Acta Crystallographica Section B
**Structural
Science**
ISSN 0108-7681

Statistical survey of hydrogen-bond motifs in crystallographic special symmetry positions, and the influence of chirality of molecules in the crystal on the formation of hydrogen-bond ring motifs

Sagi Eppel and Joel Bernstein*

Department of Chemistry, Ben-Gurion University of the Negev, PO Box 653, Be'er Sheva 84105, Israel

Correspondence e-mail: yoel@bgu.ac.il

Received 13 July 2007
Accepted 15 November 2007

A statistical survey was carried out to examine the connection between hydrogen-bond ring motifs (synthons) and crystallographic special symmetry positions. In the first part, the probability of common hydrogen-bond ring motifs to occupy specific crystallographic symmetry positions of inversion centers, rotation axes and mirror planes was examined. In the second part the probability of the occurrence of hydrogen-bond ring motifs was compared between crystals of chiral molecules (which cannot form inversion or mirror symmetry) to crystals of achiral molecules and racemic crystals. The results show that the crystallographic inversion center is a very significant component in the formation of hydrogen-bond ring motifs.

1. Introduction

The use of hydrogen-bond synthons as structure-guiding interactions for crystal engineering (Aakeröy, 1997; Desiraju, 1995; Hofmann *et al.*, 2004; Garciatellado *et al.*, 1991), as well as for other forms of molecular self assembly (Krische & Lehn, 2000; Melendez *et al.*, 2000), has been developing rapidly. While the ability to accurately predict crystal structures of molecules is still very limited (Day *et al.*, 2005), motifs that involve strong hydrogen bonds can be expected to be formed with high probability when the appropriate functional groups are used (Allen *et al.*, 1999). While the connection between molecular and crystallographic symmetry has been widely studied since the work of Kitaigorodskii (1961) by statistical (Kitaigorodskii, 1961; Brock & Dunitz, 1994; Yao *et al.*, 2002; Pidcock *et al.*, 2003; Dowdy *et al.*, 2004) and other methods, the connection between hydrogen-bond motifs and crystallographic special symmetry positions has drawn much less attention (Hofmann *et al.*, 2004; Anderson *et al.*, 2006; Allen *et al.*, 1999). This work will be divided into two parts: In the first part the probability of common hydrogen-bond ring motifs to occupy crystallographic special positions (inversion, rotations and mirrors) was examined independently for racemic crystals, crystals of achiral molecules, and crystals of chiral molecules (not racemic), using the Cambridge Structural Database (CSD; Allen, 2002). In the second part we compare the probabilities of the formation of the hydrogen-bond ring motifs in crystals of chiral molecules (which cannot form inversion or mirror symmetry) to those of crystals with achiral molecules and racemic crystals.

2. Methods of data analyses

2.1. General procedure

The analysis of probability of hydrogen-bond ring motifs to occupy crystallographic special positions was carried out in four steps:

(i) The organic crystal structures in the CSD were classified into four different groups according to their molecular symmetry type:

(*a*) ACHIRAL: structures that contain only achiral (but not *meso*) molecules;

(*b*) RACEMIC: structures that contain chiral molecules of both enantiomers in equal numbers;

(*c*) CHIRAL/ENANTIOPURE: structures that contain chiral molecules of only one enantiomer (enantiopure), or in rare cases contain both enantiomers, but not in equal numbers and therefore cannot contain inversion or mirror symmetries;

(*d*) MESO: structures that have *meso* molecules but not chiral molecules.

(ii) A group of common hydrogen-bond ring motifs was defined (Fig. 1), and every occurrence of each motif was traced in each of the crystal groups defined in the first step.

(iii) The occurrences of the hydrogen-bond ring motifs found in step (ii) were evaluated for their occupancy of crystallographic special positions. The crystallographic symmetry elements that were checked are inversion ($\bar{1}$), rotations (2,3,4) and mirrors (*m*). Mirror and rotation planes/axis vertical to the motif plane are considered independently from mirror and rotation planes/axes lying in the planes of the motif (the plane of the paper in Fig. 1).

(iv) The probability for a motif to occupy a crystallographic inversion center/rotation axis/mirror plane was calculated as a simple fraction of the total number of occurrences of the motif: $P_{\rm inv} = N_{\rm inv}/N_{\rm tot}$; $P_{\rm mir} = N_{\rm mir}/N_{\rm tot}$; $P_{\rm rot} = N_{\rm rot}/N_{\rm tot}$; $P_{\rm inv}$: probability for a motif to occupy an inversion center; $P_{\rm rot}$: probability for a motif to occupy a rotation axis; $P_{\rm mir}$: probability for a motif to occupy a mirror plane; $N_{\rm inv}$: No. of cases in which the hydrogen-bond motif occupies an inversion center; $N_{\rm mir}$: No. of cases in which the hydrogen-bond motif occupies a mirror plane; $N_{\rm rot}$: No. of cases in which the hydrogen-bond motif occupies a rotation axis; $N_{\rm tot}$: No. of times the hydrogen-bond motif appears (only cases with $N_{\rm tot} > 12$ where included).

