Subtleties in Crystal Structure Solution from Powder Diffraction Data Using Simulated Annealing: Ranitidine Hydrochloride

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ABSTRACT: Recent advances in crystallographic computing and availability of high-resolution diffraction data have made it relatively easy to solve crystal structures from powders that would have traditionally required single crystal samples. The success of direct space methods depends heavily on starting with an accurate molecular model. In this paper we address the applicability of using these methods in finding subtleties such as disorder in the molecular conformation that might not be known *a priori*. We use ranitidine HCl as our test sample as it is known to have a conformational disorder from single crystal structural work. We redetermine the structure from powder data using simulated annealing and show that the conformational disorder is clearly revealed by this method. © 2003 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 92: 244–249, 2003

Keywords: ranitidine HCl; simulated annealing; powder diffraction; structure solution; synchrotron

INTRODUCTION

Powder diffraction techniques have traditionally been used for identification and quantification of polycrystalline material and solving simple crystal structures. The information contained in a powder diffraction pattern is intrinsically less than that obtained from a single crystal, as the three-dimensional intensity distribution is compressed to one dimension. Recently, methods have been developed to solve increasingly complicated organic molecular structures from powder data by modeling the structure in direct space, using methods such as random searches,[1] Monte Carlo,[2] genetic algorithms,[3,4] and simulated annealing.[5,6] Because these methods are being improved to solve more complicated structures, it is important to understand their limitations. In particular, they depend on constructing a parameterized model of the molecule and so it is possible to encounter problems that have subtleties that are not embodied in the model. In this paper we address such a problem by using simulated annealing to determine the structure of a compound that is known to have site disorder, so that the molecule does not fit into the unit cell in a single configuration. We use the well-known ulcer medication ranitidine HCl (*N*-(2-{[5-(dimethylaminomethyl)-2-furanyl]methylthio}ethyl)-*N*′-methyl-2-nitro-1,1-ethene-diamine hydrochloride, $C_{13}H_{23}N_4O_3S^+ \cdot Cl^-$). Ranitidine HCl is an H_2-receptor antagonist used for treatment of peptic ulcers and related disorders. The crystal structure of form II ranitidine HCl is known from single crystal data,[7] and the *N*-ethyl-*N*′-methyl-2-nitro-1,1-ethenediamine moiety takes two conformations, so that there is 50% occupancy in each of two sites for two nitrogen, one carbon, and two oxygen atoms.

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EXPERIMENTAL

Ranitidine HCl powder was purchased from US Pharmacopoeia and was dried for 1 h in a vacuum at 60°C. The powder diffraction pattern was collected on beamline X3B1 of the National Synchrotron Light Source at Brookhaven National Laboratory. X-rays of wavelength 1.15 Å were selected by a double crystal Si(111) monochromator. The sample was loaded in a 1.5-mm thin-walled quartz capillary and mounted on the horizontal axis of the diffractometer. The diffracted X-rays were selected by a Ge(111) analyzer crystal on the detector arm to obtain angular resolution of $\sim 0.01^\circ$ full width at half-maximum (fwhm). Diffracted X-rays were detected by a commercial NaI scintillation detector, and the measured X-ray counts were normalized to the signal from an ionization chamber between the monochromator and sample to correct for decay and fluctuations of the incident beam intensity.

RESULTS AND DISCUSSION

Structure Solution

The cell was first indexed using the program TREOR.[8] Indexing indicated a monoclinic cell with lattice parameters $a = 18.808$ Å, $b = 12.981$ Å, $c = 7.211$ Å and $\beta = 95.047^\circ$; systematic absences indicated the space group $P2_1/n$. With the lattice indexed, we refined the powder pattern using only the lattice and profile parameters to describe the position and shape of all Bragg peaks, iteratively adjusting the intensity of each peak; this is commonly known as a LeBail fit. We performed a LeBail fit to the measured powder diffraction profile using the program FULLPROF.[9] The profile fit gave us figures of merit $R_{wp} = 6.08\%$ and $\chi^2 = 2.92$, where

$$R_{wp} = \left[\sum_{i=1}^{N_{obs}} w_i (I_{oi} - I_{ci})^2 \Big/ \sum_{i=1}^{N_{obs}} w_i (I_{oi})^2 \right]^{1/2} \quad (1)$$

and

$$\chi^2 = \sum_{i=1}^{N_{obs}} w_i (I_{oi} - I_{ci})^2 \Big/ N_{obs} - N_{var} - 1 \quad (2)$$

