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Crystal packing of alcohol amines formed by the reaction of primary amines with 1,2-epoxy-3-phenoxypropane

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For the purposes of characterizing a novel class of inorganic–organic hybrid epoxy resin materials, a series of amines were reacted with a monoepoxide (1,2-epoxy-3-phenoxypropane) under base catalyzed conditions to produce racemic mixtures of compounds with the general formula $PhOCH_2CH(OH)CH_2N(H)R$, where R = ^{n}Pr (**1**), ^{i}Pr (**2**), or ^{t}Bu (**3**). The crystal structures of these compounds were determined by X-ray crystallography. Compound **1** forms infinite sheets of centrosymmetric dimers. In contrast, as a result of intermolecular hydrogen-bonding, compounds **2** and **3** arrange as tetrameric units in non-centrosymmetric space groups. Through a review of crystal structures found in the Cambridge Crystallographic Database, compounds of the general type $X–CH(OH)CH_2N(H)R$ were investigated and a rationalization for the packing of racemic mixtures in non-centrosymmetric space groups is discussed.

Introduction

Crystal engineering is a growing area of materials chemistry research which focuses on planning the design and properties of molecular crystals.[1] Applications of crystal engineering have been proposed to include the development of pharmaceuticals, biosensors, and optical and electronic devices.[2] In general, the approach used in such research programs is a combination of analysis and synthesis wherein noted systematic patterns of crystal aggregation are exploited for the directed synthesis of compounds possessing desirable crystallographic architectures in what may be termed "engineered" molecular materials.[3,4]

To achieve the goal of designing solid-state materials with specific crystal structures, great consideration is often given to the fact that most molecular packing motifs are governed by the presence of hydrogen bonding.[5] Commonly, synthetic strategies either to direct these intermolecular forces[6] or to create them through templating routes[7] are often pursued. For the case of enantiomerically pure materials, the geometric orientation of hydrogen-bonded components causes the crystal structure to be composed of molecular chains. In racemic mixtures, however, the crystal packing is most commonly either dimeric or tetrameric as directed by the extent and relative position of the hydrogen bonding components, *e.g.*, Fig. 1.[4,8]

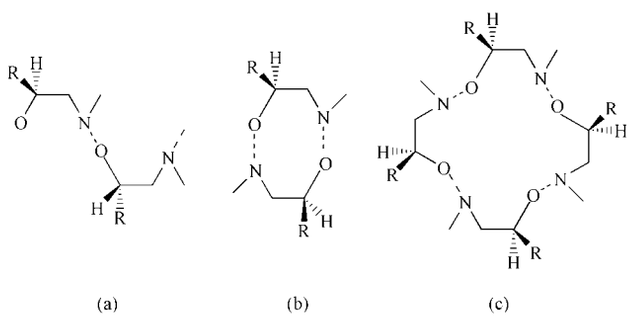

Fig. 1 Packing orientations for (a) enantiomerically pure compounds and racemic mixtures that form either (b) dimers, or (c) tetramers.

For dimeric structures, the molecules are arranged in units consisting of the two enantiomers related by a center of symmetry. In the case of the tetrameric arrangements, two molecules of each of the enantiomers are arranged in a non-centrosymmetric structure.

Molecular structure is rarely a good predictor of molecular packing due in large part to the fact that crystal structures are supermolecular entities governed by the sum of all their intermolecular interactions.[9] In the case of racemic mixtures several different interactions and factors evident in the molecular structure of a compound can be used together to predict the overall crystallographic architecture.[4] The extent of both inter- and intra-cluster hindrance, the extent of aromatic interactions,[10] and the overall linearity, or lack thereof, of the molecule can be used in combination to anticipate the packing of the final solid-state material. We have employed these various considerations to explain the observed intermolecular packing of a series of alcohol amines (**1**–**3**) previously prepared as models for the reaction of chemically functionalized alumoxanes with common di-epoxides in the method of forming inorganic–organic hybrid materials.[11] We have then expanded our review to include similar compounds found in the Cambridge Crystallographic Database. From this review, we are able to provide a rationalization for the packing of racemic mixtures in non-centrosymmetric space groups. The results and conclusions from this analysis are reported herein.