The results are given in Tables 1–4.

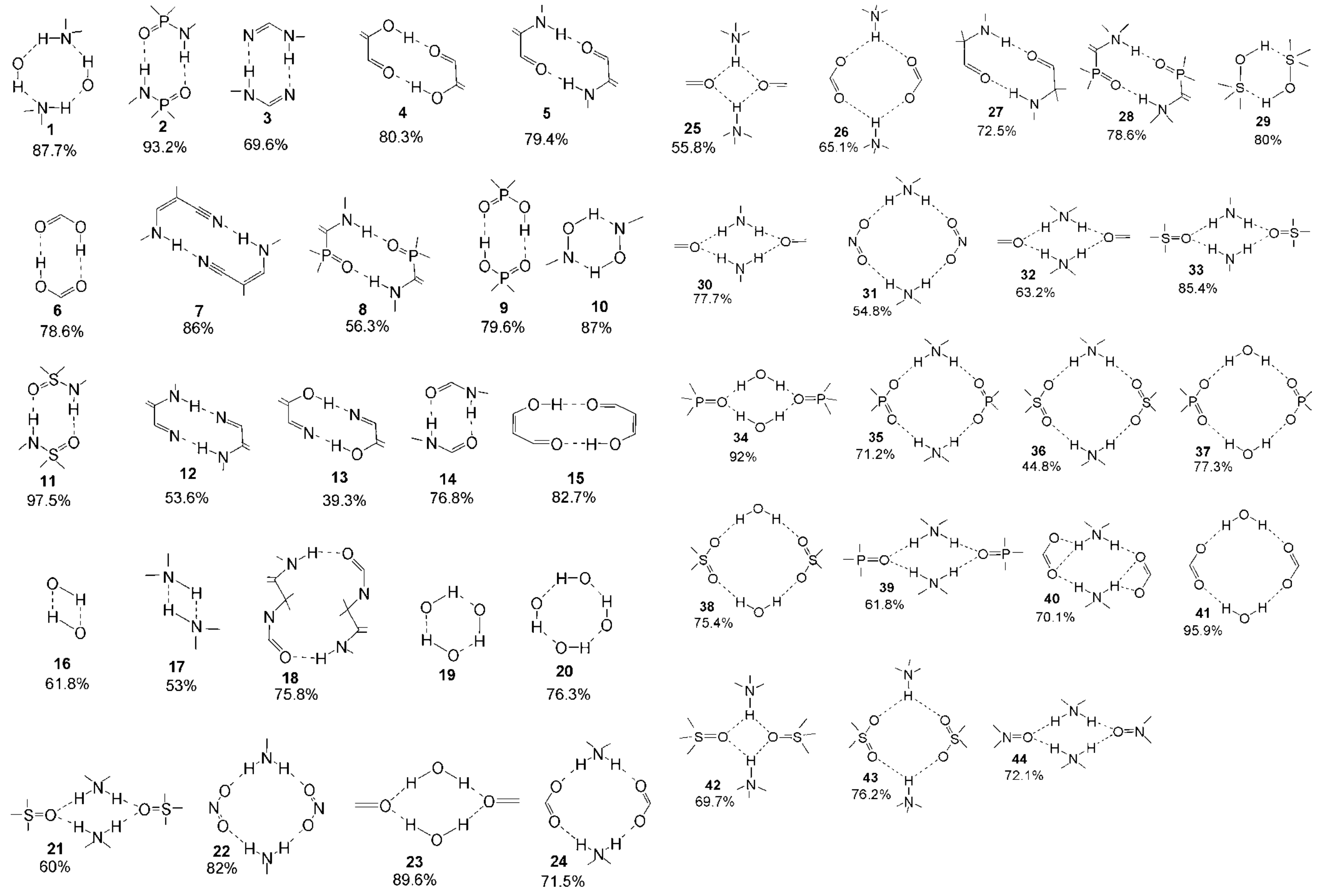

Figure 1
Hydrogen-bond ring motifs 1–44. Dashed lines represent hydrogen bonds; $P_{\rm inv}$ the probability of the hydrogen-bond motif to occupy a crystallographic inversion center (for crystals of achiral molecules) appears under the motif number.

Table 1
Probability (in %) for hydrogen-bond ring motifs to occupy crystallographic special positions, for crystal structures of achiral molecules.

Empty cells indicate zero values. The number in the first column refers to the motifs shown in Fig. 1. Cases of over 100 instances are marked with bold letters.

