Crystal Engineering and Correspondence between Molecular and Crystal Structures. Are 2- and 3-Aminophenols Anomalous?

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Abstract: Single-crystal neutron diffraction analyses of 2- and 3-aminophenols have been performed. In addition to O−H···N and N−H···O hydrogen bonds, both these structures contain previously unidentified N−H···π and C−H···O hydrogen bonds. This unusual mutual recognition pattern is not found in 4-aminophenol and other related systems. Its presence hints that the optimization of the herringbone interactions, rather than the formation of N−H···O hydrogen bonds, is the primary packing effect in these compounds. Our observations on these simple isomeric aminophenols indicate that it may not always be realistic to expect straightforward correspondences between molecular and crystal structure. The definition of the term "supramolecular synthon" recognizes this inadequacy and attempts to provide a more reliable basis for the description of crystal structures.

Introduction

An important assumption in many studies of crystal engineering is the dominance of strong hydrogen-bonding interactions of the O−H···O and N−H···O types in determining stable and predictable crystal packings. For instance, much has been said about the use of carboxyl and amide groups in the design of crystal structures.[1] More recently, elegant studies by the Ermer and Hanessian groups have shown that predictable structures can also be obtained using compounds or molecular complexes containing equal stoichiometries of −OH and −NH₂ groups.[2] This predictability arises from the 1:2 and 2:1 hydrogen bond donor:acceptor ratios in these functional groups, leading to tetrahedral configurations at both heteroatoms in the hydrogen bond network and therefore to variants of the arsenic and wurtzite structures.

At a fundamental level, these approaches seek to establish connections between molecular and crystal (supramolecular) structure. Since organic chemistry has a molecular basis, seeking such connections is almost intuitive.[3] Ideally, one would like to associate reliably functional groups with crystal structure attributes. The molecular recognition of hydroxy and amino groups has been recognized as being a step in this

direction.[4] The crystal structure of 4-aminophenol, **1** (Figure 1), shows how the tetrahedral hydrogen-bonded network is constructed.[2a] To explore this hydroxy−amino recognition further, we have determined the crystal structures of 2- and 3-aminophenols, **2** and **3**, using low-temperature neutron diffraction. These structures were determined previously using X-ray diffraction,[5] and the probable existence of the unusual N−H···π hydrogen bond in these structures prompted the present study.[6]

Experimental Section

The neutron structure determination of **2** was conducted at the pulsed neutron source, ISIS, on the Laue time-of-flight diffractometer, SXD.[7] Crystals of **2** suitable for neutron diffraction analysis were grown from ethanol. A crystal with dimensions 4.1 × 4.1 × 3.3 mm was selected for the experiment. Two position-sensitive detectors (PSDs), oriented at 2θ angles of 57° and 125°, were used. Data were collected by both detectors simultaneously at 28 different crystal orientations, yielding 56 unique frames. Data from the first high-angle frame were used to obtain orientation matrix and cell parameters. Structure factors were extracted from the frames using standard procedures,[7] and the fully anisotropic refinement was carried out using SHELXL-93.[8,9]

The neutron diffraction study of **3** was carried out at the Institut Laue Langevin reactor source using the four-circle diffractometer, D19. D19 is equipped with a large (64° × 4°) multiwire PSD. Crystals of **3** suitable for neutron diffraction analysis were grown from methanol. A crystal of dimensions 5.3 × 1.7 × 0.65 mm was selected and wrapped in thin aluminum foil and then glued to a flat-headed aluminum pin using a two-stage epoxy cement. It was mounted on the flatter of its

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(1) (a) Aakeröy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, 397. (b) Fan, E.; Vicent, C.; Geib, S. J.; Hamilton, A. D. *Chem. Mater.* **1994**, *6*, 1113. (c) MacDonald. J. C; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383. (d) Ball, P. *New Sci.* **1995** (Aug 5 issue), 40.

(2) (a) Ermer, O.; Eling, A. *J. Chem. Soc., Perkin Trans. 2,* **1994**, 925. (b) Hanessian, S.; Gomtsyan, A.; Simard, M.; Roelens, S. *J. Am. Chem. Soc.* **1994**, *116*, 4495. (c) Hanessian, S.; Simard, M.; Roelens, S. *J. Am. Chem. Soc.* **1995**, *117*, 7630.

