)	C(12)–C(11)–O(2)	118.6(6)
C(11)–C(12)–C(13)	124.3(6)	C(12)–C(13)–C(14)	121.9(6)
C(12)–C(13)–C(18)	121.0(6)	C(14)–C(13)–C(18)	117.1(5)
C(8)–C(14)–C(13)	111.2(5)	C(8)–C(14)–C(15)	110.8(5)
C(8)–C(14)–C(27)	111.2(5)	C(13)–C(14)–C(15)	110.7(5)
C(13)–C(14)–C(27)	107.3(5)	C(15)–C(14)–C(27)	105.4(5)
C(14)–C(15)–C(16)	113.1(6)	C(15)–C(16)–C(17)	111.6(6)
C(16)–C(17)–C(18)	107.6(5)	C(16)–C(17)–C(22)	108.2(6)
C(16)–C(17)–C(28)	111.7(6)	C(18)–C(17)–C(22)	107.0(6)
C(18)–C(17)–C(28)	111.6(6)	C(22)–C(17)–C(28)	110.5(6)
C(13)–C(18)–C(17)	112.1(5)	C(13)–C(18)–C(19)	114.1(5)
C(17)–C(18)–C(19)	112.6(5)	C(18)–C(19)–C(20)	113.6(5)
C(19)–C(20)–C(21)	110.6(6)	C(19)–C(20)–C(29)	110.8(6)
C(19)–C(20)–C(30)	110.2(6)	C(21)–C(20)–C(29)	110.7(6)
C(21)–C(20)–C(30)	104.0(6)	C(29)–C(20)–C(30)	110.4(6)
C(20)–C(21)–C(22)	112.6(6)	C(17)–C(22)–C(21)	112.7(6)
C(20)–C(30)–O(3)	112.7(6)	C(20)–C(30)–O(4)	124.4(6)
O(3)–C(30)–O(4)	122.9(7)		

Results and Discussion

Bond distances and bond angles are given in Table 1, the atoms and rings being labelled as shown in Fig. 1. Rings A, B, D and E adopt the expected chair conformation, whereas the unsaturated C ring adopts a distorted half-chair conformation with $\Delta C = 3.37°$.[8,9] C(8) and C(9) are displaced -0.448 and $+0.336$ Å, respectively, from the mean plane through the other four ring atoms, coplanar within ±0.008 Å. As expected, all ring junctions are *trans*. Bond distances compare well with those of the 18β-GA, in particular the longer C–C bonds, which in both cases involve mainly the –C(4)–C(5)–C(10)–C(9)–C(8)–C(14)–C(15)– fragment. Particularly relevant is the lengthening of the C(8)–C(14) bond in the C ring, with values of 1.597(9) and 1.592(5) Å for the α and β form, respectively. The main differences between the common moieties of the 18α- and 18β-GA (from ring A to ring D) concern the conformation of the C ring, with some torsion angles differing more than 10°. In the 18α-GA, the torsion angles about C(8)–C(14) and C(14)–C(13) bonds are 47.0(6) and $-16.2(8)°$, respectively, whereas in the β form they are 58.3 $-28.1°$. There is also a significant difference between the convexities of the ABCD region, which may be expressed in terms of height and angles of the O(1)C(26)C(16) triangle;[7] the values found are 2.84 Å and 120.7°, as opposed to 2.98 Å and 117.7° observed for 18β-GA, whereas the mean experimental values for steroids are 3.07 Å and 114.9°.[7] As expected, the molecular packing is completely different from that observed in 18β-GA, the water and acetone solvate molecules of which play an important role in determining the crystal packing. In our case, each molecule is linked to four

