methanol, a drop of this suspension was then deposited on a sapphire. After evaporation of the solvent the sapphire was placed in the field of view of the NIRIM. A library of single-bead NIR–Raman spectra of each of the resins was first recorded (Supporting Information), then several regions were arbitrarily selected for multispectral imaging. Since each bead appears as a collection of pixels and each pixel is a NIR–Raman spectrum of that area of the bead, comparison of these pixel spectra with the library of single-bead spectra recorded on the authentic samples confirmed the automated assignments. These results were reproducible regardless of the size and shape of the beads (Supporting Information).

The principles of dual recursive deconvolution of resin-supported combinatorial libraries have been proposed and the feasibility of the key feature of this method, the identification of the first randomized position, has been demonstrated using NIR-Raman imaging of self-encoded resin beads. The reliability of this method is very high, it has been consistently accurate over the two and a half years that we have been practicing multispectral imaging. Furthermore, any imaging technique could be applicable to the DRED method as long as the beads used display unique spectral features, and provided the loaded material does not significantly alter their spectral signature. For instance, secondary-ion mass spectrometry (SIMS)[10] and FT-IR[11] imaging are alternative approaches that we are investigating. Although, several commercially available and chemically distinct solid supports are eligible to explore the scope of DRED in combinatorial chemistry, inhomogeneities in their physical and chemical properties (e.g. swelling, porosity, size, reactivity) prompted the design of the DRED beads, a new class of resins for solid-phase synthesis.[12] The added value of the DRED method is that it is a non-invasive screening technique, it does not necessarily require sophisticated equipment, it is inexpensive, and it does not involve the development of any encoding chemistry since the DRED beads will soon become commercially available.

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Polymorphism in *p*-Hydroxybenzoic Acid: The Effect of Intermolecular Hydrogen Bonding in Controlling Proton Order versus Disorder in the Carboxylic Acid Dimer Motif**

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The phenomenon of polymorphism[1–3] is of considerable contemporary interest in the field of organic solid-state chemistry, in part because comparisons between the properties of polymorphs provide an ideal basis on which to understand relationships between solid-state properties and crystal structure. Furthermore, in the quest to develop reliable computational techniques to predict the crystal structure(s) formed by a given type of organic molecule,[4–8] studies of polymorphic systems provide stringent challenges for assessing the success of these methods. In general, the fact that the structures of organic molecular crystals usually arise from the interplay of several factors of comparable importance leads to intrinsic difficulties in attempting to predict and/or rationalize such structures. However, when one type of intermolecular interaction (or a small number of interactions) is dominant, a reliable rationalization of the observed molecular packing

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arrangement in the crystal may be possible. In this regard, crystal structures based on strong intermolecular hydrogen bonding are often amenable to straightforward structural understanding.

The hydroxy derivatives of benzoic acid represent a potentially useful family of systems in which to explore polymorphism, as the combination of hydroxy groups and carboxylic acid groups should give rise to a variety of plausible intermolecular hydrogen bonding schemes and hence different crystal packing arrangements. Indeed, two polymorphs of *m*-hydroxybenzoic acid have been reported previously,[9] and differ in their intermolecular hydrogen bonding arrangements. For *p*-hydroxybenzoic acid, on the other hand, only one crystal structure (hereafter referred to as form I) has been reported previously,[10] although the possible existence of a second polymorph (which was neither isolated nor structurally characterized) was speculated[11] on the basis of thermal analysis of samples of *p*-hydroxybenzoic acid.

Herein, we report a new polymorph (denoted form II) of *p*-hydroxybenzoic acid. Only a small number of low-quality microcrystals of this polymorph were obtained (as mixtures with other phases),[12] and the crystal structure has been determined by exploiting synchrotron X-ray microcrystal diffraction techniques.[13] Although the use of a microcrystal has led to a rather poorer quality of structural information[13] than normally expected from single-crystal X-ray diffraction studies, unambiguous information on the crystal packing arrangement and other structural aspects is nevertheless obtained. Importantly, we find that form II exhibits interesting behavior with regard to the question of order versus disorder in the carboxylic acid dimer motif, contrasting markedly with the behavior of form I.

