[Chem. Pharm. Bull.
28(5)1552—1558(1980)]

Effects of Grinding on the Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose V: Comparison with Tri-O-methyl-β-cyclodextrin Ground Mixtures[1]

YOSHINOBU NAKAI,[2] SHIN-ICHIRO NAKAJIMA,[2a] KEIJI YAMAMOTO,[2]
KATSUHIDE TERADA, and TSUTOMU KONNO[2b]

Faculty of Pharmaceutical Sciences, Chiba University[2]

(Received November 21, 1979)

Ground mixtures of aspirin, benzoic acid and *p*-acetoxydiphenyl were prepared with tri-O-methyl-β-cyclodextrin (methyl-CD). An apparent amorphous state of methyl-CD and the medicinals after grinding was indicated by X-ray diffraction analysis. Infrared analysis also indicated that the medicinal molecules were monomolecularly dispersed in the methyl-CD ground mixtures.

The infrared solution spectra of medicinals in CCl_4 were compared with the solid state infrared spectra in the carbonyl stretching absorption region. It was found that in the ground mixture of aspirin with methyl-CD, the hydroxyl group of aspirin was hydrogen-bonded with the methoxyl group of methyl-CD, while the acetoxyl group of aspirin was in a free state.

Keywords——hydrogen bonding; IR, amorphous; grinding; mechanochemistry; dispersion; cyclodextrin

An amorphous state of medicinals can be obtained by grinding them with microcrystalline cellulose. In previous papers, the authors reported that such ground mixtures showed some interesting properties, and that the medicinal molecules were dispersed monomolecularly in the ground mixtures, interacting with cellulose molecules by hydrogen bonding.[1,3]

In this study, in order to determine the role of hydroxyl groups of β-cyclodextrin and cellulose in hydrogen bond formation, tri-O-methyl-β-cyclodextrin (methyl-CD) was employed. X-Ray diffraction and infrared (IR) spectral analyses were carried out on ground mixtures of some medicinals with methyl-CD. IR spectral data obtained were compared with the IR data for the ground mixtures with β-cyclodextrin (β-CD) reported previously.[1,3c] Since methyl-CD is highly soluble in CCl_4, the solution IR spectra of methyl-CD and medicinals were compared with the solid state IR spectra of the ground mixtures.

Experimental

Materials——β-CD was purchased from Seikagaku Kogyo and used after drying at 120° for 4 hr. Methyl-CD and *p*-acetoxydiphenyl were synthesized according to the reported procedures.[4,5] Methyl-CD was recrystallized from hot water and dried at 110° for 3 hr, mp 154—158°, $[\alpha]_D^{20}$ $+155.4°$ ($CHCl_3$).[4,6] *p*-Acetoxydiphenyl was recrystallized from ether–hexane, mp 88—89°.[5] CCl_4 used as a solvent for IR spectroscopy was of spectral grade. All other materials and solvents were of analytical reagent grade.

---

1) Part IV: Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada, and T. Konno, *Chem. Pharm. Bull.*, **28**, 652 (1980).

2) Location: *1-33 Yayoicho, Chiba*; *a*) Present address: *Hospital Pharmacy, the University of Tsukuba, 2-1-1 Amakubo Sakuramura Niiharigun, Ibaraki*; *b*) Present address: *Daiichi Seiyaku Co., Ltd., 5-6-9 Narihira Sumidaku, Tokyo*.

3) *a*) Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, *Chem. Pharm. Bull.*, **25**, 3340 (1977); *b*) Y. Nakai, E. Fukuoka, S. Nakajima, and Y. Iida, *ibid.*, **26**, 2983 (1978); *c*) Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada, and T. Konno, *ibid.*, **26**, 3419 (1978); *d*) K. Yamamoto, S. Matsuda, M. Nakano, T. Arita, and Y. Nakai, *Yakugaku Zasshi*, **97**, 367 (1977).

4) B. Casu and M. Reggiani, *Tetrahedron*, **24**, 803 (1968).

5) J. Kaiser, *Ann.*, **257**, 102 (1890).

6) K. Freundedberg and M. Meyer-Delius, *Chem. Ber.*, **71**, 1596 (1938).

