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Complex Formation between Cationic Surfactants and Insoluble Drugs

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Water-insoluble drugs, 1-(2,4,6-trihydroxyphenyl)-1-propanone (flopropione) and 4-chloro-*m*-cresol, formed crystalline complexes with cationic surfactants, such as hexadecyl-, tetradecyl-, dodecyl-, and decyltrimethylammonium bromides, in a solubilized solution system when the solutions were kept at temperatures lower than 288 K and the solubilities of the crystalline complexes were significantly greater than those of only the drugs. Moreover, the complex crystals were more thermostable than only the drugs. The crystal structures of three complexes (4-chloro-*m*-cresol and hexadecyltrimethylammonium bromide (**I**), flopropione and tetradecyltrimethylammonium bromide (**II**), and flopropione and hexadecyltrimethylammonium bromide (**III**)) were analyzed by the X-ray diffraction method. These complexes were composed of the surfactant and drug molecules in a ratio of 1 : 1 (**III**) or 2 : 1 (**I** or **II**). In each crystal, the drug molecule was sandwiched by the alkyl chains of the surfactant molecules; the hydroxy group of the drug made a hydrogen bond with the bromide anion. Those structural characteristics were similar to those of the complexes between the surfactants and aromatic compounds. Such intermolecular interactions were responsible for the increased solubility and thermal stability of the complex.

Ionic surfactants in aqueous solutions aggregate to form micelles[1—4] above a certain critical concentration, called cmc.[5,6] The degree of aggregation increases when aromatic compounds are added to the solution. Cationic surfactants with quaternary ammonium salts, such as hexadecyl-, tetradecyl-, dodecyl-, and decyltrimethylammonium bromide (abbreviate as CTAB (**1**), MTAB (**2**), LTAB, and DTAB, respectively), exhibited a very high viscoelasticity when several aromatic substances, such as *p*-cresol, *o*-iodophenol, 3-hydroxybenzonitrile phenol, diphenylamine, 1-naphthylamine, and indole, were added to the aqueous solution.[7] Gigantic rod-like micelles were formed,[8,9] the shapes and sizes of which the micelles were observed in electron micrographs.[10—14] From a solution containing these gigantic micelles we obtained crystalline molecular complexes between the cationic surfactants and a variety of aromatic compounds.[15,16] Recently, we obtained molecular complexes between anionic surfactants, such as hexadecyl, tetradecyl, dodecyl, decyl, and octyl sulfate sodium salts and the aromatic compounds.[17]

Moreover, the crystal structures of the complexes were determined by an X-ray diffraction method. All of the crystals had a similar type of intermolecular interaction between the surfactant molecule and the aromatic compound, which is called the common packing pattern.[18] This interaction is responsible for the fact that water-insoluble aromatic compounds are easily dissolved in aqueous solution. This specific interaction also explains the reason why the solubility of aromatic drugs, or their lipophilicity, can be improved when surfactants are added to the solution.

We recently observed a significantly increased solubility of insoluble drugs, such as flopropione, 1-(2,4,6-trihydroxyphenyl)-1-propanone (**3**), and 4-chloro-*m*-cresol (**4**), which possess an antiseptic action for cholelithiasis and germicidal power, respectively, when the drugs formed crystalline complexes with surfactants. Crystals suitable for X-ray studies were obtained for three complexes between 4-chloro-*m*-cresol and CTAB (**I**), flopropione and MTAB (**II**), and flopropione and CTAB (**III**).

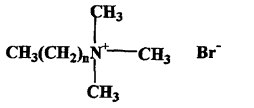
This paper reports on an improvement in the solubility due to complex formation and the crystal structures of the three complexes. The interactions between surfactants and drugs are discussed based on the crystal structures.

