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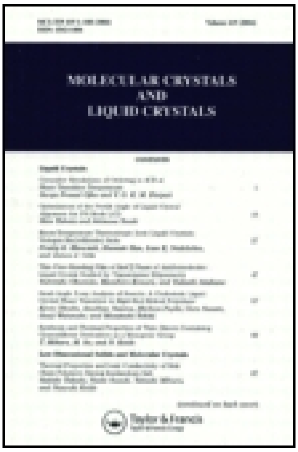

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CHOLIC ACID INCLUSION COMPOUNDS WITH AROMATIC GUESTS - SOLID-VAPOUR REACTIONS.

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Abstract Inclusion compounds of cholic acid with a variety of aromatic guest molecules may be prepared by reaction of the host with guest vapours. The structures of these compounds are identical to those produced by crystallisation methods but the rates of formation differ dependant on guest type. The crystal structure of the 1:1 inclusion compound of cholic acid•*m*-nitrotoluene is presented.

INTRODUCTION

3α,7α,12α-trihydroxy-5β-cholan-24-oic acid **1**, commonly known as cholic acid (CA) forms inclusion compounds with a wide range of guest molecules including alcohols[1,2], aliphatic esters[3] and ketones[4], lactones[5], aromatic hydrocarbons[6], substituted aromatic guests[7,8,9,10] and acetonitrile.[11]

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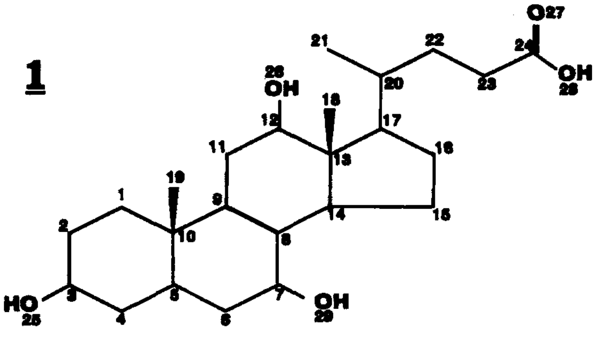

The inclusion compounds with alcohols, the hydrates[12,13] and a unique compound with acetone•3H_2O exhibit extensive host-host and host-guest hydrogen bonding as do the inclusion compounds with benzyl alcohols.[14] The crystal structures of many of the inclusion compounds are similar with curved host steroid molecules hydrogen bonded to each other in a head tail, α-face to α-face arrangement forming puckered bilayers. The hydrophilic α-face of the host molecules are largely buried in the centre of the bilayer and the hydrophobic β-face, with angular C(18) and C(19) methyl groups, is exposed on the bilayer surface. These bilayers are associated by van der Waals interactions and pack together, in the inclusion compound crystals, leaving channels in which the guest molecules are accommodated, usually without aid of short range host-guest interactions such as hydrogen bonds.

A number of reports of guest absorption phenomena from the liquid phase have been reported and it has been suggested that single crystal to single crystal[14,15] (host alone to host:guest compound) transformations occur although the experimental evidence presented suggests instead spontaneous recrystallisation, which might occur by a localised dissolution and deposition mechanism rather than an ordered intercalation process.

We have studied the decomposition kinetics of a number of CA inclusion compounds with substituted aromatic guests containing functional groups such as amino, nitro[7], nitrile[8] and ketone[4] groups. We now present the crystal structure of the 1:1 (host:guest) inclusion compound CA with *m*-nitrotoluene (CAMN) and consider the solid-vapour reactions of CA with substituted aromatic guests which result in inclusion compound formation without mediation of solvent.

EXPERIMENTAL

Good quality crystals for single crystal diffractometry were grown from solutions of CA and the guest species dissolved in dry acetone. Hot, concentrated solutions of rigorously dried host and excess guest were filtered (0.5 μm) and allowed to cool slowly to room temperature whereupon crystals of the inclusion compounds grew as colourless needles elongated along *b*. Suitable fragments for single crystal diffractometry were cut from these needles and mounted in Lindemann capillary tubes as, although the rate of guest desorption was extremely slow, the crystals were attacked by vapours of the compounds used to secure crystals to glass fibres. Preliminary cell parameters were obtained photographically and intensity data were collected on an Enraf-Nonius CAD4 diffractometer at 294 K using graphite monochromated Mo-K_α radiation (λ = 0.7107 Å) and the ω - 2θ scan mode. During data collection three reference reflections were monitored periodically to check crystal stability. The data were corrected for Lorentz-polarisation effects. Refined unit cell parameters were obtained by least squares analysis of 24 reflections measured on the diffractometer in the range $16 < \theta < 17°$. Crystal data and other experimental details are given in Table 1.

