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Polymorphism of 4-Fluorophenylpyruvic Acid Studied by X-Ray Crystallography and Vibrational Spectroscopy

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**POLYMORPHISM OF 4-FLUOROPHENYL PYRUVIC ACID STUDIED
BY X-RAY CRYSTALLOGRAPHY AND
VIBRATIONAL SPECTROSCOPY**

Key Words: 4-fluorophenylpyruvic acid, polymorphism, X-ray structure, IR spectra, Raman spectra

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ABSTRACT

Two polymorphic forms (I and II) of 4-fluorophenylpyruvic acid (F-PPA) were obtained by crystallization from different solvents, showing a melting point at 163.2 and 171.0 °C. Crystal structures of polymorphs I and II were determined by X-ray crystallography. IR and Raman spectra of the two polymorphs were measured and the spectral characteristics were compared with those of phenylpyruvic acid. The two polymorphs show similar molecular and crystal structures to each other, except for the molecular geometries of the enol and the carboxylic acid moieties. Distinct IR spectral differences which result from the crystal field splitting were observed between the two polymorphs.

INTRODUCTION

Phenylpyruvic acid (PPA) is a key compound in several metabolic sequences and is a substrate for microbial production of phenylalanine¹⁻³. Besides its biological importance, this compound has also aroused research interests in structural chemistry such as the tautomerism and the conformation⁴⁻⁸. We have investigated the tautomeric behavior of PPA and its metal salts both in solution and in the solid state by IR, Raman, and NMR spectroscopy⁹. Recently we have found that PPA crystallizes as two polymorphic forms from different solvents¹⁰. The two polymorphs showed distinct differences in IR, Raman, and solid state ¹³C NMR spectra, as well as in the thermal data. However, the detailed discussion on the spectra-structure correlation was not possible because of unavailability of X-ray crystallographic data; the PPA crystals were always obtained as mixtures of the polymorphs.

In the course of preparing single crystals for X-ray analysis, we obtained crystals of 4-fluorophenylpyruvic acid (F-PPA) in two polymorphic forms. In the present work, we have determined X-ray structures of the two polymorphs of F-PPA. IR and Raman spectra of the two polymorphs were measured and the spectral characteristics were compared with those of PPA.

EXPERIMENTAL

Materials

F-PPA was prepared by the reported procedures using 4-fluorobenzaldehyde and *N*-acetylglycine as starting materials¹¹. Its purity was checked by elemental analysis and ¹H NMR spectroscopy. Single crystals of the polymorphic forms I and II were obtained by slow evaporation of a chloroform solution and an ethyl acetate/cyclohexane/n-hexane (2:7:1) solution, respectively, of F-PPA at room temperature.

Measurement

Differential scanning calorimetry (DSC) was carried out on a differential thermal analyzer (Shimadzu, DSC-50) at a scan rate of 10 °C/min, under a stream of N₂ gas. The DSC thermograms showed that the melting points of polymorphs I and II are at 163.2 and 171.0 °C, respectively.

The IR spectra were recorded on a Perkin Elmer 1650 FT-IR spectrometer by averaging 64 scans with a resolution of 4 cm⁻¹. The spectra were measured as KBr pellets.

FT-Raman spectra were obtained on a Perkin Elmer 2000R spectrometer using the 1064 nm line of a Spectron SL300 Nd:YAG laser as an exciting source. The samples were sealed in glass capillary tubes.

X-ray crystal structure analysis

The preliminary cell dimensions and space group symmetry were determined photographically. X-ray diffraction data were obtained on a Rigaku AFC-5R diffractometer with a graphite monochromated Cu K α radiation (λ = 1.54178 Å). Intensity data were collected at room temperature (23 °C) with an ω -2θ scan mode. The data were corrected for both Lorentz and polarization effects. Table 1 summarizes the crystal data and experimental conditions for the crystal structure determination.

