

Crystal structure predictions for disordered halobenzenes

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Two existing force fields were adjusted for optimal reproduction of the crystal structures and lattice energies of halogenated benzenes and naphthalenes. Crystal structure predictions, including structures with two independent molecules, were made for 21 compounds. It was found that the two force fields, with different functional forms, led to comparable values for the energy of the experimental structures with respect to the global energy minima. These force fields were used for the prediction of disorder in *para*-substituted benzenes, without using other experimental data. This was done by artificially creating disorder in the most promising hypothetical ordered structures, and comparing the excess energy with $RT \ln 2$. Predictions of the occurrence of orientational disorder in asymmetrically substituted compounds were in agreement with experimental evidence. A comparable approach was followed to study the possibility of mixed crystals consisting of two symmetrically substituted *para*-dihalobenzenes. It appeared to be possible to estimate the randomization energy for mixtures consisting of two isomorphous compounds. However, the question whether or not such isomorphous compounds will exist in the real world could not be answered with the currently available force fields and methods.

1 Introduction

Most studies on *ab initio* crystal structure prediction have concentrated on structures which are well-ordered and homomolecular, a task which is already quite difficult.^{1,2} Yet disorder is not a rare phenomenon, and it is interesting to develop a computational model to predict its occurrence without using experimental information.

A related and more complex problem is the occurrence of mixed crystals. Heteromolecular structures have been studied for the special case of solvates.³ A solvate is just a special case of a cocrystal, with two widely different types of molecules. At the other extreme, where very similar compounds cocrystallize, an ordered cocrystal may be unfavourable with respect to a disordered mixed crystal.

Halogenated benzene derivatives are excellent simple model compounds. The *para*-substituted compounds PhClBr, PhClI and PhBrI all exhibit orientational disorder. For a symmetrically substituted compound like *p*-dibromobenzene this is, of course, impossible, but here the other case of disorder can be studied: there exists a complete range of randomly mixed crystals with the corresponding polymorph of dichlorobenzene. All structures mentioned in this paragraph are isomorphous.

Generating hypothetical disordered structures directly would be a computationally very demanding task. Rather than attempting such a fundamental approach, existing software can be used to create hypothetical well-ordered crystals as a starting point. Then a simplified model for a disordered structure can be made by taking a number of unit cells and creating the desired disorder by randomly rotating or interchanging molecules. The supercell thus obtained still forms an ordered crystal, but one can hope that it is a reasonable first approximation to the real situation.

Then, using a force field, the energies of the ordered and disordered crystals can be compared. The latter may well have a higher energy than the ordered crystal, but they will be favoured by the randomization entropy which can be easily estimated.

Generally, prediction of crystal structures is hampered by the inadequacy of the force fields used, as the energy differences between the various possible polymorphs are very small. We have argued in earlier work that this limitation is often more important than the neglect of effects of temperature and kinetics.⁴ For the detailed prediction of a disordered structure the same limitation applies, but one may hope that the occurrence of disorder itself is not sensitive to the choice of polymorph or to details of the force field. Therefore, two different force fields were used in the present work. It was found desirable to adjust the available atom–atom halogen potentials for the class of compounds studied.

2 Force field development

The simulation of chlorinated aromatic compounds has already been extensively studied, notably by the groups of Williams⁵ and Gavezzotti.⁶ Both used a Buckingham-type exponential repulsion, but Hsu and Williams included partial atomic charges whereas Filippini and Gavezzotti developed a chargeless potential. Because of the singularity at small interatomic distances neither potential can be used in our method of crystal structure generation, and to that end we used a Lennard-Jones potential based on Jorgensen and Severance's OPLS force field.⁷ Here the charges were estimated from electrostatic potential (ESP) fitting to *ab initio* wave functions for 1,4-dichlorobenzene (basis 6-31G*) and 1,4-dibromobenzene (basis STO6G).

