Inclusion and separation of picoline isomers by a diol host compound†

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Structures of the inclusion compounds formed between the host compound 1,1-bis(4-hydroxyphenyl)cyclohexane and the isomers of picoline have been elucidated. The activation energies and the kinetics of desolvation for the complexes have been determined. Competition experiments have been performed to investigate which isomer is preferentially enclathrated by the host. Lattice energy calculations explain the results of the competition experiments.

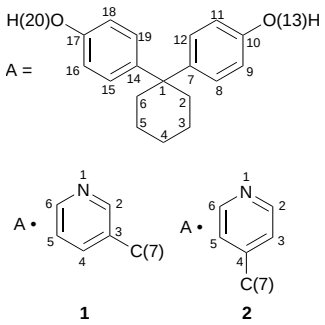
Selective enclathration by a host compound for a given guest is a molecular recognition process. This can be studied at the molecular level by mapping the interactions between host and guest in a solid inclusion compound. The resulting non-bonded interaction energies allow the calculation of lattice energies which are a measure of the relative stabilities of the host–guest networks and thus explain the preferential enclathration of a particular guest by a given host molecule. The separation of close isomers by clathrate formation is industrially attractive because it is simple, efficient and not energy intensive. The process is chemically attractive because it does not involve the breaking or forming of covalent bonds but instead relies on shape recognition of the guest by the host. Typically, the host compound is dissolved in a mixture of guest isomers, and the resulting crystalline inclusion compound is enriched with respect to a particular guest. The latter is filtered and the enriched guest released by gentle warming, so that the host can be recycled.

Host molecules may generally be classified into two types: first, those that form molecular complexes by accepting convex guests into a cavity. Examples of this kind include cyclodextrins, cavitands and carcerands, which have recently been reviewed.[1] The second type are those which form lattice inclusion compounds by packing in a manner that leaves channels or cavities in the crystal structure, and thus accommodate guest molecules. We have studied the latter type of clathrates extensively, and have employed bulky host compounds to separate a number of close isomers. In this manner, the host 1,1,2,2-tetraphenylethane-1,2-diol has been used to separate picoline, methylquinoline and lutidine isomers.[2,3] Also, cholic acid enclathrates nitrobenzene in preference to aniline,[4] and the selectivity of the bulky hydrocarbons 9,9′-bianthryl and 9,9′-spirofluorene have been reviewed by Weber.[5] Ethanol has also been extracted from a mixture of homologous alcohols by enclathration with derivatives of quininium bromide[6] and triphenylsilanol.[7]

The host compound 1,1-bis(4-hydroxyphenyl)cyclohexane forms inclusion compounds with a variety of guests. It has been used to separate the isomers of the cresols,[8] the phenylenediamines[9] and the benzenediols.[10] We now present the results of competition experiments between this host and the picolines.

Experimental

Suitable crystals of inclusion compounds **1** and **2** were obtained by slow evaporation over a period of 4 d. Many attempts were made to obtain suitable crystals of the inclusion compound of the host with 2-picoline, which crystallises as a monohydrate, but the results were unsatisfactory. Even the best crystals were of poor quality, gave a weak diffraction pattern and only yielded a partial crystal structure analysis which is therefore not reported. 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 given in Table 1. Both structures were solved by direct methods using SHELX-86[11] and refined employing full-matrix least-squares analysis using the program SHELX-93,[12] refining on



Scheme 1

F^2. The numbering scheme is shown in Scheme 1. In the final refinement for both structures all non-hydrogen atoms were treated anisotropically. The aromatic and methylene hydrogens were geometrically constrained and refined with common isotropic temperature factors. The hydroxy hydrogens were all located in difference electron density maps and refined with independent temperature factors, and with simple bond length constraints.‡

X-Ray powder diffraction (XRD) patterns were recorded in a Philips PW1050/80 vertical goniometer with a PW1394 motor control unit. The patterns were collected over a 2θ range of 6–40°.

Competition experiments

Competition experiments were conducted between the 3-picoline and 4-picoline guests as follows: a series of 11 vials was made up with mixtures of the two liquid guests, varying the mole

† Complexation with diol host compounds, Part 26.

‡ Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, *J. Mater. Chem.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 1145/45.

