

Conformations of three heterocyclic perhydropyrrolobenzofurans and polymeric assembly *via* co-operative intermolecular C—H...O hydrogen bonds

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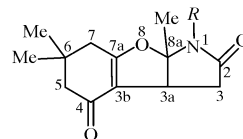
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In 1-cyclohexyl-6,6,8a-trimethyl-3a,6,7,8a-tetrahydro-1*H*-1-benzofuro[2,3-*b*]pyrrole-2,4(3*H*,5*H*)-dione, C₁₉H₂₇NO₃, (I), and the isomorphous compounds 6,6,8a-trimethyl-1-phenyl-3a,6,7,8a-tetrahydro-1*H*-1-benzofuro[2,3-*b*]pyrrole-2,4(3*H*,5*H*)-dione, C₁₉H₂₁NO₃, (II), and 6,6,8a-trimethyl-1-(3-pyridyl)-3a,6,7,8a-tetrahydro-1*H*-1-benzofuro[2,3-*b*]pyrrole-2,4(3*H*,5*H*)-dione, C₁₈H₂₀N₂O₃, (III), the tetrahydrobenzo-dihydrofuro-pyrrolidine ring systems are folded at the *cis* junction of the five-membered rings, giving rise to a non-planar shape of the tricyclic cores. The dihydrofuran and pyrrolidine rings in (I) are puckered and adopt an envelope conformation. The cyclohexene rings adopt a half-chair conformation in all the molecules, while the substituent *N*-cyclohexyl ring in (I) assumes a chair form. Short intramolecular C—H...O contacts form *S*(5) and *S*(6) motifs. The isomorphous compounds (II) and (III) are effectively isostructural, and aggregate into chains *via* intermolecular C—H...O hydrogen bonds.

Comment

Co-operativity is an important property of intermolecular interactions and, thereby, molecules assemble into polymers with distinct patterns of interactions. By the process of mutual polarization within a polymeric assembly, weaker interactions acquire greater strength than they otherwise possess. A dimer of two molecules intermolecularly connected by symmetrical hydrogen bonds is more stable than if they are connected by an isolated hydrogen bond, the stability of a tetramer is greater than that of a pair of dimers, and so on (Desiraju & Steiner, 1999; Sharma & Desiraju, 1994). Polymeric assemblies

formed by co-operative weak interactions are the subject of the present discussion. In this report, we present examples of a new class of tricyclic benzofuran derivatives with a benzofuropyrrolidine ring skeleton. The structural and conformational analyses of three compounds have been undertaken, namely 1-cyclohexyl-6,6,8a-trimethyl-3a,6,7,8a-tetrahydro-1*H*-1-benzofuro[2,3-*b*]pyrrole-2,4(3*H*,5*H*)-dione, (I), 1-phenyl-6,6,8a-trimethyl-3a,6,7,8a-tetrahydro-1*H*-1-benzofuro[2,3-*b*]pyrrole-2,4(3*H*,5*H*)-dione, (II), and 1-pyridin-3-yl-6,6,8a-trimethyl-3a,6,7,8a-tetrahydro-1*H*-1-benzofuro[2,3-*b*]pyrrole-2,4(3*H*,5*H*)-dione, (III). These chiral molecules are formally derived from a perhydrofuro(or -pyrrolo)benzofuran system, and they have previously been shown to exhibit hypoglycaemic activity (Nagarajan *et al.*, 1988).



(I) *R* = cyclohexyl, C₆H₁₁—

(II) *R* = phenyl, Ph—

(III) *R* = pyridyl, C₅H₅N—

The stereogenic centres C3a and C8a in compounds (I)–(III) (Figs. 1–3) adopt *RS* and *SR* configurations, respectively (Cahn *et al.*, 1966). The core of each molecule consists of fused tetrahydrobenzo (*A*), dihydrofuro (*B*) and pyrrolidine (*C*) rings. The C3b=C7a double bond at the *AB* ring junction is in the range 1.341 (2)–1.344 (2) Å. In each compound, the *B* and *C* rings are folded at the *BC* ring junction, which is *cis*-fused (Bucourt, 1974). The angles between the best planes through ring *B* (atoms O8/C8a/C3a/C3b/C7a) and ring *C* (atoms N1/C2/C3/C3a/C8a) are 66.4 (1), 63.8 (1) and 63.2 (1)°, respectively, while the crossed torsion angles at the junction, *i.e.*