Some parameters for chlorine and bromine, missing in the cited publications, were taken over from various sources in the literature. As a preliminary validation, energy minimizations were carried out on crystal structures of halogenated benzenes and naphthalenes. The substances and references to experimental data are given in Table 1. Enthalpies of sublimation were converted to lattice energies, considering the usual correction $2RT \approx 5.0 \text{ kJ mol}^{-1}$.⁸ The effect of the disorder in

Table 1 Substances used in the test set. ΔH is the sublimation enthalpy in kJ mol^{-1} , S (if present) denotes the symmetry of a special position occupied by the molecule, Z'' is the number of independent molecules

Substance	ΔH	Point group	S	Z''	Refcode
γ -1,4-Dichlorobenzene	66.01 ^a	$P2_1/c$	$\bar{1}$	1	DCLBEN03
α -1,4-Dichlorobenzene	64.75 ¹⁵	$P2_1/a$	$\bar{1}$	1	DCLBEN07
β -1,4-Dichlorobenzene	64.54 ^a	$P\bar{1}$	$\bar{1}$	1	DCLBEN06
1,2,4,5-Tetrachlorobenzene	83.20 ¹⁶	$P2_1/n$	$\bar{1}$	1	TCLBEN02
Pentachlorobenzene	87.12 ¹⁶	$Pca2_1$		1	PNCLBZ
1,2,3-Trichlorobenzene	75.1 ¹⁷	$P2_1/c$		2	TCBENZ
1,2,3,5-Tetrachlorobenzene	79.56 ¹⁶	$P2_1/c$		2	TCLBZN
1,3-Dichlorobenzene		$P2_1/c$		2	ABUM0Z
1,2-Dichlorobenzene		$P2_1/n$		1	ABUMIT
Hexachlorobenzene	90.50 ¹⁶	$P2_1/n$		1	HCLBNZ11
1,3,5-Trichlorobenzene	70.74 ¹⁸	$P2_12_12_1$		1	TCHLBZ
1,4-Dibromobenzene	74.23 ¹⁵	$P2_1/a$	$\bar{1}$	1	Ref. 19
1,3,5-Tribromobenzene	86.6 ²⁰	$P2_12_12_1$		1	TBRMBZ
1,2,4,5-Tetrabromobenzene		$P2_1/a$	$\bar{1}$	1	TETBBZ01
2,3,6,7-Tetrabromonaphthalene		$P2_1/c$	$\bar{1}$	1	BRNPHL
1,5-Dibromonaphthalene		$C2/c$	$\bar{1}$	1	COXLOQ
1,4-Dibromonaphthalene		$P2_1/a$		2	DBRNAQ
2-Bromonaphthalene	78.0 ²¹	$P2_1/c$		1	BRNAPT
1,2,3,5,6,7-Hexabromonaphthalene		$P2_1/c$	$\bar{1}$	1	HBRNAP
1,4,5,8-Tetrabromonaphthalene		$P2_1/c$		1	TBNAPH
α -1,4-Diiodobenzene	63.4 ¹⁷	$Pbca$		1	ZZZPRO06
β -1,4-Diiodobenzene		$Pccn$		1	ZZZPRO07
1,4-Chlorobromobenzene	69.34 ¹⁵	$P2_1/c$	$\bar{1}$	1	CBENZ
1,4-Chloriodobenzene	71.86 ¹⁵	$P2_1/c$	$\bar{1}$	1	CLIOBZ02
1,4-Bromiodobenzene	78.53 ¹⁵	$P2_1/c$	$\bar{1}$	1	KUJZUK ^b
1,2-Diiodobenzene	64.9 ¹⁷				

^a Transition enthalpy $\gamma \rightarrow \alpha$ 1.26 kJ mol^{-1} , $\alpha \rightarrow \beta$ 0.21 kJ mol^{-1} .^{22 b} No atomic coordinates given.

the three mixed *para*-dihalobenzenes on the lattice energies was neglected, as justified below (Table 5).

Most structures were reproduced well, but some were unacceptably deformed. For instance, pentachlorobenzene showed a molecular rotation of about 25° in all force fields. Therefore we adjusted the force field parameters for chlorine and bromine to reproduce the crystallographic data as well as the observed lattice energies. This was done by a two-dimensional grid search for the parameters ε and r_0 , defined in the usual way:

$$U_{\text{LJ}} = \varepsilon \left[\left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right] = \frac{C_{12}}{r^{12}} - \frac{C_6}{r^6} \quad (1)$$

$$U_{\text{Buck}} = \left(\frac{\lambda \varepsilon}{\lambda - 6} \right) \left[\frac{6}{\lambda} \exp \left(\frac{-\lambda(r - r_0)}{r_0} \right) - \left(\frac{r_0}{r} \right)^6 \right] \\ = A \exp(-Br) - \frac{C}{r^6} \quad (2)$$

where λ is a steepness parameter that is usually kept fixed to some chosen value because it is heavily correlated with ε and r_0 .

