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Volumetric measure of isostructurality

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Abstract

The numerical descriptors of isostructurality are critically reviewed and to overcome their limitations a new volumetric measure is proposed. It is defined as the percentage ratio of the overlapping volume of molecules in the analyzed structures to the average of the corresponding molecular volumes. For the calculation of this index a numerical approach is presented, which is also capable of treating disordered structures. The use of isostructurality calculations is demonstrated using a series of examples. Homologous 9-alkylthiophenanthrenes are used as simple illustrations of the necessity and applicability of the new descriptor. The structural changes in the inclusion compounds of 5-methoxysulfadiazine with chloroform, dioxane and tetrahydrofuran are analyzed and rationalized with the aid of isostructurality indices. The diverse relationships among a series of helical tubuland diols cocrystallized with simple phenols are also characterized. The modifications in molecular and crystal structures are correlated with the calculated degree of isostructurality.

1. Introduction

The similarities observed among the crystal packings of several related steroid structures (Kálmán *et al.*, 1991, 1992) prompted us to rationalize the isostructurality of organic crystals in general (Kálmán *et al.*, 1993). From the examples allocated in the current literature it became obvious that a given packing motif may *tolerate* small changes in the molecular structure without a visible effect on the already established close packing. These changes included atomic replacements and minor alterations in substitution and/or epimerization. The tolerance may be ascribed to the presence of *ca* 30% free space in close-packed structures. (Note that the packing coefficients of organic crystals are typically in the range 0.6–0.7.)

Since 1993 isostructurality has proved to be much more frequent than it was expected to be (Kálmán & Párkányi, 1997). In particular, associate crystals tend to be isostructural. Different guest molecules may be incorporated into a host lattice without substantially changing its structure. With the increasing number of known examples (predominantly binary systems) the study of isostructurality is becoming a useful tool in the deeper understanding of close-packing principles.

This, however, requires numerical descriptors to quantify the degree of similarity. In this paper we propose a new measure of isostructurality which can also handle supramolecular (binary, ternary) systems. Since crystal packing, at the first approximation, is based on the self-complementarity of molecular volumes, a measure based on the overlap of the volumes of molecules should provide physically meaningful data. Such an index also enables one to describe cases where a straightforward atom–atom correspondence cannot be established.

2. Descriptors of packing similarity

2.1. *Unit-cell similarity*

A basic prerequisite of isostructurality is the similarity of unit cells. According to Kálmán *et al.* (1993) they can be compared using

$$\Pi = [(a+b+c)/(a'+b'+c')] - 1 \qquad (a+b+c > a'+b'+c'), \tag{1}$$

where a, b, c and a', b', c' are the orthogonalized† unit-cell parameters of the related crystals. For similar unit cells $\Pi \simeq 0$. Unfortunately, the calculated values of Π depend on the orthogonalization scheme applied and thus only results obtained by the same method are comparable. As the first calculations were carried out on orthorhombic structures, this problem occurred only recently with the need to calculate a uniquely defined Π for triclinic structures. To provide a scheme that treats the axes equally, we adapted the symmetric orthogonalization method of Löwdin (1950) developed originally for the transformation of quantum chemical basis functions (see *Appendix*). All the Π values reported in this paper were determined using this orthogonalization procedure.

A more sophisticated way of comparing unit cells was proposed by Rutherford (1997). The difference in cell size is described by the mean elongation (ϵ), while the

† Orthogonalization in space groups with fixed cell angles is not necessary.

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so-called asphericity index (A) accounts for the shape distortion. The definition of ϵ is

$$\epsilon = (V'/V)^{1/3} - 1 \qquad (V' > V), \tag{2}$$

where V and V' are the volumes of the respective unit cells. The asphericity index is defined as

$$A = (2/3)\Big[1 - \textstyle\sum_{j>i}\{[(1+\epsilon)M_i - 1] \times [(1+\epsilon)M_j - 1]/3\epsilon^2\}\Big]^{1/2}, \tag{3}$$

where M_i's are the principal axes of matrix **M**, which gives the pure shear component of the transformation between the two crystallographic coordinate systems. (For more details and the derivation of the asphericity index see Rutherford, 1997, and references therein.) The closer the relationship between the structures, the closer ϵ and A are to 0. Thus, the product ϵA may also be used as a unified unit-cell similarity descriptor.

2.2. *Comparing the position of molecules in the unit cell*

Naturally, isostructurality involves not only similar unit cells, but also a similar internal arrangement of molecules. In the case of closely related molecules this means that the common atoms of the two structures are located approximately at the same coordinates. This relationship is expressed by the *isostructurality index* of Kálmán *et al.* (1993)

$$I_i(n) = \left[1 - \left(\sum \Delta R_i^2/n\right)^{1/2}\right] \times 100\%, \tag{4}$$

where ΔR_i values are the differences between the orthogonalized coordinates (Dunitz, 1979) of n identical heavy atoms in the related structures. The molecules, of course, have to be transformed to the same asymmetric unit and origin choice. This descriptor has proved to be very informative on the similarity between several steroid crystal structures, organometallic compounds of $Ph_3X{-}X'Me_3$ composition (where X, X' = Si, Ge, Sn) *etc.*, but as more complex examples have been encountered, its limits have to be taken into account:

(i) It should not be forgotten that I_i given as a percentage may even assume a *negative* value, which is impractical. Namely, the average of the coordinate differences in (4) is not limited to the crystallographic unit length (1 Å). In the beginning (Kálmán *et al.*, 1991, 1992), all the related structures investigated showed a high degree of isostructurality with low $\Pi \leq 0.010$, and I_i calculations only fitted molecules in the asymmetric units chosen to be the closest to the origin. Thus, $\langle \Delta R_i \rangle$ has never exceeded 1 Å and from such values normalized to the crystallographic unit length I_i could be calculated as a percentage with relatively high positive values.

