

The Structure of Dibenz[*b,f*]oxepin

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Abstract

The structure of dibenz[*b,f*]oxepin, $C_{14}H_{10}O$, parent molecule of a group of psychotropic drugs, has been determined by direct methods from 776 X-ray diffractometer data and refined by least squares to a final residual R of 0.115. The space group is orthorhombic, $Pnam$, with $a = 8.236$ (3), $b = 6.115$ (1), $c = 19.667$ (4) Å; $Z = 4$, $V = 990.3$ Å³; $D_m = 1.30$ (1), $D_c = 1.29$ Mg m⁻³. The molecules, located on mirror planes passing through the O atom and the midpoint of the 1.327 (6) Å C(10)–C(11) ethylenic bond, have almost planar benzene rings mutually inclined at a comparatively small dihedral angle of 134 (2)°. The heterocyclic ring, in boat conformation, has a C–O–C bond angle of 115.7 (4)° and C–O bonds of 1.390 (5) Å.

Introduction

Dibenzoxepin (DBO) is the parent molecule of some clinically active psychotropic drugs possessing central-nervous-system depressant activity (Coscia, Causa & Giuliani, 1975). For these and analogous tricyclic dibenzo derivatives, pharmacological action appears to be related to molecular conformation (Rodgers, Horn & Kennard, 1976); their behaviour in solution has been studied by NMR spectroscopy (Drake & Jones, 1978, 1981). As an aid towards estimating the influence of heterocyclic-ring conformation and dihedral angle on the activity of symmetrical dibenzo tricyclics, we have determined the crystal structure of DBO (Drake & Jones, 1977).

Experimental

From dibenzoxepin synthesized by Dr P. M. G. Bavin, SKF Laboratories (Anet & Bavin, 1957), slow evaporation (several days) from chloroform solution at room temperature yielded colourless acicular crystals (ratio of dimensions about 1:2:6) with what proved to be b -axis elongation and (001) cleavage.

X-ray oscillation and Weissenberg photographs taken with Ni-filtered Cu $K\alpha$ radiation showed the unit

cell to be orthorhombic with axial lengths $a = 8.32$, $b = 6.15$, $c = 19.5$ Å, in good agreement with those obtained subsequently by diffractometer (an Enraf–Nonius CAD-4 in the Biophysics Department, Leeds University) from three sets of 14 reflexions (see *Abstract*).

The systematic extinctions, $h0l$ with $h = 2n + 1$ and $0kl$ with $k + l = 2n + 1$, are consistent with two space groups, non-centrosymmetric $Pna2_1$ (C_{2v}^9 , No. 33), with four equivalent general positions, and centrosymmetric $Pnam$ (D_{2h}^{16} , No. 62),* with eight equivalent general positions. A statistical survey (Rogers, 1965) of the E distribution provided convincing evidence for a centric distribution of the intensities. Subsequent refinement was successful in the centrosymmetric space group $Pnam$, for which the four molecules in the cell are positioned on mirror planes through the O atom and the midpoint of the C(10)–C(11) ethylenic bond.

Intensities were collected at room temperature with graphite-monochromated Cu $K\alpha$ radiation in the moving-crystal moving-counter mode, from a crystal $0.4 \times 0.4 \times 0.3$ mm (1.1° angular width of 90% of intensity for typical reflexions) mounted in a Lindemann-glass tube with its b axis along the ϕ axis of the CAD-4 diffractometer. For each reflexion, reflexion intensity and centre background were measured over 2°, with right and left backgrounds a further 0.5° each. Intensities of the control reflexion, 223, measured after every 24 reflexions, were constant to within 6% ($\sigma = 1.3\%$). 938 unique reflexions (θ range 3–70°) were collected. Corrections were applied for Lorentz and polarization effects but not for extinction or absorption ($\mu = 0.65$ mm⁻¹ for Cu $K\alpha$); standard deviations were calculated by a Fortran IV program.

Solution and refinement of the structure

The structure was solved by direct methods with the 1972 version of *MULTAN* (Germain, Main & Woolfson, 1971).

* Corresponding standard space group $Pnma$. Equivalent positions for $Pnam$ are: $\pm(x, y, z)$; $-x, -y, \frac{1}{2} + z$; $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} + z$; $\frac{1}{2} + x, \frac{1}{2} - y, z$.