It was found that there exists a fairly large valley in (ε, r_0) space where the simulations have essentially the same quality. The values for ε especially have some arbitrariness. This problem became worse when it was attempted to parameterize iodine in the same way. Here the amount of experimental information is limited to four substances. For two of these no crystal data are available, so the lattice energy was calculated from the best hypothetical structure. This should not introduce an important error; yet it was difficult to find a value for ε that reproduced all observed lattice energies. Therefore, the iodine parameters should be considered as rather tentative.

The final Buckingham-type force field was based on the parameters from Hsu and Williams rather than the ones from Filippini and Gavezzotti. The reason is fairly trivial: the Williams force field uses combination rules for unequal atom types that allow efficient convergence acceleration for

the dispersion terms.⁹ To obtain the same accuracy in the Gavezzotti force field a cutoff distance of about 20 Å would be needed, leading to an unacceptably large computational effort. The parameter λ was kept at 13.8, as chosen by Williams.

Table 2 shows a first verification for the two force fields: the lattice energies and the geometrical shifts occurring upon energy minimization. The latter are expressed in the Williams F value:⁶

$$F = (100\Delta a/a)^2 + (100\Delta b/b)^2 + (100\Delta c/c)^2 + \Delta\alpha^2 \\ + \Delta\beta^2 + \Delta\gamma^2 + (\Delta\theta/2)^2 + (10\Delta R)^2 \quad (3)$$

where the Δ -values indicate shifts in the six cell parameters, the molecular rotation θ , and the molecular translation R , respectively (expressed in degrees and Å).

Table 3 shows the corresponding halogen nonbonded parameters. All molecules were treated in principle as fully flexible, but the force constants for stretching, bending and torsion were set fairly high to prevent excessive deformation of these fairly rigid planar structures. The optimum bond length parameters were CC = 1.39 Å, CH = 1.03 Å, CCl = 1.73 Å, CBr = 1.90 Å and CI = 2.09 Å. It is interesting to note that there is no smooth variation in nonbonded parameters: in both force fields chlorine and bromine have the same r_0 and different ε , whereas the situation is reversed between bromine and iodine.

3 Crystal structure prediction

Another essential feature of a force field is that the experimental structure should not have an excessively large energy with respect to other, hypothetical, structures. To create such sets of possible structures the UPACK program package³ has been developed in our laboratory. A recent approach¹⁰ is to generate possible structures with two independent molecules in the five space groups $P2_1/c$, $P\bar{1}$, $P2_1$, $P2_12_12_1$ and $P1$. Structures

Table 2 Lattice energies and geometry shifts upon energy minimization. L is the lattice energy in kJ mol^{-1} , F is the crystal structure disagreement factor (eqn. 3)

Substance	$-L(\text{obs})$	Lennard-Jones		Buckingham	
		$-L$	F	$-L$	F
γ -1,4-Dichlorobenzene	71.0	71.6	8	73.0	23
α -1,4-Dichlorobenzene	69.7	71.4	45	72.7	25
β -1,4-Dichlorobenzene	69.5	72.4	60	73.3	45
1,2,4,5-Tetrachlorobenzene	88.2	89.9	77	92.5	94
Pentachlorobenzene	92.1	92.6	51	94.6	81
1,2,3-Trichlorobenzene	80.1	80.5	22	82.6	24
1,2,3,5-Tetrachlorobenzene	84.6	86.7	87	88.8	97
1,3-Dichlorobenzene		68.8	16	70.0	30
1,2-Dichlorobenzene		70.7	10	71.9	14
Hexachlorobenzene	95.5	102.5	55	104.0	59
1,3,5-Trichlorobenzene	75.7	78.6	27	79.4	21
1,4-Dibromobenzene	79.3	77.4	46	77.7	14
1,3,5-Tribromobenzene	91.6	85.5	11	85.8	6
1,2,4,5-Tetrabromobenzene		99.3	99	100.3	116
2,3,6,7-Tetrabromonaphthalene		130.0	106	133.9	134
1,5-Dibromonaphthalene		104.3	9	106.0	6
1,4-Dibromonaphthalene		98.4	21	100.0	12
2-Bromonaphthalene	83.0	88.2	90	92.5	15
1,2,3,5,6,7-Hexabromonaphthalene		146.8	15	149.5	23
1,4,5,8-Tetrabromonaphthalene		126.7	45	132.7	68
α -1,4-Diiodobenzene	68.4	77.1	45	76.9	50
β -1,4-Diiodobenzene		75.4	83	75.1	98
1,4-Chlorobromobenzene	74.3	74.4	48	75.1	10
1,4-Chloriodobenzene	76.8	71.9	75	74.1	20
1,4-Bromiodobenzene	83.5	77.2		77.8	
1,2-Diiodobenzene	69.9	77.0		77.0	

