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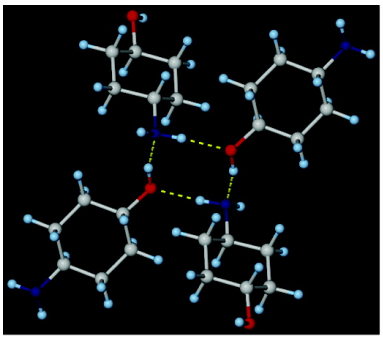

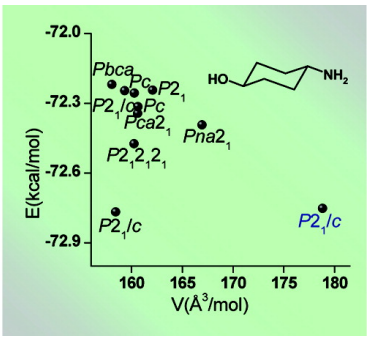

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Crystal Structure Prediction of Aminols: Advantages of a Supramolecular Synthon Approach with Experimental Structures

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Abstract: The supramolecular synthon approach to crystal structure prediction (CSP) takes into account the complexities inherent in crystallization. The synthon is a kinetically favored unit, and through analysis of commonly occurring synthons in a group of related compounds, kinetic factors are implicitly invoked. The working assumption is that while the experimental structure need not be at the global minimum, it will appear somewhere in a list of computationally generated structures so that it can be suitably identified and ranked upward using synthon information. These ideas are illustrated with a set of aminophenols, or aminols. In the first stage, a training database is created of the 10 isomeric methylaminophenols. The crystal structures of these compounds were determined. The prototypes 2-, 3-, and 4-aminophenols were also included in the training database. Small and large synthons in these 13 crystal structures were then identified. Small synthons are of high topological but low geometrical value and are used in negative screens to eliminate computationally derived structures that are chemically unreasonable. Large synthons are more restrictive geometrically and are used in positive screens ranking upward predicted structures that contain these more well-defined patterns. In the second stage, these screens are applied to CSP of nine new aminols carried out in 14 space groups. In each space group, up to 10 lowest energy structures were analyzed with respect to their synthon content. The results are encouraging, and the predictions were classified as good, unclear, or bad. Two predictions were verified with actual crystal structure determinations.

Introduction

Crystal structure prediction (CSP) has emerged as a problem of outstanding importance in supramolecular science.[1] While it is stated simply enough as the prediction of the space group, cell dimensions, and atomic fractional coordinates from the chemical diagram of a small organic molecule, the hurdles associated in so doing are numerous and the effort has been termed as being of "formidable" difficulty in at least two recent publications.[2] General or particular solutions to CSP imply a complete or partial understanding of the mechanism of crystallization (molecule → crystal), and since this is a complex phenomenon, CSP is rightly expected to be very difficult. CSP is closely connected with polymorphism;[3] accordingly, its value as a predictive tool has always raised high expectations within the corporate scientific community, and especially in the pharmaceutical industry.[4]

CSP has come of age during the past decade, with the evolution of better force fields and increase in data processing power,[5] culminating in three blind tests organized by the Cambridge Crystallographic Data Centre[6] with the aim of answering the question, "Can crystal structures be predicted?" Now, seven years and eleven molecules later, the answer is not much clearer: yes, no perhaps, sometimes.[7] Generality is still lacking, and there is a realization that while crystallization is

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(3) Selected references that show the relationship between CSP and polymorphism include: (a) Jetti, R. K. R.; Boese, R.; Sarma, J. A. R. P.; Reddy, L. S.; Vishweshwar, P.; Desiraju, G. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1963. (b) Cross, W. I.; Blagden, N.; Davey, R. J. *Cryst. Growth Des.* **2003**, *3*, 151. (c) Tremayne, M.; Grice, L.; Pyatt, J. C.; Seaton, C. C.; Kariuki, B. M.; Tsui, H. H. Y.; Price, S. L.; Cherryman, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 7071. (d) Lewis, T. C.; Tocher, D. A.; Price, S. L. *Cryst. Growth Des.* **2004**, *4*, 979. (e) Hulme, A. T.; Price, S. L.; Tocher, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 1116.
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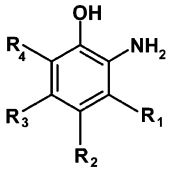
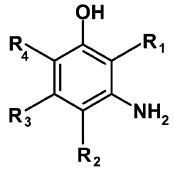
Scheme 1

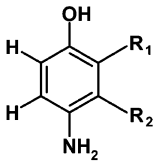
1, R = H/CH_3



2, $R_1 = R_2 = R_3 = R_4 = H$
2a, $R_2 = R_3 = R_4 = H$, $R_1 = CH_3$
2b, $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
2c, $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
2d, $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$



3, $R_1 = R_2 = R_3 = R_4 = H$
3a, $R_2 = R_3 = R_4 = H$, $R_1 = CH_3$
3b, $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
3c, $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
3d, $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$



4, $R_1 = R_2 = H$
4a, $R_2 = H$, $R_1 = CH_3$
4b, $R_1 = H$, $R_2 = CH_3$

complex, the methods inherent to CSP are very complicated.[8] Crystallization is a complex phenomenon because its outcome, the crystal structure, is only indirectly related to molecular structure as expressed as a collection of functional groups; the crystal structure obtained depends not only on the nature of these groups but also on their number and positioning.[9] CSP is a complicated exercise because the computational procedures are arduous, the sources of error are numerous, and small variations in the force field could cause major variations in the predictions. Some of these problems are put together in a basket called "kinetic factors", and while observed polymorphs are often the ones that appear faster rather than those that are the most stable,[2] computer simulation of crystallization, say through molecular dynamics, is beyond the realms of possibility.

It is in the context of addressing these inescapable kinetic issues that experimental based approaches to CSP have originated.[10,11] At the core of these approaches is the *supramolecular synthon*, which is a structural entity smaller than the complete crystal but which encapsulates a sufficient amount of critical structural information so that it serves as model for the entire crystal.[12] The structural synthon is a kinetically favored unit, and through analysis of commonly occurring or robust synthons in a group of related compounds, kinetic factors are implicitly invoked. Synthon based approaches to CSP acknowledge that crystallization is a manifestation of complexity. Rather than try to model thermodynamic and kinetic factors rigorously, one attempts to identify important synthons from experimental crystal structures and use them as positive (or negative) screens in selecting (or rejecting) computationally derived structures. CSP today is more an exercise in reranking structures rather than in predicting them because the force fields currently available are good enough so that the experimental structure is nearly always found in, say, the 500 structures that are closest to the global minimum. The idea is that while the experimental structure (kinetic polymorph) need not be the global minimum (thermodynamic polymorph), it will appear somewhere in a list of computationally generated structures so that it can be suitably identified and ranked upward using synthon information.

In the solution of a complex problem, accuracy is usually obtained at the expense of generality. The complexity inherent in crystallization means that CSP strategies could become more tractable if they are confined to groups of compounds that have similar molecular structures.[13,14] If such a group is understood well from experimental and computational viewpoints, one might consider evaluating another unknown member of the group. If the similarities are satisfactory enough, one might become confident enough to propose a crystal structure for the new compound. Any such heuristic approach needs a sufficiently large training database, and it has been estimated that, for a general supramolecular synthon based interpretation of CSP results, the Cambridge Structural Database (CSD) should contain around a million refcodes.[11c] Because the CSD will not become so large for several years, we sought to test this hypothesis and generated our own small, but within itself exhaustive, database of aminophenols, **1**. We selected the simple aminols **2**, **3**, and **4** and all 10 possible methyl substituted derivatives **2a**, **2b**, **2c**,

(6) (a) Lommerse, J. P. M.; Motherwell, W. D. S.; Ammon, H. L.; Dunitz, J. D.; Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Mooij, W. T. M.; Price, S. L.; Schweizer, B.; Schmidt, M. U.; van Eijck, B. P.; Verwer, P.; Williams, D. E. *Acta Crystallogr.* **2000**, *B56*, 697. (b) Motherwell, W. D. S.; Ammon, H. L.; Dunitz, J. D.; Dzyabchenko, A.; Erk, P.; Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Lommerse, J. P. M.; Mooij, W. T. M.; Price, S. L.; Scheraga, H.; Schweizer, B.; Schmidt, M. U.; van Eijck, B. P.; Verwer, P.; Williams, D. E. *Acta Crystallogr.* **2002**, *B58*, 647.
(7) Gavezzotti, A. *Acc. Chem. Res.* **1994**, *27*, 309.
(8) For a distinction between the terms "complex" and "complicated", see: Ottino, J. M. *Nature* **2004**, *427*, 399.
(9) Desiraju, G. R. *Science* **1997**, *278*, 404.
(10) The reader will note that prediction of crystal structures using information based on intermolecular interactions is not a new activity and that a notable attempt was made in this direction long before CSP, as it is known today, became fashionable. See: Leiserowitz, L.; Hagler, A. T. *Proc. R. Soc. London* **1983**, *A388*, 133.
(11) (a) Blagden, N.; Cross, W. I.; Davey, R. J.; Broderick, M.; Pritchard, R. G.; Roberts, R. J.; Rowe, R. C. *Phys. Chem. Chem. Phys.* **2001**, *3*, 3819. (b) Motherwell, W. D. S. *Mol. Cryst. Liq. Cryst.* **2001**, *356*, 559. (c) Sarma, J. A. R. P.; Desiraju, G. R. *Cryst. Growth Des.* **2002**, *2*, 93. (d) Hofmann, D. W. M.; Apostolakis, J. *THEOCHEM* **2003**, *647*, 17. (e) Hofmann, D. W. M.; Kuleshova, L. N.; Antipin, M. Y. *Cryst. Growth Des.* **2004**, *4*, 1395. (f) Day, G. M.; Chisholm, J.; Shan, N.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2004**, *4*, 1327. (g) Desiraju, G. R. *Curr. Sci.* **2005**, *88*, 374.
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(13) (a) Chin, D. N.; Palmore, G. T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 2155. (b) Whitesides, G. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3632.
(14) This approach contradicts Kitaigorodskii who preferred a coarse method provided it was general to a fine method which could be applied only to selected systems. Kitaigorodskii, A. I. *Molecular Crystal and Molecules*; Academic: New York, 1973; preface. We believe that CSP is so difficult that truly general solutions are almost valueless, for example, a statement that, in the predicted crystal structure, any molecule is surrounded by 12 others.