Experimental section

The synthesis and characterization of $PhOCH_2CH(OH)CH_2NH^{n}Pr$ (**1**) and $PhOCH_2CH(OH)CH_2NH^{i}Pr$ (**2**) have been reported elsewhere.[10] Solution state NMR spectra were obtained on a Bruker AC-250 spectrometer using acetonitrile-d_3 solutions (unless otherwise specified). Mass spectra were obtained on a Finnigan MAT 95 mass spectrometer operating with an electron beam energy of 70 eV for EI mass spectra.

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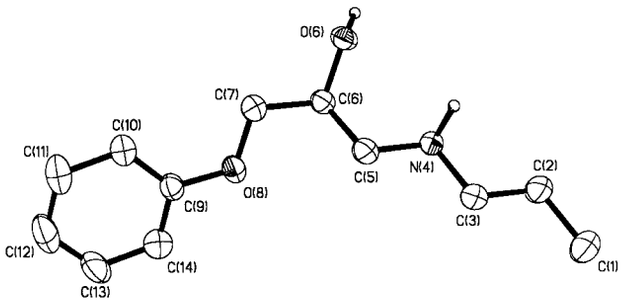


Fig. 2 The molecular structure of $PhOCH_2CH(OH)CH_2NH^nPr$ (**1**). Thermal ellipsoids shown at the 20% level, and organic hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): O(6)–C(6), 1.426(4); O(8)–C(7), 1.430(4); O(8)–C(9), 1.372(4); N(4)–C(5), 1.466(4); N(4)–C(3), 1.458(4); C(9)–O(8)–C(7), 118.3(3); C(3)–N(4)–C(5), 113.0(3).

Synthesis of $PhOCH_2CH(OH)CH_2NH^tBu$ (3)

An acetonitrile solution (10 cm^3) of *tert*-butylamine (7.8 cm^3, 74 mmol) and 1-methylimidazole (0.1 cm^3) was added to 1,2-epoxy-3-phenoxypropane (10.0 cm^3, 74 mmol) and refluxed under atmospheric conditions. After three days, the solution took on a pale red tint and the reflux was discontinued. Upon cooling the solution to −25 °C, a colorless crystalline material was obtained which was recrystallized from toluene. Mp 97–98 °C. MS (EI, %): *m*/*z* 223 (M^+, 20), 208 (M^+-CH_3, 80), 166 [$M^+-C(CH_3)_3$, 5]. IR (cm^{-1}): 3308 (s), 2975 (b), 2048 (m), 1854 (m), 1716 (m), 1598 (s), 1485 (s). ^{1}H NMR: δ 7.29 (2H, m, *o*-C*H*), 6.92 (3H, m, *m*-C*H*, *p*-C*H*), 3.87 (3H, m, OCH_2CHOH), 2.72 (4H, m, $OH+CH_2NH$), 1.07 [9H, s, $C(CH_3)_3$]. ^{13}C NMR: δ 130.6 (OC_{Ph}), 121.7 (*m*-*C*H), 115.5 (*p*-*C*H), 71.8 (*o*-*C*H), 70.1 (*C*OH), 50.8 (OCH_2), 45.7 (N*C*), 31.0 (NCH_2), 29.4 [$C(CH_3)_3$].

Crystallographic studies†

Single crystals of compounds **1**–**3** suitable for X-ray diffraction were selected directly from the analytical samples. Single crystal diffraction data were collected at ambient temperature on a Rigaku four-circle diffractometer equipped with graphite monochromated Mo-Kα radiation ($\lambda=0.71073$ Å) and corrected for Lorentz and polarization effects. Standard procedures in our laboratory have been described previously.[12] The structure was solved by direct methods (SHELX86),[13] and the model was refined using full-matrix least squares techniques.[14] The hydroxide hydrogens were located freely and refined. All the hydrogen atoms bonded to carbon were placed in calculated positions [$U_{iso}=1.3U_{(C)}$; d(C–H) = 0.95 Å] for refinement. Neutral-atom scattering factors were taken from the usual source.[15] Refinement of positional and anisotropic thermal parameters led to convergence.

