Application of Systematic Search Methods to Studies of the Structures of Urea−Dihydroxy Benzene Cocrystals

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A systematic search method that identifies trial crystal structures by manipulating a molecular model in direct-space within a defined unit cell and comparing calculated and experimental powder X-ray data and assessing calculated lattice energies has been extended to allow simulation of crystal structures having two symmetry-independent molecules within the unit cell. Overall, the methodology developed is composed of three components: first, identification of all isolated molecular-adducts that are viable in terms of intermolecular pair energy calculated using an atom−atom approach; second, clustering of all similar adducts through energy minimization and ranking of the predicted structures; third, treatment of the best molecule-pair adducts identified in a systematic search of all possible intermolecular packing arrangements. The validity of the approach is demonstrated via its application to predict the crystal structures of cocrystals of urea with the isomers of dihydroxy benzene (catechol, resorcinol, and hydroquinone).

1. Introduction

It is clear that detailed information about the intermolecular packing arrangements manifested by molecular materials within a specified crystallographic unit cell provides valuable insight into the origin of a material's solid-state properties (e.g., melting point, mechanical properties, crystal shape, and dissolution properties). Hence, such information provides, in principle, a route to a molecular design strategy aimed at controlling the crystal chemistry to enhance the performance characteristics of a phase of interest. Single-crystal X-ray diffraction provides the most widely used method for elucidating crystal structures. However, problems arise in the application of single-crystal methods to many low-symmetry organic crystals because of the difficulty in preparing crystals of sufficient size and quality in the particular polymorphic form to solve its crystal structure.[1]

A now firmly established, alternative approach is structure solution from X-ray or neutron diffraction data collected from powdered samples. For powder methods, it is accepted that good trial structures are necessary for successful determinations, and several methods for generating these initial models have been developed. The systematic search approach[1] uses a grid-based search of translations and rotations to assess all of the possible intermolecular packing arrangements in direct space. The trial structures identified as being most consistent with the available diffraction data are progressed for Rietveld refinement.[2] The systematic search approach has been successfully applied to both predict[3] (from a knowledge of unit cell parameters and space group alone) and solve from powder diffraction data the crystal structures of various materials.[4−7] Whereas this approach is well established for organic materials with asymmetric units consisting of only one molecule, further development is needed for the structure determination of many important speciality materials that have asymmetric units comprising two or more moieties, for example, materials produced as salts, hydrates, or solvates. Such forms are commonly manifested by pharmaceutical materials, so it is particularly important to develop approaches that allow their treatment for structure elucidation.

In addition to the systematic search algorithm, Harris et al.[8] have reported structures found by the Metropolis Monte Carlo method, which involves random movements of molecules within the unit cell to obtain the best overall fit to the X-ray diffraction data, and have also developed a genetic algorithm.[9,10] Another successful method using simulated annealing has been described by David and Shankland.[11]

To increase the complexity of materials amenable to structure solution from samples in powder form, one philosophy is to harness complementary structural information from other experimental techniques such as solid-state nuclear magnetic resonance spectroscopy (SSNMR). Recently we have been investigating two potential approaches to the incorporation of structural information, established from solid-state NMR measurements, directly into trial-structure generation protocols for powder X-ray diffraction data.

The first approach involves the incorporation of penalty functions, based on observed intermolecular atom−atom separation distances derived from the analysis of chemical shifts in SSNMR spectra, during trial structure generation.[12] Previously solid-state NMR data have been used to assist, a priori, in crystal structure solution from powder diffraction data by restraining the lengths of C−OH and C═O during Rietveld refinement[13] and by using the REDOR technique to measure intramolecular atom−atom distances for a molecule with conformational flexibility allowing the conformation present in the asymmetric unit to be identified.[14] However, the direct incorporation of intermolecular atom−atom distance information, derived from an analysis of chemical shifts, into a trial structure generation

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procedure employing simulated annealing is a novel approach that has been developed as a result of our research program.[12]

