Crystal Packing Calculations and Rietveld Refinement in Elucidating the Crystal Structures of Two Modifications of 4-Amidinoindanone Guanylhydrazone

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Abstract

The crystal structures of two modifications (termed *A* and *B*) of 4-amidinoindanone guanylhydrazone (AIGH), 2-(4-amidino-1-indanylideneamino)guanidine, have been determined. Modification *B*, for which single crystals were available, has been treated in the usual manner. The determination of modification *A*, for which no single crystals were available, was made on the basis of the X-ray powder pattern and *ab initio* packing calculations. It has been shown that it is possible to determine in a routine manner the crystal structure of a polar and moderately flexible molecule, which can be specified as several tautomeric forms, using a combination of high-precision computational chemistry and Rietveld refinement. The resulting *R* factor was *ca* 10%. Although the resolution of the powder diagram allowed for indexing, it is shown that the structure determination is also possible without indexing the powder diagram. The presented structure determination should be understood as an example of a new and generalized use of the Rietveld refinement where the two main problems, indexing of the powder pattern and making an initial structure guess, could be bypassed.

1. Introduction

Being a potent inhibitor of the enzyme *S*-adenosylmethionine decarboxylase, 4-amidinoindanone guanylhydrazone (AIGH), shown in Fig. 1, has been recently proposed (Stanek *et al.*, 1993) as an anticancer compound. The moderately flexible AIGH molecule has been suggested to have one fully extended planar low-energy conformation. In a salt form or under physiological conditions both amidino groups were expected to be fully protonated, giving one single conformer. In the case of the free base this may exist in several tautomeric forms, as shown in Fig. 1, and it is not clear whether one of these possible tautomers occurs exclusively or whether several tautomers may occur under different conditions (*e.g.* in different crystal modifications). Meanwhile, we have found that AIGH indeed crystallizes in the extended conformation and the free base of AIGH (*i.e.* the pure substance composed of one molecular species) exists in at least two different modifications, *A* and *B*. The crystal

structure of modification *B*, for which single crystals were available, was determined in the usual manner, as described in the following section.

For modification *A* no single crystals of sufficient quality could be grown and a crystal structure determination based on the X-ray powder diffraction was attempted. Such a Rietveld refinement (Rietveld, 1988; Young, 1995) requires that a good starting model of the crystal structure should be available. This requirement is the main reason for the rather limited use of the method in elucidating organic crystal structures. The conventional procedure is as follows: the first step consists of indexing the diffraction pattern and determining the crystal system and the lattice parameters. The resolution of a cheap in-house powder pattern is often insufficient for a reliable indexing of organic crystals and synchrotron X-ray methods must then be used. The second step consists of suggesting a crystal structure which is sufficiently close to the examined structure in the sense of some similarity between the simulated powder pattern of the suggested structure and the experimental powder pattern. Such a close estimation is usually non-trivial, even when the lattice parameters are known.

Computational methods which predict possible crystal structures on the basis of the molecular structure have only been recently developed (Gavezzotti, 1991; Gdanitz, 1992; Karfunkel & Gdanitz, 1992; Karfunkel & Leusen, 1993; Karfunkel, Rohde, Leusen, Gdanitz & Rihs, 1993; Karfunkel, Gdanitz & Leusen, 1994; Perlstein, 1994). These crystal-structure generating methods usually result in a number of stable structures (*i.e.* polymorphic structures) whose lattice energy differs by a few kJ mol^{-1}. The physical significance of the generated crystal structures depends on the precision of the underlying model for the lattice energy function. Presently, force-field methods are used as a model for the molecular crystals. A logical presumption is that if the errors in the computed lattice energies are sufficiently small, then reasonable starting structures (*i.e.* initial guesses) should be present among the predicted possible crystal structures. The crucial point behind this computational approach is that the status of the Rietveld refinement applied to organic crystals is changed from a method which works occasionally to a routine method working in an automatic manner.

Later we will demonstrate in detail the applicability of the method to the crystal structure determination of modification A. The main goal of this work is to evaluate the potential of the new approach and therefore we will also demonstrate that the same crystal structure of modification A will result, at significantly higher computational efforts, without performing any indexing (*i.e.* without knowing the lattice parameters and crystal system).

