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Vibrational Spectroscopic Studies of Cocrystals and Salts. 3. Cocrystal Products Formed by Benzenecarboxylic Acids and Their Sodium Salts

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ABSTRACT: X-ray powder diffraction, differential scanning calorimetry, infrared absorption spectroscopy, and Raman spectroscopy have been used to study the phenomenon of salt formation in four benzenecarboxylic acids (benzoic acid, phenylacetic acid, hydrocinnamic acid, and 4-phenylbutanoic acid), and in the 1:1 stoichiometric products formed by the cocrystallization of a free acid and a sodium salt. Assignments were derived for the observed peaks in both infrared absorption and Raman spectra of the reactants and their products. In all instances, it was observed that the energy of the antisymmetric stretching mode of the carbonyl group of the free benzenecarboxylic acid. In addition, the symmetric stretching mode of the benzenecarboxylic acid carbonyl group disappeared in the Raman spectrum of its sodium salt and was also absent in the Raman spectrum of the cocrystal product. It was also found that the antisymmetric carboxylate anion stretching mode, the out-of-plane carboxylate deformation mode, and the vibrational modes associated with the phenyl ring and alkane side chains were not useful spectroscopic tools to differentiate cocrystal and sodium salt, as the observed differences of these vibrational modes did not exhibit significantly consistent differences between the various forms.

Introduction

In a previous study, the existence of an interesting 1:1 saltcocrystal formed by the interaction of benzoic acid with benzylammonium benzoate was demonstrated using X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).¹ Full assignments for the infrared absorption and Raman spectra of the cocrystal were made, and by tracing the perturbations in group energies relative to the starting free acid and salt, a series of conclusions were reached regarding the intermolecular interactions existing in the cocrystal. For example, a significant alteration of the antisymmetric carbonyl stretching mode of benzoic acid was found to take place, resulting in a large shift in energy and splitting of the band. In addition, study of the energies of the phenyl ring modes enabled the deduction that formation of the cocrystal involved interactions between the phenyl rings of the benzoic acid and the benzylammonium benzoate salt that did not accompany formation of the salt from benzoic acid and benzylamine.

The principle that salts of organic molecules can form cocrystals with carboxylic acids is well established in the literature. For example, the existence of a 1:1 salt-cocrystal of fluoxetine hydrochloride and benzoic acid has been demonstrated, as have 2:1 salt-cocrystals of the drug substance with succinic and fumaric acids.² The intermolecular interactions existing in these systems represent examples of the types of anion coordination anion-templated assembly that have been recently described.³ In another work, the salt-cocrystal formed by tiotropium fumarate with fumaric acid has been shown to be more stable than were the simpler salt and saltsolvate fumarate solid forms.⁴ It is clear that such saltcocrystal systems greatly extend the scope of crystalline forms of drug substances,^{5–8} thus providing an even wider landscape for investigators seeking to improve upon the physical properties of a given drug substance.

In the preceding works in this series, in-depth studies have been conducted regarding the use of vibrational spectroscopy as a means to study the intermolecular interactions existing in the solid-state forms of salts and cocrystals.^{1,9} Other workers have used infrared absorption spectroscopy as a means to correlate intermolecular interactions in solution with the structural synthons that assemble into crystals.¹⁰ In some cases, the existence of similarities between the growth synthon and the structural synthon was detected, but in others it was deduced that the solution-phase assemblies needed to undergo significant molecular rearrangement in order to form crystal nuclei. In another study, infrared absorption spectroscopy and single-crystal diffraction studies were used to study a large number of solid-state products consisting of theophylline and interactive molecules characterized by comparable ionization constant differences.¹¹ These workers obtained 13 cocrystals, 5 salts, and 2 complexes having mixed ionization states, and ultimately proposed that screening studies be more based on identification of solid-state forms and not on pK_A differences.

In the present work, the phenomena of salt and cocrystal formation have been studied for the series of benzenecarboxylic acids whose structures are provided in Figure 1, primarily from the viewpoint of perturbations in molecular vibrations that are associated with the various species. The compounds studied in this work are characterized by an increasing degree of separation between the phenyl and carboxylate groups, enabling an investigation to be made regarding the roles of synthon formation and phenyl ring interaction.

Materials and Methods

Benzoic acid (BZA), phenylacetic acid (PAA), hydrocinnamic acid (HCA), and 4-phenylbutanoic acid (4PBA) were purchased from Sigma-Aldrich, and each free acid was wetted with methanol and ground to dryness in a mortar before use. The sodium salts of these



Figure 1. Structures of the benzenecarboxylic acids used in the present study.

carboxylic acids were prepared by dissolving 500 mg quantities of each acid in a 1:1 stoichiometric amount of 0.2 N sodium hydroxide solution, and then evaporating the solution to dryness. The recovered solids were transferred to a mortar, wetted with methanol, and then ground to dryness. Cocrystal products were prepared following the same general procedure, where accurately weighed amounts of free acid and sodium salt (1:1 stoichiometry based on nonsolvated masses) were placed in a mortar, wetted with methanol, and then ground to dryness.

XRPD patterns were obtained using a Rigaku MiniFlex powder diffraction system, equipped with a horizontal goniometer operating in the $\theta/2\theta$ mode. The X-ray source was nickel-filtered K α emission of copper (1.54184 Å). Samples were packed into the sample holder using a backfill procedure and were scanned over the range of 3.5– 40 deg 2θ at a scan rate of 0.5 deg $2\theta/\min$. Using a data acquisition rate of 1 point per second, these scanning parameters equate to a step size of 0.0084 deg 2θ .

Measurements of DSC were obtained on a TA Instruments 2910 thermal analysis system. Samples of approximately 1-2 mg were accurately weighed into an aluminum DSC pan, and then covered with an aluminum lid that was crimped in place. The samples were then heated at a heating rate of 10 °C/min from ambient temperature to termination temperatures in the range of 150–225 °C, depending on the system under study.

Fourier-transform infrared (FTIR) absorption spectra were obtained at a resolution of 4 cm⁻¹ using a Shimadzu model 8400S infrared spectrometer, with each spectrum being obtained as the average of 25 individual spectra. The data were acquired using the attenuated total reflectance sampling mode, where the samples were clamped against the ZnSe crystal of a Pike MIRacle single reflection horizontal ATR sampling accessory. Raman Systems model R-3000HR spectrometer, operated at a resolution of 5 cm⁻¹ and using a laser wavelength of 785 nm. The data were acquired using front-face scattering from a thick powder bed contained in an aluminum sample holder.