In the crystal structure[13] of form II of *p*-hydroxybenzoic acid (Figure 1), the asymmetric unit comprises two independent molecules (denoted A and B). Each of these molecules forms an $R_2^2(8)$ centrosymmetric dimer about a crystallographic inversion center, a hydrogen bond pattern (involving two O−H···O=C hydrogen bonds) that is commonly found in carboxylic acids.[16, 17] Clearly the two molecules in a given dimer are of the same type (A or B). For the centrosymmetric dimer involving molecules of type A, the O(1)···O(2) distance is 2.664(6) Å, and for that involving molecules of type B, the O(4)···O(5) distance is 2.617(6) Å (the atom labeling is specified in Figure 1). In both cases, these O···O distances are consistent with O−H···O=C hydrogen bonding. A hydrogen bonding interaction involving the hydroxy group of molecule B and the carboxylic acid group of molecule A is also clearly identified. In this interaction, the O···O distance between the hydroxy oxygen atom O(6) of molecule B and one oxygen atom O(1) of the carboxylic acid group of molecule A is 2.946(6) Å and the O−H···O angle is about 165°.[18] For the carboxylic acid group of molecule B, the shortest intermolecular O···O distances to hydroxy groups of other molecules are 3.427(8) Å and 3.439(9) Å—these O···O distances involve the same oxygen atom of the carboxylic acid group of molecule B and the hydroxy groups of two different molecules of type A (related to each other by translation along the *b* axis). However, these distances are rather long to be assigned as O−H···O=C hydrogen bonds[19] and other geometric characteristics[20] also deviate from those normally observed for strong O−H···O=C hydrogen bonds.[19] In this structure, there are no short intermolecular contacts between hydroxy groups.

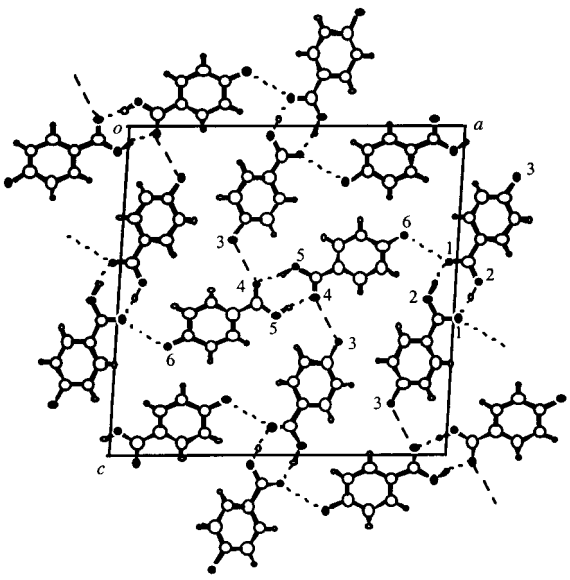

Figure 1. Crystal structure of form II of *p*-hydroxybenzoic acid viewed along the *b* axis. Dotted lines represent hydrogen bonding interactions. Molecules of type A are labeled with oxygen atoms numbered 1, 2, and 3. Molecules of type B are labeled with oxygen atoms numbered 4, 5, and 6.

In the space-averaged and time-averaged crystal structures determined from diffraction data, $R_2^2(8)$ carboxylic acid dimer motifs are often found to be disordered,[16] such that the carbon−oxygen bond lengths are intermediate between those characteristic of single bonds (corresponding to C−OH) and double bonds (corresponding to C=O) and the protons are disordered (often two sites with half occupancy are located, corresponding to equal amounts of C−O−H···O=C and C=O···H−O−C situations in the average crystal structure). We now assess the evidence for order versus disorder of the carboxylic acid dimers in form II of *p*-hydroxybenzoic acid. The carboxylic acid group in molecule A is clearly not disordered. The C−O bond lengths are 1.230(5) Å for O(1) and 1.333(5) Å for O(2), leading to the unambiguous assignment[21] of O(1) as C=O and O(2) as C−OH in an ordered carboxylic acid group. The fact that O(1) receives a hydrogen bond from the hydroxy group in molecule B is consistent with the preference for the C=O oxygen atom in an ordered carboxylic acid group (rather than the C−OH oxygen atom) to act as a hydrogen-bond acceptor. Clearly the intermolecular O−H···O=C hydrogen bond from the hydroxy group of molecule B to the carboxylic acid group of molecule A "locks" this carboxylic acid group into an ordered arrangement. Our ability to locate the hydrogen atoms of the carboxylic acid and hydroxy groups in the crystal structure determination is discussed in reference [13].