2. The crystal structure of modification B

The single crystal analysis was carried out to determine the type of tautomer in the solid state. Suitable crystals were grown by slow cooling of a hot DMF solution. The AIGH molecule in this modification, illustrated in Fig. 2, is definitely identified as tautomer of type $m1$ in Fig. 1. Crystal data are given in Tables 1 and 2, bond lengths and angles are summarized in Table 3.*

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* Lists of anisotropic displacement parameters, structure factors and the numbered intensity of each measured point on the profile have been deposited with the IUCr (Reference: SH0073). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
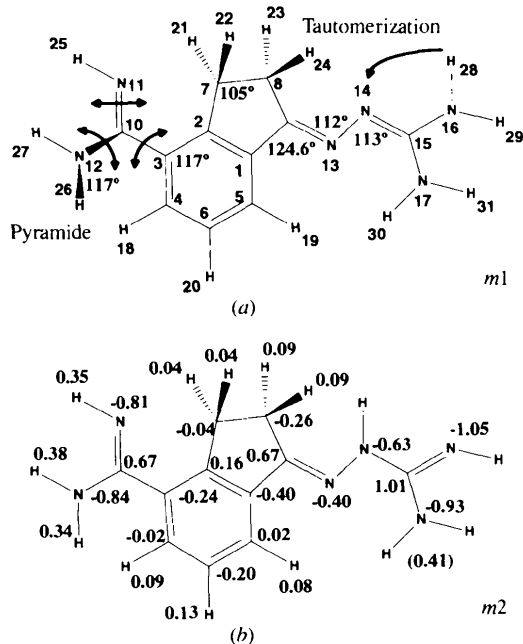

Fig. 1. The AIGH molecule, its torsional degrees of freedom and tautomeric form. (*a*) $m1$, the more stable tautomer and the atomic numbering used in reporting the final fractional coordinates. The arrows on the left-hand side show the bonds giving rise to the various conformers. Some angle values are also shown. The distance between N(13) and N(14) was 1.39 Å and the distance between these nitrogens and the neighbouring carbon was 1.29–1.30 Å. The distance between C(3) and C(10) was 1.48 Å. (*b*) $m2$, the less stable tautomer type. The figures on the atoms, however, are the electrostatic potential fitted point charges of the $m1$ tautomer used in the packing calculations (to two decimal places). The average partial charge on the guanyl hydrogens is 0.41 on each hydrogen.

Computer programs used: *SHELXS*86 (Sheldrick, 1985); *SDP* (Enraf–Nonius, 1985).

3. Structure determination of modification A on the basis of packing calculations

Although indexing is not absolutely essential for a packing-based structure determination, it is very useful in reducing the amount of computations by restricting the packing to a limited number of space groups. A powder pattern generated by a Guinier camera and shown in Fig. 3 was used for the indexing with the *TREOR*90 program (Werner, Eriksson & Westdahl, 1985). The number of lines used as an input to the indexing program was 26. The indexing results for modification A of AIGH were: triclinic, reduced lattice parameters: $a = 7.391$, $b = 7.738$, $c = 10.700$ Å, $\alpha = 79.00$, $\beta = 82.86$, $\gamma = 71.13°$; $V = 567$ Å^3, from which $Z = 2$ was derived. The figure of merit was 15. The indexing results indicate, as far as we can rely on them, that we need to pack the relevant isomers (conformers as well as tautomers) of AIGH in the space groups $P\bar{1}$ and $P1$ ($Z = 2$), the latter being much less probable.

Before proceeding to any packing calculations a series of extensive energy calculations had to be carried out on the isolated molecules in order to decide which isomers (tautomer as well as conformer) of AIGH should be considered for packing calculations. Since the differences between the lattice energies of different relevant
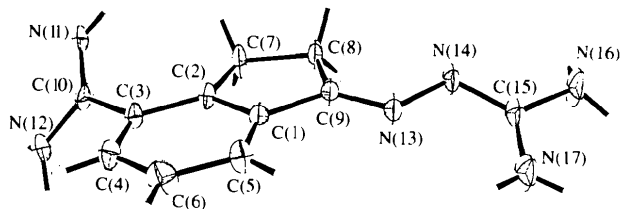

Fig. 2. An *ORTEP* (Johnson, 1976) plot with 20% displacement ellipsoids of the AIGH molecule in modification B.
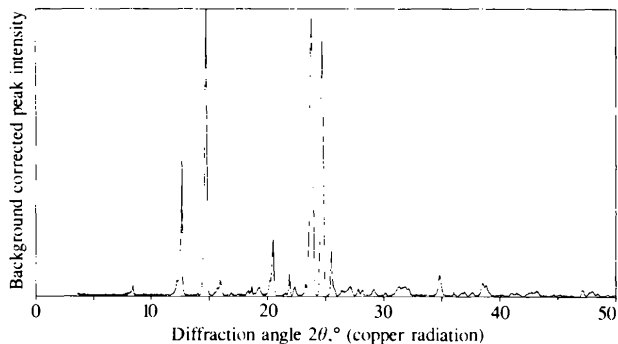

Fig. 3. The X-ray powder pattern of modification A of AIGH produced from a Guinier film and used for indexing.