with one independent molecule in many space groups should be found as special cases. Thus all structures listed in Table 1, including the four with two independent molecules and another four with space groups that were not investigated explicitly, should be recovered. This approach is costly in computer time, but just affordable for the rigid molecules studied in this work. For each compound 10 000 random structures were generated in each space group, followed by a few cycles of energy minimization and clustering. On a Gateway personal computer, equipped with a Pentium III 500 MHz processor and running under Linux, this took about 4 days for a benzene derivative and 9 days for a naphthalene derivative.

A basic requirement for a crystal structure prediction program is that it should find the experimentally observed polymorph(s). As is usually the case for simple rigid molecules, this condition was fulfilled in the present work. The experimentally observed structures with one independent molecule were found many times (N in Table 4). The exception was

2-bromonaphthalene, which was found only once. In view of the random nature of the search this means that it might just as well have been missed. The reason is probably that the experimental structure is not stable in the force fields used: energy minimization without space group restraints changed the symmetry from $P2_1/c$ to $P1$. Even the four structures with two independent molecules were found more frequently.

As always, each experimental structure was found among many hypothetical polymorphs. After the search with the Lennard-Jones force field, all structures within an energy window of 8 kJ mol^{-1} were also energy minimized with the Buckingham force field. When such a collection of structures is ordered by energy, the experimental structure has a rank R and an energy ΔE with respect to the global energy minimum. Obviously, for a successful structure prediction we would need to find $R = 1$ and $\Delta E = 0$. That situation would occur in the ideal case where the force field is perfect and the effects of temperature and crystallization kinetics can be neglected.

Table 3 Adjusted halogen nonbonded parameters. Nonbonded parameters for C and H are taken from refs. 7 (Lennard-Jones) and 5 (Buckingham)

	Lennard-Jones			Buckingham		
	Cl	Br	I	Cl	Br	I
$\epsilon/\text{kcal mol}^{-1}$	0.31	0.40	0.40	0.30	0.38	0.38
$r_0/\text{\AA}$	4.20	4.20	4.60	4.25	4.25	4.40
λ				13.8	13.8	13.8
$C_{12}/\text{Mcal mol}^{-1} \text{\AA}^{12}$	9340	12052	35905			
$C_6/\text{kcal mol}^{-1} \text{\AA}^6$	3403	4391	7579			
$A/\text{Mcal mol}^{-1}$				227.2	287.8	287.8
$B/\text{\AA}^{-1}$				3.25	3.25	3.14
$C/\text{kcal mol}^{-1} \text{\AA}^6$				3128	3962	4878
Charges C–H		–0.10/+0.10			–0.15/+0.15	
Charges C–Hal		+0.10/–0.10			+0.10/–0.10	

Table 4 Rankings and energy differences in the two force fields. N is the number of times the experimental structure was found in the search. Energy differences ΔE (kJ mol⁻¹) and rankings R refer to the experimental structure with respect to the global energy minimum

	Z''	N	Lennard-Jones		Buckingham	
			ΔE	R	ΔE	R
γ -1,4-Dichlorobenzene	1	555	1.2	7	0.0	3
α -1,4-Dichlorobenzene	1	597	1.3	8	0.3	5
β -1,4-dichlorobenzene	1	3669	0.3	2	0.0	1
1,2,4,5-Tetrachlorobenzene	1	692	0.0	1	0.0	1
Pentachlorobenzene	1	24	3.5	648	3.6	419
1,2,3-Trichlorobenzene	2	3	1.6	20	1.5	17
1,2,3,5-Tetrachlorobenzene	2	16	2.9	42	3.6	69
1,3-Dichlorobenzene	2	21	1.6	69	0.9	28
1,2-Dichlorobenzene	1	106	1.4	24	1.2	9
Hexachlorobenzene	1	277	6.8	196	5.6	170
1,3,5-Trichlorobenzene	1	671	0.7	16	1.6	42
1,4-Dibromobenzene	1	1526	1.4	6	0.7	3
1,3,5-Tribromobenzene	1	442	1.6	40	1.8	45
1,2,4,5-Tetrabromobenzene	1	444	0.4	4	0.0	2
2,3,6,7-Tetrabromonaphthalene	1	403	0.0	1	0.0	1
1,5-Dibromonaphthalene	1	73	1.4	3	0.8	4
1,4-Dibromonaphthalene	2	6	3.2	120	3.9	104
2-Bromonaphthalene	1	1	3.5	66	3.1	20
1,2,3,5,6,7-Hexabromonaphthalene	1	63	4.0	37	2.6	39
1,4,5,8-Tetrabromonaphthalene	1	229	4.3	72	2.9	20
α -1,4-Diiodobenzene	1	529	0.0	1	0.4	2
β -1,4-Diiodobenzene	1	392	1.8	16	2.3	33
1,4-Chlorobromobenzene	1	359	1.4	97	0.5	74
1,4-Chloroiodobenzene	1	263	2.2	140	0.9	50

