PERKIN 2

Complexation with diol host compounds. Part 25.[1] Selective inclusion of benzenediol isomers by 1,1-bis(4-hydroxyphenyl)cyclohexane

Mino R. Caira,[a] Alicia Horne,[a] Luigi R. Nassimbeni *,[a] and Fumio Toda[b]

[a] *Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa*
[b] *Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan*

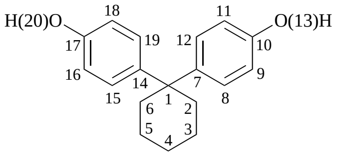
The title host compound includes all the isomers of the benzenediols. The structures with the *p*- and *o*-benzenediols have been elucidated and show that the clathrates are stabilised by hydrogen bonds. Competition experiments with the host in water suspension show that the *para*-isomer is preferentially enclathrated. Lattice energy calculations explain the results of the competition experiment.

One of the most important uses of inclusion chemistry is the separation of close isomers by enclathration. Host molecules may be broadly classified into two main types: (i) those that form molecular complexes by fitting convex guests into the concave cavity of the host (examples of this kind include cyclodextrins, cyclophanes, calixarenes, cycloveratrylenes and various carcerands[2]) and (ii) those that form lattice inclusion compounds by packing in such a manner as to leave cavities or channels in the crystal structure in which various guest molecules can reside.[3] This forms the basis of molecular recognition, a subject which has been extensively reviewed[4] and is the topic of the first three volumes of the recent publication *Comprehensive Supramolecular Chemistry*.[5] The separation of a given isomer from a mixture by formation of a host–guest compound is industrially attractive in that the procedure is simple and not energy intensive. The process generally requires the recrystallisation of the targeted isomer in the presence of the host. This can be done either directly from a mixture of guests or with an added inert solvent. The clathrate crystals are then filtered and the guest released by gentle warming. The efficiency of the process varies, but a high purity of the required isomer can usually be achieved after three or four recrystallisations. 1,1′-Binaphthyl-2,2′-dicarboxylic acid has been used to separate a variety of guests such as amides, carboxylic acids and nitriles.[6] The separation of isomeric alcohols has been achieved by selective complexation with *N*,*N*,*N*′,*N*′-tetracyclohexylfumaride and *N*,*N*,*N*′,*N*′-tetraisopropylfumaride,[7] and the structures of these hosts with cresols have been elucidated.[8,9] We have studied the structures and thermal stabilities of the clathrates formed by 1,1,2,2-tetraphenylethane-1,2-diol with lutidine guests,[10] and have discussed the relative lattice energies of the inclusion compounds formed between tri-(1-naphthyl)silanol and the isomers of xylene.[11] Enantiomers can also be separated by enclathration with chiral hosts. This process is of particular interest to the pharmaceutical industry and has been reviewed.[12,13] The host compound 1,1-bis(4-hydroxyphenyl)cyclohexane forms inclusion compounds with a wide variety of guests. It has been used to separate the cresols[14] and the isomers of phenylenediamine.[15] We now present the results of competition experiments carried out between this host and the isomers of dihydroxybenzene, both with the host in aqueous suspension of the guest mixture, and by direct solid–solid host–guest reactions.

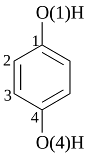
Experimental

Stoichiometric quantities of the host compound (H) and benzenediol (BD) were dissolved in ethyl acetate. Suitable crystals of the inclusion compounds, **1** and **2** were achieved by slow evaporation over a period of 5 to 7 days.

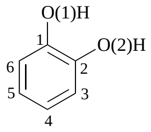
H =



1 = H : $\frac{1}{2}$



2 = H : 1



Preliminary cell dimensions and space group symmetry were determined photographically and subsequently refined by standard procedures on a CAD4 diffractometer. The intensities were collected with the ω–2θ scan mode and crystal stabilities were monitored by periodic reference reflections. Important crystal and experimental data are given in Table 1. Both structures were solved by direct methods using SHELX-86,[16] and refined using full-matrix least-squares using SHELXL-93,[17] refining on F^2. The numbering scheme used is shown on the structures given.†

Competition experiments

Competition experiments were conducted between the *o*-BD and *p*-BD guests dissolved in water, with the host in suspension. A series of 11 vials were made up with mixtures of the two guests. The mole fraction of a guest was varied from 0 to 1 in the series, keeping the host : guest ratio at 1 : 20 in each vial. The vials were shaken for 1 h, and the resulting solid inclusion compound was filtered and dried. The relative amounts of the two guests included by the suspended host in each case were analysed by HPLC using a Waters Model 510 Pump and Series 440 Absorbance detector. The column used was a Prodigy 5μ C8 (150 × 4.6 mm).