Table 1. *The determined crystal structures of modifications A and B of AIGH given as fractional coordinates*

Although modification *B* is monoclinic, all three cell angles are 90°. The atom numbering corresponds to that shown in Fig. 1. U_{eq} is defined as $(1/3)\sum_i \sum_j U_{ij} \alpha_i^* \alpha_j^* \mathbf{a}_i.\mathbf{a}_j$.

	Modification A Space group: P1̄ $a = 10.717$ Å, $\alpha = 71.78°$ $b = 7.762$ Å, $\beta = 82.838°$ $c = 7.418$ Å, $\gamma = 78.941°$			Modification B Space group: P21/c $a = 8.090$ (1) Å, $\alpha = 90°$ $b = 7.929$ (1) Å, $\beta = 90$ (1)° $c = 17.518$ (2) Å, $\gamma = 90°$			
	x	y	z	x	y	z	U_{eq}
C(1)	0.4992	0.2353	0.1120	0.2217 (4)	0.3507 (5)	0.2572 (2)	0.0264
C(2)	0.5742	0.2434	−0.0563	0.3041 (4)	0.2457 (5)	0.2058 (2)	0.0248
C(3)	0.7078	0.1914	−0.0520	0.3598 (4)	0.3138 (5)	0.1358 (2)	0.0251
C(4)	0.7623	0.1324	0.1263	0.3359 (5)	0.4844 (5)	0.1228 (2)	0.0331
C(5)	0.5522	0.1809	0.2889	0.1997 (5)	0.5212 (5)	0.2434 (2)	0.0336
C(6)	0.6853	0.1282	0.2960	0.2583 (5)	0.5883 (5)	0.1754 (2)	0.0374
C(7)	0.4907	0.3088	−0.2248	0.3100 (6)	0.0670 (6)	0.2338 (2)	0.0300
C(8)	0.3507	0.3407	−0.1380	0.2301 (5)	0.0735 (5)	0.3142 (2)	0.0274
C(9)	0.3633	0.2940	0.0749	0.1696 (4)	0.2505 (5)	0.3236 (2)	0.0260
C(10)	0.7934	0.1949	−0.2256	0.4465 (4)	0.2072 (5)	0.0780 (2)	0.0244
N(11)	0.7959	0.3328	−0.3799	0.5633 (4)	0.1000 (5)	0.0923 (2)	0.0326
N(12)	0.8784	0.0376	−0.2257	0.3969 (4)	0.2325 (5)	0.0043 (2)	0.0327
N(13)	0.2724	0.3013	0.2090	0.0805 (4)	0.3149 (4)	0.3777 (2)	0.0282
N(14)	0.1489	0.3625	0.1527	0.0471 (4)	0.2019 (4)	0.4376 (2)	0.0275
C(15)	0.0617	0.3542	0.2907	−0.0756 (4)	0.2643 (5)	0.4803 (2)	0.0289
N(16)	−0.0624	0.4209	0.2545	−0.1160 (5)	0.1770 (5)	0.5441 (2)	0.0356
N(17)	0.0954	0.2745	0.4735	−0.1605 (4)	0.4022 (5)	0.4650 (2)	0.0353
H(18)	0.8647	0.0913	0.1332	0.367 (5)	0.538 (5)	0.076 (2)	
H(19)	0.4913	0.1802	0.4167	0.143 (5)	0.600 (5)	0.278 (2)	
H(20)	0.7282	0.0860	0.4320	0.243 (5)	0.709 (5)	0.166 (2)	
H(21)	0.5037	0.2046	−0.2969	0.248 (5)	−0.013 (5)	0.198 (2)	
H(22)	0.5157	0.4345	−0.3313	0.432 (5)	0.024 (5)	0.238 (2)	
H(23)	0.2914	0.2538	−0.1664	0.141 (5)	−0.011 (5)	0.318 (2)	
H(24)	0.3038	0.4829	−0.1982	0.320 (5)	0.043 (5)	0.357 (2)	
H(25)	0.7310	0.4475	−0.3754	0.591 (5)	0.100 (6)	0.142 (3)	
H(26)	0.8789	−0.0731	−0.1068	0.296 (5)	0.299 (6)	−0.006 (2)	
H(27)	0.9370	0.0401	−0.3439	0.406 (5)	0.146 (6)	−0.030 (3)	
H(28)	−0.0898	0.4835	0.1203	−0.095 (5)	0.058 (6)	0.548 (3)	
H(29)	−0.1285	0.4103	0.3653	−0.212 (5)	0.217 (6)	0.562 (3)	
H(30)	0.1884	0.2263	0.4946	−0.132 (5)	0.479 (6)	0.431 (3)	
H(31)	0.0300	0.2691	0.5854	−0.227 (5)	0.453 (6)	0.494 (3)	

