

## Structure Study of Host–Guest Molecular Association in Solution and in the Solid State

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A correlation between the mechanism of <sup>1</sup>H NMR shift of a chiral guest by association with an optically active host compound in solution and in the solid state is revealed by an X-ray analysis of the host–guest inclusion crystal.

Optically active hosts, such as 1,6-bis(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol **1**,<sup>1,2</sup> 2,2'-dihydroxy-1,1'-binaphthyl **2**,<sup>1,2</sup> 4,4',6,6'-tetrachloro-2,2'-bis(hydroxydiphenylmethyl)biphenyl **3**,<sup>3</sup> and tartaric acid derived *trans*-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane **4a** and its derivatives **4b** and **4c**<sup>4,5</sup> can act as NMR chiral shift reagents for determining enantiomeric purity and absolute configuration of various chiral compounds.

For example, the methine proton signal of racemic-1-phenylethylamine **5a**, which appears as a quartet centred at  $\delta$  4.25 in the <sup>1</sup>H NMR spectrum<sup>†</sup> is split into two quartets centred at  $\delta$  3.63 and 3.60 in the presence of 2 equiv. of **4a**. The two signals centred at  $\delta$  3.60 and 3.63 were assigned to the methine proton of (*S*)-(–)-**5b** and the (*R*)-(+)-enantiomer **5c**, respectively, by measurement of the <sup>1</sup>H NMR spectra of the optically pure **5b** and **5c** in the presence of **4a**.

The above data can be interpreted by assuming the following molecular association of **4a** and **5** in CDCl<sub>3</sub>. In a molecular complex of **4a** and **5b** produced by their association through hydrogen-bond formation between the hydroxy group of **4a** and the amine nitrogen atom of **5b**, the methine proton of **5b** is located in the position that is shielded by a phenyl ring of **4a** and is shifted down-field. In a molecular complex of **4a** and **5c**, however, the methine proton of **5c** is

located in the position that is deshielded and is shifted up-field. In order to confirm the assumption, host–guest inclusion crystal of **4a** and **5b** was prepared and its X-ray structure was analysed.

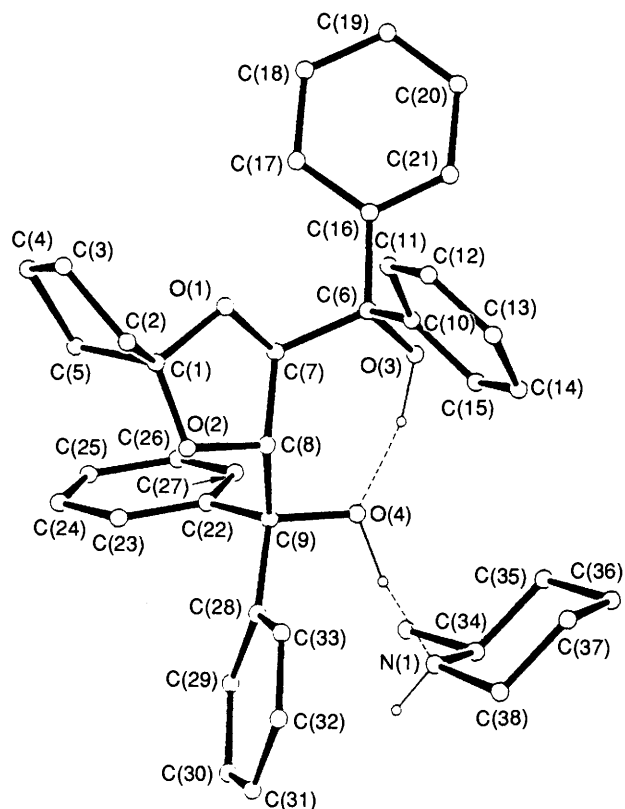
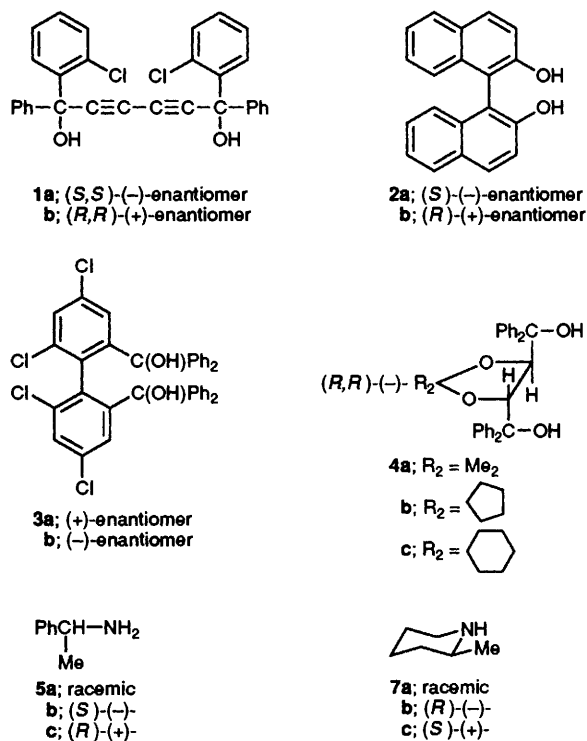
When a solution of **4a**<sup>6</sup> (5 g, 10.7 mmol) and **5a** (1.3 g, 10.7 mmol) in toluene–hexane (1 : 2, 30 ml) was kept at room temp. for 12 h, a 2 : 1 inclusion complex of **4a** and **5b** of 91% e.e. (enantiomeric excess) was obtained as colourless prisms (3.5 g, 62% yield). Recrystallisation of the inclusion crystal from toluene gave the complex **6** of pure enantiomer (3 g, 52% yield, m.p. is not clear), which upon heating *in vacuo* gave **5b** of 100% e.e. by distillation {0.32 g, 49% yield,  $[\alpha]_{\text{D}}^{25} -22.5$  (*c* 0.18, MeOH)}. The efficient optical resolution of the guest compound by inclusion complexation with optically active host compound has thus been established.<sup>7</sup>