This experiment was repeated with the *p*-BD/*m*-BD and *o*-BD/*m*-BD pairs of isomers. In these cases the method of

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† Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see ‘Instructions for Authors’, *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/81.

Table 1 Details of crystals, data collection and final refinement

Parameter	1	2
Molecular formula	$C_{18}H_{20}O_2\cdot\frac{1}{2}C_6H_6O_2$	$C_{18}H_{20}O_2\cdot C_6H_6O_2$
Molecular weight/g mol^{-1}	323.39	378.45
Space group	$C2/c$	$P\bar{1}$
a/Å	19.448(3)	6.206(3)
b/Å	10.716(2)	10.643(2)
c/Å	16.398(7)	15.418(3)
α/°	90	97.28(2)
β/°	91.75(2)	93.49(3)
γ/°	90	103.94(3)
V/Å^3	3415.8(2)	976.0(5)
Z	8	2
D_c/g cm^{-3}	1.26	1.29
D_m/g cm^{-3}	1.24(5)	1.28(5)
μ(Mo-Kα)/cm^{-1}	0.83	0.87
F(000)	1384	404
Data Collection (20 °C)		
Crystal size/mm	0.4 × 0.3 × 0.3	0.4 × 0.2 × 0.2
Range scanned, θ/°	1–25	1–25
Range of indices	h: ± 23; k: 0, 9; l: 0, 19	h: ± 7; k: ± 12; l: 1,18
Crystal decay (%)	−2.7%	3.8%
No. reflections collected	3303	3557
No. reflections observed $[I_{rel} > 2\sigma(I_{rel})]$	2304	2418
No. parameters	238	273
R_1	0.0423	0.0424
$wR2$	0.1097	0.1126
S	1.028	1.046
$\Delta\rho$ excursions/e Å^{-3}	0.194; −0.228	0.160; −0.226

Table 2 Hydrogen bond data for **1** and **2**

Compound	Donor	Acceptor	D···A/Å	D–H···A/°
1	01	020	2.725(2)	164(4)
	04	013[a]	2.649(3)	169(2)
2	013	02[b]	2.697(3)	175(2)
	01	020	2.899(2)	156(2)
	02	020[c]	2.814(2)	156(2)

Symmetry code: [a] $x - \frac{1}{2}, y + \frac{1}{2}, z$. [b] $-x, -y, -z$. [c] $-x + 1, -y + 1, -z$.

analysis was by GC using a Carlo Erba Fractovap 4200 gas chromatograph equipped with a PS255 capillary column (0.25 mm diameter) and a Spectra Physics SP4290 integrator.

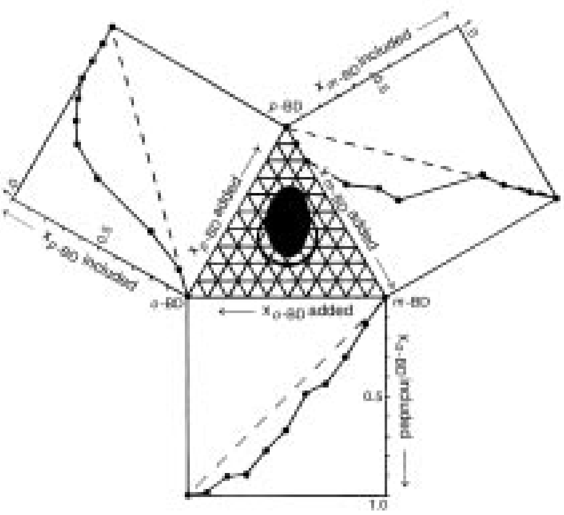

Fig. 1 Results of the competition experiments performed in water suspension

The experiment was extended to analyse simultaneous competition by all three isomers. Initial mixtures of the three guests were selected on a circle drawn on a triangular diagram representing the compositions of the isomers, as shown in Fig. 1. The equi-mixture of the guests, with mole fraction of $\frac{1}{3}$ each, representing the centre of the circle, was also analysed. The triple mixtures were shaken with the suspended host as before and the relative quantities of the included isomers were analysed by HPLC.