Results

A. Benzoic Acid, Sodium Benzoate, and their Homo-Cocrystal Product. XRPD patterns obtained for benzoic acid, sodium benzoate, and the BZA-Na-BZA cocrystal product are shown in Figure 2, where one may note that the differences in powder patterns demonstrate the existence of three different crystal structures. DSC thermograms of these substances confirmed the existence of distinctly different crystalline species. The DSC thermogram of benzoic acid consisted of a single melting endothermic transition, characterized by a temperature maximum at of 123 °C and an



Figure 2. X-ray powder diffraction patterns of benzoic acid (blue trace), sodium benzoate (green trace), and the 1:1 benzoic acid/ sodium benzoate cocrystal (red trace).



Figure 3. Infrared absorption spectra in the fingerprint region of benzoic acid (blue trace), sodium benzoate (green trace), and the 1:1 benzoic acid/sodium benzoate cocrystal (red trace).

enthalpy of fusion equal to 133 J/g. The DSC thermogram of the sodium benzoate salt consisted solely of a desolvation endotherm, which exhibited a temperature maximum of 69 °C and an enthalpy of desolvation equal to 74 J/g. These thermal characteristics may be contrasted with those of the BZA-Na-BZA cocrystal product, for which the DSC thermogram consisted of a single melting endothermic transition, having a temperature maximum at of 144 °C and an enthalpy of fusion equal to 52 J/g.

Table 1. Assignments of the Major Bands in the Fingerprint Region of the Infrared Absorption Spectra of Benzoic Acid, Sodium Benzoate, and their 1:1 Cocrystal Product

assignment	benzoic acid	benzoic acid/sodium benzoate cocrystal	sodium benzoate	assignment
C-H out-of-plane bending mode	665	652		
ring torsion mode	683	679	677	ring torsion mode
C-H deformation mode	704	706	704	C-H deformation mode
C-H rocking mode	806	798, 787		
c		820	820	out-of-plane C-H mode
		845	845	out-of-plane C-H deformation mode
out-of-plane ring bending mode	933			A
		901	920	COO ⁻ out-of-plane deformation
C-C stretching mode	1001			*
in-plane ring C–H mode	1026	1026	1028	in-plane ring C–H mode
in-plane ring C-H mode	1072	1070	1068	in-plane ring C-H mode
in-plane ring C-H mode	1128	1119		
C-H twisting mode	1186	1176		
carbonyl in-plane deformation	1257	1250		
C-C ring stretching mode	1323	1327	1308	C-C ring stretching mode
6 6		1408	1402	symmetric COO ⁻ stretching mode
OH out-of-plane deformation of COOH	1421			
C-C ring stretching mode	1452	1450		
6 6		1551	1547	antisymmetric COO ⁻ stretching mode
C-C ring stretching mode	1583			
C-C ring stretching mode	1601	1597	1595	C-C ring stretching mode
COOH stretching mode	1678	1697		2 0



Figure 4. Raman spectra in the fingerprint region of benzoic acid (blue trace), sodium benzoate (green trace), and the 1:1 benzoic acid/sodium benzoate cocrystal (red trace).

As shown in Figure 3, benzoic acid, sodium benzoate, and the BZA-Na-BZA cocrystal product exhibited a number of significant differences in the fingerprint region of their infrared absorption spectra. The molecular vibrational modes of the major absorbance peaks were assigned through the use of published compilations,^{12–14} works conducted specifically on benzoic acids^{15–18} or works covering the spectra of benzoate salts.^{19–21} The results of this analysis are provided in Table 1.

As has been noted in the previous papers,^{1,9} the degree of perturbation in the frequencies of the carbon–carbon and carbon–hydrogen modes is relatively minor across the three substances, which indicates that the basic skeletal motions are effectively the same. It is not unexpected that the most interesting changes associated with either the salt or cocrystal formation are associated with the motions of the benzoic carboxylate group. For example, the loss of the -COOH asymmetric stretching mode of benzoic acid (1678 cm⁻¹) and appearance of the antisymmetric (1547 cm⁻¹) and symmetric (1402 cm⁻¹) stretching modes of the benzoate COO⁻ ion represents the normal spectral perturbation that takes place upon formation of the carboxylate salt. All of these same vibrational modes are present in the spectrum of the BZA-Na-BZA cocrystal, with the most interesting difference being the increase in frequency of the COOH stretching mode from 1678 to 1697 cm⁻¹.

The Raman spectra of benzoic acid, sodium benzoate, and the BZA-Na-BZA cocrystal product in the fingerprint region are shown in Figure 4. The origins of the vibrational modes associated with the various Raman scattering peaks were assigned through the use of published compilations,^{22–25} works dealing specifically with benzoic acids,^{26,27} and works covering the spectra of benzoate salts.^{19,21} The results of this analysis are provided in Table 2.

As had been noted for the infrared absorption spectra, the modes associated with the carbon skeleton were not appreciably different in the Raman spectra of the three substances. Once again, the most interesting differences between the forms were found to be associated with the carboxylate group. Formation of the sodium benzoate salt was demonstrated in the Raman spectra as a loss of the weak symmetric carbonyl stretching mode (1631 cm^{-1}) of the acid and in the appearance of a carboxylate anion stretching mode in the spectrum of the salt at 1267 cm^{-1} . Formation of the BZA-Na-BZA cocrystal product was found to result in a loss of the carboxylic acid in-plane deformation mode (1287 cm^{-1}) and a shift of the carboxylate anion stretching mode from 1267 cm^{-1} to 1251 cm^{-1} . In addition, the frequency of the symmetric carboxylic acid stretching mode (1631 cm^{-1}) was found to increase to 1696 cm⁻¹ in the spectrum of the cocrystal.