crystal structures are rather small (a few kJ mol⁻¹), we assume that a value of *ca* 10 kJ mol⁻¹ is suitable as a theoretical energy cut-off for the isomers (for this type of relatively rigid molecule), *i.e.* an isomer with an (gas phase) energy of more than 10 kJ mol⁻¹ above the energy of the most stable isomer is assumed to be unable to regain this energy deficit by extra favourable packing. To this theoretical energy cut-off we must add the relative error in computing the energy of each isomer. All the relevant conformers and tautomers of AIGH have been generated with standard modelling methods and their energies computed with the *MOPAC*93 program (Stewart, 1993) using the *AM*1 as well as the *PM*3 Hamiltonians. In all cases the tautomers of type *m*1 in Fig. 1 were *ca* 34 kJ mol⁻¹ more stable than the corresponding tautomers of type *m*2. The errors in the relative *AM*1 and *PM*3 energies are sufficiently low to exclude almost certainly the existence of any tautomer of type *m*2 in any crystal modification of AIGH. Calculations with high-precision *ab initio* quantum mechanical methods (geometry relaxation with non-local density functionals at the 6-31G** basis set level) using the *Gaussian*92/*DFT* program (Frisch *et al.*, 1992) delivered an energy difference of *ca* 16 kJ mol⁻¹

in favour of the *m*1 tautomer. The error in the energy differences for this high-precision method is less than 6–7 kJ mol⁻¹ when comparing isomers so that again any crystal containing the type *m*2 tautomer can be safely excluded. The force field used for the packing of AIGH has been derived from the Dreiding force field (Rappe, Casewit, Colwell, Goddard & Skiff, 1992), as implemented in *Cerius*2 (*Cerius*2 is a registered trademark of Molecular Simulation Inc., Burlington, MA 01803-5297, USA), but corrected as follows, such that the optimized geometries of the *ab initio* calculations were reproduced: the equilibrium bond distances and angles (*i.e.* r_0 and θ_0 values in the quadratic force field terms) were shifted from their original values to those derived from the *ab initio* geometry optimization. These values are indicated in Fig. 1. The torsional barrier of the rotating amidino group has been lowered from 105 to 54 kJ mol⁻¹. Atomic point charges have been fitted to the *ab initio* calculated electrostatic potential. The four most stable AIGH conformers to be considered in the packing calculations are shown in Fig. 4.

As already stated above, the structure determination will be demonstrated for two different cases: the first presuming the above-mentioned successful indexing, the

Table 2. *Experimental details for B*

Crystal data

Chemical formula	$C_{11}H_{14}N_6$
Chemical formula weight	230.27
Cell setting	Monoclinic
Space group	$P2_1/c$
a (Å)	8.090 (1)
b (Å)	7.929 (1)
c (Å)	17.518 (2)
β (°)	90.00 (1)
V (Å^3)	1123.7 (5)
Z	4
D_x (Mg m^{-3})	1.361
Radiation type	Cu $K\alpha$
Wavelength (Å)	1.5418
No. of reflections for cell parameters	25
θ range (°)	29–49
μ (mm^{-1})	0.69
Temperature (K)	296
Crystal form	Platelet
Crystal size (mm)	0.49 × 0.45 × 0.1
Crystal colour	Colourless

Data collection

Diffractometer	Enraf–Nonius CAD-4
Data collection method	$\omega/2\theta$
Scan range (2θ,°)	6–150
Absorption correction	None
No. of measured reflections	2458
No. of independent reflections	2294
No. of observed reflections	1574
Criterion for observed reflections	$I > 4\sigma(I)$
R_{int}	0.026
θ_{max} (°)	75
Range of h, k, l	$-10 \rightarrow h \rightarrow 10$
	$0 \rightarrow k \rightarrow 9$
	$0 \rightarrow l \rightarrow 21$
No. of standard reflections	3
Frequency of standard reflections	Every 120 min
Intensity decay (%)	±4

Refinement

Refinement on	F
R	0.056
wR	0.063
S	1.18
No. of reflections used in refinement	1574
No. of parameters used	210
H-atom treatment	Only coordinates of H atoms refined
Weighting scheme	$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{max}$	0.08
$\Delta\rho_{max}$ (e Å^{-3})	0.321
$\Delta\rho_{min}$ (e Å^{-3})	−0.298
Extinction method	None
Source of atomic scattering factors	*International Tables for X-ray Crystallography* (1974, Vol. IV)

second (see the following section) ignoring any indexing results. Crystal structures were generated according to the packing protocol for the *ab initio* prediction of possible crystal structures, as described by Karfunkel & Gdanitz (1992) and Karfunkel & Leusen (1993).