Preparation of Ground Mixtures——Ground mixtures were prepared according to the procedure described previously.[3c] The weight of the mixture to be ground was 2.0 g for the β-CD ground mixture and 1.7 g for the methyl-CD ground mixture.

X-Ray Diffraction——X-Ray powder diffraction patterns were measured as described previously.[3c]

IR Absorption Studies——Spectral data were obtained with a Hitachi EPI-G3 IR double-beam spectrophotometer. Solution spectra were taken in CCl_4 using CaF_2 cells with 2 mm or 20 mm path length.

Results

Ground Mixtures of Medicinals with Methyl-CD

Figure 1 shows X-ray diffractograms of equimolar mixtures of aspirin and methyl-CD (aspirin, 11.2 weight percent). While X-ray diffraction peaks were detected in the physical mixture, the crystalline peaks decreased in intensity with increase in grinding time. A halo pattern was obtained after grinding for 30 min, indicating the production of an amorphous state of aspirin and methyl-CD. Decomposition of aspirin was rarely observed during grinding.

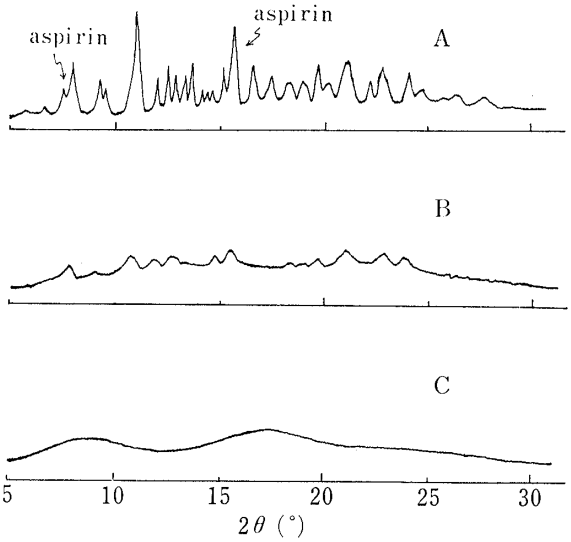

Fig. 1. X-Ray Diffraction Patterns of Equimolar Mixtures of Aspirin and Methyl-CD

A: physical mixture,
B: ground mixture (ground for 5 min),
C: ground mixture (ground for 30 min).

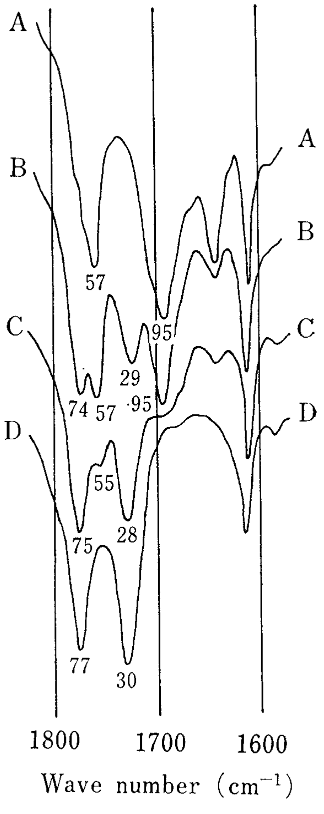

Fig. 2. IR Spectra of Equimolar Mixtures of Aspirin and Methyl-CD at Various Grinding Times

A: physical mixture,
B: ground for 5 min,
C: ground for 10 min,
D: ground for 30 min.

IR spectra of equimolar mixtures of aspirin and methyl-CD at different grinding times are shown in Fig. 2. As illustrated in Fig. 2A, peaks at 1757 cm^{-1} and 1695 cm^{-1} were assigned to an acetoxyl carbonyl stretching band (acetoxyl $\nu_{C=O}$ band) and carboxyl $\nu_{C=O}$ band in aspirin crystals, respectively. Figure 2B shows the IR curve of a mixture ground for 5 min, in which two new bands are apparent at 1774 and 1729 cm^{-1}. Increasing the grinding time caused an increase in the intensity of ~~the~~ new bands. In the IR spectra of the mixture ground for

30 min, the initially observed $\nu_{C=O}$ bands disappeared, and the new sharp bands alone were clearly observed at 1777 and 1730 cm^{-1}.