Experimental

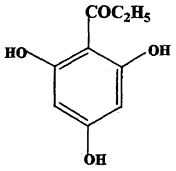
Materials. Cationic surfactants of CTAB and MTAB were crystallized from methanol–acetone solutions and then recrystallized from aqueous solutions. Flopropione and 4-chloro-*m*-cresol were purchased from Tokyo Kasei Co., Ltd. and were purified by conventional recrystallization. The structural formula of the surfactants and drugs are shown in Scheme 1.

Preparation of the Complex Crystals. Two complex crystals, **I** and **II**, were obtained from methanol solutions containing 4-chloro-*m*-cresol or flopropione and CTAB or MTAB, respectively, at temperatures lower than 288 K. Complex crystals of **III** were obtained from an aqueous solubilized solution containing CTAB and flopropione.

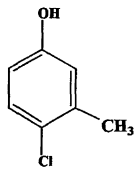
Crystal Structure Analysis. A crystal of **I** or **II** was mounted on a SMART-CCD diffractometer using Mo $K\alpha$ radiation. A crystal of **III** was mounted on a four-circle diffractometer (Rigaku-AFC5R) using Cu $K\alpha$ radiation, since the b axis is longer than 35 Å. The



n=15 (1) Hexadecyltrimethylammonium bromide
n=13 (2) Tetradecyltrimethylammonium bromide
n=11 Dodecyltrimethylammonium bromide
n=9 Decyltrimethylammonium bromide



(3) Flopropione



(4) 4-Chloro-*m*-cresol

Scheme 1. Surfactant and drug molecules.

temperature was cooled down to 223 K with Rigaku low-temperature equipment for all crystals. The crystal data and experimental details are summarized in Table 1.

The structures were solved by a direct method with the program SIR-92,[19] and were refined by a full-matrix least-squares method with the program SHELXL-97.[20] For a crystal of **I**, the 4-chloro-*m*-cresol molecule takes a disordered structure with three orientations (A, B, and C), although CTAB is ordered. The occupancy factors are 0.20(2), 0.18(1), and 0.12(3) for A, B, and C, respectively. The atomic parameters of the disordered 4-chloro-*m*-cresol molecule were refined with the isotropic temperature factor, whereas those of non-hydrogen atoms of CTAB were refined anisotropically. For **II** and **III**, all non-hydrogen atoms were refined with the anisotropic temperature factors. The C–C bonds of the alkyl chain and the N–C bonds in the cationic surfactants were restrained to 1.540 and 1.470 Å, respectively. The C–O and C=O bonds of flopropione were restrained to 1.362 and 1.221 Å, respectively. The C–Cl and C–CH_3 bonds of 4-chloro-*m*-cresol in **I** were restrained to 1.739 and 1.506 Å, respectively. The positions of the hydrogen atoms, except for those of the water molecules of **III**, were obtained geometrically and were not refined. The water hydrogen atoms were located on a difference map and the parameters were refined isotropically. The atomic-scattering factors were taken from International Tables for Crystallography.[21] The CIF data for the three crystals are deposited as Document No. 72040 at the Office of the Editor of Bull. Chem.

