Peculiar Peak Shifts in the IR Spectrum of Benzoic Acid Crystals by Compression with Methylated Additives

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The infrared (IR) peak shift in benzoic acid-additive mixtures has been studied. Benzoic acid crystals, in which benzoic acid molecules form a stable dimeric structure, showed the carbonyl stretching ($\nu_{C=O}$) band at 1688 cm^{-1}. The $\nu_{C=O}$ band of benzoic acid was shifted to a higher wavenumber of 1720 cm^{-1} when IR measurement was carried out for a physical mixture of benzoic acid with heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin (DMβCD) by KBr compression method. The shifted peak reverted to the original position when measured again by Nujol method following pulverization of the KBr disk. These phenomena were observed only in the case of using methylated polysaccharides as additives. The results of X-ray diffraction and solid-state ^{13}C-NMR spectroscopy indicated that the crystal structure of benzoic acid was not influenced by compression and the dimeric structure was maintained. From the results of IR spectra using deuterated benzoic acid, the peculiar phenomena could be explained in terms of the changes in the hydrogen bonding feature of benzoic acid in the compressed disk with DMβCD.

Key words infrared (IR) spectroscopy; compression; benzoic acid; 2,6-di-*O*-methyl-β-cyclodextrin; hydrogen bond

Infrared (IR) spectroscopy is an effective analytical method by which to investigate the molecular interaction modes and molecular states in a multicomponent dispersion system. From IR measurements, we earlier demonstrated that medicinal molecules were dispersed monomolecularly in ground mixtures with either cellulose or cyclodextrin, as well as in freeze-dried products.[2–4] It is well known that polymorphic transition, phase transition, compression and varying temperatures affect the IR absorption spectrum. Kato *et al.* reported changes in the hydrogen-bonding feature of liquid-crystalline benzoic acid derivatives during crystal-nematic and nematic-isotropic transitions.[5] Hayashi *et al.* also demonstrated a marked temperature dependence of IR spectra of benzoic acid crystals and interpreted this to indicate the coexistence of two kinds of configurations.[6,7] As for mixtures, Matsuzaki *et al.* reported a pressure-induced neutral-ionic transition in a mixed-stack charge transfer crystal of tetrathiafulvalene and iodanil.[8,9] The present study was undertaken to characterize the pressure effects on the IR spectra of carboxylic acid molecules mixed with additives. Changes in the molecular states of organic molecules by compression with the additives are discussed.

Experimental

Materials Carboxylic acids listed in Table 1 were of special reagent grade. β-Cyclodextrin (βCD), dimethyl-β-cyclodextrin (DMβCD), trimethyl-β-cyclodextrin (TMβCD) were purchased from Toshin Chemical Co. and used after heating in a vacuum at 110 °C for 6 h. Microcrystalline cellulose (Avicel® PH-101: MCC) and methylcellulose 15 cP (MC) were purchased from Asahi Chemical Industry Co., Ltd. and Nacalai Tesque Inc., respectively, and treated in a similar manner as above. d_5-Benzoic acid was purchased from Aldrich Chemical Co. Inc. and was used without further purification.

Preparation of Physical Mixture A physical mixture was prepared by manual bottle tumbling of the mixture of drug molecule and additive in a defined molar ratio.

Preparation of Benzoic Acid and DMβCD Inclusion Complex The equimolar mixture of benzoic acid and DMβCD was dissolved in distilled water at room temperature, and the solution was kept at 80 °C. Inclusion compound was obtained as precipitated crystal after filtration of the hot solution. The precipitate was dried in a desiccator with phosphorous pentaoxide for 12 h.

Preparation of Deuterated Benzoic Acid (d_6-Benzoic Acid) d_5-Benzoic acid was dissolved in D_2O and the solution was refluxed for 12 h. d_6-Benzoic acid was crystallized after cooling of the solution. Deuteration was identified by infrared absorption spectra of the O–D stretching band.

X-Ray Diffraction Measurement Powder X-ray diffraction patterns were measured using a Rigakudenki 2027 diffractometer. Conditions: target Cu, filter Ni, voltage 30 kV, current 5 mA, receiving slit 0.15 mm, count range 1000 cps, scanning speed 4°/min.