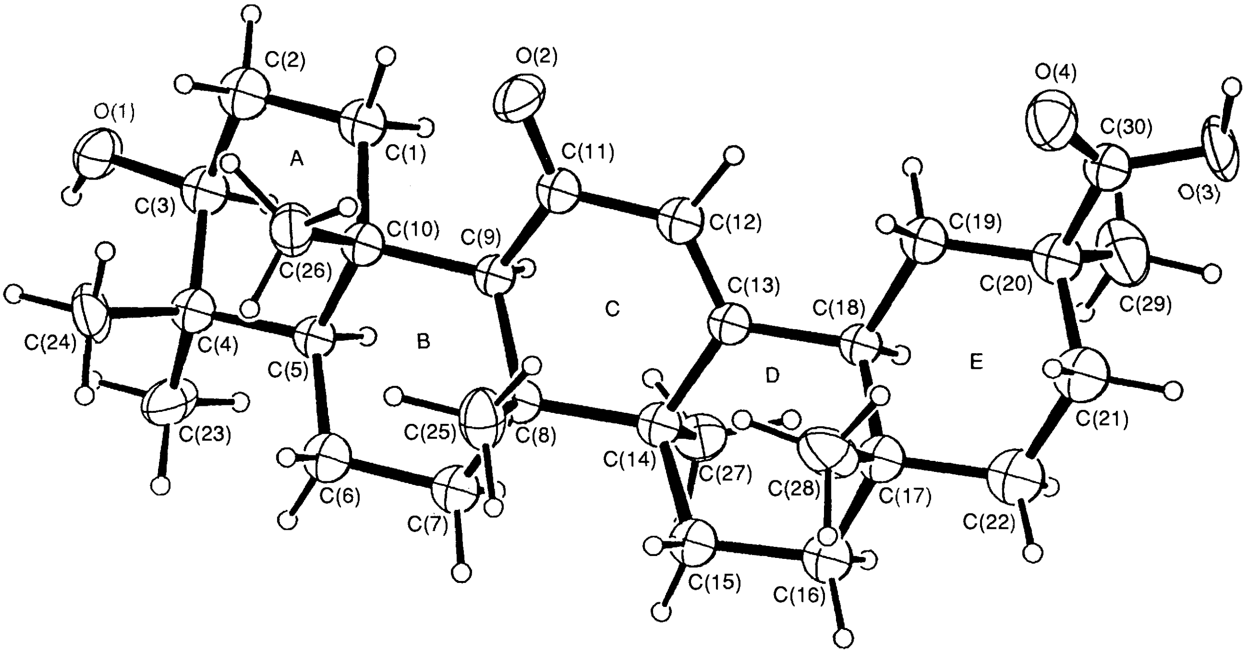

Fig. 1 ORTEP[11] drawing of the molecule with atom and ring labelling scheme. Thermal ellipsoids for non-H atoms enclose 50% probability.

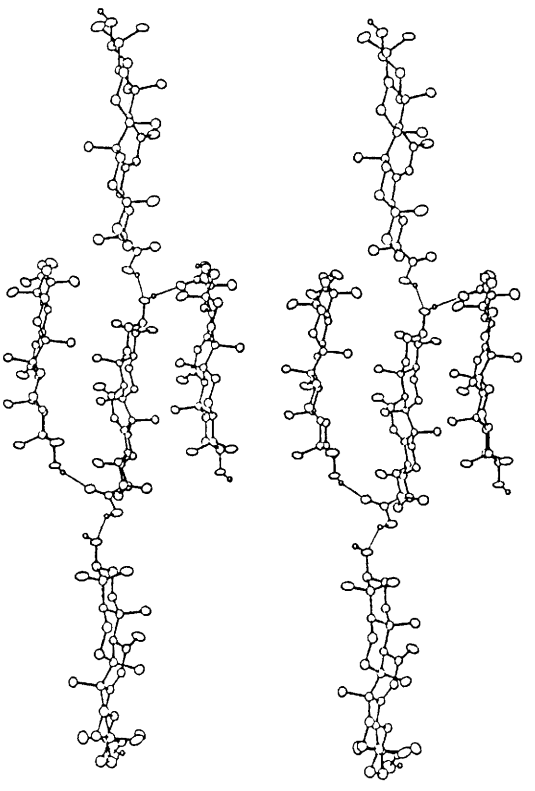

Fig. 2 Stereoview of the molecular packing. Still lines represent hydrogen bonds.

neighbouring molecules through hydrogen bonds involving the carbonyl and hydroxy functions, both of which act as bridging groups (Fig. 2). The strongest interaction involves the carboxy hydrogen [H(O3) ··· O(1) = 2.02 Å, O(3) ··· O(1) = 2.787(7) Å, ∠O(3)–H(O3) ··· O(1) = 142°] and links the molecules in linear chains parallel to the *c* axis. The weakest one occurs between the hydroxy hydrogen and the second carboxy oxygen [H(O1) ··· O(4) = 2.29 Å, O(1) ··· O(4) = 3.153(7) Å, ∠O(1)–H(O1) ··· O(4) = 168°], and, linking the molecules along the *b* axis, determines a two-dimensional network in the *bc* plane. There are few intermolecular contacts < 3.60 Å between the individual layers.

Experimental

18α-GA was purchased from Sigma (St Louis, MO, USA). All solvents were of analytical grade and were obtained from BDH (Milan, Italy).

Well-shaped but rather small crystals were obtained from very slow evaporation at room temperature of a chloroform–acetone solution of 18 α-GA.

Crystal Data.—$C_{30}H_{46}O_4$, $M = 470.34$, orthorhombic, $a = 7.835(1)$, $b = 10.489(1)$, $c = 30.393(3)$ Å, $U = 2497.7(6)$ Å^3 (by least-squares refinement on diffractometer angles of 25 automatically centred reflections, $\lambda = 0.710\,69$ Å), space group $P2_12_12_1$ (No. 19), $Z = 4$, $D_c = 1.251$ g cm^{-1}, $F(000) = 1032$. Colourless, air-stable plates. Crystal dimensions 0.32 × 0.20 × 0.07 mm, μ(Mo-Kα) 0.44 cm^{-1}.

