CRYSTAL GROWTH & DESIGN

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Hydrogen-Bonded Helical Self-Assembly of Sterically-Hindered Benzyl Alcohols: Rare Isostructurality and Synthon Equivalence Between Alcohols and Acids

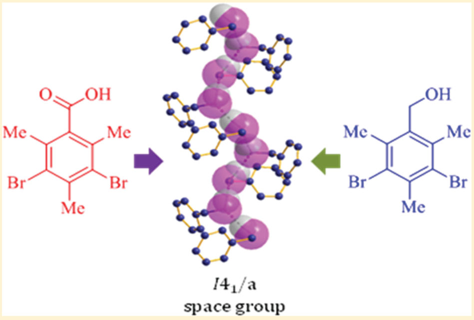
Jarugu Narasimha Moorthy,*,[†] Susovan Mandal,[†] and Paloth Venugopalan[‡]

[†]Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

[‡]Department of Chemistry, Panjab University, Chandigarh 160014, India

S Supporting Information

ABSTRACT: Hydrogen-bonded aggregation has been examined in a series of sterically hindered benzyl alcohols with an objective to explore how sterics influence the otherwise inconsistent and variable synthons generally observed for alcohols. All the sterically hindered alcohols **8−15** were found to adopt a helical hydrogen-bonded synthon, and crystallize uniformly in the rare $I4_1/a$ space group, for which the statistical prevalence in the CSD is abysmally small. Remarkably, the crystal packing in all of these alcohols is found to be isostructural to analogous sterically hindered carboxylic acids **1−4**. The reason as to why all alcohols sustain the helical motif, despite being aggregated via rather weak hydrogen bonds as compared those in analogous acids **1−4** is traceable to unique molecular topology that permits close-packing as well as exploitation of intermolecular interactions comprehensively. It is shown that sterics permit a very rare packing as well as synthon equivalence between carboxylic acids and alcohols. It emerges from the present study that the hydrogen-bonded synthons of strongly interacting functional groups are not necessarily reproducible when sterics are brought into picture. By the same token, the synthons may sustain even when the interactions are weak when close packing is ensured.



INTRODUCTION

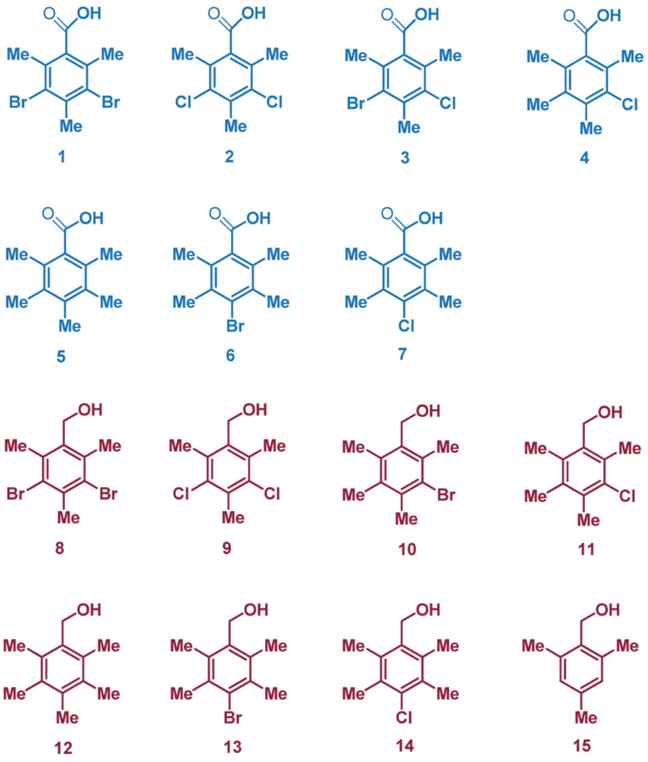
Nature abhors vacuum. In general, the molecules in crystals pack as efficiently as possible.[1] Maximization of crystal density and minimization of void volume is the enunciation of Kitaigorodskii's close packing.[1a,b] This tenet, however, is defied in compounds containing functional groups that may exploit strong hydrogen bonds.[2] The relatively high energy of hydrogen bonds as compared to van der Waals interactions in conjunction with their directionality render them to be structure-determining. Organization of rationally designed molecular modules by strong and directional hydrogen bonds in a predetermined fashion essentially constitutes *crystal engineering*.[3] Hydrogen bond-mediated aggregation is indeed the basis for the phenomenon of lattice inclusion exhibited by a variety of molecules such as urea,[4] thiourea,[5] dianin's compound,[6] cholic acid,[7] anthracene bis-resorcinol,[8] diol tubulands,[9] tetrahedral tetraarylmethanes,[10] etc.[11] Insofar as crystal engineering is concerned, identification of supramolecular synthons[3b] and the factors that affect their manifestation reliably in crystals is very important. A decade ago, we showed that simple sterically hindered benzene carboxylic acids substituted at the meta position with a weakly interacting halogen take a departure from conventional wisdom as to the self-assembly of carboxylic acids in general into either dimers or catemers; unprecedented helical assembly was demonstrated in all sterically hindered meta-halobenzoic acids **1−4**,[12] while the para-isomers as well as 2,3,4,5,6-pentamethylbenzoic acids (**5−7**) were found to exploit the dimer motif in their crystal lattices, Chart 1.