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Structure Solution and Refinement

The structure was solved by direct methods using the program SHELX-86[16] and refined by full-matrix least-squares refinement using the program SHELXL-93.[17] The weighting scheme employed was $w = [\sigma^2(F)]^{-1}$ chosen to ensure constant distribution of $<w(|F_o| - |F_c|)^2>$ with respect to $\sin\theta$ and $(F_o/F_{max})^{½}$.

TABLE 1: Crystal data, experimental and refinement parameters for CAMN.

Crystal Data	
Molecular formula	$C_{24}H_{40}O_5{\bullet}C_7H_7NO_2$
Molecular weight (gmol^{-1})	545.717
Space group	$P2_1$
a (Å)	12.442(3)
b (Å)	8.066(1)
c (Å)	14.519(2)
α (°)	90.0
β (°)	102.63(1)
γ (°)	90.0
V (Å^3)	1421.8(4)
Z	2
D_c (gcm^{-3})	1.275
μ (MoKα) (cm^{-1})	0.52
F(000)	592
Data Collection	
Crystal dimensions (mm)	0.3 x 0.3 x 0.35
Range h, k, l	±14, 9, 17
Total exposure time (h)	20.4
Intensity variation (%)	1
No. of reflections collected	2810
No. of reflections $I_{rel} > 2I\sigma_{rel}$	2324
Final Refinement	
No. of reflections (independent)	2183
No. of parameters	383
R indices: R	0.0651
wR	0.0756
S	2.34
$\Delta\rho$max (eÅ^3)	0.56
$\Delta\rho$min (eÅ^3)	-0.39

The y coordinate of one carbon atom of the host was fixed to define the origin in the polar space group $P2_1$. All non-hydrogen atoms of the host and guest were

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refined anisotropically and hydrogen atoms were placed in geometrically generated positions and refined with positional parameters riding on the host atom with each type tied to a common temperature factor. Host hydroxyl hydrogen atoms were located in electron density maps and refined with bond length restraints.

X-ray Powder Diffraction

Powder diffraction patterns were measured using Cu K_a radiation and the stepped scan mode in the range 6-36° 2θ in steps of 0.1° at a rate of 2° $(2\theta)\text{min}^{-1}$.

Thermal analysis

Thermogravimetric (TG) and differential scanning calorimetry (DSC) analyses were performed using a Perkin Elmer PC7 system. Crystalline samples were removed from mother liquor, washed with diethyl ether to remove all traces of uncomplexed guest and crushed. CA and its inclusion compounds are insoluble in diethyl ether while most of the guest species used are appreciably soluble. Samples of mass 2-5 mg were analysed in the range 30-230 °C at 20 $^{o}\text{C.min}^{-1}$ with dry nitrogen purge gas at a flow rate of 40 ml.min^{-1}.

Solid-vapour reactions

CA recrystallised from acetone or ethyl acetate was dried *in vacuo* to remove all traces of included guest, then crushed (agate mortar and pestle) and sieved. The 212-250 μm fraction was retained for reaction. A quantity of dried, sieved host was placed in a glass vial which was in turn fitted inside a larger vial which contained either liquid or powdered, solid guest and the whole immersed in a thermostated water bath. Samples were removed periodically and the extent of reaction determined from weight loss on TG analysis.

RESULTS

The molecular diagram of host and guest is presented as Figure 1 and the packing diagram as Figure 2. The conformation of the steroid side chain is puckered as indicated by the torsion angle C(20)-C(22)-C(23)-C(24) = 170.0(4)°. The compound forms the familiar tubulate clathrate structure with host bilayers packed to form infinite channels propagating in the *b* direction in which guest molecules stack in an undulating column. The A-type packing mode[3] in which C(18) methyl groups of adjacent bilayers are in close contact about the 2_1 axis at 0,y,½ is adopted. The host-host hydrogen bonding scheme is O(28)-H(28O)•••O(29)-H(29O)•••O(25)-H(25O)•••O(26)-H(26O)•••O(27).