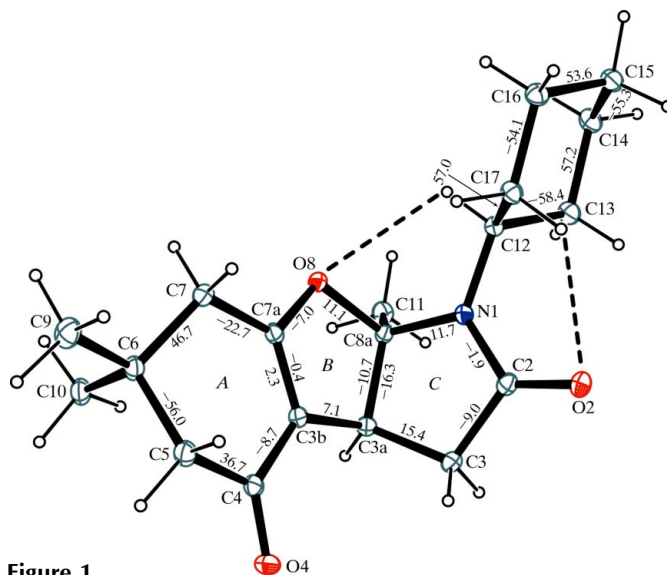


Figure 1

The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Numerical data refer to the internal torsion angles (°) of the individual rings (*s.u.* values vary between 0.1 and 0.3°). Intramolecular C—H...O short contacts are shown as dashed lines.

N1—C8a—C3a—C3b and O8—C8a—C3a—C3, are 103.2 (1) and -130.2 (1), 114.3 (1) and -121.2 (1), and 113.4 (1) and -122.3 (1) $^\circ$, respectively, in the molecules of (I)–(III).

The folding at the BC ring junction gives rise to the non-planarity of the tricyclic ring system. The structures of two analogous molecules based on a chiral tricyclic tetrahydrobenzo-dihydrofuro-tetrahydrofuran (or pyrrolidine) core, namely 1-isopropyl-6,6,8a-trimethyl-1,3a,5,6,7,8a-hexahydro-3*H*-1-benzofuro[2,3-*b*]pyrrole-2,4-dione (Narasegowda *et al.*,

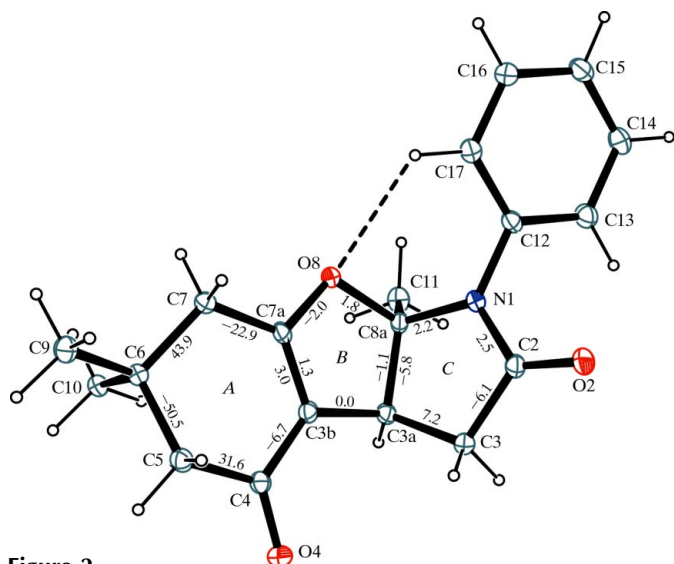


Figure 2

The molecular structure of (II), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Numerical data refer to the internal torsion angles ($^\circ$) of the individual rings (s.u. values vary between 0.1 and 0.3 $^\circ$). The intramolecular C—H...O short contact is shown as a dashed line.

