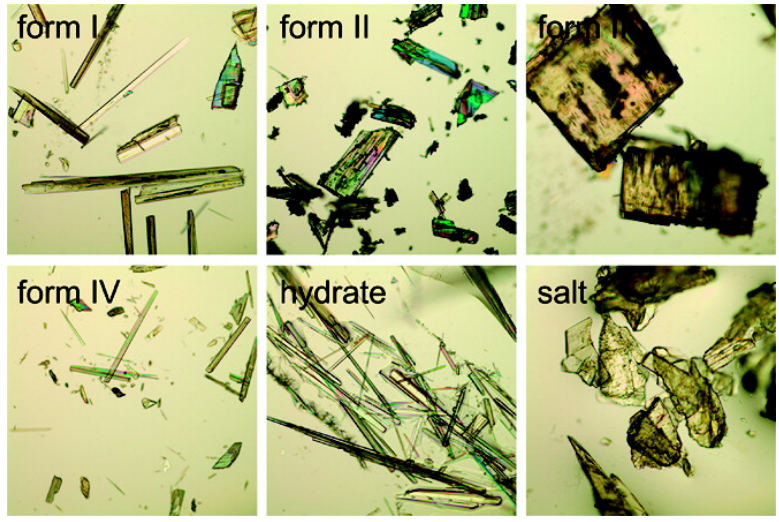
Communication

Polymorphism of an Organic System Effected by the Directionality of Hydrogen-Bonding Chains

Sihui Long, Sean Parkin, Maxime Siegler, Carolyn P. Brock, Arthur Cammers, and Tonglei Li

Cryst. Growth Des., **2008**, 8 (9), 3137-3140• DOI: 10.1021/cg800339h • Publication Date (Web): 29 July 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

CRYSTAL GROWTH & DESIGN
2008
VOL. 8, NO. 9
3137–3140

Polymorphism of an Organic System Effected by the Directionality of Hydrogen-Bonding Chains

Sihui Long,[†] Sean Parkin,[‡] Maxime Siegler,[‡] Carolyn P. Brock,[‡] Arthur Cammers,[‡] and Tonglei Li*,[†]

Department of Pharmaceutical Sciences and Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received April 2, 2008; Revised Manuscript Received July 9, 2008

ABSTRACT: Four polymorphs of 2-[methyl(phenyl)amino]nicotinic acid were discovered, and their single crystal structures were obtained at 90 K. In addition, one monohydrate and one salt were also crystallized and measured. Among the crystal structures, there are 17 crystallographically independent conformations. More interestingly, the four anhydrate forms are tessellated similarly by stacking of one-dimension hydrogen-bonding chains and, yet, the directionalities of the hydrogen-bonding chains are unique in each polymorph.

Polymorphism, as defined in McCrone's words, is "the ability of a given element or compound to crystallize as more than one distinct crystal species."[1] Some crystals are conformational polymorphs because of conformational variations of molecules in the solid state. Because of the dissimilarity in solid-state structures, polymorphs of the substance can vary significantly in their physicochemical properties. An understanding of the structure−property relationships in polymorphs has been an impetus of polymorphism studies as epitomized by the fast growing number of crystal structures in the Cambridge Structural Database (CSD)[2] as well as a vast amount of research reports including several recent books on polymorphism.[3–6]