IR Absorption Spectroscopy Measurement was carried out by KBr disk method and Nujol method using a Nicolet FT-IR spectrophotometer (5ZDX). KBr disks were prepared with a hydrostatic press at a thrust of 5.2 t/cm^2 (510 MPa) for 3 min.

Solid-State ^{13}C-NMR Measurement Solid-state ^{13}C-NMR measurements were made with a Chemagnetics CMX-360 solid-state NMR spectrometer. ^{13}C-NMR spectra were obtained using total suppression of the spinning sidebands (TOSS) method at 4.2 kHz. The contact time was usually 2 ms, and the pulse delay between scans was either 120 or 240 s. All chemical shifts were externally referenced to the methyl signal of hexamethylbenzene at 17.3 ppm.

Results and Discussion

IR Spectra of Benzoic Acid–DMβCD System Figure 1 shows the IR spectra of benzoic acid and the mixtures with DMβCD. Benzoic acid crystals (Fig. 1A) showed a carbonyl stretching vibration ($\nu_{C=O}$) band at 1696 cm^{-1} (Nujol method) and 1688 cm^{-1} (KBr disk method) both of which were assigned to the dimeric structure formed by eight-membered hydrogen bonding of the carboxylic groups.[10–12] The inclusion compound of benzoic acid and DMβCD (Fig. 1B) obtained by coprecipitation method had a stoichiometry of 1 : 1 and showed the $\nu_{C=O}$ band at a wavenumber of 1720 cm^{-1} by both the above methods, indicating that the free carbonyl group of benzoic acid existed in the hydrophobic cavity of DMβCD.[4] In a physical mixture of benzoic acid and DMβCD (Fig. 1C, D), however, significant difference in the spectra of benzoic acid was observed between Nujol method and KBr disk method. A carbonyl stretching peak was shifted

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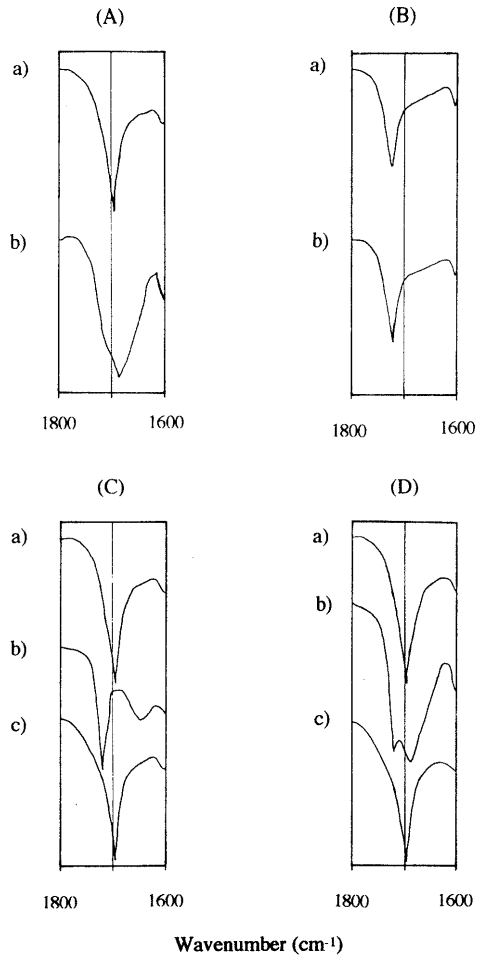

Fig. 1. IR Spectra of Benzoic Acid and DMβCD Systems

(A) benzoic acid crystals, (B) coprecipitate of benzoic acid and DMβCD (1 : 1), (C) physical mixture of benzoic acid and DMβCD (1 : 2), (D) physical mixture of benzoic acid and DMβCD (1 : 1). a) measured by Nujol method, b) measured by KBr disk method, c) measured by Nujol method after pulverization of the KBr disk (b).

to a higher wavenumber (1688→1720 cm^{-1}) in the spectra measured by KBr disk method, while the peak position measured by Nujol method was unchanged by the addition of DMβCD. Interestingly, the shifted peak reverted to the original position when the IR spectra were measured again by Nujol method following pulverization of the KBr disk. These results indicated that the remarkable $\nu_{C=O}$ peak change by compression was reversible. A peculiar peak shift was clearly observed in the DMβCD rich mixture (Fig. 1C). These phenomena were also observed in the compressed sample of benzoic acid and DMβCD mixture without KBr (not shown), indicating that the IR peak shifts by compression were independent of the presence of KBr.