In the first case packing is carried out only in the $P\bar{1}$ space group, so that the number of possible low-energy crystals is rather limited. The three most stable predicted possible crystals in this space group correspond to the $P\bar{1}$ entries in Table 4. It is immediately obvious that the most stable $P\bar{1}$ crystal has cell parameters very close to those deduced by indexing (see above). The initial trial crystal for a Rietveld refinement is derived from

Table 3. *Selected geometric parameters (Å, °) for B*

C(1)—C(2)	1.396 (5)	C(7)—C(8)	1.549 (5)
C(1)—C(5)	1.385 (5)	C(8)—C(9)	1.496 (6)
C(1)—C(9)	1.470 (5)	C(9)—N(13)	1.295 (4)
C(2)—C(3)	1.414 (5)	C(10)—N(11)	1.295 (5)
C(2)—C(7)	1.501 (6)	C(10)—N(12)	1.366 (5)
C(3)—C(4)	1.385 (6)	N(13)—N(14)	1.407 (4)
C(3)—C(10)	1.494 (5)	N(14)—C(15)	1.337 (4)
C(4)—C(6)	1.386 (6)	C(15)—N(16)	1.355 (5)
C(5)—C(6)	1.388 (5)	C(15)—N(17)	1.319 (5)
C(5)—C(1)—C(2)	122.0 (3)	C(9)—C(8)—C(7)	105.6 (3)
C(9)—C(1)—C(2)	109.0 (3)	C(8)—C(9)—C(1)	109.0 (3)
C(9)—C(1)—C(5)	129.0 (3)	N(13)—C(9)—C(1)	121.6 (4)
C(3)—C(2)—C(1)	119.0 (4)	N(13)—C(9)—C(8)	129.4 (4)
C(7)—C(2)—C(1)	111.5 (3)	N(11)—C(10)—C(3)	125.7 (3)
C(7)—C(2)—C(3)	129.4 (3)	N(12)—C(10)—C(3)	114.8 (3)
C(4)—C(3)—C(2)	118.1 (3)	N(12)—C(10)—N(11)	119.5 (3)
C(10)—C(3)—C(2)	121.4 (3)	N(14)—N(13)—C(9)	113.6 (3)
C(10)—C(3)—C(4)	120.5 (3)	C(15)—N(14)—N(13)	108.9 (3)
C(6)—C(4)—C(3)	122.3 (4)	N(16)—C(15)—N(14)	116.8 (4)
C(6)—C(5)—C(1)	118.7 (4)	N(17)—C(15)—N(14)	125.5 (4)
C(5)—C(6)—C(4)	119.8 (4)	N(17)—C(15)—N(16)	117.7 (3)
C(8)—C(7)—C(2)	104.6 (3)		

the predicted structure by a procedure, termed by us indexing correction, as follows: the cell parameters of the predicted crystal are changed to those derived from indexing, keeping the fractional coordinates of the atoms fixed (*e.g.* the length of *a* is changed from 11.26 to 10.70 Å, the closest value from the indexing mentioned above). This will bring the cell to its correct shape with
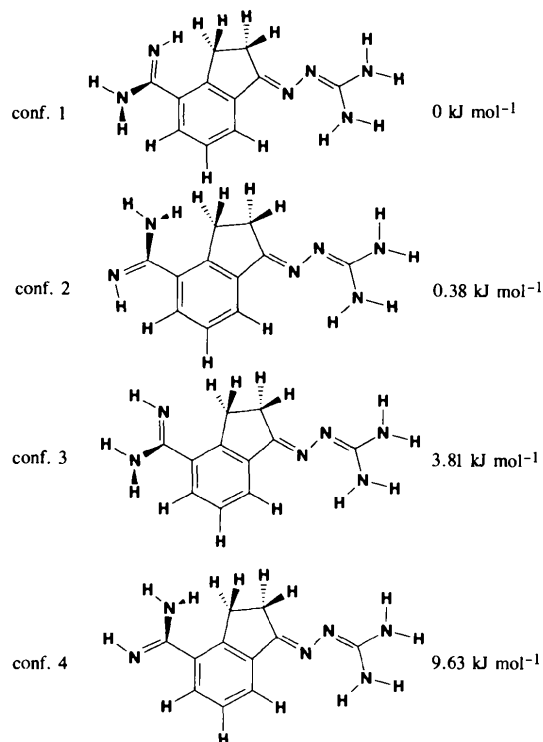

Fig. 4. The four most stable conformers of AIGH and their relative energies computed with non-local density functionals at the 6-31G** basis set level. Notice that according to the calculations the NH$_2$ group of the amidino moiety is pyramidal.

