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Selective inclusion of aliphatic alcohols by a diol host compound

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An aliphatic alcohol mixture is separated using enclathration methods, and the results are explained by means of lattice energy calculations and structural analysis.

Selective enclathration is the quintessential example of molecular recognition, as it depends on the strength and directions of non-covalent interactions which occur between host and guest molecules. This is an important procedure in industry, particularly for the resolution of optical isomers, which is of direct interest to the pharmaceutical industry. The process has been reviewed by Toda,[1] who has synthesised a variety of diol, bisphenol and diamide host compounds, and discussed their formation of inclusion compounds with a variety of guest species. For analytical purposes, the separation of optical isomers on chiral stationary phases is attracting increasing interest, and a recent article[2] discusses various chromatographic techniques which use this form of molecular recognition for both analytical determinations and large scale preparative isolation of enantiopure compounds.

We have concentrated on the separation of close isomers by selective enclathration with bulky host molecules. In this manner, the host 1,1,2,2-tetraphenylethane-1,2-diol has been used to separate picoline, methylquinoline and lutidine isomers[3,4] and the selectivities of the bulky host compounds 9,9′-bianthryl and 9,9′-spirofluorene have been reviewed by Weber.[5]

We have used the host compound 1,1-bis(4-hydroxyphenyl)cyclohexane (**H**) to separate the isomers of phenylenediamine,[6] benzenediol[7] and picoline.[7] We have used this host compound to carry out competition experiments between four aliphatic alcohols: methanol, ethanol, isopropanol and *n*-butanol, and we present the results of the structural analyses, competition experiments and lattice energy calculations.

Experimental

Suitable crystals of inclusion compounds **1**–**4** were obtained by slow evaporation over a period of 4 days. Many attempts were made to obtain suitable crystals of the inclusion compound of the host with *n*-propanol, but they were unsuccessful. Preliminary cell dimensions and space group symmetry were determined photographically and subsequently refined by standard procedures on a CAD4 diffractometer. The intensities were collected in the ω–2θ scan mode and crystal stabilities were monitored by periodic reference reflections. The important crystal and experimental data are presented in Table 1. All four structures were solved by direct methods using SHELX-86[8] and refined employing full-matrix least-squares analysis using the program SHELX-93,[9] refining on F^2. The numbering scheme is shown in Scheme 1. In the final refinement for structures **1**, **2** and **3**, all non-hydrogen atoms were treated anisotropically. For **4**, two carbon atoms of the guest molecule were refined isotropically. The hydroxy hydrogens were all located in difference electron density maps and refined with independent temperature factors, and with simple bond length constraints.

Competition experiments

Competition experiments were performed to determine the complexation selectivity of the host for the various alcohols, and were carried out as follows: a series of mixtures of two alcohol guests was made up with the mole fraction of the guests varying from 0 to 1 in steps of 0.1, always keeping the lesser guest in excess with respect to the host. Crystals of inclusion complexes were obtained by slow evaporation, were filtered and placed in vials sealed with rubber septa. The vials were heated to 150 °C in order to induce guest desolvation. On cooling of the vials, the vapours of alcohol guest condensed on the sides of the vials, and these drops were used for gas chromatographic (GC) analysis.

The competition experiments were extended to include all four alcohols simultaneously. A tetrahedron was chosen to represent the relative concentrations of the four guests. Each alcohol investigated was assigned a vertex of the tetrahedron, so that each vertex represents 100% of the corresponding alcohol, as measured perpendicularly from the opposite face. An icosahedron was placed in the centre of the tetrahedron, and the defining points of the icosahedron were chosen to represent the initial alcohol mixtures. The relative amounts of each alcohol represented by the points of the icosahedron were calculated as follows: the distance from each point of the icosahedron to each of the four planes of the tetrahedron was calculated. These distances were converted to fractions of the total distance from a vertex to a plane, and in this manner the percentages of the alcohols in the starting solutions were determined.

On completion of the competition experiments, the percentages of each alcohol included by the host were obtained by GC analysis. These percentages were converted to distances from the respective planes, and a series of final co-ordinates were obtained.

