actually the means of the e.s.d.'s of the relevant individual bond and torsion angles rather than the e.s.d.'s of the various means. The effects of such a difference in the type of statistical treatment used may be seen from the results presented for compounds (3)–(5) in Table 4. The magnitudes of the estimated errors of the mean angles now clearly preclude any comment concerning the relative degrees of flattening of the two rings in any of the four compounds.

The ring flattening under consideration arises, of course, from non-bonded interactions involving the axial substituents (*X* and *Y*) and appropriate axial hydrogens, and is necessarily accompanied by a reduction in the torsion angles *X*—C(2)—C(3)—*Y*. The observed angles for compounds (3)–(5) are listed in Table 5, together with information which shows that the departure from the 'ideal' angle of 180° arises from widely varying degrees of lateral displacement of the groups *X* and *Y*.

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A Quantitative Analysis of the Relative Importance of Symmetry Operators in Organic Molecular Crystals

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Abstract

The contribution of each symmetry operator to the lattice energy is calculated for a sample of 1068 non-hydrogen-bonded crystal structures in the most frequent space groups for organic molecules. The molecular coordination sphere is defined as the ensemble of neighbouring molecules each of which contributes more than 2% of the packing energy, and some geometrical aspects of this ensemble are studied. The frequency with which each operator is the most relevant one is estimated for each space group. It appears that some operators dominate, while others are silent by-products of the combinations of dominant ones. Pure translation gives the top contribution to the packing energy in a significant number of cases.

Introduction

The uneven distribution of organic crystal structures among space groups was recognized a long time ago by Kitaigorodski (1961), who classified the interactions among molecular objects in terms of favourable symmetry relationships. Even though a limited number of examples was then available, Kitaigorodski found that most crystal structures result from the action of one or two among a restricted set of symmetry operators, namely, the inversion centre (*I*), the twofold screw (*S*) and the glide (*G*). In this respect, the conclusion that only a few space groups are relevant to organic crystal chemistry follows naturally. This was confirmed later by analyses of space-group frequencies (Mighell, Himes & Rodgers, 1983; Donohue, 1985; Padmaja, Ramakumar & Viswamitra, 1990). Wilson (1988, 1990) has proposed quantitative rules to estimate the number of structures in each symmetry class from the type and number of symmetry operators; Scaringe (1990) has studied the distribution of structures throughout space groups, taking into account molecular symmetry, and has shown – in a beautiful confirmation of Kitaigorodski's principles – that groups containing twofold axes or mirror operators appear almost exclusively when the operator acts within the molecule, and not between molecules.

Since Kitaigorodski's time, there has been an exponential increase in the number of structure determinations which are available. This is due to the setting up of databases such as the Cambridge Structural Database (CSD; Allen, Kennard & Taylor, 1983), and the increasing speed and availability of electronic computers. Empirical formulations are available for a reasonably accurate estimation of

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lattice energies. Through these, the hope is to arrive at a semiquantitative theory of organic crystal packing.

Methods and purpose

We have assembled a database, extracted from the CSD, consisting of 391 hydrocarbon, 590 oxahydrocarbon and 459 azahydrocarbon crystal structures (see Gavezzotti, 1989, 1991*a*; Gavezzotti & Filippini 1992, respectively), for analysis of the crystal packing of organic compounds. None of these contain fully fledged hydrogen bonds, although some have weak C—H···O or C—H···N intermolecular bonds. In this work, these have been excluded, since the potential form we use here is not suitable when hydrogen bonds are present. Crystals with more than one molecule in the asymmetric unit were not considered. A data set of 1356 crystal structures resulted; for each of them, the crystal packing potential energy (PPE) was computed by the atom–atom method, which allows definition of a molecule–molecule interaction energy by an appropriate breakdown of the lattice sums:

$$\mathrm{PPE} = \textstyle\sum_i\sum_j[A\exp(-Br_{ij}) - Cr_{ij}^{-6}] = \sum_j E(j).$$