Table 1. Crystallographic Data and Structure Refinement Parameters for the Compounds in This Study

	2a	**2b**	**2c**	**2d**	**3a**
name	2-amino-3-methylphenol	2-amino-4-methylphenol	2-amino-5-methylphenol	2-amino-6-methylphenol	3-amino-2-methylphenol
crystallization	EtOH	EtOAc	EtOAc+MeCN	MeOH+benzene	EtOAc
mp [°C]	149−152	135−137	157−159	89.4	129−130
crystal system	orthorhombic	orthorhombic	monoclinic	triclinic	monoclinic
space group	*Iba*2	*Pbca*	$P2_1/c$	$P\bar{1}$	$P2_1/n$
a [Å]	21.6090(7)	7.5058(15)	8.7860(5)	8.0069(2)	6.6782(6)
b [Å]	7.4822(2)	7.7076(15)	9.9708(5)	8.0094(2)	8.1351(7)
c [Å]	8.2703(3)	22.691(5)	7.8700(4)	20.3862(5)	11.9301(10)
β [deg]	90	90	113.966(2)	84.7190(10)[a]	101.661(2)
Z	8	8	4	8	4
V [Å^3]	1337.17(7)	1312.7(4)	630.00(6)	1294.40(6)	634.76(10)
D_{calc} [mg/m^3]	1.223	1.246	1.298	1.264	1.289
R_1 [$I > 2\sigma(I)$]	0.0330	0.0390	0.0410	0.0375	0.0384

	3b	**3c**	**3d**	**4a**	**4b**
name	3-amino-4-methylphenol	3-amino-5-methylphenol	3-amino-6-methylphenol	4-amino-2-methylphenol	4-amino-3-methylphenol
crystallization	EtOAc+MeCN	EtOAc+hexane	EtOAc	EtOAc+MeCN	EtOAc+EtOH
mp [°C]	160.3	137.7	160−162	175.4	177−179
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/n$	$P2_1/n$	*Pn*	$P2_1/c$	$P2_1/n$
a [Å]	7.5998(2)	6.0239(1)	5.5990(10)	4.4894(1)	4.6823(2)
b [Å]	18.3860(5)	15.2605(3)	7.971(2)	10.4759(3)	11.5155(5)
c [Å]	9.9035(3)	7.4566(2)	7.700(2)	14.3300(4)	12.0314(5)
β [deg]	110.1720(10)	107.5570(10)	110.020(10)	93.1740(10)	96.884(2)
Z	8	4	2	4	4
V [Å^3]	1298.93(6)	653.54(2)	322.88(13)	672.91(3)	644.04(5)
D_{calc} [mg/m^3]	1.259	1.252	1.267	1.216	1.270
R_1 [$I > 2\sigma(I)$]	0.0355	0.0353	0.0393	0.0393	0.0387

[a] α, β, and γ [deg] for **2d** are 83.8860(10), 84.7190(10) and 89.1200(10), respectively.

2d, **3a**, **3b**, **3c**, **3d**, **4a**, and **4b** (Scheme 1). The crystal structures of these aminols constitute a case of moderate complexity. Conformational flexibility is limited, and this is a simplifying feature, but the possibility of nonconventional interactions (N−H···π, C−H···O, C−H···π) raises the level of difficulty.

The discussion of the experimental and computational results is as follows: (1) preparation and X-ray crystallography of the aforementioned compounds; (2) analysis of the packing in the experimental crystal structures and identification of important synthons; (3) evaluation of COMPASS (COM), DREIDING 2.21 (DRE), Universal 1.02 (UNI) and pcff_300_1.01 (pcff) force fields according to their ability to predict the experimental structure in its observed space group; (4) exhaustive polymorph prediction[15] with *Cerius*^{2} for the experimental compounds with the COM force field in at least six space groups to validate the protocol for this family of molecules; (5) application of the protocol to the CSP of nine new but related molecules; and (6) testing of the predictions for two of the new compounds with crystal structure determinations.

Experimental Section

Aminols (**2a**, **2b**, **2c**, **3a**, **3d**, and **4b**) were commercially available. Compounds **2d**, **3b**, **3c**, and **4a** were prepared according to the literature (for details including references see Supporting Information).

2-Amino-6-methylphenol, 2d. 6-Methyl-2-nitrophenol was obtained by selective nitration of 2-methylphenol followed by $SnCl_2 \cdot 2H_2O$ reduction.

3-Amino-4-methylphenol, 3b, was prepared from 4-methyl-3-nitrophenol by reduction with Pd/C and $N_2H_4 \cdot H_2O$.

3-Amino-5-methylphenol, 3c, was prepared in 70% yield according to the literature.

4-Amino-2-methylphenol, 4a. 2-Methyl-4-nitrophenol was obtained from 2-methyl-4-nitroaniline by diazotization. Hydrolysis followed by reduction afforded **4a**.

Computational. All simulations were carried out with version 4.8 of the *Cerius*^{2} molecular modeling environment[15] running on Silicon Graphics workstations. The hypothetical crystal structures were generated with a polymorph predictor (PP) module. Molecular geometries were optimized at the HF/6-31G** level using the program GAMESS-02.[16] For a PP, DRE, UNI, COM, and pcff force fields were used.[17] Force field charges were used for COM and pcff, while, for DRE and UNI, the charge-equilibrium method was used for the generation of charges. Default options were used throughout with the fine search in the Monte Carlo simulation and for clustering. All energy calculations were performed without any modifications except for the use of Ewald summation for van der Waals and Coulomb interactions. All calculations were carried out with full body minimization. More details are given in the Supporting Information.

X-ray Data Collection and Crystal Structure Determinations. Diffraction quality single crystals of all compounds were obtained by slow evaporation from solution (Table 1). The structure solution and refinements were carried out using SHELXTL programs.[18,19] In all cases the OH and NH_2 H-atoms were located in difference Fourier maps and refined isotropically. For further details, see Table 1 and the Supporting Information.

(15) *Cerius*^{2}; Accelrys Ltd., 334 Cambridge Science Park, Cambridge CB4 0WN, U.K. www.accelrys.com.

(16) Schmidt, M. W.; Balridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

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Results and Discussion

With the crystal structures of the 13 training molecules in hand, the next step is their packing analysis. The structural chemistry of the aminols has progressed in three distinct stages. A decade ago, Ermer and Eling showed that complementarity of O−H···N and N−H···O interactions leads to a saturation of hydrogen bonding potential of the OH and NH_2 functionalities in aminol **4** and related compounds.[20] Simultaneously and independently, Hanessian described similar recognition schemes in molecular complexes of diaminocyclohexanes and cyclohexane diols (supraminols).[21] A few years later, we showed that the packing of aminols **2** and **3** cannot be explained similarly and that the N−H···π interactions in these structures occur because of the need to optimize herringbone interactions.[22] This is an example of interaction interference. The levels of complexity (interference between functional groups) were even higher in our more recent study of homologated aminophenols wherein phenyl rings bearing an OH and an NH_2 substituent respectively are separated by polymethylene chains of differing lengths.[23] Here, we showed that while **2**, **3**, and **4** are distinct prototype structures, they have some commonalities at the synthon level. The addition of a Me-substituent at various positions on the aromatic ring further increases the levels of difficulty in rationalizing and predicting crystal structures in this family. This is because the supramolecular behavior of a particular functional group in a molecule depends on its nature and position and also *on the nature and position of all other functional groups*, with the added stipulation that all portions of a molecule *including the hydrocarbon residues* have supramolecular functionality.[9] Simplification of the resulting structural complexity through the identification of a few supramolecular synthons is therefore advantageous. In this context, it is very significant that we determined the crystal structures of *all* 10 isomeric methylaminophenols. This ensures that all reasonable schemes of molecular recognition that involve the OH, NH_2, CH_3, and Ph functionalities together are included, to the maximum extent possible, in our training database.

Packing Description. Although the aminols in this study are small and rigid, they display a variety of packing modes because of the high ratio of functional groups to carbon skeleton. In general, CSP of any trisubstituted benzene with three different substituents is of moderate to high difficulty.[11a] Our analysis of the packing of the 10 methylaminophenols and the 3 prototype compounds progresses from functional groups → interactions → small synthons → large synthons → crystal structure.

Hydrogen bonding is the major interaction type, and the hydrogen bonds may be classified as strong or weak; those involving only O- and N-atoms as donors and/or acceptors are better from both kinetic and thermodynamic viewpoints, owing respectively to their long-range nature and their strength. However, even from among such possibilities, some interactions are preferred. A CSD analysis of 64 aminols showed that 63 have O−H···N hydrogen bonds (version 5.25, including April 2004 updates).[24] Of these, 55 have N−H···O hydrogen bonds; in the remaining 9 all but one have a N−H···π hydrogen bridge.[25] Only 10 have an O−H···O bond and only 4 have an N−H···N, this too only if there are multiple OH or NH_2 groups present. All this indicates that the O−H···N hydrogen bond is the most readily formed interaction in this family.[26] An N−H···O hydrogen bond will then be facilitated by cooperativity. Accordingly, in 11 of the 13 aminols in our database these two types of hydrogen bond form an infinite cooperative chain O−H···N−H···O−H (synthon **I**). In the two other compounds, the cooperative arrangement of O−H···N and N−H···O bonds remains but the interactions form a closed loop, which we term a square motif (synthon **II**). In these two compounds which use synthon **II** to the exclusion of synthon **I** (**2c**, **3a**), the four aromatic rings surround the square motif, an arrangement that better accommodates the methyl substituents (Figure 1). Similar steric considerations lead to a square motif structure for the two compounds that use synthon **II** along with **I** (**4a**, **4b**).[27] Synthons **I** and **II** occurring in isolation or together constitute the simplest and smallest recognition units for the supraminols, **1**, and we term them as *small synthons*. The presence of either or both these synthons is almost compulsory within this family.

The synthon is a kinetic entity, and while we have no evidence that these small synthons exist in solution for the aminols, recent work from our group and elsewhere provide convincing evidence for the existence of synthons in solution prior to crystallization.[28] Indeed, an implicit assumption in this entire exercise is that the supramolecular synthon is important in all stages of crystallization. Identification of synthons in solution is difficult: each of the two examples cited above are very special cases, but with more examples likely soon, the fundamental basis for synthon based CSP can only become better established.

An alternative arrangement of N−H···O and O−H···N bonds gives the cyclohexane type synthon **III** which forms a part of the β-As network[20] with its nearly tetrahedral arrangement of the bonds around the O- and N-atoms. This is seen only in **4**. Between parallel hydrogen bonded networks are the connector phenyl rings that form a herringbone arrangement with C−H···O and C−H···π hydrogen bridges. We have

