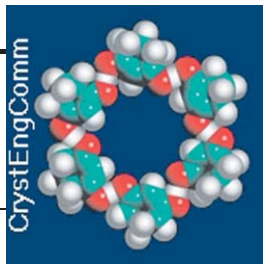
Solid state hydrogen bonding in imidazole derivatives: a persistent tape motif†



Paper

Arthur Cammers[a] **and Sean Parkin**[b]

[a]*Department of Chemistry, University of Kentucky, Lexington KY 40506-0055, USA. E-mail: a.cammers@uky.edu; Fax: 859 323 1069; Tel: 859 323 8977*
[b]*X-ray Diffraction Facility, Department of Chemistry, University of Kentucky, Lexington KY 40506-0055, USA. E-mail: spark2@uky.edu; Fax: 859 323 1069; Tel: 859 323 8984*

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The Cambridge Structural Database was mined for non N-substituted, neutral imidazole derivatives. Solid states with metal centres bound to the imidazole nitrogen atoms and ionic species were not included. The N–N, hydrogen-bound, tape motif was found to be a structural trend in the solid-state of neutral imidazole derivatives in the presence of possible competing hydrogen bonds and in highly steric environments. A chemically intuitive set of parameters was chosen to characterize the relationships between imidazole rings in the solid states. The choice of structural parameters and the values these parameters take as a function of substitution patterns of imidazole derivatives was discussed. The complexities that can arise in the crude extraction of hydrogen bond strength from solid state data was discussed.

Introduction

Presently accepted notions regarding rational design of the organic solid state are embodied in the term crystal engineering.[1] The basic tenet is that molecular organization in organic crystals should yield to the principles of rational design by the preconceived formation of non-covalent interactions in a manner analogous to the synthesis of organic molecules by the formation of covalent bonds. Both objectives require an understanding of the rules of construction.[2–7] These rules are very complex for crystals and other supramolecular entities, therefore the design of the organic solid state is tenuous.[8–10] Nevertheless, the non-covalent interactions deemed responsible for organic solid states have been categorized.[11–15] Due to their strength and directionality, hydrogen bonds have attracted the most attention of all the intermolecular forces responsible for the morphology of organic crystals.[16–21] A review of the chemical literature on molecular patterns established by hydrogen bonds identified tapes, ribbons, and sheets as dominant constructs for organic molecules bearing protic functionality.[22]

Surveys of the Cambridge Crystal Structure Database (CSD) that included imidazole derivatives and their attendant hydrogen bonds have been reported. The most pertinent of these studies to the current work mentions imidazole bond angles and bond lengths between NH and O or N atoms.[23] Studies of the Protein Crystal Structure Data Bank (PDB) have been reported of imidazole hydrogen bound *via* N atoms to all possible atoms in the context of histidine in protein crystal structures.[24,25] A comparison of imidazole solid states in protein and organic contexts appeared as a sub-theme in a review.[15] By contrast, the current study investigates the persistent occurrence of a tape motif, which is a linear molecular array that provides one molecule with two nearest neighbours linked by hydrogen bonds. These chains of hydrogen bound imidazole derivatives can be encapsulated in less descriptive terms by graph set notation as *C(4)*.[17,26] The tape motif directs NH hydrogen bond donors toward N hydrogen bond acceptors even when other suitable acceptors (O, and/or other N atoms *etc.*) are present. When only weakly interacting groups are present in the crystal, the probability for the tape structure is very high even in sterically crowded environments.

A CSD-based study of hydrogen bond donors and acceptors in neutral aromatic heterocycles indicated that nitrogen atoms tend to accept hydrogen bonds (bases) whereas oxygen atoms tend to donate hydrogen bonds (acids).[27] Imidazole enjoys advantages offered by the basicity of the nitrogen atom and the exalted acidity due to sp^2 hybridization at the nitrogen atom, allowing stable hydrogen bond donation and acceptance. Although thermodynamic parameters from statistical studies of crystal structures are qualitative at best, surveys of the bond lengths and angles of XH–Y in organic solids revealed a strong correlation between the distributions of the X–H–Y hydrogen bond angles and the stabilities of the respective interactions.[28,29] Short, hydrogen bonds tend to have wide X–H–Y bond angles (*ca.* 180°), whereas in weak interactions the distribution of hydrogen bond angles increases.