A, *B* and *C* are parameters for each type of intermolecular contact (see Gavezzotti & Simonetta, 1982, for their choice). A 7 Å cutoff was imposed on the lattice sums. *E*(*j*) is the part of PPE due to the interaction between all atoms in the reference molecule and all atoms in the *j*th symmetry-related neighbouring molecule. Only those molecules whose *E*(*j*) is more than 2% of the total PPE were considered; this is our definition of the molecular coordination sphere in the crystal. For each *E*(*j*), we call *D*(*j*) the corresponding distance between centres of mass. For each operator, the energetic relevance $E_r(j)$ is calculated as the sum of all *E*(*j*)'s from molecules related to the reference one by that operator (as obtained by adding integers to the translation vector). By ranking the operators in order of decreasing E_r, the relative importance of each in terms of crystal cohesion can be assessed in a quantitative way – at least, as quantitative as the semiempirical potentials allow (in the statistics on E_r, a subset of 1068 structures was used, screening out other structures with short contacts). Some energetic and geometrical features of the coordination sphere can be studied by a survey of the relationships between *D*(*j*) and *E*(*j*), but our main purpose here will be to determine the frequency with which each symmetry operator is top-ranking in each space group. We have restricted ourselves to *S*, *G* and *I* operators, it being understood that the translation operator *T* is present in any crystal, and to the most common space groups resulting from the combination of these operators, namely $P\bar{1}$, $P2_1$, $P2_1/c$, $P2_12_12_1$ and *Pbca*. These precautions avoid complications resulting from ill-defined operators (de Wolff, 1987) while leaving out a very small percentage of data.

Coordination sphere in molecular crystals

The average number of molecules in the coordination sphere is 12.3 (1.6), and the total energy of the ensemble is on average 97 (3)% of the PPE at 7 Å cutoff (which is usually estimated to be 80% of the total). The geometrical structure of this coordination sphere has been analyzed for hydrocarbons only (Gavezzotti, 1991*b*) by plotting the percentage energy contribution of the nearest neighbour molecule, *E*(1), against the distance between centres of mass, *D*(1). Fig. 1 shows the results for the complete data set; there is a large spread of packing modes in this respect, between a compact coordination sphere (c.c.s.), where most of the energy comes from one or a few neighbours (points in the upper part of the figure), and a scattered coordination sphere (s.c.s.), where the first neighbours are not so overwhelmingly important. Fig. 2 gives a plot of *D*(1) against the shortest molecular dimension, D_x, defined as the distance between extreme points on the van der Waals molecular envelope along the direction of the axis of maximum inertia. For the large majority of cases, *D*(1) is limited between $D_x + 1$ and $D_x - 2$ Å; note that this is a rough, but valuable, way of predicting a crystal property from a molecular property. D_x tends to be larger than *D*(1), owing to the effect of molecular interlocking in the crystal.

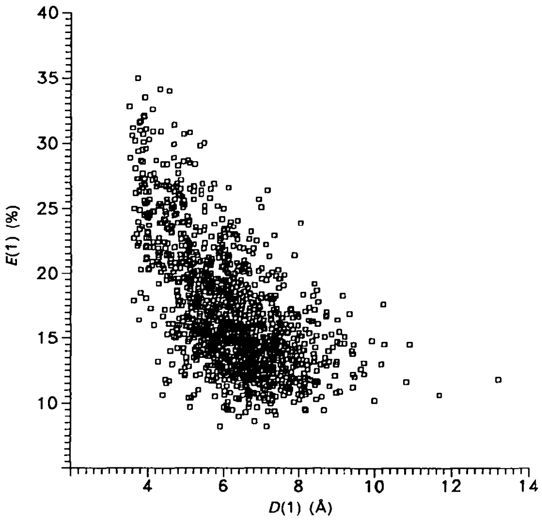

Fig. 1. A plot of the highest percentage contribution to PPE by a neighbouring molecule, *E*(1), against the distance between centres of mass, *D*(1). 1356 crystal structures.

The lower limit for both coordinates is 3.5 Å, or twice the van der Waals radius for carbon; for D_x, this value is imposed, for $D(1)$ it is an experimental result.

Relevance of operators

Table 1 shows the frequency with which each operator is top-ranking in each space group.

$P\bar{1}$

Fig. 3 shows a histogram of the energetic relevance of the T and I operators, when top-ranking, in $P\bar{1}$. The predominance of the I operator is evident; in most cases, it provides 70–80% of the PPE. In a few cases, T is 50–50 with I or overcomes it by a thin margin. Thus, $P\bar{1}$ crystals are mostly held together by interactions between molecules related by centres of symmetry, translation being an unavoidable spectator.