Solid state

Solid–solid reactions were carried out by co-grinding stoichiometric quantities of H with the guests. The solids were ground for 15 min in a stainless steel tube containing a steel ball, shaken vigorously in a Wigglebug (Grindex) apparatus. The resulting compounds were analysed by X-ray powder diffractometry (XRD).

Results and discussion

For **1**, the space group is $C2/c$ and the unit cell contains eight host and four guest molecules. The latter are located on diads at Wyckoff position **e** with the hydroxy moieties on the diad. This requires the hydrogens of the hydroxy groups to be disordered and they were both modelled with half site occupancy factors. For **2**, all the hydroxy hydrogens were located on difference electron density maps and were refined with simple bond length constraints and individual temperature factors. For both structures all the heavy atoms were refined anisotropically, and the aromatic and methylenic hydrogens were geometrically constrained and refined with common isotropic temperature factors.

The details of the hydrogen bonding in both structures are shown in Fig. 2. For **1** each hydroxy moiety of the p-BD acts as both a donor and acceptor of a hydrogen bond from the host, and guest inclusion is thus stabilised by four hydrogen bonds. For **2** the o-BD molecules are located on opposite sides of a centre of inversion and are each stabilised by three unique hydrogen bonds to the host molecules. Details of the hydrogen-bonding parameters are listed in Table 2.

The results of the competition experiments carried out in suspension are shown in Fig. 1. Each two-component result

Table 3 Complexes formed between the host, H and the isomers

	o-BD	*m*-BD	*p*-BD
From solution	√	√	√
Solid state	√	√	X

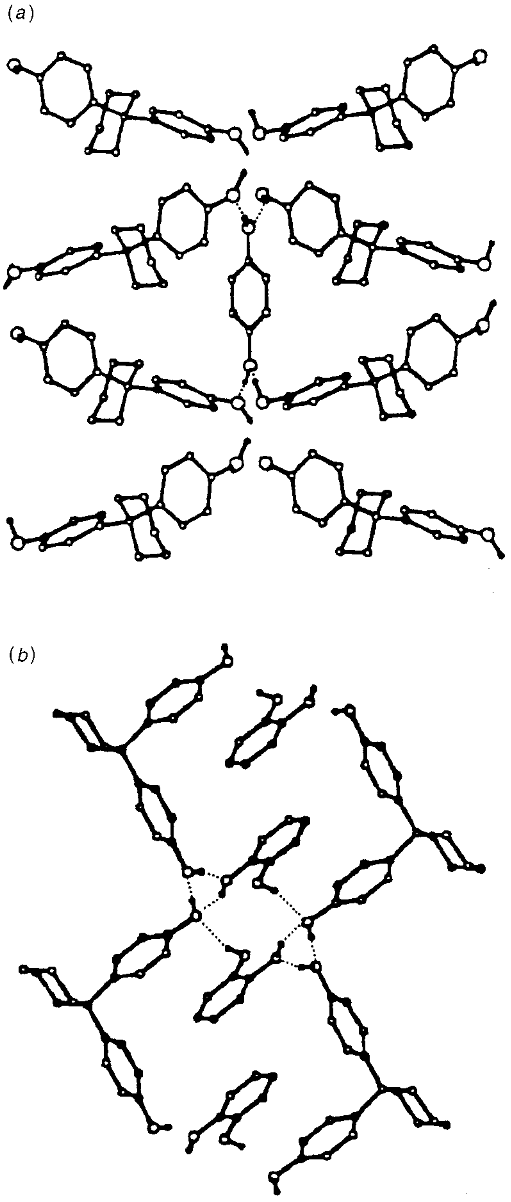

Fig. 2 (*a*) Hydrogen bonding in one member of the disordered pair of structures of **1**. (*b*) Hydrogen bonding in **2**.

shows the molar ratio of the initial solution *versus* that included by the host. For the *o*-BD/*p*-BD competition the latter is strongly favoured by the host, and an equimolar mixture results in 90% *p*-BD being included. The *p*-BD isomer is also favoured above the *meta*-isomer, but the selectivity is weaker. In the *m*-BD/*o*-BD experiment there is a small preference for the inclusion of *o*-BD, but the selectivity is poor.

The three-component experiment is shown on the equilateral triangle. The starting mixtures were located on the circle, and after inclusion moved invariably in favour of *p*-BD, as shown by the shaded ellipse.