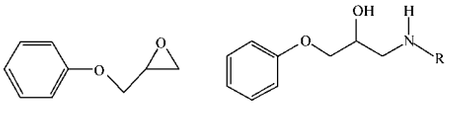
1: $C_{12}H_{19}NO_2$, $M=209.29$, monoclinic, $a=10.207(2)$, $b=4.4630(9)$, $c=26.890(5)$ Å, $\beta=94.50(3)°$, $U=1221.2(4)$ Å^3, space group $P\bar{4}2_1/c$, $Z=4$, 1981 reflections measured, 962 unique which were used in all calculations. The final R was 0.056 and R_w 0.139 [$w^{-1}=\sigma^2(|F_o|)$].

2: $C_{12}H_{19}NO_2$, $M=209.29$, tetragonal, $a=15.322(2)$, $c=11.082(2)$ Å, $U=2601.6(7)$ Å^3, space group $P2_1c$, $Z=8$, 976 reflections measured, 394 unique which were used in all calculations. The final R was 0.063 and R_w 0.155 [$w^{-1}=\sigma^2(|F_o|)$].

3: $C_{13}H_{21}NO_2$, $M=223.32$, monoclinic, $a=11.356(2)$, $b=15.550(3)$, $c=15.627(3)$ Å, $\beta=92.75(3)°$, $U=2601.6(7)$ Å^3, space group $P2_1$, $Z=8$, 12712 reflections measured, 3206 unique which were used in all calculations. The final R was 0.046 and R_w 0.069 [$w^{-1}=\sigma^2(|F_o|)$].

Results and discussion

The amines, $^nPrNH_2$, $^iPrNH_2$, and $^tBuNH_2$, were each used to ring open 1,2-epoxy-3-phenoxypropane (**I**) to yield the expected products $PhOCH_2CH(OH)CH_2NH^nPr$ (**1**),[10] $PhOCH_2CH(OH)CH_2NH^iPr$ (**2**),[10] and $PhOCH_2CH(OH)CH_2NH^tBu$ (**3**) as racemic mixtures. Single crystals of compounds **1**–**3** suitable for X-ray diffraction were grown from toluene solution. No evidence for alternative polymorphic structures was found. Although some of the substituents in compounds **1**–**3** are flexible, resulting in some increased thermal parameters, the goal of the study was to determine the relative importance of substituents in crystal structure stabilization. In this regard data collection at ambient temperatures was sufficient.



I

1 R = ^{n}Pr
2 R = ^{i}Pr
3 R = ^{t}Bu

The molecular structure of compounds **1**–**3** are shown in Fig. 2–4. All the intramolecular bond distances and angles are within the expected ranges.[16] These three molecules all belong to a general class of alcohol amines, X–CH(OH)CH_2N(H)R (**II**), where X is CH_2OPh.

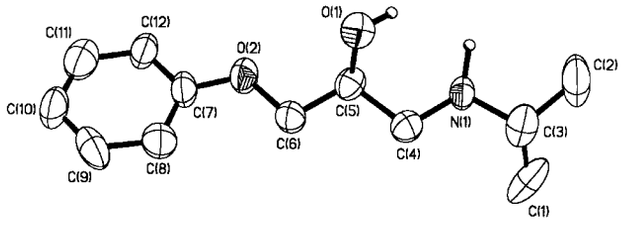


Fig. 3 The molecular structure of $PhOCH_2CH(OH)CH_2NH^iPr$ (**2**). Thermal ellipsoids shown at the 20% level, and organic hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): O(1)–C(5), 1.43(2); O(2)–C(7), 1.35(3); O(2)–C(6), 1.44(1); N(1)–C(4), 1.45(3); N(1)–C(3), 1.48(3); C(7)–O(2)–C(6), 117(1); C(4)–N(1)–C(3), 113(1).

†CCDC reference number 1145/264.