The second approach, and the motivation for the work described in this article, is the reduction in the number of parameters or range of parameter values required to undertake a grid-based systematic-search approach for defining trial crystal structures. A reduction in the range of values associated with a parameter describing the search space can be achieved, for example, if a truncated range of values for a torsion angle, describing a degree of conformational flexibility in a molecule, can be achieved. One approach is to undertake theoretical calculations of chemical shift values for the relevant atoms of an isolated molecule as a function of the torsion angle and to compare the calculated values with the experimentally observed chemical shifts. This approach has been applied successfully in a study of a polymorph of the material MNA.[15] Further, the direct measurement of hydrogen-bonding distances from a comparison of theoretical chemical shift calculations with experimentally determined chemical shifts has been achieved for MNA.[16] In principle, direct distance information of this kind allows the relative positions of two independent moieties in an asymmetric unit to be determined, removing a degree of freedom from the search space, hence reducing the number of parameters required to perform a systematic search. To evaluate the performance of a computer method encapsulating the second approach while working, in the first instance, in the absence of direct input from solid-state NMR experiments, it was decided to treat three cocrystals of urea with the dihydroxy benzenes.

In this paper, the development of the systematic search methodology for crystal systems with two molecules in the asymmetric unit is described in some detail. The approach is then validated by applying it to investigate the solid-state complexes of urea with the isomers of dihydroxy benzene, that is, resorcinol (urea), catechol (urea), and hydroquinone (urea). A full systematic search with hydroquinone−urea molecular pairs has not been undertaken at this time because of specific features of that cocrystal: whereas the urea molecules are centered on general positions within the unit cell, there are two nonequivalent half molecules of hydroquinone in the asymmetric unit. The simulated results for this cocrystal using the current methodology, with special treatment for the above features, will be presented in a further article.

2. Methodology for Direct Space Search for Two Molecules in the Asymmetric Unit

To elucidate the crystal structure of a material that has two molecules in its asymmetric unit by the systematic search method, it is necessary first to identify a large number of the plausible structures for dimers of the two source molecules. These tentative structures are then ranked in terms of their structural stability (i.e., with lowest intermolecular-pair potential energy) and used as rigid bodies when performing a systematic search for the trial structures. The whole methodology is described below.

2.1. Search of Molecular Pairs. Consider a pair of molecules, individually treated as rigid bodies, in isolation, in this case resorcinol and urea. Configurations are selected by applying translations and rotations to one molecule and rejecting or accepting a location on the basis of the criteria of atom−atom distance separation and intermolecular potential pair energy. To simplify the mathematical treatment of the molecular pair, one molecule of the pair (here resorcinol) is fixed at one coordinate location, for example, the origin of the coordinate system, while the other molecule (here urea) is subjected to a grid search,

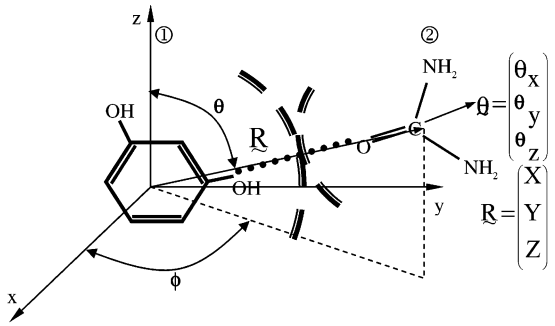

Figure 1. The Cartesian coordinate system employed for assessing molecular pairs in isolation.

defined by three translational and three rotational degrees of freedom (Figure 1).

Within a Cartesian spherical polar coordinate system, translation steps are defined by a translation magnitude, λ, and a unit vector defined by two spherical polar angles θ and ϕ (grid points are spaced at angular intervals of $\Delta\theta$ and $\Delta\phi$), and the orientation of the mobile molecule is defined by three orientation angles (θ_x, θ_y, and θ_z); hence,

$$\begin{pmatrix} x_i' \\ y_i' \\ z_i' \end{pmatrix} = \mathbf{M}\begin{pmatrix} x_i \\ y_i \\ z_i \end{pmatrix} + \lambda \underset{\sim}{\mathbf{R}} \tag{1}$$

where x_i, y_i, and z_i are the atomic coordinates of the mobile molecule at its starting location, x_i', y_i', and z_i' are the coordinates upon transformation, **M** is a rotation matrix (a function of θ_x, θ_y, and θ_z), $\underset{\sim}{\mathbf{R}}$ is the position vector of the center of coordinates of the mobile molecule, and λ is a translation magnitude that is minimized with respect to the intermolecular-pair potential energy. Hence, there is a total of six search parameters associated with the search grid. Typical van der Waals radii are used to define the minimum separation distance between the centers of the fixed and mobile molecules for each direction selected for translation of the mobile molecule. The distances so identified are used as the starting point for a one-dimensional minimization of the pair potential energy to determine the final location of the mobile molecule for a given orientation and direction of translation.