B. Phenylacetic Acid, Sodium Phenylacetate, and their Homo-Cocrystal Product. The XRPD patterns obtained for phenylacetic acid, sodium phenylacetate, and the 1:1

Table 2. Assignments of the Major Bands in the Fingerprint Region of the Raman Spectra of Benzoic Acid, Sodium Benzoate, and Their 1:1 Cocrystal Product

assignment	benzoic acid	benzoic acid/sodium benzoate cocrystal	sodium benzoate	assignment
C-C + ring deformation modes	416	398	396	C-C + ring deformation modes
ring torsion mode	611	611	609	ring torsion mode
e		673	673	symmetric COO ⁻ deformation mode
C-H out-of-plane bending mode	790	783		5
1 0		837	839	C-C + ring deformation modes
in-plane C-C deformation mode of phenyl ring	997	1001	1002	in-plane $C-C$ deformation mode of phenyl ring
in-plane C-H deformation mode	1023	1025	1026	in-plane C–H deformation mode
C-H rocking mode	1070			*
in-plane C-H deformation mode	1129	1138	1139	in-plane C-H deformation mode
*		1157	1155	C-H twisting mode
C-H in-plane bending mode	1176	1181	1179	C-H in-plane bending mode
COOH in-plane deformation mode	1287			1 0
*		1251	1267	symmetric COO ⁻ stretching mode
C-C ring stretching mode	1361	1372		
C-H twisting mode	1441	1431	1433	C-H twisting mode
0			1567	C-H ring in-plane bending mode
C-C ring stretching mode	1601	1600	1601	C-C ring stretching mode
symmetric carbonyl stretching mode	1631	1696		5 5



Figure 5. X-ray powder diffraction patterns of phenylacetic acid (blue trace), sodium phenylacetate (green trace), and the 1:1 phenylacetic acid/sodium phenylacetate cocrystal (red trace).

PAA-Na-PAA cocrystal product are shown in Figure 5, and the nonequivalence of the three powder patterns demonstrates that the structure of the cocrystal product is different than either the initial free acid or sodium salt.

While the DSC thermogram of phenylacetic acid consisted of a single melting endothermic transition (temperature maximum at of 78 °C and enthalpy of fusion equal to 113 J/g), the DSC thermogram of the sodium phenylacetate salt was quite complicated. Three overlapping desolvation endothermic transitions were noted, having temperature maxima of 59, 68, and 84 °C. The summed desolvation enthalpy of these transitions exceeded 250 J/g, and the desolvated substance was eventually found to melt with decomposition at 195 °C. The DSC thermogram of the PAA-Na-PAA cocrystal product exhibited a single melting endothermic transition, characterized by a



Figure 6. Infrared absorption spectra in the fingerprint region of phenylacetic acid (blue trace), sodium phenylacetate (green trace), and the 1:1 phenylacetic acid/sodium phenylacetate cocrystal (red trace).

temperature maximum of 43 °C (estimated enthalpy of fusion equal to 48 J/g).

As shown in Figure 6, phenylacetic acid, sodium phenylacetate, and the PAA-Na-PAA cocrystal product exhibited significant differences in the fingerprint region of their infrared absorption spectra that provides information regarding the nature of the interactions in the cocrystals. Other than an ab initio study of the vibrational modes of the phenylacetate ion,²⁸ little guidance is available in the literature to facilitate a complete assignment of the infrared absorption bands of phenylacetic acid and its derivatives. However, since this species differs from benzoic acid only by the presence of a single methylene group bridging the carboxylic acid and phenyl groups, the important

Table 3. Assignments of the Major Bands in the Fingerprint Region of the Infrared Absorption Spectra of Phenylacetic Acid, Sodium Phenylacetate, and Their 1:1 Cocrystal Product

assignment	phenyl-acetic acid	phenylacetic acid/sodium phenylacetate cocrystal	sodium phenyl-acetate	assignment
C-H out-of-plane bending mode	677	677		
ring torsion mode	698	694		
e		725	729	C-H deformation mode
COOH out-of-plane bending mode	752	748		
out-of-plane C-H deformation mode	839	843	841	out-of-plane C-H deformation mode
out-of-plane ring bending mode	924	935	932	out-of-plane ring bending mode
in-plane ring C-H mode	1030	1030	1030	in-plane ring C–H mode
in-plane ring C-H mode	1074	1074	1074	in-plane ring C–H mode
CH ₂ twisting mode	1186	1180	1186	CH_2 twisting mode
carbonyl in-plane deformation	1227	1225		2 8
C-C ring stretching mode	1337	1342	1329	C-C ring stretching mode
6 6		1390	1385	symmetric COO ⁻ stretching mode
OH out-of-plane deformation of COOH	1406			,
C-C ring stretching mode	1452	1450	1450	C-C ring stretching mode
C-C ring stretching mode	1499	1497	1497	C-C ring stretching mode
5 6 6		1537	1558	antisymmetric COO ⁻ stretching mode
COOH stretching mode	1691	1713, 1726		,

spectra bands were assigned by guidance from authoritative sources¹²⁻¹⁴ and analogy to the benzoic acid assignments. The results of this analysis are provided in Table 3.

Relative little perturbation in the frequencies of the carbon-carbon and carbon-hydrogen modes was noted in the FTIR spectra, indicating that the interactions among the phenyl groups is effectively the same for the three substances. The most dramatic changes in the spectra were observed in the antisymmetric -COOH stretching mode of the carboxylate group, where deprotonation of the carboxylic acid group to form leads to a large shift in frequency of this vibrational mode (i.e., 1691 cm⁻¹ to 1558 cm⁻¹). In the PAA-Na-PAA cocrystal, the frequency of the antisymmetric COO⁻ stretching mode of the salt was found to undergo a decrease in energy down to $1537 \,\mathrm{cm}^{-1}$, a behavior that stands in contrast to the lack of such shifting for the BZA-Na-BZA cocrystal. The antisymmetric COOH stretching mode of the acid was found to increase in energy in the cocrystal, and this band was observed to split into two components (1713 and 1726 cm^{-1}).

The Raman spectra obtained in the fingerprint region for phenylacetic acid, sodium phenylacetate, and the PAA-Na-PAA cocrystal product are shown in Figure 7. The vibrational modes associated with these Raman scattering peaks were assigned through the use of the published compilation,²²⁻²⁵ works dealing specifically with the spectra of phenylacetic acid and phenylacetate salts.^{28,29} The results of this analysis are provided in Table 4.