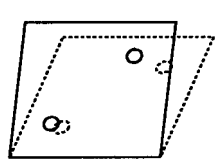


Fig. 1. The effect of unit-cell dissimilarity on the distance of equivalent points in different asymmetric units. Points with coordinates $(\frac{1}{4}, \frac{1}{4})$ and $(\frac{3}{4}, \frac{3}{4})$ are shown.

Table 1. *Isostructurality indices calculated for 9-ethylthiophenanthrene (I), 9-propylthiophenanthrene (II) and 9-butylthiophenanthrene (III)*

Structures	Π	$I_i(17)$ (%)	$I_i(17 \times 4)$ (%)	I_v (%)	$[I_v^{\max}]$ (%)
(I)–(II)	0.022	42.8	50.7	84.6	[96.1]
(II)–(III)	0.049	24.3	−33.9	65.6	[96.9]
(I)–(III)	0.073	−18.4	−61.8	57.2	[93.0]

However, with the extension of studies on isostructurality (Kálmán & Párkányi, 1997), misfits in the superposition of 'swelling/shrinking' unit cells are increasing. Therefore, it is very likely that $\langle \Delta R_i \rangle$ becomes greater than 1 Å, especially if the calculations are extended over the full unit cells, which is unavoidable for heteromolecular systems. In such cases, as shown by a two-dimensional sketch of overlapping oblique unit cells (Fig. 1), the points with coordinates $(\frac{1}{4}, \frac{1}{4})$ are much closer to each other than those at $(\frac{3}{4}, \frac{3}{4})$. In general, the ΔR_i distance between equivalent points in two unit cells increases with their distance from the common origin, fixed either at $(0, 0, 0)$ or even at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$. Of course, with increasing Π values (≥ 0.01), $I_i(n)$, but especially $I_i(n \times Z)$, where Z is the number of asymmetric units, may assume high negative values. This phenomenon is well demonstrated by the homologous series of 9-alkylthiophenanthrenes (Table 1, §4.1).

(ii) More complicated alterations to the molecule than a simple substitution exclude the changed part from the comparison since there are no common atoms there. For the same reason different guest molecules associated with the same host cannot be compared either.

(iii) In some instances, owing to small internal rotations, in the crystals not the corresponding atoms of the respective molecules are the nearest to each other. This can lead to large individual ΔR's that cannot be justified by differences in the space occupied by the molecules compared.

(iv) Although the increasing number of H atoms seems to stabilize the formation of isostructural pairs (Go & Bhandary, 1989), they are to be excluded from I_i calculations because of the limited accuracy of their coordinates.

The above experiences led us to redefine one of the conditions of isostructurality. Not the atomic coordinates (as stated earlier), but the *volumes* occupied in the unit cell should be closely related in isostructural pairs. (Obviously, it is still possible to compare certain parts of

a structure, *e.g.* one can state that host molecules are more isostructural in a given inclusion compound than guest molecules.) This viewpoint is expressed in a new *volumetric isostructurality index*

$$I_v = 2V_\cap/(V_1 + V_2) \times 100\%, \qquad (5)$$

where V_1 and V_2 are the volumes of the compared fragments and $V_\cap$ is the intersection of these volumes. As $(V_1 + V_2)/2$ is the average volume, I_v may also be expressed as the ratio of volume overlap to the average volume.

The calculation is performed on a whole unit cell to avoid the problem raised by unit-cell dissimilarity (Kálmán & Párkányi, 1997). Thus, an *averaging* is implicitly performed over the asymmetric units and the results depend on the degree of unit-cell similarity. Most I_i indices reported in this paper were *also* calculated for the whole unit cell. To emphasize this difference from the original definition we use the notation $I_i(n \times Z)$.

For identical structures we obtain $I_v = 100\%$, while with no overlap $I_v = 0\%$ is obtained. When $V_1 \neq V_2$, the theoretical maximum of I_v is

$$I_v^{\max} = (2\min\{V_1, V_2\})/(V_1 + V_2) \times 100\%, \qquad (6)$$

since $V_\cap$ cannot be greater than the smaller of the overlapping volumes.

3. Calculation of I_v

Since the analytical calculation of $V_\cap$ requires the application of extremely complicated formulae, no straightforward calculation of the novel isostructurality index (5) can be performed. To circumvent this problem we developed a numerical algorithm to calculate I_v.†

The basic idea of the calculation originates from the method of Gavezzotti (1983) to compute molecular volumes. In his algorithm the molecule is enclosed in a box of known volume and a large number of evenly distributed random points is generated in the box. The ratio of the molecular volume to the volume of the box is equal to the portion of points falling within the molecule‡ to the total number of points generated. Our method introduces only slight modifications to the above procedure to handle the intersection of two structures. Since guest molecules are frequently disordered in inclusion compounds, this algorithm is also extended to the capability of working with disordered structures.

3.1. *Input*

First, to make the structures comparable, occasionally some transformations must be performed. This may include symmetry transformations and unit-cell origin shifts. It is also possible to compare structures of different space groups by transforming both to a space group with lower symmetry. Of course, in this case more symmetry or pseudo-symmetry related molecules are compared. Then symmetry equivalent molecules are generated to fill the unit-cell box ($x, y, z \in [0; 1]$).§

From such a prepared pair of data files the program reads the unit-cell parameters, and the fractional coordinates and occupancies of each atom. Both coordinate sets are orthogonalized and the van der Waals radii of the corresponding elements are assigned to the atoms. The I_v results also depend on the arbitrary choice of orthogonalization method. For simplicity we used the standardized routine (Dunitz, 1979) which takes X parallel to crystal a, Y in the ab plane and Z perpendicular to X and Y.