In eqs. 1 and 2, I_{oi} and I_{ci} are observed and calculated intensities of the i^{th} profile point, respectively, and w_i $(=1/\sigma_i^2)$ is the statistical weight of the i^{th} profile point, which is the inverse of the variance of that observation. There are a total of N_{obs} data points in the profile, and N_{var} parameters varied in the fit.

The premise of direct space structure solution is that most bond distances and angles can be predicted by molecular mechanics or other means to required accuracy. However, torsions around single bonds cannot be predicted by such methods, so the task of direct space structure solution is essentially to twist up the molecule and locate it within the crystallographic unit cell to produce the best agreement with experimental data. The initial configuration of the molecule in this problem was obtained from the molecular modeling program CS Chem3D, where the energy of the molecule was minimized using semi-empirical quantum mechanical methods (MOPAC).[10] For ranitidine HCl, this leaves 20 parameters to solve the structure. Eleven of these parameters are the torsion angles shown in Figure 1. Three parameters (Euler angles) give the orientation of the ranitidine molecule, and the remaining six parameters are fractional coordinates that locate the ranitidine molecule and the Cl^- in the cell.

We used a locally developed simulated annealing algorithm, PSSP, to find the best agreement between calculated and observed diffraction patterns.[6,11] We define a parameter S, which is related to the weighted R factor of powder diffraction, and seek to find the solution that minimizes S. In particular,

$$S = \sum_{i=1}^{N_{obs}} [I_{li} - I_{ci}]^2 \Big/ \left[\sum_{i=1}^{N_{obs}} I_{li} \right]^2 \quad (3)$$

where I_{li} is the calculated profile of the LeBail fit at the i^{th} point. The minimum value of S is sought

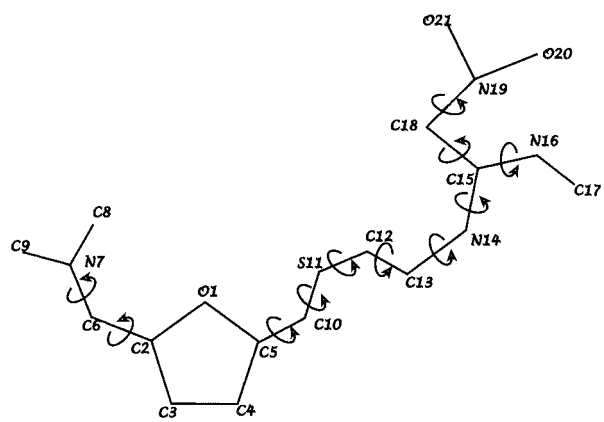

Figure 1. Sketch of the ranitidine molecule showing the 11 torsion angles that are used as internal degrees of freedom in PSSP.