The X-ray crystal structure of **6**<sup>†</sup> shows that two host molecules are related by an approximate twofold axis passing through the midpoints between O(3) and O(3') and O(4) and O(4'). All the hydrophilic groups are concentrated in the interior of the complex to make a cyclic hydrogen-bond system [...O(4)–H...N(1)–H...O(4')–H...O(3')–H...O(3)–H...] with one of the two N–H groups of **5b** free from a hydrogen bond, while the exterior of the complex is hydrophobic and no inter-complex hydrogen bond is formed. The host–guest short contacts are mainly found between the phenyl group [C(26), C(27), ...C(31)] on C(7) of **4a** on the left in Fig. 1 and the –CH(NH<sub>2</sub>)Me part of **5b**, with the methine group of **5b** shielded by the phenyl group.

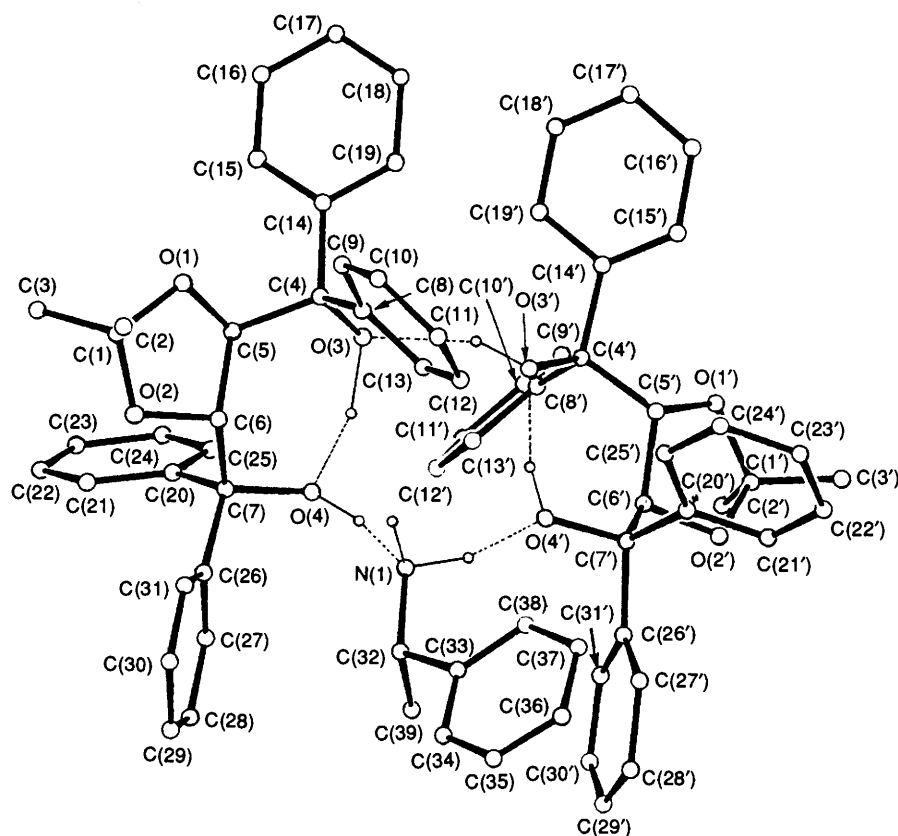
<sup>†</sup> All <sup>1</sup>H NMR spectra were measured in CDCl<sub>3</sub> at room temp. by using a 60 MHz JEOL PMX-60SI spectrometer.