Hypothetically, these correlations might afford a standard by which to measure the stabilities of the hydrogen bonds between imidazole subunits. To test this hypothesis the CSD was surveyed for non N-substituted, neutral imidazole derivatives (Fig. 1). The spatial relationships between hydrogen bonded rings were characterized as a function of substitution.

Results and discussion

The data set was small for this genre of study, especially when the set was subdivided to seek differences in substitution

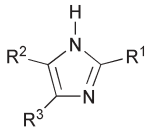

Fig. 1 The imidazole derivatives studied in this survey were neutral and un-substituted at N. Substitution patterns with R^1–R^3 as any group were included in this study.

† Electronic supplementary information (ESI) available: A list of all Cambridge Structural Database codes used in this survey. See http://www.rsc.org/suppdata/ce/b4/b405096g/

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patterns. However, the application of data sets with *ca.* 100 elements to the characterization of hydrogen bonding patterns has been reported by others,[23,29] and there has been little ambiguity in the conclusions.

This search and its attendant focused study of the CSD (CSD V5.25, Nov. 2003 with ConQuest) for metal-free, imidazole moieties produced 546 structures, from which entries possessing any of the following characteristics were removed: All duplicates; An element other than H bound to N1 (substitution by any other atom precludes formation of the tape motif); Purine derivatives (these have distinct bonding patterns of their own that are pertinent to the structure of nucleotides); Salts and imidazolium derivatives (the strength of ionic forces usually mandates the molecular arrangement within crystals).[30–32] Of the remaining 206 structures, 88 possessed the tape motif in a surprising variety of steric and heteroatom-rich environments. Co-crystals in which imidazole substructures were hydrogen bound to one another through either water or alcohols accounted for 26 structures. Molecules with OH functionality that connected the imidazole derivatives *via* hydrogen bonds offered the solid state greater variation in the attitude of one imidazole ring to another.[33] Highly steric trisubstituted imidazole derivatives (C2, C4 and C5) and heteroatom-rich derivatives tended to fulfill the hydrogen bonding requirements by inclusion of water molecules in the packing pattern.

Other intermolecular hydrogen bonding patterns competed with the imidazole tape motif in 62 structures. Some of these were peptides containing histidine. Certain substitution patterns on the imidazole ring tended to compete with the formation of the tape motif. When $R^{1,2}$ or R^3 were hydrogen bond donors or acceptors bound directly to the imidazole ring, the molecules tended to dimerize at these substituents instead of engaging in chain formation (Fig. 2).[34] These groups included but were not limited to carbonyl, thionyl, nitro, carboxylic acid derivatives (amido, cyano, carboxyalkyl), and amino. The small-ring intramolecular hydrogen bonds (putative 4- and 5-member rings in the molecules in Fig. 2) that might have resulted from these substitution patterns are not favorable, thus the dimers were favored.[35] When the substituents involved groups that were capable of forming 6- to 9-membered-ring intramolecular hydrogen bonds, these also tended to compete with the tape motif.

The stability of the neutral imidazole tape synthon, compares favorably to the achetypical, hydrogen bound, carboxylic acid cyclic dimer which has *ca.* ⅓ probability in the CSD due to competition from other hydrogen bond donors and acceptors,[34] but >0.9 probability when no other hydrogen bond functionality is present.[36,37]

Some of the CSD entries possessed unusually large numbers of molecules per asymmetric unit. When these represented multiple copies of the same hydrogen-bonding geometry (notably QENYIR, $Z' = 12$ and QENYEN, $Z' = 6$), they were reduced to a single canonical form. In others, where more than one hydrogen-bonding geometry was apparent (*e.g.* DUXSUK, $Z' = 3$; SEBCIL, $Z' = 3$), each distinct form was treated as a separate entity.