3.2. *Basic scheme of the calculation*

(i) To define a common bounding box around both structures, the maximum and minimum x, y and z coordinates are determined.

(ii) Three counters N_1, N_2 and $N_\cap$ are initialized to zero for the calculation of V_1, V_2 and $V_\cap$, respectively.

(iii) A random point is generated within the bounding box. If the point is closer to any of the atoms of molecule 1 and/or 2 than its van der Waals radius then the corresponding counter is incremented. If it is close to atoms of both molecules the counter assigned to$V_\cap$ is also increased by one. This step is repeated several times to obtain a good sampling of the bounding box (1000 points Å^{-3}).

(iv) V_1, V_2 and $V_\cap$ are calculated using the formula

$$V_i = V_{\text{box}} \times (N_i/N) \qquad (i = 1, 2, \cap), \qquad (7)$$

where N_i is the respective counter and N is the total number of random points generated. The volumetric isostructurality index is then calculated by applying (5).

3.3. *Treatment of disorder*

A distinct advantage of this numerical approach is that it is easily extendable to handle disordered structures as well. This capability is most useful for the analysis of disordered guest regions. The key of such an extension is a modification of the increments added to the counters in step (iii) of the above algorithm. Namely, values that represent the *probability* of the point being occupied are used rather than incrementing the counters Ni by one.

† The *C* program which calculates I_v for two *SHELX* files is available from the authors.

‡ A point is considered to be within the molecule if it is closer to any of its nuclei than the van der Waals radius of the corresponding atom.

§ It is more adequate to transform molecules as a whole to preclude the occurrence of physically meaningless unbound fragments. Hence, some atomic coordinates may overstep the [0; 1] interval.

The structure is divided into disordered parts (*PART* instructions in a *SHELX* file). Of course, the non-disordered part of the structure is treated with full occupancy. Depending on the position of the random point concerning the respective structure, the following increments are added to N_1 and N_2:

(i) The corresponding counter is not incremented if the point is not within the van der Waals radius of any atom in the structure investigated.

(ii) If the point is close to only one atom then the counter is incremented by the site occupation factor of this atom.

(iii) If the point is close to more atoms forming the same disordered moiety then the common site occupation factor of these atoms, *i.e.* the occupancy of the disordered part, is added to the respective counter.

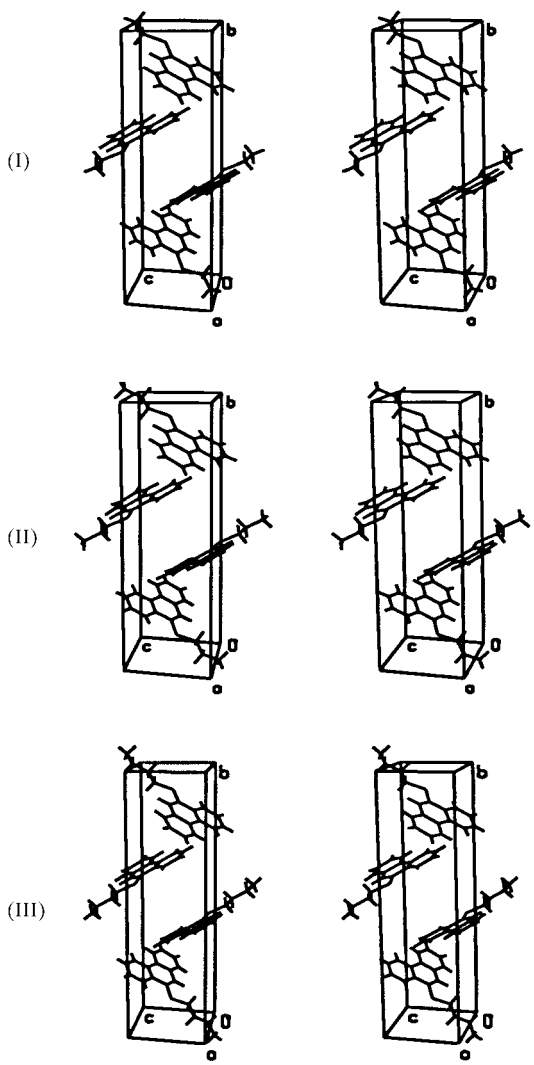


Fig. 2. Crystal packing of 9-ethylthiophenanthrene (I), 9-propylthiophenanthrene (II) and 9-butylthiophenanthrene (III).

(iv) If the point is simultaneously close to atoms that belong to different disordered parts then the counter is incremented by the sum of the occupancies of each disordered moiety involved. However, when this point is close to both non-disordered and disordered atoms, an increment greater than one is obtained. This value evidently has to be reset to one.

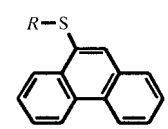
The increment of $N_\cap$ is the product of the two values obtained for N_1 and N_2, *i.e.* it is equal to the probability of the selected random point being occupied in *both* structures coincidently.

4. Results

As a benchmark of the new descriptor, I_v values were calculated for several isostructural crystal pairs (Table 2). Structures that could not sufficiently be described using I_i were selected from the literature. We compare the results obtained applying (4) and (5) and show how the latter extends the possible scope of isostructurality studies.

4.1. *Isostructurality of homologous 9-alkylthiophenanthrenes*

The homologous alkylthiophenanthrene structures were reported by Kansikas & Sipila (1997) with group *R* being ethyl (I), *n*-propyl (II) and *n*-butyl (III), respectively. All three crystallize in space group $P2_1/c$ with similar lattice parameters and molecular arrangements (Table 2, Fig. 2).



(I)–(III)

Index I_i was calculated for the 17 common heavy atoms within an asymmetric unit and for the 17×4 common heavy atoms in the unit cell, but I_v only for the four corresponding molecules (Table 1). In general, the use of a whole unit cell rather than a single molecule diminishes I_i. Therefore, it may be surprising that $I_i(17)$ for the pair (I)–(II) is smaller than $I_i(17 \times 4)$. In fact, it is not assured that the molecules closest to the origin overlap the most since the cell parameter and the fractional coordinate differences may compensate in other asymmetric units and thus lead to a better fit.