The most significant trends observed in the Raman spectra of the three substances were associated with vibrational modes of the carboxylate group. Formation of the sodium phenylacetate salt was demonstrated in the Raman spectra as a loss of the symmetric carbonyl stretching mode (1653 cm⁻¹) of the acid, and that the energy of the -COOH deformation mode of the acid (1341 cm⁻¹) shifted down to 1294 cm⁻¹ in the salt. This energy of the symmetric COO⁻ stretching mode (1294 cm⁻¹) was found to undergo only a minor shift to 1287 cm⁻¹ in the spectrum of the PAA-Na-PAA cocrystal product. However, the frequency of the symmetric carboxylic acid stretching mode was found to undergo a significant shift toward higher energy (1653 to 1721 cm⁻¹) in the cocrystal product.

C. Hydrocinnamic Acid, Sodium Hydrocinnamate, and their Homo-Cocrystal Product. The XRPD patterns obtained for hydrocinnamic acid, sodium hydrocinnamate,



Figure 7. Raman spectra in the fingerprint region of phenylacetic acid (blue trace), sodium phenylacetate (green trace), and the 1:1 phenylacetic acid/sodium phenylacetate cocrystal (red trace).

and the HCA-Na-HCA cocrystal product are shown in Figure 8, and, once again, the nonequivalence of the three powder patterns demonstrates that the structure of the cocrystal product is different than either the initial free acid or sodium salt. The DSC thermogram of hydrocinnamic acid consisted of a single melting endothermic transition (temperature maximum at of 50 °C and enthalpy of fusion equal to 96 J/g), while the thermogram of the sodium hydrocinnamate salt consisted of a broad and split desolvation endotherm (temperature maxima of 84 and 100 °C, with an overall desolvation enthalpy of approximately 66 J/g). The DSC thermogram of the HCA-Na-HCA cocrystal product consisted of a single melting endothermic transition, characterized by a temperature maximum of 123 °C and an enthalpy of fusion equal to 53 J/g.

As shown in Figure 9, hydrocinnamic acid, sodium hydrocinnamate, and the HCA-Na-HCA cocrystal product exhibited

Table 4.	Assignments of the N	Major Band	ls in the Fi	ingerprint	Region of	of the l	Raman	Spectra of	f Phenylacetic	Acid,	Sodium 1	Phenylacetate,	and (Their 1	1:1
					Co	crystal	l Produ	ct							

assignment	phenyl-acetic acid	phenylacetic acid/sodium phenylacetate cocrystal	sodium phenyl-acetate	assignment
C-C + ring deformation modes	361	378	387	C-C + ring deformation modes
ring torsion mode	475	469	471	ring torsion mode
in-plane ring deformation mode	616	615	614	in-plane ring deformation mode
ring torsion + C-H deformation modes	746	744	759	ring torsion + C-H deformation modes
C-H out-of-plane bending mode	790	783		
C-H out-of-plane bending mode	836	834	838	C-H out-of-plane bending mode
in-plane $C-\hat{C}$ deformation mode of phenyl ring	1000	1000	1000	in-plane $C-\hat{C}$ deformation mode of phenyl ring
in-plane C-H deformation mode	1026	1027	1026	in-plane C–H deformation mode
C-H in-plane bending mode	1188	1185	1194	C-H in-plane bending mode
COOH in-plane deformation mode	1341			· -
*		1287	1294	symmetric COO ⁻ stretching mode
C-C ring stretching mode	1406	1401	1409	C-C ring stretching mode
C-C ring stretching + C-H in-plane bending modes	1602	1600	1600	C-C ring stretching + C-H in-plane bending modes
symmetric carbonyl stretching mode	1653	1721		



Figure 8. X-ray powder diffraction patterns of hydrocinnamic acid (blue trace), sodium hydrocinnamate (green trace), and the 1:1 hydrocinnamic acid/sodium hydrocinnamate cocrystal (red trace).

significant differences in the fingerprint region of their infrared absorption spectra. Using the ab initio study of the vibrational modes of the hydrocinnamate (i.e., the 3-phenylpropionate) ion³⁰ in conjunction with the authoritative sources^{12–14} and analogy to the phenylacetate studies, assignments for the observed absorption bands of three species were deduced. These are provided in Table 5.

The infrared absorption bands of the free acid and sodium salt bore a significant degree of similarity to each other, with the only major difference being noted in the antisymmetric carbonyl band region. Here, the energy of the free acid stretching mode (1693 cm^{-1}) underwent a significant decrease in energy down to 1554 cm^{-1} upon formation of the sodium salt and the consequent deprotonation of the carboxylic acid group. Interestingly, in the HCA-Na-HCA cocrystal the energies of these modes were only slightly shifted relative to those of their components. The COOH



Figure 9. Infrared absorption spectra in the fingerprint region of hydrocinnamic acid (blue trace), sodium hydrocinnamate (green trace), and the 1:1 hydrocinnamic acid/sodium hydrocinnamate cocrystal (red trace).

stretching mode increased in energy to 1699 cm^{-1} , and the COO⁻ stretching mode decreased in energy to 1549 cm^{-1} .

The Raman spectra obtained in the fingerprint region for hydrocinnamic acid, sodium hydrocinnamate, and the HCA-Na-HCA cocrystal product are shown in Figure 10. As before, the vibrational modes associated with these Raman scattering peaks were assigned using the published compilation^{22–25} and the ab initio study of the vibrational modes of the hydrocinnamate ion.³⁰ The results of this analysis are provided in Table 6. Formation of the sodium hydrocinnamate salt was evidenced in the Raman spectra by the disappearance of the weak free acid symmetric carbonyl stretching mode at 1642 cm⁻¹. Formation of the HCA-Na-HCA cocrystal product caused an increase in energy of the symmetric COO⁻ stretching mode from 1270 to 1294 cm⁻¹, and in a decrease in energy of the COO⁻ out-of-plane bending mode from