							No. of instances					
Achiral		$P_{\rm inv}$	$P_{\rm rot}$		$P_{\rm mir}$		$N_{\rm tot}$	$N_{\rm inv}$	$N_{\rm rot}$		$N_{\rm mir}$	
Motif number	Graph set	Inversion centers (%)	Out-of-plane rotations (%)	In-plane rotations (%)	In-plane mirrors (%)	Out-of-plane mirrors (%)	All instances	Inversion centers	Out-of-plane rotations	In-plane rotations	In-plane mirrors	Out-of-plane mirrors
1	$R_4^4(8)$	87.7	2.7	–	–	–	73	64	2	–	–	–
2	$R_2^2(8)$	77.3	3.0	–	–	–	66	51	2	–	–	–
3	$R_2^2(8)$	**69.6**	**5.5**	–	**0.4**	–	**1125**	**783**	**62**	–	**4**	–
4	$R_2^2(10)$	**80.3**	**2.3**	–	–	–	**132**	**106**	**3**	–	–	–
5	$R_2^2(10)$	79.4	2.9	–	–		34	27	1	–	–	–
6	$R_2^2(8)$	**78.6**	**1.7**	–	**0.3**	**0.3**	**1302**	**1023**	**22**	–	**4**	**4**
7	$R_2^2(12)$	**86.0**	**1.9**	–	–	–	**107**	**92**	**2**	–	–	–
8	$R_2^2(10)$	56.3	25.0	–	–	–	16	9	4	–	–	–
9	$R_2^2(8)$	**79.6**	**1.6**	–	–	–	**186**	**148**	**3**	–	–	–
10	$R_2^2(6)$	**87.0**	**0.7**	–	–	–	**138**	**120**	**1**	–	–	–
11	$R_2^2(8)$	**97.5**	**0.8**	–	–	–	**120**	**117**	**1**	–	–	–
12	$R_2^2(10)$	**53.6**	**14.5**	–	**0.7**	–	**138**	**74**	**20**	–	**1**	–
13	$R_2^2(10)$	39.3	35.7	–	–	–	28	11	10	–	–	–
14	$R_2^2(8)$	**76.8**	**2.6**	–	**0.6**	–	**1635**	**1256**	**43**	–	**10**	–
15	$R_2^2(12)$	**82.7**	**4.5**	–	**0.8**	–	**133**	**110**	**6**	–	**1**	–
16	$R_2^2(4)$	**61.8**	**10.7**	**0.1**	**0.9**	**1.6**	**794**	**491**	**85**	**1**	**7**	**13**
17	$R_2^2(4)$	**53.0**	**13.7**	–	–	–	**183**	**97**	**25**	–	–	–
18	$R_2^2(14)$	75.8	3.2	–	–	–	62	47	2	–	–	–
19	$R_3^3(6)$	–	38.1	–	–	–	21	–	8	–	–	–
20	$R_4^4(8)$	**76.3**	**18.7**	–	**0.4**	–	**257**	**196**	**48**	–	**1**	–
21	$R_4^2(8)$	**60.0**	**1.8**	**0.9**	–	**0.9**	**110**	**66**	**2**	**1**	–	**1**
22	$R_4^4(12)$	82.0	2.0	–	2	–	50	41	1	–	1	–
23	$R_4^2(8)$	**89.6**	**2.1**	**2.1**	**0.7**	**2.1**	**144**	**129**	**3**	**3**	**1**	**3**
24	$R_4^4(12)$	**71.5**	**5.9**	**1.2**	**0.3**	–	**340**	**243**	**20**	**4**	**1**	–
25	$R_2^2(4)$	55.8	11.6	–	–	–	43	24	5	–	–	–
26	$R_2^4(8)$	65.1	9.3	–	–	–	43	28	4	–	–	–
27	$R_2^2(10)$	**72.5**	**7.3**	–	–	–	**262**	**190**	**19**	–	–	–
28	$R_2^2(10)$	78.6	3.6	–	–	–	28	22	1	–	–	–
29	$R_2^2(6)$	80.0	6.7	–	–	–	15	12	1	–	–	–
30	$R_4^2(8)$	**77.7**	**2.8**	–	–	**1**	**287**	**223**	**8**	–	–	**3**
31	$R_4^4(12)$	**54.8**	**3.2**	–	**0.8**	–	**126**	**69**	**4**	–	**1**	–
32	$R_4^2(12)$	**63.2**	**6.0**	**1.4**	–	**1.9**	**418**	**264**	**25**	**6**	–	**8**
33	$R_4^2(8)$	85.4	2.4	–	–	–	41	35	1	–	–	–
34	$R_4^2(8)$	92.0	–	4	–	–	25	23	–	1	–	–
35	$R_4^4(12)$	**71.2**	**3.8**	–	–	**0.5**	**212**	**151**	**8**	–	–	**1**
36	$R_4^4(12)$	**44.8**	**0.5**	**0.3**	–	**0.3**	**373**	**167**	**2**	**1**	–	**1**
37	$R_4^4(12)$	77.3	4.5	4.5	–	–	22	17	1	1	–	–
38	$R_4^4(12)$	75.4	–	–	–	–	65	49	–	–	–	–
39	$R_4^2(8)$	**61.8**	**1.5**	–	–	–	**136**	**84**	**2**	–	–	–
40	$R_4^2(8)$ $R_4^4(12)$	**70.1**	**7.1**	–	–	–	**154**	**108**	**11**	–	–	–
41	$R_4^4(12)$	95.9	–	4.1	–	2	49	47	–	2	–	1
42	$R_2^2(4)$	69.7	3.0	–	–	3	33	23	1	–	–	1
43	$R_2^4(8)$	76.2	–	–	–	–	21	16	–	–	–	–
44	$R_4^2(8)$	72.1	4.4	–	1.5	1.5	68	49	3	–	1	1