After a long hiatus, we wondered as to how the sterics in conjunction with halogens that may potentially involve in weaker X···X[13] and C−H···X[14] interactions influence the self-assembly of alcohols. The hydroxy compounds have long been known to interact via a varied number of supramolecular synthons, Figure 1.[15] This propensity has been intimately related to the shape and size of the compounds. Indeed, the conflict between close packing and exploitation of hydrogen bonds has been implicated for prevalence of unusually high Z′ (number of independent molecules in the asymmetric unit cell) in the crystal structures of alcohols.[15,16] Thus, we have synthesized a series of sterically hindered benzyl alcohols **8−15** (Chart 1) that are completely analogous to the set of acids **1−7** and examined their crystal packings to explore how sterics built around the hydroxyl functional group manifest in specific mode/s of hydrogen-bonded motifs/synthons. Herein, we report heretofore unprecedented and unexpected packing equivalence/isostructurality between acids and alcohols, and some insights into the origin of this intriguing feature.

Received: February 3, 2012
Revised: May 7, 2012
Published: May 8, 2012

dx.doi.org/10.1021/cg3001619 | *Cryst. Growth Des.* 2012, 12, 2942−2947

Chart 1



RESULTS AND DISCUSSION

Synthesis of Sterically-Hindered Benzyl Alcohols. The benzyl alcohols **8**, **9**, **14**, and **15** were readily prepared by reduction of the corresponding aldehydes with $NaBH_4$, see Supporting Information. The other alcohols, that is, **10**−**13**, were prepared by hydrolysis of the corresponding benzyl bromides with $CaCO_3$ in H_2O-1,4-dioxane (1:1) mixture at reflux conditions Scheme 1.

Molecular Self-Assembly and Crystal Packing of Benzyl Alcohols 8−15. All the benzyl alcohols **8**−**15** were found to be isostructural crystallizing uniquely in the tetragonal crystal system with the space group $I4_1/a$, see Table 1. The differences in terms of the molecular structure as well as crystal packing in all the compounds are unexceptional. In all of the alcohols **8**−**15**, the hydroxymethyl group is pointed almost orthogonally from that of the aromatic plane. The angle between the plane constituted by C−C−O atoms and the plane of the aromatic ring is found to vary in the range of 74−88°; the values in the region of 74° being specifically observed for alcohols that contain halogens at meta positions. In Figure 2 are shown the molecular structures of alcohols **8** and **12**, and that of the analogous benzoic acid **1**, whose structure was reported by us long ago.[12] As can be seen, the O−H bond is oriented almost orthogonally as that of the carboxylic acid group in **1**.