Table 5. Assignments of the Major Bands in the Fingerprint Region of the Infrared Absorption Spectra of Hydrocinnamic Acid, Sodium Hydrocinnamate, and their 1:1 Cocrystal Product

assignment	hydro-cinnamic acid	hydrocinnamic acid/sodium hydrocinnamate cocrystal	sodium hydro-cinnamate	assignment
C-H out-of-plane bending mode	683	694	691	C-H out-of-plane bending mode
ring torsion mode	700	696	698	ring torsion mode
C–H deformation mode	723		722	C-H deformation mode
COOH out-of-plane bending mode	756	744		
CH ₂ rocking mode	785	789	787	CH ₂ rocking mode
2 0		905	901	$C-COO^{-}$ stretching mode
out-of-plane ring bending mode	932	937	933	out-of-plane ring bending mode
1 0 0		1005	1003	COO ⁻ out-of-plane deformation
in-plane ring C-H mode	1047	1030	1028	in-plane C-H mode
in-plane ring C-H mode	1084	1078	1082	in-plane ring C–H mode
CH ₂ twisting mode	1157	1151	1163	$C\hat{H}_2$ twisting mode
COOH in-plane deformation	1219	1217		2 0
*		1240	1233	COO ⁻ in-plane deformation
C-C ring stretching mode	1302	1308	1309	C-C ring stretching mode
CH ₂ twisting mode	1358	1362	1350	CH ₂ twisting mode
OH out-of-plane deformation of COOH	1408	1408		- 0
CH ₂ scissor mode	1427	1420	1418	CH ₂ scissor mode
C-C ring stretching mode	1452	1454	1441	C-C ring stretching mode
C-C ring stretching mode	1497	1495	1496	C-C ring stretching mode
		1549	1554	antisymmetric COO ⁻ stretching mode
COOH antisymmetric stretching mode	1693	1699		. 0



Figure 10. Raman spectra in the fingerprint region of hydrocinnamic acid (blue trace), sodium hydrocinnamate (green trace), and the 1:1 hydrocinnamic acid/sodium hydrocinnamate cocrystal (red trace).

 565 cm^{-1} in the salt to 557 cm^{-1} in the cocrystal. Otherwise, the scattering bands in the various Raman spectra were remarkably consistent.

D. 4-Phenylbutanoic Acid, Sodium 4-Phenylbutanoate, and their Homo-Cocrystal Product. The XRPD patterns obtained for 4-phenylbutanoic acid, sodium 4-phenylbutanoate, and the 4PBA-Na-4PBA cocrystal product are shown in Figure 11, demonstrating by their nonequivalence that the structure of the cocrystal product is unique relative to those of the initial free acid or initial sodium salt. The DSC thermogram obtained for 4-phenylbutanoic acid consisted of a single melting endothermic transition (temperature maximum at of 52 °C and enthalpy of fusion equal to 113 J/g), while the thermogram

of the sodium 4-phenylbutanoate salt consisted of a weak desolvation endotherm (temperature maximum of 96 °C, with a desolvation enthalpy of 11 J/g). The DSC thermogram of the 4PBA-Na-4PBA cocrystal product formed by these reactants consisted of a single melting endothermic transition, having a temperature maximum of 67 °C and an enthalpy of fusion of 28 J/g.

As shown in Figure 12, 4-phenylbutanoic acid, sodium 4-phenylbutanoate, and the 4PBA-Na-4PBA cocrystal product exhibit a number of important differences in the fingerprint region of their infrared absorption spectra. In the absence of any specific studies dealing with the vibrational assignments form 4-phenylbutanoate, the assignments for the observed bands shown in Table 7 were deduced using authoritative references $^{12-14}$ and analogy to the hydrocinnamate studies. The most interesting findings were associated with the antisymmetric carbonyl region, where the energy of the free acid stretching mode at 1686 cm⁻¹ was found to undergo a peak splitting and decrease in energy to 1556 and 1573 cm^{-1} upon formation of the sodium salt. In the 4PBA-Na-4PBA cocrystal, the splitting in the COO⁻ salt vibrational modes increased to 1553 and 1582 cm⁻¹. The energy of the COOH stretching mode increased from 1686 cm⁻¹ to 1705 cm⁻¹ upon formation of the cocrystal structure. In addition, the COO⁻ in-plane deformation mode was found to shift from 1225 cm⁻¹ in the salt to 1259 cm⁻¹ in the 4PBA-Na-4PBA cocrystal.

The Raman spectra obtained in the fingerprint region for 4-phenylbutanoic acid, sodium 4-phenylbutanoate, and the 4PBA-Na-4PBA cocrystal product are shown in Figure 13. As with the infrared spectra, the vibrational modes the Raman scattering peaks were assigned using published compilations^{22–25} and by analogy to the hydrocinnamate peak assignments. The results of this analysis are provided in Table 8. Formation of the sodium 4-phenylbutanoate salt resulted in the disappearance of the weak free acid symmetric carbonyl stretching mode at 1647 cm⁻¹. Formation of the 4PBA-Na-4PBA cocrystal product caused a slight decrease in energy of the symmetric COO⁻ stretching mode from 1286 cm⁻¹ to 1282 cm⁻¹, and in a decrease in energy of the COO⁻ out-of-plane bending mode from 584 cm⁻¹ in the salt to 561 cm⁻¹ in the cocrystal.

Table 6. Assignments of the Major Bands in the Fingerprint Region of the Raman Spectra of Hydrocinnamic Acid, Sodium Hydrocinnamate, and Their 1:1 Cocrystal Product

assignment	hydro-cinnamic acid	hydrocinnamic acid/ sodium hydrocinnamate cocrystal	sodium hydro-cinnamate	assignment
C-C + ring deformation modes	336		336	C-C + ring deformation modes
ring torsion mode	447	445	449	ring torsion mode
-		557	565	COO ⁻ out-of-plane bending mode
in-plane ring deformation mode	616	613	613	in-plane ring deformation mode
ring torsion + C-H deformation modes	749	738	721	ring torsion + C-H deformation modes
C-H out-of-plane bending mode	812	820	813	C-H out-of-plane bending mode
C-COOH stretching mode	898	897		· · · · · ·
C-H out-of-plane bending mode	920	928	926	C-H out-of-plane bending mode
in-plane $C-\hat{C}$ deformation mode of phenyl ring	996	995	994	in-plane $C-\hat{C}$ deformation mode of phenyl ring
in-plane C-H deformation mode	1028	1024	1021	in-plane C-H deformation mode
C–H twisting mode	1154	1149	1157	C–H twisting mode
CH ₂ wagging mode	1200	1199	1186	CH ₂ wagging mode
		1294	1270	symmetric COO ⁻ stretching mode
C-C ring stretching mode	1409	1411	1411	C-C ring stretching mode
CH ₂ scissor mode	1448		1428	CH ₂ scissor mode
C-C ring stretching + $C-Hin-plane bending modes$	1583, 1602	1583, 1603	1583, 1603	C-C ring stretching + $C-Hn-plane bending modes$
symmetric carbonyl stretching mode	1642			-



Figure 11. X-ray powder diffraction patterns of 4-phenylbutanoic acid (blue trace), sodium 4-phenylbutanoate (green trace), and the 1:1 cocrystal of 4-phenylbutanoic acid with sodium hydrocinnamate (red trace).