Table 4 shows the actual results. It is seen that the performance of the two force fields is quite similar. We conclude that the choice of reference compounds is more important for the parameterization than the functional form of the potential. For hexachlorobenzene the relative energy is disappointingly large. Only 1,2,4,5-tetrachlorobenzene and 2,3,6,7-tetrabromonaphthalene would have been found in a genuine crystal structure prediction. In two blind tests organized recently^{11,12} a ranking up to three was accepted; this would have doubled the present success rate to 4 structures out of 24. This corresponds roughly to the general results of the blind tests, showing that the present state of the art leaves much to be desired. In a recent study of Boese *et al.*¹³ comparable ΔE values (1 to 2 kJ mol⁻¹) were found for the three dichlorobenzenes in the UNI force field of Filippini and Gavezzotti.⁶ Neither in that work nor in the present study was the correct order of the three polymorphs of *para*-dichlorobenzene reproduced.

4 Disordered crystals

4.1 Orientational disorder

Orientational disorder has been established crystallographically for the three *para*-substituted benzenes PhClBr, PhBrI and PhClI (see references in Table 1). Their structures are

isomorphous with each other as well as with PhBr₂ and α -PhCl₂, but not with either one of the two known PhI₂ polymorphs. As a possibly ordered analogue the PhHI compound monoiodobenzene (crystal structure unknown) was also studied.

Hypothetical crystal structures with one independent molecule were generated for these substances in the five space groups mentioned above. For 10 selected structures the unit cell was expanded to a supercell with 16 molecules, avoiding short axes as much as possible. Then each of the 16 molecules had a 50% chance of having its two halogen atoms interchanged, after which the energy was minimized.

Several hypothetical structures converged to exactly the same energy when the two substituents were artificially made equal to each other. Such structures form a class of isomorphs that must become equivalent upon randomization. Therefore, the selection of structures was based not only on energy: only one member of each class was used. The experimental structure was added if not already present.

For each selected structure the final energy of the disordered structure was obtained as the average of 10 randomizations. The energy differences with the ordered structures are summarized in Table 5. It is seen that the average randomization energies for the dihalogenated compounds are quite small, but that the extremes deviate considerably from the averages. Contrary to what might have been expected, significant negative values

Table 5 Average randomization energies for *para*-dihalobenzenes (kJ mol⁻¹). N is here the number of structures used. The other entries give the energy differences between the disordered structures and the corresponding ordered ones. They should be compared with a free energy decrease of $RT \ln 2 \approx 1.7$ kJ mol⁻¹ due to the randomization entropy

	N	Lennard-Jones			Buckingham		
		Average	Extremes		Average	Extremes	
PhClBr	10	0.09	-0.24	0.32	0.18	-0.01	0.62
PhBrI	11	0.12	-1.60	0.69	0.13	-0.05	0.53
PhClI	11	0.25	-0.95	1.22	0.34	-0.07	0.99
PhI	10	4.75	4.04	5.81	4.31	3.03	5.84

occur (at least, in the Lennard-Jones force field) and the ranges between the extremes vary between 0.6 kJ mol^{-1} and 2.8 kJ mol^{-1} . A positive randomization energy can be compensated by a free energy decrease of $RT \ln 2 \approx 1.7 \text{ kJ mol}^{-1}$ due to the mixing entropy.