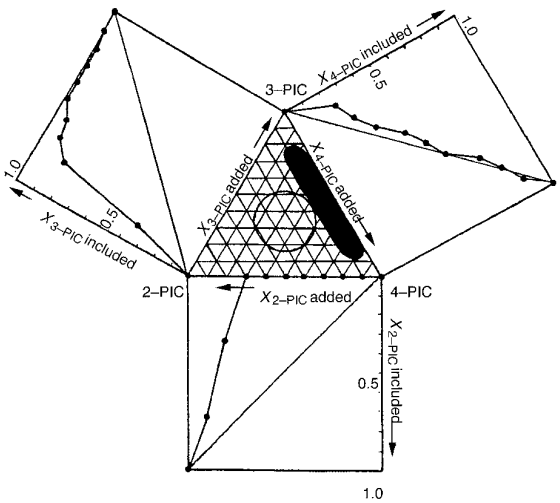


Fig. 1 Results of the competition experiments

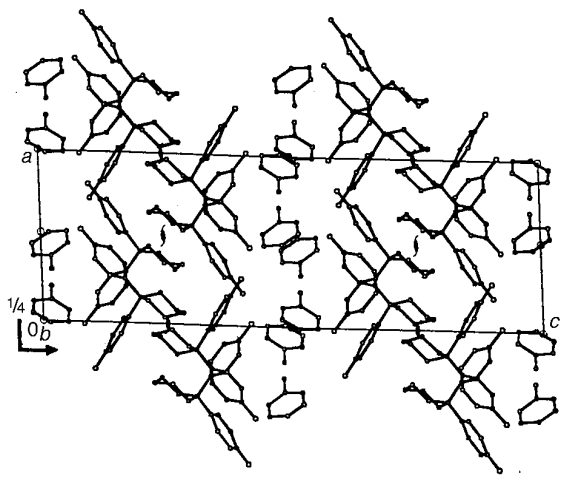


Fig. 2 Packing diagram for **1**

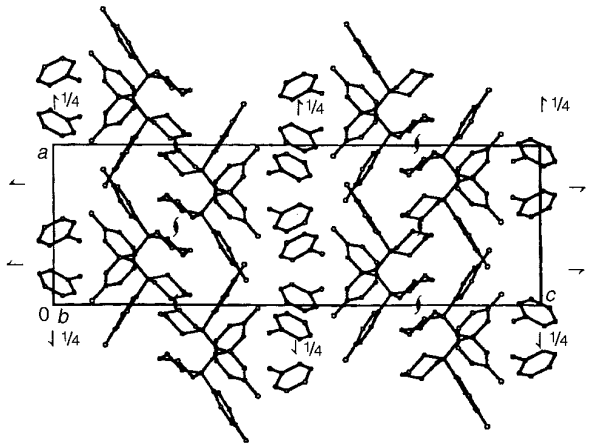


Fig. 3 Packing diagram for **2**

fraction of the guests from 0 to 1 in the series, but keeping the host : guest ratio at 1 : 20 in each vial. Crystals were obtained by slow evaporation, filtered from the mother liquor and dissolved in ethyl acetate. The relative composition of the included guests and of the mother liquors with which they were in equilibrium were determined by gas chromatography using a Varian 3300 instrument with a Supelcowax 10 column (0.2 mm diameter, 30 m length) and a Varian SP4290 integrator.

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 ⅓ each, representing the centre of the circle, was also analysed. The relative compositions of the included guests and mother liquors were analysed as before.

Thermal analysis and kinetics

Differential scanning calorimetry (DSC) and thermal gravimetry (TG) were performed on a Perkin-Elmer PC7 series system. Fine powdered specimens, obtained from continuously stirred solutions, were dried in air and placed in open platinum