(18) The crystal structure of aminol **2b** has been determined earlier; see: Kashino, S.; Tomita, M.; Haisa, M. *Acta Crystallogr.* **1988**, *C44*, 730.
(19) *SHELXTL*, version 5.1; Bruker AXS Inc.: Madison, WI, 2001.
(20) Ermer, O.; Eling, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 925.
(21) Hanessian, S.; Saladino, R. In *Crystal Design. Structure and Function*; Desiraju, G. R., Ed.; Perspectives in Supramolecular Chemistry; Wiley: New York, 2003; Vol. 7, pp 77−151.
(22) Allen, F. H.; Hoy, V. J.; Howard, J. A. K.; Thalladi, V. R.; Desiraju, G. R.; Wilson, C. C.; McIntyre, G. J. *J. Am. Chem. Soc.* **1997**, *119*, 3477.
(23) Vangala, V. R.; Bhogala, B. R.; Dey, A.; Desiraju, G. R.; Broder, C. K.; Smith, P. S.; Mondal, R.; Howard, J. A. K.; Wilson, C. C. *J. Am. Chem. Soc.* **2003**, *125*, 14495.
(24) (a) Allen, F. H.; Kennard, O. *Chem. Des. Automat. News* **1993**, *8*, 31. (b) Allen, F. H.; Motherwell, W. D. S.; Raithby, P. R.; Shields, G. P.; Taylor, R. *New J. Chem.* **1999**, *23*, 25. (c) Allen, F. H. *Acta Crystallogr.* **2002**, *B58*, 380. (d) Nangia, A. *CrystEngComm* **2002**, *4*, 93.
(25) Desiraju, G. R. *Acc. Chem. Res.* **2002**, *35*, 565.
(26) Selected references that describe the structural chemistry of supraminols include: (a) Liminga, R.; Olovsson, I. *Acta Crystallogr.* **1951**, *4*, 100. (b) Liminga, R. *Acta Chem. Scand.* **1967**, *21*, 1206. (c) Loehlin, J. H.; Etter, M. C.; Gendreau, C.; Cervasio, E. *Chem. Mater.* **1994**, *6*, 1218. (d) Toda, F.; Hyoda, S.; Okada, K.; Hirotsu. K. *J. Chem. Soc., Chem. Commun.* **1995**, 1531. (e) Loehlin, J. H.; Franz, K. J.; Gist, L.; Moore, R. H. *Acta Crystallogr.* **1998**, *B54*, 695. (f) Roelens, S.; Dapporto, P.; Paoli, P. *Can. J. Chem.* **2000**, *78*, 723. (g) O'Leary, B.; Spalding, T. R.; Ferguson, G.; Glidewell, C. *Acta Crystallogr.* **2000**, *B56*, 273. (h) Dapporto, P.; Paoli, P.; Roelens, S. *J. Org. Chem.* **2001**, *66*, 4930. (i) Lewinski, J.; Zachara, J.; Kopec, T.; Starawiesky, B. K.; Lipkowski, J.; Justyniak, I.; Kolodziejczyk, E. *Eur. J. Inorg. Chem.* **2001**, *5*, 1123. (j) Vangala, V. R.; Mondal, R.; Broder, C. K.; Howard, J. A. K.; Desiraju, G. R. *Cryst. Growth Des.* **2004**, *5*, 99. (k) Dey, A.; Desiraju, G. R.; Mondal, R.; Howard, J. A. K. *Chem. Commun.* **2004**, 2528.
(27) The square motifs may be isolated or connected with additional hydrogen bonds to form ladders. See Bhogala, B. R.; Vangala, V. R.; Smith, P. S.; Howard, J. A. K.; Desiraju, G. R. *Cryst. Growth Des.* **2004**, *4*, 647.
(28) (a) Parveen, S.; Davey, R. J.; Dent, G.; Pritchard, R. G. *Chem. Commun.* **2005**, 1531. (b) Banerjee, R.; Bhatt. P. M.; Kirchner, M. T.; Desiraju, G. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2515.

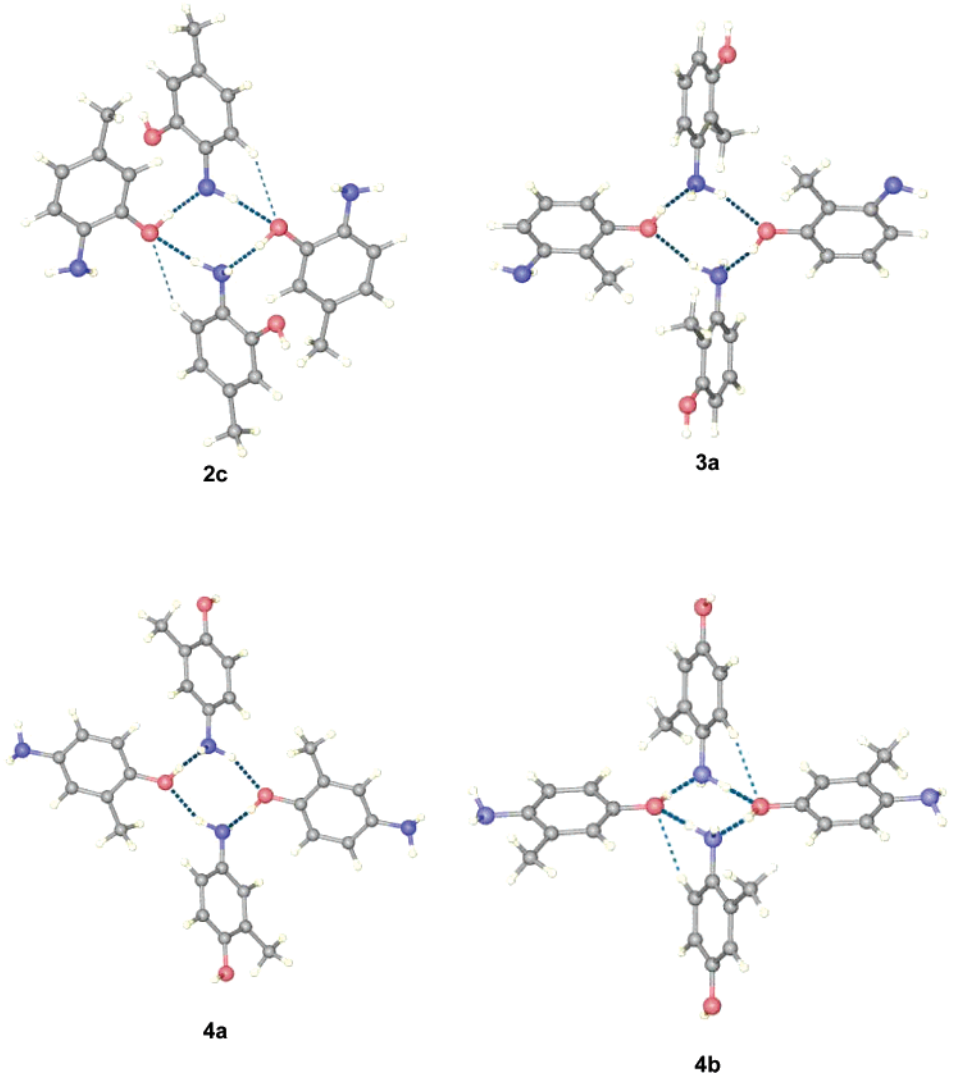


Figure 1. Crystal structures with synthon **II**.

described this structure in detail elsewhere;[22,23] in the present context, it suffices to say that the steric demands imposed by it rule it out for **4a** and **4b**.

A sterically undemanding motif is obtained in the common N−H···O dimer synthon **IV** which originates from the archetype **2**. Synthon **V**, the trimer may be visualized as originating from **II**.[29] The structures with **II** have a small intermolecular O−C−C−N torsion angle (**4a**, 61°; **4b**, 82°; **3a**, 62°; **2c**, 14°). In the 9 others, this angle is between 130° and 162°. Effectively, the π-system of the N-acceptor molecule opens up to allow for synthon **V** that incorporates a third molecule that associates with the two others with N−H···O and N−H···π bridges (Figures 2 and 3). Synthon **V** is found in 7 of these 9 structures (**2**, **2b**, **2d**, **3**, **3b**, **3c**, **3d**).

Combination of some of these synthons into larger units such as the dimer herringbone (**VI**) and the tape herringbone (**VII**) leads to more geometrical detail with concomitant loss of generality. Still, **VI** is found in three structures (**2**, **2b**, **2d**), and N−H···O dimers (**IV**) interact in an edge-to-face manner with O−H···N, C−H···O, and N−H···π bonds. The near structural equivalence of **2b** and **2** is because the H(4) atom in **2** is used neither in hydrogen bonding nor in a crowded location. Therefore it may be replaced by an Me-group with little change in the packing.[30] Aminol **2d** is related but it has $Z' = 4$ (in $P\bar{1}$). Therefore it is not used in the CSP and is not discussed further. In **2c**, the square motif **II** is surprising, and synthon **VI** might have been expected. However, **2c** has exceptional packing; it has the highest density of all the Me-substituted aminols and the shortest C−H···π hydrogen bond (d = 2.58 Å).

The tape herringbone synthon **VII**, obtained by extending trimer **V**, is found in **3b**, **3c**, and **3d** between translated molecules (7.5 Å). The tapes interact with the three donor groups along the edge forming O−H···N, C−H···O, and N−H···π bonds to the face of the next tape. **3** is a more complex variation, and the supramolecular functionality of the N−H groups is exchanged so that the N−H···π becomes an N−H···O and vice versa. Synthons **III**−**VII** constitutes more elaborate patterns of molecular recognition for the aminols, and we call them *large synthons* (Scheme 2). These patterns are not seen always and

(29) We have described recently how a synthon may "evolve" from another, and it is in this context that **II** and **V** are related. See Banerjee, R.; Desiraju, G. R.; Mondal, R.; Howard, J. A. K. *Chem.—Eur. J.* **2004**, *10*, 3373.

(30) Thomas, N. W.; Ramdas, S.; Thomas, J. M. *Proc. R. Soc. London* **1985**, *A400*, 219.

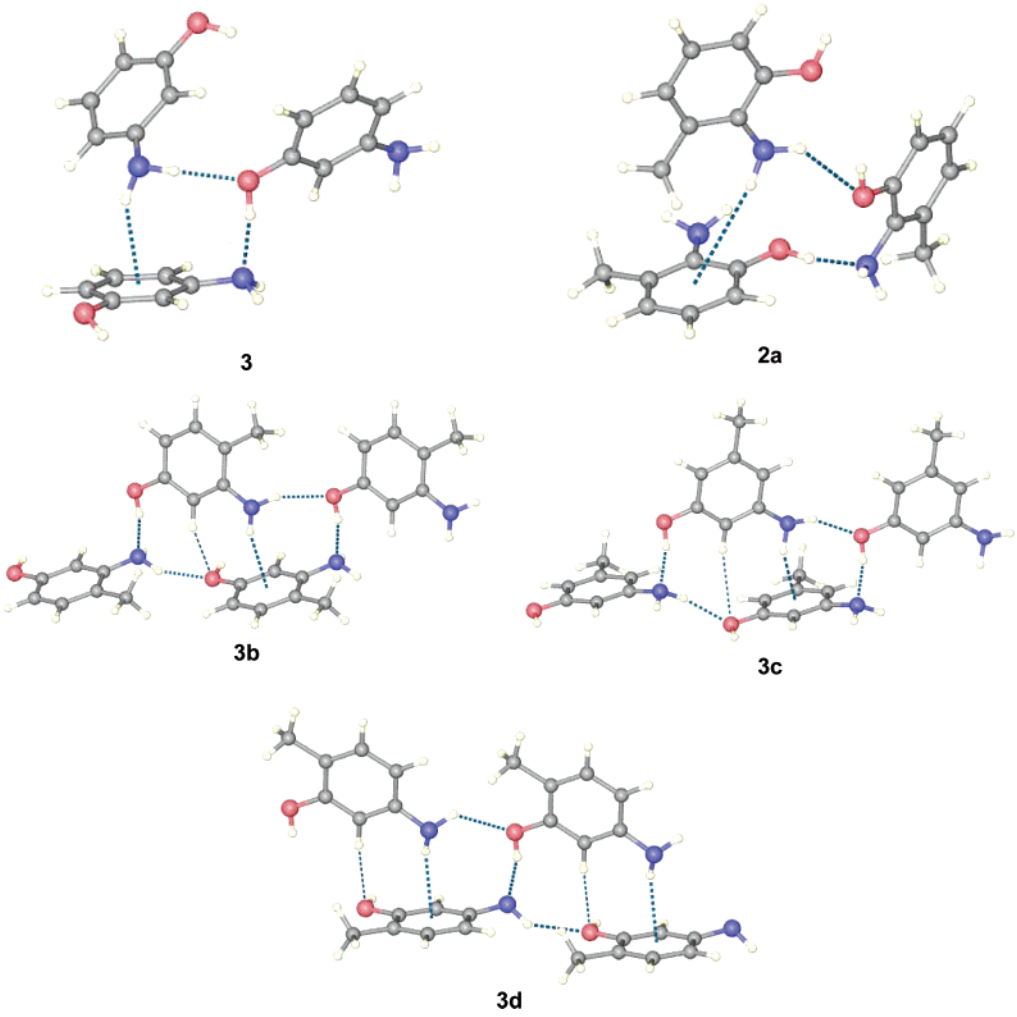


Figure 2. Crystal structures with synthon **V**.

there are variations between structures, but all in all, they represent favorable situations.

