

Selective Inclusion by Cholic Acid

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Crystallographic, thermodynamic and molecular mechanics results show that cholic acid enclathrates nitrobenzene in preference to aniline.

The structures of the inclusion compounds of cholic acid, (CA), have recently attracted considerable attention¹⁻³ but details of the mechanism of selective enclathration by cholic acid have not been discussed. We have studied the inclusion of two guests which are structurally similar: aniline and nitroben-

zene, and have carried out competition experiments of these two guests with cholic acid as host, and have analysed the selectivity by chromatographic and thermal techniques.

The crystal structures of the CA·aniline (CAAN) and the CA·nitrobenzene (CANI) inclusion compounds are compar-

able.† The unit cell parameters of the two compounds are similar and the packing motif of the host molecules is analogous as shown in Figs. 1 and 2. The guest molecules lie in channels parallel to the screw axis, but the orientation of the guests differs, with the nitro moieties of the nitrobenzene pointing away from the walls of the channel while the amino groups of the aniline are directed towards the hydrophilic pocket formed by the stacking of cholic acid. There are no close contacts between host and guest in CANI while in

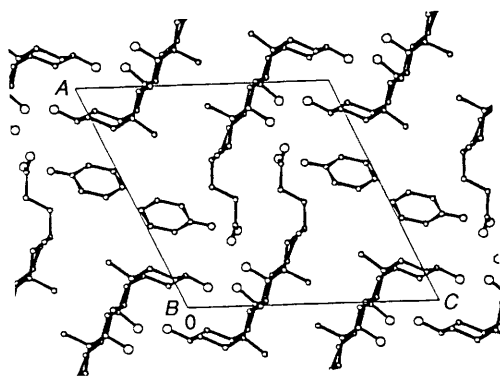
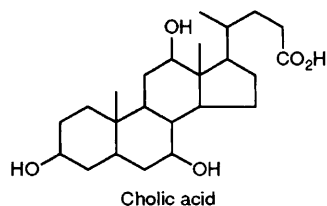


Fig. 1 Projection along [010] for structure CAAN

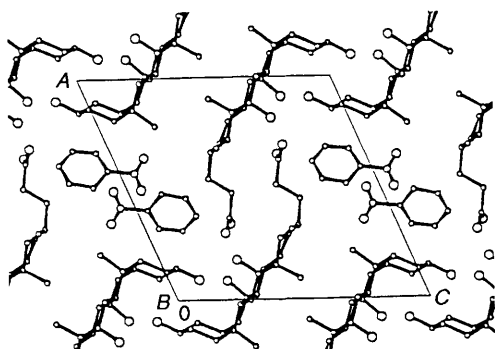


Fig. 2 Projection along [010] for structure CANI

† *Crystal data*: for both structures, intensity data were collected at room temp. on an Enraf-Nonius CAD4 diffractometer using Mo-K α , ($\lambda = 0.7107 \text{ \AA}$), radiation to $\theta_{\text{max}} = 25^\circ$.

For CAAN: $\text{C}_{24}\text{H}_{40}\text{O}_5 \cdot \text{C}_6\text{H}_7\text{N}$, $M_r = 501.71$, monoclinic space group $P2_1$, $a = 13.742(2)$, $b = 8.049(1)$, $c = 14.095(2) \text{ \AA}$, $\beta = 115.20(2)^\circ$, $Z = 2$, $D_m = 1.192 \text{ g cm}^{-3}$, $D_c = 1.181 \text{ g cm}^{-3}$, crystal size = $0.4 \times 0.5 \times 0.5 \text{ mm}$, 2784 unique reflections. Final $R = 0.0641$ for 2097 reflections with $I > 2\sigma(I)$.

For CANI: $\text{C}_{24}\text{H}_{40}\text{O}_5 \cdot \text{C}_6\text{H}_5\text{NO}_2$, $M_r = 531.69$, monoclinic space group $P2_1$, $a = 13.579(2)$, $b = 8.106(3)$, $c = 14.048(1) \text{ \AA}$, $\beta = 113.52(1)^\circ$, $Z = 2$, $D_m = 1.248 \text{ g cm}^{-3}$, $D_c = 1.245 \text{ g cm}^{-3}$, crystal size = $0.25 \times 0.25 \times 0.5 \text{ mm}$, 2807 unique reflections. Final $R = 0.0651$ for 2034 reflections with $I > 2\sigma(I)$.

Solution by direct methods was followed by least-squares refinement. In the final models the non-hydrogen atoms of the host were treated anisotropically but those of the guest, isotropically. The hydroxy hydrogens were located unambiguously in difference electron density maps and refined with bond length constraints for structure CAAN and in fixed positions for structure CANI.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

CAAN the closest contacts between the amino N atom and host hydroxy O atoms are, at 3.18 and 3.21 \AA , at the upper limit of possible hydrogen bond contact distances.