Table 1. Crystal Data and Experimental Details

No. of complex	**I**	**II**	**III**
Formula	$C_{19}H_{42}NBr/0.5C_7H_7OCl$	$2C_{17}H_{38}NBr/C_9H_{10}O_4$	$2C_{19}H_{42}NBr/2C_9H_{10}O_4/3H_2O$
Molecular weight	435.73	854.96	1147.28
Temperature/K	223	223	223
Wavelength/Å	0.71069	0.71069	1.54180
Diffractometer	SMART-CCD	SMART-CCD	AFC-5R
Radiation	Mo $K\alpha$	Mo $K\alpha$	Cu $K\alpha$
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1$	$P2_1/m$	$P\bar{1}$
a/Å	5.5232(1)	11.6511(6)	9.747(2)
b/Å	7.3944(1)	7.3421(4)	40.114(16)
c/Å	33.3594(3)	28.8002(14)	9.214(2)
α/°	90	90	93.80(3)
β/°	95.058(1)	99.491(1)	117.869(17)
γ/°	90	90	90.41(3)
Z	2	2	2
Volume/Å^3	1357.12(2)	2429.9(2)	3174.8(16)
D_{calc}/g cm^{-3}	1.066	1.168	1.200
Crystal dimensions/mm^3	$0.28 \times 0.25 \times 0.04$	$0.30 \times 0.25 \times 0.08$	$0.40 \times 0.35 \times 0.07$
Absorption correction	SADABS	SADABS	Psi-scan ($0.8374 < T < 1.000$)
$2\theta_{max}$/°	55	55	135
μ/mm^{-1}	1.571	1.705	2.041
F (000)	470	920	1236
Range of h	$-7 \rightarrow 7$	$-14 \rightarrow 15$	$0 \rightarrow 11$
Range of k	$-9 \rightarrow 9$	$-8 \rightarrow 9$	$-48 \rightarrow 48$
Range of l	$-43 \rightarrow 43$	$-37 \rightarrow 37$	$-11 \rightarrow 9$
No. of observed reflections			
Total	18276	17606	11079
Unique	6223	6006	10387
No. of refined parameters	268	302	624
R (int)	0.056	0.042	0.030
R ($I > 2\sigma$)	0.068	0.042	0.060
wR (F^2)	0.179	0.123	0.170
Goodness-of-fit on F^2	1.003	0.971	1.035
Weighting scheme [$P = (F_o^2 + 2F_c^2)/3$]	$1/[\sigma^2(F_o^2) + (0.1355P)^2]$	$1/[\sigma^2(F_o^2) + (0.0783P)^2]$	$1/[\sigma^2(F_o^2) + (0.1318P)^2]$
$\delta\rho$/e Å^{-3}	+1.66, −0.84[a)]	+0.40, −0.49	+0.80, −0.67

a) These peaks are within 1.1 Å from Br.

Soc. Jpn. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition numbers 134389-134391.

Dissolution Rates. The dissolution rates were measured for three samples: flopropione only, a mechanical mixture of the powdered surfactant and flopropione, and a complex composing a surfactant and flopropione. Each sample was first sieved with 80 mesh, and then with 48 mesh. The dissolution rate into water was measured using a dissolution analyzer (Toyama U.S.P. (NF) NTR-5S3). The sample was dissolved into degassed distilled water (500 ml) under stirring at 50 rpm. A small aliquot portion of the solution (10 ml) was taken out in each definite lapse of time and measured after filtration using a membrane filter of 0.45 mm in pore size. The amount of dissolved flopropione of each filtrate was measured by a UV spectrometer (Shimadzu UV-160).

Thermal Stability of the Complexes. Themogravimetry was carried out by using an apparatus (Rigaku TG-8120) under flowing nitrogen gas at a heating rate of 10 °C min^{-1} in the 25—160 °C region.

Results and Discussion

Crystal and Molecular Structure of I. The crystal structures viewed along the *a* and *b* axes are shown in Fig. 1, in which only the A 4-chloro-*m*-cresol molecule is shown and the disordered B and C moleucles are omitted for clarity. Since the 4-chloro-*m*-cresol molecule cannot be included in a unit cell, the *a* axis should be twice that shown by the dotted lines. The molecular structures with the numbering of the atoms are shown in Fig. 2. The alkyl groups of the hexadecyltrimethylammonium (CTA) cations with an all-*trans* conformation are arranged in an antiparallel way with each other along the *a* axis. The interaction between the cation and 4-chloro-*m*-cresol is essentially the same as those

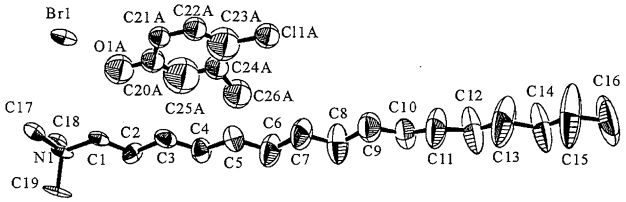


Fig. 2. Molecular structure **I** showing 50% probability displacement ellipsoids and the atomic numbering.