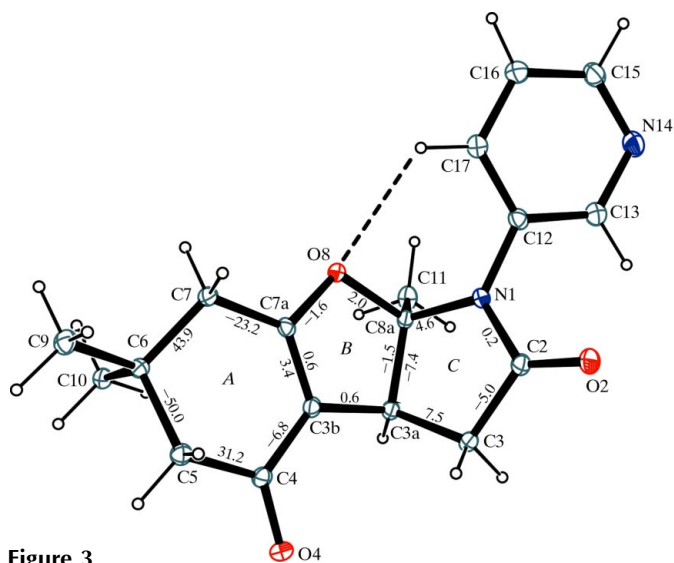


Figure 3

The molecular structure of (III), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Numerical data refer to the internal torsion angles ($^\circ$) of the individual rings (s.u. values vary between 0.1 and 0.3 $^\circ$). The intramolecular C—H...O short contact is shown as a dashed line.

2006), (IV), and 6,6,8a-trimethyl-3a,6,7,8a-tetrahydrobenzo[*b*]furo[3,2-*d*]furan-2,4(3*H*,5*H*)-dione (Nagaraj *et al.*, 2005), (V), also possess a similar non-planar shape of the tricyclic core, and the equivalent crossed torsion angles at the junctions of the five-membered rings are 99.7 (1) and -132.8 (1) (values correspond to an inverted image of the reported structure), and 104.0 (1) and -127.2 (1) $^\circ$, respectively.

The superposition of all five available structures of perhydrofuro(or -pyrrolo)benzofuran derivatives is shown in supplementary Fig. 5. The conformations of the substituent rings, *i.e.* *N*-cyclohexyl in (I), *N*-phenyl in (II) and *N*-pyridyl in (III), are described by torsion angles C8a—N1—C12—C13 of -112.4 (1), -117.2 (2) and -120.2 (1) $^\circ$, respectively.

The isomorphous compounds (II) and (III), with a difference of one atom [C14 in (II) and N14 in (III)] are isostructural. The degree of isostructurality has been quantitatively described by two descriptors, *i.e.* the unit-cell similarity index, Π , which is the difference between orthogonalized lattice parameters, and the isostructurality index, $I_i(n)$, where n is the number of distance differences between identical non-H atoms (Kálmán *et al.*, 1993). The calculated values of $\Pi = 0.019$ and $I_i(24) = 99.7\%$ indicate the structures are close to the ideal case of isostructurality.

The internal torsion angles of the heterocyclic rings are listed in Figs. 1–3. Ring A (cyclohexene) adopts a half-chair (C_2) conformation in all three molecules. However, its conformation, *i.e.* a half-chair (C_2) *versus* a sofa (C_s), is hardly distinguishable in the present structures (Bucourt, 1974). The *N*-cyclohexyl ring in (I) assumes a chair form, with the larger tricyclic system in the equatorial position. The puckering (Cremer & Pople, 1975) and asymmetric (Duax *et al.*, 1976) parameters of individual rings are provided in supplementary Table 4. The five-membered B and C rings in (I) are puckered and adopt envelope (C_s) conformations (Fuchs, 1978), with atoms C8a and C3a at the flaps of the envelopes. Atoms C8a and C3a are 0.18 (1) and 0.27 (1) Å, respectively, out of the best planes formed by the other four atoms of the ring. Rings B and C are planar in (II) and (III). The least-squares planes