We have already reported the IR spectral shift of aspirin in a ground mixture with β-CD.[3c)] In this ground mixture, the free acetoxyl $\nu_{C=O}$ band of aspirin molecules was observed at 1772 cm^{-1}, a hydrogen-bonded carboxyl $\nu_{C=O}$ band at 1715 cm^{-1} and a hydrogen-bonded acetoxyl $\nu_{C=O}$ band at 1748 cm^{-1}. As shown in curve D in Fig. 2, only two $\nu_{C=O}$ bands appeared in the aspirin methyl-CD ground mixture.

In order to investigate the effect of hydrogen bonding on the IR shift in the aspirin methyl-CD system in detail, ground mixtures of β-CD or methyl-CD were prepared using benzoic acid or *p*-acetoxydiphenyl. Figure 3 shows the IR spectra of ground equimolar mixtures of *p*-acetoxydiphenyl and either β-CD or methyl-CD. The spectra of the ground mixtures differed markedly in the shift of the $\nu_{C=O}$ band (see curves C and F). In the case of β-CD ground mixture, both upward and downward shifts of the band were observed, corresponding to free and hydrogen-bonded $\nu_{C=O}$ bands, while in the methyl-CD ground mixture the band shifted only to higher frequency and appeared at 1775 cm^{-1}.

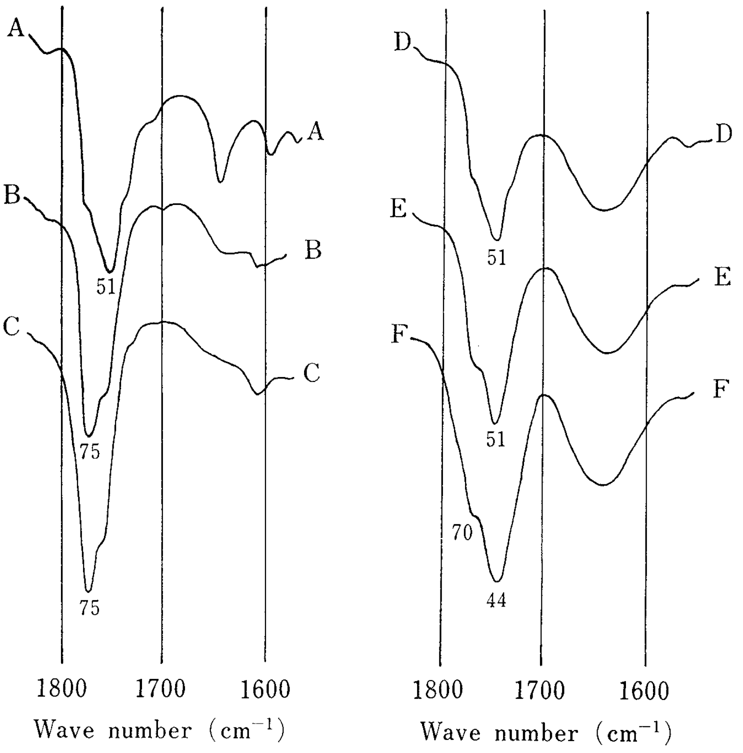

Fig. 3. IR Spectra of Equimolar Mixtures of *p*-Acetoxydiphenyl and Either Methyl-CD or β-CD

A: physical mixture with methyl-CD,
B: ground mixture with methyl-CD(ground for 2 min),
C: ground mixture with methyl-CD (ground for 15 min),
D: physical mixture with β-CD,
E: ground mixture with β-CD (ground for 4 min),
F: ground mixture with β-CD (ground for 10 min).

The acetoxyl carbonyl spectral shifts described above are consistent with those of aspirin molecules when ground with β-CD or methyl-CD.