As mentioned earlier, all alcohols **8**−**15** are isostructural. Consequently, the crystal packings are similar with marginal differences. In Figure 3 are shown the crystal packing diagrams for 3 different alcohols, that is, **8**, **12**, and **13**, together with that for the dibromo acid **1** for comparison. In all cases, the alcohols that are related by the 4_1-screw[9] along *c*-axis are found to self-assemble via strong O−H···O hydrogen bonds into a helix (Figure 4); the geometrical parameters for hydrogen bonds in all alcohols are given in Table 2. The repeat distance, that is, the pitch of the helix that corresponds to 4 residues is typically the dimension of the *c*-axis, which varies between 8.1 and 8.5 Å for all alcohols. The helical strands along the c-direction are seen to be close packed in the ab-plane. An incisive analysis shows that C−H···π interactions that operate between the methylene hydrogens and the aromatic rings of the adjacent helical strands are uniformly present in all of the structures. Otherwise, one observes C−H···Br and Br···Br interactions in the case of dibromobenzyl alcohol **8**, while no such interactions should be expected for pentamethylbenzyl alcohol **12** (Figure 3). In view of the isostructurality of all **8**−**15**, the importance of these weaker interactions in the overall crystal packing is questionable. Seemingly, they are a consequence of close packing, but not of any serious consequence in crystal packing.

Helical Assembly (4_1-Screw) and Isostructurality of Sterically-Hindered Benzyl Alcohols. Very incisive analysis

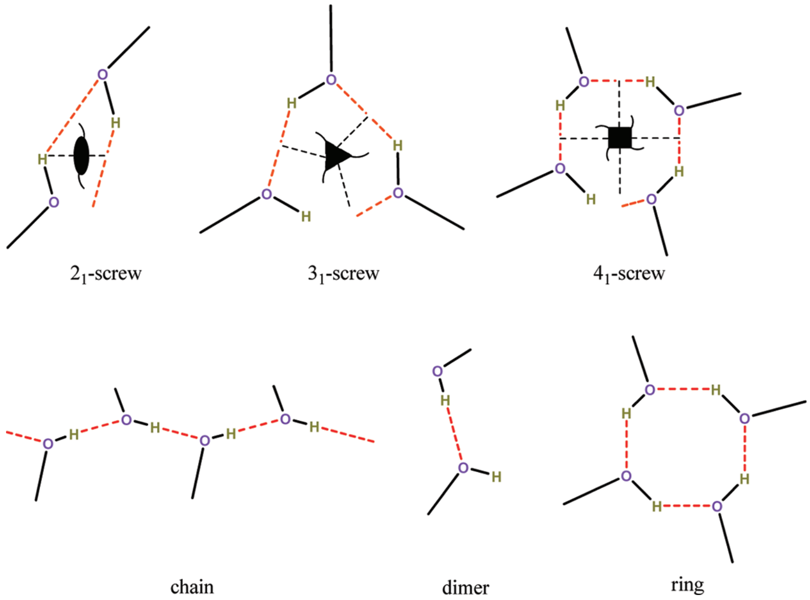
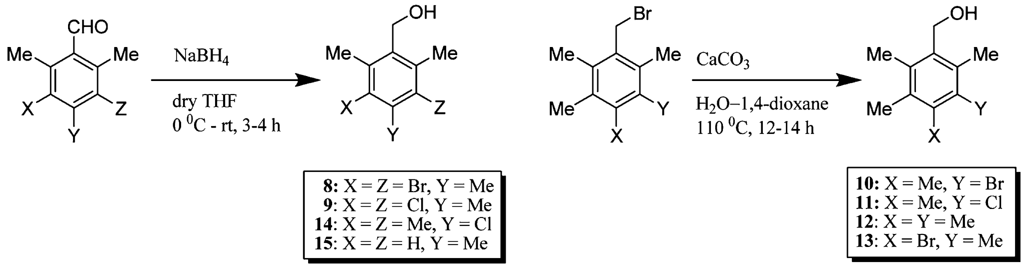


Figure 1. Typical O−H···O hydrogen bonded synthons by which alcohols in general aggregate.