Table 1 Details of crystals, data collection at 20 °C and final refinements

parameter	**1**	**2**
molecular formula	$C_{18}H_{20}O_2{\cdot}C_7H_7N$	$C_{18}H_{20}O_2{\cdot}C_7H_7N$
molecular mass/g mol^{-1}	373.05	373.05
space group	$P2_1/c$	$P2_12_12_1$
a/Å	10.684(3)	10.649(5)
b/Å	11.712(2)	11.885(2)
c/Å	32.021(4)	31.872(6)
β/°	93.39(2)	90
V/Å^3	4000.1(1)	4034.0(2)
Z	8	8
D_c/g cm^{-3}	1.200	1.190
D_m/g cm^{-3}	1.18(6)	1.18(5)
μ(Mo-Kα)/cm^{-1}	0.75	0.75
F(000)	1552	1552
crystal size/mm	0.4 × 0.4 × 0.34	0.4 × 0.4 × 0.4
range scanned, θ(°)	1–25	1–25
range of indices	h: ±12; k: 0,13; l: 0,38	h: ±12; k: ±14; l: 0,37
no. reflections collected	7152	12411
no. reflections observed	7016	8346
no. parameters	533	513
R	0.0477	0.0409
Rw	0.1134	0.1030
S	1.047	0.968
max. shift/Å	0.013	0.001
mean shift/esd	0.152	0.003
$\Delta\rho$ excursions/e Å^3	0.201; −0.264	0.154; −0.249

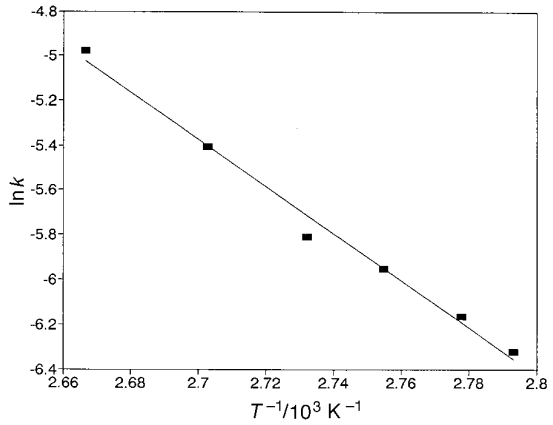


Fig. 4 Arrhenius plot for the desolvation of **1**

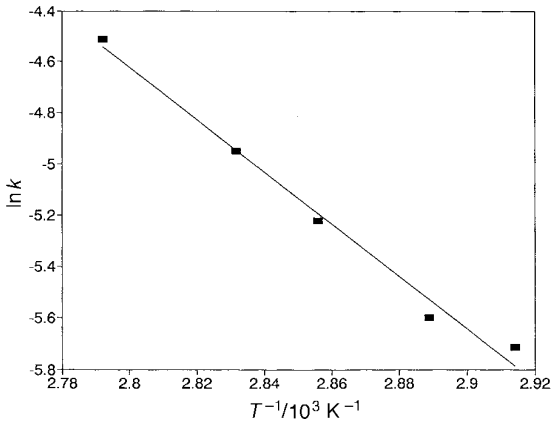


Fig. 5 Arrhenius plot for the desolvation of **2**

pans for TG experiments and in crimped, vented aluminium sample pans for DSC experiments. Sample masses in each case were 2–5 mg, and the samples were purged by a stream of nitrogen flowing at 40 ml min^{-1}. Kinetic data for the desolvation of guest were obtained both from isothermal TG experiments and nonisothermal experiments at variable heating rates.

Results and Discussion

For **1**, the space group is $P2_1/c$ with $Z=8$. There are therefore two host and two guests molecules in the asymmetric unit. The packing of the structure, shown as a projection viewed along [010], is given in Fig. 2. The cyclohexane moiety of the host is in the chair conformation and the host molecules pack in a double ribbon motif running parallel to *a*. The host molecules are stabilised by intermolecular hydrogen bonding and a given pair of host ribbons is related by a two-fold screw axis. The 3-picoline guest molecules are hydrogen bonded to the host and lie in channels parallel to *a*. For **2**, the space group is $P2_12_12_1$ with $Z=8$ and so we again have two host and two guest molecules in the asymmetric unit. However, the packing is subtly different from that of **1**. The structure, shown in Fig. 3, is again made up of double ribbons of hydrogen bonded host molecules interrupted by channels of guest molecules running parallel to *a*. However, the host double ribbons in **2** are displaced by a vector of ½(*a*) relative to one another, in order to accommodate the $P2_12_12_1$ symmetry, whereas in **1** the double ribbons are related by a centre of inversion. Details of the hydrogen bonding are presented in Table 2.