2.2. Identifying chiral enantiomers and *meso* molecules in crystals

Since the currently available CSD programs do not distinguish between crystals of chiral, racemic, *meso* and achiral molecules, it was necessary to write a new program that can identify these properties among CSD entries. All programs that were written for this study were written using Visual C++ 6 and are supplied in the supplementary material.[1]

2.3. Searching hydrogen-bond ring motifs

All searches were carried on the CSD version April 2006 for organic structures with $R < 0.10$ and no errors using *CONQUEST*, Version 1.8 (Bruno *et al.*, 2002). Structures that contain atoms with more than four bonds were excluded. The hydrogen-bond cut-off distance was defined according to the sum of the van der Waals radii and $D—\mathrm{H}\cdots A > 90°$ for angles. Bond type and charges were undefined since these often depend on the author's definition; instead all atom hybridizations (No. of bonds per atom) were included in the search.

---

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: GP5018). Services for accessing these data are described at the back of the journal.

Table 2
Probability (in %) for hydrogen-bond motifs to occupy crystallographic special positions, for racemic crystal structures.

Empty cells indicate zero values. The number in the first column refers to the motifs shown in Fig 1 (symmetry elements that are not included in the table are not represented by any of the motifs examined). Cases of over 100 instances are marked with bold letters. Only cases with $N_{\rm tot} > 12$ are included.

				No. of instances		
Racemic		$P_{\rm inv}$	$P_{\rm rot}$	$N_{\rm tot}$	$N_{\rm inv}$	$N_{\rm rot}$
Motif number	Graph set	Inversion centers (%)	Out-of-plane rotations (%)	All instances	Inversion centers	Out-of-plane rotations
1	$R_4^4(8)$	93.8	–	16	15	–
2	$R_2^2(8)$	93.2	2.3	44	41	1
3	$R_2^2(8)$	**90.4**	**2.6**	**115**	**104**	**3**
4	$R_2^2(10)$	93.8	–	16	15	–
5	$R_2^2(10)$	87.8	4.1	98	86	4
6	$R_2^2(8)$	**89.7**	**1.3**	**389**	**349**	**5**
7	$R_2^2(12)$	89.0	5.5	73	65	4
9	$R_2^2(8)$	83.3	–	48	40	–
10	$R_2^2(6)$	83.6	–	55	46	–
11	$R_2^2(8)$	89.5	2.6	76	68	2
14	$R_2^2(8)$	**86.6**	**2.9**	**724**	**627**	**21**
15	$R_2^2(12)$	83.3	5.6	18	15	1
16	$R_2^2(4)$	**61.1**	**9.1**	**396**	**242**	**36**
17	$R_2^2(4)$	75.0	–	36	27	–
20	$R_4^4(8)$	**76.1**	**20.8**	**197**	**150**	**41**
21	$R_4^2(8)$	58.3	4.2	24	14	1
23	$R_4^2(8)$	100	–	14	14	–
24	$R_4^4(12)$	**84.2**	**2.2**	**139**	**117**	**3**
27	$R_2^2(10)$	64.0	4.0	25	16	1
28	$R_2^2(10)$	79.2	4.2	24	19	1
30	$R_4^2(8)$	86.2	6.9	29	25	2
31	$R_4^4(12)$	65.0	–	20	13	–
32	$R_4^2(8)$	**78.3**	**2.9**	**138**	**108**	**4**
36	$R_4^4(12)$	**31.1**	–	**103**	**32**	–
39	$R_4^2(8)$	82.4	5.9	17	14	1
40	$R_4^2(8)$ $R_4^4(12)$	80.4	1.8	56	45	1

2.4. Checking if hydrogen-bond motif occupies a crystallographic special position

In order to identify the crystallographic site symmetry of the hydrogen-bond ring motif a program was written based on the following algorithm: For each crystal structure all the motifs and all symmetry operations (matrices) belonging to the space group of the crystal in which the motif appears are read. For each matrix the type of symmetry the matrix operation represents (inversion, rotation, mirror *etc.*) is found according to the degrees of freedom of the special positions. Special positions have one or more coordinates that remain unchanged under the application of a symmetry operation. Hence, if $\hat{S}$ describes a symmetry operation and $\mathbf{X}$ is special position then $\hat{S}\mathbf{X} = \mathbf{X}$. Special position ($\mathbf{X}$) of single point corresponds to the inversion center operation ($\hat{S}$); special positions that form a line (one degree of freedom) correspond to rotations; special positions that form a plane (two degrees of freedom) correspond to mirrors (Kitaigorodskii, 1961). Next the symmetry operation was applied to all the atoms in the motif. If the motif remained unchanged (considering all atoms of the same element as identical) then the motif occupies this crystallographic special position.