(3) (a) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Elsevier: Amsterdam, 1989. (b) Desiraju, G. R.; Gavezzotti, A. *J. Chem. Soc., Chem. Commun.* **1989**, 621.

(4) Borman, S. *Chem. Eng. News* **1995** (Dec 11 issue), 33.

(5) (a) Korp, J. D.; Bernal, I.; Aven, L.; Mills, J. L. *J. Cryst. Mol. Struct.* **1981**, *11*, 117. (b) de Rango, C.; Brunie, S.; Tsoucaris, G.; Declercq, J. P.; Germain, G. *Cryst. Struct. Commun.* **1974**, *3*, 485.

(6) Viswamitra, M. A.; Radhakrishnan, R.; Bandekar, J.; Desiraju, G. R. *J. Am. Chem. Soc.* **1993**, *115*, 4868.

(7) (a) Wilson, C. C. *J. Mol. Struct.*, in press. (b) Allen, F. H.; Howard, J. A. K.; Hoy, V. J.; Desiraju, G. R.; Reddy, D. S.; Wilson, C. C. *J. Am. Chem. Soc.* **1996**, *118*, 4081.

(8) Sheldrick, G. M. SHELXL-93, A program for the refinement of single crystal diffraction data, University of Göttingen, Germany, 1993.
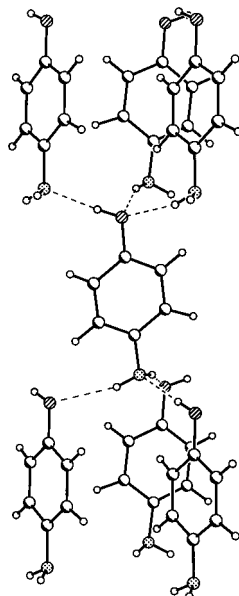
Figure 1. Tetrahedral network formed by N−H···O and O−H···N hydrogen bonds and the herringbone interactions between aromatic rings in the crystal structure of **1**.

two smallest faces such that its longest dimension was parallel with the pin. The mounted crystal was then attached to the ϕ circle of the crystal orienter.

The 117 reflections from a vertically focusing Ge monochromater crystal were used to produce a monochromatic neutron beam of wavelength 0.954 52 Å. A rough orientation matrix based on the X-ray cell was obtained from the three peaks prior to cooling. The crystal was then cooled to 100 K, and the rough orientation matrix was gradually improved using reflections scanned during the data collection. The majority of the data were collected in normal beam Weissenberg geometry. The small number of unique reflections that were missed by the normal beam scan were collected separately in equatorial plane geometry. A complete unique set of data and some equivalents were collected out to (sin θ)/λ = 0.745°. A number of higher angle data were also measured.

Integrated intensities were obtained from the raw data using the σ-(I)/I method[10] with the program PEAKINT. A Gaussian integration absorption correction was applied to the data using the program D19ABS. Corrections for absorption by the walls of the cylindrical cryostat shields were also applied. The data were refined using SHELXL-93.[8,9]

Results and Discussion

Figures 2 and 3 show the crystal structures of **2** and **3**. The presence of the N−H···π hydrogen bonds is confirmed in both structures, and details of these and other hydrogen bonds in these structures are given in Table 1. The formation of N−H···π bonds to electron-rich aromatic rings should be favored. However, it is not possible to conclude definitively if a C−C bond of the phenyl ring or the ring as a whole (centroid) is more significant with respect to N−H···π hydrogen bonding. In **2**, for example, the shorter approach (2.309 Å) to the ring centroid is the more bent one (145.0°). A longer approach of 2.421 Å to the center of the C5−C6 bond is more linear (173.9°,
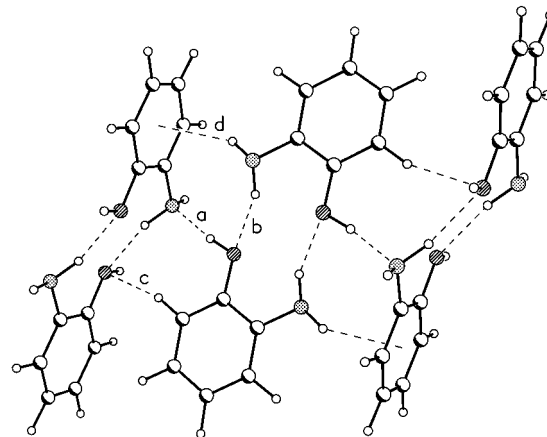
(9) Crystal data for **2**: orthorhombic, *Pbca*, $Z = 8$, $a = 19.655(2)$ Å, $b = 7.157(2)$ Å, $c = 7.770(2)$ Å, $V = 1093.0(4)$ Å^3, $D_c = 1.325$ Mg m^{-3}, $F(000) = 288$, $T = 100$ K, 8112 measured reflections, 2046 unique reflections, refinement on F^2, $R = 0.0634$, $wR_2 = 0.1439$, Gof = 1.243, all atoms anisotropic. Crystal data for **3**: orthorhombic, *Pca*2$_1$, $Z = 4$, $a = 11.226(2)$ Å, $b = 6.101(2)$ Å, $c = 8.282(2)$ Å, $V = 567.2(3)$ Å^3, $D_c = 1.276$ Mg m^{-3}, $F(000) = 144$, $T = 100$ K, 2552 measured reflections, 1227 unique reflections, refinement on F^2, $R = 0.0681$, $wR_2 = 0.0654$, Gof = 1.477, all atoms anisotropic.