IR spectra of ground equimolar mixtures of benzoic acid and either β-CD or methyl-CD are shown in Fig. 4. In the β-CD ground mixture, the carboxyl $\nu_{C=O}$ band appeared at 1706 cm^{-1}, while in the crystals it appeared at 1691 cm^{-1}. As shown by curve C in Fig. 4, the $\nu_{C=O}$

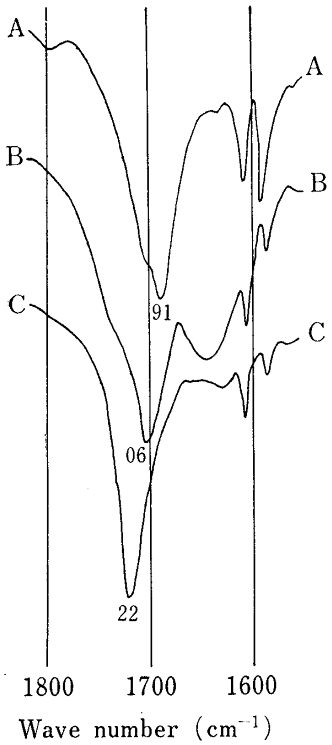

Fig. 4. IR Spectra of Benzoic Acid in Equimolar Mixtures

A: benzoic acid crystals,
B: ground mixture with β-CD (ground for 15 min),
C: ground mixture with methyl-CD (ground for 7 min).

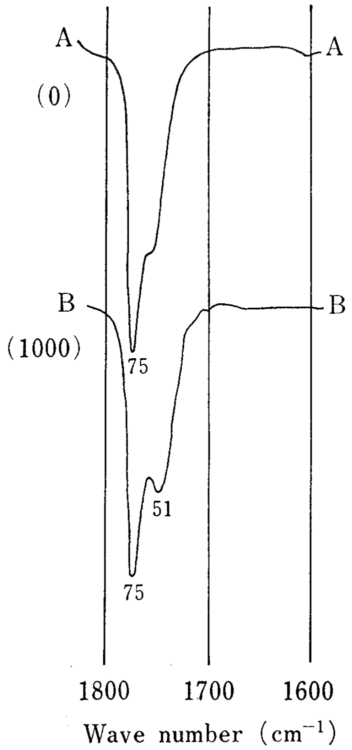

Fig. 5. IR Patterns of *p*-Acetoxydiphenyl in CCl_4 Solution Containing Butanol

The concentration of *p*-acetoxydiphenyl was 3.0×10^{-3} M. Numbers in parentheses indicate the concentration ratio of butanol to *p*-acetoxydiphenyl.

band of benzoic acid in the methyl-CD ground mixture was shifted 31 cm^{-1} to higher frequency, at 1722 cm^{-1}, and this IR pattern was very similar to the CCl_4 solution pattern (see Fig. 6C).

IR Spectra of the Medicinals in Dilute CCl_4 Solution

As it was expected that the lower peak shift observed in the β-CD and *p*-acetoxydiphenyl ground mixture (Fig. 3F) was due to hydrogen bond formation, the CCl_4 solution IR spectra were measured as reported previously.(1) Figure 5 shows the IR shift of *p*-acetoxydiphenyl in CCl_4 solution (3×10^{-3} M) in the presence of limited amounts of butanol. The free acetoxyl $\nu_{C=O}$ band of *p*-acetoxydiphenyl appeared at 1775 cm^{-1} (curve A). The new lower band at 1751 cm^{-1} in curve B indicates that *p*-acetoxydiphenyl and butanol are hydrogen-bonded in the CCl_4 solution. No band shift was observed when methyl-CD was added instead of butanol.

The IR spectra when methyl-CD was added to benzoic acid or aspirin CCl_4 solutions are shown in Fig. 6. The concentration of each medicinal was 3.0×10^{-4} M. As illustrated in Fig. 6 A—C, the addition of methyl-CD caused the carbonyl $\nu_{C=O}$ band of benzoic acid to appear at 1723 cm^{-1}, which is between the monomeric and dimeric $\nu_{C=O}$ bands. This result indicates that benzoic acid interacts with methyl-CD by hydrogen bonding. In dilute CCl_4 solution of aspirin, the acetoxyl $\nu_{C=O}$ band appeared at 1779 cm^{-1}, the monomeric carboxyl $\nu_{C=O}$ band at 1749 cm^{-1} and the dimeric carboxyl $\nu_{C=O}$ band at 1706 cm^{-1}. When methyl-CD was added to the CCl_4 solution, a new band at 1730 cm^{-1} developed, while the monomeric and dimeric bands disappeared (see curve E and F in Fig. 6). This result also suggests that the carboxyl group of aspirin is hydrogen-bonded with the methoxyl group of methyl-CD, and that the acetoxyl group is in a free state.