The identification of small and large synthons in the 13 structures in our training database is an essential part of the synthon based CSP exercise. The small synthons are of high topological but low geometrical value. Synthon **I**, for instance, is found in 11 out of 13 structures but in different geometrical arrangements. The large synthons are more defining in geometrical terms but lack generality and therefore predictive value; synthon **V** is found in barely half the cases. The absence of small synthons can therefore be used in negative tests to eliminate all those computationally derived structures that are chemically unreasonable. Large synthons lend themselves readily to positive tests, essentially ranking upward predicted structures that contain these larger and geometrically well-defined patterns. Each type of synthon therefore plays its part in CSP.

Evaluation and Selection of the Force Field. The most important decision in CSP is the choice of an appropriate force field.[17] The commercial package we used offers several, and we decided to test how well they were able to reproduce the 12 experimental crystal structures in the experimental space groups. Four force fields were evaluated (DRE, UNI, pcff, and COM). Among these, DRE and UNI are generic force fields, intended to be broadly applicable. COM and pcff are based on ab initio data, but the parameters are optimized empirically to yield good agreement with experiment.

The aminols posed some special problems: (1) The crystal packing and the intramolecular torsion angles C−C−N−H and C−C−O−H are implicitly linked. Retaining experimental angles in a rigid body PP run would lead readily to the experimental structure, while gas phase optimized angles might not necessarily lead to a good solid state packing. Noting, however, the needs for the "real" CSP that would follow, we decided to forego the rigid body assumption. We were well aware that the results might be worse with respect to reproducing known structures but (and keeping the new compounds in mind) felt that an ability to model the torsion angles even somewhat satisfactorily would be a real asset in a force field. This procedure also led to the discovery of an unsatisfactory atom typing in UNI and DRE, which gave experimentally unobserved planar NH_2 groups. (2) It is known that the charges are not updated during minimization. In the rigid body assumption this is unproblematic, but with rotation of hydrogen bonds to electronegative N- and O-atoms, the charge distribution and (more so) the dipole moments will change, affecting the quality of the results. (3) We did not use a multipole model for the modeling of electrostatic interactions, although it is superior to point charges.[31] Despite these problems, we felt confident in proceeding further since the force fields already worked quite well. With improvements in the compu-

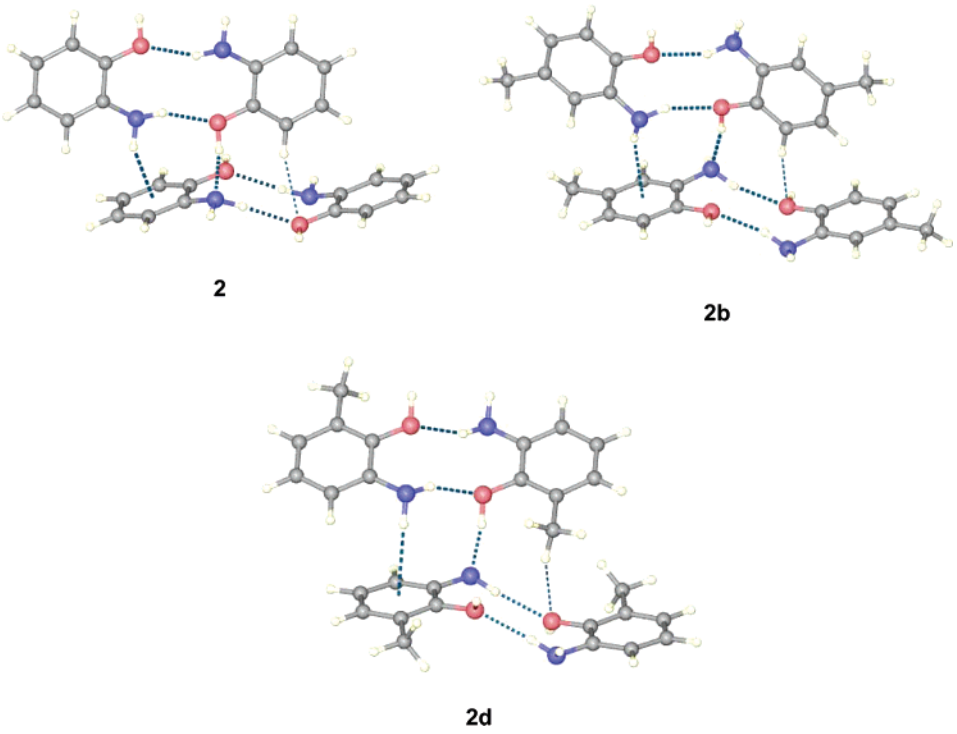


Figure 3. Crystal structures with synthons **IV** and **V**.

tational methods, parametrization of the force field, and fine-tuning of the run-time parameters, better results should be obtainable, but this is beyond the scope and the purpose of the present work.

Table 2 shows the unit cell parameters and energies for the minimized experimental structure and the lowest energy predicted structure using DRE, COM, and pcff force fields[32] for two representative compounds, **2c** and **4b**. The Supporting Information Table SI2 contains data on all 12 aminols, and Figure SI3 presents the information pictorically. If the lowest energy structure is not the same as the experimental structure, both unit cells are given. Structures predicted with the UNI force field are not given because it performed consistently worse than the others. To maintain generality and accuracy in the "real" CSP that would follow, we decided to use just one force field for all compounds[33] and to compare predicted structures with minimized experimental structures rather than with the experimental structures themselves. The use of minimized experimental structures as benchmarks deviates a little from conventional CSP wherein experimental cell parameters have to be accurately predicted.[6] Differences between the experimental and the minimized experimental structure reflect inadequacies in the force field. Synthon based CSP is slightly different from a purely computational approach in that one does not try to fine-tune force fields beyond a point and attempts to make up for this inadequacy by using elements of pattern recognition. We leave efforts to improve force fields to theoretical chemists. From an experimentalist's viewpoint, it may be said that, with improving force fields, experimental structures are more likely to be predicted closer to the global minimum but that, in the final analysis, resolution of kinetic issues cannot come through such efforts.

An overall indication of agreement between experimental and predicted structures is provided by simulated powder diffraction patterns. Figures 4 and SI4 show that COM predicted structures (for **4b**) reproduce the powder patterns, while DRE and pcff fail. Comparisons of cell parameters alone are not necessarily conclusive, as *Cerius*[2] does not perform a cell reduction. We therefore used *PLATON*[34] in Tables 2 and SI2, which compares experimentally minimized and predicted values for the 12 molecules with three force fields. After cell reduction, all cell parameters, volume, and total energy are comparable for **4b** with COM. The cell parameters predicted by DRE are close to the experimentally minimized structure but the packing is different, while pcff clearly gives an incorrect structure. A final assertion was made after a visual inspection of the crystal packing in each case. DRE works well for **4** and its derivatives. It was also able to generate experimental structures for **3**, **3a**, and **3c** (with some deviation). It does not work at all for **2** and its derivatives. Force field pcff works well for **2** and (with the exception of **2c**) is the best for this group. It also predicts **3** and **3c** but does not work with **4** and its derivatives. COM was uniformly better, and except for **4** all the structures were correctly predicted. While **2b**, **2c**, and **3a** were found with higher energy structures (0.267, 1.248, and 1.453 kcal/mol above the global minimum), this force field was able to predict the maximum number of structures with greatest accuracy and retained the topology of the synthons after minimization (see Figure SI5). Accordingly, we used COM for all further work. While this force field is acceptable,[35] the extent to which further improvements are desirable may be seen from Table SI6 which

(31) Mooij, W. T. M.; Leusen, F. J. J. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5063.
(32) **2d** is excluded here and elsewhere for reasons stated above.
(33) The use of a single force field for all predictions stems from practical considerations. Although better agreements might be obtained with different force fields in individual cases (say DRE for **4**), we prefer to sacrifice accuracy for generality. The selected force field would be used for the test compounds, and comparisons between the training and test compound structures would be more meaningful if the same force field were used throughout.
(34) Spek, A. L. *2002 PLATON, A Multipurpose Crystallographic Tool*; Utrecht University, Utrecht, The Netherlands.

Scheme 2. Supramolecular Synthons in This Study

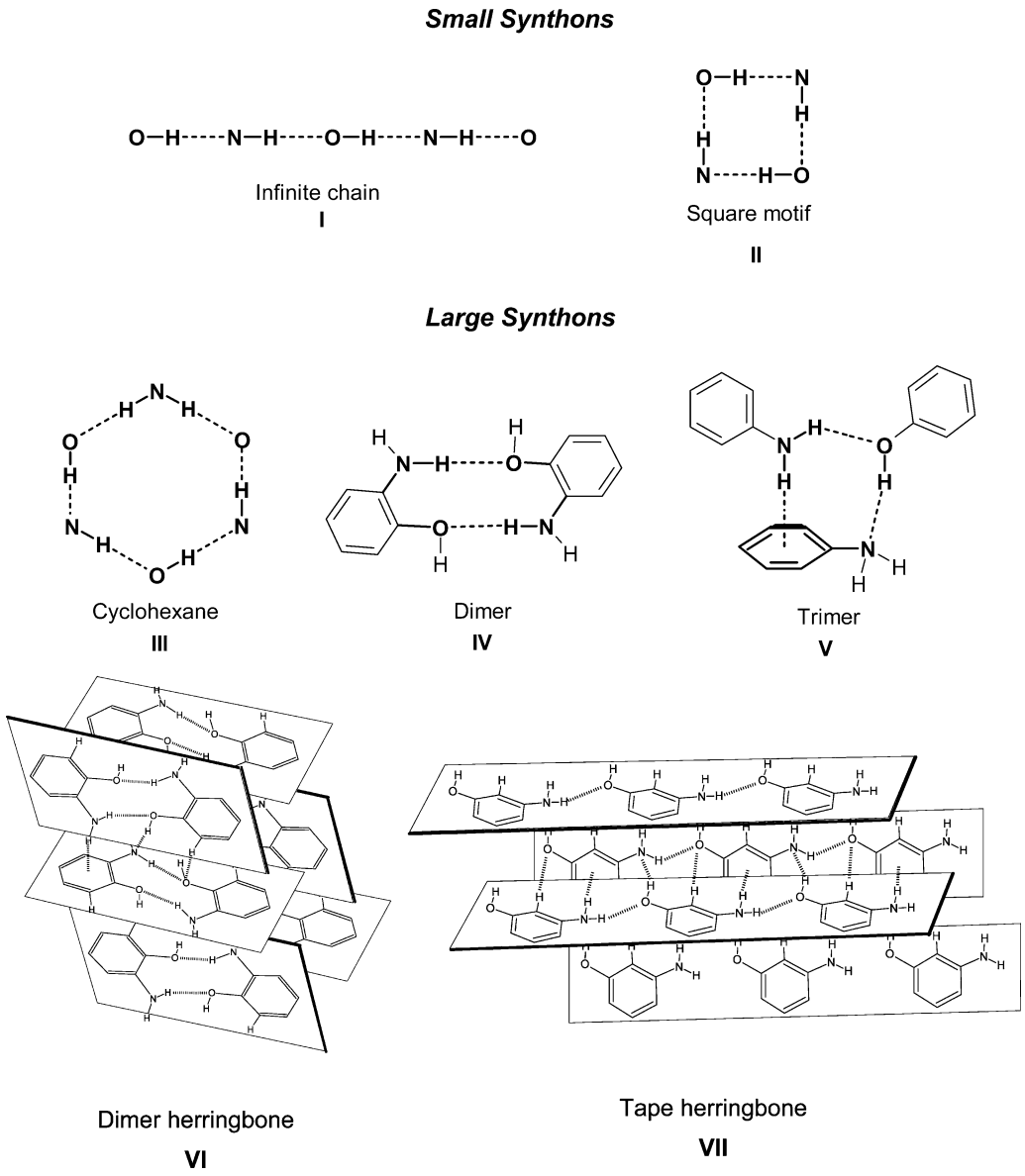


Table 2. Evaluation of Force Fields for Aminols **2c** and **4b**[a]