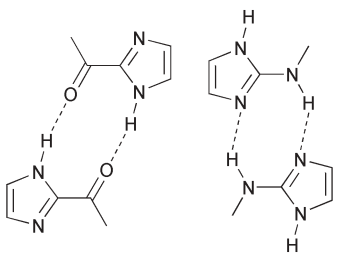

Fig. 2 Adjacent hydrogen bond donors and acceptors often resulted in dimers.

Structural characteristics

The morphology of a structural motif is governed by the relative positioning of its constituent pieces, a general description of which requires six parameters: a three-component vector and a three-component rotation. Despite its geometric rigor, such a description does not intuitively convey chemical information. Without loss of generality, the description is simplified by casting the problem in terms of carefully chosen coordinate systems. We define the donor imidazole ring as ring 1 and place an axis (x_1) along the line from the ring centroid through the donor N atom. The y_1 axis is placed perpendicular to the plane of the ring, passing through the ring centroid. Lastly, the z_1 axis completes a right-handed system by running parallel to the line through the two carbons adjacent to the donor N atom (Fig. 3a). The acceptor ring (ring 2) also has an analogous coordinate system (axes x_2, y_2, z_2). For this ring, however, it is more chemically meaningful to define a second system with axis x_2' running from the ring centroid through the acceptor N atom. The y_2' axis is again perpendicular to the ring plane (and hence is coaxial to y_2), and z_2' completes a right-handed system passing parallel to the line through the two C atoms adjacent to the acceptor N in a manner analogous to the z_1 and z_2 axes. (Fig. 3b). For all intents and purposes, these coordinate systems are orthogonal.

The parameters used to describe the intermolecular hydrogen bonding network of imidazole moieties then become r_{NN}, the interatomic N–N hydrogen bond distance and three angles θ (between x_1 and x_2'), ϕ (between y_1 and y_2') and ψ (between z_1 and z_2'), Fig. 4. The r_{NN} parameter, as the distance between two atoms is readily understandable. The θ parameter can be conceptualized as the extent to which the tape was kinked or pleated; it also measured the N–H–N bond angle of the motif. The ϕ and ψ parameters should have been sensitive to any torsional strain in the planar tape motif. The in-plane steric interactions were greatest when ϕ and ψ took on values 0 or 180°. On the other hand, these interactions were minimal at ϕ or $\psi \sim 90$ or 270°. With this in mind, we used the condensed parameters ${}^{90}\phi$, and ${}^{90}\psi$ which were symmetric about 90° (*e.g.* $\phi_{(25°)} = \phi_{(155°)} = 25°$).

There is literature precedent for imidazole π-stacking.[38–40] One might imagine that neutral imidazole would tend to stack like benzene and that this effect might have perturbed θ or the other angular parameters. Indeed, the spatial arrangement of

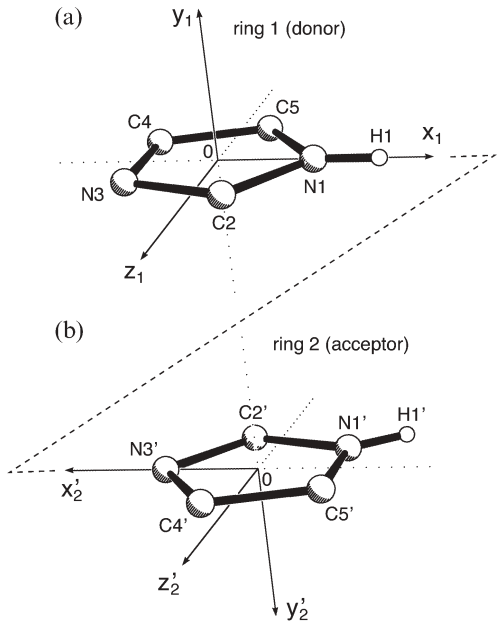

Fig. 3 Coordinate systems used to describe: (a) the donor imidazole ring; (b) the acceptor imidazole ring.