TABLE 1
Crystallographic data

Parameter	polymorph I	polymorph II
Empirical formula	$C_9H_7FO_3$	$C_9H_7FO_3$
Formula mass	182.15	182.15
Crystal system	monoclinic	monoclinic
Space group	$P2_1/a$	$P2_1/a$
Unit cell dimensions		
a (Å)=	7.3767(6)	7.3807(4)
b (Å)=	5.6430(6)	5.6456(6)
c (Å)=	19.501(2)	19.5078(8)
β (°)=	100.685(7)	100.727(4)
Cell volume	$V(\text{\AA}^3)$ =	797.7(1)
Molecules per cell	Z =	4
Density calculated	$D_c(\text{g cm}^{-3})$	1.516
=		
Max 2 θ (deg)	120.2	120.1
No. of unique reflections	1234	1338
No. of reflections measured	1349	1453
No. of reflections with	973	1116
$I > 1.20\sigma(I)$		
R	0.057	0.044
R_w	0.070	0.058
Goodness of Fit	3.42	3.18

The structure was solved by direct methods. Crystal structure analysis was performed by using the *TEXAN* crystallographic software package¹². Non-hydrogen atoms were refined anisotropically. All the H-atom positions were found from a difference Fourier map and refined isotropically.

RESULTS AND DISCUSSION

X-ray crystal structure of polymorphs I and II

Table 2 contains the final positional parameters of polymorphs I and II. Table 3 summarizes the interatomic distances, angles, selected torsional angles, and hydrogen bonding geometries of polymorphs I and II. As shown in Table 3, the

TABLE 2
Fractional atomic coordinates of polymorphs I and II.

atom	Polymorph I			$B_{eq}^{a)}$
	x	y	z	
F1	0.7974(3)	0.0401(3)	0.52168(9)	4.60(9)
O1	1.3951(3)	0.2140(4)	0.9541(1)	4.7(1)
O2	1.3775(4)	-0.1697(4)	0.9244(1)	4.8(1)
O3	1.1826(3)	0.3482(4)	0.8375(1)	4.3(1)
C1	1.3383(5)	0.0549(6)	0.9128(2)	3.6(1)
C2	1.2224(4)	0.1127(5)	0.8455(2)	3.2(1)
C3	1.1678(4)	-0.0486(6)	0.7959(2)	3.1(1)
C4	1.0650(4)	-0.0178(5)	0.7251(1)	2.7(1)
C5	1.0733(4)	-0.1994(5)	0.6773(2)	2.9(1)
C6	0.9854(4)	-0.1810(5)	0.6085(2)	3.2(1)
C7	0.8858(4)	0.0203(5)	0.5885(1)	3.0(1)
C8	0.8703(4)	0.2023(5)	0.6340(2)	3.0(1)
C9	0.9612(4)	0.1831(5)	0.7021(2)	2.8(1)
H1	1.250(6)	0.419(7)	0.876(2)	6(1)
H2	1.4541	-0.2174	0.9674	8(1)

atom	Polymorph II			$B_{eq}^{a)}$
	x	y	z	
F1	0.2975(2)	0.0399(2)	0.52156(5)	4.52(5)
O1	0.8950(2)	0.2141(3)	0.95412(7)	4.75(7)
O2	0.8774(2)	-0.1704(3)	0.92458(7)	4.81(7)
O3	0.6829(2)	0.3486(3)	0.83754(7)	4.33(6)
C1	0.8388(3)	0.0545(3)	0.91300(1)	3.57(8)
C2	0.7221(3)	0.1127(3)	0.84532(9)	3.18(7)
C3	0.6686(3)	-0.0487(3)	0.79590(1)	3.13(7)
C4	0.5651(2)	-0.0178(3)	0.72515(9)	2.66(6)
C5	0.5735(2)	-0.1993(3)	0.67710(1)	2.93(7)
C6	0.4861(2)	-0.1809(3)	0.60840(1)	3.12(7)
C7	0.3859(2)	0.0204(3)	0.58859(9)	3.03(7)
C8	0.3699(2)	0.2026(3)	0.63390(1)	3.07(7)
C9	0.4610(2)	0.1829(3)	0.70210(1)	2.84(7)
H1	0.745(4)	0.423(6)	0.878(1)	7.6(8)
H2	0.950(3)	-0.196(5)	0.970(1)	5.8(6)