Scheme 1



8: X = Z = Br, Y = Me
9: X = Z = Cl, Y = Me
14: X = Z = Me, Y = Cl
15: X = Z = H, Y = Me

10: X = Me, Y = Br
11: X = Me, Y = Cl
12: X = Y = Me
13: X = Br, Y = Me

Table 1. Crystal Data for Alcohols 8−15

	8	**9**	**10**	**11**
molecular formula	$C_{10}H_{12}Br_2O_1$	$C_{10}H_{12}Cl_2O_1$	$C_{11}H_{15}Br_1O_1$	$C_{11}H_{15}Cl_1O_1$
formula weight	308.02	219.10	243.14	198.68
solvent for crystallization	MeOH	MeOH	Et_2O	Et_2O
crystal system	tetragonal	tetragonal	tetragonal	tetragonal
space group	$I\ 4_1/a$ (No. 88)	$I\ 4_1/a$ (No. 88)	$I\ 4_1/a$ (No. 88)	$I\ 4_1/a$ (No. 88)
a (Å)	22.016(5)	21.877(2)	22.059(2)	21.960(2)
b (Å)	22.016(5)	21.877(2)	22.059(2)	21.960(2)
c (Å)	8.344(5)	8.118(1)	8.229(1)	8.121(1)
α (deg)	90.00	90.00	90.00	90.00
β (deg)	90.00	90.00	90.00	90.00
γ (deg)	90.00	90.00	90.00	90.00
volume (Å^3)	4044.0(3)	3885.4(6)	4004.7(8)	3916.7(6)
Z	16	16	16	16
calculated density (mg/m^3)	2.023	1.498	1.613	1.348
absorption coefficient (mm^{-1})	7.974	0.622	4.063	0.346
F (000)	2400	1824	1984	1696
goodness-of-fit on F^2	1.039	1.038	1.048	1.066
final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0364$, $R_2 = 0.0821$	$R_1 = 0.0396$, $R_2 = 0.1035$	$R_1 = 0.0461$, $R_2 = 0.1159$	$R_1 = 0.0395$, $R_2 = 0.1007$
R indices (all data)	$R_1 = 0.0469$, $R_2 = 0.0858$	$R_1 = 0.0448$, $R_2 = 0.1070$	$R_1 = 0.0586$, $R_2 = 0.1225$	$R_1 = 0.0416$, $R_2 = 0.1024$
	12	**13**	**14**	**15**
molecular formula	$C_{12}H_{18}O_1$	$C_{11}H_{15}Br_1O_1$	$C_{11}H_{15}Cl_1O_1$	$C_{10}H_{14}O_1$
formula weight	178.26	243.14	198.68	150.21
solvent for crystallization	C_6H_6	Et_2O	Et_2O	Et_2O + Pet ether
crystal system	tetragonal	tetragonal	tetragonal	tetragonal
space group	$I4_1/a$ (No. 88)	$I4_1/a$ (No. 88)	$I4_1/a$ (No. 88)	$I4_1/a$ (No. 88)
a (Å)	22.046(2)	22.035(2)	22.069(5)	20.924(2)
b (Å)	22.046(2)	22.035(2)	22.069(5)	20.924(2)
c (Å)	8.137(1)	8.494(1)	8.525(2)	8.102(1)
α (deg)	90.00	90.00	90.00	90.00
β (deg)	90.00	90.00	90.00	90.00
γ (deg)	90.00	90.00	90.00	90.00
volume (Å^3)	3954.7(6)	4124.4(6)	4152.2(2)	3546.9(7)
Z	16	16	16	16
calculated density (mg/m^3)	1.198	1.566	1.271	1.125
absorption coefficient (mm^{-1})	0.074	3.945	0.326	0.070
F (000)	1568	1984	1696	1312
goodness-of-fit on F^2	1.061	1.045	1.044	1.063
final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0521$, $R_2 = 0.1381$	$R_1 = 0.0294$, $R_2 = 0.0734$	$R_1 = 0.0503$, $R_2 = 0.1401$	$R_1 = 0.0711$, $R_2 = 0.1990$
R indices (all data)	$R_1 = 0.0604$, $R_2 = 0.1464$	$R_1 = 0.0361$, $R_2 = 0.0756$	$R_1 = 0.0638$, $R_2 = 0.1517$	$R_1 = 0.0771$, $R_2 = 0.2093$

