Crystal Structure and Conformation of Pakyonol, a Macrocyclic Bis(bibenzyl) Constituent of *Mannia fragrans*

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An X-ray analysis of the crystal structure of the title compound has been carried out. For the bond length of one of the ethylene bridges an unreasonably low value was calculated probably due to disorder in the crystal. The disorder was revealed by means of molecular mechanics calculations, which also threw light on further details of the conformational behaviour of the ring system.

Extensive ethnomedicinal use of liverwort extracts in Europe and Asia[1] has prompted the isolation of pure components. In addition to terpenoids and lipids macrocyclic bis(bibenzyls) are characteristic phenolic constituents of liverwort species.[2] The structure of pakyonol—a bis(bibenzyl) constituent of *Mannia fragrans*—has been elucidated by Huneck *et al.*[3] and synthesised by Nógrádi *et al.*[4] A remarkable feature of pakyonol is the highly strained macrocyclic ring caused by two *meta*,*para*-diaryl ether units. As a continuation of our work on the conformation of cyclic bis(benzyls)[5] we now report the solid-state conformational analysis of pakyonol.

Results and Discussion

Owing to the small size and the subsequently discovered disorder in the crystal, the collected data are not better than 1 Å in resolution despite the patient data collection. When we first solved and partially refined the structure from the structural parameters, it seemed obvious that there was a double bond between the atoms C(23) and C(24) (Table 1 and Fig. 1). This was contradicted by the NMR data and the synthetic methodology. To clarify this anomaly, molecular-mechanics calculations[6] were carried out and a conformational-energy curve was plotted (Fig. 2) as a function of C(20)–C(23)–C(24)–C(25) dihedral angle (θ). θ was incremented in steps of 10° in the 360° space. The potential-energy curve indicated two conformers deviating almost symmetrically from the structure yielded by X-ray crystallography.

Having considered the thermal motion parameters B_{iso} as determined by X-ray crystallography we noticed some unusually high values in the disputed structural region (Table 2). This systematic change in B_{iso} values, i.e. the increase on going from C(28) towards the undetermined structural feature, suggested the presence of two conformers in the crystal structure that could not be resolved owing to relatively low resolution and the small differences between the two structures. The lack of the resolution of the two structures results in averaging and leads to the observed unrealistic C(23)–C(24) bond length.

To lend support to this hypothesis we fitted the two structures produced by the molecular-mechanics calculation disregarding the atoms supposed to be involved in the conformational motion (Fig. 3). In fact, almost perfect fit was found for atoms from O(1) to C(22) and O(31) to C(32), while those from C(23) to C(28) seemed to assume two energetically equally probable conformations with the largest difference at C(24) as suggested by the thermal-motion parameters. The interconversion of the two conformations can conveniently be explained as the rigid-body rotation of the O(1)–C(24) fragment of the molecule around the O(1)–C(2) bond axis by about 120°

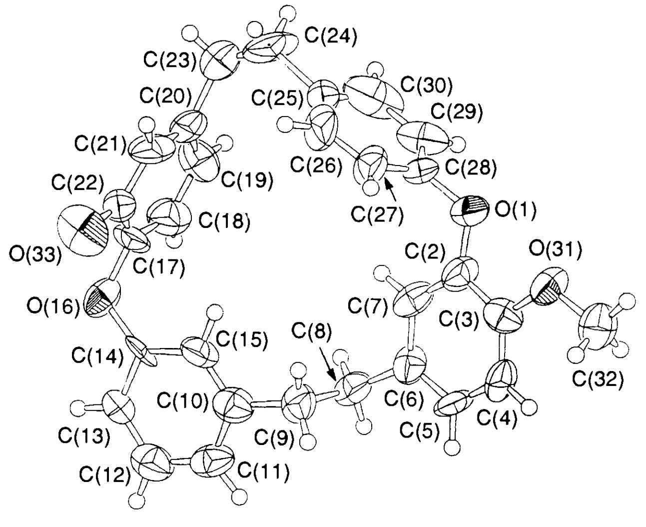

Fig. 1 The structure of pakyonol as determined from the weak dataset of diffracted intensities alone