E. Hetero-Cocrystal Products formed by the Interaction of Benzenecarboxylic Acids with the Sodium Salt of a Different Benzenecarboxylic Acid. Additional studies into the effect of cocrystal formation on the energies of the vibrational modes of the components were conducted on the mixed products formed by the cocrystallization of benzenecarboxylic acids with the sodium salt of a different benzenecarboxylic acid. A given heterococrystal product was formed by the interaction of carboxylic acid (A) with the sodium salt of carboxylic acid (B), and then another product was generated by the interaction of carboxylic acid (B) with the sodium salt of carboxylic acid (A). For cocrystal products that could be obtained in a solid form, the XRPD patterns shown in Figure 14 for the



Figure 12. Infrared absorption spectra in the fingerprint region of 4-phenylbutanoic acid (blue trace), sodium 4-phenylbutanoate (green trace), and the 1:1 cocrystal of 4-phenylbutanoic acid with sodium hydrocinnamate (red trace).

heterococrystal products were all found to differ from the XRPD patterns of their reactants, establishing the existence of authentic cocrystals.

The XRPD evaluation of these product pairs showed that in every system, the pairs of heterococrystal products exhibited exactly the same crystal structure regardless of which entity was initially present as the sodium salt and which was initially present as the free carboxylic acid. For example, an identical BZA-Na-PAA cocrystal product was obtained by the solvent-drop grinding of benzoic acid with sodium phenylacetate, or by the solvent-drop grinding of phenylacetic acid with sodium benzoate. In general, all of the heterococrystal products

Table 7. Assignments of the Major Bands in the Fingerprint Region of the Infrared Absorption Spectra of 4-Phenylbutanoic Acid, Sodiu	ım
4-Phenylbutanoate, and Their 1:1 Cocrystal Product	

assignment	4-phenyl-butanoic acid	4-phenylbutanoic acid/ sodium 4-phenylbutanoate cocrystal	sodium 4-phenyl-butanoate	assignment
C-H out-of-plane bending mode	676			
ring torsion mode	699	696	696	ring torsion mode
C–H deformation mode	729	724	732	C-H deformation mode
CH ₂ rocking mode	782	785	787	CH ₂ rocking mode
out-of-plane C-H deformation mode	855	854	851	out-of-plane C-H deformation mode
		903	906	COO ⁻ out-of-plane deformation
out-of-plane ring bending mode	931	935	934	out-of-plane ring bending mode
in-plane ring C-H mode	1033	1028	1031	in-plane C-H mode
in-plane ring C-H mode	1084	1082	1080	in-plane ring C–H mode
$C\hat{H}_2$ twisting mode	1199	1186	1189	CH_2 twisting mode
COOH in-plane deformation	1212	1221		
*		1259	1225	COO ⁻ in-plane deformation
C-C ring stretching mode	1300	1310	1314	C-C ring stretching mode
CH ₂ twisting mode	1343	1352	1354	CH ₂ twisting mode
OH out-of-plane deformation of COOH	1410	1404		
CH ₂ scissor mode	1436		1431	CH ₂ scissor mode
C-C ring stretching mode	1461	1452	1452	C-C ring stretching mode
C-C ring stretching mode	1498	1495	1496	C-C ring stretching mode
		1553, 1582	1556, 1573	antisymmetric COO ⁻ stretching mode
COOH antisymmetric stretching mode	1686	1705		-

Relative Interesty

Figure 13. Raman spectra in the fingerprint region of 4-phenylbutanoic acid (blue trace), sodium 4-phenylbutanoate (green trace), and the 1:1 cocrystal of 4-phenylbutanoic acid with sodium hydro-

850

250

450

cinnamate (red trace).

650

1050

Energy (cm⁻¹)

1250

1650

1850

1450

were found to be less crystalline than were the homococrystal products discussed in the preceding sections.

Interestingly, the PAA-Na-4PBA product was only obtained as an oil that could not be solidified under any set of circumstances, and the BZA-Na-4PBA product could only be obtained in an amorphous form. Normally, these characteristics would preclude the PAA-Na-4PBA and BZA-Na-4PBA products from being classified as cocrystals, but their respective vibrational spectra will provide a rationale for a type of cocrystal definition.

DSC analysis of the heterococrystal products revealed them to be relatively low-melting, nonsolvated solids. The BZA-Na-PAA cocrystal exhibited a melting endotherm having a temperature maximum of 72 °C (enthalpy of fusion equal to 49 J/g), which was fairly comparable to the thermal profile of the BZA-Na-HCA cocrystal (temperature maximum of 93 °C and an enthalpy of fusion of 43 J/g). The BZA-Na-4PBA cocrystal was obtained as a waxy solid for which no really definable melting endotherm could be identified in its DSC thermogram. The PAA-Na-HCA cocrystal was characterized by a melting endotherm having a temperature maximum of 63 °C (enthalpy of fusion equal to 33 J/g), while the HCA-Na-4PBA cocrystal was also obtained as a waxy solid, for which the temperature maximum of the melting endotherm was 52 °C and the enthalpy of fusion was 21 J/g. As mentioned above, the fact that the PAA-Na-4PBA product could not be obtained in solid form precluded its analysis by DSC.

Infrared absorption spectra obtained in the fingerprint region are shown in Figure 15 for the six heterococrystal systems. The spectra of the various cocrystal products exhibited a significant degree of similarity to each other, which enabled the spectral band assignments deduced for the homococrystal products to be of use in assigning the origins of the bands in the heterococrystal spectra. These assignments are collected in Table 9.