2.5. Graph-set notation

The graph-set notation (Bernstein *et al.*, 1995) was used to describe and classify the hydrogen-bond ring motifs. In this method each hydrogen-bond motif is defined by $G_d^a(n)$ notation, where G is the motif type (R ring or C infinite chain), and n is the number of atoms in the ring or in the chain repeating unit; a is the number of hydrogen-bond acceptors, d is the number of hydrogen-bond donors.

3. Results and discussion

3.1. Probability for hydrogen-bond ring motifs to occupy crystallographic special symmetry positions

From Tables 1–4 it can be seen that the inversion center plays a significant role in the structures of all the hydrogen-bond ring motifs that were examined. The probability of a motif to lie on an inversion center $P_{\rm inv}$ is between 40 and 100% for motifs in crystals of achiral molecules, 30 and 100% for racemic crystals, and 32 and 76% for crystals of *meso* molecules. In general, ring motifs with $P_{\rm inv} < 50\%$ are rare (about 5% of the motifs checked). While there does not seem to be any clear correlation between the graph set of a motif and the probability that it will occupy an inversion center ($P_{\rm inv}$), there are still some connections: motifs with graph set $R_2^2(8)$ have a relatively high probability of occupying an inversion center with $P_{\rm inv}$ between 83 and 100% for racemic and 70 and 100% for achiral. Motifs with bifurcated hydrogen bonds (one hydrogen bonded to two acceptors) exhibit a relatively lower probability of occupying an inversion center ($56 < P_{\rm inv} < 76\%$). Finally, all motifs with H_2O as the donor have higher $P_{\rm inv}$ compared with the same motif with NH_2 as the donor. This difference cannot be explained by the influence of motifs with two different NH_2 donors. A possible explanation might lie in the fact that water is a smaller molecule and therefore less limited by packing and steric effects. It can therefore fit better to the more geometrically constrained crystallographic special positions. $P_{\rm inv}$ for motifs in crystals of *meso* molecules (Table 3) are mostly similar to those of crystals of achiral molecules. The $R_2^2(4)$ motif 12 is an exception with $P_{\rm inv}$ = 32.6%, which results mainly from two crystal structures (NUNHEJ, NOHKW) that contain eight different instances of this motif, with no inversion center and are not likely to have special significance. The $R_3^3(6)$ motif 19 is the only motif checked that can contain a threefold rotation or a threefold rotation reflection point. While it has the highest probably among

Table 3
Probability (in %) for hydrogen-bond motifs to occupy crystallographic special positions, for crystal structures of *meso* molecules.

Empty cells indicate zero values. The number in the first column refers to the motifs shown in Fig 1. Cases of over 100 instances are marked with bold letters. Only cases with $N_{\rm tot} > 12$ are included.

						No. of instances					
Meso		$P_{\rm inv}$	$P_{\rm rot}$		$P_{\rm mir}$	$N_{\rm tot}$	$N_{\rm inv}$	$N_{\rm rot}$		$N_{\rm mir}$	
Motif number	Graph set	Inversion centers (%)	Out-of-plane rotations (%)	In-plane rotations (%)	In-plane mirrors (%)	All instances	Inversion centers	Out-of-plane rotations	In-plane rotations	In-plane mirrors	Out-of-plane mirrors
6	$R_2^2(8)$	75.7	6.8	–	–	74	56	5	–	–	–
14	$R_2^2(8)$	68.2	4.7	–	3.5	85	58	4	–	3	–
16	$R_2^2(4)$	32.6	10.9	2.2	–	46	15	5	1	–	–
20	$R_4^4(8)$	76.9	26.9	–	–	26	20	7	–	–	–

Table 4
Probability (in %) for hydrogen-bond motifs to occupy crystallographic special positions, for crystal structures containing chiral molecules (not racemic).

Empty cells indicate zero values. The motif number in the first column refers to the motifs shown in Fig 1. Only cases with $N_{\rm tot} > 12$ are included.

