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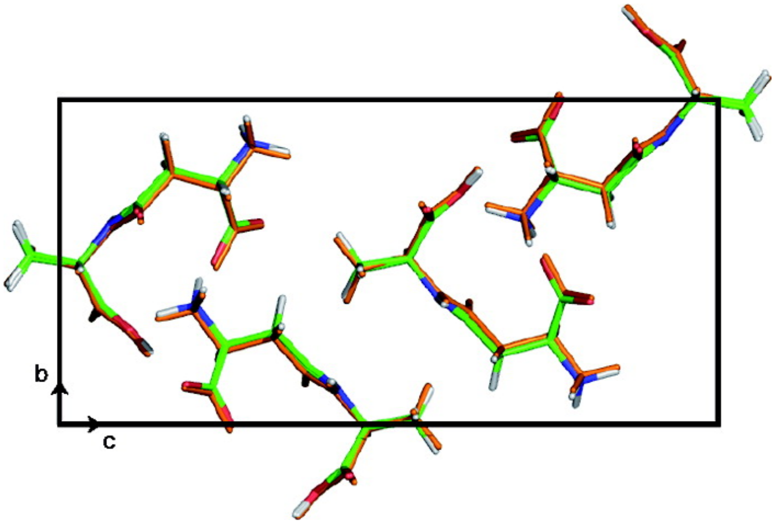

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Resolving Structures from Powders by NMR Crystallography Using Combined Proton Spin Diffusion and Plane Wave DFT Calculations

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Structural characterization of crystalline powders represents a key challenge to modern chemistry since such samples are becoming both increasingly important and widespread, notably in the areas of new materials and in the pharmaceutical industry. The development of experimental methods to study their three-dimensional atomic structure is thus an area of great current interest. Significant recent progress has been made in the application of diffraction methods,[1] and spectacular advances have been made in solid-state NMR methods for powdered solids,[2] isotopically enriched biological systems,[3] inorganic networks,[4] and organic molecular compounds.[5,6] Nevertheless de novo crystal structure determination from powders at natural isotopic abundance remains a key unsolved objective for NMR spectroscopy. Toward this end, we recently reported[7] the determination of the three-dimensional structure of a powdered organic compound, obtained by an approach that combines molecular modeling (MM) with experimental proton spin diffusion (PSD) data obtained from high-resolution solid-state ^{1}H NMR. The approach was demonstrated on powdered (microcrystalline) β-L-aspartyl-L-alanine (**1**), and we determined the crystal structure to within an average root mean square atom-to-atom distance of 0.72 Å of the known coordinates. However, although this was a big step forward, the resulting structure shown in Figure 1a clearly contained fairly large systematic deviations from the reference structure. For this method to become widespread, its accuracy must be improved.

Here, we report the combination of measured solid-state NMR chemical shifts and first principles calculations to resolve the crystal structure of **1** to within 0.13 Å of the known structure. The validity of this process is confirmed by comparing the DFT calculated chemical shifts with the experimentally measured shifts, where we observe a substantial improvement in the agreement between the calculations and experiments before and after structure optimization.

PSD data for **1** were obtained from 2D correlation experiments obtained using advanced homonuclear dipolar decoupling schemes,[8] as described in detail elsewhere.[9] The PSD constrained structure was then obtained from a combined MM/NMR-PSD approach[7] using the Xplor-NIH MM package[10] including experimental constraints obtained from comparison with back calculated PSD build up curves, as recently shown elsewhere.[7] This procedure resulted in the group of 16 structures shown in Figure 1a having the best overall agreement with the experimental constraints. This group of structures has a standard deviation of 0.14 Å, and it deviates from the reference X-ray structure[11,12] (which we assume to be correct here) by an average root mean square atom-to-atom distance for all atoms of 0.72 Å.

It can immediately be appreciated that this MM/PSD-NMR structure contains significant systematic deviations, notably in the positions of the polar carboxyl groups. These deviations are not surprising since (i) these groups are not protonated and so are not strongly constrained by the PSD-NMR data, and (ii) systematic deviations are in any case expected since the phenomenological description of the PSD process is not perfect. To improve the structures, we need at this point a more accurate relation between the trial structures and the experimental observables. In the following, we show that this can be provided by DFT calculation of chemical shifts.

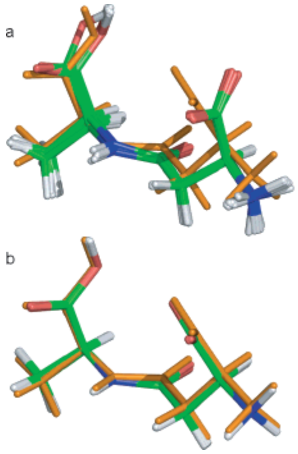

Figure 1. Comparison between the structure of **1** determined by X-ray diffraction (orange) and (a) the 16 structures obtained from the MM/PSD-NMR refinement, and (b) the 16 structures refined using the plane wave DFT/NMR chemical shift approach described here. The figure shows one of the four equivalent molecules in the unit cell.