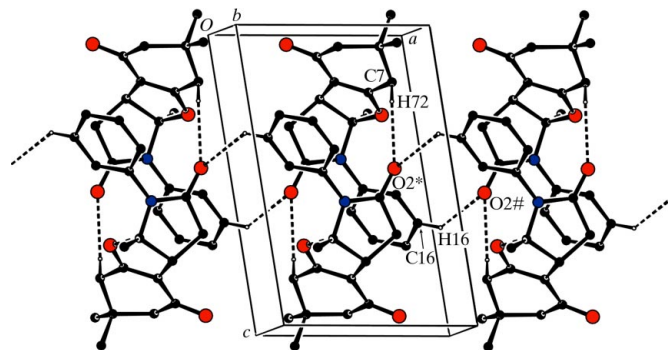


Figure 4

The crystal packing, showing the co-operative C—H...O hydrogen-bonded polymeric association of isostructural compounds (II) and (III), viewed along the *a* axis. The representative diagram corresponds to the packing in (II). Atoms labelled with an asterisk (*) or a hash (#) are at the symmetry positions $(-x+1, -y+1, -z+1)$ and $(x+1, y, z)$, respectively. Intermolecular C—H...O hydrogen bonds are shown as dashed lines.

formed by atoms of rings *A* and *B* (C3a/C3b/C4/C5/C7/C7a/O8/C8a) and ring *C* (N1/C2/O2/C3/C3a/C8a) intercept at an angle of 65.8 (1)° in (II) and 64.2 (1)° in (III).

The parameters for intramolecular short contacts and intermolecular hydrogen bonds are given in Tables 1–3. The conserved intramolecular C—H···O short contacts in (I)–(III) were observed between the donors of the *N*-substituents and atom O8 of ring *B* (Figs. 1–3). The short contact C12—H12···O8 forms an *S*(5) motif (Bernstein *et al.*, 1995) in (I), while *S*(6) motifs are formed by C17—H17···O8 in (II) and (III). Additionally, an intramolecular C17—H17···O2 contact forms an *S*(6) motif in (I). The crystal packing in (I) is entirely due to van der Waals interactions. The crystal structures of isostructural compounds (II) and (III) are held together primarily by intermolecular C—H···O hydrogen bonds (Tables 2 and 3), forming chains of rings along [100] (Fig. 4). The significance of the co-operativity of weak intermolecular interactions for molecular self-assembly is elucidated in the present examples.

Experimental

The synthetic procedures used for the preparation of compounds (I)–(III) are as described in the literature (Nagarajan *et al.*, 1988). Single crystals suitable for X-ray diffraction were grown by slow evaporation of solutions containing the following solvents (in a 1:1 ratio): for (I), ethanol and water; for (II), dichloromethane and hexane; for (III), benzene and hexane.

Compound (I)

Crystal data

$C_{19}H_{27}NO_3$	$V = 848.50 (3) \text{ \AA}^3$
$M_r = 317.42$	$Z = 2$
Triclinic, $P\bar{1}$	$D_x = 1.242 \text{ Mg m}^{-3}$
$a = 9.4708 (2) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 10.2139 (2) \text{ \AA}$	$\mu = 0.08 \text{ mm}^{-1}$
$c = 10.7512 (2) \text{ \AA}$	$T = 120 (2) \text{ K}$
$\alpha = 105.804 (1)^\circ$	Plate, colourless
$\beta = 99.141 (1)^\circ$	$0.24 \times 0.16 \times 0.03 \text{ mm}$
$\gamma = 116.320 (1)^\circ$	

Data collection

Nonius KappaCCD area-detector diffractometer	18064 measured reflections
φ and ω scans	3327 independent reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2003)	2990 reflections with $I > 2\sigma(I)$
$T_{\min} = 0.891$, $T_{\max} = 0.998$	$R_{\text{int}} = 0.039$
	$\theta_{\max} = 26.0^\circ$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0495P)^2 + 0.3127P]$
$R[F^2 > 2\sigma(F^2)] = 0.039$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.107$	$(\Delta/\sigma)_{\max} = 0.001$
$S = 1.12$	$\Delta\rho_{\max} = 0.30 \text{ e \AA}^{-3}$
3327 reflections	$\Delta\rho_{\min} = -0.32 \text{ e \AA}^{-3}$
316 parameters	
All H-atom parameters refined	