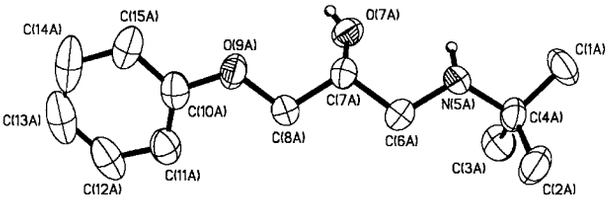


Fig. 4 The molecular structure for one of the four independent molecules of $PhOCH_2CH(OH)CH_2NH^tBu$ (**3**). Thermal ellipsoids shown at the 20% level, and organic hydrogen atoms are omitted for clarity. Average bond lengths (Å) and angles (°): O(7)–C(7), 1.400(6)–1.420(7); O(9)–C(8), 1.416(4)–1.430(5); O(9)–C(10), 1.365(5)–1.380(6); N(5)–C(4), 1.486(6)–1.519(5); N(5)–C(6), 1.440(5)–1.467(6); C(10)–O(9)–C(8), 117.4(4)–119.1(4); C(6)–N(5)–C(4), 115.4(4)–117.8(5).

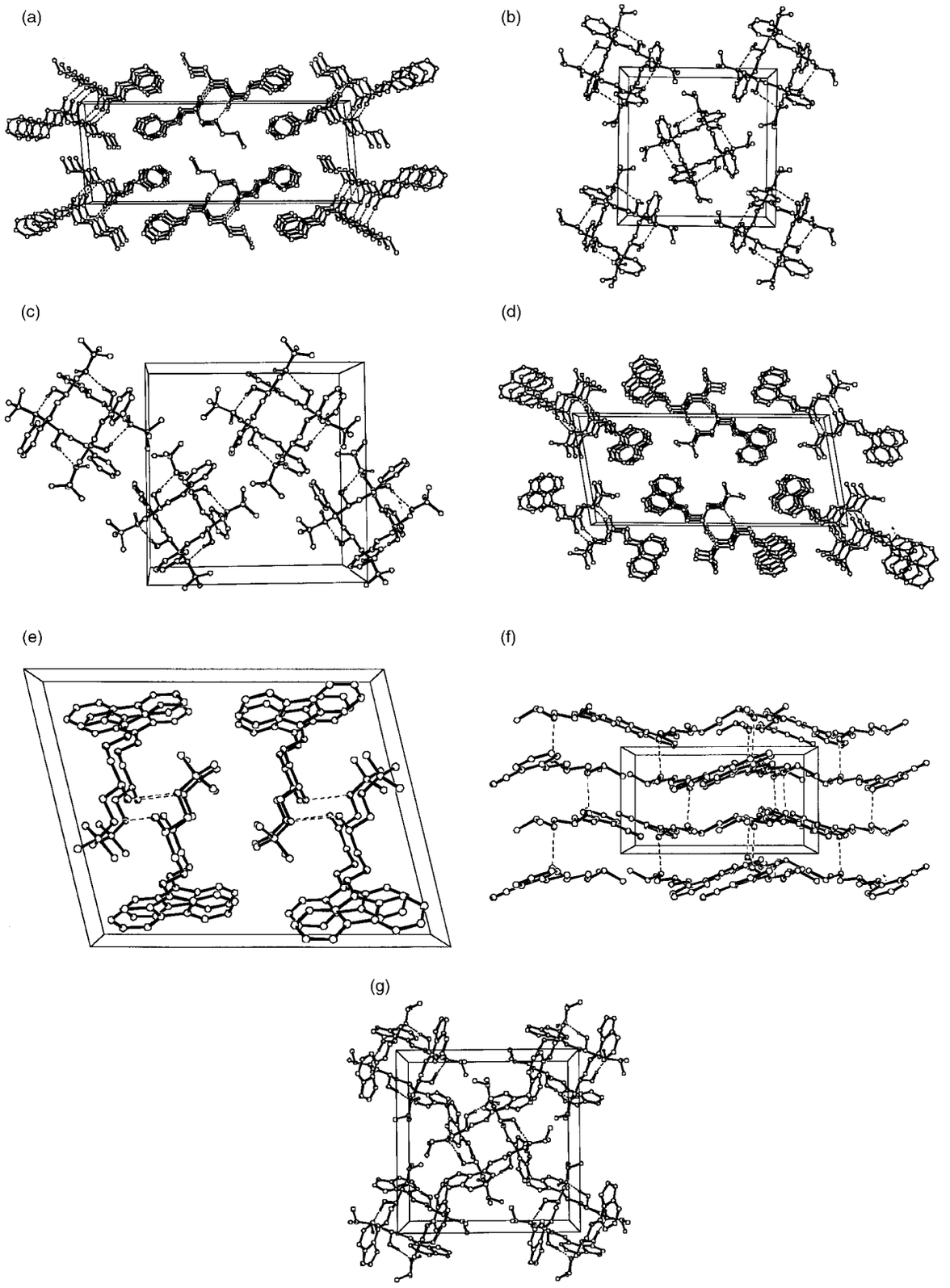
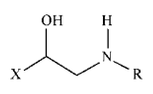