The relative compositions of the included guests and of the mother liquors with which they were in equilibrium were determined by gas chromatography using a Philips PYE Unicam Series 304 chromatograph equipped with a 10% OV101 on Chromosorp column (1 m). This apparatus was linked to a Waters 746 Data Module integrator.

Thermal analysis

Differential scanning calorimetry (DSC) and thermogravimetry (TG) were performed on a Perkin-Elmer PC7 series system. All samples were dried in air, and lightly crushed before analysis. The samples were placed in open platinum pans for TG experiments and in crimped, vented aluminium sample pans for DSC experiments. Sample masses in each case were

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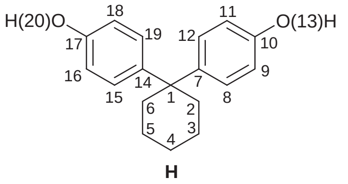
Table 1 Crystal data, experimental and refinement parameters

	1	**2**[a]	**3**	**4**
molecular formula	$C_{18}H_{20}O_2{\cdot}CH_4O$	$C_{18}H_{20}O_2{\cdot}C_2H_6O$	$C_{18}H_{20}O_2{\cdot}C_3H_8O$	$C_{18}H_{20}O_2{\cdot}C_4H_{10}O$
M_r/g mol^{-1}	300.38	314.41	328.43	342.46
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a/Å	6.276(2)	6.293(2)	6.3207(6)	6.285(8)
b/Å	10.895(4)	10.859(2)	10.881(2)	10.784(2)
c/Å	12.887(8)	13.420(3)	14.301(3)	14.789(3)
α/°	90.34(5)	84.73(2)	86.59(1)	98.14(2)
β/°	101.52(5)	77.91(2)	79.43(1)	92.24(1)
γ/°	102.18(3)	78.96(2)	79.51(1)	101.07(1)
V/Å^3	842.9(7)	878.8(4)	950.4(3)	971.5(3)
Z	2	2	2	2
D_c/g cm^{-3}	1.18	1.18	1.15	1.17
D_m/g cm^{-3}	1.16(2)	1.16(3)	1.13(2)	1.15(3)
μ(Mo-Kα)/cm^{-1}	0.80	0.78	0.75	0.76
F(000)	324	340	356	372
crystal size/mm	0.35 × 0.35 × 0.25	0.45 × 0.4 × 0.4	0.4 × 0.4 × 0.25	0.4 × 0.35 × 0.35
range scanned θ/°	1–25	1–25	1–25	1–25
range of indices	h: ±7; k: ±12; l: 0, 15	h: ±7; k: ±12; l: 0,15	h: ±7; k: ±12; l: 0,16	h: ±7; k: ±12; l: 0,17
crystal decay (%)	−5.2	−7.1	−6.54	−9.13
no. reflections collected	3116	3233	3483	3563
no. reflections observed	2970	3088	3337	3418
no. parameters	219	227	224	236
R_1	0.0587	0.0482	0.0816	0.0891
wR_2	0.1602	0.1328	0.2283	0.2398
S	1.010	1.003	1.019	1.219
$\Delta\rho$ excursions/e Å^{-3}	0.214; −0.311	0.333; −0.177	0.581; −0.337	1.025; −0.807

[a] This structure has previously been reported by Bond *et al.*,[15] but has been redetermined for the purposes of this paper. Cell data obtained from the two structure solutions are in good agreement.



Scheme 1 **1** = **H**·methanol, **2** = **H**·ethanol, **3** = **H**·isopropanol, **4** = **H**·*n*-butanol

2–5 mg, and the samples were purged by a stream of nitrogen flowing at 40 ml min^{-1}. The mass losses observed in the TG traces on heating complexes **1**–**4** from 30–200 °C confirmed that in each complex the host : guest ratio was 1 : 1. Endotherms were observed in the DSC traces at the temperatures corresponding to the mass loss steps observed in the TG traces.