The results of the competition experiments are shown in Fig. 1. Each two-component result shows the mole ratio of the initial solution *versus* that included by the host. For the 2-picoline/3-picoline competition the latter is strongly favoured by the host, and an equimolar mixture results in 98% 3-picoline being included. 4-Picoline is also convincingly favoured over 2-picoline, but in the 3-picoline/4-picoline experiment no significant selectivity is observed. The three-component experiment is shown on the equilateral triangle. The starting mixtures were located on the circle, and after inclusion they invariably moved away from the 2-picoline component, as shown by the shaded area.

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[13,14] 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 shown in eqn. (1),

$$V(r)=a\exp[(-br)/r^d-c/r^6] \quad (1)$$

where r is the interatomic distance and the coefficients a–d are those given by Giglio[15] and recently reviewed by Pertsin and Kitaigorodsky.[16] In addition, we have incorporated a hydrogen bonding potential into our calculations. This is a simplified version of that used by Vedani and Dunitz,[17] using the potential shown in eqn. (2),

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

where R is the distance between the hydrogen and the acceptor, and θ is the donor–A···acceptor angle. Further details are given in a previous paper[18] in which the relative stabilities of a series of inclusion compounds between bulky hydroxy hosts and 1,4-dioxane were analysed.

For both structures **1** and **2** we selected a representative host–guest pair and carried out the appropriate summations of all the host···host, host···guest and guest···guest interactions. For **1** we obtained a value of −261.9 kJ mol^{-1}, while **2** yielded a very similar value of −261.4 kJ mol^{-1}. As stated earlier, we did not obtain a fully refined structure of the 2-picoline inclusion compound, because although the atomic

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

compound	donor	acceptor	D—H/Å	D···A/Å	D—H···A (°)
1	O20A	N1GA[a]	0.96(3)	2.664(3)	171.8(3)
	O13B	N1GB[b]	0.98(3)	2.647(3)	167.8(3)
	O13A	O20A[c]	0.93(3)	2.733(3)	171.1(3)
	O20B	O13B[d]	0.94(4)	2.735(3)	170.6(4)
2	O13A	N1GA[e]	0.95(2)	2.676(3)	168.7(4)
	O20B	N1GB[f]	0.974(4)	2.678(3)	174.1(3)
	O20A	O13A[c]	0.938(3)	2.723(3)	168.8(3)
	O13B	O20B[d]	1.00(4)	2.728(3)	169.3(3)

Symmetry operations: [a] $-x+1, -y+1, -z$. [b] $-x, -y+1, -z$. [c] $x-1, +y, +z$. [d] $x+1, +y, +z$. [e] $x-½, -y-½, -z$. [f] $x-½, -y+½, -z$.

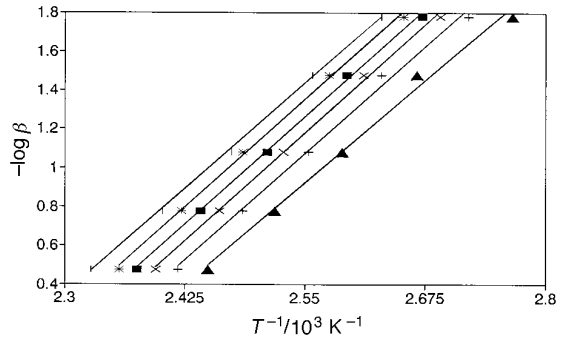


Fig. 6 Plot of $-\log \beta$ *versus* T^{-1} for several percentages of decomposition of **1**: (▲) 6.25, (+) 9.38, (×) 12.5, (■) 15.63, (∗) 18.75 and (|) 21.87 mass% loss