$P2_1$ *and* $P2_12_12_1$

Fig. 4 shows the pertinent histograms. For $P2_1$, S is by far the most relevant operator, as I was in $P\bar{1}$; however, in $P2_1$ T is top-ranking in 19% of the cases, as against 13% in $P\bar{1}$. The trend continues in $P2_12_12_1$, where T is top-ranking in 26% of cases. Although it should be remembered that each of the three S operators was considered separately, the relative importance of T is striking: in a significant number of cases, it provides about 50% of the cohesion energy.

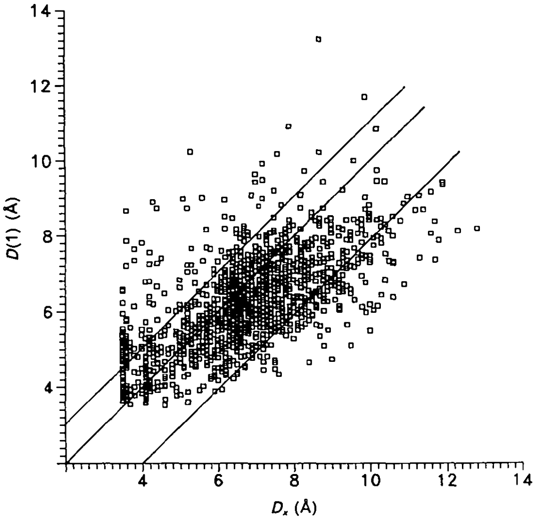

Fig. 2. A plot of $D(1)$ (see caption to Fig. 1) against the shortest molecular dimension, D_x. Straight lines represent $D(1) = D_x + 1$, $D(1) = D_x$, and $D(1) = D_x - 2$. 1356 crystal structures.

Table 1. *Frequency with which each operator is top-ranking in each space group*

Space group	Z	No. of structures	Frequency (%) T	I	S	G
$P\bar{1}$	2	121	13	87	–	–
$P\bar{1}$	1	37	100			
$P2_1$	2	93	19	–	81	–
$P2_12_12_1$	4	206	26	–	74	–
$P2_1/c$	4	410	15	37	27	21
$P2_1/c$	2	118	45		55	
$Pbca$	8	61	2	16	15	67
$Pbca$	4	22	0		100	

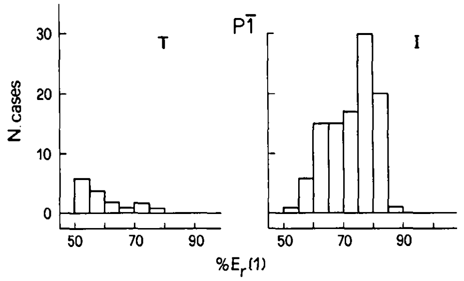

Fig. 3. Space group $P\bar{1}$, $Z = 2$. Histograms of the energetic relevance of each operator.

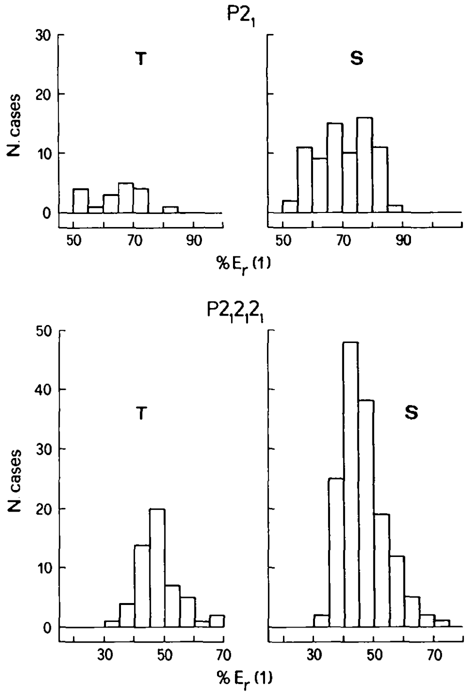

Fig. 4. Space groups $P2_1$ and $P2_12_12_1$. Histograms of the energetic relevance of each operator.