Figure 2 shows effects of compression on the powder X-ray diffraction pattern of the physical mixture of benzoic acid and DMβCD. Since the diffraction peak positions were identical between the two patterns (Fig. 2a, b), the three dimensional molecular arrangement of benzoic acid was not influenced by compression. Furthermore, the difference in the X-ray diffraction pattern of the compressed sample from that of the inclusion compound (Fig. 2c) suggests that the IR peak shift by compression was not attributable to the inclusion compound formation

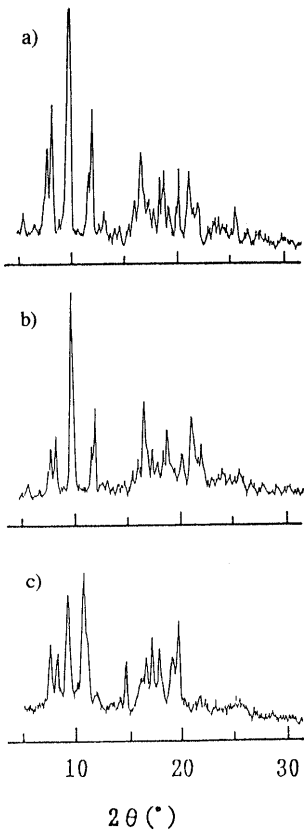

Fig. 2. Powder X-Ray Diffraction Patterns of Benzoic Acid–DMβCD Systems at a Molar Ratio of 1 : 1

a) physical mixture, b) after compression of a), c) inclusion compound prepared by coprecipitation method.

between benzoic acid and DMβCD.

IR Spectra of Carboxylic Acid–DMβCD Systems IR peak positions of $\nu_{C=O}$ band in carboxylic acid–DMβCD (molar ratio 1 : 1) systems by compression are listed in Table 1. In the cases of *o*-, *m*-, *p*-fluorobenzoic acid and decanoic acid, slight $\nu_{C=O}$ peak change was observed after compression. When phenylpropionic acid was used, a peculiar peak shift was observed by compression. When the IR spectrum was measured again by Nujol method following pulverization of the KBr disk, however, the shifted peak position showed incomplete reversion to the original position. Only benzoic acid crystals showed a remarkable and reversible peak shift by compression.

IR Spectra of Benzoic Acid–Additive Systems Other additives, βCD, TMβCD, MCC and MC were used to investigate $\nu_{C=O}$ peak shift by compression and pulverization. Figure 3 shows IR spectra of benzoic acid in the physical mixture with each additive at 1 : 14 molar ratio of benzoic acid to glucose unit. In the cases of the TMβCD and MC mixture, the reversible peak shift was observed. Since MC did not form an inclusion compound with benzoic acid, the IR peak shift by compression with DMβCD was not necessarily attributable to inclusion of benzoic acid into the DMβCD cavity. On the contrary, in the mixtures with βCD and MCC, the $\nu_{C=O}$ bands of benzoic acid were observed at the same position as benzoic acid crystals, showing the absence of any interaction between the two components in each mixture. Figure 4 also shows IR spectra of benzoic acid mixed with methyl-

Table 1. IR Peak Position of $\nu_{C=O}$ Band in Carboxylic Acid–DMβCD (Molar Ratio 1 : 1) Systems by Compression

	Wavenumber (cm^{-1}) KBr method		Nujol method[a]
	Without additive	Physical mixture	After pulverization
Benzoic acid	1688	1720	1696
o-Fluorobenzoic acid	1694	1715	1706
m-Fluorobenzoic acid	1687	1725	1702
p-Fluorobenzoic acid	1683	1715	1698
o-Chlorobenzoic acid	1690	1690	
m-Chlorobenzoic acid	1700	1700	
p-Chlorobenzoic acid	1682	1682	
o-Bromobenzoic acid	1683	1684	
m-Bromobenzoic acid	1686	1686	
p-Bromobenzoic acid	1679	1678	
o-Iodobenzoic acid	1690, 1677	1690, 1675	
m-Iodobenzoic acid	1683	1683	
p-Iodobenzoic acid	1679	1679	
o-Hydroxybenzoic acid	1686	1686	
m-Hydroxybenzoic acid	1687	1686	
p-Hydroxybenzoic acid	1675	1675	
o-Toluic acid	1686	1686	
m-Toluic acid	1686	1686	
p-Toluic acid	1680	1680	
Phthalic acid	1686	1686	
Isophthalic acid	1690	1690	
Terephthalic acid	1677	1676	
Phenylpropionic acid	1698	1735	1735, 1712
Decanoic acid	1692, 1701	1708, 1732	1712
Stearic acid	1701	1701	