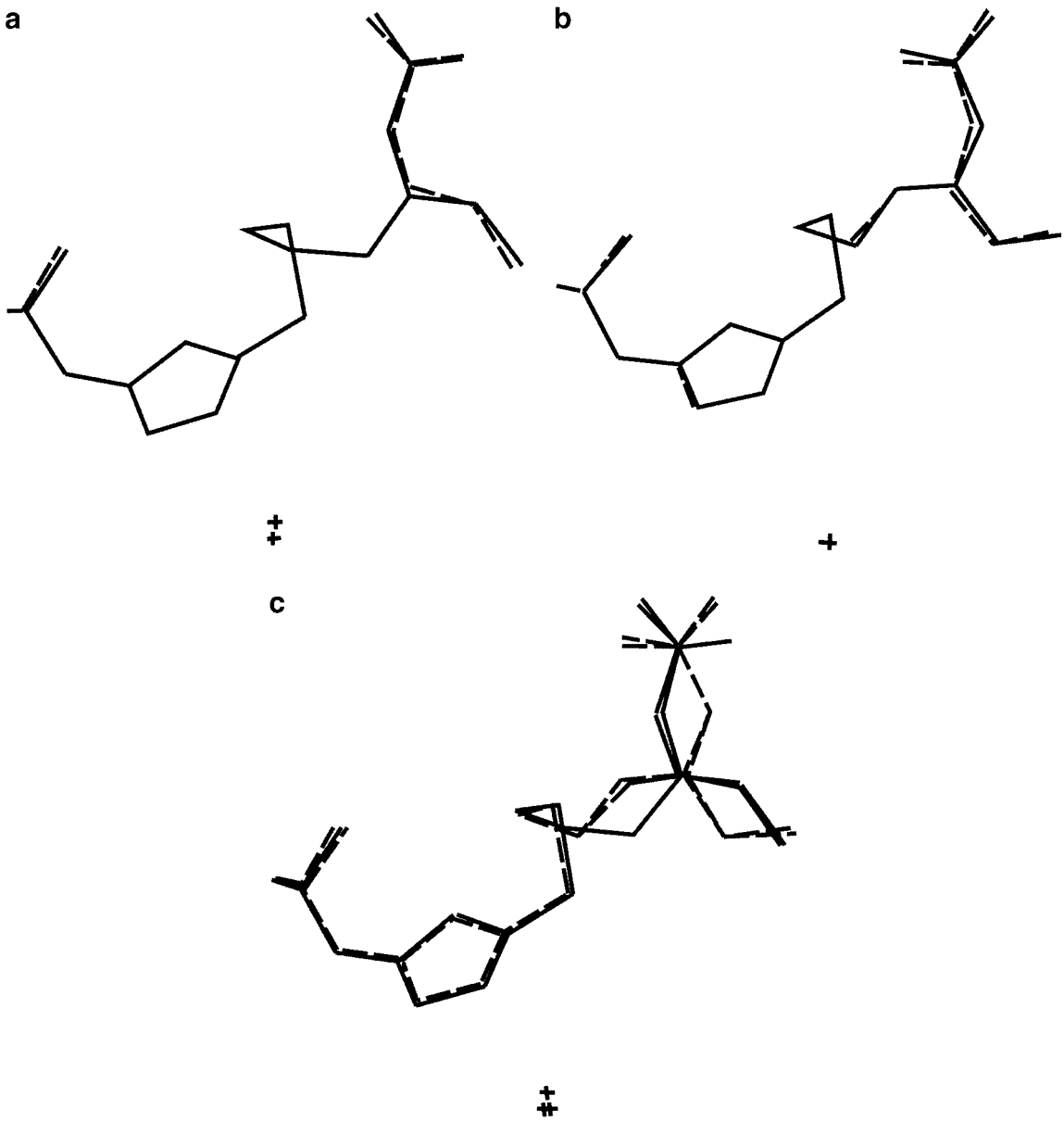

Figure 2. (a) The two solutions obtained from PSSP with $S = 0.046$ and 0.048. (b) Two solutions for which $S = 0.057$ and 0.058, having a different conformation. (c) All four solutions obtained from PSSP superimposed. The views are along the crystallographic a^* direction.

by simulated annealing, where we hypothesize that S represents the energy of an imaginary physical system that is minimized by raising its temperature to some high value and gradually lowering it, allowing it to seek the configuration(s) of lowest energy. A description of how S can be economically calculated from integrated intensities, without loss of information by overlapping peaks, has been published elsewhere.[11]