Here we use geometry optimization by the CASTEP program,[13] a DFT-based code (but other programs providing the same functionality could be used). The crucial difference for the application here between this code and other quantum chemical techniques is that the charge density and wave functions are described using a plane wave basis set and so the translational symmetry of the system is implicit. In contrast to cluster methods, this method allows for a fully solid-state treatment of the system under investigation. This approach has recently been applied with some considerable success to the calculation of NMR parameters from known crystal structures in a variety of systems, where the method is found to provide remarkably accurate predictions of solid-state NMR chemical shifts.[6] On the other hand, so far, DFT approaches have never been used to determine structures. Indeed, DFT methods are currently not capable of determining complex structures de novo, from random starting points, since the parameter space is very large, and calculation times are currently prohibitive. For example, we note that, in addition to the position and orientation in the unit cell, **1** has eight torsion angles that are freely rotatable, so the DFT optimization is not trivial. However, if the starting point for a suitable DFT optimization is taken as the end point of the

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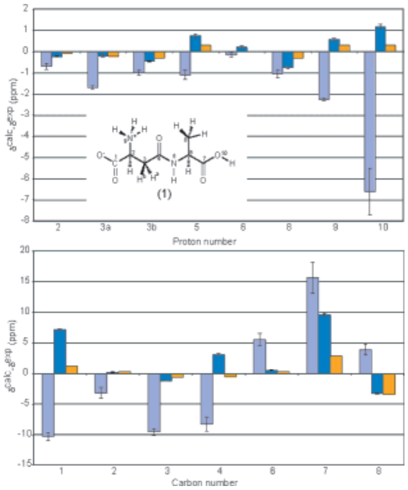

Figure 2. Differences between measured and calculated chemical shifts for ^{1}H (top) and ^{13}C (bottom) with reference to the numbering scheme shown in the inset. Light blue shows the result for the 16 MM/PSD-NMR input structures, dark blue shows the result for the structures resulting from plane wave DFT refinement, and orange shows the result for the X-ray structure (with optimized proton positions[12]). In the first two cases, the bar is positioned at the average value obtained for the 16 calculated structures, and the error bar indicates the standard deviation within the 16 structures. The estimated error in the measurement of the experimental shifts is ±0.1 ppm for ^{13}C, and from ±0.01 to ±0.15 ppm for ^{1}H (see Supporting Information).

MM/PSD-NMR procedure, then the DFT method should be able to correctly refine the structure. The accuracy of plane wave DFT for the calculation of structural parameters is today excellent,[14] and we expect the result of such an optimization to be in close agreement with the crystal structure. Without a comparison to experiment, however, such a DFT optimization procedure would have no real value. The calculation of chemical shifts and comparison to experimental chemical shift data is thus essential to validate the resulting structures.

In Figure 2 the data in light blue show the comparison with experimentally determined values of all the ^{1}H and ^{13}C chemical shifts calculated using CASTEP for 16 structures within the ensemble resulting directly from the MM/PSD optimization shown in Figure 1a (without optimizing the proton positions). It can be appreciated that the differences are fairly large, with the root mean square difference between the experimental and the average of the calculated values being 2.64 ppm for ^{1}H and 9.5 ppm for ^{13}C. The details of the chemical shift calculations using GIPAW[15] and "ultrasoft" pseudopotentials[16] are given in the Supporting Information. The geometry of these 16 starting structures was then DFT optimized in the full crystalline environment using the basis set described in the Supporting Information, and chemical shifts were recalculated. The resulting ensemble of structures is shown in Figure 1b, and the chemical shift differences compared to the measured experimental values are shown in dark blue in Figure 2. The difference in chemical shifts for the optimized structures is substantially reduced: to 0.63 ppm for ^{1}H and 5.0 ppm for ^{13}C, *indicating that the resulting structures are in better agreement with the experimental data than the starting point*. Indeed, we see from Figure 1b that the resulting structures are now *essentially identical to the crystal structure*, deviating from the reference structure by an average root mean square atom-to-atom distance of only 0.13 Å. Notably, there no longer appears to be any obvious systematic difference between the structures. The deviation can be compared to X-ray vibrational B factors for the heavy atoms, which yield an average uncertainty in the positions of ~0.12 Å (see Supporting Information).

This result illustrates the remarkable accuracy of current DFT methods in describing the structure of solids and in predicting NMR chemical shifts. Importantly, we note that the procedure is self-consistent, in that we can calculate the agreement of the structures obtained by CASTEP with the PSD data. As expected, the CASTEP optimized structures have a higher χ^{2}_{PSD} value[7] for the agreement with the PSD data than the starting structures, but the increase in the χ^{2}_{PSD} value is relatively modest (from 16.1 to 21.4). On the other hand, we note that chemical shifts calculated for the DFT/NMR chemical shift structures hardly deviate from the measured values any more than do the chemical shifts shown in Figure 2 calculated for the X-ray structure itself.[12] This clearly validates the idea that this is a substantially more accurate method than the purely PSD approach.

In conclusion, the plane wave DFT based optimization method used here, in conjunction with validation through calculation of solid-state chemical shifts, allows the determination of crystal structures from powder samples using starting approximate structures provided from molecular modeling using PSD-NMR data. This ensemble results in a strategy for accurate NMR based de novo structure determination for molecules in powders at natural isotopic abundance. There is clearly room for improvement both in the DFT/NMR chemical shift protocol and the MM/PSD-NMR step, so it seems likely that this method will develop and become widespread in the future.

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Supporting Information Available: Tables of measured and calculated chemical shifts, coordinate files, and experimental details for calculations and NMR measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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