Table 4. *Some low lattice-energy crystals of AIGH predicted by the packing calculations in various space groups*

The column Conf. no. refers to the conformers in Fig. 4. In the case where indexing is presumed one should consider only the entries corresponding to the known space group ($P\bar{1}$ in the case of modification A of AIGH).

Mod. no.	Space group	Conf. no.	Lattice E (kJ mol^{-1})	a (Å)	b (Å)	c (Å)	α (°)	β (°)	γ (°)
1	$P\bar{1}$	1	−609.2	11.26	7.45	7.41	75.13	79.75	79.76
2	$P\bar{1}$	1	−602.1	10.53	809	705	83.28	85.18	84.94
3	$P\bar{1}$	1	−582.8	8.25	12.02	7.39	83.94	73.43	70.55
4	$P21/a$	1	−611.3	16.41	6.96	10.07	90	87.3	90
5	$P21/a$	2	−603.2	12.17	7.31	15.39	90	118.5	90
6	$P21/c$	2	−591.5	11.19	12.18	8.48	90	93.26	90
7	$P21/c$	1	−585.2	12.53	14.85	7.43	90	69.56	90
8	$P2_12_12_1$	2	−586.1	12.63	7.48	14.26	90	90	90
9	$Pna2_1$	2	−576.3	12.35	14.52	8.03	90	90	90
10	$P21/m$	2	−565.1	8.02	33.04	7.09	90	65.67	90
11	$Pca2_1$	2	−563.2	15.76	9.07	8.71	90	90	90
12	$P2/c$	2	−562.8	23.11	4.68	13.28	90	70.10	90

slightly deformed molecules. In a subsequent step the lattice energy is minimized with respect to the molecular geometry under the constraint of the fixed unit cell (*i.e.* only the cell content is optimized). We will term such crystals as indexing corrected crystals in contrast to the predicted force-field minimized crystals. In the case of modification A of AIGH the resulting indexing corrected crystal is so close to the experimental one that a Rietveld refinement is trivial (see Fig. 5). The R factor prior to the structural refinement (*i.e.* prior to the change of a lattice parameter or atomic positions) is already as low as 27%, as one can see in Fig. 5. The refinement has been carried out with the *DBWS* program (Wiles & Young, 1981), where rigid-body motions and internal coordinates were manipulated in an interactive manner (see below). The final refinement delivered an R factor of *ca* 10%, as shown in Fig. 5. Such low R factors are considered to be very satisfactory in the Rietveld refinement of organic crystals. The final cell parameters and the fractional coordinates of modification A are given in Table 1. Of particular interest is the geometrical difference between the predicted force-field minimized structure and the final structure after the refinement. This is shown in Fig. 6, but one should bear in mind that in the present case we started the structural refinement from a much better indexing corrected trial structure. It is also interesting to note that the second best predicted $P\bar{1}$ crystal given in Table 4 will lead to the same final crystal. The predicted third best $P\bar{1}$ structure is, however, too different from the experimental structure to be useful as a trial structure.

4. Packing-based structure determination of modification A without indexing

In the second case, where it is assumed that no results from a successful indexing are available, the procedure is as follows: The conformers of the target molecule are packed in all meaningful space groups, starting usually from the most frequent (*i.e.* from the $P21/c$
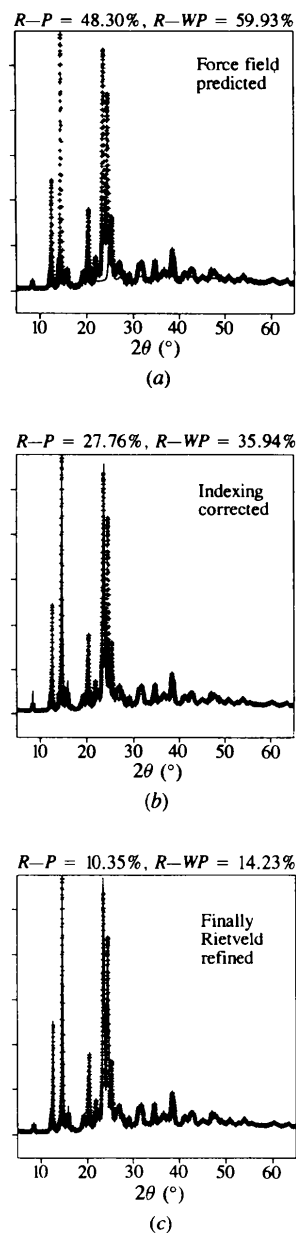
R–P = 48.30%, R–WP = 59.93%