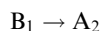
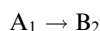
The correlation between the individual values from the two force fields is not large. However, both force fields agree unequivocally that the three dihalobenzenes should be rotationally disordered (as observed) and predict that iodobenzene should be ordered. Interestingly, knowledge of the exact structure is not necessary: the 10 or 11 hypothetical structures with lowest energy all lead to this conclusion.

4.2 Mixed crystals

The situation for mixed crystals is more complex. Let us imagine that in a certain structure of a mixture A/B all molecules A are converted into B or *vice versa* (in the computer this is easy!). After relaxation of the resulting structures into their equilibrium geometries we shall find certain polymorphs (A_1 or B_1 , respectively) of the pure compounds, schematically:



Which polymorphs are found may well depend on the mixing ratio. Then repeating the procedure for the pure compounds can lead to different structures:



This interesting phenomenon was observed occasionally in our calculations on hypothetical structures. However, continuously mixable systems must be isomorphous at all compositions. Therefore this study was limited to systems with $A_1 = A_2$ and $B_1 = B_2$. Then it is expected that mixed crystals are only possible if A/B, A_1 and B_1 are all favoured by a low energy relative to their respective global minima, so as to make the occurrence of these polymorphs plausible.

This work was further limited to mixtures of 50% A and 50% B. Fig. 1 illustrates the three possibilities for the crystallization of such a mixture: (1) two crystals of the pure substances A and B; (2) an ordered cocrystal with relative energy ΔE_{cocr} with respect to (1); (3) a mixed crystal (being a disordered cocrystal) with relative energy ΔE_{rand} with respect to (2). The sum of ΔE_{cocr} and ΔE_{rand} is the mixing energy, ΔE_{mix} . In principle, each of the three possibilities might correspond to the lowest energy. But the free energy of the mixed crystal is lowered by $RT \ln 2$ due to the mixing entropy.

Hypothetical ordered crystal structures were generated for systems A/B where A and B are *para*-dihalobenzenes. For 5000 structures the computing time was about 2 days. Large sets of ordered cocrystals A/B, often close together in energy, were found that corresponded to the same couple of structures A_i and B_i . This is not surprising, since there are many ways in which the molecules A and B can be interchanged in a lattice while still maintaining crystallographic symmetry; usually

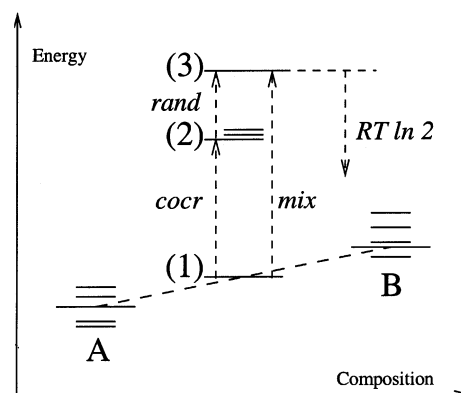


Fig. 1 Energy levels for crystals of two pure substances, A and B, where two polymorphs are selected. For the 1 : 1 mixture (1) represents two separate crystals, (2) the corresponding ordered cocrystal, and (3) is the average energy of an essentially continuous set of disordered structures from (2). The vertical arrows on the left side denote the energy of cocrystallization and of randomization. The sum of these two, the relative energy of the mixed crystal, should be compared with $RT \ln 2$.

there were recognizable strings of A and B running parallel in some direction. Out of each set, only the structure with lowest energy was selected, and only if its energy as well as the energies of the limiting structures A_i and B_i were less than 3 kJ mol^{-1} above their respective global minima. For that structure the unit cell was expanded to a supercell with 16 molecules, as explained above for the case with orientational disorder. But now these 16 molecules were interchanged at random, after which the energy was minimized.

Again, for each selected structure the final energy of the disordered structure was obtained as the average of 10 randomizations. The results are summarized in Table 6. For the systems $\text{PhCl}_2/\text{PhBr}_2$ and $\text{PhBr}_2/\text{PhI}_2$ the two force fields agree that mixed crystals should be expected, provided that isomorphous polymorphs can be combined. Experimentally, this situation is observed in $\text{PhCl}_2/\text{PhBr}_2$ but for the iodine compounds no suitable isomorphs are known. For the $\text{PhCl}_2/\text{PhI}_2$ system the theoretical conclusions are uncertain: the Buckingham force field predicts consistently mixed crystals, whereas the Lennard-Jones force field finds (with a few exceptions) that demixing into crystals of the two pure substances will occur (Fig. 2).

