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Morphotropism: link between the isostructurality, polymorphism and (stereo)isomerism of organic crystals

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An ongoing analysis of the supramolecular self-assembly of disubstituted cycloalkanes has led to the discovery of seven packing patterns built up from hydrogen-bonded homo- and heterochiral chains of racemic molecules, associated in either antiparallel or parallel arrays [Kálmán *et al.* (2001). *Acta Cryst.* B**57**, 539–550]. Two further patterns have been revealed in the close packing of analogous alicyclic β-amino acids [Fábián *et al.* (2005). *Cryst. Growth Des.* **5**, 773–782]. Since each pattern is represented by at least one crystal structure, the chemical similarity and crystallographic forms of these crystals have facilitated the recognition that these patterns differ by one or two rotation(s) of the common motifs (*e.g.* dimers, tetramers, helices *etc.*), or the whole pattern may rotate through 180° in an oblique unit cell. Such non-crystallographic – with the exception of polymorphism – virtual rotations as a whole may be denoted by the expression *morphotropism*. According to Kitaigorodskii [(1961), *Organic Chemical Crystallography*, pp. 222–231. New York: Consultants Bureau], morphotropism is an attempt to keep the packing coefficient above 0.6 whenever there are alternative possibilities for the structures of closely related molecules. It has been found that crystals of stereoisomers are also frequently related by such virtual rotations. Similarly, non-crystallographic rotations effect bridges between homostructural crystals [Kálmán *et al.* (1993*b*). *Acta Cryst.* B**49**, 1039–1049] and occasionally hallmark the polymorphism of organic compounds [Kálmán *et al.* (2003) *J. Am. Chem. Soc.* **125**, 34–35]. In polymorphs, however, such rotations really transform one molecule into another in order to achieve a better packing mediated by solvents, temperature *etc.*

1. Introduction

In his seminal book *Organic Chemical Crystallography*,[1] Kitaigorodskii (1961) dealt with, among other topics, the isomorphism of organic molecules. His examples were mainly halo compounds with molecular similarities, which he considered to be sufficient to give rise to isomorphous crystals. From this conclusion, he jumped directly to the suggestion that 'it is therefore of some interest to determine the intermolecular spacing in non-isomorphous crystals of compounds with similar molecules. We explain the morphotropic step as due to the impossibility of maintaining a sufficiently high packing coefficient for isomorphous substitution'. He referred to tetra-*p*-ethoxyphenyltin {[$Sn(C_2H_5OC_6H_4)_4$]}, which, unlike

[1] The original Russian issue was published by the Publishing House of the Academy of Sciences of the USSR in Moscow in 1955.

Table 1
A list and labels of compounds (depicted in Fig. 1) discussed in the text.

(I*a*), (I*b*)	*cis*- and *trans*-2-Hydroxycyclooctanecarboxylic acids
(II*a*)	(1*R**,2*S**,4*R**)-4-*tert*-Butyl-2-hydroxycyclopentanecarboxylic acid
(II*b*)	(1*R**,2*S**,4*S**)-4-*tert*-Butyl-2-hydroxycyclopentanecarboxylic acid
(II*c*)	(1*R**,2*S**,5*R**)-5-*tert*-Butyl-2-hydroxycyclopentanecarboxylic acid
(III*b*)	*trans*-2-Hydroxycyclopentanecarboxylic acid
(IV*a*)	*cis*-2-Hydroxycyclohexanecarboxylic acid
(V*a*), (V*b*)	*cis*- and *trans*-2-Hydroxycycloheptanecarboxylic acids
(V*b*)$^{(p)}$, (V*b*)$^{(a)}$	Homostructural dimorphs of (V*b*)
(VI*b*)	(1*R**,2*R**,4*S**)-4-*tert*-Butyl-2-hydroxycyclopentanecarboxamide
(VII*a*), (VII*b*)	*cis*- and *trans*-2-Hydroxycyclopentanecarboxamides
(VIII*b*)	*trans*-2-Hydroxycycloheptanecarboxamide
(IXα), (IXβ)	Homostructural polymorphs of glycine
(Xα), (Xβ)	Anhydrous polymorphs of nitrofurantoin
(XIα), (XIβ)	Isostructural dimorphs of *trans*-13-azabicyclo[10.2.0]tetradecan-13-one
(XII*a*)	*cis*-2-Aminocyclopentanecarboxylic acid
(XIII*a*), (XIII*b*)	*cis*- and *trans*-2-Aminocyclohexanecarboxylic acids
(XIV*a*)	*cis*-2-aminocycloheptanecarboxylic acid
(XV*a*)	*cis*-2-Aminocyclooctanecarboxylic acid
(XVI*a*), (XVI*b*)	*cis*- and *trans*-2-Aminocyclohex-4-enecarboxylic acids

the tetragonal crystals of the closely related $[Sn(C_6H_5)_4]$, $[Sn(CH_3C_6H_4)_4]$ and $[Sn(CH_3OC_6H_4)_4]$, is monoclinic. He stated that the observed rearrangement maintains the packing density at *ca* 0.67. Otherwise, it would have dropped below 0.6. The essence of morphotropism remained unexplored, however.

More than 30 years later, we wrote a paper[2] on the isostructuralism of organic molecules in terms of Kitaigorodskii's early perception (Kálmán *et al.*, 1993*a*). Among the examples was on a packing rearrangement which was observed twice in a series of organometallic compounds related by isostructurality. While $Me_3Si–SiPh_3$ (Párkányi & Henge, 1982) and its analogs $Me_3Si–GePh_3$ (Párkányi *et al.*, 1986) and $Me_3Ge–SiPh_3$ (Pannell *et al.*, 1990) form trigonal crystals (common space group, $P\bar{3}$), the isomeric $Me_3Ge–SnPh_3$ and $Me_3Sn–GePh_3$ are pseudohexagonal with the orthorhombic space group $Pna2_1$ (Pannell *et al.*, 1992). In the former case, the $Me_3E–E'Ph_3$ dumbbells related by a center of symmetry are antiparallel, whereas in the orthorhombic pair of structures they are stacked in a parallel array. Continuing these investigations, we found that the crystals of $Me_3Ge–GePh_3$ (Párkányi *et al.*, 1994), $Me_3Sn–SnPh_3$ (Párkányi *et al.*, 1996) and some others, such as $Me_3Pb–SnPh_3$ and $Me_3Pb–PbPh_3$ (Preut & Huber, 1976), are again trigonal with the space group $P\bar{3}$. A 180° rotation of the $R_3Ge–SnR'_3$ dumbbells, perpendicular to the respective $E–E'$ bond, was attributed (Kálmán & Párkányi, 1997) to the 0.19 Å difference in the covalent radii of Ge and Sn with respect to those of 0.11 and 0.06 Å observed between the Ge–Si and Pb–Sn pairs, respectively. In accordance with Kitaigorodskii's perception, we claimed that 'in these pseudohexagonal unit cells, the bumps of the molecules stacked with similar orientation along the polar *c*-axis fit perfectly into the hollows of the adjacent columns generated by glide planes, thereby forming new efficient close packing'.

Although the $P\bar{3} \rightarrow Pna2_1$ rearrangement is a 180° rotation of every second dumbbell in the unit cell, we did not feel (Kálmán & Párkányi, 1997) these examples to be sufficient for morphotropism to be regarded as a rotation of motif(s) in general, as suggested by the mirror translation of the Greek words 'morphos' (shape) and 'trópos' (turn) or 'tropé' (turning). Neither the symmetrical spirosulfurane (Kálmán *et al.*, 1973) nor the analogous spiroselenourane (Dahlén, 1974), with parallel (space group *Fdd*2) and antiparallel (space group *C*2/*c*) molecules sitting on twofold axes, compelled us to recognize the importance of non-crystallographic rotations in crystal chemistry. Now, 50 years after Kitaigorodskii's publication, the present paper aims to explore the essence of morphotropism. Several forms of morphotropism between isostructural crystals, polymorphs and stereoisomeric pairs are presented, recognized in a survey of the crystal structures of 2-hydroxycycloalkanecarboxylic acids, analogous carboxamides, alicyclic β-amino acids and their β-lactam derivatives determined in our laboratory. These molecules, together with a few examples of morphotropism found by chance in the literature, are listed in Table 1 and depicted in Fig. 1.

First, we recognized that the racemic crystals of these compounds are built up from hydrogen-bonded homo- or heterochiral chains in either antiparallel or parallel arrays (Kálmán *et al.*, 2001, 2002*a*). They form seven packing patterns, which can be transformed into each other directly or indirectly (Kálmán *et al.*, 2002*b*). Several pairs of crystals with different degrees of isostructurality were discerned (Kálmán *et al.*, 2001, 2002*a*,*b*). Novel forms of polymorphism and isostructurality were then observed, which could be attributed to non-crystallographic rotations between common motifs (Kálmán *et al.*, 2003, 2004). Finally, a study of the isostructurality of four *cis*-alicyclic β-amino acids, tested against ring deformation (the cyclohexane ring was replaced by the cyclohexene ring) and stereoisomerism (Fábián *et al.*, 2005), revealed two different forms of close packing, differing in the non-crystallographic rotations of a common motif. Bearing in mind the antiparallel *versus* parallel fits of the $Me_3E–E'Ph_3$ dumbbells (Kálmán & Párkányi, 1997) mentioned above, the novel examples must be regarded as *morphotropes*. This led belatedly (by 50 years) to the elucidation of the morphotropism exhibited by isomers, isostructures and polymorphs.