a) $B_{eq} = (4/3) \sum_i \sum_j \beta_{ij} a_i^* a_j^* (a_i a_j)$

TABLE 3
Selected structural parameters of polymorph I and polymorph II

Parameters	Polymorph I	Polymorph II
Bond lengths/Å		
<i>r</i> (C1-O1)	1.227(4)	1.226(2)
<i>r</i> (C1-O2)	1.310(4)	1.312(2)
<i>r</i> (C1-C2)	1.464(4)	1.473(3)
<i>r</i> (C2-O3)	1.363(4)	1.366(2)
<i>r</i> (C2-C3)	1.334(4)	1.332(3)
<i>r</i> (C3-C4)	1.458(4)	1.459(2)
<i>r</i> (O2-H2)	0.959(2)	0.95(3)
<i>r</i> (O3-H1)	0.92(4)	0.94(3)
Bond angles/°		
ϕ (O1-C1-O2)	123.8(3)	124.3(2)
ϕ (O1-C1-C2)	119.8(3)	119.5(2)
ϕ (O2-C1-C2)	116.4(3)	116.2(2)
ϕ (C1-C2-O3)	113.4(3)	113.2(2)
ϕ (C1-C2-C3)	123.0(3)	122.8(2)
ϕ (C2-O3-H1)	105(3)	107(2)
ϕ (C2-C3-C4)	129.7(3)	129.5(2)
ϕ (C1-O2-H2)	119.9(3)	112(2)
ϕ (C3-C2-O3)	123.5(3)	124.0(2)
Dihedral angles/°		
τ (H1-O3-C2-C3)	-171.7	-175.0
τ (H1-O3-C2-C1)	5.6	2.0
τ (O3-C2-C1-O1)	-2.8(5)	-2.6(3)
τ (O3-C2-C1-O2)	175.6(5)	178.2(2)
τ (C3-C2-C1-O1)	174.6(3)	174.4(2)
τ (C3-C2-C1-O2)	-4.4(5)	-4.8(3)
τ (C4-C3-C2-C1)	-175.0(3)	-175.3(2)
τ (C4-C3-C2-O3)	2.1(6)	1.4(3)
τ (H2-O2-C1-O1)	0.4	2.8
τ (H2-O2-C1-C2)	179.3	-178.0
τ (C5-C4-C3-C2)	160.9(3)	161.2(2)
τ (C9-C4-C3-C2)	-18.2(5)	-17.7(3)
Hydrogen bonding geometries		
<i>r</i> (H1...O1)	2.049	2.052
<i>r</i> (O3...O1)	2.623	2.622
ϕ (O3-H1...O1)	119.6	117.8
<i>r</i> (H2...O1')	1.717(2)	1.71(3)
<i>r</i> (O2...O1')	2.649(3)	2.646(2)
ϕ (O2-H2...O1')	162.6	170.7
τ (O2-H2...O1'-C1')	17.2	66.0

two polymorphs show practically identical molecular and crystal structures. The molecular structure and packing in the unit cell of polymorph I are illustrated in Figs. 1 and 2. Both polymorphs are crystallized in the monoclinic space group with four molecules in a unit cell. F-PPA molecules take the enol form with an intramolecular hydrogen bonding between the enolic hydrogen and the carbonyl oxygen. The molecules are linked together by the intermolecular hydrogen bondings through the carboxylic acid groups. These hydrogen bonds make a centrosymmetric dimer, which is normally seen in carboxylic acids. The carboxylic acid group and the olefinic C=C group are almost co-planar, and the C3-C2-C1-O2 torsion angle is -4.4° and -4.8°, respectively, for polymorphs I and II. The phenyl ring is tilted about 20° toward the olefinic group τ (C5-C4-C3-C2) is 160.9° and 161.2°, respectively, for polymorphs I and II). Similar molecular and crystal structures were reported for *p*-hydroxyphenylpyruvic acid (HO-PPA)¹³.