*P*2$_1$/*c*

Fig. 5 shows the histograms for $Z = 4$. The order of importance of the four operators is: *I* (top-ranking in 37% of cases), *S* (27%), *G* (21%), *T* (15%). The contribution of *I*, when top-ranking, ranges from 35 to 60% PPE, while *S*, *G* and *T* peak between 35 and 45%. It is surprising that pure translation overrides the coalition of the three most powerful symmetry operators in as much as 15% of cases.

For $Z = 2$ (Fig. 6) *T* is equivalent to *I* and *S* to *G*, due to the presence of a molecular centre of symmetry. These two operators have an almost equal share of top positions (45% $T = I$, 55% $S = G$). The distribution of the percentage contribution is wide, ranging from 55 to 80% for both operators.

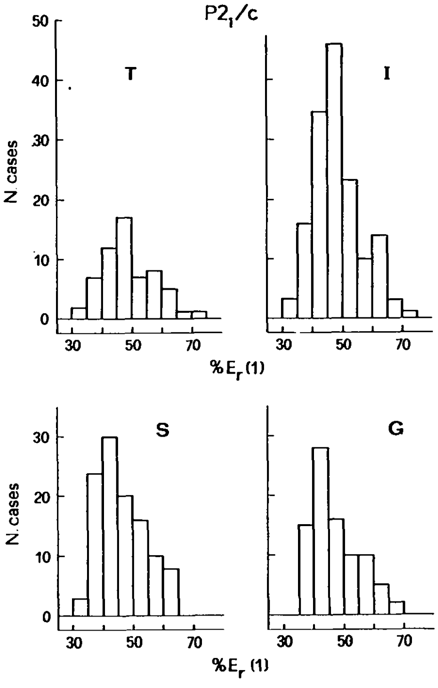

Fig. 5. Space group *P*2$_1$/*c*, $Z = 4$. Histograms of the energetic relevance of each operator.

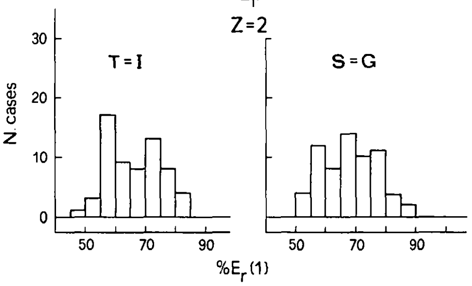

Fig. 6. Space group *P*2$_1$/*c*, $Z = 2$ (all molecules are centrosymmetric). Histograms of the energetic relevance of each operator.

Pbca

In this space group, *T* is never top-ranking; a modest 16 and 15% pertain to *I* and *S*, respectively, while *G* dominates by far (Fig. 7).

Discussion

Here we introduce a method to estimate, in a quantitative way, the relative importance of symmetry operators in organic crystals. Our present results depend to some extent on the choice of parameters for the PPE calculations, but we believe that this dependence only influences the details. As a first general result, it emerges clearly that some operators in some space groups are silent, that is, they do not contribute significantly to the packing, but appear as unavoidable products of the combination of other operators.

In an f.c.c. packing of spheres, the coordination number is exactly 12. As demonstrated in a previous section, the average number of molecules in the coordination sphere is also 12, but the close-packing of organic molecules usually requires symmetry operators like *I*, *S* or *G* to interlock the complex molecular objects. Our results demonstrate that pure translation is the most important operator in a significant percentage of organic crystal structures; therefore, pure translation must be quite effective in producing close packing.

I is the most important operator in $P\bar{1}$, and *S* in *P*2$_1$ and *P*2$_1$2$_1$2$_1$; *I* is such in *P*2$_1$/*c*, although *S* is close to it. *G* is clearly less important in this last space group, while it is by far the most relevant in *Pbca*. It must be therefore that the combination of three glide planes inhibits the action of other operators in *Pbca*. When $Z = 4$, *Pbca* reduces to *P*2$_1$2$_1$2$_1$ for a centrosymmetric molecule; translation