(10) Wilkinson, C.; Khamis, H. W.; Stansfield, R. F. D.; McIntyre, G. J. *J. Appl. Cryst.* **1988**, *21*, 471.

Figure 2. O−H···N (a), N−H···O (b), C−H···O (c), and N−H···π (d) interactions in the crystal structure of **2**. Notice synthons **5** and **7**.
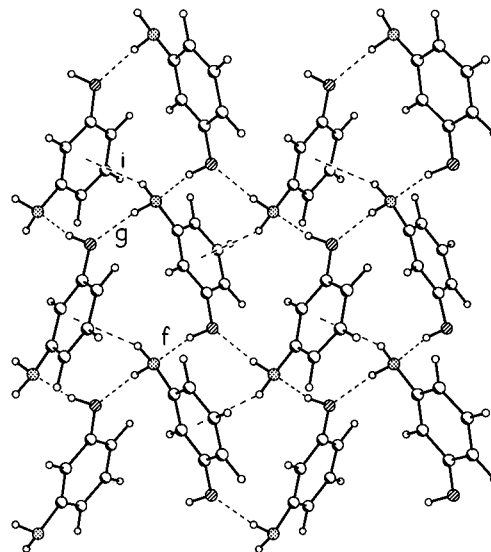

Figure 3. Crystal structure of **3** down [010]. Notice synthon **6**.

interaction e in Table 1). A similar geometry (interaction j) is obtained in **3**. Such an ambiguity does not exist for the intermolecular O−H···π hydrogen bond in 2-ethynyladamantan-2-ol wherein the OH group is shown to definitely point toward the center of the alkyne bond rather than to either of the C atoms that constitute this bond.[7b] The N atoms are distinctly tetrahedral in both structures, with the perpendicular distances from the basal plane to the apex of the pyramid being 0.331 and 0.358 Å in **2** and **3**, respectively. Inspection of Figures 2 and 3 reveals that the N−H···π hydrogen bonds would not be so effective if the N atoms were planar, and perhaps this is the driving force for pyramidalization.

Surprisingly, the hydroxy−amino recognition pattern as observed elsewhere by Ermer and Hanessian is not found in these simple compounds. In **2**, the hydroxy and amino groups form a centrosymmetric arrangement. Each −OH group donates a hydrogen bond to an −NH$_2$ group (O−H···N, interaction a in Table 1) and accepts one (N−H···O, interaction b) from another. The fourth coordination site is occupied by a C−H···O hydrogen bond (interaction c). Each −NH$_2$ group similarly donates (interaction b) and accepts (interaction a) a strong hydrogen bond. The second amino H atom participates in the N−H···π hydrogen bond (interaction d). Interestingly, both the O and N atoms have a tetrahedral environment, but unlike in **1**, the hydrogen bonding is not exclusively of the strong type. A very similar situation prevails in the structure of **3** with adjacent N−H···O-bonded molecules related by a screw axis. The N−H···π hydrogen bond is again present (interaction i) along