The 145 E values >1.4 generated 1651 \sum_2 phase relations; an E map for the set with highest CFOM contained plausible positions for all eight non-hydrogen atoms in the asymmetric unit and one spurious peak. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1962). Following full-matrix least-squares refinement with *CRYLSQ* of *XRAY 72* (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) from a residual $R = \sum |F_o| - |F_c| / \sum |F_o|$ of 0.26 to $R = 0.15$ for $Pnam$, all H atoms were clearly identified by a Fourier difference synthesis. Refinement with 772 reflexions [$|F| > 3\sigma(|F|)$] and with unit weighting, anisotropic thermal parameters for non-hydrogen atoms in $Pnam$, and isotropic ones for H atoms in $Pnam$ and for all atoms in $Pna2_1$, reduced R to 0.115 for $Pnam$ and 0.124 for $Pna2_1$. For the non-centrosymmetric space group, however, shifts and errors were much larger than for $Pnam$ so that, although the mirror-plane-averaged $Pna2_1$ parameters are close to those for the $Pnam$ structure, it was concluded that the space group is $Pnam$. Accordingly the final atomic coordinates* in Table 1 and corresponding bond lengths and angles (Tables 2 and 3), uncorrected for any small rotational oscillations (Fig. 1), are for $Pnam$. In the final stages of refinement,

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36285 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final fractional atomic coordinates and equivalent isotropic thermal parameters (\AA^2) (with *e.s.d.*'s in parentheses)

$$B_{eq} = \frac{2}{3}\pi^2 (U_{11} + U_{22} + U_{33}).$$

| | x | y | z | B_{eq} |
|-------|------------|-------------|------------|-----------|
| C(1) | 0.2231 (7) | 0.6552 (9) | 0.3945 (3) | 3.9 (3) |
| C(2) | 0.3139 (8) | 0.5251 (10) | 0.4365 (3) | 4.7 (3) |
| C(3) | 0.3648 (7) | 0.3198 (9) | 0.4146 (3) | 4.3 (3) |
| C(4) | 0.3165 (6) | 0.2461 (9) | 0.3511 (2) | 3.6 (2) |
| O(5) | 0.1626 (6) | 0.2858 (6) | 0.2500 | 3.3 (2) |
| C(11) | 0.0854 (6) | 0.7341 (8) | 0.2837 (2) | 3.5 (2) |
| C(12) | 0.1764 (5) | 0.5878 (7) | 0.3291 (2) | 3.0 (2) |
| C(13) | 0.2213 (6) | 0.3773 (7) | 0.3098 (2) | 3.0 (2) |
| H(1) | 0.175 (5) | 0.793 (7) | 0.410 (2) | 1.1 (1.0) |
| H(2) | 0.359 (6) | 0.575 (9) | 0.481 (3) | 3.5 (1.4) |
| H(3) | 0.441 (6) | 0.219 (8) | 0.443 (2) | 3.5 (1.4) |
| H(4) | 0.359 (5) | 0.110 (7) | 0.334 (2) | 1.4 (1.1) |
| H(11) | 0.025 (5) | 0.840 (6) | 0.309 (2) | 0.3 (0.9) |

Table 2. Bond lengths (with *e.s.d.*'s in parentheses)

| | | | |
|-------------|-------------|-------------|-------------|
| C(1)–C(2) | 1.369 (8) Å | C(12)–C(1) | 1.405 (7) Å |
| C(2)–C(3) | 1.392 (8) | C(11)–C(10) | 1.327 (6) |
| C(3)–C(4) | 1.385 (7) | C(1)–H(1) | 0.98 (4) |
| C(4)–C(13) | 1.385 (7) | C(2)–H(2) | 0.99 (5) |
| C(13)–O(5) | 1.390 (5) | C(3)–H(3) | 1.04 (5) |
| C(13)–C(12) | 1.391 (6) | C(4)–H(4) | 0.96 (4) |
| C(12)–C(11) | 1.468 (6) | C(11)–H(11) | 0.95 (4) |

Table 3. Bond angles (with *e.s.d.*'s in parentheses)

| | | | |
|-------------------|------------|-------------------|------------|
| C(12)–C(1)–C(2) | 122.1 (5)° | C(13)–O(5)–C(14) | 115.7 (4)° |
| C(1)–C(2)–C(3) | 120.1 (5) | C(12)–C(1)–H(1) | 115 (2) |
| C(2)–C(3)–C(4) | 119.1 (5) | C(2)–C(1)–H(1) | 112 (2) |
| C(3)–C(4)–C(13) | 120.2 (5) | C(1)–C(2)–H(2) | 123 (3) |
| C(4)–C(13)–C(12) | 121.8 (4) | C(3)–C(2)–H(2) | 116 (3) |
| C(4)–C(13)–O(5) | 117.4 (4) | C(2)–C(3)–H(3) | 123 (3) |
| O(5)–C(13)–C(12) | 120.7 (4) | C(4)–C(3)–H(3) | 118 (3) |
| C(13)–C(12)–C(1) | 116.6 (4) | C(3)–C(4)–H(4) | 119 (3) |
| C(13)–C(12)–C(11) | 122.3 (4) | C(13)–C(4)–H(4) | 120 (3) |
| C(1)–C(12)–C(11) | 121.1 (4) | C(12)–C(11)–H(11) | 111 (2) |
| C(12)–C(11)–C(10) | 127.4 (4) | C(10)–C(11)–H(11) | 122 (2) |