We have carried out guest competition experiments by dissolving with heating the cholic acid in known mixtures of the guests and analysing the ensuing crystalline inclusion compounds. The latter were heated in a sealed vial and the mixture of gaseous guests evolved was analysed by gas chromatography. The selectivity curve obtained is shown in Fig. 3, which shows that nitrobenzene is preferentially enclathrated over aniline: starting with a 50% mole fraction of liquid guests, the ensuing crystals enclathrate 80% nitrobenzene. Similar results were obtained when the evolved gases were allowed to condense at room temperature and subsequently analysed.

Interestingly, this selectivity process can be followed by differential scanning calorimetry (DSC). When the crystalline inclusion compounds are subjected to heating at a constant rate of $20^\circ \text{C min}^{-1}$ in vented pans under a constant flow of N_2 , the DSC curve shows a single endotherm corresponding to guest release. The onset temperature of the endotherm varies with % nitrobenzene in the crystal, as shown in Fig. 4.

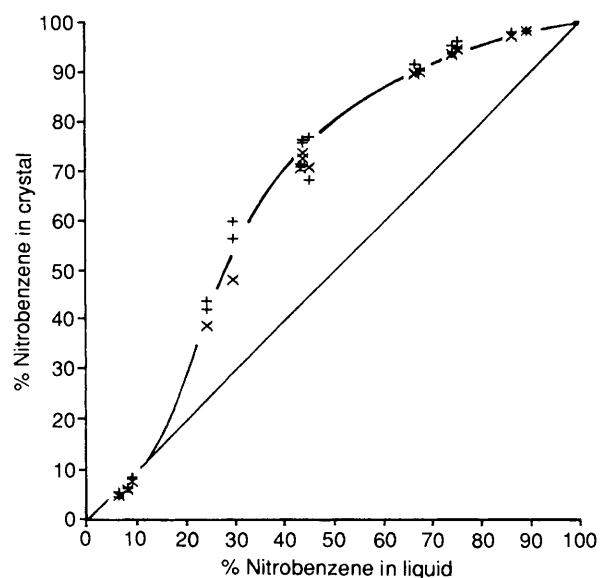


Fig. 3 Selectivity curve of cholic acid with mixtures of nitrobenzene and aniline; \times , evolved gases; $+$, condensate

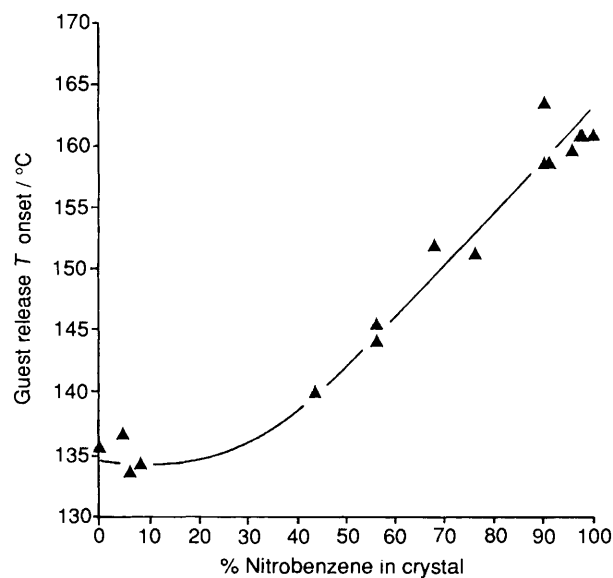


Fig. 4 Onset temperature of guest release vs. % nitrobenzene

Remarkably, we find a linear relationship between onset temperature and % nitrobenzene in the crystal for a wide range of guest composition.

The objective of carrying out thermal analysis is to reconcile thermodynamics with structure. Thus, it should, in principle, be possible to find a relation between the measured enthalpies of the guest release reactions and the host-guest interactions which occur in the crystal structure. This should also explain the results of the competition experiments.

We used the program EENY⁴ to evaluate the van der Waals energy using empirical atom pair potential curves. The coefficients of the atom-atom potentials are of the form: $U(r) = a\exp(-br)/r^d - c/r^6$, where r is the distance between atom pairs and the coefficients a , b , c , d are those given by Giglio⁵ and recently reviewed by Pertsin and Kitaigorodsky.⁶

We used this method to evaluate the potential energy of a single guest molecule surrounded by appropriate host molecules and obtained values of -20.9 and -15.7 kJ for the nitrobenzene and aniline compounds, respectively. The enthalpies of the guest release reaction follow the same trend, with $\Delta H = 36.4$ kJ mol⁻¹ for CANI and 19.1 kJ mol⁻¹ for CAAN.

It is gratifying to note that the minimised energy, derived from the crystallographic results, follows the trend of measured enthalpies of the guest release reaction, both of which indicate that the nitrobenzene clathrate is the more stable. This explains the enrichment of nitrobenzene which occurs in the competition experiments.

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