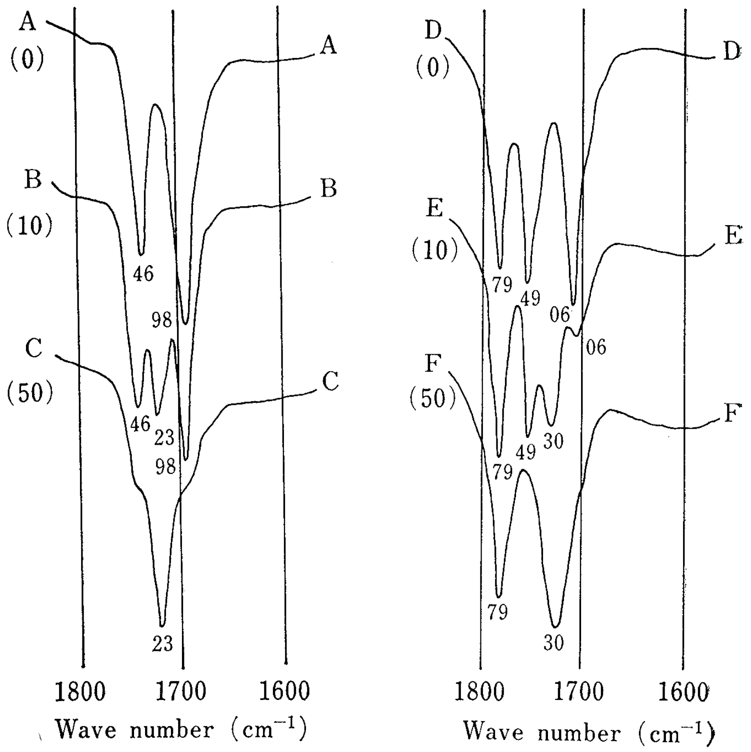

Fig. 6. IR Patterns of Benzoic Acid or Aspirin in CCl_4 Solution Containing Various Amounts of Methyl-CD

The concentration of benzoic acid or aspirin was 3.0×10^{-4} M.
Numbers in parentheses indicate the concentration ratio of methyl-CD to benzoic acid or aspirin.
A—C: benzoic acid,
D—F: aspirin.

Discussion

To investigate hydrogen bond formation between medicinals and either β-CD or methyl-CD in ground mixtures, the solid state IR spectra and the solution IR spectra were compared.

The acetoxyl $\nu_{C=O}$ absorption wave numbers of *p*-acetoxydiphenyl are summarized in Fig. 7. An only upper mark means a shoulder band. The band shift observed in the CCl_4 solution spectra upon the addition of butanol is attributable to hydrogen bond formation. Therefore, the two bands in the β-CD ground mixture can be assigned as a hydrogen-bonded band (1744 cm^{-1}) and a free band (1770 cm^{-1}).

The band at 1775 cm^{-1} in the spectrum of the methyl-CD ground mixture is considered to be due to free acetoxyl $\nu_{C=O}$.

The carboxyl $\nu_{C=O}$ absorption wave numbers for benzoic acid are summarized in Fig. 8. In crystals of benzoic acid, the acid group is dimerized$^{7)}$ by strong hydrogen bonding. Marked shifts were observed in cases C and F in Fig. 8, indicating dissociation of the dimer and the formation of hydrogen bonding between the hydroxyl group of benzoic acid and the methoxyl group of methyl-CD.$^{8)}$ Thus, it is established that in the methyl-CD ground mixture the benzoic acid molecules are dispersed in monomolecular form. In the β-CD ground mixture, the carboxyl $\nu_{C=O}$ band appeared at 1706 cm^{-1} (case B), as reported in the preceding paper.$^{3c)}$ The difference of peak shift between cases B and C is ascribed to the difference in the forms of hydrogen bonding, as discussed below for aspirin.