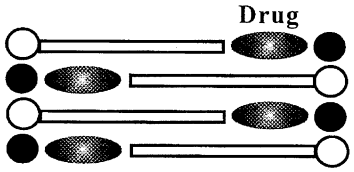


Fig. 3. Common packing pattern.

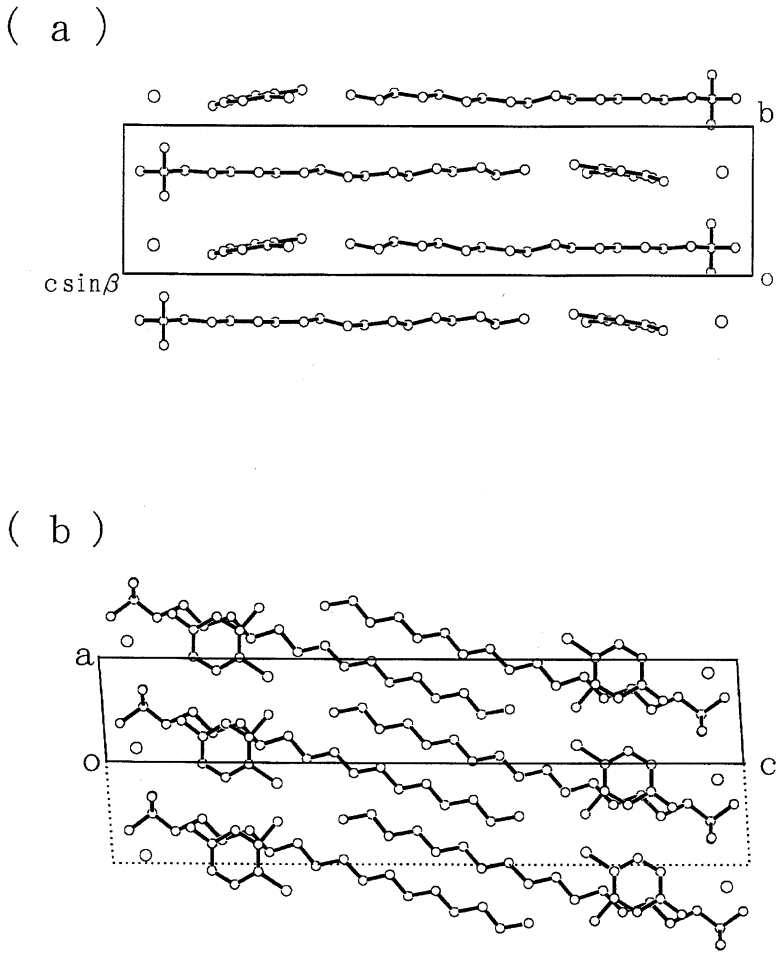


Fig. 1. Crystal structures of **I** viewed along; a), the *a* axis and b), the *b* axis.

observed in the related complex crystals, which is called as "common packing pattern" (Fig. 3). The 4-chloro-*m*-cresol molecule is sandwiched by the alkyl groups of the CTA cation. The hydroxy groups of the disordered 4-chloro-*m*-cresol seem to make hydrogen bonds with the bromide anion. The distances of Br···O1A, O1B, and O1C are 2.75(3)—3.58(3) Å.

Crystal and Molecular Structure of II. The crystal structure viewed along the b axis is shown in Fig. 4. All of the molecules lie on the crystallographic mirror planes. There is one flopropione and two MTAB's, A and B, in an asymmetric unit. The molecular structures along with the numbering of atoms are shown in Fig. 5. The benzene ring of flopropione is sandwiched by the alkyl groups of the A-MTA cation, which is similar to the common packing pattern observed in related complex crystals (Fig. 3). Since the flopropione molecule is so large an extra MTA cation and a bromide anion of B are necessary to maintain the common packing pattern. An intermolecular hydrogen bond is made between the O–H group of flopropione and the bromide anion of A (3.253(3) Å).