For molecule B, the carbon−oxygen bond lengths in the carboxylic acid group are 1.273(7) Å for O(4) and 1.299(7) Å for O(5). The fact that these bond lengths in the average crystal structure are intermediate between C−O single and C=O double bonds suggests that this carboxylic acid group is disordered. Presumably any intermolecular interactions in-

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volving the carboxylic acid group of molecule B (in particular, the rather long contacts to the hydroxy groups of molecules of type A discussed above) are insufficient to "lock" the carboxylic acid group of molecule B into an ordered arrangement.

For comparison, the crystal structure of form I of *p*-hydroxybenzoic acid[10] also contains carboxylic acid dimers with the $R_2^2(8)$ hydrogen bond motif, but there is no direct hydrogen bonding between hydroxy groups and carboxylic acid groups (Figure 2). Instead, the hydroxy groups engage in

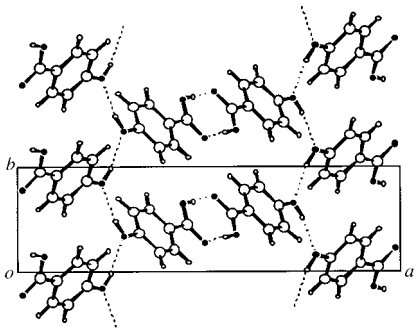

Figure 2. Crystal structure of form I of *p*-hydroxybenzoic acid (data from reference [10]).

O–H···O–H hydrogen bonds with other hydroxy groups, constructing chains that extend through the crystal.[22] The two carbon–oxygen bond lengths in the carboxylic acid group are equal (1.266 Å) (there is one molecule in the asymmetric unit), and the hydrogen atom of the carboxylic acid group is found to be distributed (with half occupancy) between two sites. These facts clearly indicate that the carboxylic acid group is disordered.

The subject of proton disorder in carboxylic acid dimers has aroused much interest from structural and dynamic viewpoints,[23–30] and it is clear that the two polymorphs of *p*-hydroxybenzoic acid represent an ideal basis for systematic studies of this property. Thus, from the X-ray diffraction data reported here, form I exhibits proton disorder, whereas form II has two crystallographically independent carboxylic acid dimers, one of which is clearly ordered and the other disordered.[31] Future neutron diffraction studies, also as a function of temperature, will provide more details on structural aspects of the proton order/disorder, whereas other techniques (solid-state NMR and inelastic and quasielastic neutron scattering) will lead to an understanding of dynamic aspects. Inter alia, these variable temperature studies will allow the static versus dynamic character of the disorder to be probed, as well as the question of whether polymorphic phase transformations are observed in this system. Such future advances will be facilitated by the ability to prepare form II as a monophasic sample, ideally comprising larger single crystals than the microcrystals available in the present work.