		experimental			predicted		
	FF	reduced cell parameters (Å, deg)	*V* (Å^3)	energy kcal/mol/ molecule	reduced cell parameters (Å, deg)	*V* (Å^3)	energy kcal/mol/ molecule
2c	DRE	8.034, 8.295, 10.513, 112.95	645.13	4.981	1st, 4.734, 11.197, 12.220, 93.84	646.32	28.192
	COM	7.338, 9.054, 10.084, 112.88	617.23	−36.010	1st, 5.768, 9.318, 11.194, 91.03	601.58	−37.249
					8th, 7.738, 9.054, 10.084, 112.9	617.21	−36.011
	pcff	7.497, 9.034, 10.459, 114.88	644.62	−25.309	1st, 5.121, 8.377, 15.228, 94.14	651.48	−24.162
4b	DRE	5.456, 10.985, 11.776, 96.13	701.80	−21.491	1st, 5.548, 9.799, 12.390, 92.56	672.91	−22.453
	COM	5.245, 9.925, 11.983, 93.09	622.92	−46.485	1st, 5.244, 9.928, 11.983, 93.10	622.90	−46.485
	pcff	4.909, 10.732, 12.328, 95.99	645.97	−36.057	1st, 7.411, 7.595, 11.792, 105.55	639.41	−35.520

[a] For cases where the global minimum unit cell is not the same as the experimental cell and a local minimum structure corresponding to the experimental can be found, both are given with the ranking of the latter. A similar table pertaining to all training database compounds is given in Table SI2.

compares the reduced cell parameters for experimental and minimized structures.

Compilation of the CSP Protocol. With an appropriate force field in hand, the expectation was that if CSP of a known crystal structure was satisfactory, the force field would not lead one completely astray for an unknown but related crystal structure. The CSP protocol is based on the use of COM to reproduce the experimental crystal structures of the training database compounds. Such an exercise is ideally done in a number of space groups (and the experimental space group if it is not in the list of selected space groups). We selected $P2_1$, $P2_1/c$, $C2/c$, $Pca2_1$, $Pna2_1$, and *Pbca* because they are the most

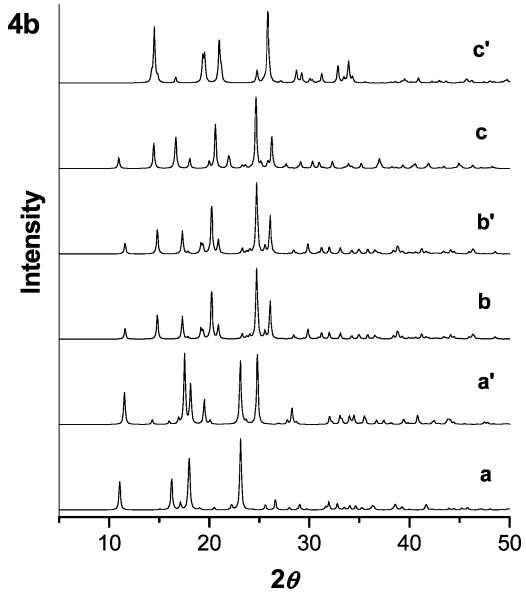


Figure 4. X-ray powder patterns of crystal structure of **4b** simulated with different force fields. Experimentally minimized structures: a, DRE; b, COM; c, pcff. Predicted structures: a′, DRE; b′, COM; c′, pcff. For similar illustrations for all training aminols, see Figure SI4 in the Supporting Information.

common. Triclinic space groups were excluded because none of the 12 training compounds adopt them.[36] Because crystallization is subject to kinetic factors, the experimental structure need not correspond to the global energy minimum.

Table 3 gives the 10 lowest energy structures for aminol **2b** as a representative example. Table SI7 gives the corresponding information for all 12 experimental compounds. Figure 5 is an energy−volume (EV) graph for the 12 compounds. For half the compounds (**3**, **3b**, **3c**, **3d**, **4a**, **4b**), the experimental packing is also the global minimum. For the others (**2**, **2a**, **2b**, **2c**, **3a**, **4**), the situation is less clear-cut and other structures are favored in the CSP. The worst result was obtained for **2c**, where the experimental packing is #13 in energy ranking. However, and in totality, these results are promising, and one might say that polymorphism is uncommon for aminophenols (for polymorph screening, see the Supporting Information). The confidence with which this statement can be made increases with the energy gap between the lowest energy packing and the second one. If one of the predicted structures is well separated from the rest (**2a**, **3**, **3b**, **3c**, **4**, **4b**), it can be considered to be the most stable polymorph. This is ideal, but the global minimum is often close to many nearby structures (**3a**, **3d**) so that no discrimination is possible (**2**, **2b**, **2c**, **4a**). The fact that polymorphs predicted as stable for **2a** and **4** are not found experimentally shows the importance of kinetic factors; of course, compounds such as **4a** might pose problems with any method. We stress that such issues cannot be resolved by faster computation or better force fields and suggest that it is here that the supramolecular synthon approach comes into its own. The chemist may compile a protocol that will rerank the predicted structures on the basis of chemical information. The question then becomes, "What minimum protocol would lead to a maximum number of correct predictions?" Once the protocol is proven to work acceptably within the database, it may be applied to new compounds.

In our protocol, the absence of small synthons in the predicted structures is used as a negative indicator, and the presence of large synthons, as a positive one. The O−H···N−H···O−H connectivity, either as an infinite chain (**I**) or as a square motif (**II**), is a sine qua non in this family.[37] Computationally predicted structures containing only O−H···O and/or N−H···N bonds must therefore be treated cautiously. Among the large synthons, **III** is uncommon in the database but we cannot rule it out in new compounds. Again, **VI** and **VII** are common in our database, but one should be prepared to see simpler versions of them (**IV** and **V**) in new compounds. Accordingly, we carried out a detailed evaluation of the low energy structures vis-à-vis their synthon content. The information is given in Table 3 for the representative **2b** (for all 12 compounds are in the Supporting Information Table SI7).

The 10 lowest energy structures for **2b** are in three space groups and are close in energy and net volume. All 10 structures contain synthon **I**, and none can be rejected outright. The fifth, sixth, eighth, and ninth structures do not contain a large synthon, and so they were given lower priority. The six others contain dimer synthon **IV**. Of these, five also have synthon **V**. The tenth (with **IV** but not **V**) lacks an N−H···π interaction and was down-ranked. The five remaining structures (first, second, third, fourth, seventh) were further considered. The first, second, and fourth lack the C−H···O interaction necessary for synthon **VI**; in the third a C−H···O is present but in a distorted orientation (2.652 Å, 141.8° and 2.796 Å, 165.4°). Only in the seventh ranked structure is distortion of (the large) synthon **VI** completely absent, leading to its reranking as the predicted packing. Such a prediction is confirmed by comparison with minimized experimental cell parameters and fractional coordinates, which match to the second decimal place. Our final ranking for these 10 low energy structures is therefore 7, 3, (1,2,4), 10, (5,6,8,9) wherein groups such as (1,2,4) and (5,6,8,9) represent sets within which the differences are only with respect to higher order packing features. The 10 lowest energy structures for each of the 11 other compounds were analyzed similarly. The results are summarized briefly:

2: The structures are close in energy and density. The fourth structure does not have large synthons and was down ranked. The first (and third as a stacking variation) have synthons **I**, **IV**, and **V**, but the dimer herringbone is distorted. In the second (experimental structure) and the fifth and seventh, which are stacking variations, this distortion is completely absent. Considering the distortion as unacceptable, the correct packing is predicted.

2a: The experimental structure (*Iba*2) is found only tenth ranked, but a packing in $Pca2_1$ with the same secondary structure has an equivalent packing and is fifth in energy. The third was down ranked, while the fourth was discarded. The square motif in the second structure allows it to retain precedence, and we

(35) Rationalization as to why COM performs the best is obtained by considering the weaker N−H···π types of hydrogen bonds, which are ubiquitous in the 2- and 3-aminophenols. In COM all hydrogen bonds are implicitly parametrized in the electrostatic terms and so the weak edge-to-face hydrogen bonds that are characteristic of the tape and dimer structures are modeled better. In contrast, the β-As sheets contain only strong hydrogen bonds that elude the parametrization of COM. The success of DRE with aminol **4** is also understood, as these interactions are parametrized in this force field.

(36) We note that the 13th compound with $Z' = 4$ (**2d**) adopts a triclinic space group.

(37) Synthon **II** is unique in that it need not be incorporated into any larger synthon. It can be linked to itself (ladder motif) or not at all. Therefore it may also serve as a positive discriminant when it appears in a predicted packing.

Table 3. Ten Lowest Energy Crystal Structures for Aminol **2b**[a,b]

rank	rerank	space group	energy kcal/mol/ molecule	net volume Å^3	cell parameters Å/deg	structural description
1	3	$P2_1/c$	−36.018	153.13	9.013, 5.776, 11.774, 87.84	Synthons **I**, **IV**, and **V** present, lacks C−H···O for synthon **VI**, therefore disfavored.
2	3	$P2_1/c$	−35.973	154.71	8.946, 5.755, 13.161, 65.96	Variation of structure 1 in stacking of layers.
3	2	$P2_1/c$	−35.908	157.15	8.595, 5.805, 12.735, 81.59	Synthons **I**, **IV** and **V** present, C−H···O different to synthon **VI**, therefore disfavored.
4	3	*Pbca*	−35.678	158.76	5.834, 8.501, 25.607	Variation of structure 1 in stacking of layers.
5	5	*Pbca*	−35.559	150.43	7.635, 28.655, 5.500	Synthon **I** without any large synthons. Similar to **2a** in packing.
6	5	*Pbca*	−35.552	149.71	7.582, 28.720, 5.500	Variation of structure 5 in stacking of layers.
7	**1**	***Pbca***	**−35.411**	**157.96**	**7.917, 21.757, 7.335**	**Experimental: synthons I, IV, V, and VI present without distortion.**
8	5	$Pca2_1$	−35.357	152.00	5.432, 14.585, 7.674	Variation of structure 5 in stacking of layers.
9	5	*Pbca*	−35.288	151.71	25.625, 5.870, 8.069	Synthon **I** without any large synthons.
10	4	$P2_1/c$	−35.263	148.79	14.493, 5.520, 7.549, 99.80	Synthons **I** and **IV** present, lacks N−H···π for synthon **V** and **VI** therefore disfavored.