PSSP starts out by performing Monte Carlo searches to sample the configuration space at some high temperature. Random starting parameters give S in the range 20–50; starting temperature (dimensionless) was chosen as 50, so that essentially all moves would be accepted. We used $N_{obs} = 100$ reflections in the simulated annealing calculations, to a minimum d of 2.66 Å. The algorithm computed 10^6 structures (requiring

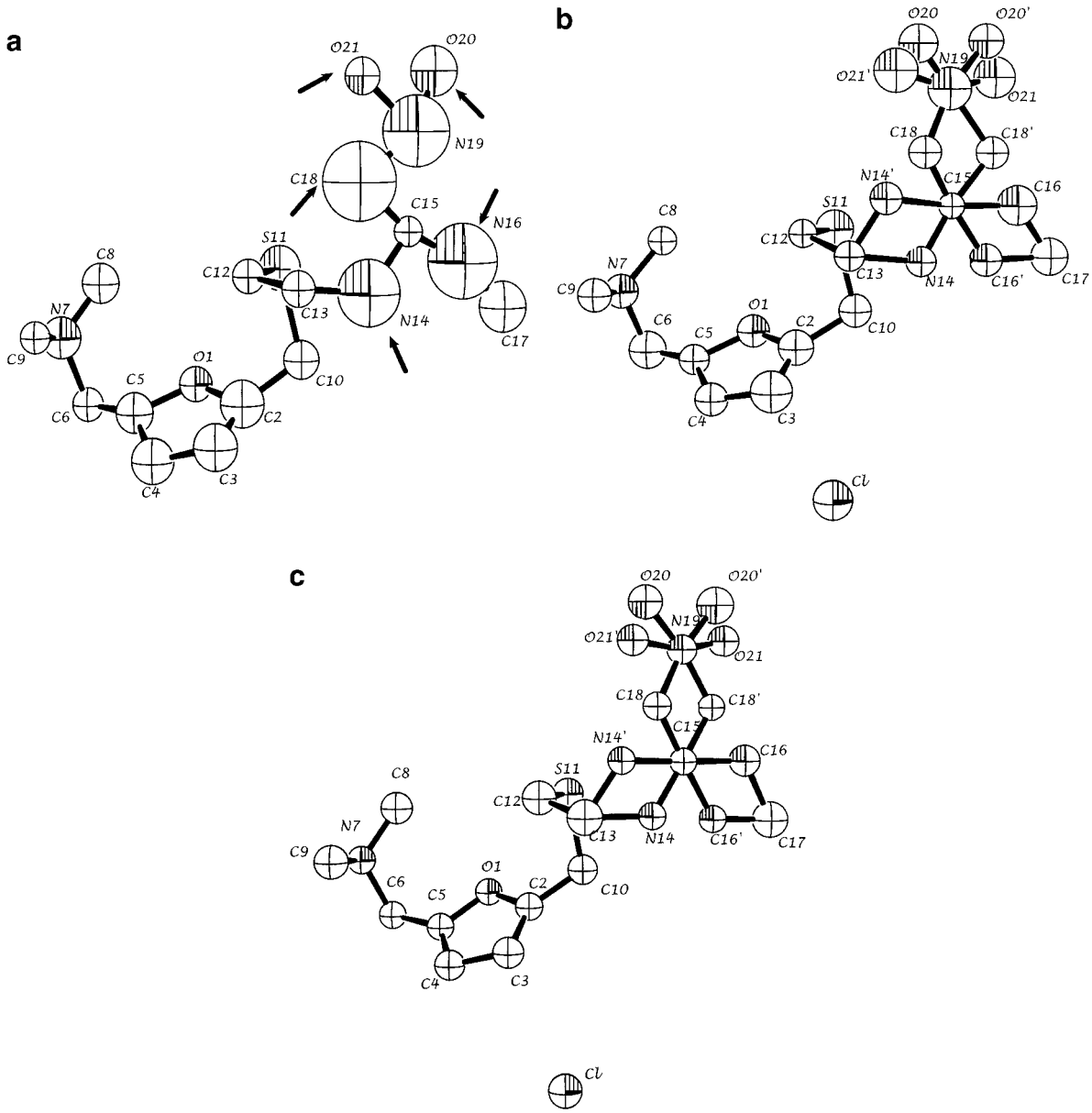

Figure 3. (a) Refined structure of the molecule obtained from *ab initio* powder structure solution for a single molecular configuration. Spheres are 50% density contours of isotropic thermal parameters. Arrows indicate the five atoms that are configurationally disordered. (b) Refined structure with both positions of disordered atoms N14, C16, C18, O20, and O21 indicated. (c) Single crystal solution (coordinates from ref. 7). All views are along the crystallographic a^* direction.

~1 h on a 650 MHz Pentium) before repeatedly lowering the temperature by 20% until a final temperature of 0.001 (dimensionless) was reached. We carried out 50 such calculations and obtained four solutions, for which $S = 0.048$, 0.046, 0.057, and 0.058. The unsuccessful trial runs typically had $S > 0.1$.

The structures of the four solutions that came from PSSP, without refinement, are shown in Figure 2. It is immediately seen that there are two pairs of very similar solutions. In all cases, the backbone from C8 and C9 to C13 is essentially identical, but there are two different locations found for atoms N14, N16, C18, O20, and O21,