in 1994 by Brock and Duncan on the aggregation of alcohols[15] in general are the following: (i) hydrogen-bonded aggregates of alcohols are largely rings and chains, (ii) if the compounds are relatively thin, they can be related by 2_1-screw, glide planes, and translation rarely, and (iii) in sterically hindered molecules, the difficulty in organizing molecules by 2-fold axes or inversion symmetry may manifest in crystal structures with high Z' or aggregation of the molecules around screw or rotation inversion axes of order 3, 4, or 6 in trigonal or tetragonal space groups. Subsequent analyses by Taylor and Macrae in 2001[17] were found to be in conformity with the inferences by Brock and Duncan;[15] the former observed that the helical chains are common for secondary and tertiary monoalcohols suggesting thereby that sterics could be very relevant in the helical self-assembly. It was also observed that 3-fold helices are more frequently observed than 4-fold helices. In 2003, Muir and co-

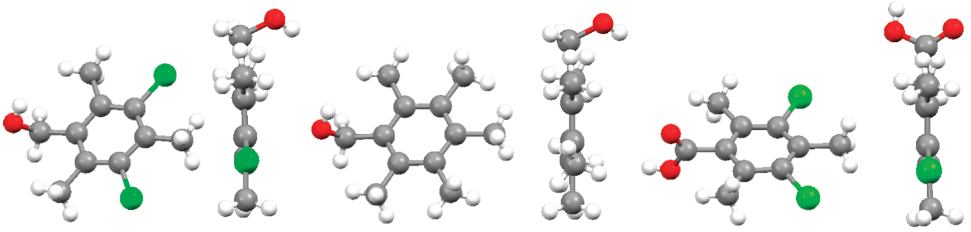


Figure 2. X-ray determined molecular structures of benzyl alcohols **8** and **12** (left and center pairs), and dibromobenzoic acid **1** (right pair).

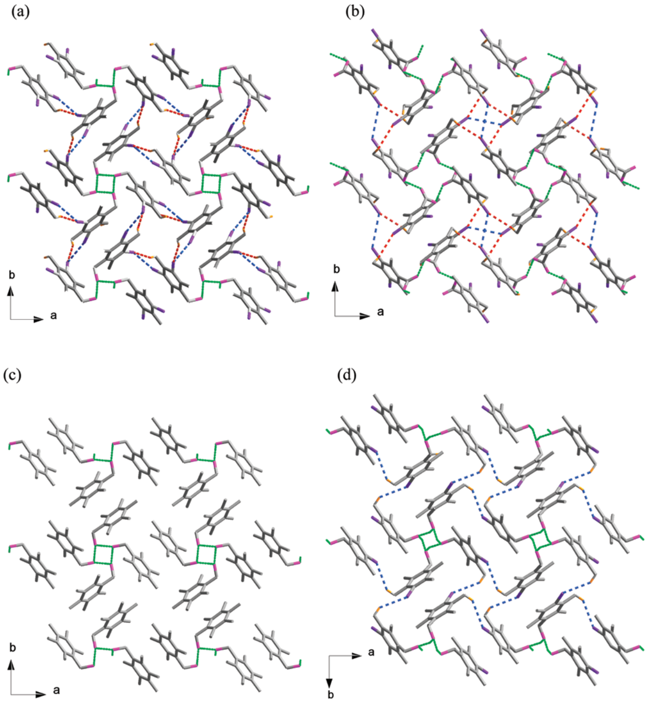


Figure 3. Comparison of the crystal packings of (a) 3,5-dibromo-2,4,6-trimethylbenzyl alcohol **8**, (b) 3,5-dibromo-2,4,6-trimethylbenzoic acid **1**, (c) 2,3,4,5,6-pentamethylbenzyl alcohol **12**, and (d) 4-bromo-2,3,5,6-tetramethylbenzyl alcohol **13**. Notice that in all the structures O–H···O hydrogen bonds have been shown with broken green line, while Br···Br and C–H···Br have been shown in blue and red color, respectively.