The atom−atom force field parameters were taken from Nemethy et al.,[17] while the atomic point charges were calculated using MOPAC AM1 method.[18] The total pair potential energy was obtained from

$$E = \sum_{i=1}^{M_i}\sum_{j=1}^{M_j}\left[\left(-\frac{A_{ij}}{r_{ij}^{6}} + \frac{B_{ij}}{r_{ij}^{12}}\right) + \left(-\frac{C_{ij}}{r_{ij}^{10}} + \frac{D_{ij}}{r_{ij}^{12}}\right) + \frac{g_i g_j}{D r_{ij}}\right] \tag{2}$$

where A_{ij}, B_{ij}, C_{ij}, and D_{ij} are atom−atom force field parameters for atoms i and j in the first and second molecules, g_i and g_j are atomic point charges, D is the dielectric parameter, and r_{ij} is the central distance between atoms i and j. In this formulation,[18] the 6−12 potential term was used to model the isotropic van der Waals component for all atoms except those when hydrogen bonding was used where a 10−12 formulation was employed.

By applying the one-dimensional minimization procedure for all possible orientations of the mobile molecule at every grid cell, the locations of urea, together with rotation angles and polar angles, were used to provide the coordinates of all calculated resorcinol−urea pairs with their corresponding minimized intermolecular potential energy. It is clear that finer grid cells

for polar angles and rotation angles will definitely help the pair search algorithm determine the desired location of the second molecule, hence finding the best pair structures for systematic search to elucidate crystal structures. However, because of the limitation of computer speed, the molecular pair search can only be carried out over a relatively coarse grid of cells for both polar and rotation angles. To balance the CPU time requirements against the possibility of finding more accurate pair structures, relatively coarse grid cells were used to achieve moderate accuracy with acceptable CPU time consumption, while further refinement of the calculated pair structures was carried out by pair energy minimization, hence, to some extent, compensating the effect of relatively coarse grid cells on the accuracy of the molecule pairs found.

It should be noted that the molecular pair search performed here only takes into account the intermolecular potential energy of the pair without including the crystal binding energy (packing force); therefore, one can expect that the molecular pair with top ranked pair energy may not necessarily represent the best moiety for packing into a crystal structure. With this in mind, an appropriate pair energy window was set up to hold as many as possible pair structures so that the molecular pair most similar to the moiety from crystal structure could be captured.

2.2. Optimization and Clustering of Molecular Pairs. Because the number of molecular pairs within this energy window can be huge however, performing systematic searches for all pairs obtained within the energy window given current CPU capacity is clearly unrealistic. Furthermore, many molecular pairs may yield nearly identical structures after the application of crystal symmetry operations. Overall, a reduction in number via further analysis of the molecular pairs in the energy window is clearly needed to reduce, substantially, the number of molecular pairs for treatment in subsequent systematic searches. The approach used in this work was to optimize the calculated pair structures within the energy window using the Cerius[2] package[19] employing the same force field parameters used in the molecular pair searches. Through optimization, the molecular adducts were grouped in terms of their configuration and pair potential energy. Further analysis clustered the optimized pairs to eliminate repeated or symmetry-related structures.

By superimposing the fixed molecule of any two adducts, the relative locations of urea molecules then indicate whether the two adducts can be clustered into same group. The root-mean-square (rms) distance between the atoms of two urea molecules from two pairs provides the clustering criteria. If rms is equal to zero or less than a small value, the two adducts are treated as the same or very similar and then clustered into same group. The representatives of each cluster group, together with all nonclustering pairs, form the final subset of molecular pairs, which will be ranked in terms of the minimized pair energy. The top ranked pair structures in this subset are subsequently examined individually in the full systematic-search procedure.