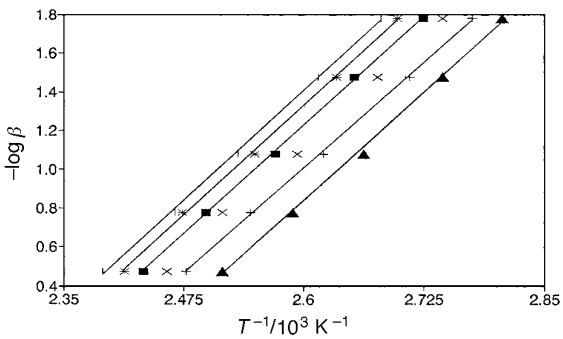


Fig. 7 Plot of $-\log \beta$ *versus* T^{-1} for several percentages of decomposition of **2**: (▲) 6.25, (+) 9.37, (×) 12.5, (■) 15.63, (∗) 18.75 and (|) 12.87 mass% loss

positions of the host and water were located unambiguously, the guest molecule exhibited high thermal motion and yielded unsatisfactory molecular parameters. We therefore constructed an idealised 2-picoline molecule and superimposed it as a rigid structure on the difference electron density map calculated from the structure factors derived from the host alone. We then calculated the lattice energy as before and obtained the substantially higher value of -198.6 kJ mol^{-1}. These are gratifying results because they explain the non-selectivity of the host for the 3-picoline *versus* the 4-picoline, in that their inclusion compounds have practically the same lattice energies. They also justify the selectivities of these two isomers over the 2-picoline in that the latter compound has a smaller lattice energy, and thus results in the effective rejection of this isomer in the three-component competition experiment.

Kinetics of desolvation

For both **1** and **2**, a series of mass loss *versus* time curves were obtained for the desolvation reaction, over a temperature range of 70–102 °C. The data were reduced to fractional reaction α *versus* time curves. For both systems the curves showed a deceleration. Various appropriate kinetic models[19] were tested for linearity and all the data best fitted the equation representing the contracting area model *R*2: $1-(1-\alpha)^{1/2}=kt$ over the complete α range. Plots of $\ln k$ *versus* $1/T$ for **1** and **2** are shown in Fig. 4 and 5. These yielded activation energies of 87(4) and 85(5) kJ mol^{-1} respectively.

Thermogravimetry at various heating rates provided another method to estimate the activation energy of the guest-release reaction. We used the method developed by Flynn and Wall[20] which has previously been applied to similar compounds.[21] The decomposition curves for both **1** and **2** were recorded at various heating rates, β, ranging from 1 to 20 °C min^{-1} and the corresponding semilogarithmic plots of $\log \beta$ *versus* $1/T$ are shown in Fig. 6 and 7. For **1**, the slopes of the lines

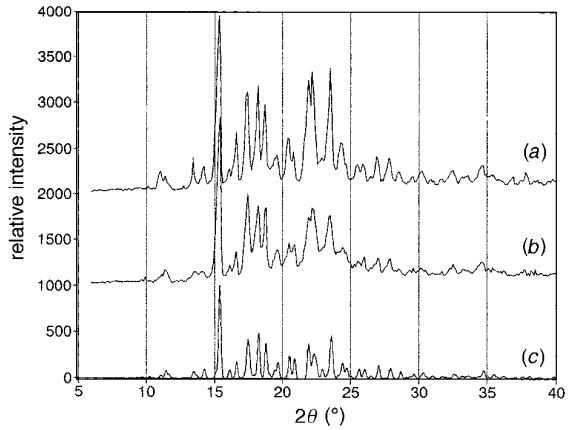


Fig. 8 (*a*) Experimental powder pattern of sample obtained by fast stirring of host in 3-picoline. (*b*) Experimental powder pattern of host exposed to 3-picoline vapour. (*c*) Calculated powder pattern for compound **1**.

correspond to activation energies varying from 77 to 81 kJ mol^{-1} while for **2** the corresponding values vary from 79 to 82 kJ mol^{-1}. The similarity in the activation energy values obtained by these different methods is satisfying.

We are conscious of the fact that different methods of preparation of inclusion compounds can lead to a variety of structures with inconsistent host : guest ratios. We therefore checked that the powdered samples used for the kinetic experiments had the same crystal structure as those of the single crystals. This was achieved by recording the powder diffraction pattern of the inclusion compounds grown as microcrystalline powders by fast stirring, and comparing these to the patterns calculated from the atomic coordinates derived from the structure solutions using the program LAZY PULVERIX.[22] These patterns match very well both in peak position and relative intensity. Interestingly, we also formed the inclusion compounds by exposing the host to a vapour of the guest, which yielded essentially the same XRD patterns as before. The powder diffraction results for **1** are shown in Fig. 8. Similar results were obtained for **2**.

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