2. The forms of morphotropism

2.1. Rotation of dimers

Four of the seven patterns built up from either heterochiral or homochiral chains of racemic molecules in an antiparallel array are characterized by dimers (Kálmán *et al.*, 2002*a*), described by the graph-set notation $R_2^2(12)$ (Etter, 1990; Bernstein *et al.*, 1995). They are distinguished by their acceptor groups (either OC or OH) which can be interconverted by a simultaneous 180° rotation of the COOH and

[2] This was a contribution to the A. I. Kitaigorodskii Memorial Issue on Molecular Crystal Chemistry (Hargittai & Kálmán, 1993).

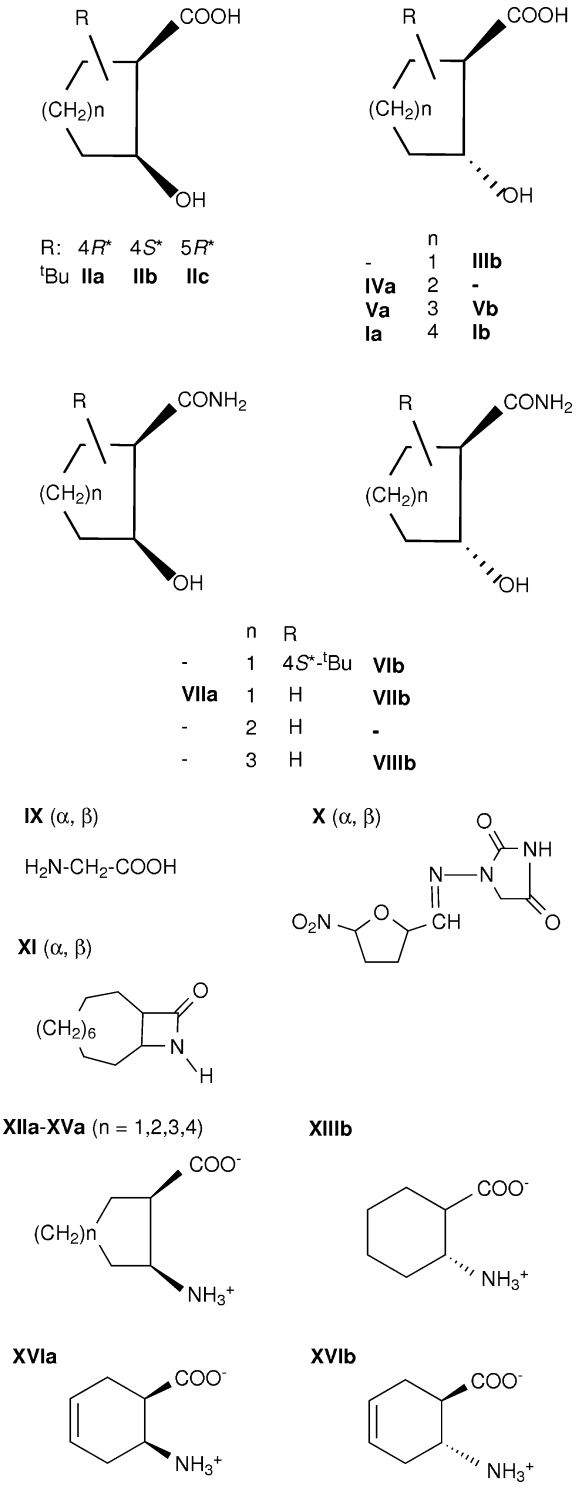

Figure 1
Chemical line drawings of the molecules labeled from (I*a*) to (XVI*b*).

OH moieties. Separately, these dimer motifs may exist in lateral associations held together by $R_4^4(12)$ tetramers, while their linear association is the same, since either type generates the other dimer. This linear array, demonstrated by *trans*-2-hydroxycyclooctanecarboxylic acid (I*b*),[3] is therefore unique (Kálmán *et al.*, 2002*b*). It is the basic pattern (**1**) from which (Fig. 2) the others can be deduced by non-crystallographic rotations of the OC or OH dimers.

To visualize such rotations the symbolic (topological) presentation of the packing patterns that we have introduced (Kálmán *et al.*, 2002*a*,*b*) is convenient. To simplify the homologous 1,2-disubstituted alicyclic (cyclopentane → cyclooctane) monomers (Fig. 3*a*), the saturated rings are omitted, while the functional groups are depicted by graphical symbols. A straight line represents an OH group, a circle a CO group and a triangle (in carboxamides) an NH_2 group (Fig. 3*b*). To distinguish between the C1-*R* and C1-*S* enantiomers the symbols are converted into black or white triangles (Fig. 3*c*). The hydrogen bonding in the heterochiral OC and OH dimers is denoted by dotted lines (Fig. 3*d*). In the topological descriptions, the OC and OH dimers simply rotate around their center of symmetry through either 90 or 180°. We apply these symbols in the analysis of pattern **1** depicted in Fig. 4(*a*), which shows the two parallel molecular ribbons in which the OC and OH dimers alternate. These dimers are taken to rotate through 90 or 180° as follows:

(i) A rotation of every second dimer (either OC or OH) through 90° results in their lateral association **2** with the alternatives ***2a*** and ***2b*** held together by $R_4^4(12)$ tetramers of C_i symmetry (Fig. 4*b*). The sub-patterns ***2a*** (OC) and ***2b*** (OH) retain the triclinic space group $P\bar{1}$ from **1**.

(ii) The motifs in sub-patterns ***2a*** and ***2b*** are stacked in a parallel orientation, which, similarly to the R_3E–$E'R_3'$ dumbbells (Kálmán & Párkányi, 1997), can be rearranged in an antiparallel mode by a 180° rotation of every second dimer in unison. In the novel sub-patterns ***3a*** and ***3b*** (Fig. 4*c*), the symmetry of the $R_4^4(12)$ tetramers alters from C_i to C_2, while the space group changes from $P\bar{1}$ to $C2/c$.

(iii) The rearrangement of sub-patterns ***3a*** and ***3b*** is continued if the antiparallel motifs are rotated through 90° around their main axis in unison. Thus, once again, two linear associations ***4a*** and ***4b*** are obtained (Fig. 4*d*), in which the heterochiral dimers are separated by homochiral dimers, which in the crystalline state readily polymerize into infinite helices.[4] These packing patterns (***4a*** and ***4b***) display monoclinic symmetry with the space group $P2_1/c$. The three patterns **2**, **3** and **4** (except for ***2a***) are exemplified by the crystal structures listed in Table 2.

Although the symbolic descriptions of the crystal structures do have advantages and predictive power, they conceal the relevant three-dimensional information, *e.g.* the planar and folded conformations of the dimers cannot be seen. In addition, it must be remembered that dimers rotate through 90° around their main axes,[5] while their 180° rotation takes place perpendicularly to their main axes (see Fig. 2*a* *versus* *b*). Nevertheless, these symbols enable us to describe the morphotropism observed between the crystal structures which are 'non-isomorphous'.

[3] The *cis* and *trans* isomers are distinguished by bold *a* and *b*.

[4] To diminish the empty channels in the unit cell, *i.e.* to increase the close-packing coefficient, the principal factor in Kitaigorodskii's realm.

[5] The main axis is defined by a vector between the remotest CH_2 groups of the opposite cycloalkane rings.

Table 2
Packing patterns and their space groups assumed by the investigated disubstituted cycloalkane molecules.

↔: isostructural pairs and groups; $\leftarrow^{2}\rightarrow$: with alternating (two-dimensional layers); (\), (/): with different orientations in oblique unit cells.

Patterns	Space groups	Molecules
1	$P\bar{1}$	(I*b*)
2*b*	$P\bar{1}$	(II*b*)
3*a*	$C2/c$	(/) (III*b*) ↔ (IV*a*) (60%)
3*b*	$C2/c$ ($I2/c$)	(IV*a*) (40%) ↔ (\) (V*a*)
4*a*	$P2_1/c$	(VI*b*)
4*b*	$P2_1/c$	(I*a*)
5	$Pca2_1$, $Pbca$	(VII*b*) $\leftarrow^{2}\rightarrow$ (VIII*b*)
6	$P2_1/c$	(/) (II*a*) ↔ (\) (VII*a*)
7	$P2_1/n$ ($Pna2_1$, $Pn2_1a$)	(I*c*), [(V*b*)(^{p}) $\leftarrow^{2}\rightarrow$ (V*b*)(^{a})]
8a	$P\bar{1}$	(/) (XII*a*) ↔ (XIII*a*) ↔ (XIV*a*) ↔
8b	$P\bar{1}$	↔ (\) (XV*a*)
9a	$P2_1/c$	(/) (XVI*a*) ↔
9b	$P2_1/c$	↔ (\) (XIII*b*) ↔ (XVI*b*)

Kitaigorodskii (1961) guessed that the best way to find morphotropism is the study of isostructural crystals surrounded by 'non-isomorphous' relatives. This guess is substantiated by the homologs (III*b*), (IV*a*) and (V*a*) (space group $C2/c$), which are isostructural (Kálmán *et al.*, 2002*a*), while the fourth member of the series, *cis*-2-hydroxycyclooctanecarboxylic acid (I*a*), forms crystals in the space group $P2_1/c$ (Kálmán *et al.*, 2002*b*). The sub-patterns ***3a*** and ***4a*** are related by a dimer rotation through 90°. It is noteworthy that the sub-pattern ***4a*** and the basic pattern **1** are related directly by a rotation of the OC dimers (Fig. 3*d*) through 180° (Figs. 4*a* and *d*). In other words, the structures of (I*a*) and (I*b*), differing only in the chirality of the C2 atom, can be virtually converted into another by a non-crystallographic rotation. Thus, they may be regarded as morphotropes.