Similarly, **4b** also acts as a chiral shift reagent. For example, the methyl  $^1\text{H}$  signal of racemic 2-methylpiperidine **7a**, which appears as a doublet centred at  $\delta$  1.09, is split into two doublets centred at  $\delta$  0.82 and 0.87 in the presence of an equimolar amount of **4b**. The two signals centred at  $\delta$  0.82 and 0.87 were assigned to the methyl proton of (*R*)-(-)-**7b** and (*S*)-(+)-enantiomer **7c** respectively, by measurement of the  $^1\text{H}$  NMR spectra of the optically pure **7b** and **7c** in the

presence of **4b**. The splitting of the methyl proton signal of **7a** in the presence of **4b** can also be interpreted as a host-guest molecular association in  $\text{CDCl}_3$ . In a molecular complex of **4b**



**Fig. 2** ORTEP drawing of host-guest (1 : 1) complex of **4b** and **7c**. Hydrogen bonds are shown by dotted lines. Hydrogen bond distances ( $\text{\AA}$ ): O(3)-O(4) 2.614(3); O(4)-N(1) 2.683(4).



**Fig. 1** ORTEP drawing of host-guest (2 : 1) complex of **4a** and **5b**. Hydrogen bonds are shown by dotted lines. Hydrogen bond distances ( $\text{\AA}$ ): O(4)-N(1) 2.730(7); N(1)-O(4') 2.955(7); O(4')-O(3') 2.652(5); O(3')-O(3) 2.860(5); O(3)-O(4) 2.677(4).

and **7b**, the methyl proton of **7b** is located in the position shielded by a phenyl ring of **4b** and is shifted downfield. In a molecular complex of **4b** and **7c**, however, the methyl proton of **7c** is located in the position deshielded and is shifted up-field. In order to confirm the assumption, an inclusion crystal of **4b** and **7c** was prepared and its structure was studied by X-ray analysis.

When a solution of **4b** (5 g, 10.2 mmol) and **7a** (2 g, 20.2 mmol) in toluene-hexane (1 : 1, 20 ml) was kept at room temp. for 3 h, a 1 : 1 inclusion complex of **4b** and **7c** of 42% e.e. was formed as colourless needles (5.4 g, 90% yield). Three recrystallisations of the crude complex from toluene gave the complex **8** of pure enantiomer (1.6 g, 30% yield, m.p. is not clear), which upon heating *in vacuo* gave **7c** of 100% e.e. {0.26 g, 26% yield,  $[\alpha]_D^{25} +4.5$  ( $c$  0.85, MeOH)}.

The X-ray crystal structure analysis of **8**† showed that the hydrophilic groups of **4b** and **7c** are suited to make a hydrogen-bond network [O(3)-H...O(4)-H...N(1)]. Similarly to the complex of **4a** and **5b**, **6**, the exterior of the complex of **4b** and **7c**, **8** is mostly hydrophobic with no inter-complex hydrogen bond (NH of **7c** does not take part in the hydrogen bond). The phenyl ring [C(28), C(29), ...C(33)] on C(9) of **4b** interacts

mainly with N(1)-C(38) moiety of **7c** and no short contact is found between the methyl group of **7c** and the phenyl rings of **4b**.