Apparently, I_i and I_v indices change in a parallel manner. The former, which is based on atomic coordinates (4), is much more sensitive than the latter, calculated from molecular volumes (5). Despite the visible close-packing similarity, negative I_i's are obtained, whereas the I_v scale remains reasonable. (One should bear in mind that the statistical nature of the calculation accounts for a *ca* $\pm 0.2\%$ uncertainty shown by the I_v indices.)

Table 2. *Space groups, unit-cell parameters and packing coefficients of the structures analyzed*

Structure	Space group	*a*	*b*	*c*	*β*	p.c.
(I)	$P2_1/c$	9.054	20.644	6.659	98.10	0.69
(II)	$P2_1/c$	9.067	21.123	7.007	99.12	0.70
(III)	$P2_1/c$	9.010	23.124	6.888	97.81	0.69
(IV)	$P2_1/c$	8.403	7.489	14.025	97.18	0.69
(V)	$P2_1/c$	8.473	7.437	13.952	94.51	0.71
(VI)	$P2_1/c$	12.282	13.920	10.068	99.51	0.68
(VII)	$P2_1/c$	12.279	13.938	10.037	99.55	0.67
(VIII*a*)	$P2_1/c$	8.129	19.077	11.256	101.56	0.68
(VIII*b*)	$P2_1/c$	8.020	19.187	11.175	98.89	0.69
(VIII*c*)	$P2_1/c$	8.056	19.500	11.252	98.72	0.69
(IX*d*)	$P2_1/c$	6.927	12.696	19.286	94.82	0.66
(X*d*)	$P2_1/c$	6.875	13.244	19.878	97.56	0.68
(X*e*)	$P2_1/c$	6.871	13.255	20.021	96.64	0.69
(X*f*)	$P2_1/c$	6.896	13.145	20.598	97.21	0.68
(XI*g*)	$P2_1/c$	6.908	13.754	19.561	102.90	0.66

An interesting conclusion can be drawn from the comparison of I_v and $I_v^{\max}$ values. Although the relative change in the molecular volumes between (I) and (II) is larger than between (II) and (III), the former pair shows a closer relationship in the crystal phase. Thus, the more similar molecular volumes do not necessarily lead to more similar crystal packings.

As indicated by the packing coefficients (p.c. in Table 2), the first methylene group added to *R* in (II) tightens its packing. The second, however, diminishes it again, which means that molecules are *necessarily* displaced in (III) to avoid possible strains induced by the longer chain. Also, this displacement is properly reflected by the smaller (II)–(III) isostructurality index compared with $I_v^{\max}$.

4.2. *Test calculations on non-isostructural crystals*

Obviously, the theoretical minimum of $I_v = 0$ is never obtained in a calculation, since there is always some overlap even between unrelated structures. To estimate a reasonable lower limit of the I_v index, test calculations were performed on crystal pairs retrieved from the Cambridge Crystallographic Database (Allen & Kennard, 1993) possessing similar unit cells with the same space group, but showing no other structural relationship.

As an example, acetyl benzoyl peroxide (IV) (Karch *et al.*, 1975) and 2,6-dimethoxy-1,4-oxathiane 4,4-dioxide (V) (Estrada & López-Castro, 1991) are presented. Despite the similarity of their unit cells (Table 2, $\Pi = 0.001$) and an $I_v^{\max}$ of 99.4%, the volumetric isostructurality index for these structures is only 22.6%. Similarly, the unit cells of 6-phenyl-4-oxa-8,9-10,11-dibenzotricyclo[5,4,0,$0^{1,6}$]undeca-2,8,10-triene-5-one (VI) (van Arendonk *et al.*, 1978) and *rel*-(1*R*,4*R*,9*R*)-1-acetyl-9-(*t*-butylthio)-9-cyano-1,4-dihydro-1,4-ethanonaphthalene (VII) (Döpp *et al.*, 1989) are almost the same ($\Pi = 0.004$) and $I_v^{\max} = 99.1\%$. Nevertheless, I_v is only 30.2%.

From these examples it is apparent that volumetric isostructurality indices of ~50% still indicate pronounced structural resemblance, whereas around 30% they can be obtained from randomly overlapping structures.

4.3. *Inclusion compounds of 5-methoxysulfadiazine*

The inclusion properties of 5-methoxysulfadiazine (VIII) were studied by Caira & Mohamed (1993). The solvates formed with chloroform (VIII*a*), tetrahydrofuran (VIII*b*) and 1,4-dioxane (VIII*c*) are isostructural. The different guest molecules are incorporated into an almost unaltered host lattice (Fig. 3).