[a] For similar data on all 12 compounds in the database, see Table SI7. [b] The structure in bold font is the experimental structure.

would have predicted this structure in a blind test. The many different and unexpected patterns for this compound suggest that there might be problems in packing (perhaps because of a 1,2,3 juxtaposition of substituents). The choice remains difficult, and no simple synthon protocol can predict the crystal structure correctly (and probably no simple computational procedure either).

2c: The experimental packing is the thirteenth in the EV diagram and has synthon **II**. The fourth ranked structure also has **I** and **II**, but it is unusual in that the OH and NH_2 groups point toward each other. The 11 other structures have disfavored arrangements with a multitude of stacking patterns. If the fourth is discarded, the protocol leads to the correct structure although it is 1.2 kcal/mol down in ranking. We had a strong suspicion that the experimental structure of **2c** is a kinetic polymorph, and we recrystallized it from various solvents (EtOH, EtOAc, 1:1 EtOAc−MeCN) and by sublimation but no other polymorph was obtained. It should be noted that the experimental structure has a short C−H···π interaction of only 2.575 Å and a C···C close contact of 3.236 Å, which are difficult to reproduce computationally. We feel that **2c** is a special case.

3: The experimental structure was found to be the best ranked, and its selection would have been unproblematic using any type of CSP. The fourth is a possibility.

3a: The experimental packing is found ranked fifth. The fourth can be discarded, and two others are suspect because the C−C−O−H torsion angle is inclined toward the Me-group. However, we would have predicted the lowest energy structure containing **II** with N−H···O connections and is 1.5 kcal/mol more stable than the experimental structure. A short H···H contact below 2.2 Å in the experimental structure hints that computational methods might be unreliable. Such a difficulty has been noted for the rigid imide molecule in CSP2001.[6b]

3b: The experimental structure is the best ranked. The second and fifth are unfavorable because they have no synthon larger than **I**. The third and fourth have a square motif **II** and a tape herringbone, respectively. The calculation was done with $Z' = 2$, and structures ranked second, third, and fifth can be transformed into higher symmetry space groups with $Z' = 1$.

3c: The experimental structure is the best ranked and is followed closely by two structures that differ in their layer stacking.

3d: A variation of the experimental structure, with a distorted tape herringbone, is the best-ranked. The next best is a structure that resembles **3**. The third has a square motif, while the fourth is a variation of the experimental packing. The fifth shows only synthon **I**, while the sixth and eighth are stacking variations of the square motif in the third. The seventh, ninth, and tenth are rejected because of missing small synthons. The outcome of this prediction depends on how much distortion is acceptable for synthon **VII**. But the best-ranked structure is the one closest to the experimental packing.

4: The experimental packing is not reproduced with COM. But the first, fifth, and ninth ranked structures have the cyclohexane synthon **III** and show a structural variation of the experimental packing, which is a cubic ZnS structure rather than wurtzite. Of the remaining structures only the second has a plausible structure with a square motif. The rest may be rejected.

4a: The first and third have N−H···O linked square motif synthons as does the experimental packing, but they differ by the conformation of the OH group which unexpectedly points toward the Me-group. The remaining structures are rejected or disfavored because they miss small or large synthons.

4b: The best ranked structure is the experimental one. Of the remaining nine only the third and eighth ranking has plausible packing with a square motif.

How does one evaluate the level of success? For seven compounds (out of 12), the lowest energy structure is the experimental packing (**3**, **3b**, **3c**, **4b**) or a distortion thereof (**3d**, **4**, **4a**). In all cases, our protocol would also have given the same result. In the five other compounds, the experimental structure is not the lowest energy structure. For **2** and **2b**, the second and seventh structures respectively were reranked correctly with the synthon protocol. For **2c** and **3a** the fourth and first would have been predicted by us, whereas the thirteenth and fifth would have been correct. However, in both cases the experimental structure was the second after our reranking (#13→#2, #5→#2). For **2a** the second ranked packing with a square motif would have been predicted by our protocol, while the fifth, with a stacking variation of the experimental packing, and the tenth, with the experimental packing in an uncommon space group, would have been reranked to second and third place. These results are encouraging because in all cases the experimental structure appears among the three best-ranked solutions.

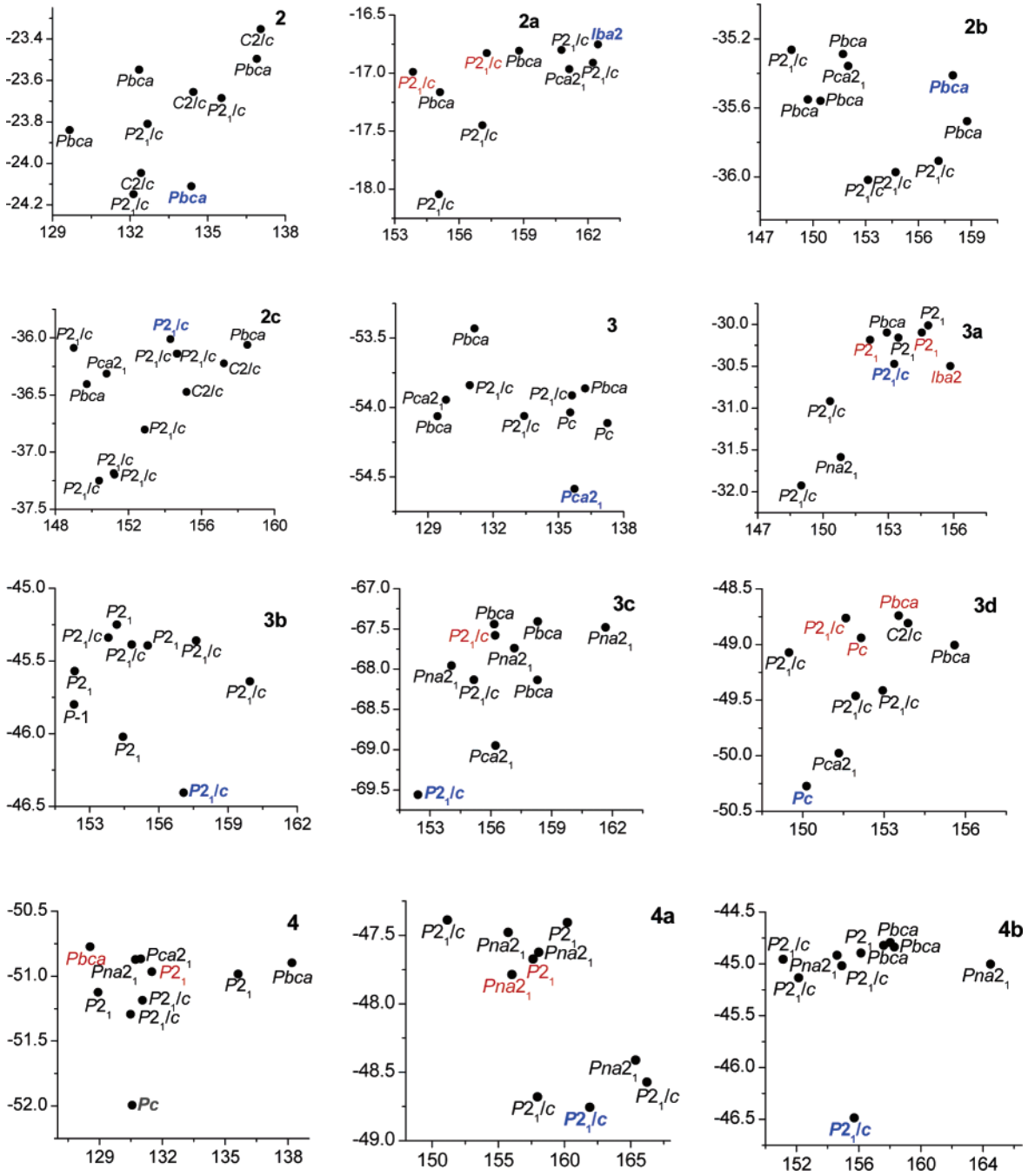
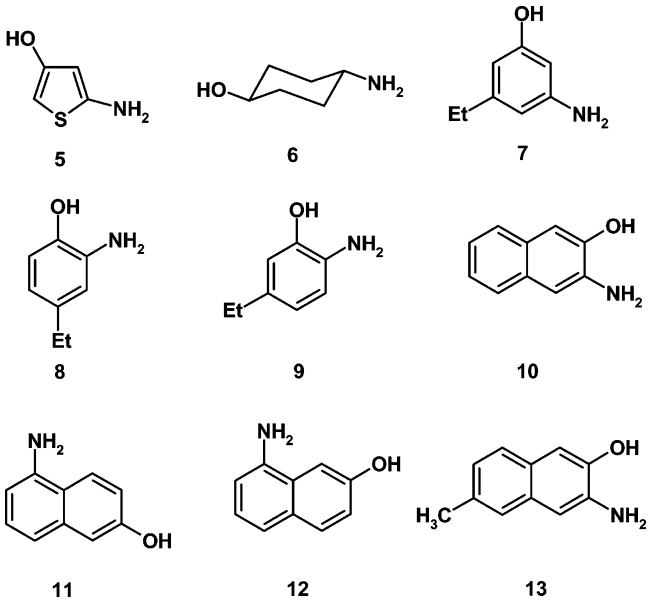


Figure 5. Plots of lattice energy (kcal/mol/molecule) versus net volume (Å^3) for 12 experimental crystal structures. Color codes blue and red indicate experimental and rejected structures, respectively.

Of course, one could be critical and state that, in the five cases where synthon based interpretation of CSP results became necessary, the correct structure only appeared as the #1 structure in two of them. One could also say that this CSP was not truly "blind". It could even be argued that in 7 of the 12 cases, synthon based CSP was unnecessary because computational CSP gave the correct answer. To this, it may be countered that if one were told only that computational CSP gave the correct answer in 7 out of these 12 cases, *it would be virtually impossible to say (without the synthon information) which 7 were thus predicted correctly*. To summarize, these predictions are only the first step (dry run) for the "real" CSP still to follow. If the protocol had not been so tuned to give correct (or nearly correct) predictions for the training structures, the next (and final) step would surely give many incorrect results (summary table for 12 aminols, see Table SI8.)

Use of the Protocol in Polymorph Prediction. The Synthon Approach. In the selection of appropriate aminols for this exercise, two caveats are pertinent: (1) the molecules chosen should resemble the molecules in the training database, but one could also extend the molecular similarity beyond a certain limit to test the robustness of the protocol; (2) the aminols should be "blind" in the best sense of the word, and their crystal structures, unknown. We carried out CSP on approximately 20 such molecules. For each of these, CSP was carried out in 14 space groups ($P\bar{1}$, $P2_1$, *Pc*, $P2/c$, $P2_1/c$, *C*2, *Cc*, $C2/c$, $P2_12_12_1$, $Pca2_1$, $Pna2_1$, *Pbca*, *Pbcn*, and *Iba*2). In each case, the starting point is the ab initio optimized molecular structure. As previously,

Scheme 3. Test Molecules for CSP



the rigid body approximation was not used. Therefore only the relative energies of various predicted structures are comparable. From these 20 molecules, a subset of nine is presented (Scheme 3; see also Scheme SI12 for the remaining 11 test molecules). These constitute, to our mind, a fair and concise pick of good, unclear, and bad results for synthon based CSP. The nine structures are discussed with reference to structural information in Table 4 and the EV diagrams in Figure 6. Detailed structural information is given in Table SI9.