				No. of instances	
Chiral		$P_{\rm rot}$		$N_{\rm tot}$	$N_{\rm rot}$
Motif number	Graph set	Out-of-plane rotations (%)	In-plane rotations (%)	All instances	Out-of-plane rotations
3	$R_2^2(8)$	17.5	–	40	7
4	$R_2^2(10)$	7.7	–	13	1
5	$R_2^2(10)$	**20.8**	–	**144**	**30**
6	$R_2^2(8)$	16.2	–	99	16
11	$R_2^2(8)$	13.0	–	23	3
14	$R_2^2(8)$	**16.7**	–	**288**	**48**
16	$R_2^2(4)$	**15.9**	–	**773**	**123**
17	$R_2^2(4)$	25.0	–	24	6
19	$R_3^3(6)$	17.3	–	52	9
20	$R_4^4(8)$	**28.0**	–	**107**	**30**
24	$R_4^4(12)$	**12.6**	**0.6**	**175**	**22**
27	$R_2^2(10)$	36.8	–	19	7
30	$R_4^2(8)$	53.8	–	13	7
31	$R_4^4(12)$	5.2	–	58	3
32	$R_4^2(8)$	**8.4**	–	**190**	**16**
36	$R_4^4(12)$	11.9	–	42	5
39	$R_4^2(8)$	31.3	–	16	5
40	$R_4^2(8)$ $R_4^4(12)$	14.6	–	89	13

motifs of achiral molecules to contain the rotation axis ($P_{\rm rot}$ = 38%), it contains no single rotation reflection point.

The probability of a motif to lie on a rotation axis varies widely among different motifs, with $5 < P_{\rm rot} < 54\%$ for motifs appearing in the chiral group, and $2 < P_{\rm rot} < 38\%$ in crystals of achiral molecules. However, in all cases where $P_{\rm rot} > 30\%$ the number of instances of the motif is less than 30 ($N_{\rm tot} < 30$); hence the statistics are less reliable. Note that there is a negative correlation between the $P_{\rm inv}$ and $P_{\rm rot}$; hence motifs that have a high probability of occupying an inversion center have a low probability to occupy a rotation axis and *vice versa*. This can be explained by the fact that the appearance of inversion and rotation together in the same motif is possible only in crystallographic 2/*m* symmetry, and since the retention of mirror symmetry is relatively rare (Kitaigorodskii, 1961), the appearance of an inversion center will usually exclude the existence of rotation axis and *vice versa*. It is clear from Tables 1–4 that rotation axes that lie in the plane of the motif (in-plane rotation axis) and mirror planes do not play any significant role in the structures of any of the motifs that were surveyed ($P_{\rm mir} <$ 3.5% for all; Kitaigorodskii, 1961). However, the formation of a motif with mirror plane or in-plane rotation depends much on the symmetry of the molecules that form the motif, since the mirror plane/rotation axis must pass through the molecule, and therefore puts larger constraints on the motif and the molecule compared with inversion and the off-plane rotation.

3.2. The influence of molecular chirality on the formation of hydrogen-bond ring motifs in the crystal

Another feature that was examined is the effect of the chirality of the molecules in the crystal on the probability of formation of hydrogen-bond ring motifs in the crystal. Since the inversion center apparently plays an important role in the structures of all the motifs studied here, it is clear that for crystal structures of chiral molecules, which cannot have inversion centers, the ring motifs will be less likely to form, even compared with crystal structures of the same substance but with both enantiomers (Sørensen & Larsen, 2003). To determine the effect of inversion center on the formation of hydrogen-bond ring motifs we determined the structural probability $P_{\rm s}$ (Allen *et al.*, 1999), which refers to the probability that a crystal structure of molecules with some functional groups will contain a specific hydrogen-bond motif composed of these functional groups. For example, one might want to determine the probability that a crystal with a carboxylic group would exhibit the carboxylic acid dimer [$R_2^2(8)$ motif 4, Fig. 1]. The structural probability $P_{\rm s}$ of a motif is calculated by dividing the number of crystal structures in which this specific motif is formed ($N_{\rm m}$), by the number of crystal structures that contain the functional groups that are necessary to form this motif $N_{\rm p}$

Table 5
The structural probability (P_s in %) for a hydrogen-bond ring motif to appear in crystals of achiral molecules, chiral molecules (not racemic), *meso* molecules and racemic crystals (§2.1).

P_s for cases in which $N_p < 20$ appear in parentheses. The motif number in the first column refers to the motifs in Fig. 1. Dashed entries indicate zero values.