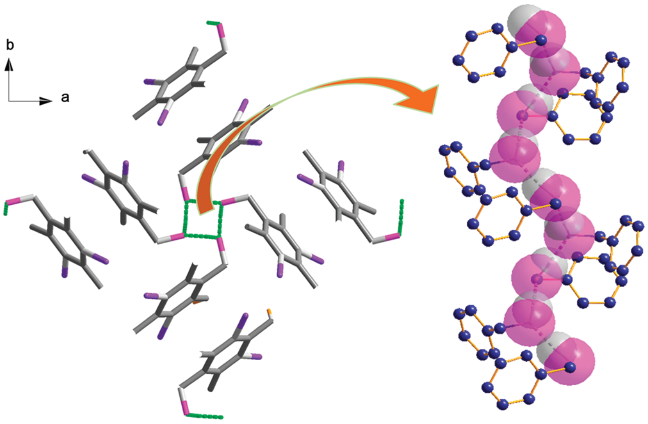


Figure 4. Partial drawing of molecular packing in 3,5-dibromo-2,4,6-trimethylbenzyl alcohol **8** (left) and the O–H···O hydrogen-bonded self-assembly into 4_1-screw helix. Please note that the aromatic hydrogens, bromines, and methyl groups have been removed in the helix for clarity.

workers analyzed the aggregation with a particular emphasis on tertiary alcohols and showed that trigonal and tetragonal space groups are more prevalent for tertiary alcohols as compared to all other structures in the database.[18] In the backdrop of this literature on hydrogen-bonded assembly of alcohols in general and our own observation of dramatic influence of sterics on benzene carboxylic acids,[12] it was instructive to enquire into how sterically hindered benzyl alcohols aggregate vis-à-vis unhindered parent benzyl alcohols. Further motivation for comprehensive investigations into the steric effects on benzyl alcohols was also the following. A quick perusal of the CSD revealed that the synthons that are typically observed for simple benzyl alcohols, for example, *p*-chloro/bromo/methyl benzyl alcohols, are linear chains and 2_1-screw-related zigzag chains.[19] Curiously, the X-ray crystal structures of sterically hindered 2,4,6-trimethylbenzyl alcohol and any of its derivatives are unknown as revealed by the CSD search. From a thorough CSD analysis, we recognized that 1,4-bis(hydroxymethyl)-benzene crystallizes in $P2_1/n$ space group,[20] while its sterically hindered 1,4-bis(hydroxymethyl)durene (OJEZUY) analog was found to crystallize in $I4_1/a$ space group.[21]

Clearly, the crystal structures of all benzyl alcohols **8–15** show that sterics divert the otherwise generally observed chain/zigzag motif, and that minor substitutional changes do not affect the aggregation via 4_1-helix. What is it that causes the 4_1-screw helical synthon in sterically hindered benzyl alcohols to be so robust as to be reliably observed in a series of derivatives? Indeed, the crystallization of all of the benzyl alcohols **8–15** in $I4_1/a$ space group is quite intriguing when the fraction of total number of alcohols as a whole that crystallize in this space group is considered. Our analysis of CSD (as of 2012) reveal that the number of structures in CSD that correspond to the string "C–C–OH" is 35 689, of which only 73 are found to crystallize in $I4_1/a$; this amounts to 0.20% of the total number of alcohols (Table 3).

The reason for helical aggregation around 4_1-axis appears to be traceable to orthogonality of C–C–O bond with respect to the aromatic *bulky* moiety; for all the alcohols, the angle between C–C–O plane and the plane of the aryl ring varies between 74° and 88° (Table 2), while the angle in sterically unhindered alcohols that crystallize in $P2_1$ or $P2_1/c$ or $P2_1/a$ are typically in the range of 34–51°.[19] Seemingly, this orthogonality of the aryl ring with respect to the C–C–O plane of C–C–OH that self-assembles via O–H···O hydrogen bonding permits best packing with each of the aryl ring stacked almost perpendicular to the ab-plane along the *c*-axis. The aryl rings do not tilt much into the ab-plane thereby allowing efficient organization along the *c*-axis; the angles between the planes of the aryl rings that are related by 4_1-screw axis varies between 81° and 90° for all alcohols (Table 2). As was prophetically inferred by Brock and Duncan,[15] the alcohols **8–15**, which are bulky, cannot presumably be linked up by C_2-axis, inversion

