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Examples of successful crystal structure prediction: polymorphs of primidone and progesterone

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Abstract

The field of crystal structure prediction and its potential value to the pharmaceutical industry is described. The process of structure prediction employed here is summarized and the results of its application to primidone and progesterone are reported. It is shown that the process successfully generates the known polymorphs of these molecules, starting from the molecular structure alone. Observations related to the application of the structure prediction process are reported.

Keywords: Crystal structure prediction; Polymorph selection; Polymorphism

1. Introduction

In recent years, a number of independent attempts have been made to design molecular modelling approaches which predict the crystal structures of organic molecules from their molecular structures (Gavezzotti, 1991; Gdanitz, 1992; Karfunkel and Gdanitz, 1992; Perlstein, 1992; Catlow et al., 1993; Chang et al., 1993; Holden et al., 1993; Shoda et al., 1995; Van Eijck et al., 1995; Van Eijck and Kroon, 1997; Chaka et al., 1996; Gavezzotti et al., 1997). The motivation for this work is derived from a need to understand the phenomenon of polymorphism, in which one molecular structure can exist in more than one pure crystalline form. Different polymorphs have different physicochemical properties. In the field of pharmaceutical science one important aspect of this phenomenon is that different polymorphs can have different dissolution rates and hence polymorph selection can affect bioavailability. Pragmatically, in the fields of pharmaceutical process and formulation development, it is also important to verify that a selected polymorph is the most stable option. Predictive molecular modelling could assist in this verification.

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Ideally, a 'polymorph predictor' would generate all of the possible crystal forms of a molecule, rank them in terms of free energy and offer a measure for which structures were most likely to form under various conditions of crystallisation. To date, it could be argued that the available modelling technology is some way from achieving this ideal (Gavezzotti, 1994). However, a number of approaches referred to above have led to qualified success. Some of these have relied on the user having quite detailed expertise in the field of crystallography; requiring that appropriate building blocks are assembled from small numbers of molecules, before potential crystal structures are generated. Arguably the most general approach is that devised by Gdanitz (1992) and developed by Karfunkel, Gdanitz and co-workers (Karfunkel and Gdanitz, 1992; Karfunkel and Leusen, 1992; Gdanitz et al., 1993). This methodology has been implemented as a commercial program, C^2 Polymorph (Leusen, 1996). The work reported here forms part of an evaluation of this methodology. Although computers are becoming faster, the approach of Gdanitz is founded on intensive calculations in which thousands of potential packing arrangements are investigated. As a consequence, a comprehensive set of structure predictions for one molecule can currently take a number of weeks, if not months. Evaluation has therefore taken place at a detailed level for a small molecule, acetic acid (Payne et al., 1998a), and at a less detailed level for aspirin (Payne et al., 1998b). Neither of these molecules has more than one confirmed, experimentally realised polymorph. The purpose of this paper is to report on structure predictions for slightly larger pharmaceutically active molecules, which are known to have two polymorphs. The work demonstrates the potential of the chosen predictive approach through the location of all four known crystal structures.

2. The molecules

Primidone (Boon et al., 1951) is an anticonvulsant which occurs in two polymorphic forms, A and B (Daley, 1973; Summers and Enever, 1976). The crystal structure of form A is monoclinic, and can be obtained from the Cambridge Structural Database (CSD) as refcode EPHPMO (Yeates and Palmer, 1975; Cambridge Crystallographic Data Centre, 1998). The structure of form B is orthorhombic and has been solved recently (Payne et al., 1996). Some crystallographic details of these two structures are contained in Table 1. Primidone has a strong propensity to hydrogen bonding, and this is reflected in the packing arrangements of the crystal structures and hence their crystal habits (crystals of A are rhombohedral, those of B are thin hexagonal plates). Fig. 1a–c are images of the molecular structure of primidone and the hydrogen bonding motifs in forms A and B, respectively. Note that form A has two types of hydrogen bond: one creating dimers and the other linking those dimers into

Table 1
Some crystallographic details of polymorphs A and B of primidone and α and β of progesterone[a]

Structure	Space group	*a*	*b*	*c*	*β*	*ρ*	Energy
Primidone A	$P2_1/c$	12.25	7.09	14.81	117.82	1.276	–
A_min	$P2_1/c$	11.62	7.43	14.27	112.53	1.274	−297.15
Primidone B	Pbca	10.27	7.92	27.54	90.00	1.296	–
B_min	Pbca	10.38	7.69	28.33	90.00	1.282	−290.45
α-Progesterone	$P2_12_12_1$	6.25	12.59	22.49	90.00	1.180	–
α_min	$P2_12_12_1$	6.50	12.83	22.37	90.00	1.118	−5.70
β-Progesterone	$P2_12_12_1$	12.56	13.80	10.34	90.00	1.166	–
β_min	$P2_12_12_1$	12.88	13.92	10.55	90.00	1.103	−5.47

[a] Data are also included for the force field minimised counterparts of these crystal structures: A_min, B_min, α_min and β_min. Unit cell dimensions are given in Å, *β*-angles in °, density, *ρ*, in g/cm^3, energy in kcal/mol.