Differences in the molecular structure are seen both in the enol and carboxylic acid moieties. The dihedral angle τ (O3-C2-C1-O2) is 175.6° for polymorph I and 178.2° for polymorph II. The O3-H1 bond length is shorter in polymorph I; this distance is 0.92 Å compared to 0.94 Å in polymorph II. The carboxylic C-O-H angle is larger in polymorph I; the bond angle C1-O2-H2 is 119.9° and 112°, respectively, for polymorphs I and II. Furthermore, the largest difference is observed in the intermolecular hydrogen bonding geometry; these polymorphs differ in the twisting angle of the carboxylic OH (the difference between the dihedral angles, τ (O2-H2...O1'-C1'), is 48.8°).

Infrared and Raman Spectra

Figures 3 and 4 show the IR and Raman spectra of the F-PPA polymorphs. When these spectra are compared with those of the PPA polymorphs¹⁰, marked similarities are found between the band frequencies and the spectral patterns in the regions of 3500-3100 cm⁻¹, 1700-1620 cm⁻¹, and 1250-1190 cm⁻¹. Therefore, the

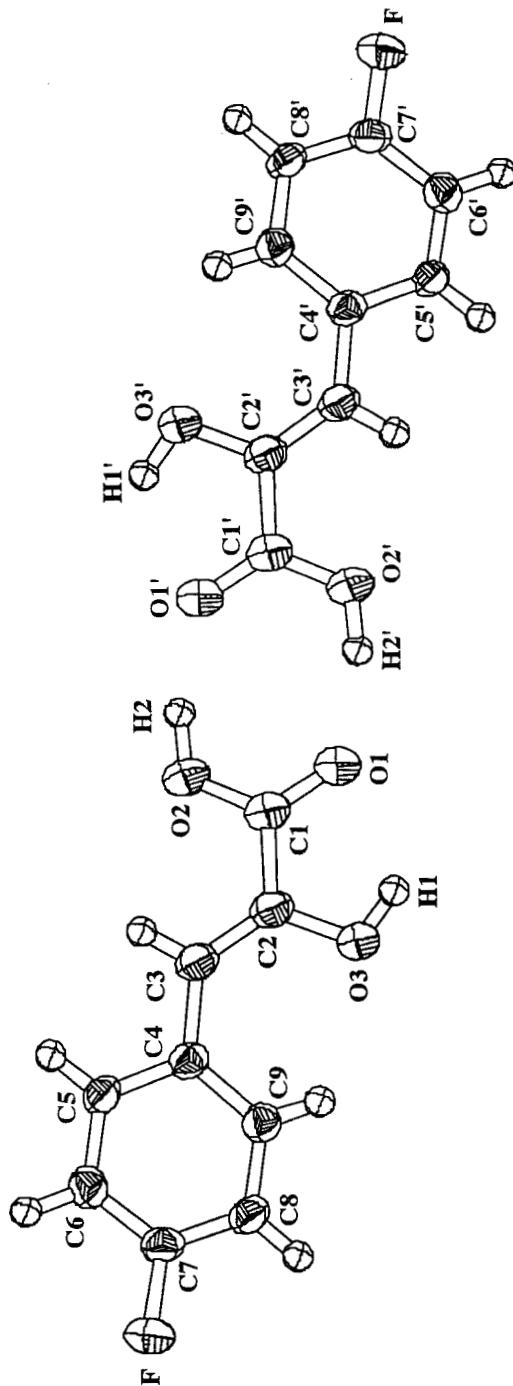


FIG. 1 Molecular structure of polymorph I with the numbering of the atoms. Thermal ellipsoids of the non-hydrogen atoms are scaled to enclose 50 % probability. The spheres of the hydrogen atoms are drawn in an arbitrary scale.