Results and Discussion

The crystal structures of complexes **1**–**4** were analysed, and were found to be essentially isostructural.‡ All have a host : guest ratio of 1 : 1 and crystallise in the triclinic space group $P\bar{1}$ with $Z = 2$. The structures of **1** and **2** are well refined, but those of **3** and **4** exhibited relatively high thermal motion of the guest molecules. This resulted in somewhat higher final R values, a feature common in the structures of many inclusion compounds. Their packing is characterised by the host forming a double ribbon motif with the guest located in channels running parallel to [100], as shown in Fig. 1. The consistency in the crystal packing is reflected in the small variation of the unit cell parameters a (6.276–6.3207 Å) and b (10.784–10.895 Å) in the four structures. However, a significant increase of the cell parameter c occurs: from 12.887 Å in **1** to 13.420 Å in **2**, to 14.301 Å in **3**, and finally to 14.789 Å in **4**. This variation

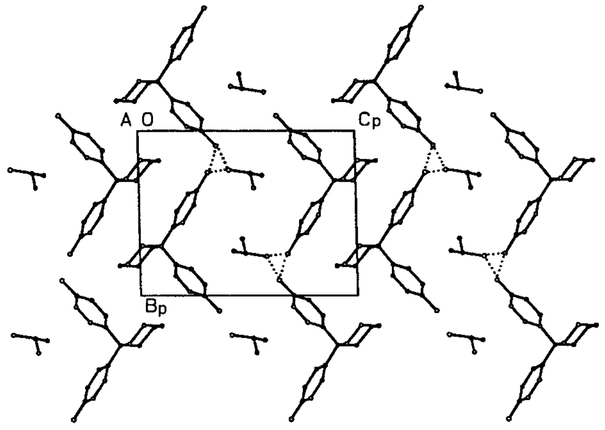


Fig. 1 Packing diagram of complex **3**, viewed along [100], with hydrogen bonding interactions inserted

Table 2 Details of hydrogen bonding

complex	donor	acceptor	D—H/Å	D···A/Å	D—H···A/°
1	O1G	O20^a	0.94(5)	2.664(4)	162(5)
	O13	O1G	0.98(7)	2.666(4)	176(6)
	O20	O13^b	1.00(5)	2.672(4)	177(4)
2	O13	O1G^c	0.99(3)	2.583(4)	173(3)
	O1G	O20^e	0.85(3)	2.782(3)	166(3)
	O20	O13^b	0.94(3)	2.706(3)	172(3)
3	O20	O1G^f	0.96(5)	2.595(5)	156(5)
	O1G	O13^g	0.98(4)	2.735(4)	173(5)
	O13	O20^b	0.94(5)	2.677(4)	172(4)
4	O13	O1G^h	1.00(4)	2.626(4)	172(3)
	O1G	O20^i	0.83(3)	2.774(4)	169(4)
	O20	O13^b	0.87(4)	2.708(4)	170(4)

Symmetry code: (*a*) $x+1, y+1, z$; (*b*) $x, y-1, z$; (*c*) $x-1, y, z$; (*e*) $x, y+1, z$; (*f*) $-x, -y+1, -z+1$; (*g*) $-x+1, -y, -z+1$; (*h*) $-x+1, -y+2, -z$; (*i*) $-x, -y+1, -z$.
D = Donor; A = Acceptor.

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‡Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 1145/93.

in *c* occurs since the 'layers' of host molecules along *c* are stabilised mainly by weak van der Waals forces, and therefore their periodicity may be relatively easily increased. This increase in the spacing between the layers occurs in order to accommodate the larger guest molecules between the layers. Details of the hydrogen bonding interactions in structures **1**–**4** are presented in Table 2.