2.3. Systematic Unit Cell Search Procedure. In the systematic search procedure employed in this study, a fast, efficient, and reliable filter for the selection of trial structures is obtained by using the in-built chemical sense and calculated lattice energies to decide upon the suitability and ranking of potential arrangements. Generally speaking, a twin track approach, that is, ranking trial structures both on lattice energy and goodness of fit to the observed X-ray diffraction data, was used to solve crystal structures from X-ray powder diffraction data.[1] The lattice energy, E_{latt}, was calculated by summing, pairwise, all of the atom−atom interactions between a central molecule and all of the surrounding molecules (e.g., Williams[20] and Kitaigorodski et al.[21]). With a lattice having n atoms in the central molecule and n' atoms in each of the N surrounding molecules, the lattice energy was calculated by

$$E_{\text{latt}} = \frac{1}{2}\sum_{k=1}^{N}\sum_{i=1}^{n}\sum_{j=1}^{n'}V_{kij} \tag{3}$$

where the factor $^1/_2$ reflects the pairwise nature of intermolecular forces; $n = n'$ in most cases, but in the case of molecular complexes, they will be different. V_{kij} is the interaction potential between atom i in the central molecule and atom j in the surrounding molecule k. As a very reasonable approximation, a truncated lattice is built during the systematic search on the basis of reduced radial cutoff distances of 25 Å because, for electronically neutral molecular materials, the near coordination spheres contribute the majority of the lattice energy.[4] Further detailed description of the systematic search procedure can be found in the literature.[1,4,7] All of the trial structures resulting from the systematic search on the subset of pair structures from the asymmetric unit were subjected to lattice energy minimization using force field parameters employed in the systematic search. In this work, the top-ranked structures, before and after lattice energy minimization, were compared with the structures determined by single-crystal methods. The comparison was made in terms of X-ray diffraction profiles that were calculated both for the top-ranked structures and the single-crystal structures.

3. Results and Discussion

3.1. Molecular Pair Structure Search and Optimization. The step of polar angle θ was 10°, and the corresponding step of polar angle ϕ was calculated by $\Delta\theta/(\pi \sin\theta)$, $0° < \theta < 180°$, to generate a distribution of grid cells in such a way that each grid cell covered a similar size of area on the spherical surface. The steps of orientation angles of urea were chosen to be 20° with the range of variation from 0° to 360°. The total number of one-dimensional minimizations of the pair potential energy was approximately 1.9 million. The one-dimensional minimization algorithm uses the Broyden−Fletcher−Goldfarb−Shanno variant of Davidon−Fletcher−Powell minimization method[22] and a line search subroutine with line searches and backtracking method.[22]

A total of 16 191, 14 458, and 13 207 pair structures were found with an upper energy cutoff of −7.0 kcal/mol for resorcinol−urea pairs and −6.0 kcal/mol for catechol−urea and hydroquinone−urea pairs, respectively. The energy distributions are plotted in Figures 2, 3, and 4. It can be seen that the numbers of pairs found in the pair structure search decrease with the decrease in the pair potential energy. The numbers of resorcinol−urea pairs are dramatically reduced from 7008 to 236 when the pair energy varies from the range between −8.0 and −9.0 kcal/mol to the range between −9.0 and −10.0 kcal/mol, which indicates that a strong hydrogen bond is only located in a small number of grid cells and orientation angles given the mesh size and orientation angle steps used in these calculations. Similar trends were found for the other two cases.

The energy distributions after potential energy optimizations and clustering of the pair structures are also shown in Figures 2−4 for the pairs of urea with resorcinol, catechol, and hydroquinone. The optimizations totally changed the energy distributions and narrowed their ranges of energy. The majority of the resorcinol−urea pairs within the energy window were

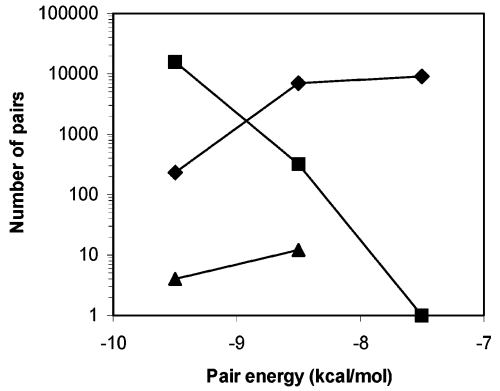

Figure 2. Energy distributions of resorcinol−urea pairs with energy cutoff of −7 kcal/mol: (◆) before minimization; (■) after minimization; (▲) after clustering with tolerance of 0.5.