---

7) G.A. Sim, J.M. Robertoson, and T.H. Goodwin, *Acta Cryst.*, **8**, 157 (1955).
8) H. Hirota, *Kagaku to Kogyo*, **20**, 56 (1967).

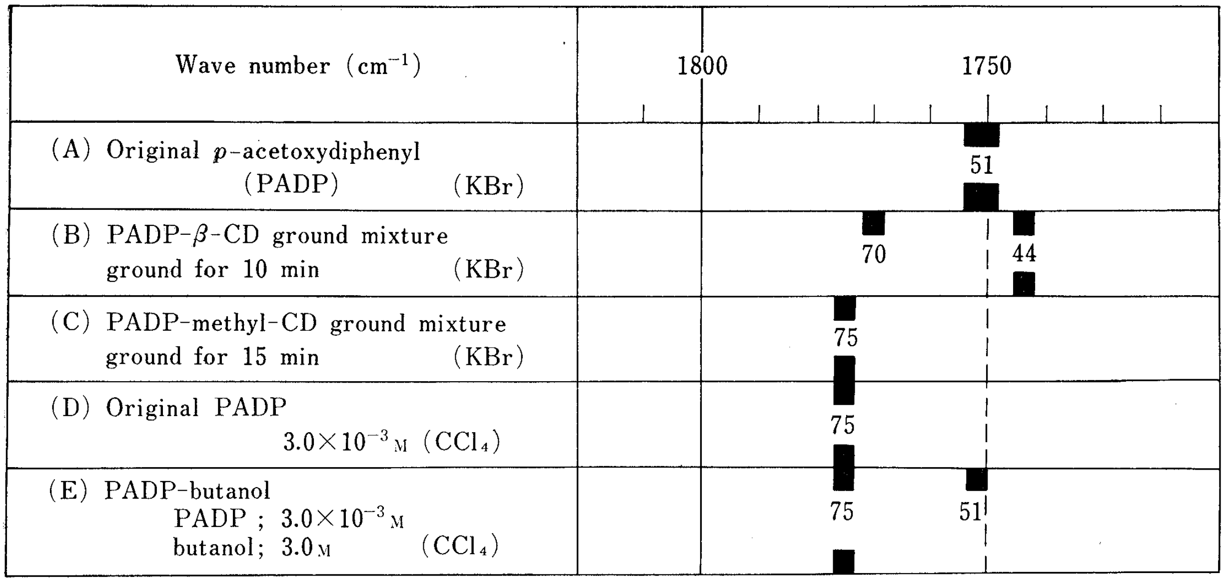

Fig. 7. Comparison of Carbonyl Stretching Vibrations of p-Acetoxydiphenyl in Various States