The same overall trends noted in the infrared spectra of the homococrystals were observed in the spectra of the heterococrystals. Most importantly, the energies of the carbonyl antisymmetric stretching modes were observed to undergo increases in the cocrystals relative to the energies in the respective benzenecarboxylic acids. While the frequency of this absorption band was observed over an approximate frequency range of $1700-1730 \text{ cm}^{-1}$ in the homococrystal systems, a smaller degree of shifting (approximate frequency range of $1690-1700 \text{ cm}^{-1}$) was noted for the heterococrystal systems. Given that the reduced masses of the bonds involved is comparable in the systems, one concludes that the force constant of the

Table 8.	Assignments of the Major Bands in the Fingerprint Region of the Raman Spectra of 4-Phenylbutanoic Acid, Sodium 4-Phenylbutanoate, and Thei
	1:1 Cocrystal Product

assignment	4-phenyl-butanoic acid	4-phenylbutanoic acid/ sodium 4-phenylbutanoate	sodium 4-phenyl-butanoate	assignment
	460	471	. phonyr outuriouto	
ring torsion mode	468	4/1	4/6	ring torsion mode
C-C + ring deformation modes	508	494	511	C-C + ring deformation modes
		561	584	COO out-of-plane bending mode
in-plane ring deformation mode	616	613	615	in-plane ring deformation mode
ring torsion + C-H deformation modes	747	746	750	ring torsion + C-H deformation modes
C-H out-of-plane bending mode	810	807	814	C-H out-of-plane bending mode
C-COOH stretching mode	888	896		÷ -
C-H out-of-plane bending mode	912	928	930	C-H out-of-plane bending mode
in-plane $C-\hat{C}$ deformation mode of phenyl ring	997	995	997	in-plane $C-\hat{C}$ deformation mode of phenyl ring
in-plane C-H deformation mode	1028	1023	1027	in-plane C-H deformation mode
C-H rocking mode	1059	1060	1057	C-H rocking mode
C-H twisting mode	1155	1151	1152	C-H twisting mode
C-H in-plane bending mode	1182	1183	1176	C-H in-plane bending mode
CH ₂ wagging mode	1206	1200	1202	CH ₂ wagging mode
2 88 8		1282	1286	symmetric COO ⁻ stretching mode
CH ₂ twisting mode	1343	1332		.,
C-C ring stretching mode	1407	1412	1417	C-C ring stretching mode
CH ₂ scissor mode	1439	1442	1437	CH_2 scissor mode
C-C ring stretching + $C-Hin-plane bending modes$	1582, 1602	1582, 1603	1581, 1601	C-C ring stretching + $C-Hin-plane bending modes$
symmetric carbonyl stretching mode	1647			



Figure 14. X-ray powder diffraction patterns of the five heterococrystal products formed by the interaction of a benzenecarboxylic acid with the sodium salt of a different benzenecarboxylic acid and which could be obtained in solid form. The spectra are labeled to indicate the identity of each cocrystal product.

carbonyl antisymmetric stretching modes is less perturbed in the heterococrystal systems relative to the homococrystal systems. This conclusion would imply that the energetics of heterococrystal interaction are less than those of homococrystal interaction, which would in turn be



Figure 15. Infrared absorption spectra in the fingerprint region of the six heterococrystal products formed by the interaction of a benzenecarboxylic acid with the sodium salt of a different benzenecarboxylic acid. The spectra are labeled to indicate the identity of each cocrystal product.

consistent with the lower degrees of crystallinity observed for the homococrystal products.

The energies of most of the other vibrational modes were found to be fairly similar in the homococrystal and heterococrystal products. For example, the degree of

Table 9. As	ssignments of the Ma	jor Bands in the Finger _l	print Region of the Infra	ared Absorption Spectra	of the Mixed Cocrystal 1	Products of Benzenecarb	oxylic Acids
	benzoic acid/ Na- phenyl-acetate	benzoic acid/ Na-hydro-cinnamate	benzoic acid/ Na-4-phenyl-butanoate	phenylacetic acid/ Na-hydrocinnamate	phenylacetic acid/ Na-4-phenyl-butanoate	hydrocinnamic acid/ Na-4-phenyl-butanoate	
acid assignment	cocrystal	cocrystal	cocrystal	cocrystal	oil	cocrystal	salt assignment
C-H out-of-plane bending mode	654	677	662	677	099	670	C-H out-of-plane bending mode
ring torsion mode	692/698	698	698	694	696	698	ring torsion mode
C-H deformation mode	721	712	710	725	727	719	C-H deformation mode
COOH out-of-plane bending mode	762	752	752	748	744	748	
CH ₂ rocking mode	797	789	797	787		791	CH ₂ rocking mode
out-of-plane C-H deformation mode	841	845	847	850	841	856	out-of-plane C-H deformation mode
	899	922	906	901	908	903	COO ⁻ out-of-plane deformation
out-of-plane ring bending mode	924	943	933	926		939	out-of-plane ring bending mode
in-plane ring C-H mode	1024	1024	1024	1030	1030	1028	in-plane C-H mode
in-plane ring C-H mode	1068	1070	1070	1066	1074	1080	in-plane ring C-H mode
in-plane ring C-H mode	1146			1144	1146	1144	in-plane ring C-H mode
CH ₂ twisting mode	1173	1175	1175	1178			CH ₂ twisting mode
COOH in-plane deformation	1203	1211	1200	1194	1196	1209	
	1259	1240	1227	1215	1246	1259	COO [–] in-plane deformation
CH ₂ deformation mode	1273	1275	1277		1279	1286	CH ₂ deformation mode
C-C ring stretching mode	1315	1315	1315	1306		1306	C-C ring stretching mode
CH ₂ twisting mode			1352			1337	CH ₂ twisting mode
	1387		1387	1354	1387	1366	symmetric COO ⁻ stretching mode
OH out-of-plane deformation of COOH	1404	1404	1406	1400		1406	
CH ₂ scissor mode				1420		1431	CH ₂ scissor mode
C-C ring stretching mode	1452	1450	1450	1452	1452	1450	C-C ring stretching mode
C-C ring stretching mode	1493	1493	1493	1495	1495	1495	C-C ring stretching mode
	1556	1553	1556	1556	1560	1553	antisymmetric COO ⁻ stretching mode
C-C ring stretching mode	1605	1597	1601	1602		1601	C–C ring stretching mode
COOH antisymmetric stretching mode	1697/1707	1693	1680/1699	1697/1728	1693	1693	

shifting in the carboxylic acid anion modes in the component salts upon formation of the cocrystals was found to be comparable in both categories.

It is significant to note that even though the PAA-Na-4PBA and BZA-Na-4PBA products were not obtained in a crystalline solid-state form, their infrared absorption spectra exhibited peaks that were shifted from those of their reactants in a manner entirely consistent with the authentic cocrystal products. This finding would indicate that a similar type of supramolecular synthon existing in the crystalline cocrystal products must also exist in the PAA-Na-4PBA and BZA-Na-4PBA products, even though these materials were not obtained in a crystalline form.