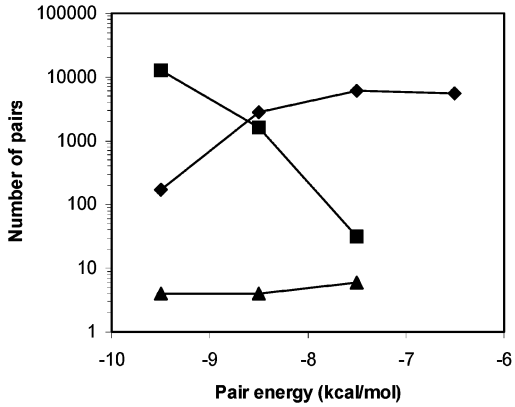

Figure 3. Energy distributions of catechol−urea pairs with energy cutoff of −6 kcal/mol: (◆) before minimization; (■) after minimization; (▲) after clustering with tolerance of 0.5.

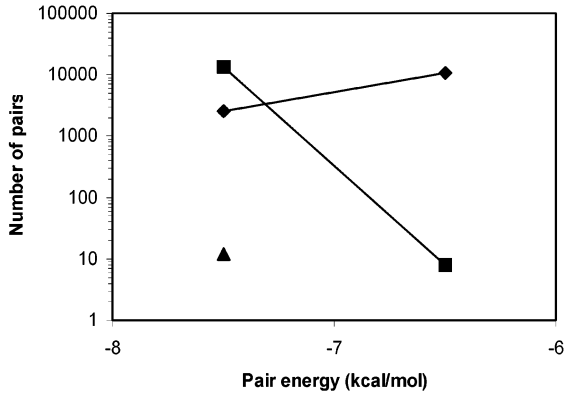

Figure 4. Energy distributions of hydroquinone−urea pairs with energy cutoff of −6 kcal/mol: (◆) before minimization; (■) after minimization; (▲) after clustering with tolerance of 0.5.

located in the energy range between −9.0 and −10.0 kcal/mol, about 98% of total 16 191 resorcinol−urea pairs (Figure 2). Similar conclusions can be drawn from Figures 3 and 4 for the catechol−urea and hydroquinone−urea pairs. These findings indicate that the optimizations successfully relaxed constraints due to the finite grid cell size and the orientation angle steps.

3.2. Clustering and Grouping the Optimized Pairs. The root-mean-square (rms) distance between atoms of urea compounds from any two pairs, calculated with eq 2, determines whether two pairs can be classified into the same cluster. The criterion of the rms tolerance was set at 0.5 with a smaller tolerance generating more clusters. The effect of the rms tolerance on the number of clusters is plotted in Figure 5 for

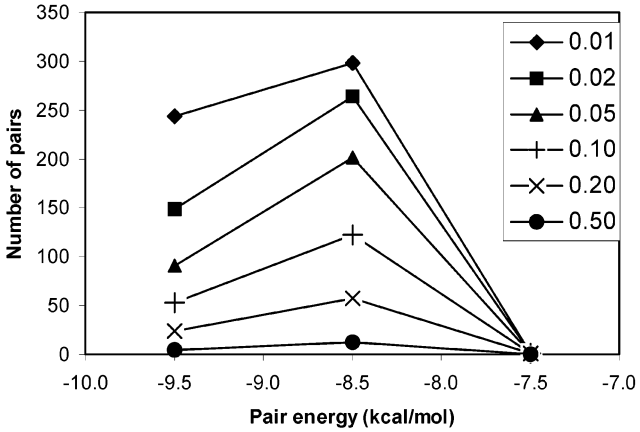

Figure 5. The effect of rms tolerance on the number of clusters for resorcinol−urea pairs after clustering.

TABLE 1: Number of Pair Structures of Dihydroxy Benzene−Urea Before and After Clustering

Section A: Resorcinol−Urea

	before clustering	after clustering (rms tolerance)					
		0.01	0.02	0.05	0.10	0.20	0.50
number of pairs	16191	543	414	293	176	82	16
average number of pairs in one cluster	1	∼30	∼39	∼55	∼92	∼197	∼100

Section B: Catechol−Urea

	before clustering	after clustering (rms tolerance)					
		0.01	0.02	0.05	0.10	0.20	0.50
number of pairs	14458	653	507	307	177	65	14
average number of pairs in one cluster	1	∼13	∼21	∼41	∼77	∼209	∼1100