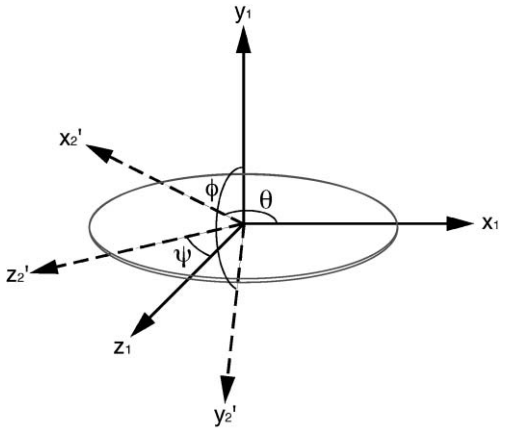

Fig. 4 Angular parameters used to classify the tape motifs in crystalline imidazole derivatives. For the sake of clarity, the coordinate systems for the donor (solid axes) and acceptor rings (dashed axes) have been shifted to a common origin.

the solid state of the parent compound, imidazole (*e.g.* IMAZOL06), had an edge-to-face packing motif similar to that of benzene. The stacking interactions between the rings propagate in a plane orthogonal to the direction of the propagation of the tape motif (the directionality of the hydrogen bond). In the direction of the stacking motif, ring faces meet ring edges. The stacking interactions result in a pleated tape ($\theta = 162°$) with high values for the dihedral parameters, ($^{90}\phi$, $^{90}\psi$: 60°, 57°). Upon examining the solid state structure in imidazole it became obvious that the stacking interactions would not abide any substituents larger than hydrogen. Scanning the solid states of the imidazole derivatives in this study for stacking interactions revealed no particular stacking motif.

As mentioned above, the inclusion of water molecules in the crystal is one way to satisfy the hydrogen bonding requirements and maximize structural freedom between imidazole derivatives in highly steric environments. However, the dominant way in which neutral imidazole derivatives maintained hydrogen bonds by reducing the R^1/R^2 steric interactions was to modify the ϕ and ψ parameters away from the planar tape motif (see Fig. 4 then Fig. 5).

Figs. 6A and B graph population distributions as a function of the $^{90}\phi$ and $^{90}\psi$ parameters and substitution patterns. Tri-substituted derivatives favored large $^{90}\phi$ angles (50–90°) in response to non-continuum steric crowding at C2, C4, and C5. The tri-substituted derivatives possessing $^{90}\phi$ angles below 45° in Fig. 6A were all 2-subsitituted benzimidazole derivatives. These benzannulated derivatives would have exerted less of a steric effect in the planar tape than tri-substituted derivatives in which R^1, R^2 and R^3 were alkyl.

Mono- and di-substituted derivatives discriminated $^{90}\phi$ and $^{90}\psi$ angular values to a lesser extent than the tri-substituted derivatives, but they favored small angles instead of large angles. In the tape motif each sequential C2 (R^1) position was disposed on the opposite side of the tape as the previous one, as shown in Fig. 5. This zigzag pattern affected the angular values of $^{90}\phi$ and $^{90}\psi$ as a function of substitution pattern in the

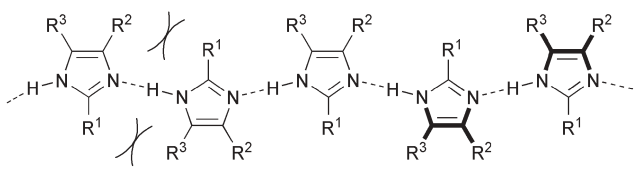

Fig. 5 Steric interactions in the coplanar tape (left side) between the pairs R^1/R^2 and R^1/R^3 had the greatest effect on ϕ and ψ. Large substituents at R^1 and R^2 and/or R^3 caused the rings to twist out of planarity (right side) to alleviate these steric interactions.