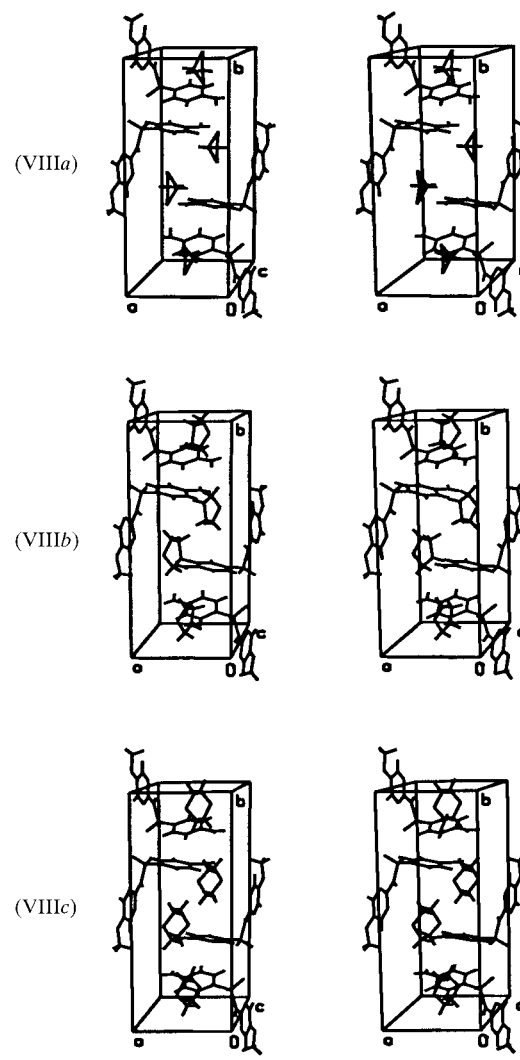


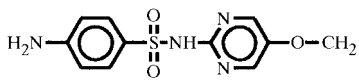
Fig. 3. Stereoview of inclusion compounds of 5-methoxysulfadiazine with chloroform (VIII*a*), tetrahydrofuran (VIII*b*) and dioxane (VIII*c*).

Table 3. *Isostructurality of inclusion compounds of 5-methoxysulfadiazine with chloroform (VIIIa), tetrahydrofuran (VIIIb) and 1,4-dioxane (VIIIc)*

I_i can be calculated only for the 19 heavy atoms of the host molecules.

Structures	Π	$I_i(19 \times 4)$ (%)	I_v^{host} (%)	I_v^{guest} (%)	I_v (%)
(VIII*b*)–(VIII*c*)	0.011	71.0	90.6	86.5 [95.6]	89.7 [98.6]
(VIII*a*)–(VIII*b*)	0.001	70.1	91.0	77.1 [96.2]	87.7 [99.4]
(VIII*a*)–(VIII*c*)	0.010	59.3	87.6	75.3 [91.7]	84.8 [97.9]

Interestingly, the chemically unrelated solvent ($CHCl_3$) also gives the same packing as the cyclic ethers, although its looser fit is emphasized by disorder. The host molecule itself and its clathrate with acetylsalicylyc acid (Caira, 1994) are not isostructural either with these associates or each other.



(VIII)

The study of these isostructural inclusion compounds (Kálmán & Párkányi, 1997) was limited to the inspection of host molecules by the restrictions implicit in the definition of I_i. In contrast, the descriptor I_v allows for the comparison of regions occupied by such dissimilar molecules as dioxane and tetrahydrofuran, as well as for a systematic treatment of disorder shown by chloroform.

As expected, the highest I_v value is obtained for the associates with dioxane and tetrahydrofuran (Table 3). In accordance with the similar solvent volumes (VIII)–chloroform is closer to the tetrahydrofuran solvate. However, the sequence of I_i indices computed for the host molecules differs from the sequence of I_v^{host} values, suggesting that such small differences between isostructurality indices are of limited significance.

Neglecting these minor deviations, I_v and I_v^{host} values move together with I_v^{max}. On the other hand, I_v^{guest} for the (VIII*a*)–(VIII*b*) pair is small compared with the corresponding maximum value. This shows that in spite of the similar volumes, chloroform and tetrahydrofuran, owing to their different shapes, cannot occupy the same volume. The smaller change in I_v^{host} shows that the host structure damps guest alteration effects.

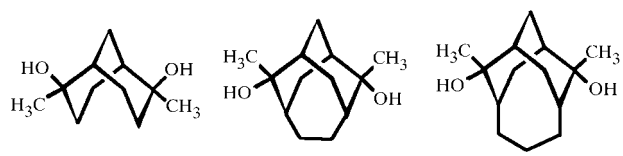
The relationship $I_v^{host} > I_v^{guest}$ corresponds to loosely bound guest molecules *versus* a relatively rigid hydrogen-bonded host lattice. One may anticipate that the comparison of full and partitioned isostructurality indices can give a general hint on the stiffness of those fragments with respect to packing forces.

4.4. *Cocrystalline compounds of tubuland diols*

The helical tubuland diols (IX), (X) and (XI) were cocrystallized with simple phenols by Ung *et al.* (1994). The resulting cocrystals provide an outstandingly good subject of our examinations through the variation of both host and guest molecules (*d*: *p*-chlorophenol, *e*: *p*-hydroxythiophenol, *f*: *p*-methoxyphenol and *g*: phenol).

Table 4. *Isostructurality of cocrystals of (X) with p-chlorophenol (Xd), p-hydroxythiophenol (Xe) and p-methoxyphenol (Xf)*

	Π	I_v (%)	I_v^{host} (%)	I_v^{guest} (%)
(X*d*)–(X*e*)	0.004	92.5 [99.3]	92.7	91.1 [97.9]
(X*e*)–(X*f*)	0.012	86.7 [99.3]	87.7	83.7 [97.6]
(X*d*)–(X*f*)	0.010	83.0 [98.6]	83.8	79.6 [95.5]



(IX) (X) (XI)

The compounds of 2,7-dimethyltricyclo[4.3.1.1^{3,8}]-undecane-*syn*-2,*syn*-7- diol (X) with *p*-chlorophenol (X*d*), *p*-hydroxythiophenol (X*e*) and *p*-methoxyphenol (X*f*) equally crystallize in space group $P2_1/c$, assuming 1:1 host:guest ratio (Table 2).

The volumes of the solvent molecules increase in the order (X*d*), (X*e*) and (X*f*). In terms of I_v^{max}, (X*e*) is midway between the others (Table 4). Contrasting the similar maximum values, the isostructurality indices for the (X*d*)–(X*e*) and (X*e*)–(X*f*) pairs differ significantly. Here, a similar situation is encountered again as with the phenanthrene thioethers [(I), (II) and (III)]. A small increase in the guest volume ($d \rightarrow e$) is tolerated by the crystal without a major displacement of the molecules, whereas an even larger molecule does not fit in the same space (X*f*) and thus the packing distorts more (see also the packing coefficients in Table 2).