Data Collection and Processing.—CAD4 diffractometer, ω–2θ mode with ω scan width = $(0.50 + 0.35 \tan \theta)°$, ω scan speed 1.0–2.7° min^{-1}, graphite-monochromated Mo-Kα radiation: 2540 unique reflections measured ($1.5 \leqslant \theta/° \leqslant 25$; $+h$, $+k$, $+l$) giving 1383 with $I \geqslant 2\sigma(I)$. Empirical absorption correction based on the ψ scan[8] (max., min. transmission factors = 0.96, 0.93). No crystal decay during data collection.

Structure Analysis and Refinement.—Direct methods (SHELX 86[9]) and full-matrix least-squares refinements (SHELX 76[10]). Oxygen and methyl carbons anisotropic, all other C atoms isotropic (because of the low reflection: parameter ratio). All H atoms located in ΔF maps, and then fitted at ideal positions (C–H = 1.05 Å), except O-bonded hydrogens maintained in observed positions. The weighting scheme $w = 1.18/[\sigma^2(F_o) + 0.0029F_o^2]$ with $\sigma(F_o)$ from counting statistics gave satisfactory agreement analyses. Final R and R' value were 0.055 and 0.061. No attempts were made to determine the absolute configuration. For the sake of easier comparison, we have assumed the configuration to be the same as 18β-GA, the absolute configuration of which has not actually been established.

Table 2 Final fractional co-ordinates

Atom	*x*	*y*	*z*
C(1)	−0.0345(9)	0.4893(6)	0.8175(2)
C(2)	−0.0283(9)	0.4853(7)	0.8678(2)
C(3)	0.1200(9)	0.4038(7)	0.8832(2)
O(1)	0.1116(6)	0.3971(5)	0.9302(1)
C(4)	0.2945(9)	0.4526(6)	0.8666(2)
C(5)	0.2840(9)	0.4593(6)	0.8151(2)
C(6)	0.4487(9)	0.4932(6)	0.7913(2)
C(7)	0.4394(9)	0.4550(6)	0.7427(2)
C(8)	0.2923(8)	0.5220(6)	0.7183(2)
C(9)	0.1249(8)	0.5086(6)	0.7455(2)
C(10)	0.1358(9)	0.5401(6)	0.7962(2)
C(11)	−0.0176(9)	0.5760(6)	0.7209(2)
O(2)	−0.1277(7)	0.6426(5)	0.7380(2)
C(12)	−0.0262(9)	0.5539(6)	0.6737(2)
C(13)	0.0971(8)	0.4993(6)	0.6503(2)
C(14)	0.2659(9)	0.4575(6)	0.6712(2)
C(15)	0.4188(9)	0.4883(6)	0.6401(2)
C(16)	0.385(1)	0.4510(7)	0.5921(2)
C(17)	0.2268(9)	0.5171(6)	0.5739(2)
C(18)	0.0735(8)	0.4723(6)	0.6012(2)
C(19)	−0.0974(9)	0.5190(6)	0.5825(2)
C(20)	−0.125(1)	0.4828(7)	0.5342(2)
C(21)	0.031(1)	0.5187(7)	0.5066(2)
C(22)	0.198(1)	0.4696(7)	0.5264(2)
C(23)	0.429(1)	0.3520(8)	0.8791(2)
C(24)	0.345(1)	0.5795(7)	0.8884(2)
C(25)	0.339(1)	0.6643(7)	0.7117(2)
C(26)	0.150(1)	0.6842(7)	0.8056(2)
C(27)	0.2616(9)	0.3088(6)	0.6748(2)
C(28)	0.245(1)	0.6613(8)	0.5748(2)
C(29)	−0.165(1)	0.3409(8)	0.5297(3)
C(30)	−0.2697(9)	0.5627(7)	0.5144(2)
O(3)	−0.3428(7)	0.5067(5)	0.4803(2)
O(4)	−0.3094(7)	0.6666(5)	0.5269(3)

Scattering factors were from SHELX 76.[10] All calculations were carried out on a VAX 6310 computer. Final atomic co-ordinates for non-H atoms are given in Table 2. Full lists of atomic temperature factors, positional and thermal parameters for H atoms, selected least-squares planes and torsion angles have been deposited at the Cambridge Crystallographic Data Centre.*

Acknowledgements

We thank the *Centro Interdipartimentale Grandi Strumenti* of Modena University for the X-ray data collection, and the *Centro Interdipartimentale di Calcolo Automatico e Informatica Applicata* for computing facilities.

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Paper 1/03049C
Received 20*th June* 1991
Accepted 12*th September* 1991

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* For details of the CCDC deposition scheme, see 'Instructions for Authors (1992)', *J. Chem. Soc., Perkin Trans. 2*, issue 1.