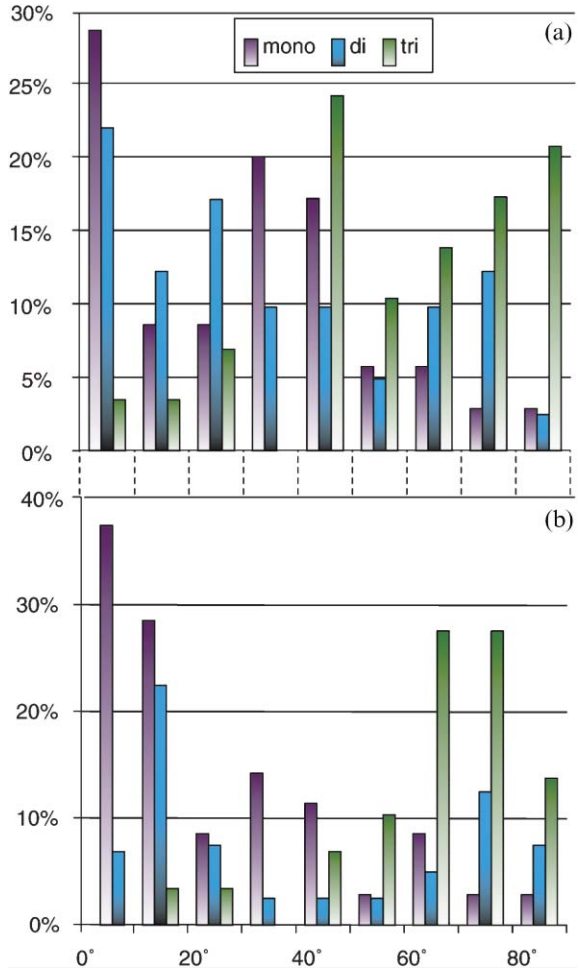

Fig. 6 Population as a function of angular parameters and substitution (10° bins), A: $^{90}\phi$, B: $^{90}\psi$.

di-substituted derivatives in the following way. The (4,5)-di-substituted imidazole derivatives (R^1 = H; R^2 and $R^3 \neq$ H) tended to possess small $^{90}\phi$ angular values in the solid state. The tape motif of the 4,5-di-substituted pattern was nearly planar because R2 and R3 only interact with H between imidazole molecules. Some examples of this can be found in the solid states of (4,5)-dichloroimidazole (JORYIY) $^{90}\phi = 3.4°$; (4,5)-di-i-propylimidazole (NEMYUZ) $^{90}\phi = 4.9°$; and (4)-chloro-(5)-nitroimidazole (PEPFUL) $^{90}\phi = 4.0°$. However, when steric crowding in (4,5)-derivatives increased, the planar tape was destabilized: (4,5)-di-*t*-butylimidazole (DTBIMZ) $^{90}\phi = 75.8°$ and others (SEBCIL and DUXSUK). Likewise, the (2,4)-di-substituted imidazole derivatives must possess R^1/R^2 steric interactions in planar tape motifs, so the solid states of these tended to deviate from the planar motif by adopting large $^{90}\phi$ and $^{90}\psi$ values. Examples of these were found in the solid states of (2,4)-dinitroimidazole (TEVHEH) $^{90}\phi = 57.0°$ and (2)-methyl-(4)-nitroimidazole (MENOIM) $^{90}\phi = 26.2°$).