Table 2. Geometrical Parameters for the Intermolecular Interactions Observed in the Crystals of Alcohols **8**−**15**

compound	$d_{O\cdots O}$[a] (Å)	$\theta_{O-H\cdots O}$[a] (°)	$d_{O-H\cdots O}$[a] (Å)	$d_{X\cdots X}$[b] (Å)	$\theta_{C-X\cdots X}$[b] (°)	$d_{C-H\cdots X}$[c] (Å)	$d_{C-H\cdots \pi}$[d] (Å)	$\theta_{aryl-CCO}$[e] (°)	$\theta_{(tilting)}$[f] (°)
8	2.75(1)	173.4(2)	1.94(1)	3.63(1)	75.2(1)	2.99(1)	3.11(1)	74.2(2)	82.6(1)
9	2.74(1)	173.7(1)	1.93(1)				3.08(1)	74.6(1)	82.1(1)
10	2.74(1)	175.8(2)	1.92(1)	3.60(1)	75.3(1)	2.87(1)	3.12(1)	74.8(2)	81.9(1)
11	2.74(1)	178.1(1)	1.92(1)				3.10(1)	74.4(1)	81.7(1)
12	2.76(1)	176.6(1)	1.94(2)				3.11(1)	76.3(1)	81.3(1)
13	2.71(1)	163.1(1)	1.91(1)			2.93(1)	3.16(1)	87.4(1)	84.7(1)
14	2.74(1)	167.0(1)	1.93(1)			2.85(1)	3.18(1)	88.0(1)	85.1(1)
15	2.75(1)	169.7(1)	1.94(1)				2.88(1)	85.6(1)	89.9(1)

[a] For O−H···O hydrogen bond. [b] For halogen···halogen interactions. [c] Distance of C−H···X interaction. [d] For closest C−H···π interaction. [e] The angle between the aryl ring and the plane constituted by the C−C−O(H) atoms. [f] Angle between the planes of the aryl rings related by 4_1-screw axis.

Table 3. Statistical Analysis of Alcohols in the CSD as of 2012

search string	total hits	hits with $I4_1/a$ space group	percentage
C−C−OH	35689	73	0.20
C−CH_2−OH	6843	26	0.38
C−C(C)H−OH	14331	19	0.13
C−$C(C)_2$−OH	8174	16	0.20
C−OH	46300	105	0.23

symmetry, translation and $2_1/3_1$ screw axes. Thus, the fact that sterics that impart a particular shape appears to be crucial for the helical self-assembly based on O−H···O hydrogen bonding, which is unaffected by the presence/absence of weakly interacting groups that are remotely located from the hydroxyl group.

Synthon (Packing) Equivalence of Sterically-Hindered Benzyl Alcohols with Analogous Acids. As mentioned at the outset, sterically hindered benzene carboxylic acids that contain at least one halogen at the meta position were shown by us to undergo helical assembly and crystallize in $I4_1/a$ space group.[12] In fact, all of the alcohols **8**−**15** are isostructural to those of acids **1**−**4**. To the best of our knowledge, the observed isostructurality between acids and alcohols is unprecedented. The acids in general are strong hydrogen bond donors as well as acceptors, while alcohols are relatively weaker donors and acceptors; this is amply reflected in the significantly shorter (2.4−2.55 Å) O···O distances in acids **1**−**4** than in alcohols **8**−**15** (2.71−2.75 Å), cf. Table 2. What is the origin of packing equivalence of acids **1**−**4** with those of all alcohols **8**−**15**? Why is it that replacement of halogens at 3,5-positions of the acids with methyl groups as in **5** and location of a halogen at para position as in **6** and **7** leads to dimeric motif, while similar substitutional changes do not affect the helical assembly of alcohols **8**−**15**? It is ironic that the strongly hydrogen-bonded helical motif in **1**−**4** is readily perturbed, while the rather less strongly aggregated alcohols sustain the helical propagation! The fact that the sterically hindered acids, despite being strongly connected, are worst affected with weakly interacting groups suggests that the crystal packing in **1**−**4** seemingly corresponds to critical threshold at which there is a best trade-off between close-packing and exploitation of strong as well as weak interactions. This sensitive limit appears to be readily perturbed with minute of changes, as reflected by the crystal packings of **5**−**7** in which the dimer motif is observed. In other words, the acids **1**−**4** appear to represent systems that are "sensitive" from the point of view of crystal packing, although carboxyl hydrogen in each case is involved in hydrogen bonding. Despite maximization of hydrogen-bonding interactions, the packing appears to be unstable/inefficient such that the helical synthon is readily compromised with any perturbation that imparts little gain in terms of the lattice energy. In contrast, the molecular organization in analogous alcohols appears to be free from any stress and is seemingly "relaxed" with best of close-packing and hydrogen bonding. In spite of relatively weaker hydrogen-bonding interactions, the packing is conserved for similar changes in the substitution pattern. Evidently, the close-packing is not much affected. In line with these considerations, the packing indexes, as revealed by PLATON, for some of the alcohols **8**−**15** and acids **1**−**7** (Table 4) show that the helical organization of the molecules with extra carbonyl oxygen in acids **1**−**4**, when compared with alcohols, renders the packing little poorer. In essence, the rare packing equivalence for acids **1**−**4** and alcohols **8**−**15**, divergence for **5**−**7** point out subtle interplay between close-packing and exploitation of hydrogen-bonded synthons in the crystal packing. It emerges from the present study that the hydrogen-bonded synthons of strongly interacting functional groups are not necessarily reproducible when sterics are brought into picture. By the same token, the synthons may sustain even when the interactions are weak when close packing is ensured.