Table 1

compound	interaction[a]	X-ray			neutron		
		D (Å)	d (Å)	θ (deg)	D (Å)	d (Å)	θ (deg)
2-aminophenol	a. O−H···N	2.780	1.772	169.2	2.787(2)	1.782(4)	172.7(3)
	b. N−H···O	3.114	2.221	153.4	3.113(2)	2.141(4)	156.6(3)
	c. C−H···O	3.650	2.686	160.6	3.620(2)	2.577(4)	160.6(3)
	d. N−H···π	3.260	2.458	146.2	3.199	2.309	145.0
	e. N−H···π	3.487	2.577	172.4	3.438	2.421	173.9
3-aminophenol	f. O−H···N	2.749	1.883	161.1	2.753(3)	1.758(5)	168.0(4)
	g. N−H···O	3.011	1.957	153.4	3.030(3)	2.024(6)	165.6(5)
	h. C−H···O	3.359	2.625	131.7	3.323(3)	2.524(7)	129.0(5)
	i. N−H···π	3.341	2.410	161.9	3.328	2.409	148.7
	j. N−H···π	3.534	2.584	167.9	3.522	2.504	171.8

[a] Interactions d and i are to the center of the phenyl ring while interactions e and j are to the center of the C−C bond.
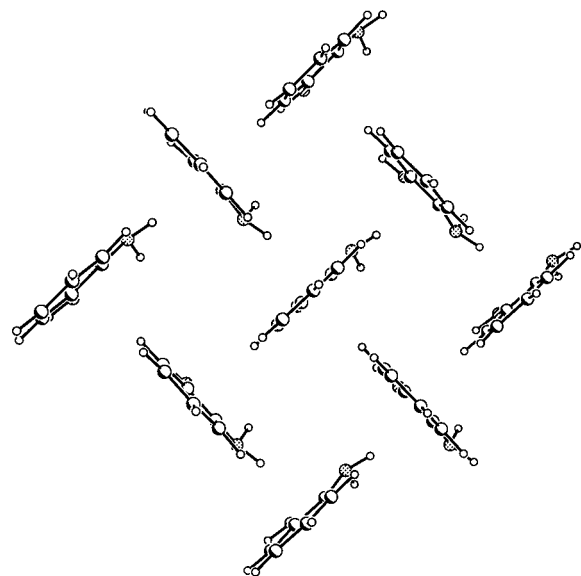

Figure 4. Herringbone interactions in **2**. Note that the arrangement of aromatic rings is similar to that in the structure of benzene.

with the other interactions (f, g, and h) as in **2**, and the tetrahedral environment around the O and N atoms is maintained. The cooperative scheme of hydrogen bonds in both structures may be noted.[11] In contrast, there are no significant N−H···π interactions in **1** because the shortest N−H···π distance is as long as 4.466 Å. In a more general context, we have used this opportunity to suggest geometrical criteria for attractive N−H···π interactions. Studies with the Cambridge Structural Database (CSD)[12] show that N−H···π geometries may be structurally significant when the H···X distance, d (X = ring centroid), is less than 2.6 Å and additionally the N−H···X angle, θ, is between 130° and 180°.

To understand why these "anomalous" structures are obtained, it is instructive to consider the packing of aromatic rings in the structures of **2** and **3**. Figure 4 shows that the phenyl rings in **2** are arranged in a herringbone fashion, and it has been previously pointed out that this arrangement is almost identical to the arrangement of aromatic rings in crystalline benzene.[13,14] Herringbone interactions are identified by their characteristic T-shaped geometry, and their importance in the crystal structures of aromatic compounds has been discussed repeatedly in the past.[15] In the present instance, we do not distinguish between herringbone geometries in which the inter-ring angles are around 90° and those where this angle is around 60°.[13,16] Figure 5
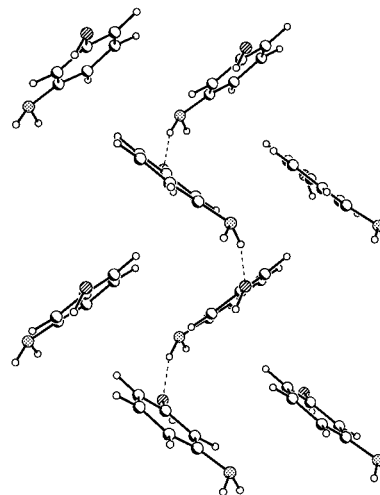

Figure 5. Herringbone interactions in the crystal structure of **3**.