Section C: Hydroquinone−Urea

	before clustering	after clustering (rms tolerance)					
		0.01	0.02	0.05	0.10	0.20	0.50
number of pairs	13207	1016	622	323	170	63	12
average number of pairs in one cluster	1	∼13	∼21	∼41	∼77	∼209	∼1100

resorcinol−urea, and the numbers of pair structures before and after clustering for resorcinol−urea, catechol−urea, and hydroquinone−urea pairs are listed in Table 1, sections A, B, and C, respectively. As can be seen from Figure 5, the number of clusters reduced from 543 to 16 when the rms tolerance was increased from 0.01 to 0.50. When the rms tolerance equals 0.01, around 30 pairs were clustered into each cluster, while the average number of pairs clustered into each cluster increased to about 1000 with an rms tolerance of 0.50 (Table 1, section A).

If the systematic search procedure for crystal structure determination were to be directly applied to the 16 191 pair structures in the energy window, the total CPU time required would be 10 794 h (∼450 days or 1.23 years) with 40 min CPU time for each search, which is definitely unrealistic. However, after optimization and clustering with an rms tolerance of 0.50, only 16 pair structures were left for full crystal structure searching, which only required 10.7 h (0.44 day). The CPU time saving is massively 99.9%. If the extra CPU time required for optimizing and clustering is taken into account, the total CPU time saving is still over 99.8%. For the pairs of urea with

TABLE 2: Unit Cell Parameters of the Cocrystals of Urea with Resorcinol and Catechol

structure	*a* [Å]	*b* [Å]	*c* [Å]	α [deg]	*β* [deg]	*γ* [deg]	space group	unit cell volume [Å^3]	asymmetric units per cell [*Z*]	density [g cm^{-3}]
resorcinol−urea	7.142	7.798	15.428	90.0	90.000	90.0	$P2_12_12_1$	859.236	4	1.315 46
catechol−urea	19.219	6.249	7.180	90.0	97.898	90.0	$P2_1/c$	854.135	4	1.323 32

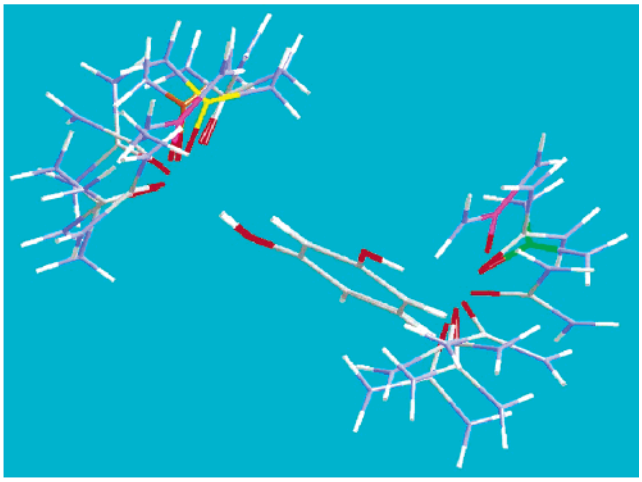

Figure 6. Comparisons between the total 16 pair structures and the asymmetric unit from crystal structure[23] of resorcinol−urea. For the pair from the crystal, the carbons are colored magenta; for the first, second, and third top-ranked pairs, the carbons are colored yellow, green, and brown, respectively.

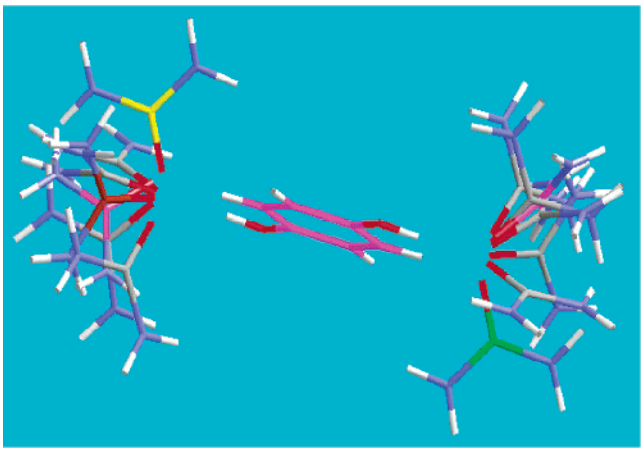

Figure 7. Comparisons between the total 12 pair structures and the asymmetric unit from crystal structure[24] of hydroquinone−urea. For the pair from the crystal, the carbons are colored magenta; for the first, second, and third top-ranked pairs, the carbons are colored yellow, green, and brown, respectively.