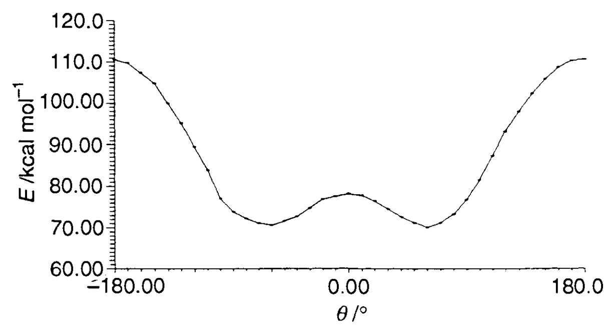

Fig. 2 Calculated potential-energy curve of pakyonol

Table 1 Selected structural parameters of pakyonol as determined by a 'standard' crystallographic procedure

Bond length/Å	C(20)–C(23) 1.55(2) C(23)–C(24) 1.23(2) C(24)–C(25) 1.51(3)
Bond angle/deg	C(20)–C(23)–C(24) 128(2) C(23)–C(24)–C(25) 127(2)
Torsion angle/deg	C(20)–C(23)–(24)–C(25) 10(6)

(*i.e.*, 60° both directions from the crystallographic or average structure).

Lists of atomic coordinates, bond lengths, bond angles, torsion angles and thermal parameters have been deposited in separate tables and are available on request from the Cambridge Crystallographic Data Centre.*

The most interesting feature of the solid-state structure of pakyonol is the relative orientation of the four rings and the connecting bridges. Table 3 shows the interplanar angles formed by the four rings and permits the following conclusions. (1) The *meta*-substituted rings are nearly coplanar and the connecting ethylene bridge is in an antiperiplanar conformation. (2) The planes of the *meta*- and *para*-substituted rings are perpendicular. The connecting ether oxygens seem to show a slight delocalisation of their non-bonding pairs (*cf.*, bond lengths and angles). (3) The *para*-substituted rings form an angle of 78° in the disordered crystal structure. The connecting ethylene bridges are in (+) and (−) *gauche* conformations, respectively.

The packing of the molecules in the crystal seems to be governed by two major factors: (1) Along the crystal axis *a* there is a linear chain of hydrogen-bonded molecules. The hydrogen bond is formed between the O(33)–H(26)•••O(1) atoms and can be characterised with an O(33)•••O(1) non-bonding distance of 3.01(1) Å and an O(33)–H(26)•O(1) angle of 160°. (2) The linear chains of the neighbouring unit cells form a plated sheet which presents spatial complementarity to the neighbouring sheets formed by symmetrically related molecules.

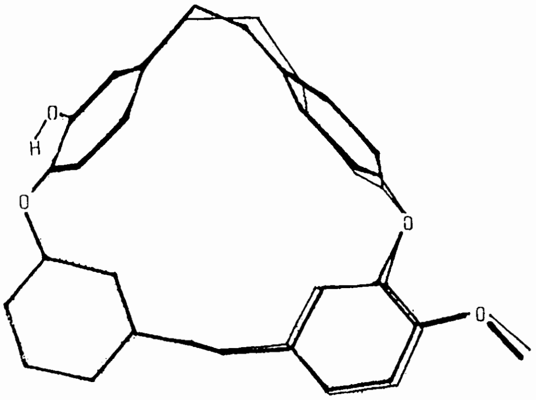

Fig. 3 Superposition of the two lowest-energy conformers of pakyonol

Table 2 B_{iso} thermal parameters as determined by the X-ray diffraction (see Fig. 1)

Atom	B_{iso}
C(30)	10(1)
C(29)	7(1)
C(28)	4.8(7)
C(27)	5.6(9)
C(26)	8(1)
C(25)	10(2)
C(24)	21(2)
C(23)	9(1)
C(20)	5.4(8)

Experimental

Crystals of this kind of compound seem to be fairly hard to obtain and small crystals of the title compound could only be formed by slow evaporation of methanol from the solution.

Crystal Data.—$C_{29}O_4H_{26}$, $M = 438.52$. Orthorhombic, $a = 10.967(3)$ Å, $b = 26.260(3)$ Å, $c = 8.443(3)$ Å, $V = 2431.7(8)$ Å^3, by least-squares refinement on diffractometer angles for 24 automatically centred reflections in the range $41.3 < 2\theta < 52.9$, Cu-Kα radiation ($\lambda = 1.541\ 78$ Å), space group $P2_12_12_1$, $Z = 4$, $D_{calc} = 1.198$ g cm^{-3}. Transparent columns. Crystal dimensions 0.15 × 0.08 × 0.07 mm, $\mu = 5.01$ cm^{-1}.