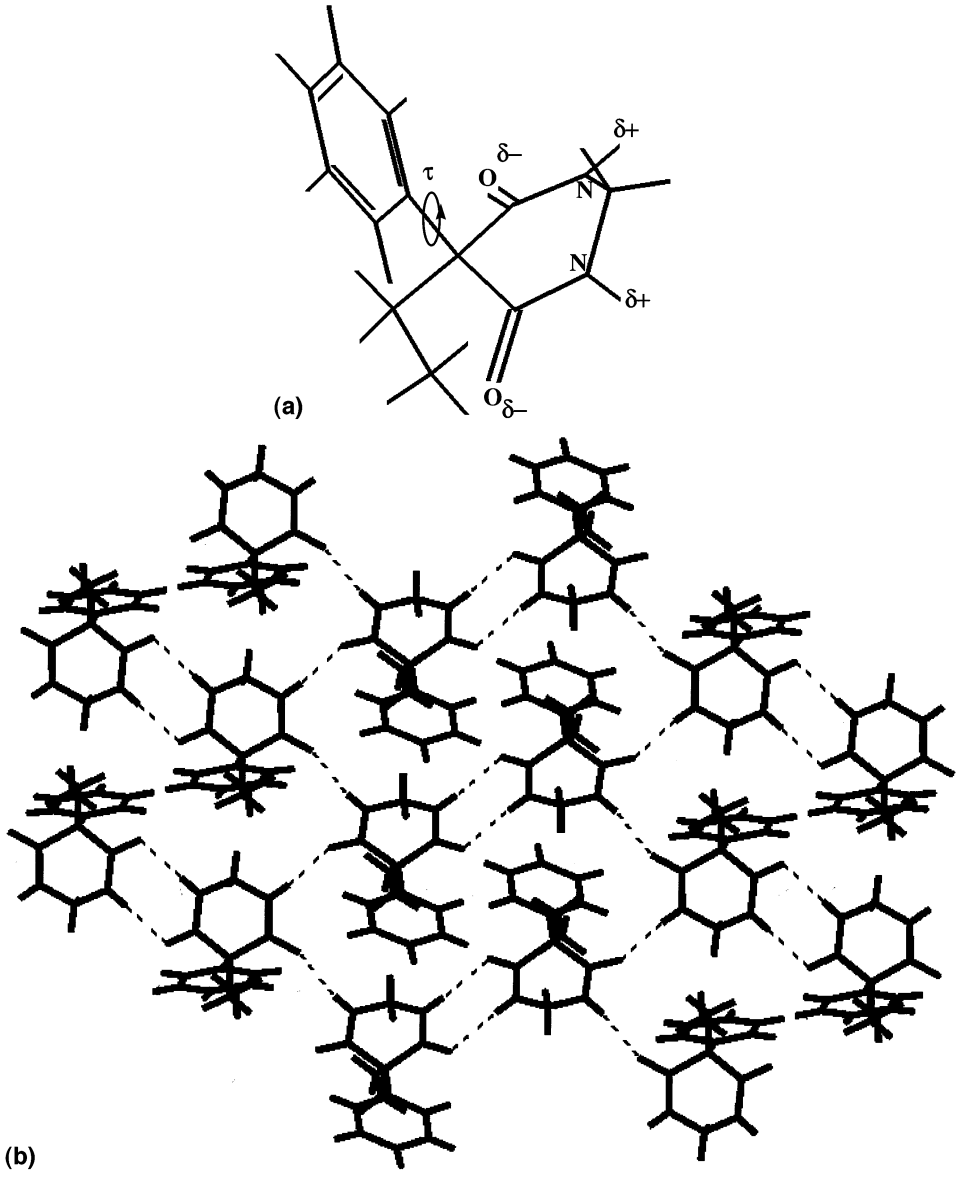

Fig. 1. (a) The molecular structure of primidone. (b) The hydrogen bonding motifs of primidone A. (c) The hydrogen bonding motifs of primidone B.

sheets of molecules. Form B has one type of hydrogen bond forming sheets.

Progesterone is a steroid used to treat abnormalities of the menstrual cycle and pregnancy. It exists in two crystal forms of equal physiological activity, which are readily interconverted. The α-form has the highest melting point (129°C compared with 121°C for β). It therefore might be expected to be the most thermodynamically stable. The relative stability of the two forms is confirmed by the work of Muramatsu et al. (1979), who reported α to be 1.1 kcal/mol more stable than β. They also stated that the conformational differences between molecules in the two forms are very small. The α-form is orthorhombic and tends to a prismatic morphology. The crystal

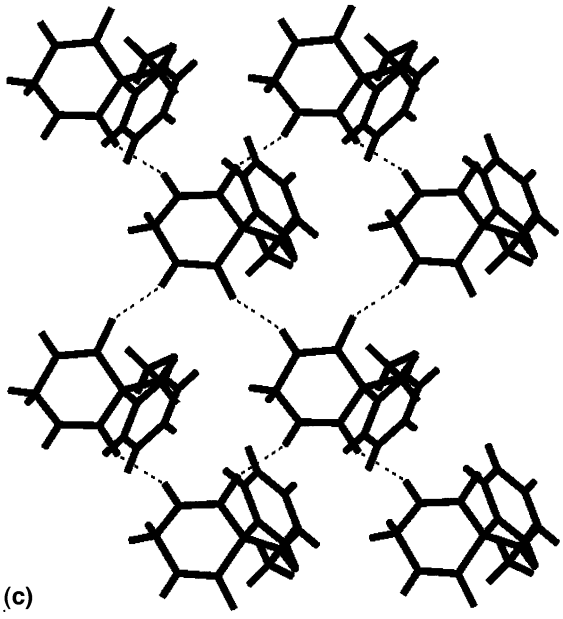

Fig. 1. (*Continued*)

structure of α-progesterone is available as refcode PROGST01 in the CSD. The β-form is also orthorhombic, but its crystals are needle-like. Its crystal structure is refcode PROGST10 in the CSD (Campsteyn et al., 1972). Some crystallographic information regarding these forms is contained in Table 1. The molecular structure of progesterone is shown in Fig. 2a, whilst the crystal structures of the two forms are shown in Fig. 2b Fig. 2c. Neither form contains molecular interactions that would normally be regarded as hydrogen bonds, because, whilst progesterone has ketone hydrogen bond acceptors, it has no conventional hydrogen bond donors.

3. The process of polymorph prediction

The generation of potential polymorphs for a particular molecule requires a process that will identify a set of most stable crystal structures. In C^2 Polymorph this process is addressed by attempting to generate all possible structures and then ranking them according to their energy, those with the lowest energy being the most stable.

The first stage of the process is to choose a molecular conformation to enter into the program. In making this choice the following questions should be asked:

- Is the molecule flexible?
- Does this lead to a number of potential conformers which differ with regards to building a crystal structure?
- Should the conformer(s) be optimised?
- To what level of theory should optimisation take place?

If the molecule is inflexible there will be only one conformation to deal with and the choice comes down to one of optimisation. If it is flexible, it may be possible to decide on the conformation(s) that should be packed. This is achieved by mapping energy as a function of torsion angles about rotatable bonds (see, for example, Payne et al., 1998b), or employing other tools for conformational analysis (see, for example, Kolossvary and Guida, 1996; Gianpaolo et al., 1997; Weiser et al., 1997). The amount of time spent in predicting polymorphs will be directly proportional to the number of conformers chosen. It is recommended that a chosen conformer is optimised using high level quantum mechanics (QM) calcu-