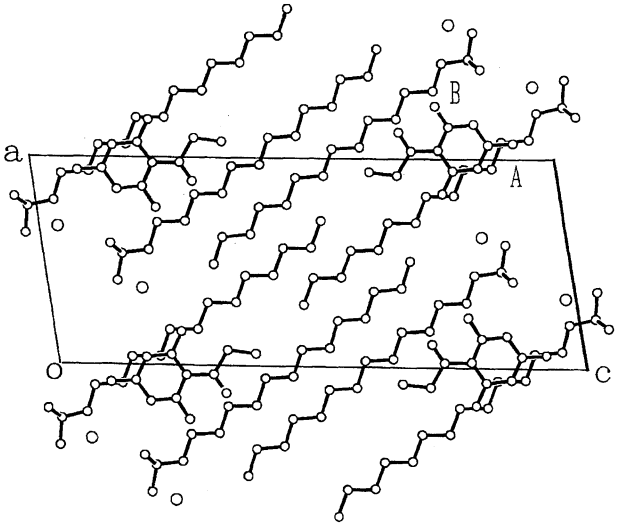


Fig. 4. Crystal structure of **II** viewed along the *b* axis.

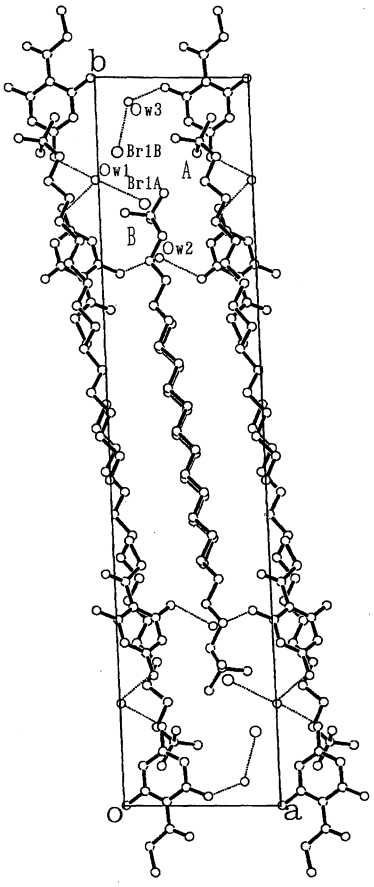


Fig. 6. Crystal structures of **III** viewed along the *c* axis.

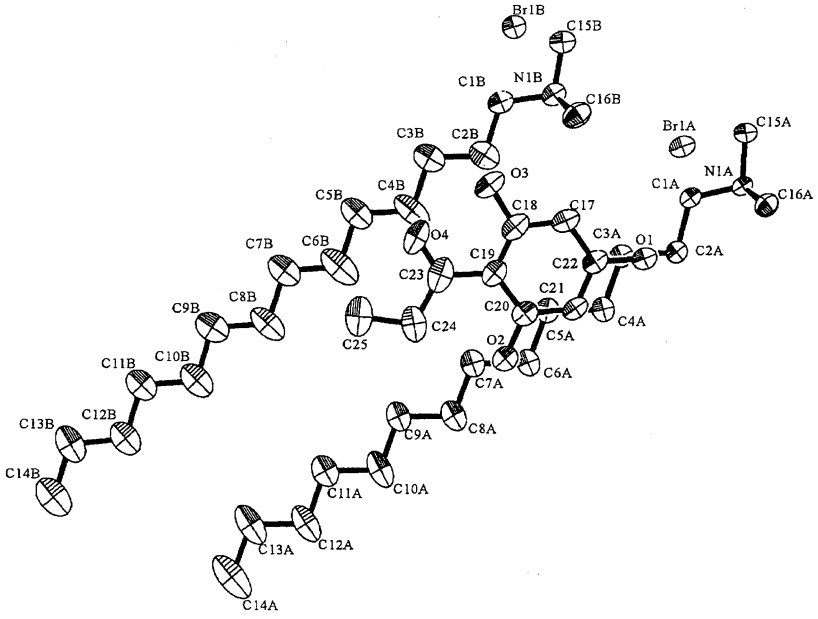


Fig. 5. Molecular structure **II** showing 50% probability displacement ellipsoids and the atomic numbering.

