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Inclusion Compounds of Cholic Acid with a Variety of Organic Substances

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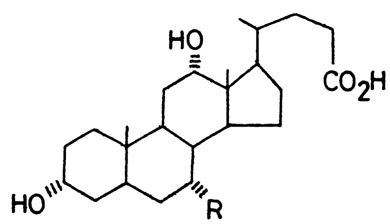
Cholic acid was found to form inclusion compounds with a great variety of organic substances, such as aliphatic, alicyclic and/or aromatic alcohols, ketones, aldehydes, ethers, carboxylic acids, esters, and nitriles. The molar ratios of host to guest components were 1:1 in almost all cases.

It has been long known that deoxycholic acid, a steroidal bile acid, forms crystalline intermolecular compounds with a great variety of organic substances, called choleic acids.[1,2] The extensive studies on the crystal structures of the compounds established that they are lattice inclusion compounds of the channel type.[3] However, there are only a few reports on an ability of other related bile acids to form such inclusion compounds.[1] For example, Mylius reported about one century ago that cholic acid (3α, 7α, 12α-trihydroxy-5β-cholan-24-oic acid) forms the intermolecular compounds only with several alcohols such as methanol and ethanol.[4] Another example of forming the compounds with dyestuffs was pointed out by Cilento.[5]

In a series of our extensive studies on the inclusion polymerization using deoxycholic acid and apocholic acid,[6,7] we found an ability of some steroidal bile acids and their derivatives to form the inclusion compounds. The present paper is concerned with the inclusion compounds of cholic acid with a great variety of organic substances.



R = OH ; cholic acid
R = H ; deoxycholic acid

The recrystallization of cholic acid from liquid guest components afforded the inclusion compounds in almost all cases. In case of viscous or solid guest components we added a solvent such as acetone or acetone-ether. For example, the inclusion compounds of cholic acid with acetonitrile, ethyl acetate, and acetophenone were obtained by recrystallization of cholic acid from the guest components themselves. Figure 1 shows the diagrams of both differential thermal analysis (DTA) and thermogravimetry (TG) of the resulting compounds. We can see two endothermic peaks in the DTA diagrams. One peak at higher temperature (200 °C) corresponds to the melting point of pure cholic acid. Another peak at lower temperature is based on the release of the guest molecules from the host lattice, as indicated by the weight loss in the simultaneous TG measurement.

The release behavior varies from one case to another. In case of acetonitrile the release occurred rapidly at 103 °C, which is by 21 °C higher than the boiling point of acetonitrile. But the compound with ethyl acetate is unstable, because the release of the guest molecules occurred gradually even at the beginning of the measurement. In case of acetophenone the release temperature can be recognized clearly in spite of the high boiling point of the guest compound. These results indicate that the release of guest components from the host lattice depends on the strength of the interaction between host and guest molecules.

The molar ratios of these three compounds were estimated to be 1:1 on the basis of the TG and ^{1}H-NMR measurements.

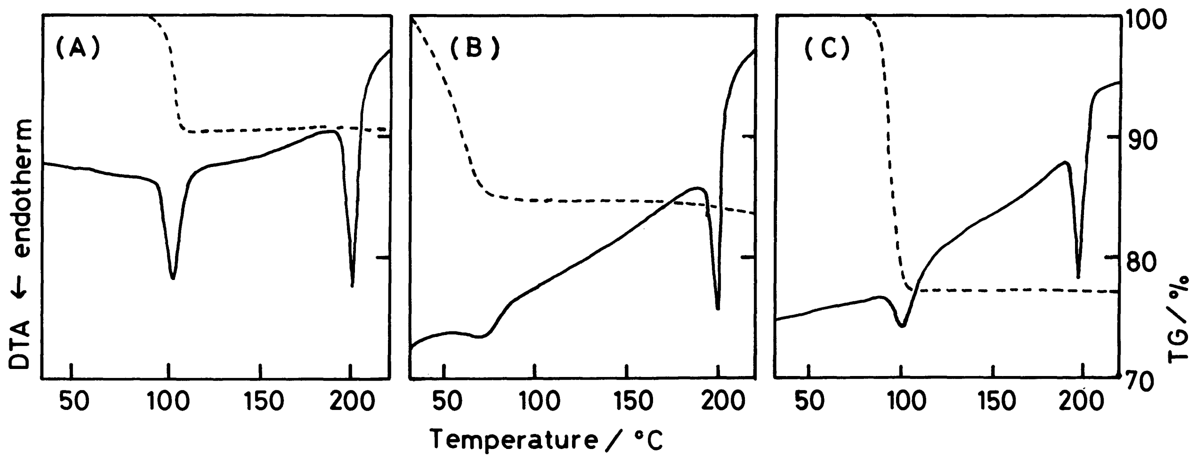
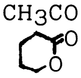
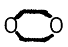