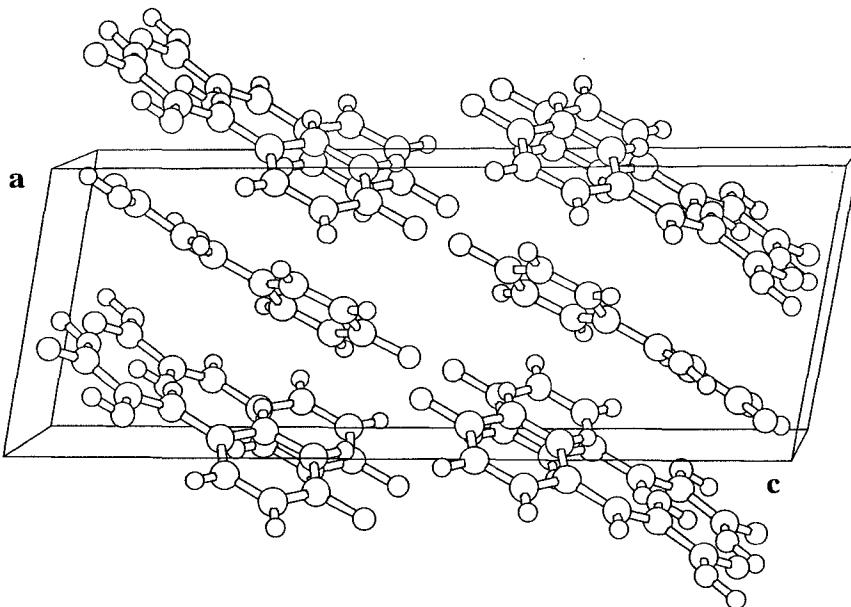


FIG. 2 Molecular packing in the unit cell of polymorph I.

PPA polymorphs probably have structures similar to those of the F-PPA polymorphs. Table 4 gives the comparison of these IR bands between F-PPA and PPA. The largest difference between the F-PPA polymorphs is in the hydrogen bonding by which the two molecules form the ring dimer, as discussed above. The bond length of the enol group is also different between the two forms. Spectral differences come from such characteristics of the crystal structure. The differences in the bond angle $\phi(C1-O2-H2)$ and the dihedral angle $\tau(O2-H2...O1'-C1')$ affect the coupled mode of the C-O stretching and the O-H bending of the carboxyl group to give different frequencies (1212 and 1238 cm^{-1}) between the two polymorphs. The respective enol OH stretching bands are observed at 3478 and 3458 cm^{-1} for these polymorphs, corresponding to the magnitude of the O-H bond lengths.