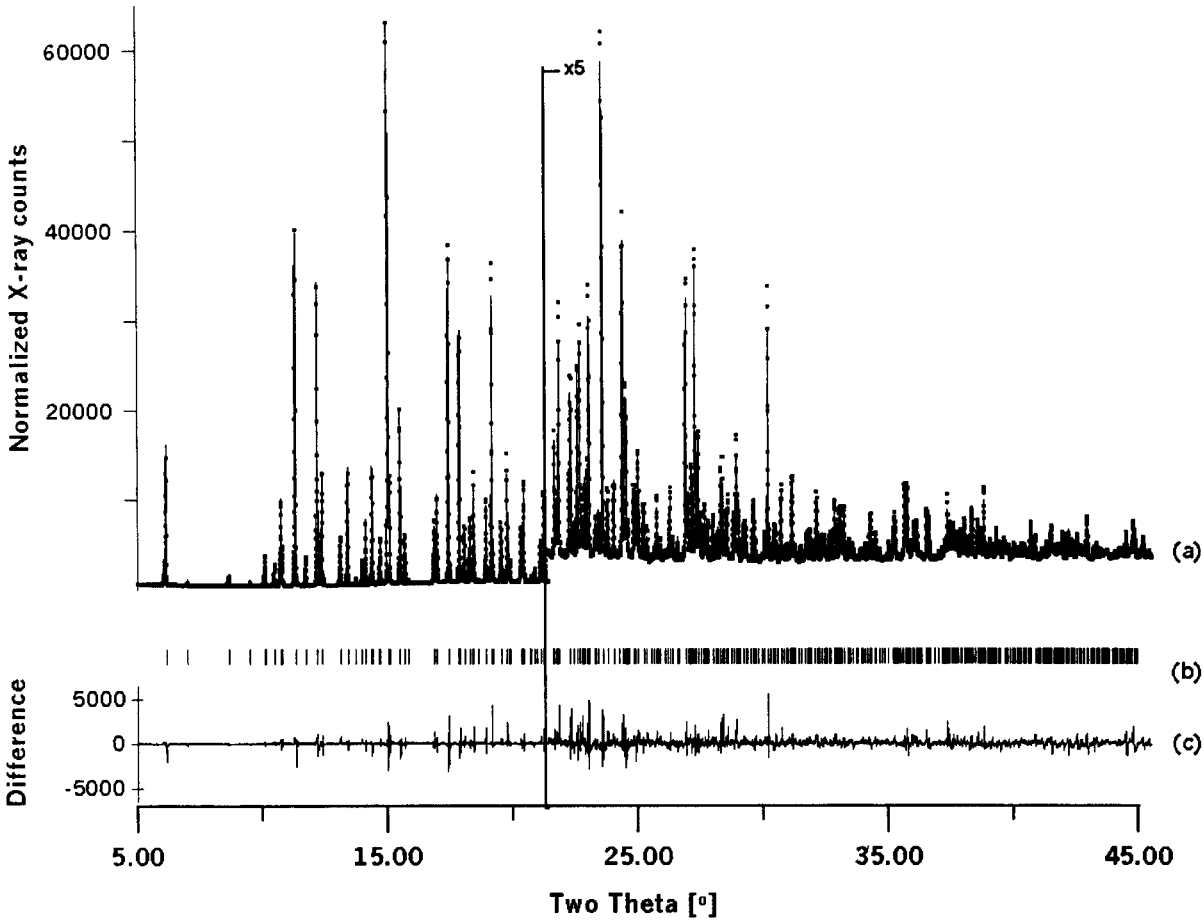

Figure 4. Scattered X-ray ($\lambda = 1.1508$ Å) intensity from ranitidine HCl as a function of diffraction angle 2Θ. Shown are (a) the observed pattern (dots) and the best Rietveld-fit profile (line), (b) peak positions, and (c) the difference curve between observed and calculated profiles.

which are precisely the atoms that had 50% occupancy in two different sites in the single crystal solution. This result suggests that PSSP has found the two distinct conformations known from the single crystal structure, without any imposed bias.

We obtained Rietveld refinements from each of the four PSSP solutions using GSAS.[12] We refined 96 variables, including the lattice parameters, profile parameters, fractional coordinates, and individual isotropic thermal parameters for each nonhydrogen atom, and typically obtained $R_{wp} = 11.12$ and $\chi^2 = 10.56$. These refinements required application of soft restraints on certain bond distances and angles to obtain a stable solution. In the powder solution we notice unusually large thermal parameters for the atoms N11, N16, C18, N19, and O21 (Figure 3a) which are in the fragment of the molecule containing the atoms that are known to be disordered from the single crystal study.[7] It is unrealistic that adjacent bonded atoms would have vastly different thermal parameters in the absence of disorder, which is also a strong indication that the model being used is not a correct description of the crystal structure.