The model employed here focuses on ΔE_{mix} , which is essentially the same as the excess enthalpy (ΔH^E) used in thermodynamical measurements. For the system $\text{PhCl}_2/\text{PhBr}_2$ the excess enthalpy has been measured to be 1.1 kJ mol^{-1} relative to the liquid mixture, which was assumed to behave ideally.¹⁴ The value in Table 6 is 4 to 5 times lower. It is not known whether this disappointing result is due to inadequacies of the force fields or to an overly simplistic computational model. One deficiency is obvious: the model does not represent the excess entropy (ΔS^E) which is the mixing entropy relative to $R \ln 2$. In the real world that quantity is not negligible. For

Table 6 Average randomization energies for mixed crystals of *para*-dihalobenzenes (kJ mol^{-1}). N is the number of structures used. ΔE_{cocr} is the energy of the ordered cocrystal with respect to two separate crystals, and ΔE_{rand} is the energy increase upon its randomization. Their sum, ΔE_{mix} , should be compared with a free energy decrease of $RT \ln 2 \approx 1.7 \text{ kJ mol}^{-1}$ due to the mixing entropy (see Fig. 1)

	N	Lennard-Jones			Buckingham		
		ΔE_{cocr}	ΔE_{rand}	ΔE_{mix}	ΔE_{cocr}	ΔE_{rand}	ΔE_{mix}
$\text{PhCl}_2/\text{PhBr}_2$	9	0.06	0.17	0.23	0.05	0.21	0.26
$\text{PhBr}_2/\text{PhI}_2$	10	0.43	0.56	0.99	0.12	0.21	0.33
$\text{PhCl}_2/\text{PhI}_2$	10	0.83	1.03	1.86	0.50	0.50	1.00

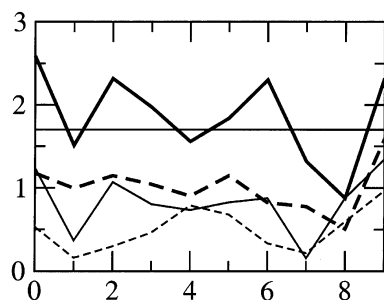


Fig. 2 Energy effects (kJ mol^{-1}) for 10 hypothetical mixed crystals of *p*-dichlorobenzene and *p*-diiodobenzene. Dashed lines: Buckingham potential; solid lines: Lennard-Jones potential. Thin lines: ΔE_{coor} ; bold lines: ΔE_{mix} . The lines do not imply any directionality from left to right, but they allow instant comparison between ΔE_{mix} and the horizontal line at $RT \ln 2 \approx 1.7 \text{ kJ mol}^{-1}$.

1 : 1 mixtures of *para*-dihalobenzenes an empirical relation¹⁴ has been found:

$$\Delta H^E / \Delta S^E \approx 500 \text{ K.} \quad (4)$$

So far, we have not been able to reproduce such an entropy effect by molecular modelling.

5 Conclusions

Force-field calculations allow an estimate of the energy effect of simple orientational disorder. This can be done by artificial randomization of the hypothetical structures with lowest energy, without knowing which polymorphs are experimentally observable. In the examples studied here, the range in energy effects between the various structures was small enough to predict whether or not entropy effects offset any energy increase on randomization. Identical conclusions were obtained from two different force fields, one using the Lennard-Jones 12–6 potential and the other using the Buckingham exponential form. It should be noted that both force fields were parameterized on the same set of halogenated benzenes and naphthalenes, and that the results of our crystal structure predictions suggest that the composition of that set is more important than the functional form.

The problem of predicting whether or not two substances can produce mixed crystals is more complex. The fact that in the case of the $\text{PhCl}_2/\text{PhI}_2$ mixture the results depend on the choice of force field can be dismissed as an unfortunate borderline case of mixing energies that happen to be of the same order of magnitude as $RT \ln 2$. Nevertheless, the calculated values for the mixing energies may be too low, as seen for the $\text{PhCl}_2/\text{PhBr}_2$ mixture. More fundamentally, the occurrence of mixed crystals is only possible under the condition that isomorphous polymorphs of two compounds exist. At present it is nearly impossible to predict whether or not that condition will be satisfied. However, the procedure to predict positional

disorder in structures of pure compounds should be extendable to larger structures, including flexible molecules and other mixing ratios than 50%.

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