shows the corresponding arrangement of rings in **3**. The formation of the unusual hydrogen bond network in these compounds is understood then as a result of the need to establish a herringbone arrangement. It has been stated that the N−H···π hydrogen bond is uncommon because it can occur only in acceptor-poor systems.[17] In the present context, the acceptor atoms are present but inaccessible because of the constraints imposed by the formation of the particular herringbone geometry. Alternatively, the formation of the weaker N−H···π and the C−H···O bonds in these systems at the expense of the stronger N−H···O bonds would hint that *the optimization of the herringbone interactions rather than the formation of N−H···O hydrogen bonds is the primary structural effect in these compounds.* According to such an argument, the tetrahedral hydrogen-bonded network in **1** follows not only from the hydrogen bond capabilities of the −OH and −NH₂ groups as visualized by Ermer but also from the fact that the establishment of a preferred herringbone arrangement in this structure (Figure 1) does not interfere with such a tetrahedral hydrogen bond network. Further, one may now contrast the aromatic hydroxy−amino systems of Ermer and the aliphatic hydroxy−amino systems of Hanessian. Both these systems display tetrahedral supramolecular arrangements, but one could infer that these arrangements are more likely in aliphatic systems where an N−H···π hydrogen bond cannot exist.

The observed crystal structures of **2** and **3** optimize several types of interactions. The structure of **2** is especially noteworthy

(11) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer: Berlin, 1991.

(12) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 204.

(13) Zorkii, P. M.; Zorkaya, O. N. *J. Struct. Chem.* **1995**, *36*, 704.

(14) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.

(15) (a) Robertson, J. M. *Proc. R. Soc. London,* **1951**, *A207*, 101. (b) Kitaigorodskii, A. I. *Molecular Crystal and Molecules*; Academic Press: New York, 1973. (c) Williams, D. E. *J. Chem. Phys.* **1965**, *45*, 3770. (d) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995. (e) Gavezzotti, A.; Desiraju, G. R. *Acta Crystallogr.* **1988**, *B44*, 427.

(16) Gavezzotti, A. *Chem. Phys. Lett.* **1988**, *161*, 67.

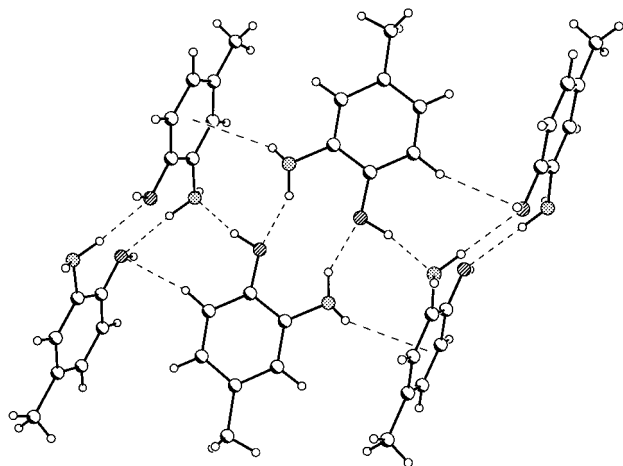(17) Hanton, L. R.; Hunter, C. A.; Purvis, D. H. *J. Chem. Soc., Chem. Commun.* **1992**, 1134.

Figure 6. Synthons **5** and **7** in the crystal structure of **4**. Compare this with Figure 2.
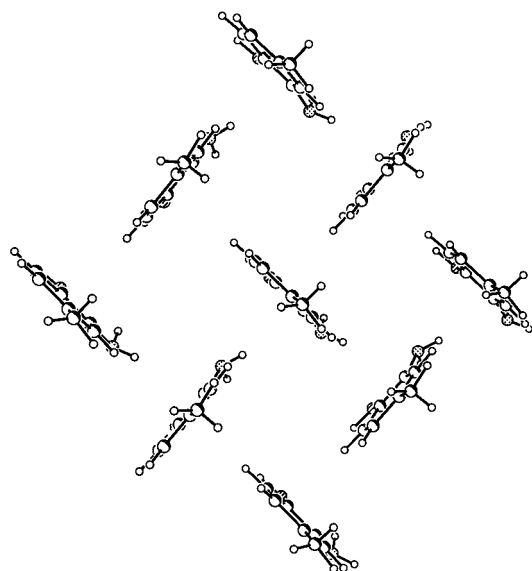