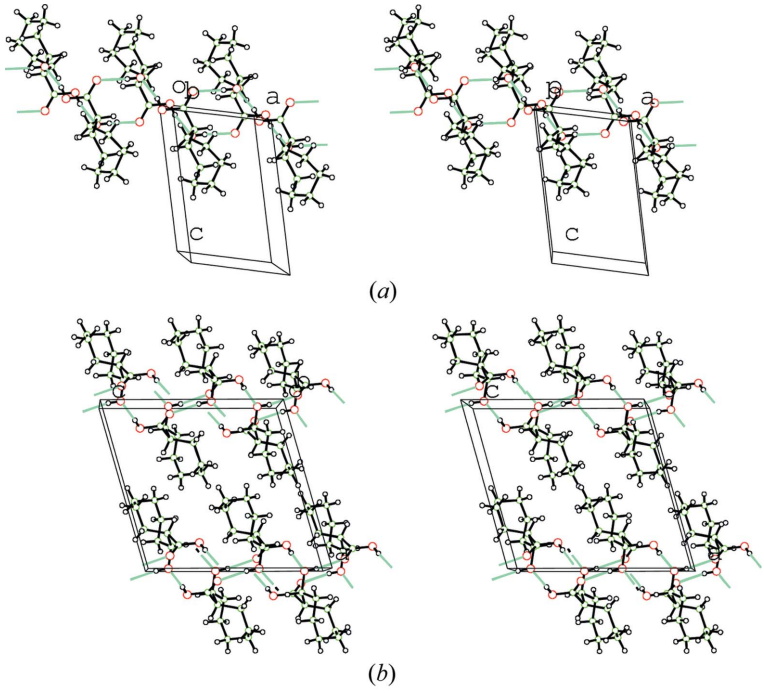

Figure 2
Stereoviews of the molecular packing of (I*b*) ($P\bar{1}$) and (I*a*) ($P2_1/c$). They are related by the type of rotation from **1** → ***4b***. Their common motif is the folded OC dimer located between planar OH dimers in (I*b*) and between helices in (I*a*). (Reproduced from Kálmán *et al.*, 2002*b*.)

2.2. Rotation of helices

In order to increase the packing coefficient the homochiral dimers in patterns ***4a*** and ***4b*** polymerize into helices, which can be seen if they are shown in two dimensions (Fig. 5). The antiparallel helices with opposite chirality are held together by the retained (either OC or OH) dimer motifs. In (1*R**,2*R**,4*S**)-4-*tert*-butyl-2-hydroxycyclopentanecarboxamide (VI*b*) (Kálmán *et al.*, 2001), the helices are held together by OH dimers (Fig. 5*b*). In contrast, in the *tert*-butyl free *trans*-2-hydroxycyclopentanecarboxamide (VII*b*), a 180° rotation of either of the enantiomorphic (back and white) helices forms a polar crystal with the space group $Pca2_1$. In this pattern (**6**), the parallel helices are held together by glide planes enclosing heterochiral rings (Fig. 5*c*) described by the graph-set notation $R_4^3(18)$. Of course, the non-crystallographic rotation between the structures (Figs. 5*b* and *c*) of the related (VI*b*) and (VII*b*) molecules is only *virtual*. However, these virtual rotations shed light upon the packing similarities of closely related compounds.

In an alternative step, the antiparallel helices in pattern **4** may also reassemble in a lateral stacking mode (pattern **5**) by a 90° rotation around the twofold screw axes (Fig. 4*e*), as demonstrated by *cis*-2-hydroxycyclopentanecarboxamide (VII*a*) (Kálmán *et al.*, 2001). In pattern **5**, the helices are held together by $R_4^4(12)$ tetramers of C_i symmetry. Accordingly, the stereoisomers (VII*a*) with monoclinic crystals (space group $P2_1/c$) and (VII*b*) with orthorhombic crystals (space group $Pca2_1$) are morphotropes again. These stereoisomers are related by two consecutive virtual rotations.

2.3. Rotations of tetramers

The polar layers (pattern ***6b***) in parallel stacking, observed in (VII*b*), may also be rearranged into an antiparallel array. A 180° rotation of every second layer of the tetrameric $R_4^3(18)$ rings gives rise to antiparallel stacking (Kálmán *et al.*, 2004). The non-isomorphous (Table 3) two dimensional isostructurality of the parallel (space group $Pca2_1$) and the antiparallel (space group $Pbca$) stackings of (VII*b*) and the (VIII*b*) (*trans*-2-hydroxycycloheptanecarboxamide) are depicted in Fig. 6 taken from Kálmán *et al.* (2004).

Pattern **7** is the parallel association of heterochiral chains (Kálmán *et al.*, 2001, 2002*a*). The molecules, invariably linked by hydrogen bonds, form exclusively heterochiral tetramers described by the graph-set notation $R_4^4(18)$. These rings are antidromic (see Appendix *A*), which generates dipoles. However, the dipoles must cancel out over the whole crystal by antiparallel stacking of either

Table 3
Crystal data on selected morphotropic pairs (isostructures and polymorphs).

	a (Å)	*b* (Å)	*c* (Å)	α (°)	β (°)	γ (°)	*V* (Å^3)	Space group
(VII*b*)	8.250 (2)	8.410 (2)	9.879 (2)	90	90	90	685.4 (3)	$P2_1ca$
(VIII*b*)	8.248 (1)	19.679 (3)	10.581 (1)	90	90	90	1717.4 (4)	$Pbca$
(V*b*)(^{p})	21.184 (3)	6.824 (1)	5.892 (2)	90	90	90	851.7 (3)	$Pna2_1$
(V*b*)(^{a})	21.185 (2)	6.826 (1)	5.889 (1)	90	90	90	851.6 (2)	$Pn2_1a$
(IXα)	5.0993 (3)	11.9416 (6)	5.4608 (3)	90	111.784 (2)	90	308.78 (3)	$P2_1/n$
(IXβ)	5.077 (4)	6.268 (6)	5.379 (9)	90	113.2	90	157.3 (5)	$P2_1$
(Xα)	6.774 (1)	7.795 (2)	9.803 (1)	106.68 (1)	104.09 (2)	92.29 (1)	477.6 (2)	$P\bar{1}$
(Xβ)	7.840 (5)	6.486 (1)	18.911 (6)	90	93.17 (3)	90	960.2 (7)	$P2_1/n$
(XIα)	5.858 (1)	7.629 (1)	28.237 (3)	90	97.97 (1)	90	1249.7 (3)	$P2_1/c$
(XIβ)	5.962 (1)	7.267 (1)	28.689 (1)	90	94.90 (1)	90	1238.4 (3)	$P2_1/c$

molecular layers or crystal domains (Jeffrey & Saenger, 1991), as demonstrated by the polymorphs (Table 3) of *trans*-2-hydroxycycloheptanecarboxylic acid (V*b*) (Kálmán *et al.*, 2003). The possible stacking forms of pattern **7**, together with the rearrangement **3** $\rightarrow$ **7** are described in Appendix *B*.

A curious property of the polymorphs of (V*b*) with their virtually identical unit cells is that their upper halves cannot be distinguished, while the lower halves differ by a 180° rotation around a non-crystallographic axis perpendicular to the layers (Kálmán *et al.*, 2003). In other words, if we rotate one of the unit cells around the *a* axis, then the lower halves become identical while the upper halves differ by a rotation through 180.° Consequently, dimorphs (V*b*)$^{(p)}$ and (V*b*)$^{(a)}$ [where $^{(p)}$ and $^{(a)}$ denote the parallel and antiparallel stackings] are isostructural in two dimensions with an alternating layer orientation; their polymorphism is the archetype of morphotropism. Explicitly, the polymorphs (V*b*)$^{(p)}$ and (V*b*)$^{(a)}$ differ simply in a 180° rotation of every second layer in the unit cell. Such a phenomenon is rare, but not unique. While studying the isostructurality of polymorphs (Fábián & Kálmán, 2004), we found that two (α and β) of the three polymorphs of glycine exhibit a similar relationship. In polymorph (IXβ) (Table 3), the layers of $H_3N^+CH_2COO^-$ zwitterions, held together by four N—H$\cdots$O hydrogen bonds, are stacked in the parallel mode, which gives rise to the space group $P2_1$ (Iitaka, 1960). In polymorph (IXα), with a unit cell doubled along the orthogonal *b* axis, every second layer becomes antiparallel by a rotation through 180°. Since the molecules are achiral, this structure is centrosymmetric, space group $P2_1/n$ (Langan *et al.,* 2002). These morphotropic polymorphs are also isostructural, with an alternating layer orientation in two dimensions.