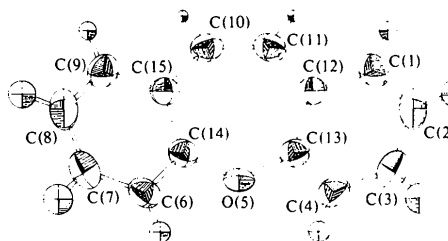


Fig. 1. Geometry of the dibenz[*b,f*]oxepin molecule obtained with *ORTEP* (Johnson, 1965); thermal ellipsoids are drawn at the 50% probability limit.

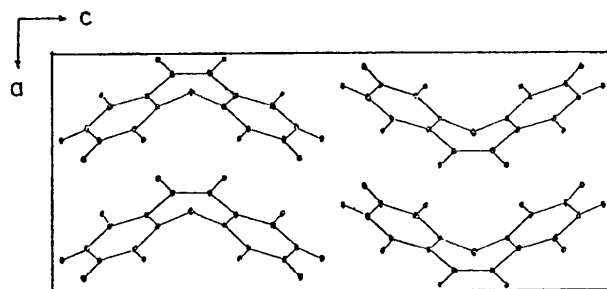


Fig. 2. Molecular packing viewed along b .

weighting $w = 1/\sigma^2(F)$ gave $R'' = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2} = 0.061$.

Description and discussion of the structure

The overall saddle shape of the DBO molecule (Fig. 1) consists of a heterocyclic ring in boat conformation flanked by closely planar benzene rings, the latter having a mutual inclination (below the hull of the boat) of $134 (2)^\circ$; Fig. 2 shows the molecular packing within the unit cell, consistent with easy cleavage parallel to (001). Several tricyclic compounds, inclined and planar, crystallize with closely similar cell dimensions, and with use in the space group of a mirror plane bisecting the central ring (Table 4). Despite the approximate isomorphism of DBO, dibenzazepine (DBA) (Reboul, Cristau, Soyfer & Estienne, 1980; Schäffer, 1971; Wimmer, 1963, quoted in Hoppe, 1969) and phenothiazine (with a six-membered central ring), their crystal structures appear to have been

Table 4. Comparison of crystallographic data for dibenz[*b,f*]oxepin and related compounds

| Compound | Unit-cell dimensions (Å) | Space group | Dihedral angle (°) | References |
|-----------------------------------|--|-------------|--------------------|---|
| DBO | <i>a</i> 8.24, <i>b</i> 6.12, <i>c</i> 19.67 | <i>Pnam</i> | 134 | This work |
| DBA | <i>b</i> 8.24, <i>c</i> 6.05, <i>a</i> 20.46 | <i>Pmnb</i> | 144 | Reboul <i>et al.</i> (1980) |
| Phenothiazine | <i>a</i> 7.92, <i>c</i> 5.89, <i>b</i> 20.97 | <i>Pnma</i> | 159 | Wimmer (1963) (quoted in Hoppe, 1969), Schäffer (1971) |
| [Phenothiazine Monoclinic form | | | 153 | McDowell (1976) |
| Dibenzofuran | <i>a</i> 7.65, <i>b</i> 5.90, <i>c</i> 19.32 | <i>Pnam</i> | 180 | Bell, Blount, Briscoe & Freeman (1968)] |
| Carbazole | <i>a</i> 7.76, <i>c</i> 5.74, <i>b</i> 19.15 | <i>Pnma</i> | 180 | Banerjee (1973) |
| Fluorene | <i>a</i> 8.49, <i>c</i> 5.72, <i>b</i> 18.97 | <i>Pnma</i> | 180 | Kurahashi, Fukuyo, Shimada, Furusaki & Nitta (1969) Burns & Iball (1955) |

solved independently. With a dihedral angle of 134°, DBO is less nearly planar than its analogues in which —O— is replaced by >NH (144° in DBA) or >C=O (141°), according to a preliminary report (Shimanouchi, Hata & Sasada, 1968) of the structure of dibenzo[*b,f*]tropone, and appreciably less nearly planar than phenothiazine (159°) (McDowell, 1976). In the structure of DBO, there are no abnormally close interatomic distances between adjacent molecules.