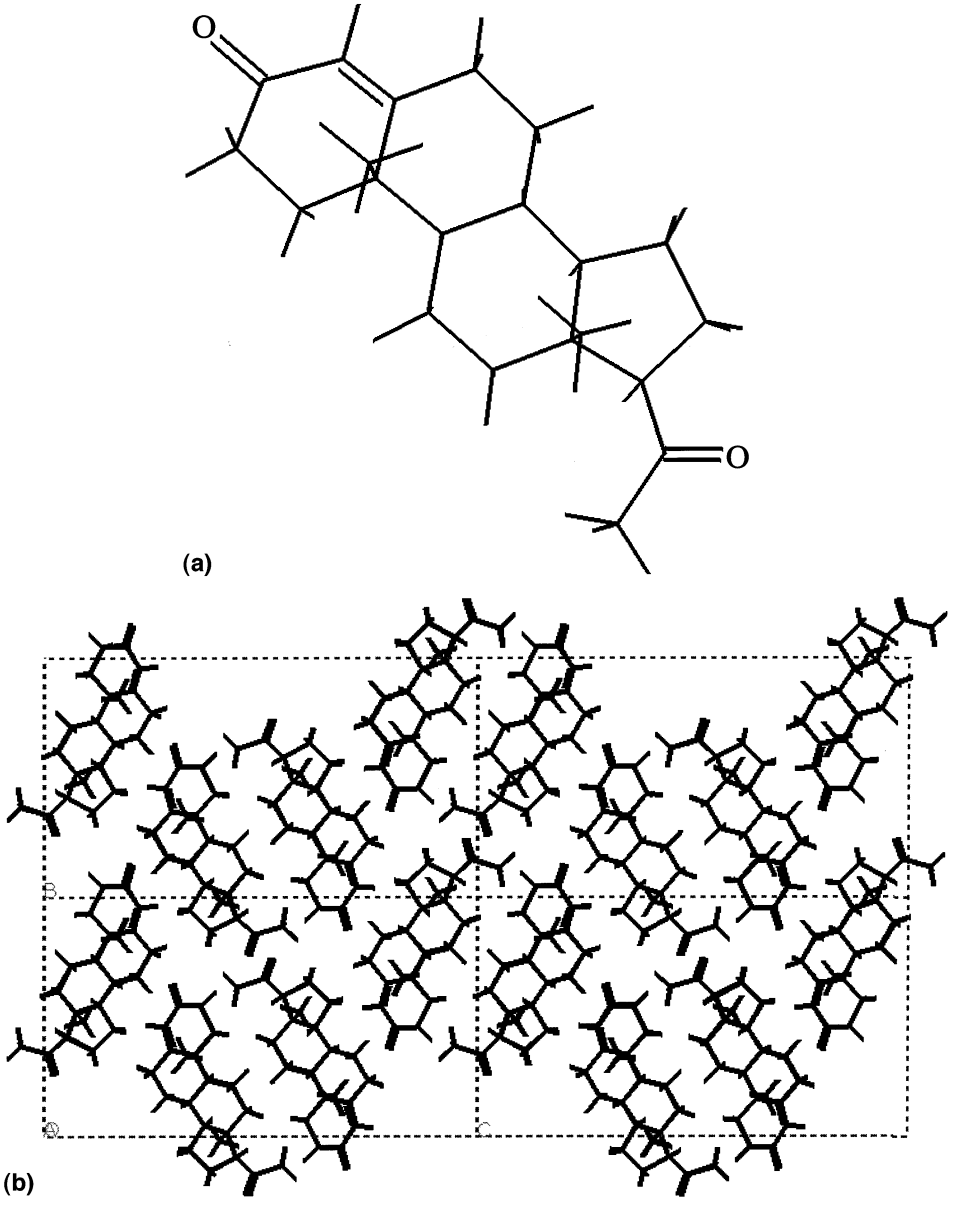

Fig. 2. (a) The molecular structure of progesterone. (b) The crystal structure of α-progesterone. (c) The crystal structure of β-progesterone.

lations so that bond lengths and angles are set to appropriate theoretical values (Karfunkel and Gdanitz, 1992). Here, conformers are optimised according to the restricted Hartree–Fock formalism (RHF) at the 6-31G** level, using the QM program Gaussian92 (Frisch et al., 1993). It is worth noting, however, since a later stage of the prediction process involves applying an empirical 'force field' to the molecular geometry, that this level of optimisation seems excessive and can take days of computer time (even for medium sized molecules with 30–50 atoms). Previously, detailed work on acetic acid brought the need for high level QM calculations into question (Payne et al., 1998a).

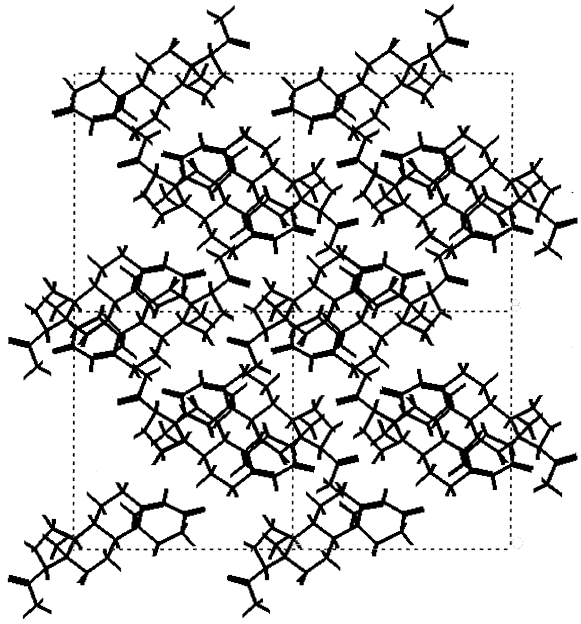

Fig. 2. (*Continued*)

A further consideration before making a predictive run is how to calculate the charges on individual atoms. Ideally, this is achieved using QM and fitting charges, located at the atom centres to the electrostatic potential (ESP) around the molecule. Such charges are termed 'ESP charges'.

The second stage of the prediction process is to generate thousands of crude crystal structures for a molecular conformer using a Monte Carlo (MC) search algorithm, in conjunction with simulated annealing (SA) and the Metropolis acceptance criterion. The Dreiding 2.21 empirical force field is used to measure the relative stability of structures (Mayo et al., 1990) and the electrostatics are based on the atom-centred charges. The search is constrained by the symmetry operations of a chosen space group. There are three important parameters that can be set by the user at this stage of the process:

- N_accept: the number of structures that are accepted for the system to be considered a 'melt'.
- Heat_Factor: defines the rate of heating during the attainment of a 'melt'.
- Cool_Factor: similarly defines the rate of cooling. This parameter is particularly important, as it affects the number of MC moves per unit temperature of SA. Reducing Cool_Factor increases the probability of locating all possible structures.

The values used for these parameters, and others governing the predictive method, are listed in Table 2.

The MC–SA procedure can generate many thousands of crude structures of which a significant number will be similar. Thus, a 'clustering' process is applied to reduce the number of struc-

Table 2
The values used for important C^2 Polymorph user-definable parameters in all structure prediction runs described in this paper

Parameter	Value
N_accept	12
Heat_Factor	0.025
Cool_Factor	0.002
Tolerance	0.15
RMSF	0.001

Table 3
Information on the ten most stable structures predicted using the primidone A conformer in $P2_1/c$[a]

Frame number	*a*	*b*	*c*	*β*	*ρ*	Energy	Similarity versus form A	Similarity versus A_min
1	10.20	16.72	6.98	92.31	1.219	−298.9	0.251	0.255
2	7.72	21.62	7.11	99.76	1.239	−298.4	0.234	0.218
3	7.12	21.84	7.68	79.33	1.235	−298.1	0.247	0.227
4	15.30	11.17	6.88	100.15	1.252	−297.6	0.294	0.305
5	15.30	11.17	6.88	100.15	1.252	−297.6	0.239	0.241
6	7.69	21.67	7.31	72.80	1.246	−297.4	0.222	0.224
7	11.64	7.44	14.56	64.84	1.271	−297.1	0.229	0.185
8	11.62	11.36	9.11	97.05	1.215	−296.9	0.249	0.232
9	9.11	11.37	11.63	95.48	1.210	−296.9	0.264	0.252
10	12.12	9.77	10.90	73.38	1.172	−296.5	0.441	0.446

[a] Unit cell dimensions are given in Å, β-angles in °, density, ρ, in g/cm^3, energy in kcal/mol.

tures. The important parameter for clustering is termed 'tolerance'. The lower this value, the more similar a structure must be to the reference structure to be deemed to have the same packing arrangement. Its value would ideally cluster structures that would fall into the same minimum on the potential energy hypersurface—i.e. represent the same final crystal structure.