catechol and hydroquinone, similar CPU time saving (over 99%) can be achieved after optimizing and clustering with a tolerance of 0.50. The representative pair structures obtained with a tolerance of 0.5 comprise an average of all contributing pairs, which would otherwise be distinct given increasingly smaller tolerance values. Because it was still possible to locate the observed crystal structures despite this inherent approximation, the use of a tolerance of 0.5 can be seen to be justified at least empirically.

Figures 6 and 7 show a comparison of the clustered pair structures of resorcinol−urea and hydroquinone−urea, obtained from pair searches, and the pair structures from their corresponding cocrystal structures determined experimentally.[23,24] As expected, the hydrogen-bond interactions between the two molecules are clearly apparent in all of the trial molecular pairs. Furthermore, the locations of the urea molecules in some

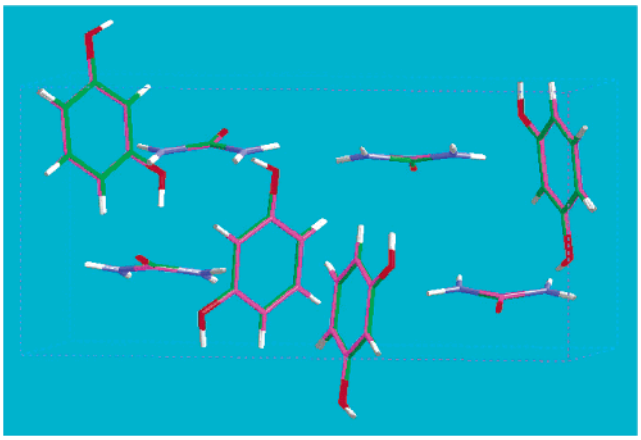

Figure 8. Comparisons of structures from systematic search after optimization and Cambridge Crystal Structure Database (CSD) with optimized resorcinol for resorcinol−urea cocrystal.[23] For the structure from CSD, the carbons are colored magenta; for the best structure from systematic search after lattice energy minimization, the carbons are colored green).

calculated pairs are very close to those of the urea in the asymmetric unit from the known crystal structures, which indicates that with the very small number of trial asymmetric units identified by the molecular pair search the full systematic search should generate good trial structures for the elucidation of the cocrystal structures. Similar results have been found for the pair structures of catechol−urea (not shown here).

3.3. Systematic Search Validation. The systematic search performs 11.664 million steps with a total of 5832 rotational steps about the *x*, *y*, and *z* axes for each translational search of total 2000 steps along the *x*, *y*, and *z* axes. The short atom−atom distance cutoff in the present study was 2.2 and 1.7 Å for normal and hydrogen-bonding interactions, while the high lattice energy cutoff was set to be −10.0 kcal/mol and used to eliminate unrealistic crystal structures.

The unit cell parameters of resorcinol−urea and catechol−urea are listed in Table 2. A lattice energy window was set up with energy cutoff of −10.0 kcal/mol, which contained about 2000 crystal structures for each run. Given the granularity of the grid employed for the systematic searches, lattice energy optimization was employed as a final step to rank the trial crystal structures generated through the systematic searches prior to comparisons being made with the observed crystal structures.

The comparisons between the structures obtained from the systematic search after optimizations and the experimentally determined crystal structures of resorcinol−urea[23] and catechol−urea[25] are shown in Figures 8 and 9, and their corresponding X-ray diffraction patterns are plotted in Figures 10 and 11. Taking the resorcinol−urea for example, the best calculated crystal structure, referring to agreement with the powder diffraction data, is the 15th top-ranked structure in terms of the optimized lattice energy, which corresponds to the 448th top-ranked structure in terms of the lattice energy before optimization, and the energy was reduced from −16.8 to −30.8 kcal/mol. The optimization displaced and reorientated the resorcinol−urea pair into its most stable packing position, hence producing the most similar X-ray diffraction pattern to that calculated from