Variation of the Aromatic System. The EV diagram for **5** is crowded, in terms of both energy and net volume. Six of the seven best-ranked structures do not show a small synthon and may be rejected. The second, which is the exception, features only an infinite chain. The eighth also has infinite chains, but running parallel and linked by N−H···O, as has been previously described as being of the narsarsukite type.[27] The ninth is a variant of the eighth, and the chains run antiparallel and give synthon **II**. Neither arrangement was seen in the database group. The tenth surprisingly shows a tape herringbone synthon with only a slightly distorted orientation, which might even be expected since the N−H···π would be more oriented toward the electron rich sulfur. This tenth packing was reranked as #1, followed by the narsarsukite packings. A possible issue here is that the S-atom could act as an additional hydrogen bond acceptor. The second ranked structure has such hydrogen bonding. We feel, however, that N−H···S hydrogen bonds to thioether-S (as opposed to thione-S) is not so important, and there is some precedent for this.[38] As for **6**, the EV diagram is very crowded with the exception of the second packing, which is also separated by its lower density. Despite this, we reranked it #1 because it has an N−H···O linked square motif such as that found in **4a** and **4b**. The fourth, which is a variation of the second with the infinite chains running parallel, was reranked #2. All other packings display only the infinite chain and no larger synthons, and the seventh, which is close to the β-As structure with a very long N−H···O (*d*, 3.06 Å), was reranked #3. That the EV diagrams are crowded in a small energy window for both **5** and **6** points to an unspecific force field or computational procedure. That many predicted packings are classified as the same (or mostly not describable at all) by the synthons of the database group points to molecular structures that are beyond the scope of the synthon protocol. In cyclohexane **6**, might the conformational issues be important? Experimental results from the Hanessian group[21] show that both axial and equatorial conformations may be found in the same structure, but we did not include this aspect in our modeling because the complexity level would rise unacceptably. For all these reasons, we classify both these predictions as "unclear". While this paper was being refereed, we were able to determine the crystal structure of **6**; our synthon based prediction was correct, and the details are discussed later in this paper.

Methyl → Ethyl Exchange. For **7** the EV diagram is moderately crowded. The eighth and tenth can be rejected, and the first, fourth, and ninth only show synthon **I**. In the second, sixth, and seventh structures, a dimer synthon **IV** is found, which is unusual for 3-aminophenols because it leads to a close H···H contact across the inversion center. Also, while the packing generally has the dimer herringbone arrangement, it lacks the N−H···π interaction that is necessary for synthon **VI**. The remaining structures, namely the third and fifth with synthon **II**, were reranked as #1 and #2. We would term this prediction as "bad" because we were compelled to opt for a low-density structure that does not have enough by way of larger synthons, in the absence of any meaningful alternative.

It might be recollected that the difference in crystal packing for aminols **2b** and **2c** is not really understandable. While the 4-substituted **2b** has the dimer herringbone **VI**, the 5-substituted **2c** has a different and unusual packing with a short C···C separation. **2b** is analogous to **2**. It is argued that the H(4) atom in **2** does not play any specific role in the packing and that H→Me exchange causes no structural change. On similar steric grounds, **2c** could also just as easily have adopted a similar structure. Why does it not do so? The ethyl analogues **8** and **9** were selected to further examine this question. Aminol **8** has a crowded EV diagram although there is a big gap of 0.531 kcal/mol after the three best-ranked packings. All predicted structures are somewhat unsatisfactory. For **9** the EV diagram is less crowded. The third structure has no large synthons, and the fifth and seventh have only an infinite chain. All the remaining, but one, are of the distorted herringbone dimer type. The solitary exception is the ninth which has only a square motif. The cell parameters are more telling in that they are nearly equal to those of **2c** (**2c**: 7.337, 9.054, 10.084 Å, 112.84°; **9**: 7.533, 9.985, 10.145 Å, 111.66°; the second axis is the axis within the Me→Et exchange). This similarity hints that **9** will pack with synthon **II** like **2c** and maintains the analogy between methyl and ethyl derivatives, while the true packing for **8** (similar to that of **2b**?) might still be hidden in a higher energy structure, as in **2b**.

These predictions are in the "unclear" category, and they raise a general problem of synthon based interpretation of CSP results. If the test molecule is sufficiently dissimilar to those in the training database, it is clear that all the larger synthons in the latter will not replicate themselves faithfully in the former. But one does not know a priori the actual degree of molecular similarity/dissimilarity. So does one assume that the molecules are similar and, therefore, search for large synthons in the blind CSP, not find them, and then rule out a (correct) packing of the actually dissimilar molecule? Or does one assume that the molecules are dissimilar and, therefore, accept a structure only

Table 4. Ten Lowest Energy Crystal Structures for Aminols **9** and **12**[a,b]

rank	rerank	space group	energy kcal/mol/ molecule	net volume Å^3	cell parameters Å/deg	structural description and prediction
1	2	*C*2/*c*	−37.005	182.44	9.151, 6.682, 24.589, 76.10	Synthon **I**, **IV**, **V**, and **VI** lacking CH···O but with aliphatic CH···π.
2	3	*C*2/*c*	−36.573	181.12	9.160, 6.677, 24.276, 90.38	Variation of structure 1 in stacking of layers.
3	0	*Pca*2$_1$	−36.164	182.34	4.652, 15.491, 10.121	Rejected because small synthons not found.
4	4	*C*2/*c*	−36.093	189.54	9.100, 5.879, 29.370, 74.80	Variation of structure 1. More tilt between dimers.
5	6	*Pca*2$_1$	−35.654	180.45	5.353, 16.406, 8.219	Synthon **I** without large synthons.
6	5	*C*2/*c*	−35.563	180.36	35.157, 6.675, 6.150, 99.13	Synthons **I** and **IV** present, lacks N−H···π for synthon **V** and **VI**, therefore disfavored.
7	6	*P*2$_1$2$_1$2$_1$	−35.561	175.04	4.652, 25.196, 5.973	Synthon **I** without large synthons.
8	5	*C*2/*c*	−35.535	179.83	6.379, 6.916, 34.345, 108.29	Variation of structure 6.
9	**1**	***P*2$_1$/*c***	**−35.519**	**177.32**	**9.985, 10.145, 7.533, 111.66**	**Synthon II.**
10	5	*P*2$_1$/*c*	−35.513	184.52	7.171, 6.302, 17.104	Variation of structure 6.
1	**1**	***P*2$_1$/*c***	**58.753**	**186.40**	**16.435, 5.537, 9.173, 116.72**	**Synthon II, similar to 3a and 4b.**
2	3	*P*2$_1$2$_1$2$_1$	59.362	186.27	7.872, 5.447, 17.376	Synthon **I** without large synthons.
3	3	*P*2$_1$	59.455	188.56	7.930, 5.534, 8.777, 78.26	Synthon **I** without large synthons. Variation of structure 2 in stacking of layers.
4	2	*P*2$_1$/*c*	59.462	185.59	15.807, 5.305, 9.032, 78.55	Variation of structure 1.
5	3	*Pna*2$_1$	59.486	186.72	17.714, 5.361, 7.865	Synthon **I** without large synthons.
6	0	*P*2$_1$2$_1$2$_1$	59.556	185.43	9.560, 5.374, 14.437	Rejected because small synthons not found.
7	3	*Pna*2$_1$	59.602	189.88	17.820, 7.895, 5.398	Synthon **I** without large synthons. Variation of structure 5.
8	3	*Pbca*	59.779	189.47	9.068, 18.327, 9.120	Synthon **I** without large synthons.
9	3	*P*2$_1$/*c*	60.080	190.52	7.951, 5.268, 20.822, 119.08	Synthon **I** without large synthons.
10	3	*P*2$_1$/*c*	60.083	190.82	7.854, 18.302, 5.310, 90.07	Synthon **I** without large synthons.

[a] For similar data on all 9 compounds in the database, see Table SI8. [b] The structure in bold font is the preferred predicted structure.

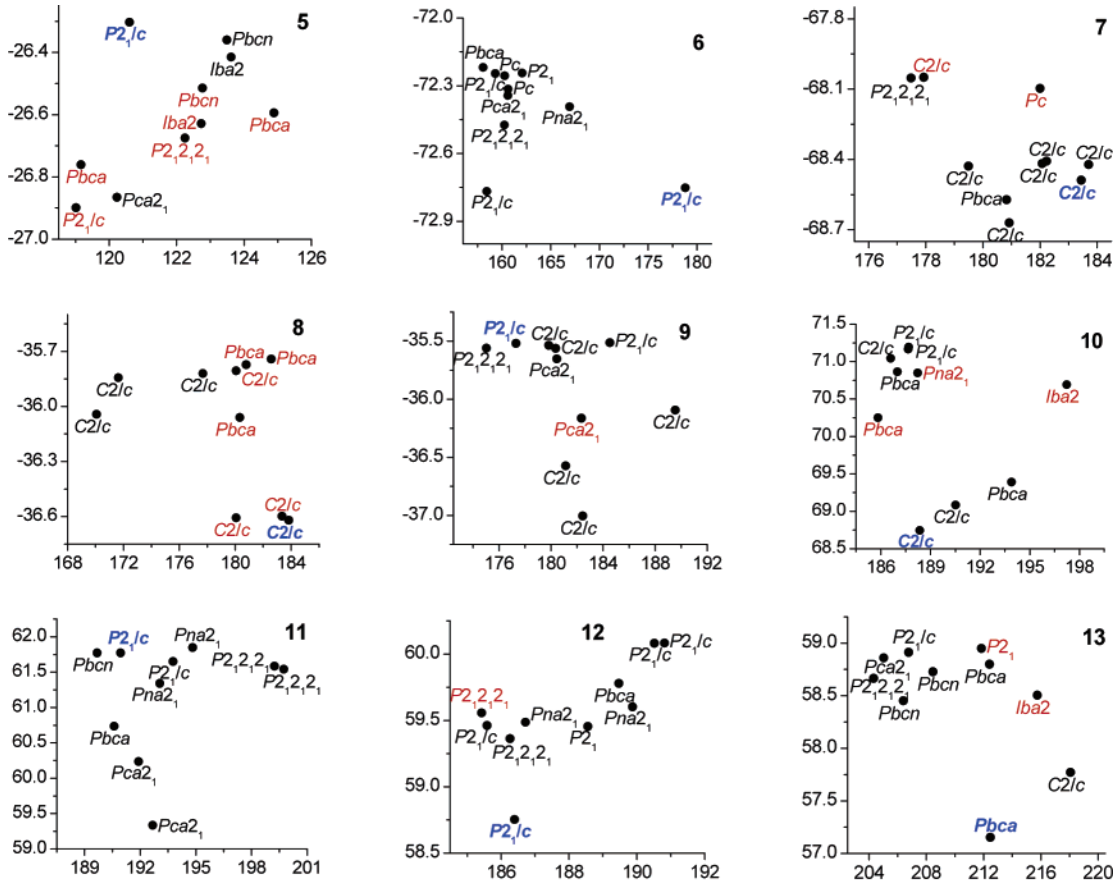


Figure 6. Plots of lattice energy (kcal/mol/molecule) versus net volume (Å^3) for CSP of 9 test structures. Blue and red codes indicate plausible and rejected structures.

on the basis of smaller synthons, to find that the correct packing in the (actually similar) molecule is at a higher energy and therefore hidden? In both cases, one arrives at an incorrect answer. In the particular case of Me→Et exchange, one might

Table 5. Comparison of Cell Parameters and Lattice Energies for Experimental Verification of Aminols **12** and **6**

aminol		cell parameters (Å/deg)	volume (Å^3)	reduced cell parameters (Å/deg)	volume (Å^3)	energy (kcal/mol/molecule)
12	experimentally minimized	9.173, 5.537, 14.788, $\beta = 96.92$	745.92	5.537, 9.173, 14.788, $\gamma = 96.92$	745.6	58.754
	predicted	16.435, 5.537, 9.173, $\beta = 116.72$	745.61	5.537, 9.173, 14.788, $\gamma = 96.92$	745.6	58.753
6	experimentally minimized	5.163, 11.476, 11.335, $\beta = 92.87$	670.85	5.163, 11.335, 11.476 $\gamma = 92.87$	670.8	−73.069
	predicted	12.134, 11.583, 5.180, $\beta = 100.78$	715.27	5.181, 11.583, 12.135, $\gamma = 100.78$	715.3	−72.752

assume that the molecules in the training and test databases are not really similar and that one should be content to see similarities at the level of the small synthons.