The I_v^{guest} indices calculated for only the heavy atoms would be approximately 5% smaller for (X*f*), showing that the volume of H atoms cannot be disregarded in the volume of the methoxy group. (Usually, omitting H atoms leads to only 1–2% difference in the resulting I_v.)

In these binary crystals host molecules are more isostructural than guest molecules, but the differences between their respective isostructurality indices are much smaller than in the solvates of (VIII). While guest molecules are located in open channels in (VIII*a*), (VIII*b*) and (VIII*c*), in the inclusions of host (X) they form separate molecular layers (Fig. 4). The layers are interconnected by → (host → host → guest) → hydrogen-bond chains, hence the guest molecules are also held tightly in these crystals.

The 2,6-dimethylbicyclo[3.3.1]nonane-*exo*-2,*exo*-6-diol *p*-chlorophenol cocrystal (IX*d*) was also reported to be isostructural with (X*d*)–(X*f*) (Fig. 5). In principle, this structure can be obtained from (X*d*) by removing a linking dimethylene group from the host molecule. In

practice, the molecule turns around and the single carbon linkage moves into the position of the missing atoms, while its original place remains unoccupied by the host. This *ca* 180° rotation is accompanied by a significant translation of the molecules. The relatively small isostructurality indices (Table 5) also emphasize how much the structure is rearranged. Nevertheless, the packing arrangement and the hydrogen-bonding network are unaltered.

Surprisingly, (IX*d*) is more similar to (X*e*) than to (X*d*). The effects of host and guest changes are probably better compensated in the former case. It also seems to be reasonable that the need of a different host for being complementary to the same guest leads to an increased displacement. This may also explain the low I_v^{host} value obtained for (IX*d*) and (X*d*).

Table 5. *Isostructurality of the p-chlorophenol associate of (IX) with cocrystals of (X) and p-chlorophenol (Xd), p-hydroxythiophenol (Xe) and p-methoxyphenol (Xf)*

	Π	I_v (%)	I_v^{host} (%)	I_v^{guest} (%)
(IX*d*)–(X*d*)	0.027	72.7 [95.4]	69.1 [93.4]	76.2 [99.3]
(IX*d*)–(X*e*)	0.031	74.8 [94.7]	72.1 [93.2]	77.1 [97.2]
(IX*d*)–(X*f*)	0.044	71.9 [94.0]	71.4 [93.6]	69.3 [94.9]

The structure of (IX*d*) is clearly the farthest from (X*f*). While the larger *p*-methoxyphenol guest expands the cell compared with (X*d*), replacement of the host with (IX) shrinks it. The combined effect of these opposite changes gives rise to a further decrease of isostructurality.

Even smaller isostructurality indices were obtained between the inclusions of (X) and the phenol solvate of 2,8-dimethyltricyclo[5.3.1.1^{3,9}]dodecane-*syn*-2,*syn*-8-diol (XI*g*). The host molecule (XI) can be formed by adding a CH_2 group to (X), whereas phenol is smaller than any of the guests of (X). Thus, one would predict that some 'guest regions' of (X*d*)–(X*f*) are occupied by the enlarged host in (XI*g*) and that host molecules are simultaneously shifted towards the released guest space. Indeed, the overall isostructurality index I_v is greater than either I_v^{host} or I_v^{guest} for all three pairs, proving the validity of this assumption (Table 6).

The (X*d*)–(X*f*) *versus* (XI*g*) I_v values decrease as the size of the guest molecule increases in the order (X*d*), (X*e*) and (X*f*). A careful observation of the crystal structure (Fig. 6) reveals that the elongated ring protrudes towards the *para* hydrogen of the phenol molecules. Increasing the size of the *para* substituent of the guest molecule in (X) cocrystals thus repels the host molecule further away from its position in (XI*g*).

The Π descriptor of unit-cell similarity gives misleading results for (XI*g*), because the more than 0.5 Å lengthening of axis *b* is compensated by a similar shortening of axis *c*. The more complicated description of Rutherford (1997) would presumably reflect the dissimilarity of cells.

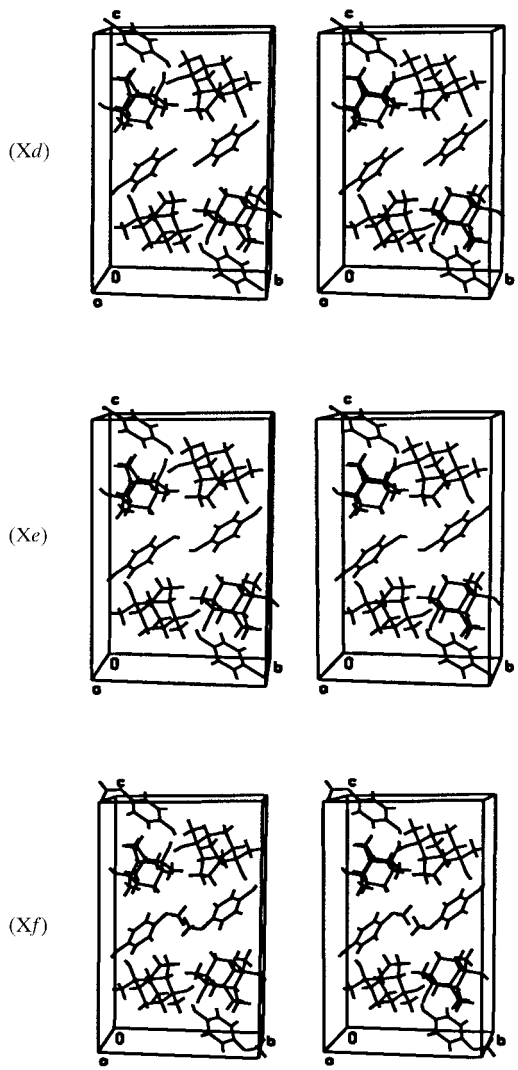


Fig. 4. Cocrystalline compounds of 2,7-dimethyltricyclo[4.3.1.1^{3,8}]undecane-*syn*-2,*syn*-7-diol (X) with *p*-chlorophenol (X*d*), *p*-hydroxythiophenol (X*e*) and *p*-methoxyphenol (X*f*).