Force field predicted

2θ (°)

(*a*)

R–P = 27.76%, R–WP = 35.94%

Indexing corrected

2θ (°)

(*b*)

R–P = 10.35%, R–WP = 14.23%

Finally Rietveld refined

2θ (°)

(*c*)

Fig. 5. Comparison of the simulated powder pattern of various crystals with the experimental powder pattern (+++) of modification A of AIGH. The powder pattern used for the Rietveld refinement was measured with a powder diffractometer. The resolution in 2θ for the computations was 0.01°. (*a*) The powder pattern of the lowest $P\bar{1}$ crystal predicted in the packing calculations (first entry in Table 4). Only background, scale and peak-shape parameters have been adjusted for the comparison resulting in an R factor of *ca* 48%. The positions of some lines are shifted since the error in the lattice parameters is significant. (*b*) Comparison of the powder pattern of the indexing corrected best $P\bar{1}$ crystal with the experimental powder pattern. The cell parameters from the indexing are enforced on the best predicted $P\bar{1}$ crystal. Background, scale and peak-shape parameters have been adjusted. The R factor is already as low as 27%. (*c*) The final result of the Rietveld refinement. The non-structural parameters considered in the refinement were background (three coefficients), scale, peak-shape (pseudo-Voigt), displacement and preferred orientation (March–Dollase).

space group). The results now correspond to Table 4 (the list of predicted possible structures is in reality much larger). Since presumed cell parameters are not available, we must take the predicted minimized structures as the first trial. The predicted force-field minimized structures are not as close to the experimental structure as the indexing corrected structures and the situation is now more complicated since upon structure refinement one may end up with a structure which does not correspond to the experimental one (*i.e.* convergence to another local minimum of the difference between experimental and simulated powder patterns). Comparing the simulated powder spectra of the predicted structures of Table 4 with the experimental spectrum resulted usually in rather large R factors, out of which the lowest R factor of *ca* 48% originated from the second most stable $P\bar{1}$ modification, as shown in Fig. 5. To our surprise the initial trial consisting of this predicted $P\bar{1}$ force-field structure (*i.e.* second entry of Table 4) converged upon an interactive Rietveld refinement to the same crystal derived already in the previous chapter (see Table 1). By an interactive Rietveld refinement we mean that during the manual structural changes (rigid-body motions, torsions and bond angle changes), a large crystal segment is seen on the screen so that close contacts (or other chemically unreasonable features) can be observed during the manipulations. Thus, any structural change giving rise to chemical nonsense is suppressed, although the R factor would have been dropped by such a change.

5. Discussion and summary

The crystal structures of two modifications of AIGH, a polar and moderately flexible molecule with several possible tautomers, have been determined and their fractional coordinates reported in Table 1. One modification, termed A, for which no single crystals were available, has been determined by a Rietveld refinement. The initial trial structure for the refinement was derived from a set of *ab initio* predicted low lattice-energy structures. The novelty of this work is that this structure determination utilized an ordinary in-house powder pattern and was also possible without referring to any indexing of the powder pattern. The degree of geometrical deviation between the predicted (*i.e.* force-field optimized) and experimental structures is shown in Fig. 6 and one could argue that this deviation is too large to always ensure a convergence of the refinement to the right crystal. Recently, we (Karfunkel, Rohde, Leusen, Gdanitz & Rihs, 1993) proposed a new method for calculating the similarity between two powder patterns. In the conventional Rietveld refinement the difference between two powder spectra is defined by the squared difference spectra. When the peaks of the simulated powder pattern and the experimental one do not overlap (a very common situation), attempts to refine the structure using the conventional sum-of-squares difference measure will usually fail. The difference measure we have proposed is independent of an overlap between the corresponding peaks of the powder patterns to be compared. This new algorithm has not yet been implemented in any of the Rietveld refinement programs and therefore we will not go into details. The point to be mentioned here is that an initial trial structure which differs from the experimental structure to the extent shown in Fig. 6 will have no convergence problem when the new difference measure is used.
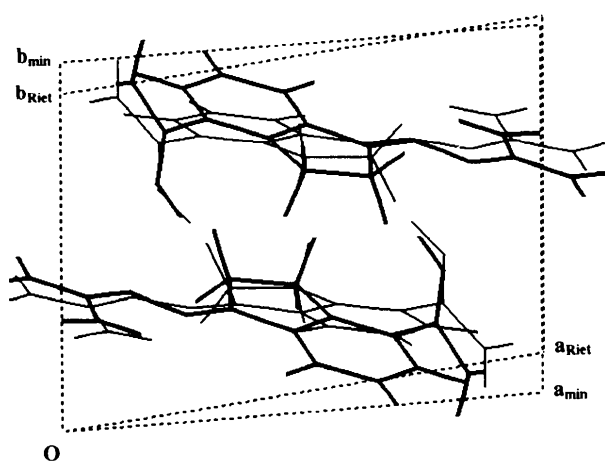