Next, each crude structure which survives clustering is subjected to energy minimisation, using Dreiding 2.21, in which all of the degrees of freedom, including the conformation of the molecule and the unit cell parameters, are allowed to relax. The symmetry elements of the chosen space group are retained. Minimisation terminates after a user-defined level of RMSF, the root mean squared force for convergence (see Table 2). The effectiveness of a force field can be gauged by comparing the unit cell parameters of a known crystal structure with those of the force field minimised crystal structure. Changes of less than 5% are generally accepted as an indication that the force field performs well for the structure in question. Table 1 contains the values of these parameters for primidone A, primidone B, α-progesterone, β-progesterone and their minimised counterparts: A_min, B_min, α_min and β_min. It demonstrates that Dreiding 2.21 is an acceptable force field. It has known limitations (Payne et al., 1998a,b), but was the only available option for C[2] Polymorph when this work was initiated.

Primidone has a number of rotatable bonds, one of which adopts a significantly different torsion value in the known forms (see τ in Fig. 1a). In primidone A, τ is 27.4°, whilst in primidone B it is 68.4°. In this study RHF/6-31G** optimised versions of these conformers were used in the pursuit of the known forms. Separate predictive runs were required for A and B, as they occupy different space groups ($P2_1/c$ and Pbca, respectively). The significance of the conformational flexibility of this molecule was tested subsequently, by seeking form A in $P2_1/c$, with the conformer of form A.

Progesterone, typically for a steroid, has limited flexibility. As a consequence, the conformers in the α- and β-forms are similar enough that they were considered identical for the purpose of polymorph prediction. Both forms were sought using the optimised crystal structure conformer of α. Since α and β occupy the same space group, $P2_12_12_1$, it was possible to search for both polymorphs simultaneously.

The similarity of a predicted structure to a known form was calculated using a 'similarity' measure described in the Cerius[2] program manual as "examining the partial radial distribution functions between pairs of force field atom types of the two structures being compared" (Molecular Simulations Inc, 1995). The smaller the value of this similarity measure, the more similar are the structures being compared.

4. Results and discussion

4.1. Primidone

An initial view of structures generated when the optimised crystal structure conformer of primidone A was used to predict in $P2_1/c$ was disappointing. It was evident that:

- The first few structures had unit cell parameters, which were quite different to those of form A.
- A visual comparison of X-ray powder patterns for the 20 most stable predicted structures with the pattern of form A did not reveal close similarities.
- Similarity measures for the predicted structures versus the crystal structure of form A produced high values (> 0.2).

Table 3 contains the unit cell parameters and similarity measures for the ten most stable predicted structures from this run.

However, further investigation suggested that the predictive run had located a structure close to that of form A. Frame 7 (the seventh most stable predicted structure) had:

- Unit cell parameters close to form A and almost identical to form A_min.
- A powder pattern almost identical to that of A_min.
- A similarity measure of < 0.2 versus A_min.

Fig. 3 contains a comparison of the powder patterns of form A, A_min and frame 7. When the molecular model of frame 7 is appropriately oriented, it is seen to have the same packing arrangement as form A. An important conclusion from these observations is that, whilst the packing arrangement of form A was located by C^2 Polymorph, it would have been difficult to recognise this fact from readily available experimental data—i.e. an X-ray powder pattern from form A. However, once the most similar structure had been recognised, it was possible to obtain a better fit to the powder pattern of form A, using the process known as Rietveld refinement (Young, 1993). This process automatically modifies unit cell and other parameters to minimise the least square difference (R factor) between an experimental powder pattern and that simulated for a given packing arrangement. This process was carried out using frame 7 refined against the powder pattern of form A (Fig. 4) over the range shown, varying background, zero point and peak shape (the relative atomic co-ordinates were not varied). This gave an R factor of 25% after 200 iterations. Despite the fact that this final R factor is still rather poor, qualitatively at least by visual inspection of the powder patterns, there does seem to be reasonable agreement (Fig. 4). It was not thought necessary to further refine the structure in view of

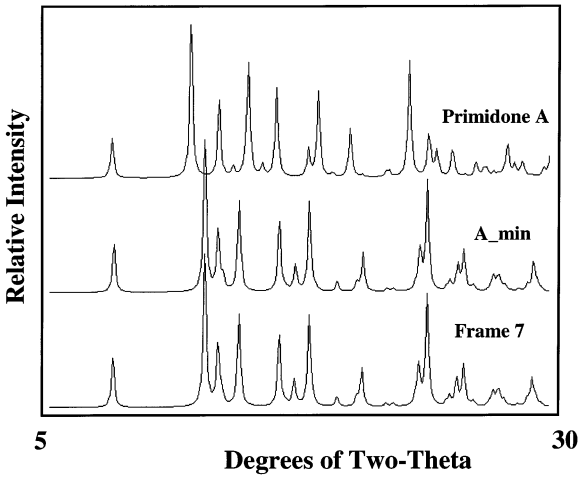

Fig. 3. A comparison of the simulated X-ray powder patterns of primidone A, A_min and frame 7 from Table 3.

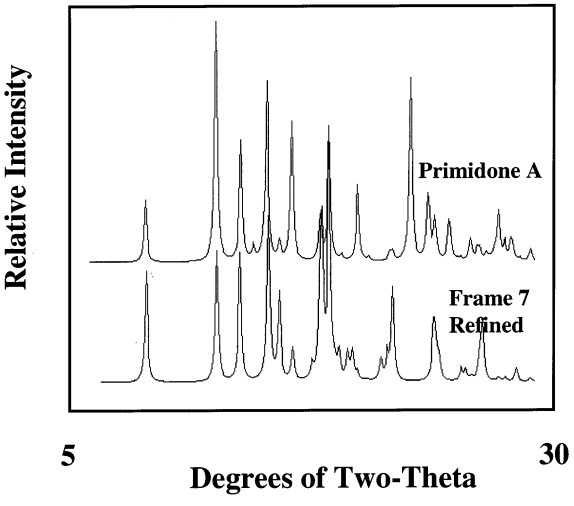

Fig. 4. The results of Rietveld refinement on frame 7 with respect to the simulated X-ray powder pattern of primidone A.