Lattice energy calculations

The potential energy environment of the guest molecules in the host structural environment was studied using empirical atom pair potentials. The program HEENY[10,11] was used to calculate intermolecular non-bonded interactions. HEENY calculates atom-pair potentials using van der Waals energy of the form

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

where *r* is the distance in Å between any pair of atoms and *a*, *b*, *c*, and *d* are coefficients calculated by Giglio,[12] and reviewed by Pertsin and Kitaigorodsky,[13] to yield $U(r)$ in kcal mol^{-1}. In addition, hydrogen bonding potentials have been incorporated into the calculations. A simplified version of that used by Vedani and Dunitz[14] was employed, using the potential

$$U_{\mathrm{hb}}=[(A/R^{16})-(C/R^{10})]\cos^{2}\theta$$

where U_{hb} is the energy associated with the hydrogen bond, *R* the distance between the hydrogen atom and the acceptor, θ the angle donor—H···acceptor and the constants *A* and *C* are related to the well-depth $U_{\min}$ and the equilibrium distance R_{o} by $A=-5R_{\mathrm{o}}^{12}U_{\min}$ and $C=-6R_{\mathrm{o}}^{10}U_{\min}$.

A mixing scheme was introduced to allow the full non-bonded potential U_{norm} to take effect as θ deviates from the ideal angle of 180° such that

$$U_{\mathrm{total}}=U_{\mathrm{hb}}+(1-\cos^{2}\theta)U_{\mathrm{norm}}$$

For each structure, we selected a representative host–guest pair and carried out the appropriate summations of all the host···host, host···guest, and guest···guest interactions. The calculated lattice energies of the four structures indicate that complex **3** [−268(1) kJ mol^{-1}] is most stable, followed by **4**