Fig. 1. DTA (——) and TG (- - -) diagrams of the inclusion compounds of cholic acid with acetonitrile (A), ethyl acetate (B), and acetophenone (C).

Furthermore, it was found that cholic acid forms the inclusion compounds with over fifty different guest compounds. A partial list is given in Table 1. It can be seen that cholic acid forms the inclusion compounds with a variety of organic substances, such as aliphatic, alicyclic and/or aromatic alcohols, ketones, aldehydes, carboxylic acids, esters, nitriles, amines, nitro compounds, and halides. In addition, we obtained the inclusion compounds with other organic compounds having longer, more bulky alkyl groups or multiple aromatic groups. However, aliphatic, alicyclic or aromatic hydrocarbons seem not to be included into the host lattice.

The inclusion compounds had a definite stoichiometry with a 1:1 molar ratio of host to guest components except alcohols on the basis of the TG, ^{1}H-NMR, and UV-VIS measurements. The thermal properties of the inclusion compounds varied from one case to another. In case of liquid guest molecules except acetone, both the release temperatures and the melting point of cholic acid itself were observed. However, in case of benzophenone as a solid guest, an endothermic peak was observed at 170 °C while the melting point of cholic acid itself was not found. The peak is a new melting point which is different from the melting points of the guest compound and cholic acid itself.

Table 1. Release temperature and molar ratio of the inclusion compounds of cholic acid with a variety of organic substances

Guest	Release temperature[a)] °C	Molar ratio Host:Guest	Guest	Release temperature[a)] °C	Molar ratio Host:Guest
CH_3OH	133	1 : 2	CH_3CO_2H	113, 134	1 : 1
n-C_4H_9OH	172	1 : 2	$CH_3CO_2CH_2CH_3$	62	1 : 1
$PhCH_2OH$	120	1 : 2		104	1 : 1
CH_3COCH_3	nc [b)]	1 : 1	$PhCO_2CH_2CH_3$	82, 145	1 : 1
$PhCOCH_3$	101	1 : 1	CH_3CN	103	1 : 1
PhCOPh	170 [c)]	1 : 1	PhCN	135	1 : 1
PhCHO	118	1 : 1	$PhNH_2$	115	1 : 1
	78	1 : 1	$CH_3CH_2NO_2$	51	1 : 1
$PhOCH_3$	66, 92	1 : 1	$CHCl_3$	92	1 : 1

a) Temperature at which the guest molecule is released from the host lattice on the basis of DTA and TG measurements.

b) nc means not clear.

c) The inclusion compound melted.

Since cholic acid tends to form the stable inclusion compounds with organic substances having polar functional groups, it is considered that hydrogen bonds between host and guest molecules play an important role for the stabilization of such host-guest compounds. In this sense, the inclusion compounds of cholic acid should be classified as an example of coordinatoclathrates,[8] like the derivatives of binaphthyl and diacethylene diol.[9,10]

In this concern, Johnson and Schaffer reported the crystal structure of cholic acid-ethanol compounds.[11] Ethanol molecules are accommodated into the host lattice by hydrogen bonds. But in this crystal structure there are only small cavities for the guest molecules. Therefore, cholic acid should have another crystal structures. On the other hand, deoxycholic acid accommodates the guest molecules into the hydrophobic channels running through the host lattice.[3] The cholic acid inclusion compounds are in contrast to deoxycholic acid ones with respect to the interaction between the host and guest components.

The methyl esters of cholic acid and deoxycholic acid are also found to form the inclusion compounds with a great variety of organic substances.[12] The detailed study on the inclusion ability and their crystal structure will be reported in a near future.

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