The N–N hydrogen bond distance, r_{NN}, and the N–N hydrogen bond angle (θ) were the most chemically intuitive structural parameters. The distance parameter did not vary much with substitution. The mono-, di- and tri-substituted imidazole derivatives had average r_{NN} values 2.89 ± 0.1, 2.90 ± 0.1 and 2.94 ± 0.2 Å, respectively. It was not surprising that the average r_{NN} of the more substituted derivatives increased slightly over the less substituted derivatives. To the extent that changes in torsional parameters did not dissipate steric clashes, these interactions in the more substituted derivatives should have pushed the molecules apart. Modification of θ could also decrease steric interactions. Fig. 7 is a stereodiagram showing pair-wise modification of θ and the

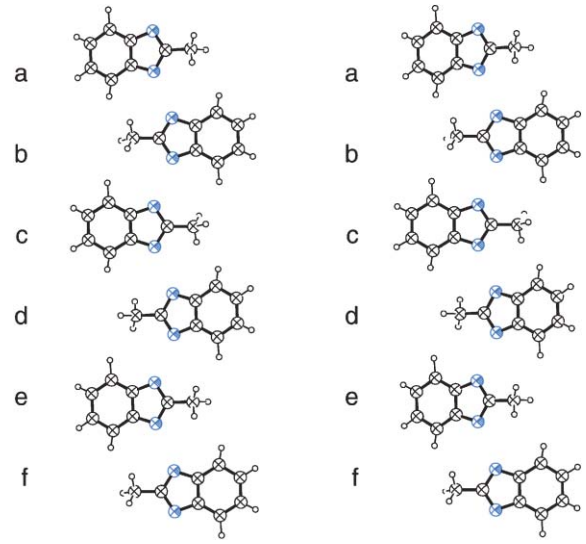

Fig. 7 Stereodiagram of 2-methylbenzimidazole (KOWYEA01) showing how the parameters θ, $^{90}\phi$ and $^{90}\psi$ decreased steric interaction between groups. Molecular pairs ab, cd and ef modified the ϕ and ψ parameters ($\theta = 180^\circ$, $^{90}\phi = 26.8^\circ$, $^{90}\psi = 26.7^\circ$) to decrease steric interactions. Molecular pairs bc and de modified the θ parameter ($\theta = 177.5^\circ$, $^{90}\phi = 0.0^\circ$, $^{90}\psi = 0.0^\circ$) for analogous steric changes.

torsional parameters ϕ and ψ. A value for θ less than that of the un-pleated motif ($\theta = 180^\circ$) resulted in decreased steric interaction between CH_3 and the benzene ring between a pair of 2-methylbenzimidazole molecules. Likewise, in the next pair along the tape motif, changes in ϕ and ψ decreased the in-plane, steric interactions.

All substitution patterns had increased populations at θ values between 145 and 165°, but the mono-, di- and tri-substituted derivatives had $\theta = 152 \pm 50$, 162 ± 25, and $161 \pm 30^\circ$, respectively (Fig. 8). This is opposite to the trend of bond length as a function of substitution. In this survey, imidazole derivatives formed intermolecular hydrogen bonds that were strong enough to compete with non-ionic hydrogen bonds of the type C=O···HX (X=O, N). This raised the question of how the results obtained here could be reconciled with Desiraju's compelling conclusion that hydrogen bond angles correlate with their bond lengths.[28] Strong R_3C–OH–O=C hydrogen bonds maximize the population distribution at $\theta = 180^\circ$; however, the distribution in Fig. 8 flattens out at $\theta \sim 140^\circ$. None of the interactions from strong hydrogen bonds to van der Waals interactions have this kind of profile with respect to θ.