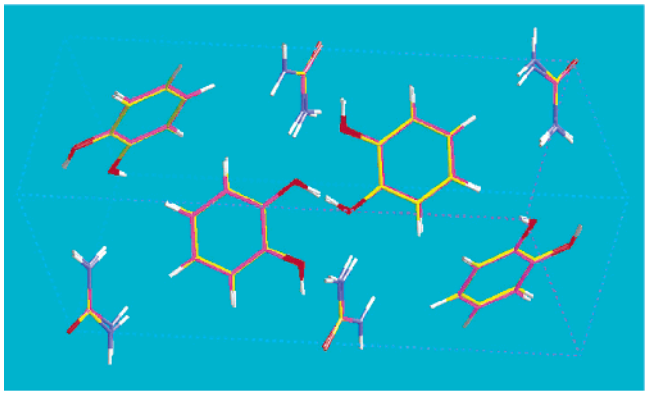

Figure 9. Comparison of catechol−urea cocrystal structures. For the structure from Hammond et al.,[25] the carbons are colored magenta; for the best structure from systematic search after lattice energy minimization, the carbons are colored yellow).

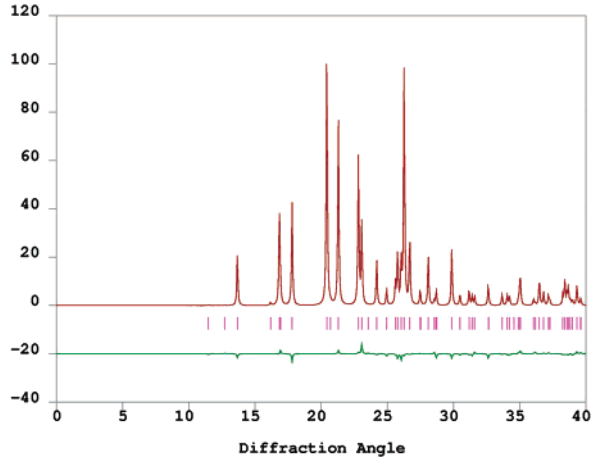

Figure 10. Calculated X-ray diffraction pattern for best structure for resorcinol−urea from systematic search after lattice energy minimization (red) and difference with diffraction pattern calculated for structure from CSD[22] (green).

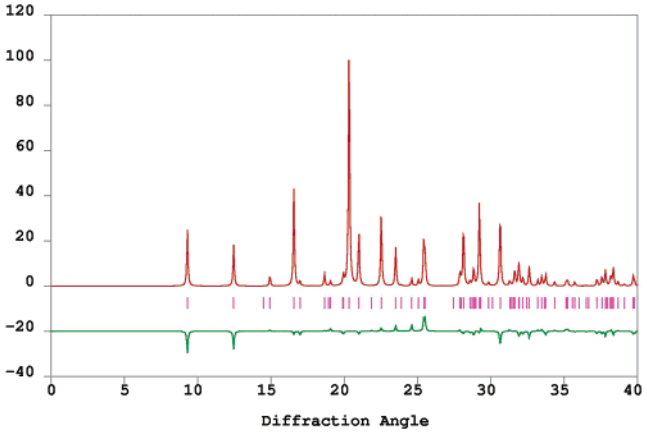

Figure 11. Calculated X-ray diffraction pattern for best structure for catechol−urea from systematic search after lattice energy minimization (red) and difference with diffraction pattern calculated for structure from Hammond et al.[24] (green).

the structure identified by single-crystal methods (Figure 10). With such a small difference between the calculated and experimentally determined crystal structures of resorcinol−urea and catechol−urea (see Figures 9−11), the Rietveld fitting method[2] could utilize the modeled structures with confidence to determine structures of the cocrystals.

4. Conclusions

The further development of the systematic search method for dealing with more than one molecule per crystallographic asymmetric unit has been validated through detailed studies on urea−dihydroxy benzene cocrystals. The developed method employs "prescreen" techniques, pair structure search, optimization, and clustering, to identify a very small number of pair structures representing all distinguishing pair groups from a data set involving $>10^{10}$ steps yielding a massive ca. 99% reduction in computing time compared to methods not including the prescreen techniques. Further application of the method for structure determination of organic salts and solvates is currently being developed opening a way forward to an improved understanding of the crystal science associated with (pseudo-)polymorphic and related effects.

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