a) Peak position was listed only in the system in which peak shift was observed.

ated CDs at the molar ratio of benzoic acid to CDs of 1 : 1 (1 : 7 molar ratio of benzoic acid to glucose unit). The $\nu_{C=O}$ peak shift of the TMβCD mixture was more remarkable than that of DMβCD mixture. The results shown in Figs. 3 and 4 reveal that the presence of numerous methoxyl groups in additives appeared to be an important factor for carbonyl peak shift to higher wavenumber.

Solid-State ^{13}C-NMR Spectra of Benzoic Acid–DMβCD Systems Solid-state ^{13}C-NMR spectroscopy was carried out to investigate the molecular states of benzoic acid in the mixture (Fig. 5). The chemical shifts observed at 130.9 and 172.5 ppm in benzoic acid crystals (Fig. 5a) were assigned to the benzene-ring carbon and carbonyl carbon, respectively. In the inclusion compound of benzoic acid and DMβCD (Fig. 5b), the chemical shift of carbonyl carbon appeared at a higher magnetic field of 167.2 ppm, corresponding to the change into the free-state of carbonyl group of benzoic acid by inclusion in the DMβCD cavity, in agreement with the result of IR spectroscopy (Fig. 1B). In the ^{13}C-NMR spectrum of compressed disk measured after adequate pulverization[13] (Fig. 5d), the chemical shifts due to carbons of benzoic acid were observed at the same position as those observed in benzoic acid crystals or the physical mixture. These results indicated that the dimer structure of benzoic acid molecules still remained after compression with DMβCD, and that the IR peak shift was not attributable to the inclusion compound formation between benzoic acid and DMβCD as reported previously.[2]

Change in the Molecular State of Benzoic Acid Dimer Breakage of hydrogen bonding or formation of a different kind of hydrogen bonding must be responsible for IR

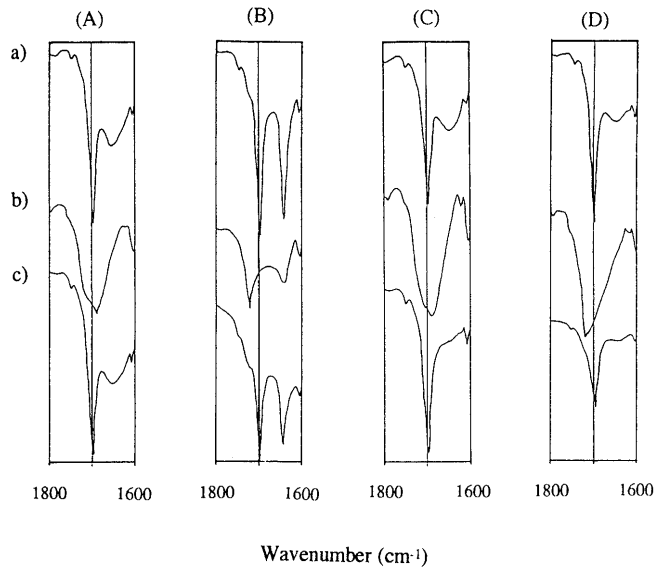

Fig. 3. IR Spectra of the Mixture of Benzoic Acid with Additives

(A) βCD, (B) TMβCD, (C) MCC, (D) MC. (1 : 14 molar ratio of benzoic acid to glucose unit) a) measured by Nujol method, b) measured by KBr disk method, c) measured by Nujol method with pulverized KBr disk (b).