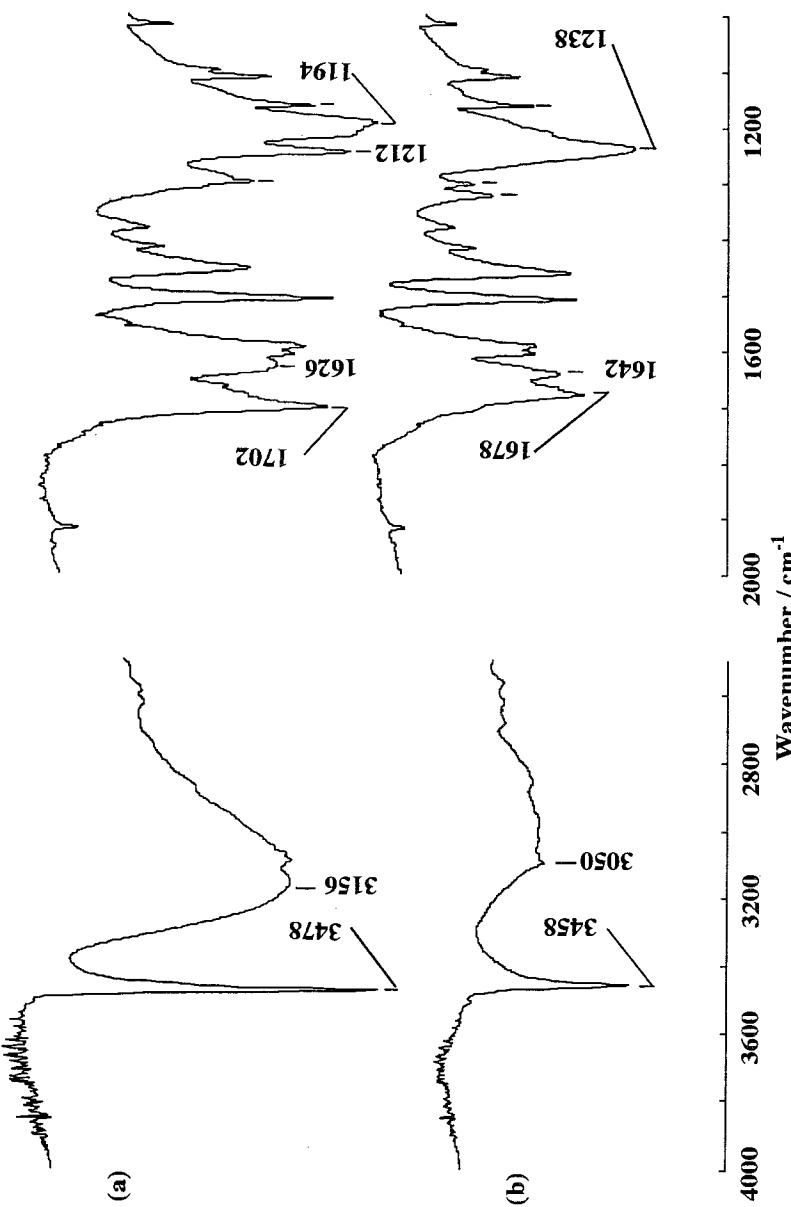


FIG. 3 Infrared spectra of (a) polymorph I and (b) polymorph II of F-PPA.