The interpretation of the  $^1\text{H}$  NMR spectra by assuming the molecular association described above is supported by the X-ray structures of these two complexes, **6** and **8**. Interestingly, the relative orientation of **4a** on the left and **5b** in Fig. 1 resembles that of **4b** and **7c** in Fig. 2. Moreover, the same type of host-guest arrangements have been found in the 1 : 1 inclusion complex crystal of **4a** with (*R*)-(-)-6-methyl-[4.4.0]dec-1-en-3-one and with (*R*)-(-)-methylbicyclo-[4.4.0]dec-1-ene-3,7-dione.<sup>8</sup> Thus, these results may suggest that the host-guest association of **4b** with **7c** and **4a** (on the left in Fig. 2) with **5b** may reflect approximately host-guest interactions in  $\text{CDCl}_3$ . An important feature of the host-guest association in this orientation is that the complex is stabilised by a hydrogen-bond formation of a hydroxy group of a host molecules as a donor with N atom of a guest molecule as an acceptor, and the van der Waals interactions between the phenyl rings of a host molecule and a guest molecule.

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† Crystal data for **6**:  $2(\text{C}_{31}\text{H}_{30}\text{O}_4)$   $\text{C}_8\text{H}_{11}\text{N}$   $M = 1054.28$ , orthorhombic, space group  $P2_12_12_1$ ,  $a = 20.308(6)$ ,  $b = 17.173(2)$ ,  $c = 17.042(2)$  Å,  $U = 5943(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.17$  g cm<sup>-3</sup>,  $\mu = 0.71$  cm<sup>-1</sup>. 5780 Reflections with  $2\theta < 50.0^\circ$  were recorded on a Rigaku AFC-6A four-circle diffractometer using graphite monochromated Mo-K $\alpha$  radiation. Of these, 3566 with  $F > 3\sigma(F)$  were judged as observed. The structure was solved using SHELX-86.<sup>9</sup> The hydrogen atoms of the methyl group on C(32) could not be located because of large thermal motion. Full-matrix least-squares refinement with anisotropic temperature factors for non-hydrogen atoms and isotropic hydrogens converged to  $R = 0.057$  and  $R_w = 0.084$ .<sup>10</sup>

Crystal data for **8**:  $\text{C}_{33}\text{H}_{32}\text{O}_4\text{C}_6\text{H}_{13}\text{N}$   $M = 591.76$ , orthorhombic, space group  $P2_12_12_1$ ,  $a = 22.796(4)$ ,  $b = 15.436(2)$ ,  $c = 9.298(3)$  Å,  $U = 3272(1)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.20$  g cm<sup>-3</sup>,  $\mu = 0.71$  cm<sup>-1</sup>. 3261 Reflections with  $2\theta < 50.0^\circ$  were recorded on a Rigaku AFC-6A four-circle diffractometer using graphite-monochromated Mo-K $\alpha$  radiation. Of these, 2404 with  $F > 3\sigma(F)$  were judged as observed. The structure was solved using SHELX-86.<sup>9</sup> Full-matrix least-squares refinement with anisotropic temperature to  $R = 0.045$  and  $R_w = 0.074$ .<sup>10</sup> For both structures, atomic coordinates, bond distances and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

## References

- 1 F. Toda, K. Mori, J. Okada, M. Node, A. Itoh, K. Oomine and K. Fuji, *Chem. Lett.*, 1988, 131.
- 2 F. Toda, K. Mori and A. Sato, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4167.
- 3 F. Toda, R. Toyotaka and H. Fukuda, *Tetrahedron Asymmetry*, 1990, **1**, 303.
- 4 K. Tanaka, M. Ootani and F. Toda, *Tetrahedron Asymmetry*, 1992, **3**, 709.
- 5 C. von dem Bussche-Hunnelfeld, A. K. Beck, U. Lengweiler and D. Seebach, *Helv. Chim. Acta*, 1992, **75**, 438.
- 6 D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, *Helv. Chim. Acta*, 1987, **70**, 954.
- 7 F. Toda and K. Tanaka, *Tetrahedron Lett.*, 1988, **29**, 551.
- 8 L. R. Nassimbeni, M. L. Niven, K. Tanaka and F. Toda, *J. Crystallogr. Spectrosc. Res.*, 1991, **21**, 451.
- 9 G. M. Sheldrick, SHELX86: Program for the automatic solution of crystal structures, University of Göttingen, Germany, 1986.
- 10 W. R. Busing, K. O. Martin and H. S. Levy, ORFLS. Oak Ridge National Laboratory Report, ORNL-TM-305, 1965.