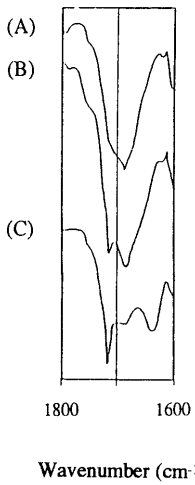

Fig. 4. IR Spectra of Benzoic Acid Mixed with Methylated CDs at 1 : 1 Molar Ratio Using KBr Disk Method

(A) βCD, (B) DMβCD, (C) TMβCD.

peak shift of the carbonyl stretching vibration band of benzoic acid. The experimental result, however, indicated that the crystal structure of benzoic acid was not affected by the compression.

Hayashi *et al.* reported that the $\nu_{C=O}$ peak of benzoic acid crystals was shifted at 1710 cm^{-1} to below 147 K.[6,7] This phenomenon was attributed to the coexistence of two kinds of configurations of benzoic acid accompanied by the proton transfer along two hydrogen bonds of carboxylic acid dimer.[6] In the cases of *o*-, *m*-, *p*-chlorobenzoic acid and bromobenzoic acid, which did not show IR peak change by compression (Table 1), temperature dependent IR peak shift was also reported and the enthalpy difference between the two configurations of each sample was larger than that of benzoic acid, which was estimated as approximately 0.4 kJ mol^{-1}.[7]

It is assumed that the proton transfer can occur easily when the movement of proton is small as in the case of

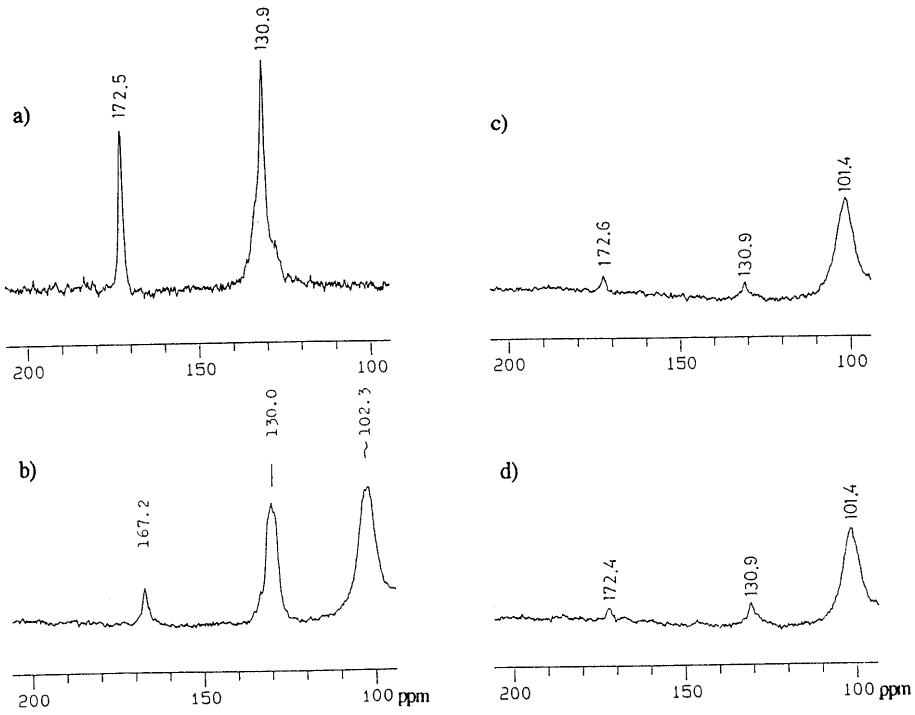

Fig. 5. Solid-State ^{13}C-NMR Spectra of Benzoic Acid–DMβCD Systems

a) benzoic acid crystals, b) inclusion compound (1 : 1), c) physical mixture before compression (molar ratio = 1 : 1), d) after compression.