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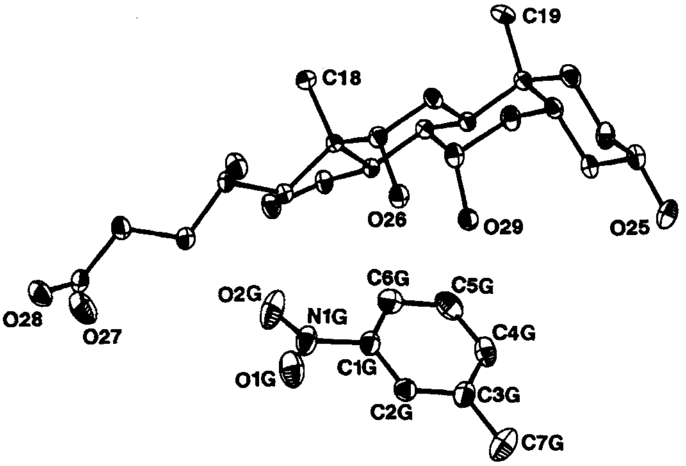

FIGURE 1: Molecular diagram of CA and *m*-nitrotoluene with thermal ellipsoids at 30 % probability. Numbering of the host follows conventional steroid numbering.

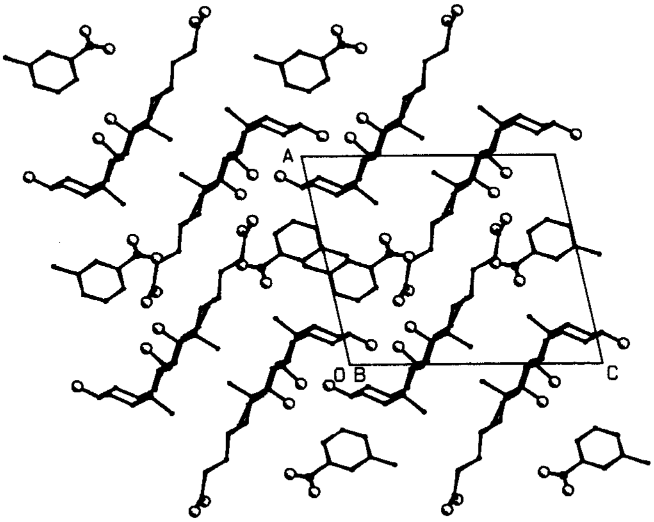

FIGURE 2: Packing diagram of CA•*m*-nitrotoluene viewed as a projection of (101). Oxygen and nitrogen atoms are represented by large open and filled circles respectively.

Cholic acid forms 1:1 inclusion compounds with a large number of substituted aromatic guest species. These compounds may be prepared in the conventional manner by crystallisation from solutions of the host and guest or, in some cases, by reaction of dry powdered host with vapours of the guest. We have noted this phenomenon in the formation of acetonitrile inclusion compounds of CA and its O(28) methyl ester and experiments with substituted aromatic guest species are

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detailed in Table 2.

TABLE 2: Guest species tested for solid-vapour reactivity.

Guest	Structure	m.p. (°C)	b.p. (°C)	$t_{\frac{1}{2}}$ @31 °C (days)
Aniline	7	-6.2	184.4	44
Benzonitrile	8	-12.9	189.6	27
Nitrobenzene	7	5.7	210.6	110
o-Nitrotoluene	-	-4.1	222.3	not absorbed
m-Nitrotoluene	this paper	5.7	231.9	not absorbed
p-Nitrotoluene	18	51.9	238.3	not absorbed
p-Toluidine	18	44.5	200.4	47
p-Bromophenol	-	64.0	238	> 120
Acetophenone	15	20.5	202.5	not absorbed
Propiophenone	9	21.0	218.0	not absorbed

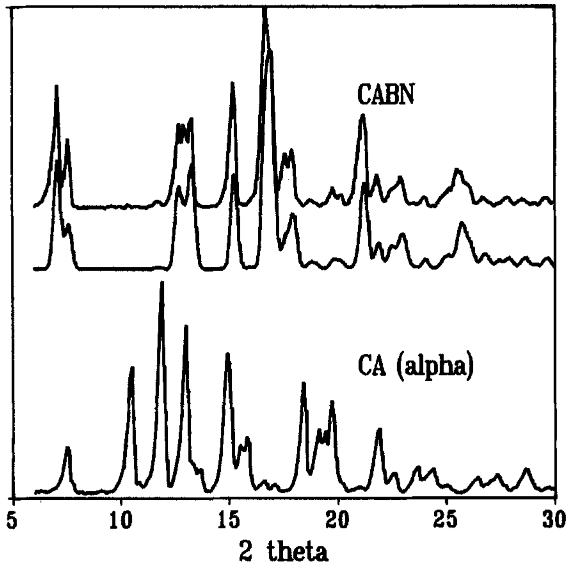

FIGURE 3: Powder XRD traces of pure CA (bottom) and the 1:1 inclusion complex with benzonitrile formed by crystallisation (top, lower) and absorption (top, upper).