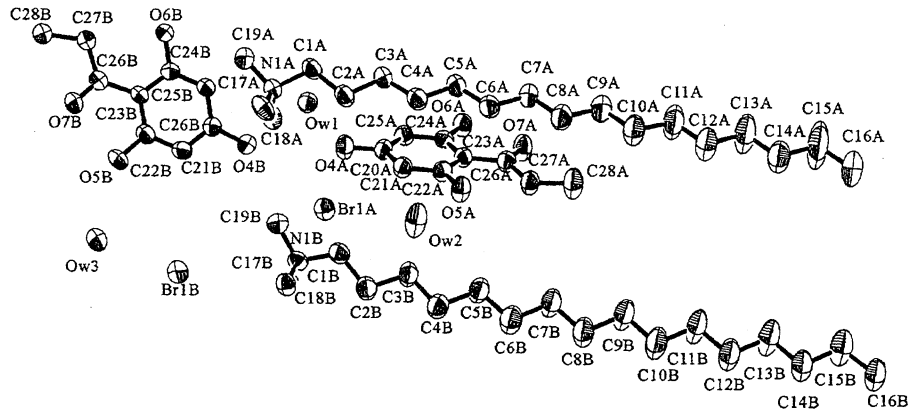


Fig. 7. Molecular structure **III** showing 50% probability displacement ellipsoids and the atomic numbering.

Crystal and Molecular Structure of III. The crystal structure viewed along the c axis is shown in Fig. 6. There are two crystallographically independent CTAB's and flopropiones (A and B) and three solvent water molecules (Ow1, Ow2, and Ow3) in an asymmetric unit. The molecular structures of two flopropione and CTAB molecules, and three water molecules are shown in Fig. 7. Both of the CTA cations take an all-*trans* conformation. The interaction between the CTA cation A and the flopropione molecule A is essentially the same as that of the "common packing pattern". On the other hand, the packing of the B flopropione and the B cation are different from the common pattern. The flopropione molecule has many hydrogen donor groups, which make hydrogen bonds with the solvent water molecules. The hydrogen bond distances between the flopropione molecules or the bromide anions and the water molecules are as follows: O5A···Ow2, 2.631(5) Å, Ow2···Br1A, 3.208(4) Å, O5B···Ow3, 2.925(5) Å, and Ow3···Br1B, 3.228(4) Å, respectively. These hydrogen donor groups and water molecules make a wide hydrophilic region in the crystal structure. This may cause a different packing of the alkyl groups of CTAB in the crystal.

Increased Dissolution Rate by Complex Formation. Figure 8 shows the dissolution rates of the three samples, flopropione only, the simple mechanical mixture of the powdered flopropione and CTAB, and the powdered complex crystals between flopropione and CTAB. The dissolution rate of the complex is significantly greater than that of the other two. This suggests that the complex species may be