2.4. Rotation of molecules in a heterochiral chain

The polymorphism of (V*b*) originates from the parallel stacking of the heterochiral chains of molecules (pattern **7**) formed by antidromic rings (Appendix *A*). In contrast, the *cis* isomer (V*a*) crystallizes in the space group *C*2/*c* (sub-pattern ***3b***). However, as described in Appendix *B*, the sub-patterns ***3a*** and ***3b*** may be equally transformed into pattern **7** by a 180° rotation of the molecules in every second chain in unison. From this, it follows that the stereoisomers (V*a*) and (V*b*) are also related *via* morphotropism.

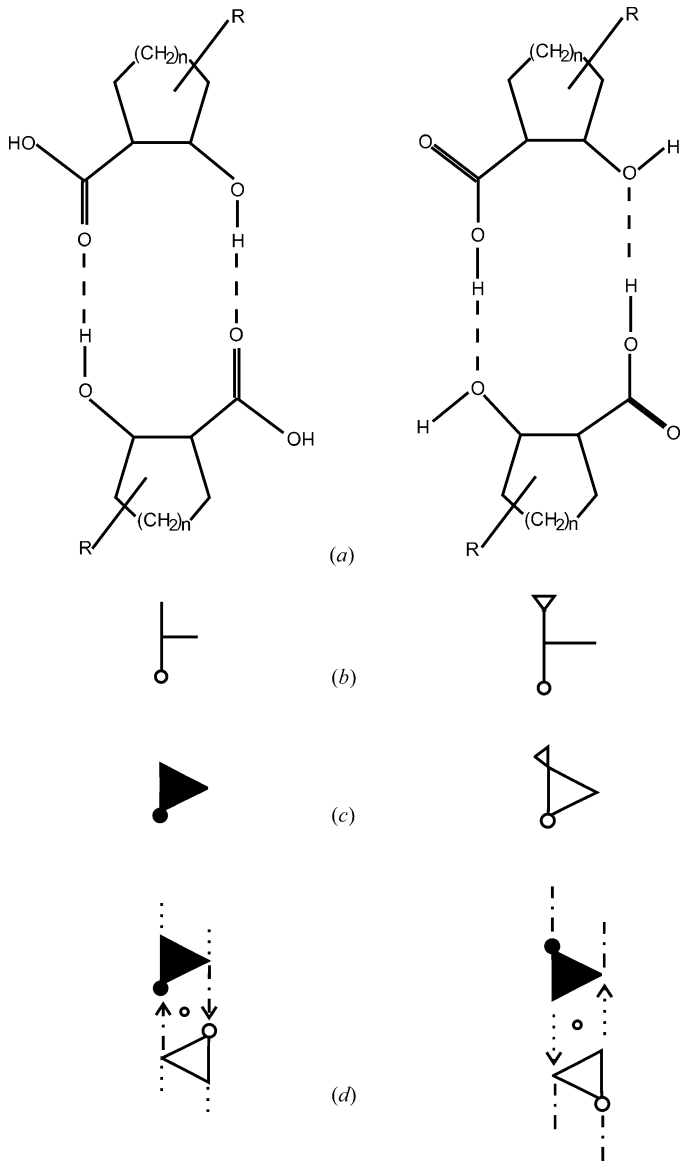

Figure 3
The basic forms of the OC (left) and OH (right) cyclic dimers observed for 2-hydroxycycloalkanecarboxylic acids and analogous carboxamides. Detailed explanations are given in the text. (Reproduced from Kálmán *et al.*, 2002*b*.)

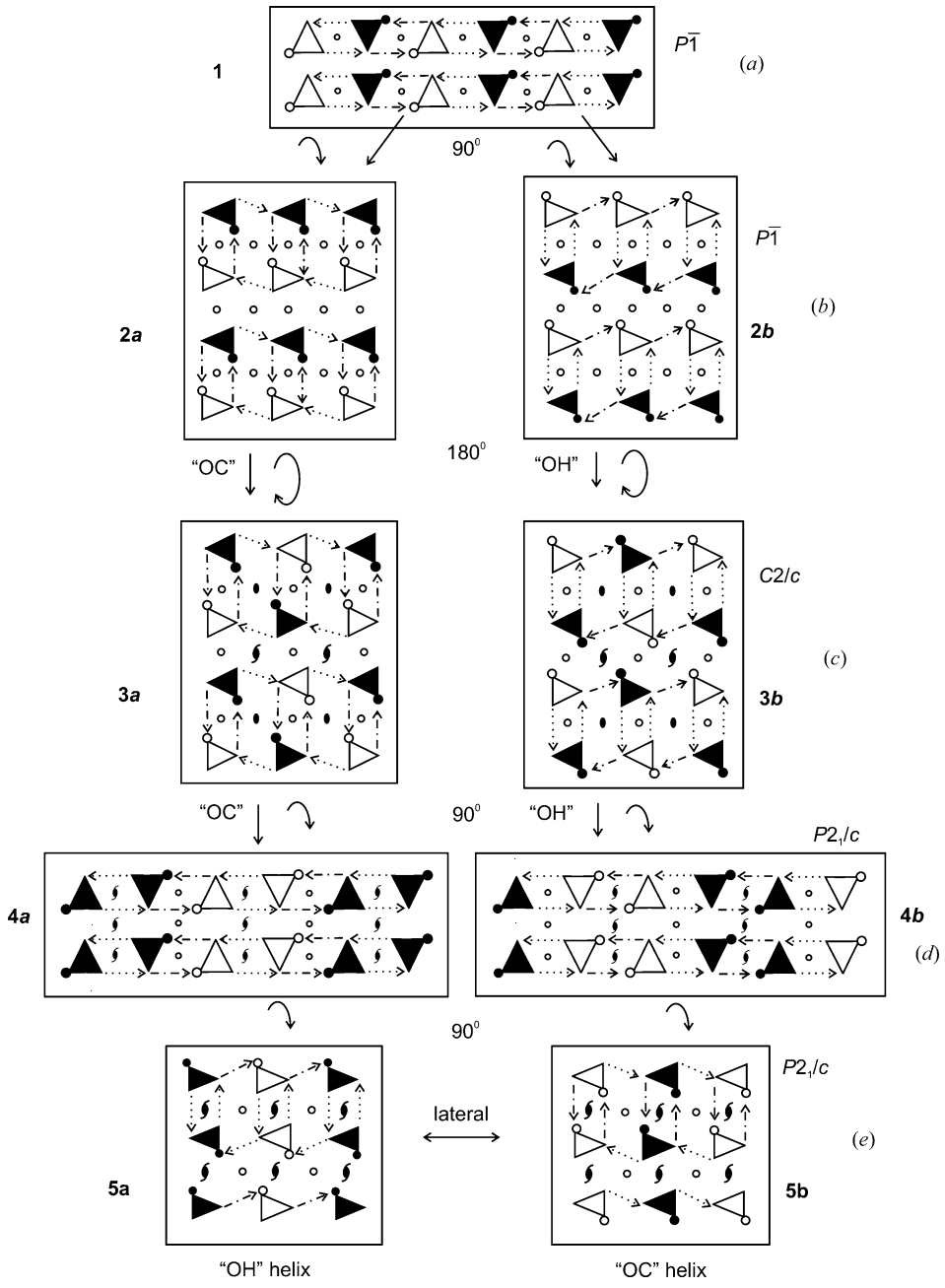

Figure 4
Topological patterns of the supramolecular self-organization of small molecules held together by their common hydrogen bonds. (*a*) Heterochiral dimers in a linear array (pattern **1**); (*b*) OC and OH dimers in a lateral array (sub-patterns **2*a*** and **2*b***); (*c*) dimers in a lateral, but antiparallel array (sub-patterns **3*a*** and **3*b***); (*d*) homochiral helices held together by heterochiral dimers in a linear array (sub-patterns **4*a*** and **4*b***); (*e*) enantiomeric helices, held together by tetramers in a lateral array (sub-patterns **5*a*** and **5*b***).