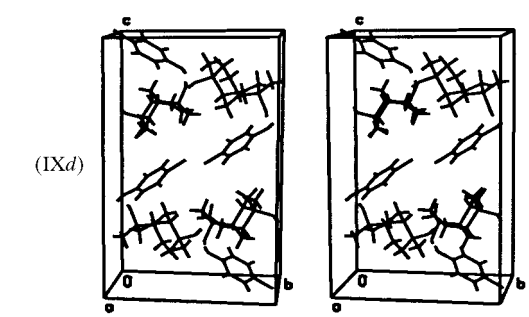


Fig. 5. Structure of the cocrystals of 2,6-dimethylbicyclo[3.3.1]nonane-*exo*-2,*exo*-6-diol with *p*-chlorophenol (IX*d*).

Table 6. *Isostructurality of the phenol solvate of (XI) with (X), p-chlorophenol (Xd), p-hydroxythiophenol (Xe), p-methoxyphenol (Xf), and with (IX), p-chlorophenol (IXd) cocrystalline compounds*

	Π	I_v (%)	I_v^{host} (%)	I_v^{guest} (%)
(XI*g*)–(X*d*)	0.003	70.0 [99.8]	69.2 [96.5]	64.5 [92.4]
(XI*g*)–(X*f*)	0.013	61.8 [98.7]	61.5 [96.2]	51.2 [88.0]
(XI*g*)–(X*e*)	< 0.001	65.9 [99.3]	65.1 [96.6]	58.7 [90.4]
(XI*g*)–(IX*d*)	0.031	54.3 [95.3]	49.7 [89.9]	55.3 [93.0]

The difference between structures (IX*d*) and (XI*g*) is so large that I_v drops to 54.3%. This rather low value indicates the borderline between isostructurality and homostructurality (Kálmán *et al.*, 1993). Although the sum of host and guest volumes is similar ($I_v^{\max} = 95.3\%$), as is the relative arrangement of molecules, the condition of molecular *isometricity* is poorly satisfied. The relatively small packing coefficient of 0.66 for both structures also suggests that they can be considered as distortions of the more ideal binary packing of (X) in opposite directions.

Ung *et al.* (1994) reported on other cocrystalline compounds of (IX) and (X) which are expected to be either isostructural or homostructural with those discussed above on the basis of their X-ray powder patterns. In the 2:1 clathrate of (IX) with hydroquinone the guest molecule occupies the place of two phenol molecules without altering the packing motif. The *c* axis, however, shortens from ~20 to ~16 Å, thus the resulting structure is only homostructural with the others. A detailed description of the factors determining these structures, which is beyond the scope of this paper, has already been given (Ung *et al.*, 1994).

5. Conclusions

The limitations of the isostructurality index I_i (4) lead us to introduce a new measure of isostructurality I_v (5), which is based on the overlap of molecular volumes. This new descriptor extends the scope of isostructurality studies to the analysis of weakly isostructural, non-orthogonal, heteromolecular and disordered structures also. The results of such an investigation provide useful data for interpreting the close-packing rules.

The results for 9-alkylthiophenanthrenes show that a stepwise homologous extension of a molecule can either result in an increase of the packing coefficient or displacement of molecules. The former is achieved by inserting the newly added atoms to the space unoccupied by the smaller molecules. If there is no more room for new atoms then molecules are displaced relative to each other, but the isostructurality may still be retained.

In heteromolecular crystals the roles of host and guest changes were studied using volumetric isostructurality indices. From I_v values information was extracted on the stiffness of intermolecular interactions and on the degree and structural consequences of alterations in host–guest complementarity.

Presumably, isostructurality calculations accompanied by a careful structural interpretation of the results may become a useful tool in understanding the factors determining a series of related crystal structures.

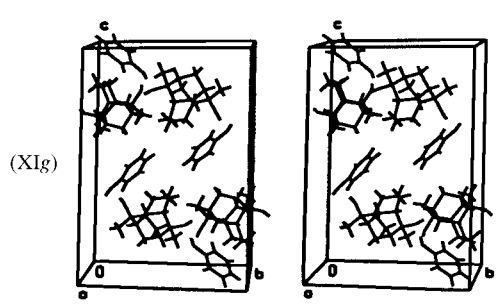


Fig. 6. Crystal structure of 2,8-dimethyltricyclo[5.3.1.1^{3,9}]dodecane-*syn*-2,*syn*-8-diol phenol solvate (XI*g*).