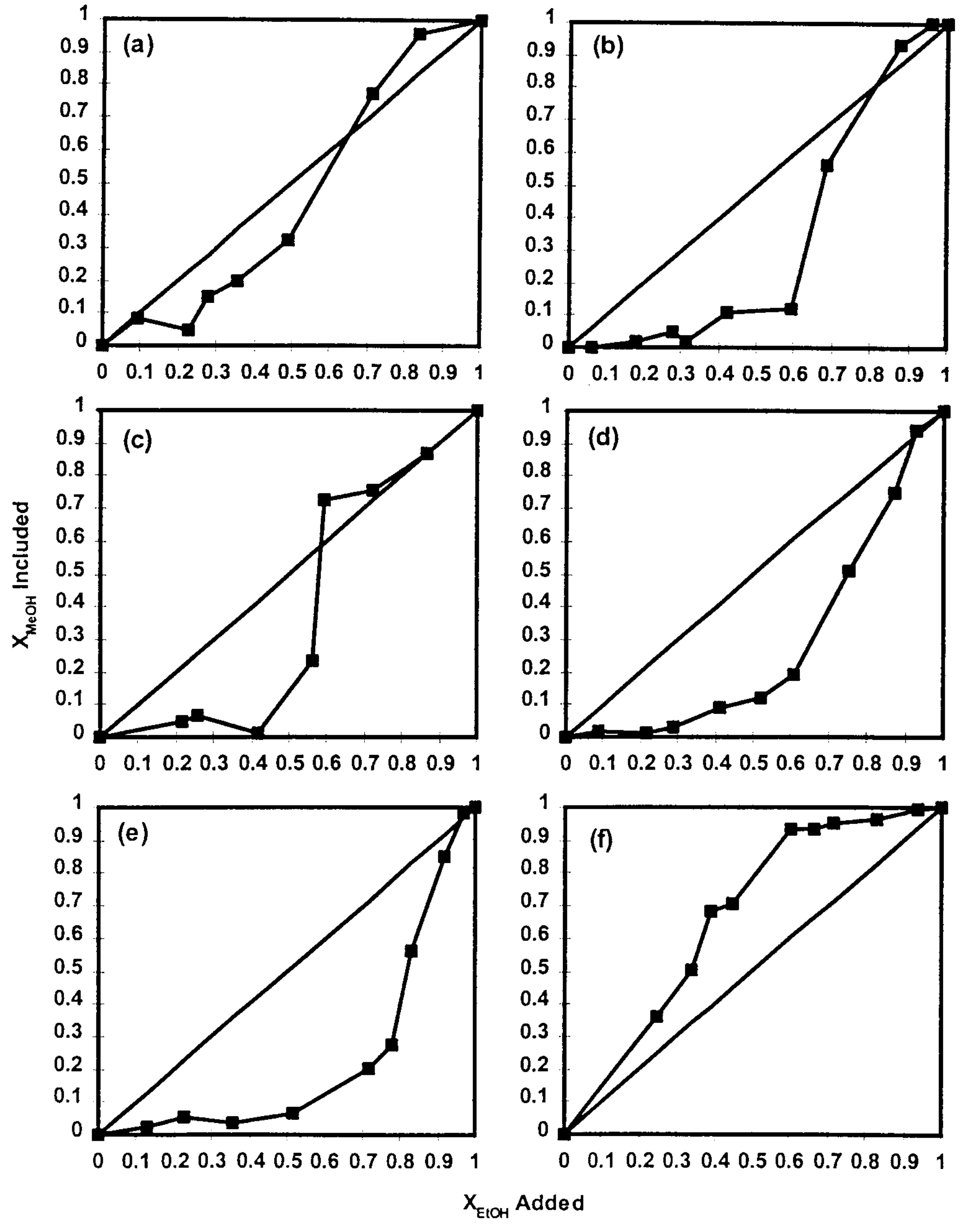

Fig. 2 Results of the two-component competition experiments: (a) methanol *vs.* ethanol; (b) methanol *vs.* isopropanol; (c) methanol *vs.* *n*-butanol; (d) ethanol *vs.* *n*-isopropanol; (e) ethanol *vs.* *n*-butanol; (f) isopropanol *vs.* *n*-butanol

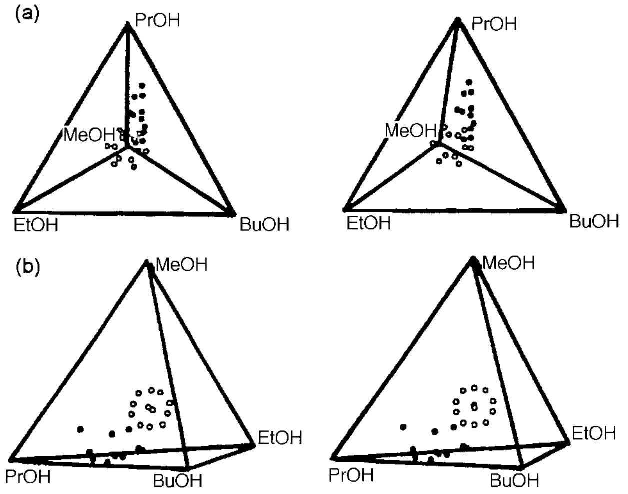

Fig. 3 Results of the four-component competition experiments, presented in stereo. The unshaded circles represent the starting concentrations, while the shaded circles represent the concentrations of the four components included by the host. (a) View of the tetrahedron perpendicular to the ethanol/isopropanol/*n*-butanol plane; (b) side view of the tetrahedron.

[−258(1) kJ mol^{-1}]. Complexes **1** [−216(1) kJ mol^{-1}] and **2** [−215(1) kJ mol^{-1}] have similar lattice energies, and therefore are of similar stability.

The relative stabilities of the complexes were reflected by the results obtained from the competition experiments. The two-component results, illustrated in Fig. 2, show that there is no significant selectivity between MeOH and EtOH, but the selectivity between the other pairs of alcohols is as follows: Bu^{n}OH > MeOH, Pr^{i}OH > MeOH, Pr^{i}OH > EtOH, Bu^{n}OH > EtOH and Pr^{i}OH > Bu^{n}OH. This trend agrees with the lattice energy values, with the most stable complexes forming preferentially. The results of the four-component competition experiments are presented in Fig. 3, and agree well with the previous observations. A migration of the starting icosahedron occurs away from the vertices representing methanol and ethanol, and towards the vertex representing isopropanol. A less pronounced migration occurs away from the *n*-butanol vertex toward the isopropanol vertex. This result is expected, since the lattice energy of **3** is only *ca.* 10 kJ mol^{-1} lower than that of complex **4**.

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