Raman spectra obtained in the fingerprint region are shown in Figure 16 for the six heterococrystal systems. As has been noted for their infrared absorption, the spectra of the various cocrystal products exhibited a significant degree of similarity to each other, which also facilitated the deduction of spectral band assignments for the heterococrystal spectra through comparison to the assignments reached for the spectra of the homococrystal products. Assignments deduced in this manner are collected in Table 10, and most of the trends contained in the table have been discussed above. The main effect of cocrystal formation in these systems was a slight decrease in energy of the symmetric COO⁻ stretching mode, and a decrease in energy of the COO⁻ out-of-plane bending mode.

Discussion

A number of interesting trends emerged from study of the vibrational spectra of benzenecarboxylic acids, their sodium salts, and the 1:1 products formed by the cocrystallization of the acid and its salt. Many other infrared spectroscopic studies have established that the antisymmetric stretching mode of the carboxylic acid carbonyl group undergoes a drastic shift to lower energies upon formation of its salt form. In the present work, the general trend has emerged that this same vibrational mode shifts to higher energies when the benzenecarboxylic acid forms a cocrystal with its sodium salt.

One may deduce from the present analysis that for salt and cocrystal systems involving carboxylic acid groups that the energy of the antisymmetric stretching mode of the carbonyl group can be used to deduce the nature of the species formed. When the free acid absorption band (approximate frequency range of $1680-1690 \text{ cm}^{-1}$) disappears entirely and becomes replaced by the corresponding anion band (approximate frequency range of $1550-1600 \text{ cm}^{-1}$), one has observed the formation of a salt species. On the other hand, when the free acid absorption band undergoes a small shift toward higher energy (approximate frequency range of $1700-1730 \text{ cm}^{-1}$), one has observed the formation of a cocrystal species.

The same set of observations were made in a previous work involving benzoic acid, the benzylammonium benzoate salt, and their 1:1 cocrystal.¹ In that work, formation of the salt was evidenced by the loss of the free acid absorption band at 1678 cm^{-1} and the observation of the corresponding anion band at 1514 cm^{-1} . In the 1:1 cocrystal formed by these two



Figure 16. Raman spectra in the fingerprint region of the six heterococrystal products formed by the interaction of a benzenecarboxylic acid with the sodium salt of a different benzenecarboxylic acid. The spectra are labeled to indicate the identity of each cocrystal product.

compounds, the free acid absorption band was observed to increase in energy to 1694 cm^{-1} .

In most systems, the energy of the antisymmetric carboxylate anion stretching mode decreased when the cocrystal was formed using its sodium salt. However, this trend was not shown to exist in the benzoic acid/sodium benzoate cocrystal, and the energy of this band increased slightly on passing from the salt form to the cocrystal. In the previous work,¹ the energy of this vibrational mode was found to decrease in the benzoic acid/benzylammonium benzoate cocrystal relative to that in the benzylammonium benzoate salt form.

The vibrational frequencies of the symmetric carboxylate anion stretching mode were not found to be useful spectroscopic tools to differentiate cocrystal and sodium salt, as the observed differences between the two forms were effectively random and as many increases were detected as decreases. The energy of the out-ofplane deformation mode proved to be equally ineffective in this regard as the vibrational frequency was equivalent in both the salt form and in the cocrystal. Neither of these vibrational modes was particularly useful for differentiation purposes in the corresponding Raman spectra.

Finally, while significant differences in energy among the multitude of vibrational modes associated with the phenyl ring and alkane side chain were observed to exist in the spectra of the free acid, its sodium salt, and their cocrystal product, no general trends emerged from the spectral assignments that could serve as form differentiation selection rules.

Table	10. Assignments of	f the Major Bands in the	Fingerprint Region of	the Raman Spectra of t	the Mixed Cocrystal Pro	ducts of Benzenecarboxy	lic Acids
	benzoic acid/ Va phenyl-acetate	benzoic acid/ Na-hvdro-cinnamate D	benzoic acid/ Ja-4-phenyl-butanoat	phenylacetic acid/ e Na-hvdrocinnamate	phenylacetic acid/ Na-4-phenyl-butanoate	hydrocinnamic acid/ Na-4-phenvl-butanoate	
acid assignment	cocrystal	cocrystal	cocrystal	cocrystal	óil	corystal	salt assignment
C-C + ring deformation modes	398	398	397	378	396	402	C-C + ring deformation modes
ring torsion mode	472	458	483	468	473	489	ring torsion mode
C-C + ring deformation modes	518	522	525	516	516	514	C-C + ring deformation modes
,	572	564	585	561	559	561	COO [–] out-of-plane bending mode
In-plane ring deformation mode	615	612	612	613	613	613	In-plane ring deformation mode
ring torsion + C-H deformation	760	746	743	746	746	744	ring torsion + C-H deformation
modes							modes
C-H out-of-plane bending mode	791	662	789	784	807	809	C-H out-of-plane bending mode
C-H out-of-plane bending mode	839	836	837	832	834	835	
C-COOH stretching mode	904	899	006	895	006	897	
C-H out-of-plane bending mode	920	935	923	924	930	929	C-H out-of-plane bending mode
in-plane C-C deformation mode	866	995	995	995	966	995	in-plane C-C deformation mode of
of phenyl ring							phenyl ring
in-plane C-H deformation mode	1025	1022	1022	1023	1024	1023	in-plane C-H deformation mode
C-H rocking mode			1064				C-H rocking mode
C-H twisting mode	1155	1153	1152	1152	1152	1151	C-H twisting mode
C-H in-plane bending mode	1174	1175	1175			1180	C-H in-plane bending mode
CH ₂ wagging mode	1200	1199	1201	1191	1196	1198	CH ₂ wagging mode
	1286	1273	1288	1273	1292	1291	Symmetric COO [–] Stretching Mode
C-C ring stretching mode	1412	1414	1409	1405		1416	C-C ring stretching mode
CH ₂ scissor mode			1440	1432	1437	1440	CH ₂ scissor mode
C-C ring stretching + C-H in-plane bending modes	1584, 1600	1584, 1602	1586, 1602	1585, 1603	1584, 1603	1583, 1603	C-C ring stretching + C-H in-nlane hending modes
Symmetric carbonyl stretching mode	1701	1712	1691	1707		1701	

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