		Structural probability $P_s = N_m/N_p$				No. of structures that have the possibility to form the motif N_p				No. of structures with motif N_m			
Motif number	Graph set	Meso (%)	Racemic (%)	Achiral (%)	Chiral (%)	Meso	Racemic	Achiral	Chiral	Meso	Racemic	Achiral	Chiral
1	$R_4^4(8)$	1.8	1.5	1.4	0.3	113	1044	4249	3333	2	16	61	9
2	$R_2^2(8)$	–	52.5	58.1	14.7	–	80	105	34	–	42	61	5
3	$R_2^2(8)$	(35)	32.4	30.5	6.4	20	324	3065	598	7	105	935	38
4	$R_2^2(10)$	–	31.4	32.4	11.4	3	51	386	105	–	16	125	12
5	$R_2^2(10)$	2.5	17.8	6.2	5.5	40	528	497	2144	1	94	31	117
6	$R_2^2(8)$	45.7	39.5	33.7	5.1	116	864	3316	1686	53	341	1118	86
7	$R_2^2(12)$	–	47.1	33.3	–	1	140	306	15	–	66	102	–
8	$R_2^2(10)$	–	–	(76.5)	–	–	2	17	1	–	–	13	–
9	$R_2^2(8)$	(20)	38.0	37.3	10.2	15	108	432	98	3	41	161	10
10	$R_2^2(6)$	(66.7)	46.1	29.5	7.7	3	102	421	78	2	47	124	6
11	$R_2^2(8)$	(36.4)	41.7	19.9	8.5	11	163	562	212	4	68	112	18
12	$R_2^2(10)$	(5.6)	2.3	7.4	2.4	18	88	1614	451	1	2	120	11
13	$R_2^2(10)$	–	(12.5)	9.0	(15.4)	–	8	266	13	–	1	24	2
14	$R_2^2(8)$	36.2	35.9	25.8	5.7	185	1796	5288	4303	67	645	1362	246
15	$R_2^2(12)$	–	7.5	9.7	1.1	15	239	1305	369	–	18	126	4
16	$R_2^2(4)$	5.1	5.8	5.1	4.6	633	5861	13 425	12 182	32	339	683	562
17	$R_2^2(4)$	1.7	0.9	1.1	0.3	401	3890	15 421	6358	7	34	170	17
18	$R_2^2(14)$	–	4.8	21.5	–	2	21	246	79	–	1	53	–
19	$R_3^3(6)$	0.5	0.1	0.1	0.3	633	5861	13 425	12 182	3	6	18	42
20	$R_4^4(8)$	4.1	3.1	1.8	0.8	633	5861	13 425	12 182	26	182	247	101
21	$R_4^2(8)$	–	42.9	36.0	8.0	5	35	225	100	–	15	81	8
22	$R_4^4(12)$	(50)	–	7.8	–	2	30	516	37	1	–	40	–
23	$R_4^2(8)$	5.8	3.3	7.7	0.4	69	426	1750	1941	4	14	134	7
24	$R_4^4(12)$	(29.4)	45.0	36.7	12.2	17	220	630	997	5	99	231	122
25	$R_2^2(4)$	2.5	0.7	2.8	0.2	81	539	1428	1735	2	4	40	4
26	$R_2^4(8)$	–	2.2	4.6	0.3	31	277	769	1153	–	6	35	3
27	$R_2^2(10)$	(50)	26.4	31.2	9.8	6	87	744	173	3	23	232	17
28	$R_2^2(10)$	(33.3)	65.4	59.1	(9.1)	6	26	44	11	2	17	26	1
29	$R_2^2(6)$	(50)	(60)	18.7	(5.6)	2	5	75	18	1	3	14	1
30	$R_4^2(8)$	2.6	6.9	11.3	1.4	38	379	1996	855	1	26	226	12
31	$R_4^4(12)$	–	23.3	23.8	19.7	3	30	235	61	–	7	56	12
32	$R_4^2(8)$	9.7	29.8	26.6	10.7	31	342	1063	1359	3	102	283	145
33	$R_4^2(8)$	–	9.1	6.8	3.3	3	22	561	61	–	2	38	2
34	$R_4^2(8)$	(10.5)	13.6	10.5	2.0	19	66	237	102	2	9	25	2
35	$R_4^4(12)$	(20)	21.3	40.6	4.5	5	47	283	89	1	10	115	4
36	$R_4^4(12)$	(40)	48.6	48.9	18.6	5	35	225	97	2	17	110	18
37	$R_4^4(12)$	(9.1)	9.7	12.3	3.5	11	31	171	86	1	3	21	3
38	$R_4^4(12)$	(30)	11.4	13.4	1.0	10	35	329	96	3	4	44	1
39	$R_4^2(8)$	(16.7)	26.3	28.7	6.5	6	57	289	107	1	15	83	7
40	$R_4^2(8)$ $R_4^4(12)$	(17.6)	21.8	18.7	7.7	17	220	630	997	3	48	118	77
41	$R_4^4(12)$	(13.3)	8.2	11.3	0.9	15	97	399	458	2	8	45	4
42	$R_2^2(4)$	–	–	7.7	–	20	58	272	147	–	–	21	–
43	$R_2^4(8)$	–	–	5.5	–	20	58	272	144	–	–	15	–
44	$R_4^2(8)$	–	21.9	19.5	11.1	3	32	241	63	–	7	47	7