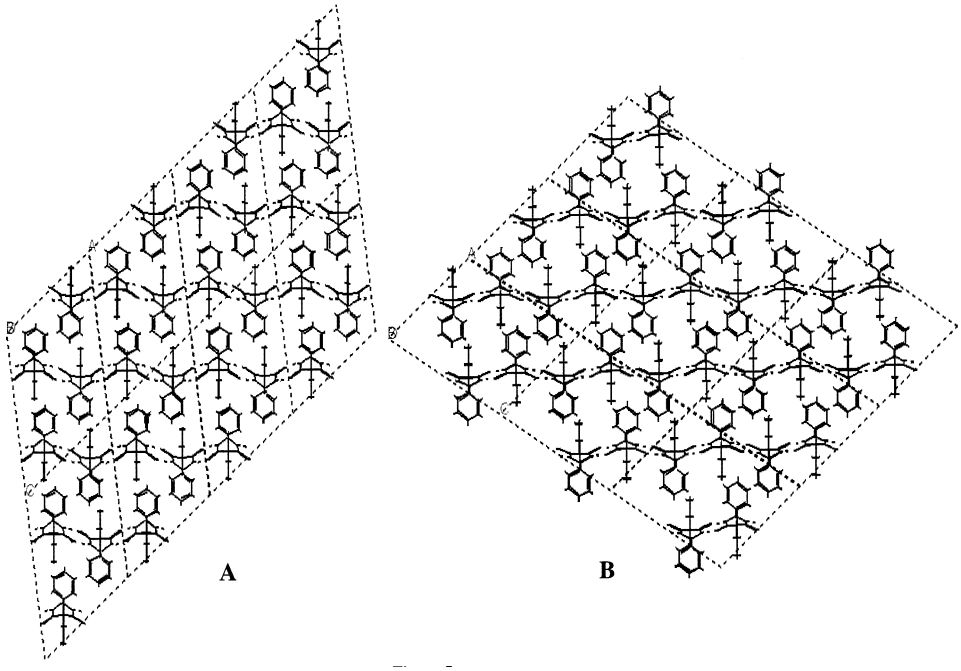

Fig. 5. Comparison of the crystal structure of primidone A (A) versus the most likely packing arrangement, frame 7 (B).

Table 4
Information on the ten most stable structures predicted using the primidone B conformer in Pbca[a]

Frame number	*a*	*b*	*c*	ρ	Energy	Similarity versus form B	Similarity versus B_min
1	13.83	21.53	7.67	1.270	−290.7	0.234	0.233
2	28.29	10.38	7.70	1.283	−290.5	0.253	0.163
3	21.46	7.68	13.82	1.273	−290.5	0.256	0.237
4	13.95	21.20	7.60	1.289	−289.5	0.258	0.206
5	21.55	7.49	14.26	1.260	−289.2	0.263	0.238
6	7.75	11.99	26.59	1.174	−289.1	0.292	0.265
7	29.32	10.28	7.66	1.256	−288.0	0.258	0.212
8	11.99	27.19	7.87	1.130	−288.0	0.287	0.252
9	21.46	11.71	10.01	1.153	−287.8	0.267	0.253
10	7.64	28.09	10.80	1.252	−287.5	0.258	0.208

[a] Unit cell dimensions are given in Å, density, ρ, in g/cm^3, energy in kcal/mol.

the low quality of the powder pattern which was obtained from a laboratory instrument (Siemens D5000 using Bragg–Brentano geometry). To add further evidence that the frame 7 is the same structure as the crystal structure, the two structures are shown side by side in Fig. 5 for comparison. These show excellent agreement, having the same hydrogen bonding pattern, but in the predicted structure (frame 7) the chains are tilted slightly more into the plane of the paper. It should be noted that the cell angle β for the crystal structure is 117.82° (Table 1) and that for frame 7 is 64.84° (Table 3), reflecting the different appearance of the unit cell in Fig. 5.

The packing arrangement of primidone form B was located as frame 2 when the optimised form B conformer was used to predict in Pbca. It should be noted that the unit cell lengths for

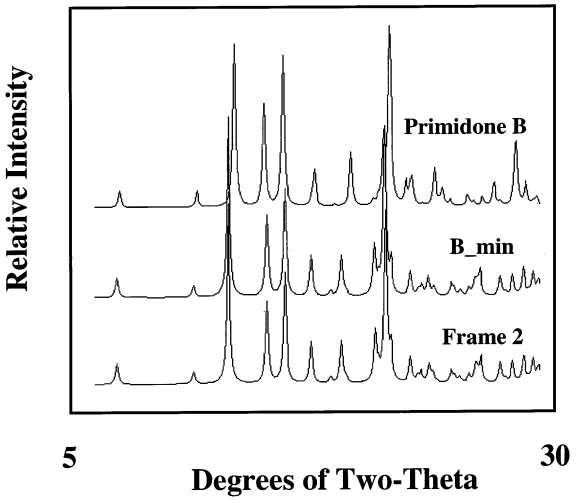

Fig. 6. A comparison of the simulated X-ray powder patterns of primidone B, B_min and frame 2 from Table 4.

frame 2 are virtually identical in value to B_min, but are switched around. These are in fact the same crystal structures but with different settings of the same space group, Pbca. This is confirmed by the data in Table 4 and the powder patterns in Fig. 6.

Prediction with the B conformer in $P2_1/c$ located the packing arrangement of form A, again in seventh place in the stability ranking (see Table 5 and Fig. 3). Note should be taken of the fact that other structures located in this run were different from those listed in Table 3. Thus, if the aim of the work had been to generate an exhaustive list of possible structures for primidone in $P2_1/c$, it would not have been achieved in one predictive run. Indeed, it is not possible to be sure that the two runs reported here achieve this aim. This irreproducibility of predictive runs has been observed before (Payne et al., 1998a,b), and can be rationalised in terms of the stochastic nature of the MC methodology employed in the predictive method. The problem is compounded for molecules of increasing size and flexibility. The concern remains as to how a user knows when a search for alternative polymorphs is complete: multiple runs using the same search parameters may be required until new structures cease to be located.

Table 6
Information on the ten most stable structures from a first predictive run using the force field optimised, α-progesterone conformer in $P2_12_12_1$[a]

Frame number	*a*	*b*	*c*	*ρ*	Energy
1	12.80	6.48	22.49	1.120	−5.68
2	10.52	12.94	13.93	1.102	−5.47
3	13.01	9.94	14.83	1.089	−5.38
4	8.49	18.79	11.80	1.109	−5.37
5	21.24	7.60	11.55	1.120	−5.37
6	12.80	23.26	6.24	1.125	−5.37
7	15.85	15.31	7.89	1.091	−5.2
8	7.20	14.48	18.30	1.095	−5.19
9	12.96	9.97	14.84	1.089	−5.18
10	6.50	10.13	28.99	1.094	−5.18

[a] Unit cell dimensions are given in Å, density, *ρ*, in g/cm^3, energy in kcal/mol.

Table 5
Information on the ten most stable structures predicted using the primidone B conformer in $P2_1/c$[a]

Frame number	*a*	*b*	*c*	*β*	*ρ*	Energy	Similarity versus form A	Similarity versus A_min
1	7.13	21.85	7.65	101.40	1.235	−290.6	0.232	0.227
2	6.93	16.80	10.21	87.33	1.221	−290.4	0.260	0.273
3	7.14	21.70	7.71	100.50	1.235	−290.4	0.246	0.215
4	7.67	21.63	7.28	106.80	1.254	−290.0	0.242	0.241
5	9.11	11.34	11.61	95.28	1.214	−289.8	0.329	0.331
6	9.12	11.34	11.61	84.35	1.214	−289.7	0.257	0.257
7	11.61	7.44	14.50	64.74	1.280	−289.7	0.245	0.182
8	13.89	7.52	11.43	104.45	1.254	−289.4	0.254	0.243
9	14.01	7.47	11.32	75.68	1.264	−289.3	0.248	0.249
10	10.86	9.77	12.07	106.38	1.179	−288.4	0.235	0.230

[a] Unit cell dimensions are given in Å, *β*-angles in °, density, *ρ*, in g/cm^3, energy in kcal/mol.