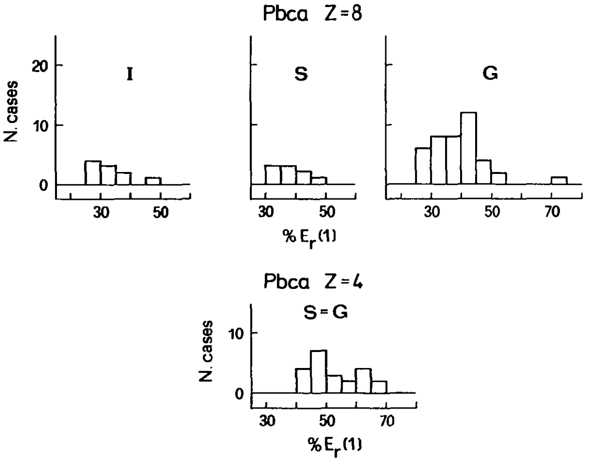

Fig. 7. Space group *Pbca*. All molecules are centrosymmetric when $Z = 4$. Histograms of the energetic relevance of each operator.

is never top-ranking, while it is such in a significant percentage of $P2_12_12_1$ structures for non-centrosymmetric molecules.

The question of what is the most important symmetry operator in an absolute sense is a difficult one, since it is not easy to discern the real effectiveness of each operator in producing close-packed arrays from the effects of the interactions among operators, as dictated by their location in space ('encumbered' operators; Wilson, 1988). Nevertheless, a global analysis of the distribution of organic molecules among space groups, together with the present results, suggest (although no quantitative proof may be given) that the order of importance is $I > S > G > T$. Our results for $P2_1/c$ are, in this respect, exemplary. We note that the importance increases with the number of coordinates whose sign is changed by the operator (3 for I, 2 for S, 1 for G and zero for T).

Of the 177 centrosymmetric molecules in our sample, 67% choose to crystallize in $P2_1/c$, $Z = 2$, 21% in $P\bar{1}$, $Z = 1$, and only 12% in $Pbca$, $Z = 4$; these percentages are quite similar to those found by Scaringe (1990).

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5-Spirocycloalkane Isoxazolines: Structures and Thermal Behaviour

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Abstract

(1): 3-Phenyl-4,5-dihydroisoxazole-5-spirocyclopropane, $C_{11}H_{11}NO$, $M_r = 173.21$, monoclinic, $P2_1/n$, $a = 10.052\ (4)$, $b = 5.732\ (8)$, $c = 16.091\ (10)$ Å, $\beta = 99.41\ (4)°$, $V = 915\ (1)$ Å^3, $Z = 4$, $D_x = 1.26$ g cm^{-3}, $\mu = 0.76$ cm^{-1}, $F(000) = 368$, $T = 298$ K, final $R = 0.094$ for 407 observed reflections $[I > 3\sigma(I)]$. (2): 3-Phenyl-4,5-dihydroisoxazole-5-spirocyclobutane, $C_{12}H_{13}NO$, $M_r = 187.24$, orthorhombic, $P2_12_12_1$, $a = 5.845\ (2)$, $b = 8.887\ (2)$, $c = 19.236\ (5)$ Å, $V = 999.2\ (5)$ Å^3, $Z = 4$, $D_x = 1.24$ g cm^{-3}, $\mu = 0.74$ cm^{-1}, $F(000) = 400$, $T = 298$ K, final $R = 0.066$ for 679 observed reflections $[I > 3\sigma(I)]$. (3): 3-Phenyl-4,5-dihydroisoxazole-5-spirocyclopentane, $C_{13}H_{15}NO$, $M_r = 201.27$, orthorhombic, $P2_12_12_1$, $a = 8.057\ (10)$, $b = 11.169\ (5)$, $c = 12.251\ (9)$ Å, $V = 1102\ (2)$ Å^3, $Z = 4$, $D_x = 1.21$ g cm^{-3}, $\mu = 0.71$ cm^{-1}, $F(000) = 432$, $T = 298$ K, final $R = 0.075$ for 502 observed reflections $[I > 3\sigma(I)]$. 5-Spirocyclopropane and 5-spirocyclobutane isoxazolines undergo thermal rearrangement to give mainly 2-phenyl-5,6-dihydropyrid-4-one and 2-phenyl-5,6,7,8-tetrahydro-4*H*-azepin-4-one respectively under rather different experimental conditions. Geometrical parameters of the 5-spirocyclopropane and 5-spirocyclobutane isoxazolines, derived from the X-ray analysis, were used to justify the origin of their different thermal behaviour.

Introduction

Thermal rearrangement of the 5-spirocycloalkane isoxazolines (1) and (2) has recently provided a new route to dihydro-4-pyridone (4) (Guarna, Brandi, De

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