Table 1

Hydrogen-bond and short-contact geometry (\AA , $^\circ$) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C12—H12···O8	1.00 (2)	2.52 (2)	2.920 (2)	103 (1)
C17—H17···O2	1.01 (2)	2.55 (2)	3.153 (2)	118 (1)

Compound (II)

Crystal data

$C_{19}H_{21}NO_3$	$V = 799.89 (6) \text{ \AA}^3$
$M_r = 311.37$	$Z = 2$
Triclinic, $P\bar{1}$	$D_x = 1.293 \text{ Mg m}^{-3}$
$a = 7.2348 (2) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 10.1212 (5) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$c = 11.6287 (6) \text{ \AA}$	$T = 120 (2) \text{ K}$
$\alpha = 77.031 (2)^\circ$	Plate, colourless
$\beta = 79.285 (3)^\circ$	$0.20 \times 0.14 \times 0.03 \text{ mm}$
$\gamma = 76.872 (3)^\circ$	

Data collection

Nonius KappaCCD area-detector diffractometer	14845 measured reflections
φ and ω scans	3132 independent reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2003)	2562 reflections with $I > 2\sigma(I)$
$T_{\min} = 0.903$, $T_{\max} = 0.997$	$R_{\text{int}} = 0.047$
	$\theta_{\max} = 26.0^\circ$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0532P)^2 + 0.358P]$
$R[F^2 > 2\sigma(F^2)] = 0.044$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.117$	$(\Delta/\sigma)_{\max} = 0.001$
$S = 1.07$	$\Delta\rho_{\max} = 0.19 \text{ e \AA}^{-3}$
3132 reflections	$\Delta\rho_{\min} = -0.27 \text{ e \AA}^{-3}$
292 parameters	
All H-atom parameters refined	

Table 2

Hydrogen-bond and short-contact geometry (\AA , $^\circ$) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C17—H17···O8	1.00 (2)	2.49 (2)	3.066 (2)	116 (2)
C7—H72···O2 ⁱ	0.96 (2)	2.49 (2)	3.275 (2)	140 (2)
C16—H16···O2 ⁱⁱ	0.98 (2)	2.46 (2)	3.243 (3)	138 (2)

Symmetry codes: (i) $-x + 1, -y + 1, -z + 1$; (ii) $x + 1, y, z$.

Compound (III)

Crystal data

$C_{18}H_{20}N_2O_3$	$V = 778.13 (4) \text{ \AA}^3$
$M_r = 312.36$	$Z = 2$
Triclinic, $P\bar{1}$	$D_x = 1.333 \text{ Mg m}^{-3}$
$a = 7.2330 (2) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 9.8165 (3) \text{ \AA}$	$\mu = 0.09 \text{ mm}^{-1}$
$c = 11.6008 (3) \text{ \AA}$	$T = 120 (2) \text{ K}$
$\alpha = 78.541 (2)^\circ$	Prism, colourless
$\beta = 78.992 (2)^\circ$	$0.19 \times 0.14 \times 0.09 \text{ mm}$
$\gamma = 77.302 (1)^\circ$	

Data collection

Nonius KappaCCD area-detector diffractometer	13914 measured reflections
φ and ω scans	3040 independent reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2003)	2769 reflections with $I > 2\sigma(I)$
$T_{\min} = 0.913$, $T_{\max} = 0.992$	$R_{\text{int}} = 0.035$
	$\theta_{\max} = 26.0^\circ$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0478P)^2 + 0.3717P]$
$R[F^2 > 2\sigma(F^2)] = 0.039$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.104$	$(\Delta/\sigma)_{\max} = 0.006$
$S = 1.07$	$\Delta\rho_{\max} = 0.29 \text{ e \AA}^{-3}$
3040 reflections	$\Delta\rho_{\min} = -0.20 \text{ e \AA}^{-3}$
288 parameters	
All H-atom parameters refined	

Table 3

Hydrogen-bond and short-contact geometry (Å, °) for (III).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C17—H17 \cdots O8	0.99 (2)	2.50 (2)	3.060 (2)	116 (2)
C7—H72 \cdots O2 ⁱ	0.99 (2)	2.49 (2)	3.295 (2)	138 (1)
C16—H16 \cdots O2 ⁱⁱ	0.97 (2)	2.54 (2)	3.268 (2)	132 (2)

Symmetry codes: (i) $-x + 1, -y + 1, -z + 1$; (ii) $x + 1, y, z$.