The ability to predict two polymorphs with the conformer of one indicates that there is little or no energy barrier between them. This ability is partly due to a predictive process that includes sufficient flexibility for a molecule to adopt either conformation, depending on the influences that adjacent molecules in the crystal structure have on each other. In a previous paper it was shown that an energy barrier of ≈ 4 kcal/mol (as calculated using Dreiding 2.21) between conformers of aspirin could not be surmounted by C^2 Polymorph. For primidone, calculations of the gas phase energy of the molecule as a function of torsional differences indicate that there is no barrier between the conformers of forms A and B.

4.2. Progesterone

A first predictive run, using the optimised conformation of α-progesterone in $P2_12_12_1$, did not locate crystal structures similar (i.e. with similarity measures < 0.2) to either of the known polymorphs. A second identical run also failed to locate the known crystal structures.

As an exploratory trial, an α-form conformer (no charges assigned) was minimised using Dreiding 2.21, and RHF/6-31G** ESP charges were calculated for its atomic centres. A first predictive run with this conformer yielded the ten most stable structures whose unit cell parameters are contained in Table 6.These data suggest that the run located structures which are similar to α_min and β_min as frames 1 and 2, respectively. This suggestion is supported by the plots of similarity measures, α versus α_min, β and β_min in Fig. 7. Although it should be noted that for the similarity measure of the α-form versus α_min is much higher > 0.2 than that for the β-form (Fig. 7). This cannot be explained, since one might expect the α-form to have a lower similarity measure. because the starting structure used was the α-conformation/charges. Fig. 8a and Fig. 8b can be compared to Fig. 2b and Fig. 2c, respectively, to show that the packing arrangements of these predicted structures are very similar to those of the known polymorphs. A second predictive run with this 'Dreiding' conformer was performed, using precisely the same starting conditions as the first. The similarity measures for this run are given in Fig. 9. Unit cell parameters for this set of predicted structures are contained in Table 7. Although the results of this second run are qualitatively similar to those of the first, a structure similar to α_min being located as frame 1,

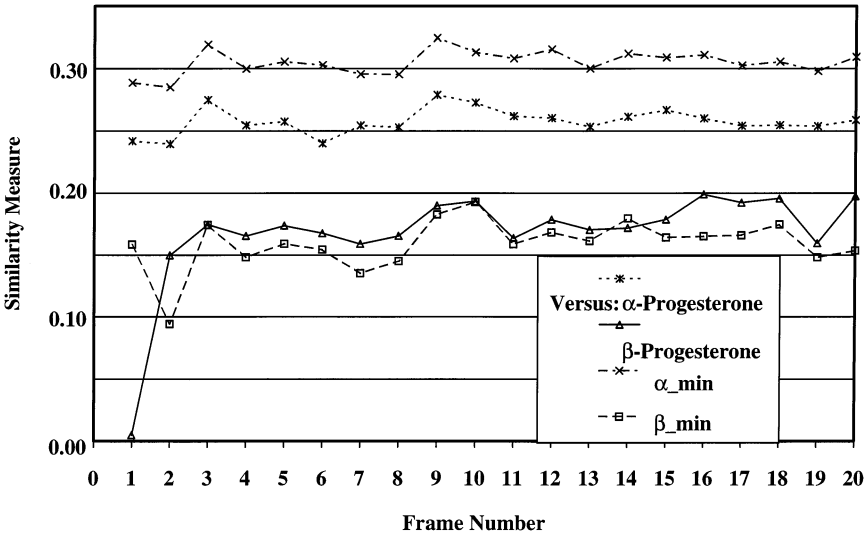

Fig. 7. The similarity measures against α-progesterone, α_min, β-progesterone and β_min for the 20 most stable structures from a first predictive run using the α-progesterone conformer in $P2_12_12_1$.

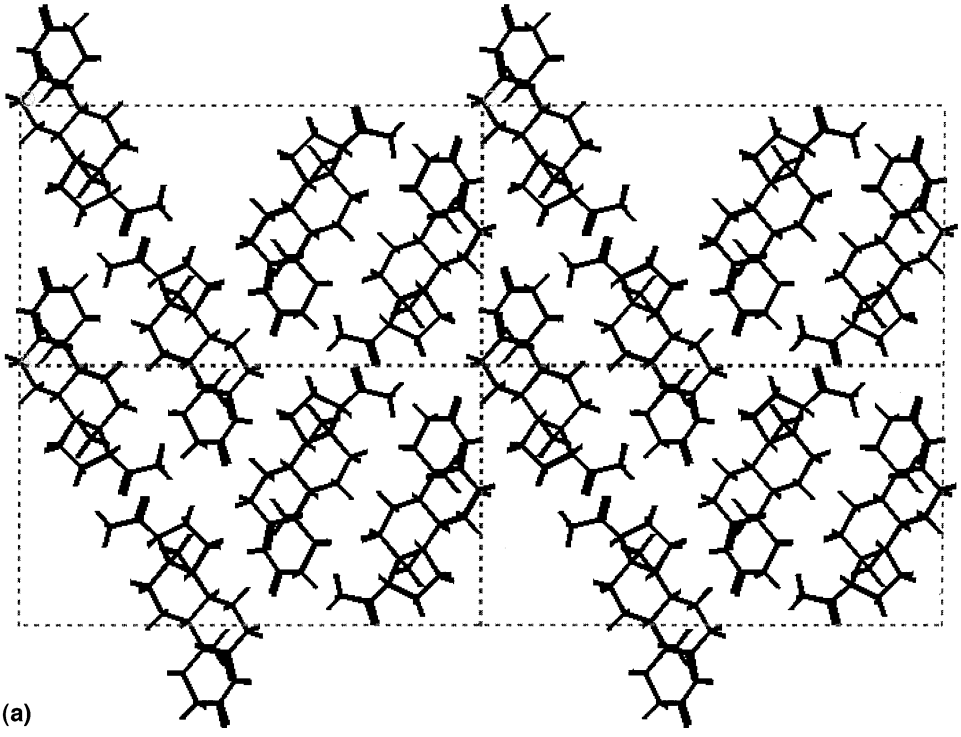

Fig. 8. (a) The structure of frame 1 from Table 6. (b) The structure of frame 2 from Table 6.

frames 3 and 4 exhibit similarity to β_min. Thus, as frame 2 in the second run is new, it is clear that the original run was not exhaustive. Further, the frames ranked 1 and 4 by energy in the second run are subtly different to those associated with α and β in the first run. These observations suggest that:

- The clustering process, as applied to these studies, is more discriminating than would be ideal for locating structures that be known or be realisable experimentally. This is in keeping with previously reported comments regarding an approach of grouping predicted structures visually by way of their packing arrangement when seeking distinct polymorphic forms (Payne et al., 1998a,b).
- It is not always critical to optimise a conformation using high level QM methods to locate potential polymorphs of a compound.
- These predictive runs do not represent an exhaustive search. There are likely to be more crystal structures that C2 Polymorph can locate for progesterone, even in $P2_12_12_1$.