Fig. 5 Crystal packing diagram for compounds **1** (a), **2** (b), **3** (c), **4** (d), **5** (e), **6** (f), **7** (g).



II

Despite the similarity in the structural core of compounds **1**–**3**, and the formation of O–H···N hydrogen bonded networks, their extended structures, and crystal systems are dissimilar. Compound **1** forms centrosymmetric dimers and based upon the hierarchical levels of crystal architecture proposed by Whitesides and co-workers,[17] may be described as having a structure consisting of a series of head-to-tail dimers (*primary* level) forming a series of rods (*secondary* level) which are parallel but contain no inter-rod contacts (*tertiary* level), see Fig. 5a. In contrast, compounds **2** and **3** arrange as tetrameric

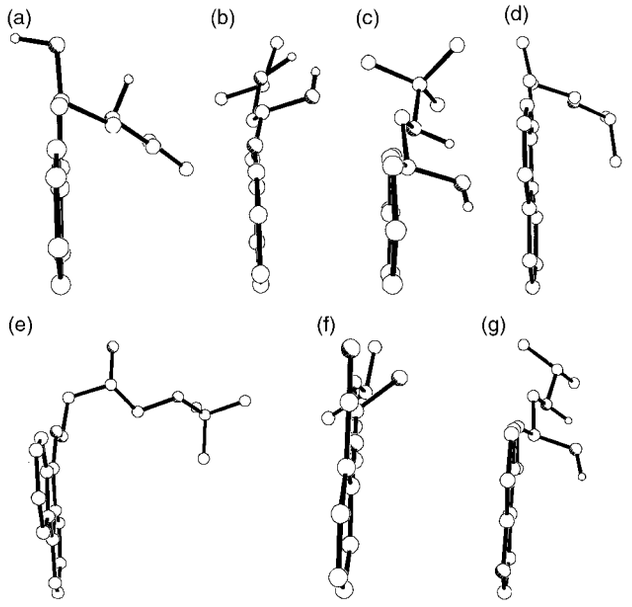
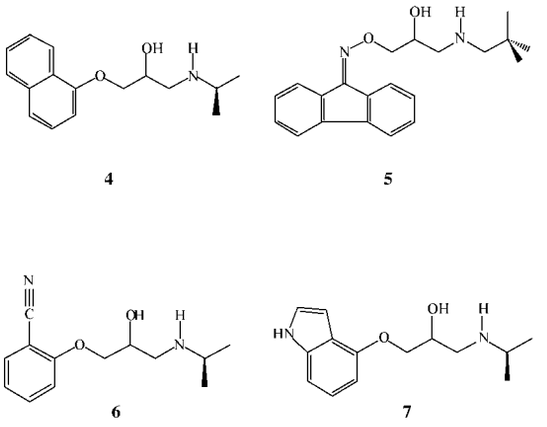


Fig. 6 Core structures of compounds **1** (a), **2** (b), **3** (c), **4** (d), **5** (e), **6** (f), **7** (g) viewed along their backbones and showing the relative conformation of the X–C–C–N–R unit.

units (Fig. 5b and c) in non-centrosymmetric space groups ($P\bar{4}2_1c$ and $P2_1$, respectively). The observation of a non-centrosymmetric space group, despite the presence of a racemic mixture within the crystal lattice for both compounds **2** and **3**, is of interest with regard to crystal engineering. In particular, the observation that a racemic mixture of compound **3** crystallizes in a polar space group (*i.e.*, $P2_1$) is of particular importance with regard to nonlinear optical properties. We note that the shape of the unit cell in compound **3** is very similar to the tetragonal unit cell observed for compound **2**. Since racemic mixtures are easier to synthesize than optically pure compounds it would be useful to gain an understanding of the factors that determine the crystallization of racemates in non-centrosymmetric, and particularly, polar space groups.