Table 4. Packing Indexes for Some of the Benzoic Acids **1**−**7** and Benzyl Alcohols **8**−**15**[a,b]

compound	packing index (%)	compound	packing index (%)
1	66.7	**9**	72.8
2	66.2	**12**	72.4
6	65.0	**13**	70.5
7	64.5	**14**	68.2
8	73.1	**15**	66.9

[a] As calculated by the program PLATON. [b] The packing indexes were not calculated for the disordered structures.

CONCLUSIONS

We have investigated hydrogen-bonded self-assembly in a series of sterically hindered benzyl alcohols with a view to inquire about how sterics influence the hydrogen-bonded synthons of hydroxyl groups. Contrary to the noted propensity of alcohols to aggregate via different synthons, the sterically hindered benzyl alcohols **8**−**15** were found to adopt helical hydrogen-bonded synthon, and crystallize uniformly in the rare $I4_1/a$ space group, for which the statistical prevalence in the CSD is abysmally small. The reason as to why all alcohols sustain the helical motif, despite being aggregated via rather weak hydrogen bonds as compared to those in analogous acid **1**−

4, is traceable to unique molecular topology that permits close-packing as well as exploitation of intermolecular interaction comprehensively. It is shown that sterics permit a very rare packing as well as synthon equivalence between carboxylic acids and alcohols.

EXPERIMENTAL SECTION

Crystal Structure Determinations and Refinement. The crystals suitable for X-ray analysis were grown in each case by slow evaporation of their solutions in the solvents mentioned in Table 1. A good quality crystal in each case was mounted in a glass capillary, cooled to 100 K, and the intensity data were collected on a Bruker Nonius SMART APEX CCD detector system with Mo-sealed Siemens ceramic diffraction tube (λ = 0.71073 Å) and a highly oriented graphite monochromator operating at 50 kV and 30 mA. The data were collected on a hemisphere mode and processed with Bruker SAINTPLUS. Empirical absorption correction was made using Bruker SADABS. The structure was solved in each case by Direct Methods using SHELXTL package and refined by full matrix least-squares method based on F^2 using SHELX97 program.[22] For benzyl alcohols **10** and **11**, the halogen and methyl groups at meta positions were found to be statistically disordered. The refinement for these cases was accomplished with associating partial occupancies for methyl carbon and halogen atoms. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in their ideal positions with fixed isotropic U values and were allowed to ride with their respective non-hydrogen atoms. The crystal data and details of refinement are included in Table 1.

ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic information files (CIF), NMR spectral data, and spectral reproductions. This information is available free of charge via the Internet at http://pubs.acs.org/.

AUTHOR INFORMATION

Corresponding Author

*E-mail: moorthy@iitk.ac.in.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

J.N.M. is thankful to DST (Department of Science and Technology), India for funding. S.M. is grateful to CSIR for a senior research fellowship.

DEDICATION

Dedicated to Prof. T. N. Guru Row. IISc., Banaglore on the occasion of his 60th Birthday

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