Although two initial runs with a QM optimised conformation were unsuccessful, two successive runs with a force field optimised conformation located the known polymorphs. The stochastic nature of the predictive process means that it is not possible to conclude that one conformation was better for the process than the other. Further prediction with the QM optimised conformer might have located the known polymorphs.

5. Conclusions

- The packing arrangements of all four crystal forms discussed in this paper were located by C^2 Polymorph.
- It would have been difficult to identify the correct packing arrangements by comparison with experimental X-ray powder data alone—i.e. if crystal structure and hence minimised crystal structures had not been available a priori.

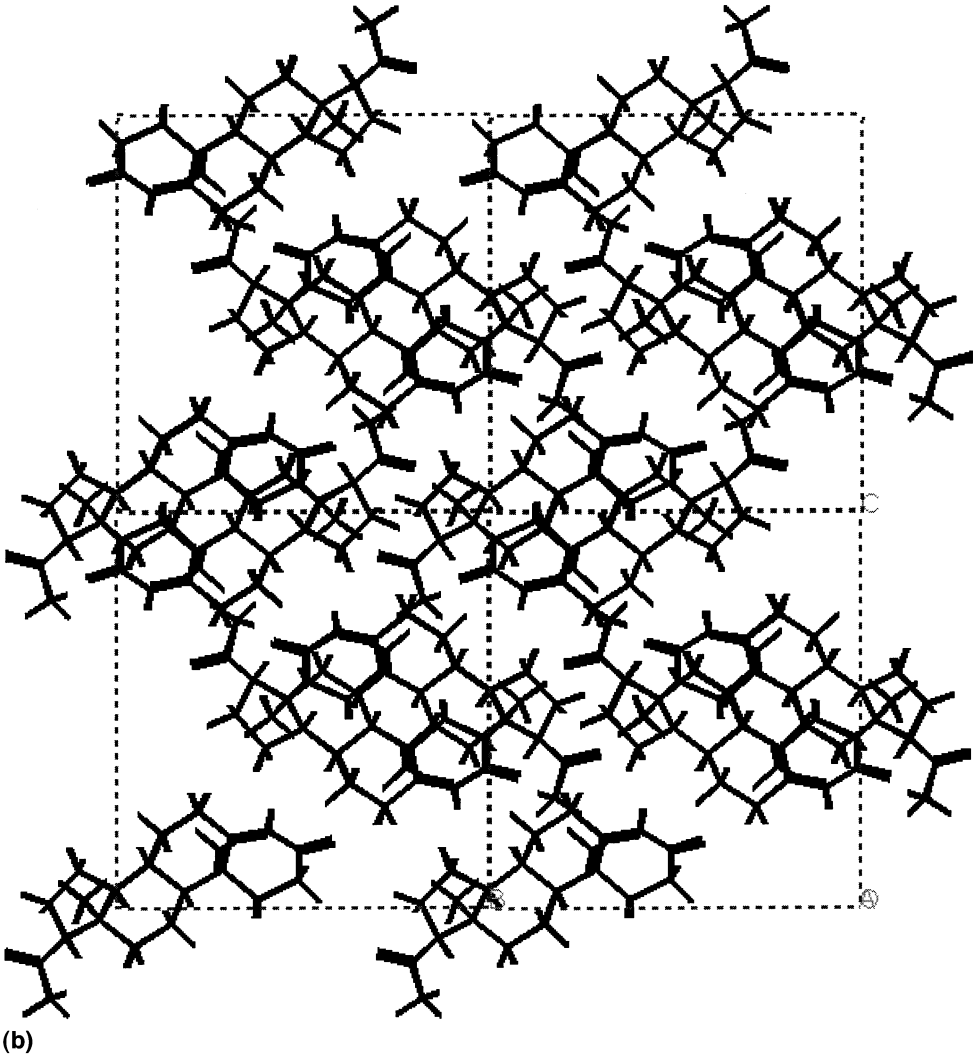

Fig. 8. (*Continued*)

- Once located, the correct packing arrangement could be refined to produce a crystal structure approaching that of the known form, using Rietveld refinement.
- The predictive runs reported here do not represent an exhaustive list of the structures C^2 Polymorph is capable of generating in the chosen space groups. Prediction of all potential forms would require multiple runs in these and other space groups.
- For primidone, it was possible to locate both known polymorphs using the conformer of form B. This would not necessarily be true in general for polymorphs with conformational differences.
- For progesterone, a force field optimised conformer was an adequate molecular starting point for the predictive methodology to locate both known polymorphs.

In general, the work reported here has shown

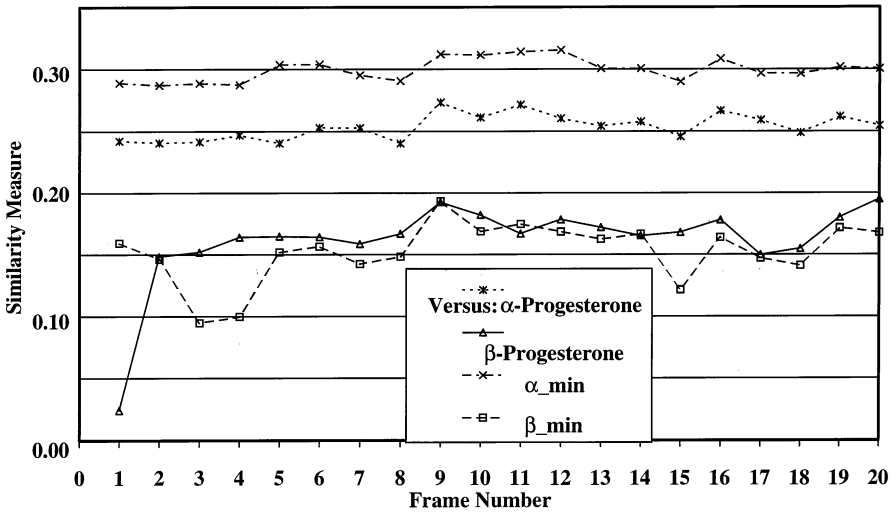

Fig. 9. The similarity measures against α-progesterone, α_min, β-progesterone and β_min for the 20 most stable structures from a second predictive run using the α-progesterone conformer in $P2_12_12_1$.

that polymorph prediction, using the method of Gdanitz (1992), offers an opportunity to investigate the potential crystal structures that a particular compound might adopt. However, there are a number of observations that demonstrate the need for considerable thought in its application and further development of the method.