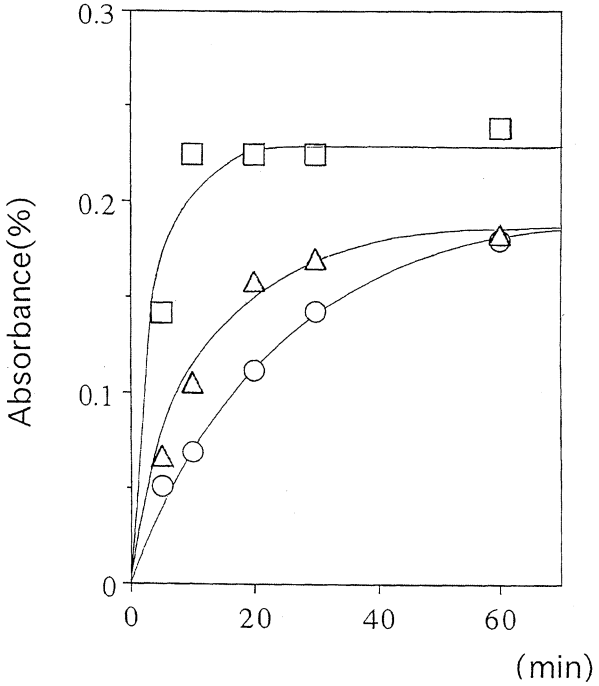


Fig. 8. Dissolution rates of three samples; flopropion only (–○–), the simple mechanical mixture of the powdered flopropion and CTAB (–△–), and the powdered complex crystals, CTAB/flopropione (–□–).

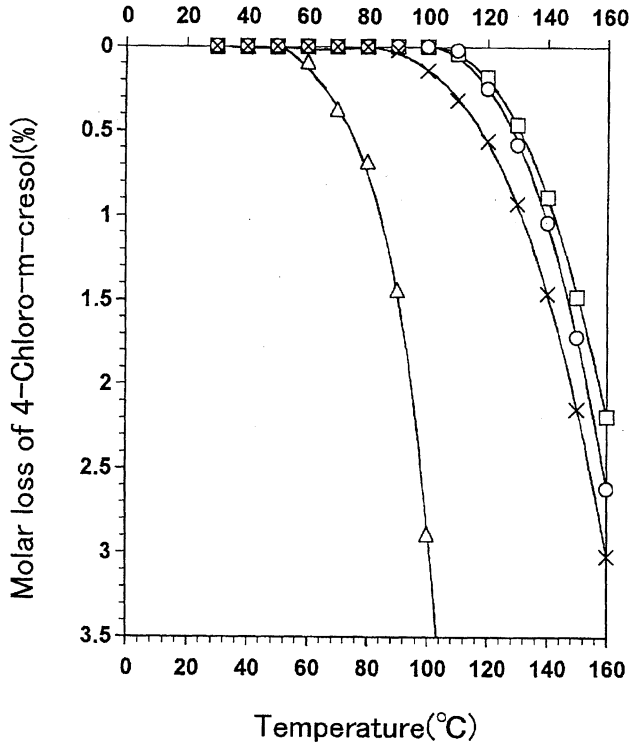


Fig. 9. Molar loss of 4-chloro-*m*-cresol in the complex crystals with CTAB (-□-), MTAB (-○-), and LTAB (-×-) compared with the pure crystal of 4-chloro-*m*-cresol (-△-).

tightly kept as an entity in solution, inducing such a condition that the surfactant molecule may partly prevent the solvent water molecules from direct contact to the flopropione molecules. In fact, we have already established that the surfactant complexes have different values of cmc or Krafft point from the corresponding ones of their component surfactant molecules.[22] The rate of the mechanical mixture is slightly greater than that of only flopropione. This may be explained by two factors: One is that the same structure as that of the complex may be formed when the powdered samples of both components are mechanically mixed;[23] the other is that the dissolved CTAB may form a complex with dissolved flopropione in solution.

Thermal Stability. Figure 9 shows the molar loss of 4-chloro-*m*-cresol in the crystals of 4-chloro-*m*-cresol only and its complexes with CTAB, MTAB, and LTAB with increasing temperature. The vaporization of 4-chloro-*m*-cresol is clearly prevented when it forms complexes with surfactants; the thermal stability depends on the length of the alkyl chains of the surfactants.

These results clearly indicate that the complex formation of insoluble drugs with surfactants increases the solubility and thermal stability. This may be applicable to improve the characteristics of drugs.

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