Considering that the four solutions can be superimposed with two distinct conformations of the fragment containing atoms N11, N16, C18, O20, and O21, it is natural to try a Rietveld refinement using a starting model where both of these conformations are considered to have half occupancy. This method gave a significantly better fit, yielding $R_{wp} = 8.39\%$ and $\chi^2 = 5.88$. (We also carried out refinements starting from the known model of disorder from single crystal results and obtained an essentially identical fit, with $R_{wp} =$

8.43 and $\chi^2 = 5.61$.) The molecule obtained from our model and the published structure from single crystal work are shown in Figures 3b and 3c, respectively. If we put in the hydrogen atoms in the model, we get an even better agreement with the acquired data, with $R_{wp} = 7.41$ and $\chi^2 = 4.51$; this is the Rietveld refinement shown in Figure 4. Neither this work nor the single crystal diffraction can reveal whether this disorder is static or dynamic, the magnitude of the reorientation time, or the short-range correlations that may occur between neighboring molecules.

CONCLUSIONS

We have shown that it is possible to find a stable, refinable structure of ranitidine HCl using powder data. The molecular disorder in the crystal structure is clearly seen in two different ways: distinct solutions have nearly identical figures of merit, and Rietveld refinements that do not incorporate the conformational disorder lead to unrealistic thermal parameters. The solutions can be combined to give a disordered structure with acceptable thermal parameters, which is identical to the previously known structure determined with single crystal data. We have also shown in such cases it is crucial to analyze several solutions obtained from simulated annealing calculations to obtain the detailed crystal structure.

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