Table 7
Information on the ten most stable structures from a second predictive run using the force field optimised α-progesterone conformer in $P2_12_12_1$[a]

Frame number	*a*	*b*	*c*	*ρ*	Energy
1	22.48	6.48	12.80	1.120	−5.68
2	12.81	6.49	22.45	1.118	−5.65
3	12.94	10.52	13.93	1.102	−5.47
4	13.01	10.47	13.92	1.101	−5.47
5	23.26	6.24	12.80	1.125	−5.33
6	22.43	10.40	8.22	1.090	−5.27
7	18.30	14.48	7.20	1.095	−5.19
8	13.62	7.43	18.96	1.088	−5.18
9	28.99	10.13	6.50	1.094	−5.18
10	12.80	19.96	7.52	1.087	−5.17

[a] Unit cell dimensions are given in Å, density, ρ, in g/cm^3, energy in kcal/mol.

References

Boon, W.R., Carrington, H.C. and Vasey, C.H., 1951. US Patent 2,578,847.

Cambridge Crystallographic Data Centre, 1998. QUEST3D. Cambridge Crystallographic Data Centre, Cambridge.

Campsteyn, H., Dupont, L., Dideberg, O., 1972. Crystal and molecular structure of progesterone. Acta Crystallogr. B 28, 3032–3042.

Catlow, R.A., Thomas, J.M., Freeman, C.M., Wright, P.A., Bell, R.G., 1993. Simulating and predicting crystal structures. Proc. R. Soc. London Ser. A 442, 85–96.

Chaka, A.M., Zaniewski, R., Youngs, W., Tessier, C., Klopman, G., 1996. Predicting the crystal structure of organic molecular materials. Acta Crystallogr. B 52, 165–183.

Chang, Y.-L., West, M.-A., Fowler, F.W., Lauher, J.W., 1993. An approach to the design of molecular solids. Strategies for controlling the assembly of molecules into two-dimensional layered structures. J. Am. Chem. Soc. 115, 5991–6000.

Daley, R.D., 1973. Primidone. In: Florey, K. (Ed.), Analytical Profiles of Drug Substances, vol. 2. Academic Press, New York, pp. 409–437.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Gill, P.M.W., Johnson, B.G., Wong, M.W., Foresman, J.B., Robb, M.A., Head-Gordan, M., Replogle, E.S., Gomperts, R., Andres, J.L., Raghavachari, K., Binkley, J.S., Gonzalez, C., Martin, R.L., Fox, D.J., Defrees, D.J., Baker, J., Stewart, J.J.P., Pople, J.A., 1993. Gaussian 92/DFT, Revision G.1. Gaussian, Inc, Pittsburgh, PA.

Gavezzotti, A., 1991. Generation of possible crystal structures from the molecular structure for low-polarity organic compounds. J. Am. Chem. Soc. 113, 4622–4629.

Gavezzotti, A., 1994. Are crystal structures predictable? Acc. Chem. Res. 27, 309–314.

Gavezzotti, A., Filippini, G., Kroon, J., Van Eijck, B.P., Klewinghaus, P., 1997. The crystal polymorphism of tetrolic acid ($CH_3C \equiv CCOOH$): a molecular dynamics study of precursors in solution, and a crystal structure generation. Chem. Eur. J. 3, 893–899.

Gdanitz, R.J., 1992. Prediction of molecular crystal structures by Monte Carlo simulated annealing without reference to diffraction data. Chem. Phys. Lett. 190, 391–396.

Gdanitz, R.J., Karfunkel, H.R., Leusen, F.J.J., 1993. The prediction of yet-unknown molecular crystal structures by solving the packing problem. J. Mol. Graph. 11, 275–276.

Gianpaolo, B., Emanuela, G., Zaliani, M.P., 1997. SONHICA (simple optimized non-hierarchical cluster analysis): a new tool for analysis of molecular conformations. J. Comp. Chem. 18, 1295–1311.

Holden, J.R., Du, Z., Ammon, H.L., 1993. Prediction of possible crystal structures for C-, H-, N-, O-, and F-containing organic compounds. J. Comp. Chem. 14, 422–437.

Karfunkel, H.R., Gdanitz, R.J., 1992. Ab initio prediction of possible crystal structures for general organic molecules. J. Comp. Chem. 13, 1171–1183.

Karfunkel, H.R., Leusen, F.J.J., 1992. Practical aspects of predicting possible crystal structures on the basis of molecular information only. Speedup J. 6, 43–50.

Kolossvary, I., Guida, W.C., 1996. Low mode search. An efficient, automated computational method for conformational analysis: application to cyclic and acyclic alkanes and cyclic peptides. J. Am. Chem. Soc. 118, 5011–5019.

Leusen, F.J.J., 1996. Ab initio prediction of polymorphs. J. Cryst. Growth 166, 900–903.

Mayo, S.L., Olafson, B.D., Goddard, W.A., 1990. DREIDING: a generic force field for molecular simulations. J. Phys. Chem. 94, 8897–8909.

Molecular Simulations Inc, 1995. Cerius^2, Release 2.0. Molecular Simulations Inc, San Diego, CA.

Muramatsu, M., Iwahashi, M., Takeuchi, U., 1979. Thermodynamic relationship between α- and β-forms of crystalline progesterone. J. Pharm. Sci. 68, 175–177.

Payne, R.S., Roberts, R.J., Rowe, R.C., McPartlin, M., Bashal, A., 1996. The mechanical properties of two forms of primidone predicted from their crystal structures. Int. J. Pharm. 145, 165–173.

Payne, R.S., Roberts, R.J., Rowe, R.C., Docherty, R., 1998. The generation of crystal structures of acetic acid and its halogenated analogues. J. Comp. Chem. 19, 1–20.

Payne, R.S., Rowe, R.C., Roberts, R.J., Charlton, M.H. and Docherty, R., 1998b. Potential polymorphs of aspirin. J. Comp. Chem. (in press).

Perlstein, J., 1992. Molecular self-assemblies: Monte Carlo predictions for the structure of the one-dimensional translation aggregate. J. Am. Chem. Soc. 114, 1955–1963.

Shoda, T., Yamahara, K., Okazaki, K., Williams, D.E., 1995. Molecular packing analysis of benzene crystals. Part 2. Prediction of experimental crystal structure polymorphs at low and high pressure. J. Mol. Struct. 333, 267–274.

Summers, M.P., Enever, R.P., 1976. Prepartion and properties of solid dispersion system containing citric acid and primidone. J. Pharm. Sci. 65, 1613–1617.

Van Eijck, B.P., Mooij, W.T.M., Kroon, J., 1995. Attempted prediction of the crystal structures of six monosaccharides. Acta Crystallogr. B 51, 99–103.

Van Eijck, B.P., Kroon, J., 1997. Fast clustering of equivalent structures in crystal structure prediction. J. Comp. Chem. 18, 1036–1042.

Weiser, J., Holthausen, M.C., Fitjer, L., 1997. HUNTER: a conformational search program for acyclic to polycyclic molecules with special emphasis on stereochemistry'. J. Comp. Chem. 18, 1264–1281.

Yeates, D.G.R., Palmer, R.A., 1975. The crystal structure of primidone. Acta Crystallogr. B 31, 1077–1082.

Young, R.A. (Ed.), 1993. The Rietveld Method. Oxford University Press, Oxford.

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