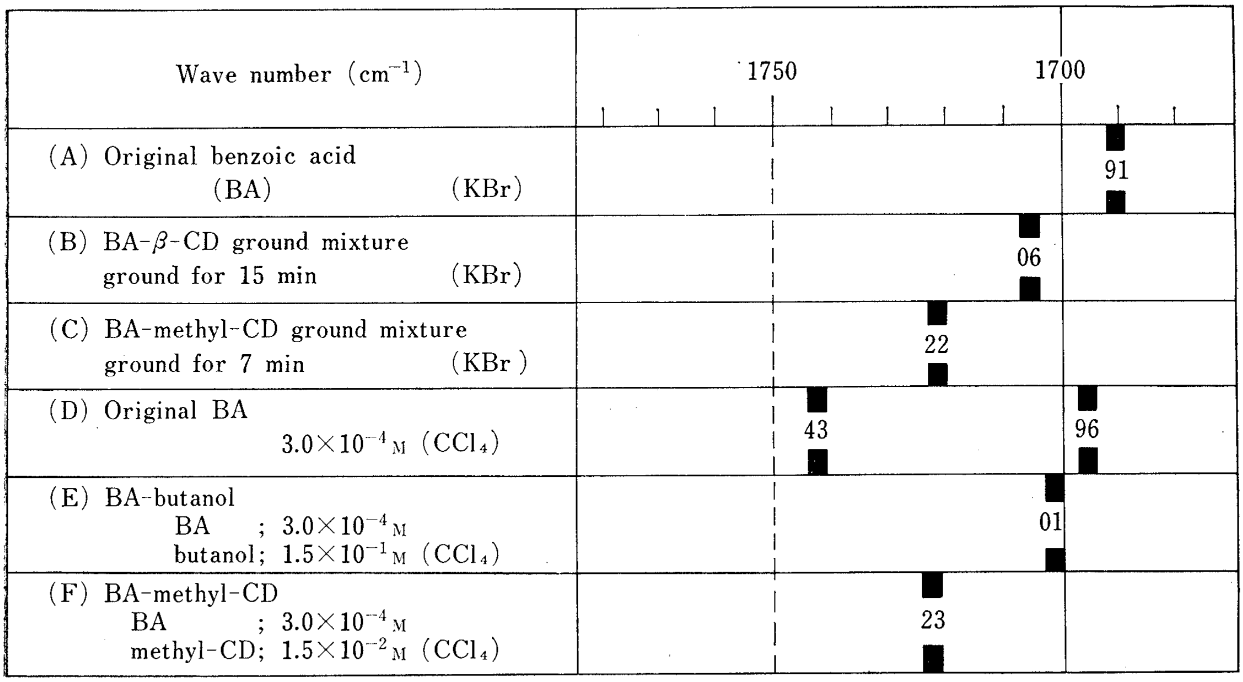

Fig. 8. Comparison of Carbonyl Stretching Vibrations of Benzoic Acid in Various States

The absorption wave numbers of carbonyl bands of aspirin under various conditions are summarized in Fig. 9. Dimerization occurs in the crystals of aspirin as in the case of benzoic acid.[9] Case G in Fig. 9 shows the IR spectral shift when dibuthyl ether was added to dilute aspirin CCl_4 solution. This shift coincides in position with those in cases C and F, and can be explained as follows. As the oxygen atom of the ethers has large electron negativity, it acts as a proton acceptor, and the carboxylic OH group of aspirin (monomeric) acts as a proton donor, leading to hydrogen bonding between them, as shown in Chart 1. The hydrogen bond formation results in a decrease in the double bond character of the carboxyl C=O group. Thus, the carboxylic $\nu_{C=O}$ band is shifted to lower frequency, from 1753 to 1728 cm^{-1}.

---

9) P.J. Wheatley, *Acta Cryst.*, **17**, 6036 (1964).