Many of the aromatic guests known to form inclusion compounds show reactivity in spite of their low vapour pressures under the conditions of experiment. Reaction isotherms for solid-vapour reactions of those aromatic species which were spontaneously absorbed are presented in Figure 4.

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The stoichiometry and structure of the compounds produced by solid-vapour reaction were shown to be identical with those formed by conventional crystallisation methods. Stoichiometry was confirmed by weight loss % on TG analysis and ^{1}H-NMR analysis and structure by comparison of X-ray powder diffraction patterns. Figure 3 illustrates the match between powder patterns of compounds formed by solid-vapour or crystallisation methods. The structure of the CA host alone[19] is quite different from that of the tubulate clathrate inclusion compounds and the rearrangement of host molecules required includes the formation of new host-host hydrogen bonds and extensive rotation of host molecules relative to each other. Interestingly, of the smaller, more volatile guest molecules known to form inclusion compounds with CA, only acetonitrile[11] and the alcohols (methanol, ethanol, *i*-propanol) show appreciable solid-vapour reactivity.

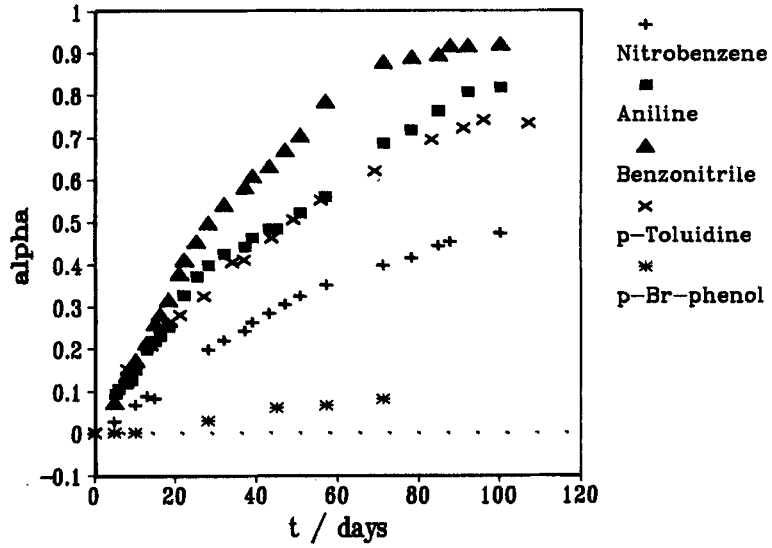

FIGURE 4: Adsorption isotherms for aromatic guests which react with CA at 31 °C to form 1:1 inclusion compounds.

The adsorption isotherms for the various aromatic guests which show appreciable reactivity at room temperature approximate first order rate law curves and the difference in rate of reaction reflects the order of volatility of the compounds i.e. benzonitrile > aniline > *p*-toluidine > nitrobenzene > *m*-nitrotoluene > *p*-nitrotoluene. This validates the assumption of a first order reaction mechanism although the concept of 'molecularity' clearly cannot be extended to reactions where one reactant is in the solid state. Surprisingly some aromatic guests included from solution, notably *m*- and *p*-nitrotoluene proved unreactive under the conditions of the experiment and it is possible that there exists some threshold vapour pressure below which reaction does not proceed.

The similarity in the mechanism of adsorption, as judged from the shape of the reaction isotherms is to be expected given the isostructurality of the inclusion compounds formed and the 1st order mechanism implied is consistent with the dependance on guest vapour pressure. Neither of the aromatic ketone guests, acetophenone or propiophenone, are absorbed from the vapour phase in spite of being readily included from solution. Studies of the kinetics of decomposition of these compounds[8,9] reveals that the mechanism of decomposition of the inclusion compounds with aromatic guests also differs from that of the aromatic ketones and this bears further study.

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