The paradox disappeared upon examining the correlation

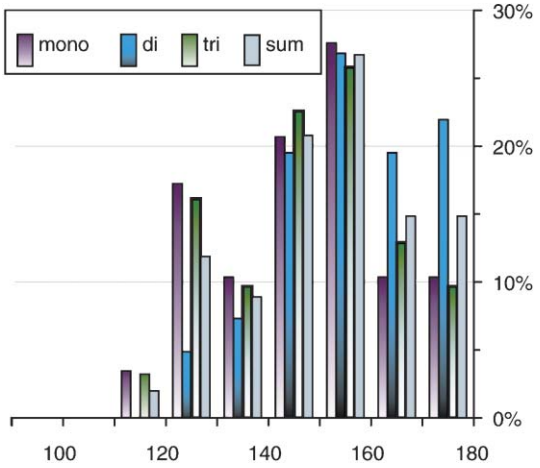

Fig. 8 The normalized population distribution of θ as a function of substitution.

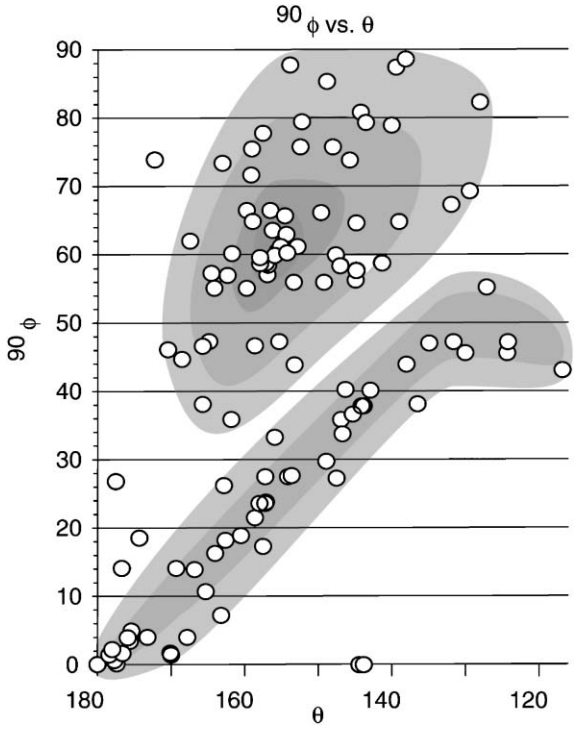

Fig. 9 The structural parameter θ as a function of $^{90}\phi$ in degrees. The shaded areas include >95% of the points. The two points on the θ axis (*ca.* 144°, 0°) were due to 2,2′-bis-imidazole and the group at (155°, 60°) were due to 2,2′-bis-imidazole derivatives.

between the parameters θ and ϕ (Fig. 9). These two parameters varied in a heuristic manner while the hydrogen bond distance remained largely unchanged. These distances indicated a strong hydrogen bond, comparable to the type C–O–H–X (X = N, O). Fig. 9 shows a general decrease in $^{90}\phi$ with increased θ. Thus bond angles and the torsional angles in this study changed to optimize hydrogen bonding as a function of substitution. These results raise a caveat to the extraction of hydrogen bond strength by the broad application of correlations between hydrogen-bond distance and hydrogen-bond angle in a sterically complex context.

Conclusions

Chemically significant parameters were developed to analyze and characterize a hydrogen-bond tape motif in neutral imidazole derivatives. The parameter defining the length of the hydrogen bond, r_{NN} changed little with substitution. Synergistic changes in the bond angle parameter and torsional parameters as a function of steric interactions were observed. Due to the steric effect, the hydrogen bond angles in solid-state imidazole chains were more broadly distributed and, on average, smaller than hydrogen-bond donors and acceptors of comparable bond strength. Using bond angle distributions to gauge hydrogen-bond strength in solid-state studies should be done with possible interference of steric interactions in mind. Thus for example, the distribution profile of hydrogen bond angles for cyclic imide derivatives compared with R_2C=N might more strongly reflect steric interactions instead of differences in native hydrogen bond acceptance between the two subsets.

This study also indicates that imidazole establishes the N–N hydrogen-bond tape motif in the presence of heteroatoms and in sterically restrictive environments. Neutral imidazole should therefore be a useful synthon for crystal engineering because its preferred mode of intermolecular association generally lies within definable bounds that change predictably as a function of substitution.

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