2.5. Rotation of molecules in different patterns

2.5.1. Polymorphism of planar molecules. Polymorphism is often attributable to the conformational difference(s) assumed by a molecule under different circumstances (solvent, pressure, temperature *etc.*). However, planar molecules such as nitrofurantoin (X) may also crystallize in two anhydrous[6] forms, α and β (Table 3), obtained either from hot acetic acid–water or from hot acetone solution (Pienaar *et al.*, 1990*b*). In the monoclinic polymorph (Xβ), the molecules form infinite helices held together by N—H···O hydrogen bonds (Fig. 7*a*). If the achiral molecules, similarly as in the rearrangement **3*a*** ⇒ **7** (see Appendix *B*), rotate through 180° on either side of the twofold screw axis in unison, they form centrosymmetric $R_2^2(8)$ dimers with the molecules stacked on the other side of the disappearing helix in (Xα) (Fig. 7*b*). Overall, the phase transition between the nitrofurantoin polymorphs (Xα) and (Xβ), mediated by the solvents, is a real rotation of the molecules.

2.5.2. Polymorphism *via* non-crystallographic rotation of a macroring. Two polymorphs of *trans*-13-azabicyclo[10.2.0]-tetradecan-13-one (XI) present a unique example of isostructurality, differing only in the orientation of a given hydrogen bond with respect to the β-lactam bond (Fábián *et al.*, 2004). This slight difference is attributable to the twofold rotation of the $C_{12}H_{22}$ ring of C_2 symmetry, which is hardly noticeable in the crystal structure. Both polymorphs are monoclinic (space group $P2_1/c$) and their orthogonal axes accommodate the homochiral helices of azetidin-2-one moieties linked by N—H···O hydrogen bonds. The *b* axis is considerably longer in (XIα) [7.629 (1) Å] than in (XIβ) [7.267 (1) Å], which is attributed to the different orientations of the O lone-pair electrons that accept the hydrogen bond. The hydrogen-bond arrangement may be either antiperiplanar (XIα) or synperiplanar (XIβ) with respect to the endocyclic amide bond of the planar β-lactam ring. The formation of (XIα) and (XIβ) from different solvents (methanol *versus* acetone) is facilitated by the almost perfect C_2 symmetry of the 12-membered rings (Figs. 8*a* and *b*). A non-crystallographic rotation of the molecules through 180° around the molecular C_2 axis tilted by *ca* 45° with respect to the twofold screw axis alters only the orientation of the O=C—N—H moiety. The polymorphs

[6] Nitrofurantoin also forms two monohydrates, described by Pienaar *et al.* (1990*a*).

(XIα) and (XIβ) (Table 3), characterized by a high degree of isostructurality (unit-cell similarity index Π = 0.008, volumetric index I_v = 75%; Fábián & Kálmán, 1999), are again related by a non-crystallographic rotation of the β-lactam molecules.

2.5.3. Non-crystallographic rotations in oblique unit cells.

(i) The four unit cells (space group, $P\bar{1}$) of the *cis*-alicyclic β-amino acids [(XII*a*) $\rightarrow$ (XV*a*)] display the superposition of patterns **1** and **2*b*** (in the following, pattern **8**). Nevertheless, while the dimers of (XII*a*), (XIII*a*) and (XIV*a*) exhibit a high degree of isostructurality, with the same orientation in the oblique unit cells, the dimer of (XV*a*) rotates through 180° around a non-crystallographic axis parallel to the *c* axis (Fábián *et al.*, 2005). The different dimer orientations [(XV*a*) *versus* (XII*a*) $\rightarrow$ (XIV*a*)] in the oblique unit cells, denoted by sub-patterns **8*a*** and **8*b*** (Table 2), account for an improved close packing of (XV*a*) bearing the largest cycloalkane ring. Consequently, (XV*a*) is homostructural (Kálmán *et al.*, 1993*b*) with (XII*a*), (XIII*a*) and (XIV*a*). However, this basic form of morphotropism compelled us to identify similar phenomena in other crystals we studied earlier.

(ii) To present comparable stereoviews of the packing similarity of (III*b*), (IV*a*) and (V*a*), the unit cell of (V*a*), determined with the space group *C*2/*c*, was transformed into a body-centered form with the non-standard space group *I*2/*c* (*cf.* Fig. 8 in Kálmán *et al.*, 2002*a*). From this it follows that the isostructurality of (V*a*) differs from that of (III*b*) and (IV*a*) by a rotation of the OH dimers through 180° in the oblique unit cell.

(iii) In one of our earlier observations (Kálmán *et al.*, 1993*b*), 5- and 7-chloroindol-3-ylacetic acids (Kojic Prodic *et al.*, 1992) were described as homostructural in their oblique unit cells. These substitutional isomers were found to have similar close packing *via* a non-crystallographic symmetry (*cf.* Fig. 10 in Kálmán *et al.,* 1993*b*). These isomers can also be regarded as morphotropes, related by an approximately 180° virtual rotation of the molecules around the shorter diagonal of the oblique *ac* plane.

(iv) At the beginning of these investigations, we reported (Kálmán *el al.*, 2000) on the peculiar isostructurality of (1*R**,2*S**,4*S**)-4-*tert*-butyl-2-hydroxycyclopentanecarboxylic acid (II*a*) with its *tert*-butyl free carboxamide derivative (VII*a*). Although the molecules differ in the *tert*-butyl group and the $CONH_2$ *vs* COOH functions, their close packing is similar if one of the oblique unit cells rotates through 180° by a turn of the orthogonal crystal axis upside down (*cf.* Fig. 14 in Kálmán *et al.*, 2001).

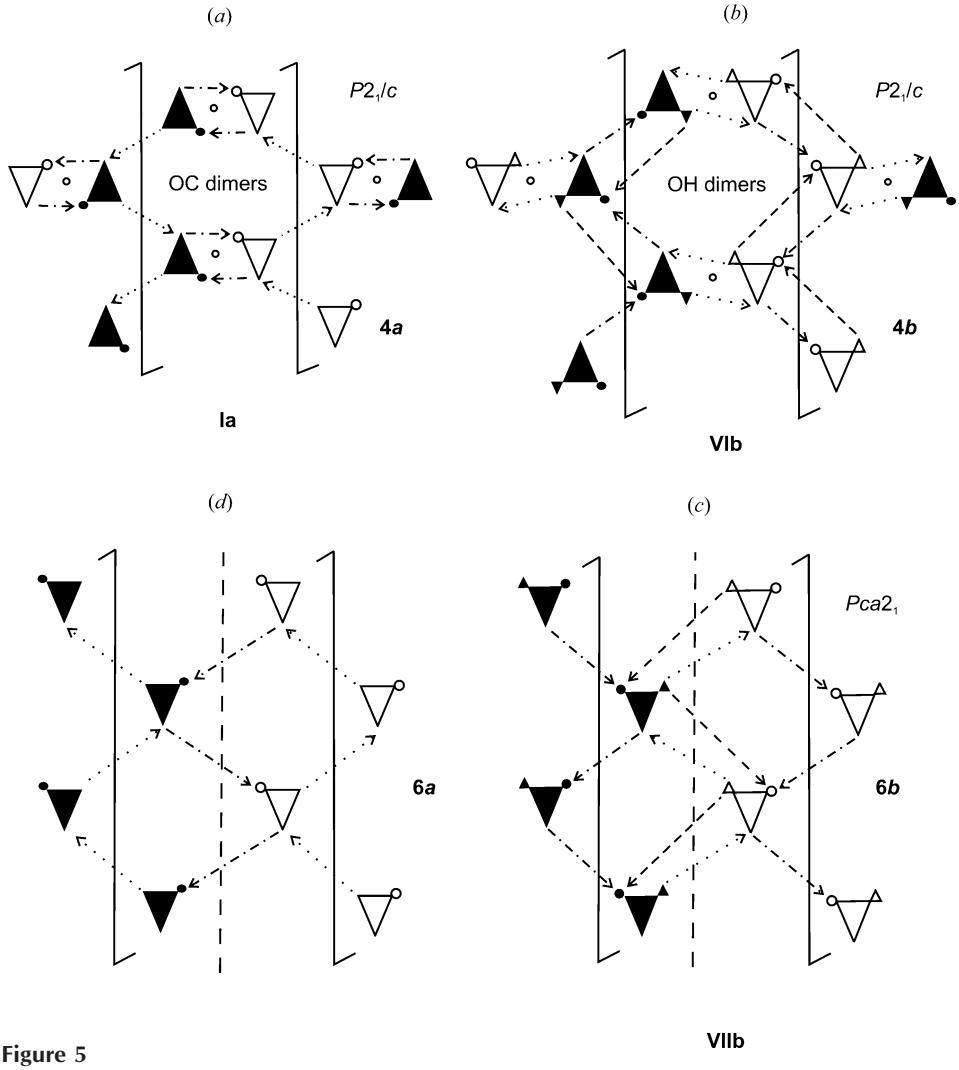

Figure 5
(*a*) and (*b*) Two-dimensional description of helices held together by dimers in an antiparallel array (sub-patterns **4*a*** and **4*b***) or (*c*) and (*d*) separated by glide planes in a parallel array (sub-patterns **6*a*** and **6*b***). Sub-pattern **6*a*** has not been observed in crystals so far.