In the central ring, the carbon atoms C(12,13,14,15) lie accurately in one plane, roughly parallel to, and 0.5–0.6 Å distant from, that defined by atoms O(5), C(10) and C(11). Deviations (e.s.d.'s 0.01 Å) from the mean plane, equation $7.770x + 2.08y = 2.322$, passing through all seven atoms of this ring are O(5) –0.45, C(10) and C(11) –0.17, C(12) and C(15) 0.24, and C(13) and C(14) 0.17 Å. Within the 'boat', the C(13), O(5), C(14) 'bow' and C(15,10,11,12) 'stern' planes make angles of 57 (2)° and 24 (2)° with the C(12,13,14,15) plane and 99 (2)° with each other. For DBA the corresponding angles are 48, 21 and 112°, and for the carbonyl analogue dibenzo[*b,f*]tropone, the corresponding angles are 37, 20 and 123°, respectively (Ibata, Shimanouchi & Sasada, 1975). Chemical reactions and ¹H NMR behaviour in solution (Bavin, Bartle & Jones, 1968) would suggest that any aromatic character in the seven-membered ring is weak. It is certainly non-planar and there is a marked alternation in DBO between single and double bonds along the sequence C(12)–C(11)=C(10)–C(15), 1.468 (6), 1.327 (6), 1.468 (6) Å, continued with an aromatic C(12)–C(13) and a 1.390 (5) Å C(13)–O(5) single bond, in remarkably close agreement with the corresponding bond lengths in DBA [1.469 (6), 1.328 (7), 1.469 (6) Å for the ethylenic region, 1.399 (5) Å aromatic, and C–N = 1.411 (5) Å]. Following the observation of differential effects in solution between the ¹H NMR resonances of the benzene-ring H atoms in DBO and DBA (Drake & Jones, 1977), it has been suggested (Haigh, 1976) that small paramagnetic ring currents may be carried even by such appreciably non-planar central rings.

The C atoms of the benzene rings (Table 5) lie within ±0.02 Å of planarity and there is a slight twist (2°)

Table 5. Parameters of the mean plane through benzene C atoms and deviations (e.s.d. 0.01 Å) of benzene-ring atoms from the plane

Equation of plane through C(1,2,3,4,12,13)

$$6.865x + 2.375y + 7.727z = 3.907$$

Deviations

| | | | |
|-------|--------|------|---------|
| C(1) | 0.01 Å | H(1) | –0.15 Å |
| C(2) | 0.02 | H(2) | 0.09 |
| C(3) | –0.02 | H(3) | 0.09 |
| C(4) | 0.00 | H(4) | 0.10 |
| C(12) | –0.02 | | |
| C(13) | 0.02 | | |

between the planes through the two halves, C(1,2,12) and C(3,4,13). Of the H atoms, H(1) deviates most from the aromatic-ring plane; it is attached to the only hydrogenated C atom on this ring whose C–C–C angle deviates significantly from 120°. As a result, intramolecular separations H(11)···H(1) and H(1)···H(2) are nearly equalized at 2.4 (1) Å, similar to the distances between neighbouring H atoms in the benzene rings. O(5)···H(4) = 2.55 (6) Å is rather too long for intramolecular hydrogen bonding; the ring-to-ring H(4)···H(6) approach is 3.30 (6) Å. Of the benzene-ring bond lengths, averaging 1.387 (5) Å as in typical benzene C–C bonds, only C(1)–C(12) and C(1)–C(2) differ from each other by more than 3σ.

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Topography of Cyclodextrin Inclusion Complexes.

XVI.* Cyclic System of Hydrogen Bonds: Structure of α -Cyclodextrin Hexahydrate, Form (II): Comparison with Form (I)

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Abstract

The cyclic hexasaccharide α -cyclodextrin (α -CD; cyclohexaamylose) crystallizes from water as the hexahydrate in two different forms with the same space group $P2_12_12_1$ but cell constants $a = 14.858$ (3), $b = 34.038$ (7), $c = 9.529$ (2) Å (form I) and $a = 13.70$ (1), $b = 29.35$ (2), $c = 11.92$ (1) Å (form II). Final R for form (II) is 3.8% for all the 4860 reflections. Form (I) grows preferentially and has been described previously [Klar, Hingerty & Saenger (1980). *Acta Cryst.* **B36**, 1154–1165]. In form (I), the α -CD annulus encloses a pair of water molecules and

four water molecules are located 'outside'. The α -CD molecule is distorted, the O(2)···O(3) hydrogen-bonding ring is disrupted at one glucose moiety which is rotated out of alignment with the other glucose units and associated glucosidic torsion angles φ and ψ indicate high-energy distortion. The α -CD in form (II) crystals has an almost identical conformation, with one water molecule and an O(6) hydroxyl of a symmetry-related α -CD included while five water molecules are located 'outside'. It is concluded that this distorted α -CD is intrinsically associated with the 'empty' water complex and that upon complexation with guest molecules, α -CD changes its conformation to a 'round, undistorted' molecule with the ring of O(2)···O(3) hydrogen bonds fully established, a model for the 'induced-fit'-type complex formation.

* For part XV, see Chacko & Saenger (1980).