Fig. 6. An overlay of a force-field minimized crystal predicted from the packing entry (entry 2 in Table 4) and the resulting Rietveld refined crystal. Cell parameters as well as orientation differ significantly. The thicker lines correspond to the force-field predicted structure prior to refinement.
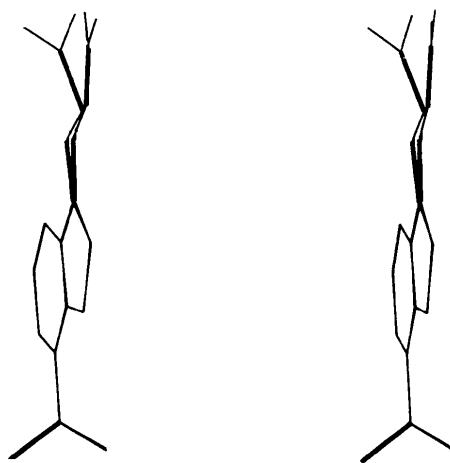

Fig. 7. A stereoview of the AIGH molecules in the two determined modifications. The molecules are superimposed at the atoms of the indanone rings. The AIGH geometry in modification B is bent to an extent which could not be treated correctly by the force field parameters in use. The distortion of the guanido 'side arm' in modification B is clearly indicated in the shown superposition.

The key feature of the presented method is our ability to predict in a reliable manner possible crystal structures. There is still a controversy about the question whether crystal structures are predictable (Gavezzotti, 1994) and since such predictions are based on the lattice energy the question is reduced to the relative error in computing this quantity. In a recent article (Filippini & Gavezzotti, 1993) the correlation between computed lattice energies and experimental heat of sublimations for 122 organic crystals (without hydrogen bonds) had been discussed. In spite of a very simple interaction model the average absolute discrepancy between predicted and calculated heats of sublimation was 7.5 kJ mol^{-1}. Based on these results we are very optimistic about the achievable reliability of packing predictions. Our optimism is based on the large error compensation in computing lattice energy differences, since we have to compare the different packing of only the same molecule. The amount of computational efforts for a reasonable force-field parameterization of a given molecule on the basis of precise *ab initio* quantum chemical calculations is considerable, but methods to do this routinely are emerging (Aleman, Canella, Franco & Orozco, 1991).

How good then was the force field used for AIGH in this work? In the performed quantum chemical energy calculations we assumed that the extended guanylhydrazone side arm (Fig. 1, atoms numbered 13–17) is more or less planar and no attempts to parameterize the out-of-plane bending of this side arm have been undertaken. Instead, we used the transferable crude force parameters of the original Dreiding force field. Our force field is, therefore, not suitable for crystals in which the AIGH molecule is significantly deformed. The AIGH molecule in modification *A* is, fortunately, planar. In modification *B*, however, AIGH is strongly bent (see Fig. 7) and indeed, optimizing the geometry of the experimental crystal of modification *B* with our force field resulted in a lattice energy which was *ca* 25 kJ mol^{-1} higher than the lowest predicted *P*21/*c* modification. In other words, with the force field in use it is impossible to determine the crystal structure of modification *B via* a Rietveld refinement simply because among the predicted possible crystals serving as a source of initial trial structures, that leading to the experimental structure is missing.

Finally, an interesting and uncommon feature of the two elucidated AIGH modifications should be mentioned: the number of intermolecular hydrogen bonds in the two modifications is different. In modification *B* the AIGH crystal gains one additional hydrogen bond at the cost of the strain energy resulting from the unusually large deformation of the AIGH molecule.

The presented calculations (*ab initio* quantum chemical as well as the packing calculations) consumed enormous amounts of computational resources, but one should bear in mind that the computational costs drop about an order of magnitude every 3 years. Thus, we believe that the presented structure determination example of AIGH on the basis of an ordinary powder pattern and packing calculations will evolve toward a reliable and cheap routine method in the near future.

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