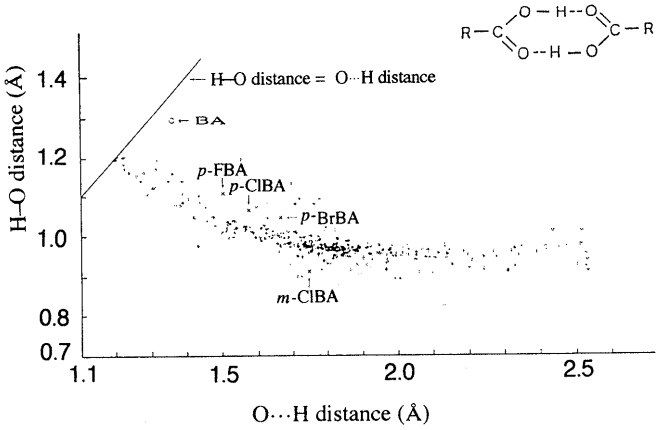

Fig. 6. Correlation of H–O and O···H Distance on the H–O···H Hydrogen Bondings of Carboxylic Acid Dimers

This figure was made on the basis of a distances of 499 hydrogen bonds by neutron diffraction measurement.[14–17] BA, benzoic acid; *p*-FBA, *p*-fluorobenzoic acid; *p*-ClBA, *p*-chlorobenzoic acid; *p*-BrBA, *p*-bromobenzoic acid; *m*-ClBA, *m*-chlorobenzoic acid.

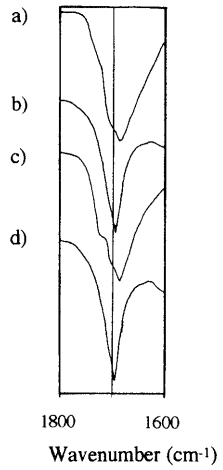

Fig. 7. IR Spectra of d_6-Benzoic Acid Mixed with DMβCD

a) d_6-benzoic acid measured by KBr disk method, b) d_6-benzoic acid measured by Nujol method, c) d_6-benzoic acid–DMβCD (1 : 1) measured by KBr disk method, d) measured by Nujol method with pulverized KBr disk (c).

Table 2. Hydrogen Bond Lengths of Carboxyic Acids

	Bond length (Å)[a]			
	O···O	H–O	O···H	Δd_{OH}[b]
Benzoic acid	2.65	1.29	1.36	0.07
o-Fluorobenzoic acid	2.58	1.07	1.51	0.44
m-Fluorobenzoic acid	2.63	1.06	1.57	0.51
p-Fluorobenzoic acid	2.62	1.11	1.51	0.40
Decanoic acid	2.64	1.04	1.60	0.56

a) See ref. 12, 19—22. *b*) Δd_{OH} = H···O distance − O–H distance.

the configurational change, that is, when the H···O distance and O–H distance on the H···O–H hydrogen bonding of dimeric structure of carboxylic acid become close. To investigate the possibility of proton transfer by compression, we examined whether proton transfer can occur in benzoic acid crystals. Recently, H···O and O–H bond lengths in H···O–H hydrogen bonds were estimated by low-temperature neutron diffraction technique with high precision.[14] Figure 6 shows the correlation of H···O and O–H distances on the H···O–H hydrogen bonding of carboxylic acid dimers, which was made on the basis of 499 hydrogen bond distances by neutron diffraction measurement by Sasada.[15] The H···O and O–H distances are equal on the solid line represented in the figure. The H···O and O–H distances of benzoic acid were calculated as 1.36 and 1.29 Å, respectively.[12] The difference of these bond distances (Δd_{OH}) of benzoic acid (0.07) was small enough compared with that of *m*-chlorobenzoic acid

(0.83 Å), *p*-chlorobenzoic acid (0.49 Å) and *p*-bromobenzoic acid (0.55 Å).[16-18] Hydrogen bond lengths and Δd_{OH} of the carboxylic acids which showed IR peak change by compression (see Table 1) are listed in Table 2. Although the O···O distances of these drugs were almost equal, the Δd_{OH} of benzoic acid was much smaller than that of the others. This suggests that the proton transfer may occur easily in benzoic acid crystals.

As the proton transfer was thought to be affected by the mass of proton, deuterated benzoic acid (d_6-benzoic acid) was synthesized. Figure 7 shows the IR spectra of d_6-benzoic acid mixed with DMβCD.

When proton was substituted for deuterium in the dimeric structure, no peak shift was observed. This was ascribed to the isotope effect, that is, heavy deuterium was not as easy to transfer as hydrogen.

We conclude from the present study that compression of benzoic acid with methylated polysaccharide induced the proton transfer in the hydrogen bonded eight-membered ring of dimeric benzoic acid molecules, causing $\nu_{C=O}$ peak shift.

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References and Notes

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