Data Collection and Processing.—Data were collected on a Rigaku AFC6S (sealed tube) diffractometer using the ω–2θ scan technique with a scan rate 4.0 deg m^{-1} (in omega) and a scan range of $(1.68 + 0.30 \tan\theta)°$. 2837 reflections were measured ($0 < 2\theta < 150$) 1088 with $I > 1.5\sigma(I)$. Three standard reflections were measured after each 150 reflections and showed no change in intensity. The intensities were corrected for Lorentz and polarisation effects.

Structure Analysis and Refinement.—Structure solution was by direct methods using the SAPI91 program[7] in the TEXSAN package,[8] structure expansion was by Fourier techniques.[9] The refinement was carried out by full-matrix least-squares on $|F|$. The function minimised was $\Sigma w(|F_o| - |F_c|)$. All hydrogen atoms were placed in calculated positions using a riding model. A DIFABS[10] absorption correction was applied. All non-hydrogen atoms were refined with anisotropic thermal parameters. Calculations were carried out on a Silicon Graphics R3000 workstation. The final cycle of the refinement included 319 variables and converged with $R = 0.066$ and $R_w = 0.092$ for the 1088 reflections with $I > 1.5\sigma(I)$. The weighting scheme was defined as $w^{-1} = \sigma^2(F)$, final difference Fourier synthesis: $-0.25 < \Delta\rho < 0.24$ e Å^{-}3.

Molecular Mechanics Calculation.—Molecular mechanics calculations were carried out on an IBM 80486 computer using the MM2/MMX program.[6] The potential-energy curve was generated by incrementing θ[C(20)–C(23)–C(24)–C(25)] in the

Table 3 Dihedral angles between least-squares planes

Plane	Atoms defining plane	Mean deviation/Å
1	O(1)–C(2)–C(3)–C(4)–C(5)–C(6)–C(7)–C(8)	0.0296
2	O(16)–C(9)–C(10)–C(11)–C(12)–C(13)–C(14)–C(15)	0.0155
3	O(16)–C(17)–C(18)–C(19)–C(20)–C(21)–C(22)–C(23)	0.0113
4	O(1)–C(24)–C(25)–C(26)–C(27)–C(28)–C(29)–C(30)	0.0168

	ω/deg			
Plane	1	2	3	4
2	11.50			
3	85.38	96.19		
4	94.87	93.37	77.69	

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* For full details of the deposition scheme, see 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1.

360° space in steps of 10°. The steric energy was minimised to within 0.0001 kcal mol^{-1} at each step, the average movement was 0.000 05 Å $atom^{-1}$, the maximum movement was 0.000 23 Å $atom^{-1}$ in the last step of minimisation. The minimum-energy conformers of pakyonol were fitted by the least-squares method (average deviation expected for C(24): 0.19 Å RMS deviation: 0.28 Å), the average deviation for C(24) was 1.4 Å.

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References

1 Y. Asakawa, *Rev. Latinoamer. Quim.*, 1984, **14**, 109.
2 Y. Asakawa in *Progress in the Chemistry of Organic Natural Products* eds. W. Herz, H. Griseback and G. W. Kirby, Springer, New York, 1982, Vol. 42.
3 S. Huneck, J. D. Conolly, D. S. Rycroft and N. Woods, *J. Chem. Res.* (*S*), 1988, 79.
4 M. Nógrádi, B. Vermes, M. Kajtár-Peredy and P. Novikov, *Liebigs Ann. Chem.*, 1990, 299.
5 M. Kajtár-Peredy, G. M. Keserű and M. Nógrádi, *J. Chem. Soc., Perkin Trans. 2*, 1993, 563.
6 MMX is a generalised version of Allinger's MM2 (*QCPE* program Nos. 343 and 318) program, extended by W. Still, adapted to Microsoft FORTRAN by G. Gajewski and K. Gilbert.
7 Fan Hai-Fu (1991) Structure Analysis Programs with Intelligent Control, Rigaku Corporation, Tokyo, Japan.
8 TEXSAN *Crystal Structure Analysis Package*, Molecular Structure Corporation (1985 and 1992).
9 P. T. Beurskens, G. Admiraal, G. Beurkens, W. P. Bosman, S. Garcia-Granada, R. O. Gould, J. M. M. Smlts and C. Smykalla, (1992) The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.
10 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **39**, 158.

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