$$P_s = N_m/N_p. \quad (1)$$

Table 5 gives the structural probability P_s for the motifs in Fig. 1. Cases with $N_p < 20$ were included in parentheses and are not considered in the discussion. The structural probability P_s of ring motifs to appear in crystals with chiral molecules is much lower than in crystals of enantiomeric pairs and achiral molecules. P_s for ring motifs in the chiral group is generally between 2 and 10 times lower than P_s of the same motif in racemic crystals and crystals of achiral molecules. While the effect of the inversion center on the formation of the hydrogen-bond ring motif is not surprising by itself (Sørensen & Larsen, 2003; Davis *et al.*, 1996), the size of the effect is rather surprising and shows that symmetry considerations, as they come to play in relating to inversion centers, are of immense significance in the formation of the ring motifs in crystals. Therefore, symmetry considerations should not be neglected when considering the reasons for the formation of these motifs. This fact should be emphasized considering that much of the previous work done on the theoretical (Hofmann *et al.*, 2004; Steiner, 2002), statistical (Allen *et al.*, 1999) and experimental (Desiraju, 1995) reasons for the formation of hydrogen-bond ring motifs in crystals did not assign much consideration to the effect of symmetry. The $R_4^4(12)$ motifs 31, 36 and 24 have the highest P_s value in crystals of chiral molecules. However, none of the interactions checked for chiral molecules give P_s of over 20% and for most of them P is less than 10%. Hence, there is lower potential for utilization of any of these synthons for crystal engineering of chiral molecules (or noncentrosymmetric crystals). Also note that for almost all motifs P_s of racemic crystals is much closer to the P_s of crystals with achiral molecules than to P_s of the crystal of the chiral molecules. This supports the idea that the difference in probability results only or mostly from the inability to utilize inversion symmetry when crystallizing from an enantiopure solution.

4. Conclusion

The probability for common hydrogen-bond ring motifs (synthons) to occupy crystallographic symmetry positions was examined and the results (Fig. 1 and Tables 1–4) show that the probability of hydrogen-bond ring motifs to occupy an inversion center is usually between 50 and 100% depending on the hydrogen-bond motif. Also the probability of ring motifs to be formed in crystals of chiral molecules was compared with the probability of these motifs to be formed in crystals of achiral molecules and racemic crystals. The probability of all these hydrogen-bond ring motifs to be formed in crystals of chiral molecules is much lower, which indicates that the inversion center plays a significant role in the formation of hydrogen-bond ring motifs.

This work is supported by a US–Israel Binational Science Foundation grant No. 2004118.

References

Aakeröy, C. B. (1997). *Acta Cryst.* B**53**, 569–586.

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Allen, F. H., Motherwell, W. D. S., Raithby, P. R., Shields, G. P. & Taylor, R. (1999). *New J. Chem.* **23**, 25–34.

Anderson, K. M., Kamyar, A., Hiu-wan, Y., Goeta, A. E. & Steed, J. W. (2006). *Cryst. Growth Des.* **6**, 2109–2113.

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed.* **34**, 19.

Brock, C. P. & Dunitz, J. D. (1994). *Chem. Mater.* **6**, 1118–1127.

Bruno, I. J., Cole, J. C., Edgington, P. R., Kessler, M., Macrae, C. F., McCabe, P., Pearson, J. & Taylor, R. (2002). *Acta Cryst.* B**58**, 389–397.

Davis, R. E., Whitesell, J. K., Wong, M.-S. & Chang, N.-L. (1996). *Perspect. Supramol. Chem.* **2**, 63–106.

Day, G. M. *et al.* (2005). *Acta Cryst.* B**61**, 511–527.

Desiraju, G. R. (1995). *Angew. Chem. Int. Ed.* **34**, 2311–2327.

Dowdy, S. M., Wearden, S. & Chilko, D. M. (2004). *Statistics for Research*, 3rd ed. New York: Wiley Interscience.

Garciatellado, F., Geib, S. J., Goswami, S. & Hamilton, A. D. (1991). *J. Am. Chem. Soc.* **113**, 9265–9269.

Hofmann, D. W. M., Kuleshova, L. N. & Antipin, M. Y. (2004). *Cryst. Growth Des.* **4**, 1395–1402.

Kitaigorodskii, A. I. (1961). *Organic Chemical Crystallography*. New York: Consultants Bureau.

Krische, M. J. & Lehn, J. M. (2000). *Structure and Bonding*, Vol. 96, *Molecular Self-Assembly*, pp. 3–29. Heidelberg: Springer.

Melendez, R. E., Carr, A. J., Linton, B. R. & Hamilton, A. D. (2000). *Structure and Bonding*, Vol. 96, *Molecular Self-Assembly*, pp. 31–61. Heidelberg: Springer.

Pidcock, E., Motherwell, W. D. S. & Cole, J. C. (2003). *Acta Cryst.* B**59**, 634–640.

Sørensen, H. O. & Larsen, S. (2003). *Acta Cryst.* B**59**, 132–140.

Steiner, T. (2002). *Angew. Chem. Int. Ed.* **41**, 48–76.

Yao, J. W., Cole, J. C., Pidcock, E., Allen, F. H., Howard, J. A. K. & Motherwell, W. D. S. (2002). *Acta Cryst.* B**58**, 640–646.