In a consideration of the molecular structures of compounds **2** and **3** *versus* **1**, it is immediately obvious that the conformations of the X–C–C–N–R backbones are dissimilar. The nitrogen center in compound **1** is positioned *gauche* to the CH_2OPh group (Fig. 6a). In addition, compound **1** has a nearly linear molecular arrangement of the backbone. In contrast, the nitrogen centers in compounds **2** and **3** are positioned *anti* to the CH_2OPh group (Fig. 6b and c) and consequently, has a non-linear overall backbone conformation. It would appear that the observation of a non-centrosymmetric space group is related to the conformation of the X–C–C–N–R backbone. However, it is unclear, from this limited group, as to whether this relationship holds for the general class of alcohol amines, X–CH(OH)CH_2N(H)R. With this in mind additional structures were surveyed from the Cambridge Crystallographic Database. These were (naphthyl)$OCH_2CH(OH)CH_2N(H)^iPr$ (**4**),[18] (fluoren-9-yl)$NOCH_2CH(OH)CH_2N(H)^tBu$ (**5**),[19] (C_6H_4-2-CN)$OCH_2CH(OH)CH_2N(H)^iPr$ (**6**),[20] and (indol-4-yl)$OCH_2CH(OH)CH_2N(H)^iPr$ (**7**).[21]



Compounds **4** ($P2_1/a$) and **5** ($P2_1/c$) have crystal structures consisting of centrosymmetric head-to-tail dimers (*primary* level), arranged in a series of rods (*secondary* level), see Fig. 5d and 5e, respectively. In contrast, racemates of compounds **6** ($P2_12_12_1$) and **7** ($P\bar{4}2_1c$) both crystallize in non-centrosymmetric space groups. While compound **7** is arranged as tetrameric units (Fig. 5g) in an analogous manner to compounds **2** and **3**, compound **6** exists as dimers which are arranged as sheets, see Fig. 5f. Despite the differences in crystal packing, a consideration of the orientation of the X–CH(OH)CH_2N(H)R backbones of compounds **4**–**7** (Fig. 6d–g) confirms the relationship of centrosymmetric to non-centrosymmetric structures. Thus, if the nitrogen center is positioned *gauche* to the X group, a centrosymmetric structure is observed. Conversely, if the nitrogen center is positioned *anti* to the X group a non-centrosymmetric structure is observed. Unfortunately, from the foregoing, it is not clear as to what factors, if any, control the conformation of the X–CH(OH)CH_2N(H)R backbone.

If we accept that the crystal symmetry of alcohol amines, X–CH(OH)CH_2N(H)R, is determined by the conformation of the X–CH(OH)CH_2N(H)R backbone, it would be desirable to predict the conformation, and hence crystal symmetry, based solely on the molecular structure. In this regard, a summary of the crystal packing motifs and all relevant considerations involved in the solid state arrangements is given in Table 1. For systematic descriptive purposes the X groups in compounds **1**–**3** (CH_2OPh) and **6** ($CH_2OC_6H_4$-2-CN) are considered "small", while the fused aromatic rings in **4**, **5**, and **7** are considered "large". A similar description is given for the amine's alkyl substituent, *i.e.*, R = ^{n}Pr and $CH_2{}^t$Bu are "long", whereas Y = ^{i}Pr and ^{t}Bu are both considered "short/bulky". Based on the analysis of the size and/or bulk of the substituents X and R, a pattern is observed that allows for the possible prediction of