2.6. Non-crystallographic rotations in alicyclic β-amino acids

We have seen that the isostructurality of *cis*-alicyclic β-amino acids [(XII*a*), (XIII*a*) and (XIV*a*)] is differentiated by a rotation of the (XV*a*) dimers through 180° around a non-crystallographic axis in their oblique unit cells (Fábián *et al.*, 2005). We now show that these β-amino acids are also linked to their stereoisomers and unsaturated derivatives by other virtual rotations, as follows:

After successful syntheses and crystallizations, the study of the cyclohexane homolog (XIII*a*) could be extended to its *trans*

isomer (XIII*b*) and their cyclohexene derivatives (XVI*a*) and (XVI*b*). Since they form zwitterions, each NH_3^+ moiety forms three hydrogen bonds of the OC type with carboxylic O atoms, one of which is bifurcated. Two infinite rows of the heterochiral $R_2^2(12)$ dimers of (XIII*a*), depicted by the topological symbols in Fig. 9(*a*), are held together by two hydrogen bonds and crosslinked by the third hydrogen bond. In this two-dimensional network, two kinds of centrosymmetric tetramers, $R_4^4(12)$ and $R_4^2(8)$, furnish the lateral connections between the ribbons. A rotation of every second dimeric motif in pattern **8** through 180° generates homochiral dimers (Fig. 9*b*), which polymerize into antiparallel helices (Fig. 9*c*). In this stacking (pattern **9**), the homochiral 'triangles' are located around a twofold screw axis and linked together by two hydrogen bonds (dotted lines) with alternating orientations. The $R_2^2(12)$ dimers formed along the helices are free of symmetry. The enantiomeric helices are crosslinked again by the third hydrogen bond, preserving the alternating $R_4^4(12)$ and $R_4^2(8)$ tetramers from the pattern **8**. The antiparallel helices held together by the tetramers of C_i symmetry form a layer perpendicular to the folded plane of **8**. This novel pattern **9** is exemplified by three crystal structures, (XIII*b*) and the *cis–trans* isomers of (XVI), described above.

A comparison of the structures [(XIII*a*), (XIII*b*)] and [(XVI*a*), (XVI*b*)] reveals an important relationship between them:

(i) (XIII*a*) and its stereoisomer (XIII*b*) are linked by the type of virtual rotation **8** → **9**.

(ii) Similarly, (XIII*a*) and its cyclohexene derivative (XVI*a*) are linked by the same type of rotation **8** → **9**.

(iii) Additionally, their *trans* isomers (XIII*b*) and (XVI*b*) are isostructural.

Although the unit cells of the stereoisomers [(XVI*a*), (XVI*b*)] are rather similar (Π = 0.011; Fábián & Kálmán, 1999), the crystals should differ. From this it follows that pattern **9** must have alternative sub-patterns, ***9a*** and ***9b*** (Table 2), which differ by a non-crystallographic rotation of the helical motif along the *a* axis in the oblique unit cell of either (XVI*a*) or (XVI*b*) (Fig. 10). Overall, this difference in the locations of the stereoisomers in an oblique unit cell serve to optimize their close packing.

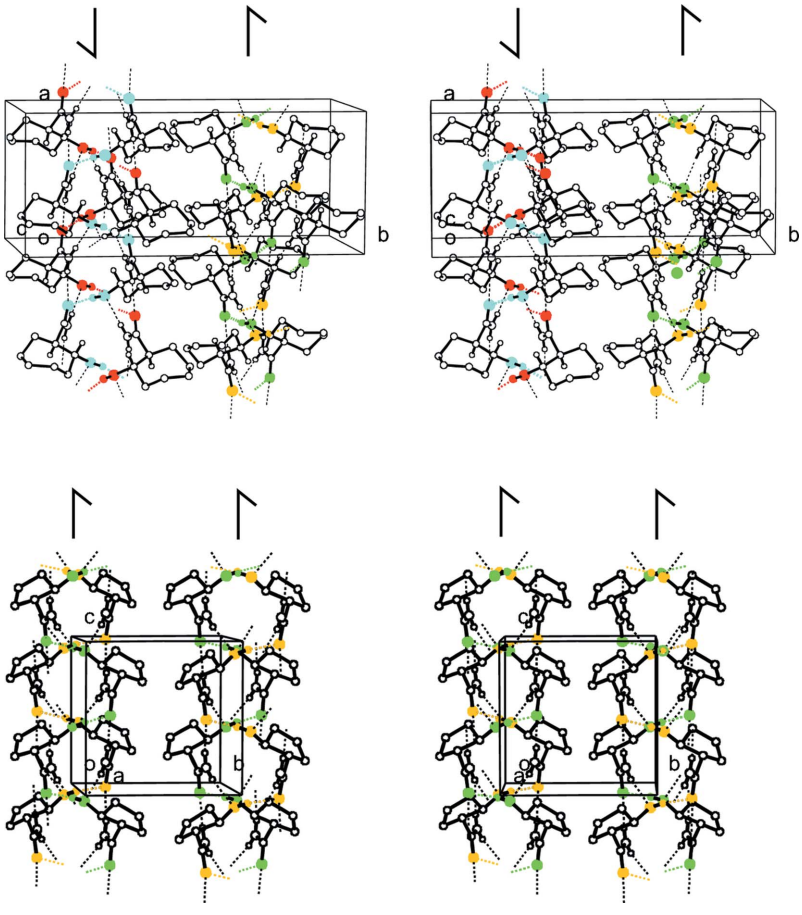

Figure 6
Stereoview of the close packing of (VII*b*) and (VIII*b*). The alternating two-dimensional isostructurality is revealed by the antiparallel helices in (VIII*b*) *versus* the parallel helices in (VII*b*). In both structures, the enantiomers denoted by 4*R* are held together by the hydrogen bonds shown in green, whereas the helices with 4*S* configuration are shown by yellow hydrogen bonds. The antiparallel double helix in (VIII*b*) is indicated in blue (4*R*) and red (4*S*). (Reproduced from Kálmán *et al.*, 2004.)

3. Conclusions

It has been demonstrated that several of the hydrogen-bonded crystal structures of disubstituted cycloalkanes are related by non-crystallographic rotations of their *basic motifs* (dimers, helices, ribbons and tetramers). They form a network which relates directly or indirectly to the packing patterns. This fact-gathering work was complemented by a small number of examples taken from the literature. Accordingly, morphotropism involves the rotation of motifs which transforms one *packing pattern* into another and *vice versa*.

The forms of morphotropism that have been observed were as follows:

(i) A rotation of identical motifs through 90 or 180° in unison, *e.g.* (i) hydrogen-bonded molecules rotate upside down in a helix, (ii) or all dimers rotate by 90° around their main axis in unison.

(ii) A rotation of every second motif of a packing pattern through 90° or 180°, *e.g.* (*a*) every second dimeric motif in a lateral array rotates around its center of symmetry through 180° (*b*) or hydrogen-bonded molecules (in the case of polymorphism) rotate upside down in unison, but only on either side of the respective twofold screw axis.

(iii) A rotation of the whole pattern through 180°, *e.g.* a 180° rotation of infinite layers of hydrogen-bonded tetramers upon each other forming either antiparallel or parallel layer stacking. The axis of such a rotation may be perpendicular to [dimorphs $(Vb)^{(p)}$ and $(Vb)^{(a)}$]

or tilted with respect to a screw axis [dimorphs (XIα) and (XIβ)] or parallel to a direction in an oblique unit cell [(XII*a*)–(XIV*a*) *versus* (XV*a*)].

Although the present work still comprises predominantly fact-gathering, it ascertains that two or more crystals are morphotropes if their packing patterns differ only by one (or occasionally two) non-crystallographic rotation(s) of their common motifs. In other words, the packing patterns of chemically similar molecules with isometric shapes may be related by a few non-crystallographic rotations. In particular, stereoisomers form crystals, the patterns of which differ only in a non-crystallographic rotation. It explains how *cis* and *trans* isomers, with a configurational difference, are able to form closely related packing patterns. Homostructural crystals may also show morphotropism whenever the 'second' layer rotates through 180°, or the whole pattern rotates through 180° in an oblique unit cell.

The most important discovery is the morphotropism of polymorphs. While two chemically similar (isomeric or homostructural) crystals are related by a virtual rotation of the common motif, such a non-crystallographic rotation between polymorphs really transforms one molecule into another. The four rather different morphotropic polymorphs described above (Table 3) are enantiotropic, *i.e.* their reversible phase transitions are solvent-mediated.