Phenyl → Naphthyl Exchange. Naphthalene **10** is analogous to **2** in that many elements of the molecular structure are retained; only the aromatic system is enlarged. The fourth, fifth, and sixth structures may be rejected, and the seventh does not show any synthon larger than the infinite chain. The first three are very similar to each other in that they display the expected dimer herringbone, although the motif is distorted in a manner that would be unusual, if one goes by the training database. The second is not as good because the C−H···O is missing. The eighth, ninth, and tenth have an unusual OH group conformation and form dimers with O−H···O hydrogen bonds. As they are also higher in energy by 1.5 kcal/mol, they were not considered. It is easy to accept #1, and one might confidently classify this prediction as "good".

Similarly, **11** is analogous to the prototype **3**. Structures ranked second, fourth, fifth, sixth, ninth, and tenth only show a linear chain. The first and second have an additional trimer synthon **V** and pack similar to **3**. Another combination of **I** and **V** is found in the eighth but without any similarities to known structures. The outstanding packing in this prediction has rank #7 and displays an adaptation of the tape herringbone that is suited to the larger displacement of functional groups in **11** relative to **3**. In addition to the known interactions, it features an additional and excellent C−H···π bond of the H(4)-atom while H(3) is incorporated into the C−H···O bond. This prediction is tempered by a large energy gap of 2.3 kcal/mol, but we still feel confident enough to rerank #7 to #1, with the first and third to follow, adding that polymorphism might become an issue. Again, one might classify this prediction as "good". In compound **12**, the sixth is rejected and seven others have only a linear chain. The first ranked structure and the fourth which is a variation have a square motif. Both are similar to **3a** and **4b**. The energy gap between #1 and #2 is 0.609 kcal/mol. This leads to a rather confident prediction of the first ranked structure. Since we confirmed this prediction with an experimental crystal structure determination, we do not classify it as "good", "unclear", or "bad".

Aminol **13** is the naphthyl analogue of **2b**, and its study might verify the near isostructural relationship between **2** and **2b**. It has a fair EV diagram with the first and second ranked packings clearly separated from the rest. These two are also ranked highest synthonwise because they contain **I**, **IV**, **V**, and **VI**; the fourth and tenth can be rejected outright, while the third, sixth, seventh, and ninth show only a linear chain **I**. The fifth and eighth also have only synthon **I**, but the arrangement of molecules is as close as a vicinal aminol can get to the tape herringbone synthon. Therefore they are ranked higher at #3 and #4. We consider this prediction to be "good". We have noted earlier in this section that the H→Me exchange in going from **2** to **2b** does not change the essential packing. The cell parameters of **10** and **13** support this hypothesis.[39] A summary of all nine test molecules is given in Table SI10.

Experimental Verification. At the end of the study, it was felt appropriate to verify two of the blind predictions with experimental structure determinations. The two compounds selected were naphthalene aminol, **12**, and cyclohexane aminol, **6**, because they are commercially available. For compound **12** the computationally predicted structure is also the structure predicted via the synthon approach (Table 5; see also Figure SI11). However, even in such cases (#1 → #1), the double confirmation of the prediction is welcome. The synthon approach is not superfluous, but rather it strengthens a prediction that could be called into question for a variety of reasons.[40] When we determined the crystal structure, we found that the experimental structure[41] was identical to the experimentally minimized crystal structure; in other words, the prediction was correct. As for compound **6**, the experimental structure determination itself posed problems because the crystals were hygroscopic and nearly intractably twinned. However, when we determined the crystal structure (in response to a referee comment),[42] we were gratified to note that our prediction was correct (Table 5, Figure SI11). More significantly, and this argues in favor of synthon based analysis in CSP, our predicted structure was originally ranked #2 in terms of energy but then upgraded by us to the #1 position in our synthon based reranking. The reader will also note (and appreciate) that our predicted packing has the lowest density, and this too is counterintuitive. Perhaps we were too self-critical when we originally classified this prediction as "unclear", and it is possible that the COM force field is already at a point where it may be used reliably for synthon based CSP of all aminols.

(38) Allen, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Crystallogr.* **1997**, *B53*, 696.

(39) Predicted cell parameters of **10** and **13** are: **10**, #1: *C*2/*c* 5.851 Å, 8.888 Å, 14.892 Å, 97.07°, 101.33°, 90.00°, 753.4 Å^3. **10**, #2: *Pbca* 5.845 Å, 8.883 Å, 29.879 Å, 1551.2 Å^3. **13**, #1: *Pbca* 5.922 Å, 8.697 Å, 33.007 Å, 1699.8 Å^3. **13**, #2: *C*2/*c* 5.832 Å, 8.794 Å, 17.407 Å, 97.51°, 99.64°, 90.00°, 872.3 Å^3.

(40) We feel at the present time that *any* CSP result may be called into question, and this has nothing to do with the quality of the effort that is being put into this problem worldwide but rather is inherent to the complexity and difficulty of the problem.

(41) Crystal data for **12**: ($C_{10}H_9NO$), $M = 159.18$, pale pink blocks, mp 204−207 °C, monoclinic, $a = 12.415(2)$ Å, $b = 4.1719(7)$ Å, $c = 15.511(3)$ Å, $\beta = 108.804(3)°$, $V = 760.5(2)$ Å^3, $T = 100(2)$ K, space group $P2_1/n$, $Z' = 1$, $\mu = 0.091$ mm^{-1}, $\lambda = (\text{Mo K}_\alpha) = 0.710\ 73$ Å, 5450 total reflections of which 1497 were independent, 1214 observed [$I > 2\sigma(I)$], 121 parameters, R_1 [$I > 2\sigma(I)$] = 0.0564, $wR_2 = 0.1533$.

(42) Crystal data for **6**: ($C_6H_{13}NO$), $M = 115.17$, colourless blocks, mp 111 °C, monoclinic, $a = 5.259(2)$ Å, $b = 11.954(5)$ Å, $c = 11.730(4)(3)$ Å, $\beta = 95.486(8)°$, $V = 734.1(5)$ Å^3, $T = 298(2)$ K, space group $P2_1/n$, $Z' = 1$, $\mu = 0.070$ mm^{-1}, $\lambda = (\text{Mo K}_\alpha) = 0.710\ 73$ Å, twinned crystal, 3661 total reflections, 3683 data, 1853 observed [$I > 2\sigma(I)$], 91 parameters, R_1 [$I > 2\sigma(I)$] = 0.0660, $wR_2 = 0.1697$.

Conclusions

The supramolecular synthon concept recognizes the complexities inherent in crystallization. Likewise, the synthon approach to CSP recognizes that the kinetic issue is not easily resolved with exhaustive computation. In synthon based CSP, the better the information, the more reliable will be the CSP. Further, one could also consider whether there is any need for more fine-tuning of atom potentials, leaving aside the question of whether it is possible or even meaningful. Finally, we note that as the amount of structural information in crystallographic databases increases, structural prediction would gradually move toward fingerprinting.

The following general points emerge from this study: (1) Synthon based interpretation of CSP results is a valuable adjunct to computational CSP because it biases the results of the latter in chemically reasonable ways. (2) In synthon based CSP, the force field is a working rubric that achieves accuracy without sacrificing generality, to the extent possible. The force field should not be so coarse that the results are erroneous, but it also need not be calibrated so fine that precise agreements are obtained only for a limited number of structures. (3) As an experimental method, this sort of CSP is advantageous and especially suited to cases where CSP is needed for one or a small number of chemically related compounds. This is typical of the pharmaceutical industry, where the researcher is more concerned with whether a particular compound will show additional polymorphs rather than whether a general solution for CSP will be found across a broad range of chemical space. (4) The analysis of several, or in the present case all, members of a family of structurally related compounds might be compared to a polymorphism screening, in that the packing landscape[43] has been exhaustively surveyed.[11c] As with the use of different solvents or methods of crystallization, molecular level variations within a family will favor or disfavor certain arrangements of molecules but the crystal structures are related or at least connected. An observed crystal structure of one of the members of the family is a putative structure of another. (5) There is an urgent case for crystallographers to deposit unpublished crystal structures in the CCDC, so that the size of the CSD increases as rapidly as possible. This would obviate the need to synthesize and characterize the training set compounds prior to the CSP as we have done here. However, we do not foresee an early resolution of this difficulty.

(43) (a) Blagden, N.; Davey, R. J. *Cryst. Growth Des.* **2003**, *3*, 873. (b) Gavezzotti, A. *CrystEngComm* **2003**, 439. (c) Kirchner, M. T.; Reddy, L. S.; Desiraju, G. R.; Jetti, R. K. R.; Boese, R. *Cryst. Growth Des.* **2004**, *4*, 701.

The following points emerge from this study, specific to the aminols: (1) Polymorphism is not so common in this family of compounds. We had long suspected this to be the case,[23−25,29] but the present study confirmed it repeatedly. This could be because all the important hydrogen bond donors and acceptors are situated in flexible functional groups (OH, NH_2). Therefore fine-tuning of all hydrogen bonds is possible in the packing. In particular, this fine-tuning can take place within the kinetically favored synthon **I**. Therefore the kinetic and thermodynamic polymorphs are more likely to be one and the same leading to an absence of polymorphism. (2) Changing the connector group between OH and NH_2 causes significant changes in the synthon profile, especially the change from an aromatic connector to an aliphatic one, but the prediction is still secure. (3) A Me→Et substitutional change, considered to be one of the simplest changes in molecular chemistry, has deep-seated supramolecular consequences. (4) A phenyl→naphthyl substitutional change, in contrast, is easy to handle and predict in supraminols.

Our experiences with these substitutional exchanges is suggestive. Why does a Me→Et change lead to unpredictable changes at the supramolecular level, but why is the phenyl→naphthyl change much more robust? Our inability to answer such questions illustrates that the grammar of supramolecular chemistry is, at a fundamental level, different from that of molecular chemistry. Put another way, the molecular → supramolecular transition represents a change to systems of higher complexity and emergence, and the supramolecular synthon concept is one of the ways in which such complexity may be approached.

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Supporting Information Available: Detailed Experimental Section, crystallographic table (Table SI1), Table SI2, Figure SI3, Figure SI4, Figure SI5, Table SI6, Table SI7, and Summary Table SI8 for aminols **2**, **2a**, **2b**, **2c**, **3**, **3a**, **3b**, **3c**, **3d**, **4**, **4a**, and **4b**. For the predicted structures **5**−**13**, see Table SI9, Summary Table SI10, and Figure SI11 for **12** and **6**, Scheme SI12 (PDF). 213 coordinate files for predicted crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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