Table 1 Summary of crystal packing motifs and relevant packing directors

Compound	R	Size/bulk	X	Size/bulk	N alignment[a]	Centrosymmetric	Motif
1	^{n}Pr	Long	CH_2OPh	Small	*gauche*	Yes	Dimer
5	$CH_2{}^t$Bu	Long	CH_2ON(fluoren-9-yl)	Large	*gauche*	Yes	Dimer
4[b]	^{i}Pr	Short/bulky	CH_2O(naphthyl)	Large	*gauche*	Yes	Dimer
7[b]	^{i}Pr	Short/bulky	CH_2O(indol-4-yl)	Large	*anti*	No	Tetramer
2	^{i}Pr	Short/bulky	CH_2OPh	Small	*anti*	No	Tetramer
3	^{t}Bu	Short/bulky	CH_2OPh	Small	*anti*	No	Tetramer
6	^{i}Pr	Short/bulky	$CH_2O(C_6H_4$-2-CN)	Small	*anti*	No	Sheets

[a]N alignment is in relation to the X group and represents the geometry of the hydrogen bonding center. [b]See text for an explanation of the reasons these compounds with similar packing directors have different crystal packing motifs.

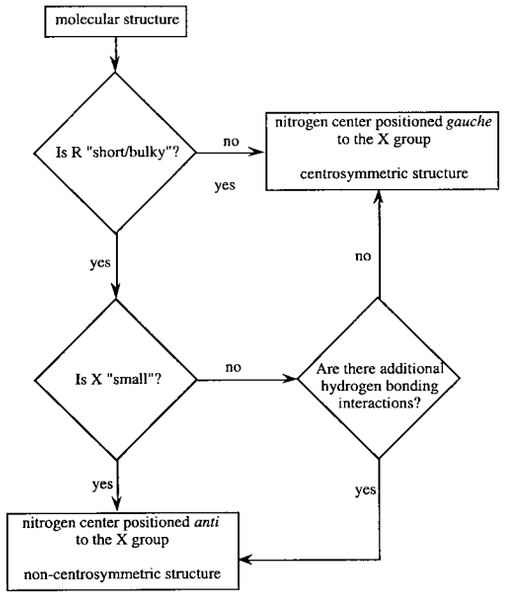


Fig. 7 A simple flow diagram for the prediction/rationalization of crystal structures of alcohol amines X-CH(OH)CH_2N(H)R.

crystal symmetry and molecular packing based upon molecular structure.

The most important factor to consider in attempting to predict the presence, or absence, of a center of symmetry in the crystal structure of a racemic mixture of an alcohol amine is the size and bulk of the end-groups. Thus, if the alkyl group (R) is "long" (irrespective of the size of the X group), the nitrogen center is positioned *gauche* to the X group and a centrosymmetric crystal structure is obtained. If the alkyl group is "short/bulky" and the X group "large" then a centrosymmetric crystal structure is also obtained. If the alkyl group is "short/bulky" and the X group "small" then the nitrogen center is positioned *anti* to the X group and a non-centrosymmetric crystal structure is also observed. The only exception to this trend is the structure of (indol-4-yl)$OCH_2CH(OH)CH_2N(H)^iPr$ (**7**) which should be expected to be similar to (naphthyl)OCH_2-$CH(OH)CH_2N(H)^iPr$ (**4**) based upon the relative size of the indol-4-yl and naphthyl substituents. Thus, the nitrogen center would be expected to be positioned *gauche* to the X group, but it is *anti*. However, compound **7** has additional hydrogen bonding between the indole NH group and the alcohol oxygen. Presumably this additional interaction forces an *anti* arrangement of the nitrogen center with respect to the (indol-4-yl)OCH_2 group. Albeit using only this somewhat limited basis set, a simple flow diagram may be generated for the prediction/rationalization of centrosymmetric *versus* non-centrosymmetric crystal structures of racemic mixtures of alcohol amines, X–CH(OH)CH_2N(H)R, Fig. 7.

Clearly, the foregoing analysis is limited in scope, but it appears to work well for describing the crystal packing of racemic compounds formed from the reaction of amines with epoxy resins. It should be noted that while the molecular structure of an alcohol amine, X–CH(OH)CH_2N(H)R, appears to control the packing of racemic mixtures in non-centrosymmetric space groups, there does not appear to be a ready explanation as to the crystallization of racemic mixtures in polar space groups. However, if it was desirable to prepare compounds that crystallize in polar space groups for nonlinear optical properties, the present scheme would minimize the number of synthetic targets to be considered.

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