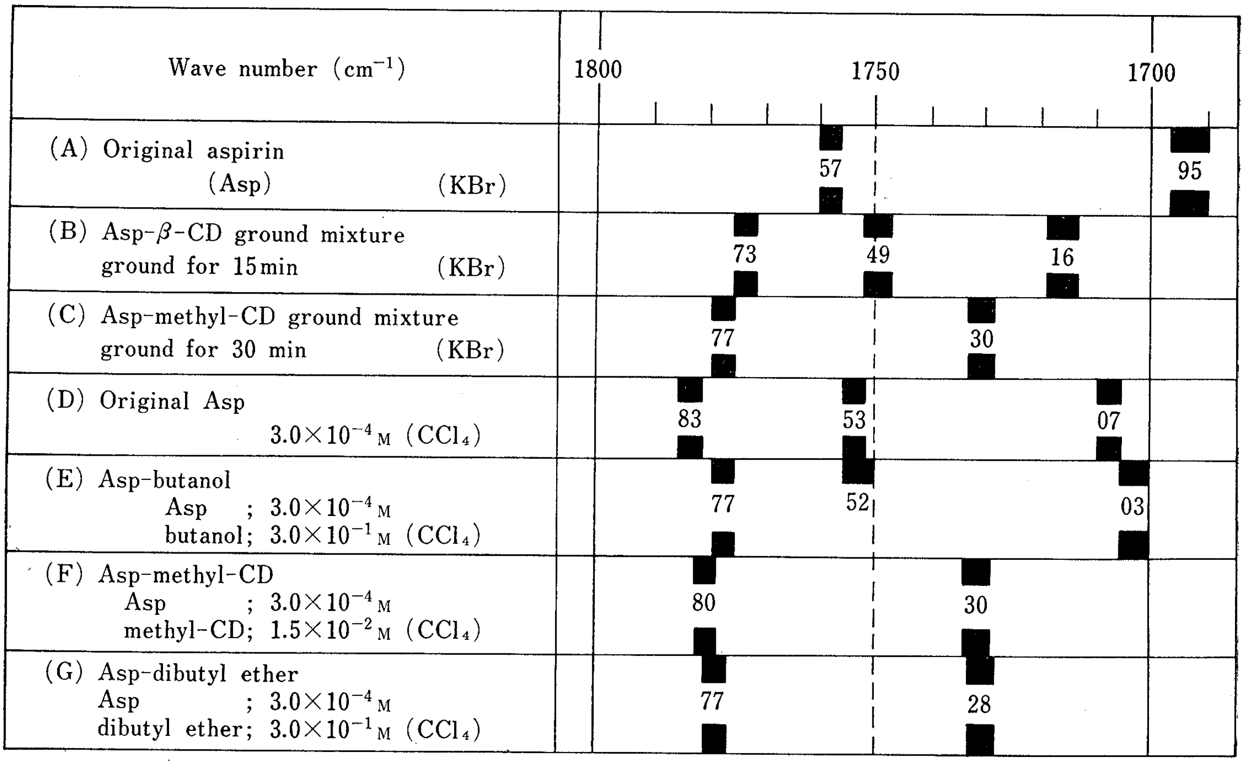

Fig. 9. Comparison of Carbonyl Stretching Vibrations of Aspirin in Various States

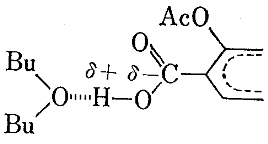

Chart 1

The peak shift observed in case F, that is, when methyl-CD was added to the aspirin CCl$_4$ solution, can be interpreted in terms of hydrogen bond formation as shown in Chart I. The hydroxyl group of aspirin interacts with the methoxyl group of methyl-CD by hydrogen bonding, while the acetoxyl group does not interact with methyl-CD. The carboxyl $\nu_{C=O}$ band at 1730 cm^{-1} is attributable to this intermolecular hydrogen bond formation.

The results for the aspirin methyl-CD ground mixture, case C, can be considered in a similar manner. Consequently, the band at 1777 cm^{-1} is assigned to free acetoxyl $\nu_{C=O}$ and the band at 1730 cm^{-1} is assigned to the carboxyl $\nu_{C=O}$ affected hy hydrogen bonding.

IR spectra and X-ray diffraction analyses showed that the medicinal molecules exist in a monomolecular dispersed state in the ground mixture of methyl-CD, as in the β-CD ground mixture reported previously.[1] The extent of the IR peak shift, however, differs in the β-CD and methyl-CD systems. This indicates a difference in the modes of hydrogen bonding in the two systems. In the aspirin methyl-CD ground mixture, the hydroxyl group of aspirin (as a proton donor) is hydrogen-bonded with the methoxyl group of methyl-CD, and the acetoxyl group of aspirin is in a free state. On the other hand, in the β-CD ground mixture, the carboxyl carbonyl group of aspirin (as a proton acceptor) is hydrogen-bonded with the hydroxyl group of β-CD (as a proton donor), and the acetoxyl group of aspirin exists in both free and hydrogen-bonded states.

Comparison of the IR spectra also revealed that the solid state spectra of the methyl-CD ground mixtures corresponded closely with the CCl$_4$ solution IR patterns of methyl-CD and medicinals. In the ground mixtures and in CCl$_4$ solution, the medicinals probably interact with methyl-CD molecules in the same way, and this suggests complex formation of methyl-CD and medicinal molecules in the ground mixtures.

Acknowledgement The authors thank Drs. H. Ishii and N. Ikeda for valuable advice on the preparation of tri-O-methyl-β-cyclodextrin and *p*-acetoxydiphenyl.