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[12] Microcrystals (for typical crystal size, see reference [13]) of form II of *p*-hydroxybenzoic acid were obtained during preparation of inclusion compounds between deoxycholic acid and *p*-hydroxybenzoic acid, using methanol as solvent. The crystals were very small and of very poor quality.
[13] Single-crystal X-ray diffraction data were recorded for a microcrystal of form II of *p*-hydroxybenzoic acid on Station 9.8 at the Synchrotron Radiation Source (Daresbury Laboratory). This microcrystal diffraction station comprises a Siemens SMART CCD detector and goniometer system. Crystal size $0.10 \times 0.07 \times 0.05\ mm^3$; $T = 296(2)$ K; $\lambda = 0.68850$ Å; monoclinic, $P2_1/n$; $a = 18.66(2)$, $b = 3.860(4)$, $c = 18.82(3)$ Å, $\beta = 93.511(6)^\circ$; $V = 1353(3)$ Å^3; $Z = 8$. The structure was solved by using SHELXS[14] and refined by using SHELXL[15] ($R_1 = 0.131$; $R_w = 0.365$). The aryl rings were refined as idealized hexagons (including hydrogen atoms). In the difference Fourier map, the strongest peak (0.5 e Å^{-3}) represented the position of the hydrogen atom of the carboxylic acid group of molecule A (the ordered carboxylic acid group—see text), and this hydrogen atom was then included in the refinement in a fixed position corresponding to standard geometry. The hydrogen atom of the carboxylic acid group of molecule B and the hydrogen atoms of the hydroxy groups were not located among the next highest peaks in the difference Fourier map. As only microcrystals of form II of *p*-hydroxybenzoic acid were available for the X-ray diffraction experiments, it is necessary to recognize that the intrinsically poorer data quality has resulted in relatively high values of *R* factors. Nevertheless, by maintaining the discussion and interpretation at a level commensurate with the reliability of the refined structural information, reliable conclusions on structural properties are nevertheless reached.
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[20] The geometries of these C(4)-O(3)-H···O(4)-C(14)-C(8) contacts are: a) O(3)···O(4) distance 3.439(9) Å; O(3)···O(4)-C(14) angle

112.2(4)°; C(4)-O(3)···O(4) angle 107.6(3)°; O(3)···O(4)-C(14)-C(8) dihedral angle −60.3(6)°; b) O(3)···O(4) distance 3.427(8) Å; O(3)···O(4)-C(14) angle 153.3(4)°; C(4)-O(3)···O(4) angle 123.3(4)°; O(3)···O(4)-C(14)-C(8) dihedral angle 25.5(1.3)°. Note that C(4)-O(3)-H is the hydroxy group of molecule A and O(4)−C(14) is in the carboxylic acid group of molecule B.

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Structure Determination of an Oligopeptide Directly from Powder Diffraction Data**

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In recent decades, single-crystal X-ray diffraction techniques have underpinned many major breakthroughs in structural biology, although it is well recognized that an intrinsic limitation of these techniques is the requirement to prepare single crystals of sufficient size, quality, and stability to allow diffraction data of sufficiently high quality to be measured. In solid-state and materials sciences, similar limitations are encountered in the scope and applicability of single-crystal diffraction methods, but much progress has been made in recent years in the use of powder diffraction data as an alternative means of obtaining structural information. Herein, we apply a new methodology for structure determination from powder diffraction data to determine the crystal structure of the oligopeptide Phe-Gly-Gly-Phe (Figure 1), which demonstrates the opportunity for future extensions to more complex systems of interest in structural biology. In this regard, we note that knowledge of the structural properties and interactions in model oligopeptide systems can yield fundamental insights towards understanding structural properties of polypeptide sequences in proteins.[1–6]

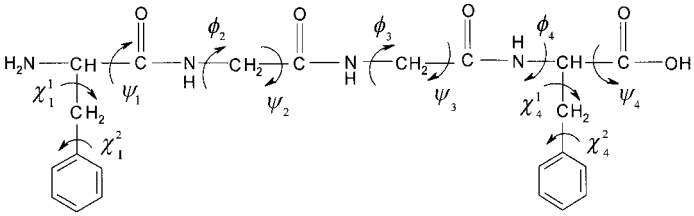

Figure 1. The molecular structure of Phe-Gly-Gly-Phe, showing the variable torsion angles in the genetic algorithm structure solution calculation.

In principle, powder diffraction data contains the same information as single-crystal diffraction data, but with the three-dimensional diffraction data compressed into one dimension. As a consequence, there is generally substantial overlap of peaks in the powder diffraction pattern, leading to severe difficulties in extracting the same quality of diffraction data (and hence structural information). Although the challenges in determining structures directly from powder diffraction data are considerable, new techniques and strat-

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