Figure 7. Herringbone interactions in the crystal structure of **4**. Compare this with Figure 4.

in that the melting point difference between **2** (175°) and **1** (189°) is one of the smallest between isomeric *ortho-* and *para-*disubstituted benzenes. To the extent that melting points provide a measure of packing efficiency, we examined the packing coefficients of **1**, **2**, and **3.** These are, respectively, 0.714, 0.752, and 0.729. The higher values for **2** and **3** indicate that these anomalous structures do not suffer from any marked packing deficiencies. To obtain an idea of the generality of these structures, the CSD[12] was again examined and revealed that 4-methyl-2-aminophenol, **4**[18] (mp 141°), and 4-chloro-2-aminophenol[19] have structures very similar to that of **2**. Figures 6 and 7 show two views of the crystal structure of **4**. The similarity between the structures of **2** and **4** extends to the same networking of strong and weak hydrogen bonds.[20] Which of these aminophenol structures then is anomalous, **2** (and **3**) or **1**?

Our observations on these simple molecules indicate that straightforward correspondences between molecular and crystal

(18) Kashino, S.; Tomita, M.; Haisa, M. *Acta Crystallogr.* **1988**, *C44*, 730.

(19) The crystal structure of 4-chloro-2-aminophenol has been determined to a low accuracy (Ashfaquzzaman, S.; Pant, A. K. *Acta Crystallogr.* **1979**, *B35*, 1394) and so is not discussed in any further detail here.

(20) Note that two of the cell edges of **2** and **4** are nearly identical. Cell parameters of **4**: $a = 7.7803$ Å, $b = 22.901$ Å, $c = 7.5962$ Å, $\alpha = \beta = \gamma = 90°$.
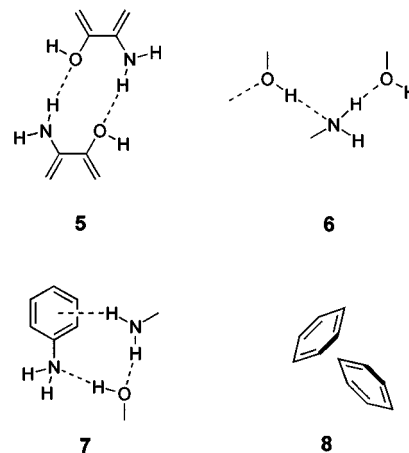

Figure 8. Supramolecular synthons in the structures of 2- and 3-aminophenols.

structure often do not exist. When these seemingly exist, they are the result of effective insulation between different sets of significant intermolecular interactions. In the present case, these sets correspond to hydrogen-bonding and herringbone interactions. When such insulation is absent, or in other words when the interactions interfere with one another, unexpected crystal structures could arise. A major problem in crystal engineering is that it is often difficult to anticipate, at least from a casual inspection of molecular structural features, when such insulation will or will not be present. This among other reasons has led to the suggestion for the definition of supramolecular synthons,[14] the most significant of which are the *smallest* structural units within which is encoded the *maximum* information inherent in the mutual recognition of molecules to yield solid state supermolecules, that is, crystals. The terms "smallest" and "maximum" are of significance here. Molecular functional groups such as $-OH$ and $-NH_2$ and supramolecular fragments like $-O-H\cdots NH_2$ and $-N(H)H\cdots O-H$ are also structural units, that is, molecular and supramolecular synthons, but they are too small to uniquely determine the molecule $\rightarrow$ crystal relationship. In the present context of the crystal structures of the isomeric aminophenols, perhaps more meaningful structural units would be synthons **5**–**8** (Figure 8). A CSD survey shows that the synthons **5** and **7** are specific to the title crystal structures and compound **4**, whereas synthon **6** is quite general and is observed in many structures that contain hydroxy and amino groups.

In conclusion, we emphasize that (a) molecular features such as functional groups do not necessarily correspond in a simple manner with arrangements of molecules in crystals, (b) strong hydrogen bonding of the $O-H\cdots N$ and $N-H\cdots O$ types need not control crystal packing to the exclusion of other factors, and (c) the definition of the term "supramolecular synthon" recognizes the inadequacy of present molecule $\rightarrow$ crystal transforms and attempts to provide a supramolecular basis for the description of supramolecular structures.