The results of the solid–solid experiments are summarised in Table 3. We have shown unequivocally that the H·1*o*-BD and H·1*m*-BD complexes are formed by co-grinding stoichiometric quantities of host and guest. An example is shown in Fig. 3 which gives a comparison of the X-ray diffraction pattern of the product of the solid–solid reactions with the calculated X-ray pattern derived from the crystal structure. Interestingly, we did not obtain the inclusion compound by co-grinding the host with *p*-BD, and the X-ray powder diffraction pattern was simply the sum of the individual components.

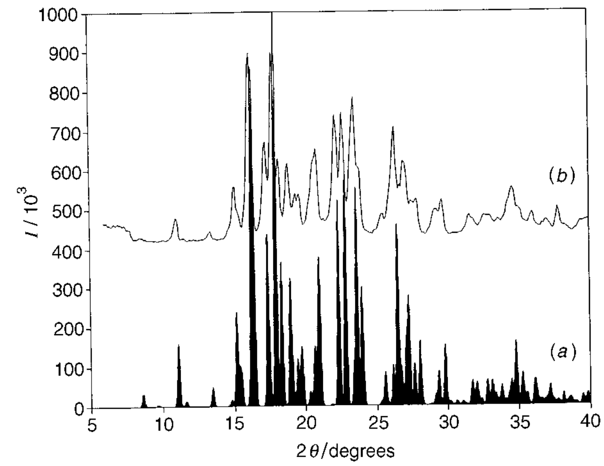

Fig. 3 (*a*) Calculated powder pattern for compound **2**. (*b*) Experimental powder pattern: H + *o*-BD ground.

The patterns obtained from the H·1*o*-BD and H·1*m*-BD are identical and we conclude that the inclusion compounds are isomorphous.

The mechanism of the solid–solid reaction is not well understood, but may well involve an initial attack on the host surface by guest vapour, followed by interdiffusion of the host and guest molecules. We note that at room temperature the vapour pressure of *p*-BD, 0.04 Pa, is one tenth that of *m*-BD and one hundredth that of *o*-BD. We suggest that this may be the primary factor for failure of the host–*p*-BD reaction.

Lattice energy calculations

When considering the selectivity of a particular host for a given guest from a mixture of isomers, an important parameter to be evaluated is the lattice energy. There are two principal interactions that are responsible for the packing of the molecules: van der Waals forces and hydrogen bonds.

The potential energy of the lattice was calculated by the method of atom–atom potentials. The program HEENY[18,19] uses empirical atom pair potential curves to evaluate non-bonded van der Waals interactions. The coefficients of the atom–atom potentials are of the form given in eqn. (1), where *r*

$$V(r) = a\exp(-br)/r^{d} - c/r^{6} \qquad (1)$$

is the interatomic distance and the coefficients *a*, *b*, *c*, *d* are those given by Giglio[20] and recently reviewed by Pertsin and Kitaigorodsky.[21] In addition we have incorporated a hydrogen bonding potential into our calculations. This was a simplified version of that used by Vedani and Dunitz,[22] using the potential [eqn.(2)] where *R* is the distance between the hydrogen and the

$$V_{\mathbf{H\text{-}bond}} = (A/R^{12} - c/R^{10})\cos^{2}\theta \qquad (2)$$

acceptor, and θ is the donor–H···acceptor angle. Further details are given in a previous paper[23] in which we analysed the relative stabilities of a series of inclusion compounds between bulky hydroxy hosts and 1,4-dioxane.

We selected a representative host–guest pair and carried out the appropriate summations of all host···host, host···guest and guest···guest interactions. For **1** we obtained a value of -264 kJ mol^{-1}, while **2** yielded -250 kJ mol^{-1}. These values are of the same order as those obtained for the packing potentials of hydrocarbons as discussed by Gavezzotti.[24] Our result is gratifying, in that the inclusion compound formed by the *p*-BD has a more negative lattice energy than that formed by the *o*-BD. We failed to grow single crystals of the host with *m*-BD, and thus could not carry out a detailed energy analysis of the latter compound. However, since this compound is isomorphous with the H·*o*-BD, their lattice energies are likely to be very similar.

This therefore explains the results of the competition experiments that the *p*-BD is invariably included by the host in favour of the two other isomers, and indicates the association between structural features and the preferential formation of a complex.

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