Larger-than-expected values of residual electron density were observed in (I) and (III) [the values of $\Delta\rho_{\max}$ and $\Delta\rho_{\min}$ were 0.75 and -0.88 e Å^{-3} , respectively, in (I), and 0.82 and -0.87 e Å^{-3} , respectively, in (III)]. This was attributed to the presence of a few poorly fitting low-angle reflections [(011), ($\bar{1}\bar{1}1$), (020), (111) and ($\bar{2}\bar{1}2$) in (I), and ($\bar{1}\bar{1}2$), (100), ($\bar{1}\bar{1}1$), (022), (013), (122) and (012) in (III)], which appeared to have been truncated by the beam stop. These reflections were omitted during the final cycles of refinement. The residual electron density was then featureless and the residual factor R dropped from 0.053 to 0.039 in (I), and from 0.056 to 0.039 in (III) for observed data.

H atoms were located in difference maps and were refined freely. Refined methine, methylene and methyl C—H distances are as follows: for (I), 0.99 (2), 0.97 (2)–1.01 (2) and 0.96 (2)–1.02 (2) Å; for (II), 0.97 (2), 0.96 (2)–1.01 (2) and 0.97 (2)–1.03 (2) Å, with aromatic C—H = 0.96 (2)–1.00 (2) Å; for (III), 0.99 (2), 0.97 (2)–1.02 (2) and 0.98 (2)–1.02 (2) Å, with aromatic C—H = 0.97 (2)–1.01 (2) Å.

For all compounds, data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997) and *COLLECT*; data reduction: *DENZO* and *COLLECT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997), *PLATON* (Spek, 2003) and *INSIGHTII* (Accelrys, 2002); software used to prepare material for publication: *SHELXL97* and *PLATON*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3014). An additional figure and table are also available. Services for accessing these data are described at the back of the journal.

References

- Accelrys (2002). *INSIGHTII*. Version 2000.2. Accelrys Inc., 9685 Scranton Road, San Diego, CA 92121-3752, USA.
- Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Bucourt, R. (1974). *Topics in Stereochemistry*, Vol. 8, edited by E. L. Eliel & N. Allinger, pp. 159–224. New York: John Wiley.
- Cahn, R. S., Ingold, C. K. & Prelog, V. (1966). *Angew. Chem. Int. Ed. Engl.* **5**, 385–415.
- Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
- Desiraju, G. R. & Steiner, T. (1999). *The Weak Hydrogen Bond in Structural Chemistry and Biology*. New York: Oxford University Press Inc.
- Duax, W. L., Weeks, C. M. & Rohrer, D. C. (1976). *Topics in Stereochemistry*, Vol. 9, edited by E. L. Eliel & N. Allinger, pp. 271–383. New York: John Wiley.
- Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
- Fuchs, B. (1978). *Topics in Stereochemistry*, Vol. 10, edited by E. L. Eliel & N. Allinger, pp. 1–94. New York: John Wiley.
- Kálmán, A., Párkányi, L. & Argay, G. (1993). *Acta Cryst.* **B49**, 1039–1049.
- Nagaraj, B., Yathirajan, H. S., Nagaraja, P. & Lynch, D. E. (2005). *Acta Cryst.* **E61**, o1041–o1042.
- Nagarajan, K., Talwalker, P. K., Nagana Goud, A., Shah, R. K., Shenoy, S. J. & Desai, N. D. (1988). *Indian J. Chem. Sect. B*, **27**, 1113–1123.
- Narasegowda, R. S., Yathirajan, H. S., Lynch, D. E., Narasimhamurthy, T. & Rathore, R. S. (2006). *Acta Cryst.* **E62**, o1328–o1329.
- Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
- Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
- Sharma, C. V. K. & Desiraju, G. R. (1994). *J. Chem. Soc. Perkin Trans. 2*, pp. 2345–2352.
- Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
- Sheldrick, G. M. (2003). *SADABS*. Version 2.10. Bruker AXS Inc., Madison, Wisconsin, USA.
- Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.