Finally, it is also noteworthy that the revealed forms of non-crystallographic rotations occur in the most frequent centrosymmetric space groups $P2_1/c$ (12), $P\bar{1}$ (7), $C2/c$ (3) and $Pbca$ (1), followed by $Pna2_1$ (2) and $Pca2_1$ (1). Even their numbers (in parentheses) among the structures discussed above correspond roughly to the population (%) of these space groups archived in the Cambridge Structural Database (CSD; October 1997 issue; Allen, 2002): 35.4, 19.4, 7.2, 3.8, 1.54, 0.73%, as demonstrated by statistics reported earlier by

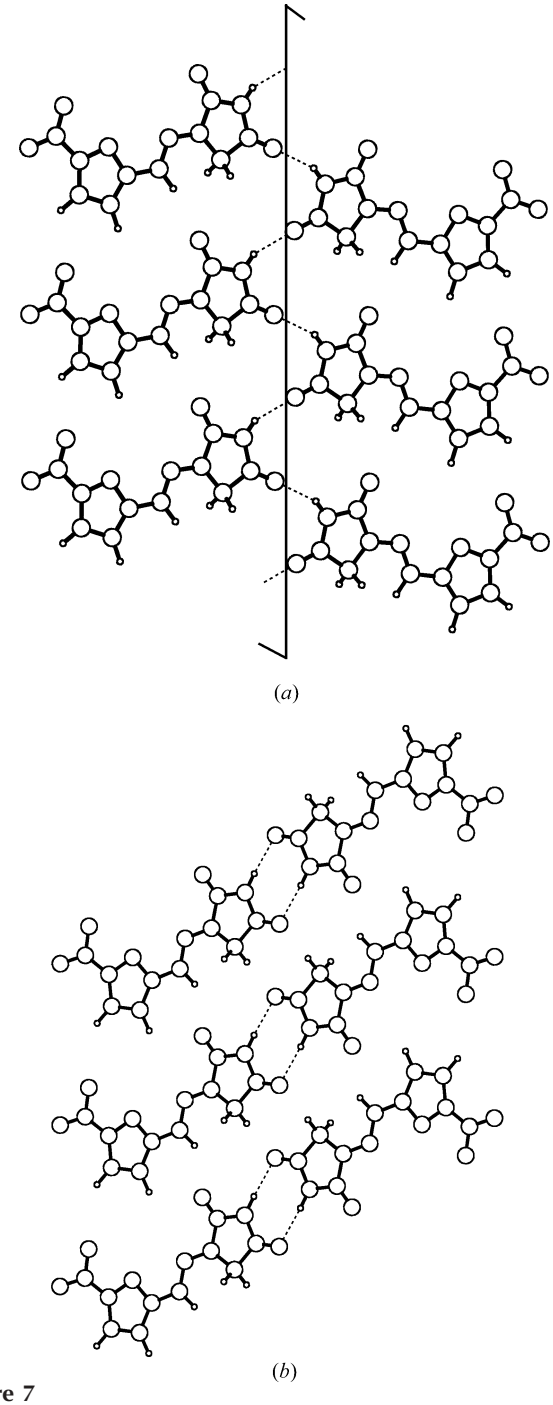

Figure 7
The triclinic (Xα) and monoclinic (Xβ) polymorphs of nitrofurantoin (Pienaar *et al.*, 1990*a*). A 180° rotation of the molecules on the right side of the helix (Fig. 6*a*) perpendicular to the twofold screw axis results in a rearrangement which forms $R_2^2(8)$ dimers in the triclinic unit cell (Fig. 7*b*).

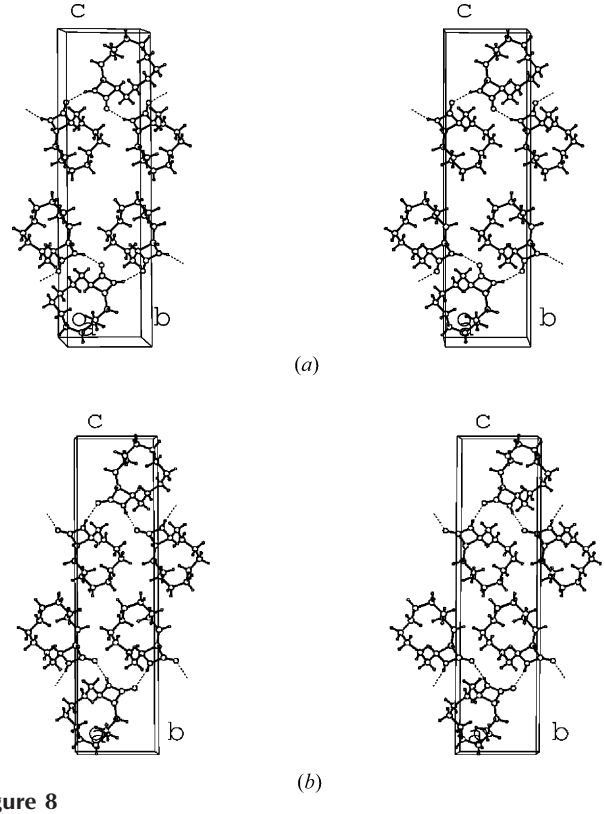

Figure 8
Stereoviews of the close packing of the polymorphs α and β of (XI) in space group $P2_1/c$. In the unit cells (*a*) and (*b*), the positions of the cyclododecane rings are the same; only the positions of the C═O and N—H groups are interchanged. (Reproduced with kind permission from Fábián *et al.*, 2004.)

Kálmán (1999). This observation once again underscores the fundamental connections between the most frequent space groups (Brock & Dunitz, 1994). This conclusion is substantiated by the variety (four) of close packing in the space group $P2_1/c$ found between the investigated disubstituted cycloalkanes. Enantiomeric helices are crosslinked:

(i) by dimers (pattern **4**) (I*a*) and (VI*a*);

(ii) by tetramers (pattern **5**) (II*a*) and (VII*a*);

(iii) by two kinds of tetramer (sub-pattern **9*a***) (XIII*b*), (XVI*a*) and (XVI*b*);

(iv) or they are perpendicular to the layers formed by heterochiral tetramers (pattern **7**) (II*c*).

These remarks and the observations described above suggest that the standard forms of the 230 space groups are no longer enough to describe structural properties (*cf.* the *transitional* space groups between triclinic and pseudo-monoclinic crystals described in Kálmán, 1998; Kálmán & Argay, 1998). Thus, the

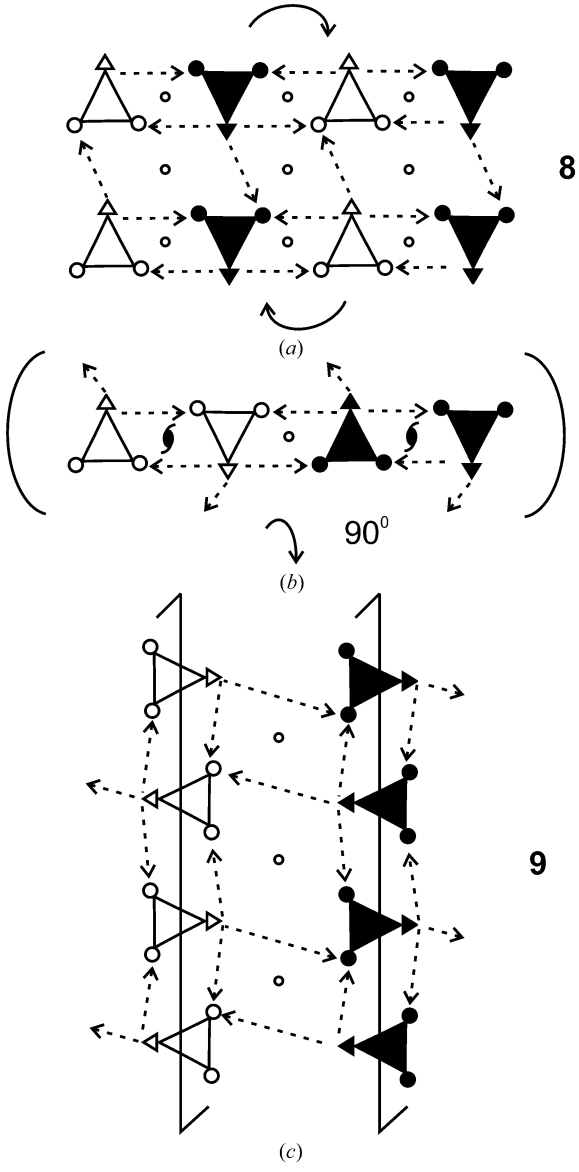

Figure 9
Topological presentation of the close packing of *cis*-alicyclic β-amino acids (*a*) and the results of the type of rotation 8 $\rightarrow$ 9 in one (*b*) and two dimensions (*c*). Since β-amino acids are zwitterions, their symbolic presentation denotes the NH_3^+ group with a small triangle rotated through 180° to that of NH_2 groups in carboxamides, depicted in Fig. 3(*b*), while the COO^- moiety is denoted by two small circles. The molecules forming helices are linked by two NH$\cdots$O hydrogen bonds along the twofold screw axes. They enclose symmetry-free $R_2^2(8)$ dimers. The enantiomeric helices are cross-linked by the third N—H$\cdots$O hydrogen bond, simultaneously enclosing the $R_4^4(12)$ and $R_4^2(8)$ tetramers.