APPENDIX *A*
The application of Löwdin orthogonalization for crystal structures

The symmetric orthogonalization method (Löwdin, 1950) is well known among quantum chemists and is usually described in textbooks of quantum chemistry (*e.g.* Szabo & Ostlund, 1982). It transforms a set of non-orthogonal, *i.e.* overlapping set of vectors $\{\mathbf{a}_i\}$ to an orthonormal vector set $\{\mathbf{x}_i\}$ that fulfills the equations:

$$\mathbf{x}_i \cdot \mathbf{x}_j = \delta_{ij},$$
$$\sum_i |\mathbf{x}_i - \mathbf{a}_i|^2 \rightarrow \min. \tag{8}$$

To apply this procedure for cell axes let us define $\{\mathbf{a}_i\}$ as the set of unit cell translation vectors. Let us form the metric tensor $\mathbf{S}$, where $S_{ij} = \mathbf{a}_i \cdot \mathbf{a}_j$. The orthogonal directions (vectors of unit length) that are closest to the directions of the original vectors can then be obtained as

$$\mathbf{x}_i = \sum_j \left(\mathbf{S}^{-1/2}\right)_{ji} \mathbf{a}_j, \tag{9}$$

where $\mathbf{S}^{-1/2}$ is the matrix for which $\mathbf{S}^{-1/2} \cdot \mathbf{S}^{-1/2} = \mathbf{S}^{-1}$, *i.e.* its square equals to the inverse of $\mathbf{S}$. The orthogonalized cell axis lengths are calculated as the dot product of the original vectors and the corresponding orthonormal ones, *i.e.* as the projection of the original axes to the orthogonal directions.

$$a_i^{\text{orth}} = \mathbf{x}_i \cdot \mathbf{a}_i = \left(\sum_j \left(\mathbf{S}^{-1/2}\right)_{ji} \mathbf{a}_j\right) \cdot \mathbf{a}_i$$
$$= \sum_j \left(\mathbf{S}^{-1/2}\right)_{ji} S_{ji} \tag{10}$$

Unfortunately, the eigenvectors and eigenvalues of **S** are needed for the calculation of $\mathbf{S}^{-1/2}$ and we were unable to derive a formula to obtain them from the unit-cell parameters. Thus, the calculation can only be performed numerically, *e.g.* with the aid of a computer algebra package.†

To illustrate the application of this method in the calculation of Π, we describe the Löwdin orthogonalization of the cell parameters of (I) (Table 2).

$$a = 9.054\ \text{Å} \quad b = 20.644\ \text{Å} \quad c = 6.659\ \text{Å}$$
$$\alpha = 90^\circ \quad \beta = 98.10^\circ \quad \gamma = 90^\circ$$

In this case the metric tensor can be calculated as:

$$\mathbf{S} = \begin{pmatrix} a^2 & ab\cos\gamma & ac\cos\beta \\ ab\cos\gamma & b^2 & bc\cos\alpha \\ ac\cos\beta & bc\cos\alpha & c^2 \end{pmatrix} = \begin{pmatrix} 81.975 & 0 & -8.495 \\ 0 & 426.175 & 0 \\ -8.495 & 0 & 44.342 \end{pmatrix}$$

In order to calculate the $-1/2$ power of **S**, we write it as a product of three matrices (eigenvalue decomposition)

$$\mathbf{S} = \mathbf{U}\mathbf{D}\mathbf{U}^T = \begin{pmatrix} 0.978 & 0 & 0.210 \\ 0 & 1 & 0 \\ -0.210 & 0 & 0.978 \end{pmatrix} \times \begin{pmatrix} 83.804 & 0 & 0 \\ 0 & 426.175 & 0 \\ 0 & 0 & 42.514 \end{pmatrix} \times \begin{pmatrix} 0.978 & 0 & -0.210 \\ 0 & 1 & 0 \\ 0.210 & 0 & 0.978 \end{pmatrix},$$

where **D** has the eigenvalues of **S** in its diagonals, whereas **U** contains the eigenvectors of **S** as column vectors.

The $-1/2$ power of **D** is obtained by taking the square root of the reciprocal of the diagonal elements.

$$\mathbf{D}^{-1/2} = \begin{pmatrix} 1/(83.804)^{1/2} & 0 & 0 \\ 0 & 1/(426.175)^{1/2} & 0 \\ 0 & 0 & 1/(42.514)^{1/2} \end{pmatrix} = \begin{pmatrix} 0.1092 & 0 & 0 \\ 0 & 0.04844 & 0 \\ 0 & 0 & 0.1534 \end{pmatrix}$$

$\mathbf{S}^{-1/2}$ can now be determined as

$$\mathbf{S}^{-1/2} = \mathbf{U}\mathbf{D}^{-1/2}\mathbf{U}^T = \begin{pmatrix} 0.978 & 0 & 0.210 \\ 0 & 1 & 0 \\ -0.210 & 0 & 0.978 \end{pmatrix} \times \begin{pmatrix} 0.1092 & 0 & 0 \\ 0 & 0.04844 & 0 \\ 0 & 0 & 0.1534 \end{pmatrix} \times \begin{pmatrix} 0.978 & 0 & -0.210 \\ 0 & 1 & 0 \\ 0.210 & 0 & 0.978 \end{pmatrix} = \begin{pmatrix} 0.1112 & 0 & 0.0091 \\ 0 & 0.04844 & 0 \\ 0.0091 & 0 & 0.1514 \end{pmatrix}.$$

Finally, the orthogonalized axes are calculated according to (10).

$$a^{orth} = \sum_{j=1}^{3} \left(\mathbf{S}^{-1/2}\right)_{j1} S_{j1} = 0.1112 \times 81.975 + 0 \times 0 + 0.0091 \times (-8.495) = 9.038$$

$$b^{orth} = \sum_{j=1}^{3} \left(\mathbf{S}^{-1/2}\right)_{j2} S_{j2} = 0 \times 0 + 0.04844 \times 426.175 + 0 \times 0 = 20.644$$

$$c^{orth} = \sum_{j=1}^{3} \left(\mathbf{S}^{-1/2}\right)_{j3} S_{j3} = 0.0091 \times (-8.495) + 0 \times 0 + 0.1514 \times 44.342 = 6.636$$

† A utility to perform this calculation in the *MuPAD* computer algebra system, which is free for non-commercial users (http://www.mupad.de), is available from the authors on request. An orthogonalization program is also available as C++ source code or as Linux/i386 or SGI IRIX executable.

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