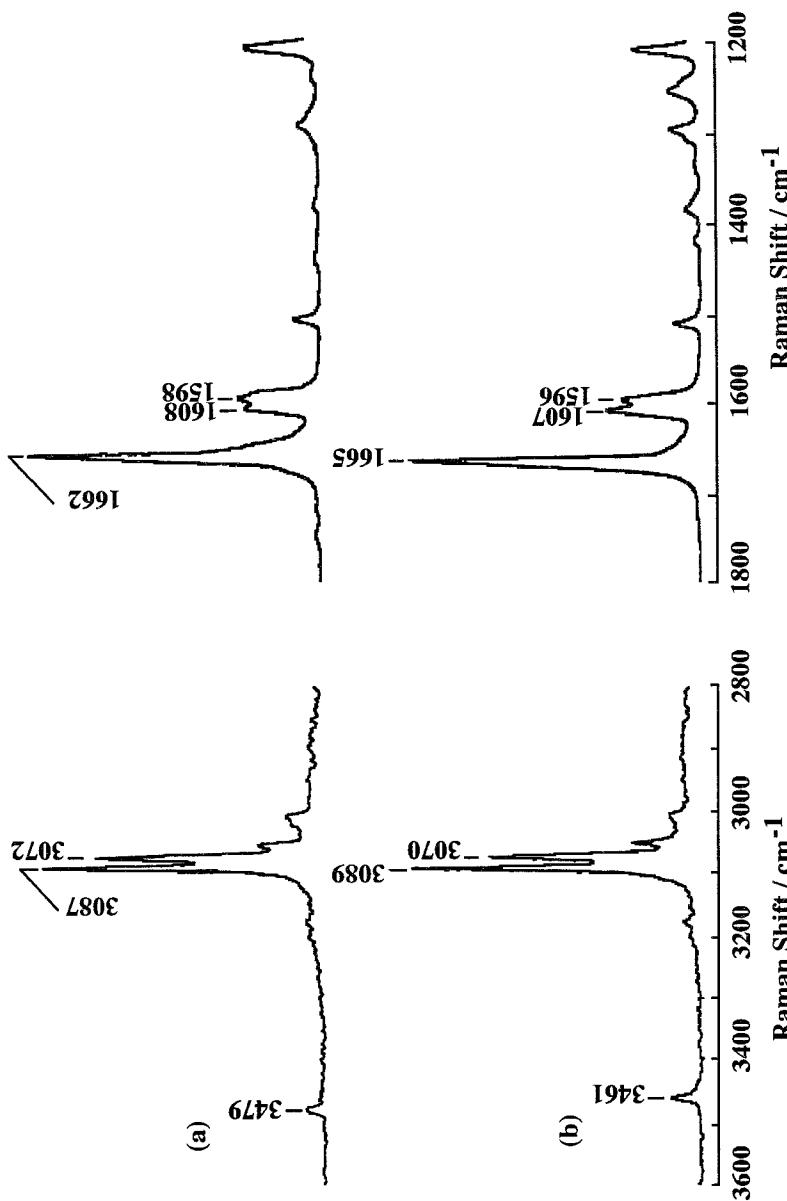


FIG. 4 Raman spectra of (a) polymorph I and (b) polymorph II of F-PPA.

TABLE 4
Selected IR frequencies (cm^{-1}) of phenylpyruvic acid polymorphs

Polymorphs of F-PPA		polymorphs of PPA ^{a)}		Assignment
I	II	I	II	
3478 s	3458 s	3476 s	3458 s	$\nu(\text{OH})/\text{enol}$
3156 m,br	3050 w,br	3150 m,br	3050 w,br	$\nu(\text{OH})/\text{carboxyl}$
1702 vs	1678 vs	1700 vs	1680 vs	$\nu(\text{C=O})/\text{carboxyl}$
1665 w	1666 sh	1660 w	1660 w	$\nu(\text{C=C})$
(1662 vs) ^{b)}	(1665 vs) ^{b)}	(1660 vs) ^{b)}	(1660 vs) ^{b)}	
1626 m	1642 m	1623 m	1645 m	$\nu(\text{C=O})/\text{carboxyl}$
1212 s	1238 vs	1218 s	1251 vs	$\nu(\text{C-O})+\delta(\text{OH})/\text{carboxyl}$
1194 vs		1196 vs		$\nu(\text{C-O})+\delta(\text{OH})/\text{enol}$

^{a)} Previous work¹⁰

^{b)} Raman bands

Two bands are observed in the C=O region for F-PPA as reported for PPA¹⁰. The higher-frequency one is straightforwardly assigned to the C=O stretching vibration. However, the assignment of the lower-frequency band still remains open, although we have already discussed this problem for PPA and suggested an explanation¹⁰. The C=C stretching vibration, which is expected in this region, appears around 1665 cm^{-1} as a weak or shoulder band in the infrared spectrum. This assignment was confirmed by the observation of a very strong Raman band around 1665 cm^{-1} and by the fact that the corresponding infrared band for PPA shows an expected isotope shift of 26 cm^{-1} on $2\text{-}^{13}\text{C}$ substitution¹⁰. A hydrogen-bonded carboxyl pair is located closely to the nearest neighbor with their planes diagonally faced in the unit cell, as seen in Fig. 2. Therefore, it is reasonable to consider the interaction between the transition dipoles¹⁴; the two bands observed may be ascribed to splitting which arises from such interaction between the two molecules which are transferred to each other by the glide plane. HO-PPA also has similar spectral features⁷ and a similar crystal structure for the carboxylic moieties¹⁸. Probably such crystal field splittings are characteristic of phenylpyruvic acids which have the crystal structures discussed above. The

crystals of *trans*- and *cis*-cinnamic acids^{15,16}, which are the model compounds of the enol form of phenylpyruvic acids, belong to the same crystal system, but their molecular arrangements are appreciably different from those in F-PPA and HO-PPA crystals; these cinnamic acids show the normal C=O bands. Although the splitting in polymorph I is larger than that in polymorph II, the mean frequency of the two bands are almost the same for both forms. The C=O band lengths are the same as given in Table 3.

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