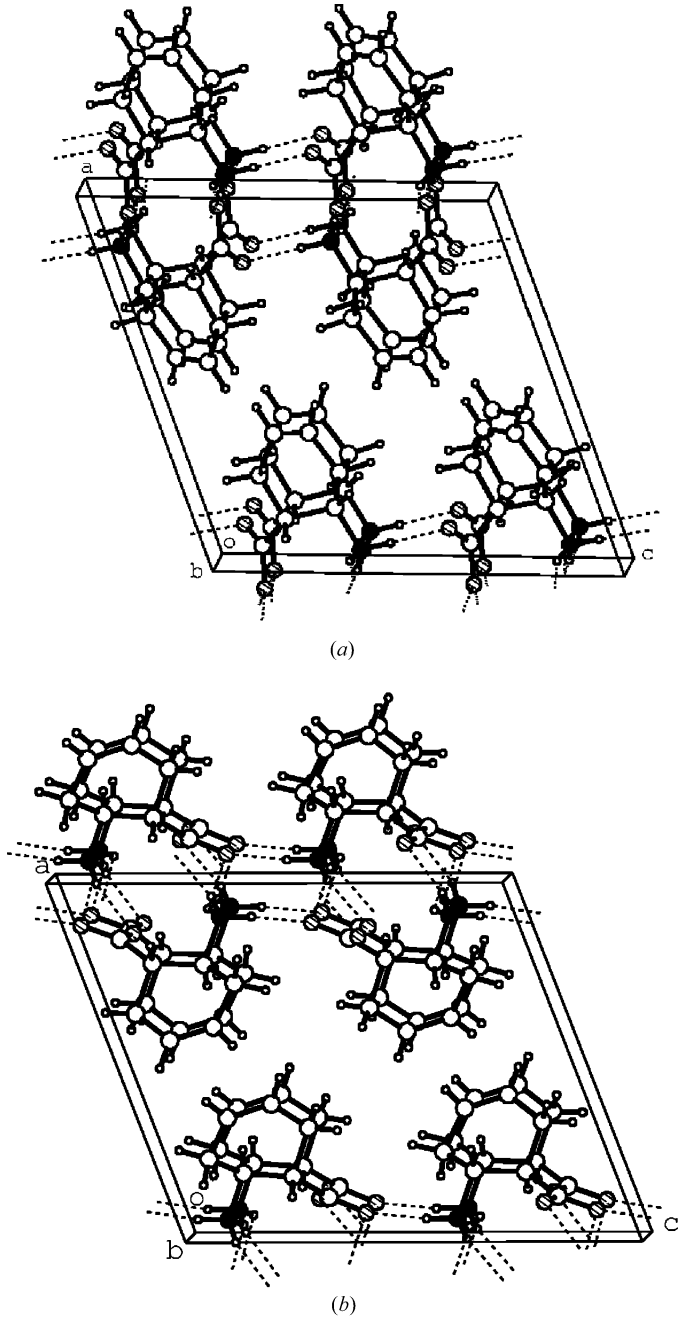

Figure 10
Projections of the unit cells of the *cis* and *trans* isomers of 2-aminocyclohex-4-enecarboxylic acids (XVI*a*) and (XVI*b*) (Fábián *et al.*, 2005). Apart from configurational differences in the helix formation, they differ by a 180° rotation of the helices parallel to the *a* axis in either of the two (slightly different) oblique unit cells.

use of non-standard space groups such as $P2_1/n$, $I2/c$, $Pn2_1a$, *etc.* is not only a matter of choice of the three principal axes. Each of them has its meaning in describing a relevant structural relationship. For example, the non-standard space group *I*2/*c versus C*2/*c* indicates the virtual rotation of the common motif between (IV*a*) and (V*a*) in their 'isomorphous' obligue unit cells. No such distinction can be made, however, between the close packings of (XIV*a*) *versus* (XV*a*) in the triclinic (space group $P\bar{1}$) and (XVI*a*) *versus* (XVI*b*) in the monoclinic unit cells (space group $P2_1/c$). From these it follows that we must become accustomed to an increasingly generalized description of crystals, as suggested by Desiraju (2003).

As far as the future is concerned, the author hopes that the differences in the crystal structures of similar molecules will be better understood from studies of non-crystallographic rotations, whenever they are recognized. Since such a study has not been made so far, a search for such rotations, hopefully in numerous crystals archived in the CSD, may be informative in crystal engineering.

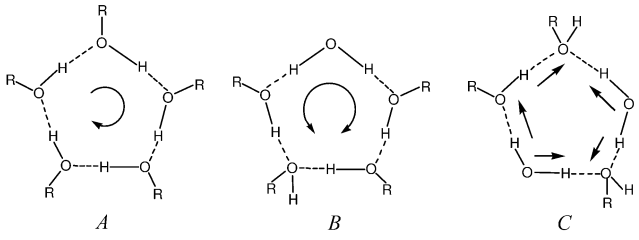

Figure 11
Homo-, anti- and heterodromic rings.

APPENDIX *A*
Definition of the homo-, hetero- and antidromic rings formed by hydrogen bonds of the type O—H···O

The homodromic (*A*), antidromic (*B*) and heterodromic (*C*) rings for cyclodextrin hydrates defined in the book '*Hydrogen Bonding in Biological Structures*' (Jeffrey & Saenger, 1991, p. 38) may be seen in Fig. 11. These definitions for pentamers have been adapted for the tetramers observed in the structures discussed here.

APPENDIX *B*
Dipole extinctions in antidromic rings *via* three forms of layer stacking

The simplest stacking form is an overlap of the identical subpatterns **7*a*** and **7*b*** (Figs. 12*c* and *d*), deduced from **3*a*** and **3*b*** (Figs. 12*a* and *b*) by a rotation of each molecule in their second row through 180°. They are held together by a twofold screw axis which leaves the ring dipoles parallel [polymorph $(Vb)^{(p)}$, space group $Pna2_1$]. Consequently, the antiparallel alignment of the domains cancels out the dipole moment. The second form [polymorph $(Vb)^{(a)}$] is an overlap of the identical **7*a*** and **7*c*** (Figs. 12*c* and *e*) held together by a screw axis perpendicular to the dipole vector which leaves the ring dipoles antiparallel. To this form a non-standard space group $Pn2_1a$ had to be ascribed (Kálmán *et al.,* 2003). The third form – demonstrated by (II*c*) (1*R**,2*S**,5*R**)-5-*tert*-butyl-2-hydroxycyclopentanecarboxylic acid (Kálmán *et al.,* 2001) – is an overlap of the identical subpatterns **7*b*** and **7*c*** (Figs. 12*d* and *e*), held together by the twofold screw axes which are perpendicular to them.

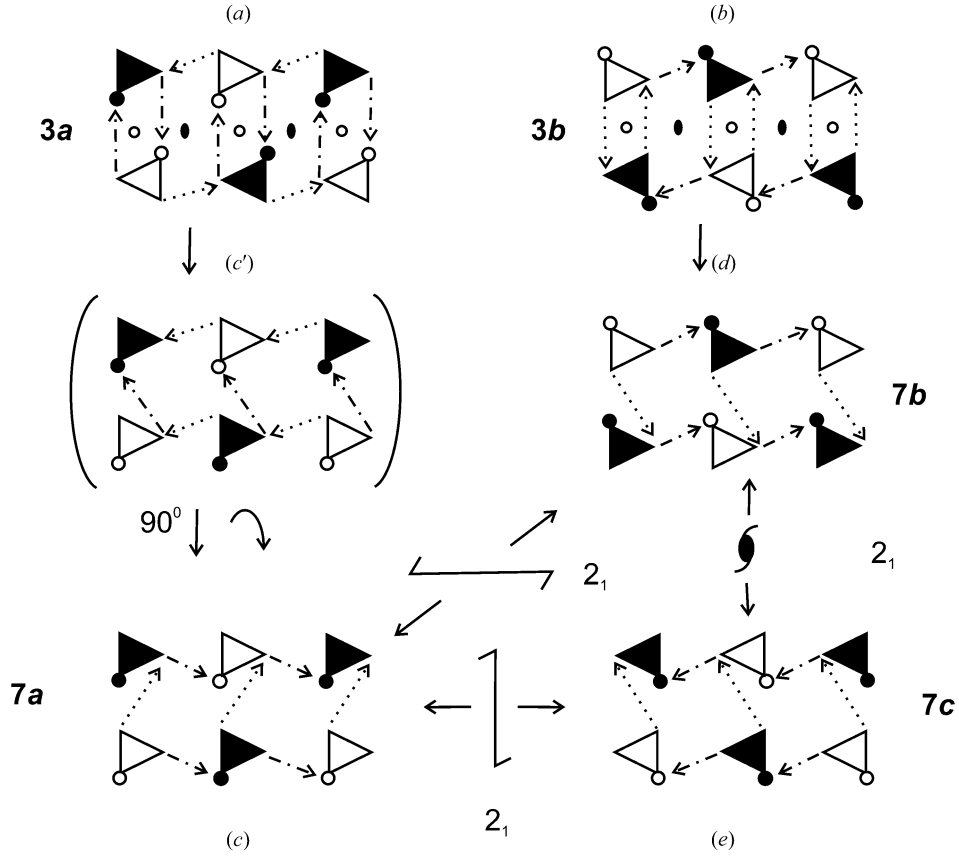

Figure 12
The parent sub-patterns (*a*) **3*a*** and (*b*) **3*b***, and (*c*), (*c*′), (*d*) and (*e*) four different settings of pattern **7** formed by antidromic rings described by the graph-set notation $R_4^4(18)$.

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