The polymorphic formation of a given substance lies in a compromise between inter- and intramolecular interactions which can be affected by crystallization conditions. A number of diarylamines are known to be polymorphic.[7–9] During our systematic investigation of these compounds, we have discovered four polymorphs (I, II, III, and IV), one monohydrate, and one hydrochloride salt of 2-[methyl(phenyl)amino]nicotinic acid (2-MPNA), shown in Figure 1a, from different growth conditions. Single crystal structures were solved at 90 K with $R1$ values smaller than 0.059 and the crystallographic data are listed in Table 1. For the details of experimental procedures, see Supporting Information. It is known that organic systems with four or more well-characterized polymorphs are scarce.[10] 2-MPNA is particularly unusual not only in the exhibition of extensive polymorphism, but also in the total number of crystallographically independent conformations in the four polymorphs, which stands at 17 ($Z' = 1, 3, 3, 10$ for forms I, II, III, and IV, respectively). The number increases to 19 if the monohydrate ($Z' = 1$) and salt ($Z' = 1$) are included. Furthermore, all of the crystal structures consist of respectively equal numbers of *R* and *S* enantiomeric conformations that stem from the chirality of the tertiary amino group (N7). In all the structures except form IV, the *R* and *S* conformations are mirror images (e.g., Figure 1c) that are directly related by crystallographic symmetry operations (i.e., glide plane). In the case of form IV, there are five different *R* and five different *S* enantiomeric conformations presented in the asymmetric unit ($Z' = 10$); however, no *R*/*S* mirror pair can be identified and no reflection symmetry is present in the space group ($P2_1$). Organic crystals with high Z' are not commonly seen;[11,12] a survey of crystal structures with $Z' \geq 10$ in the 2008 CSD resulted in 30 hits; 20 were organic and 10 organometallic.[13]

The 19 symmetry-independent conformations differ in three torsion angles designated as $\tau1$, $\tau2$ and $\tau3$ (Figure 1b and Table 2). An *R* enantiomeric conformation has all three angles negative while an *S* has them positive. As a result of glide-reflection symmetry, the absolute values of $\tau1$-$\tau3$ of each *R*/*S* pair in all but form IV are exactly the same; the slightly different values in form IV are due to the lack of reflection symmetry relating the *R* and *S* molecules, probably caused by subtle variations in the local intermolecular interaction environment. In all molecules, the C−C bond between COOH and the pyridinyl ring is single as indicated by the bond length (average distance: 1.488 (5) Å). This suggests rotation about the C−C bond is permitted. In addition, due to the steric hindrance caused by the methyl group, the atom N7, which bridges the two aromatic rings, is no longer conjugated with either ring. Figure 2 illustrates conformational energy scans of single *R* enantiomeric conformer versus the three torsion angles respectively. It appears that each angle has two energy minima. For $\tau1$, the global energy minimum is located at −157.5° and the second minimum at 35.0° (7 kJ/mol higher). For $\tau2$, the two values are −142.5° and 62.5° with the latter being 35 kJ/mol higher in energy. For $\tau3$, because of the 2-fold symmetry of the phenyl ring along N7−C8, the two *iso*-energetic values are 45.0° and −137.5° despite a small energy difference seen in the figure, which is an artifact caused by the calculations where only $\tau3$ was allowed to change while other angles and bond distances were kept constant (this is also the case for evaluating $\tau1$ and $\tau2$, respectively). The torsion angles of all *R* conformers as listed in Table 2 clearly show the molecules reside very closely in the basin defined by the energy minima of the three torsion angles. The similarity in their conformations is further illustrated by the inset figure in Figure 2. The monohydrate form indicates similar yet noticeably different $\tau1$ from those in the anhydrate forms, plausibly a result of change in the molecular energy and hydrogen bonding pattern thanks to the relocation of

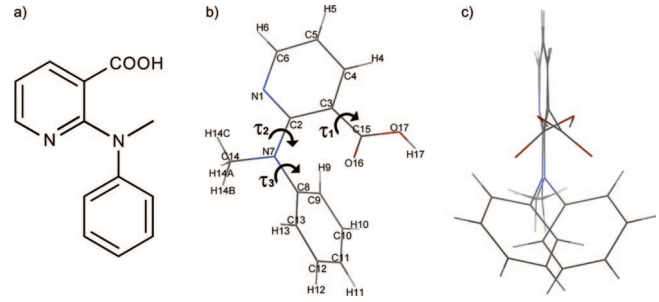


Figure 1. *R*-2-[methyl(phenyl)amino]nicotinic acid (a) with atoms labeled as in the crystals and torsion angles marked (b) and superimposed enantiomeric conformers found in form I indicating their mirror symmetry (c). Note that the lone pair of electrons on N7 points inward in (b).

* To whom correspondence should be addressed. Phone: (859) 257-1472. Fax: (859) 257-7585. E-mail: tonglei@uky.edu.
[†] Department of Pharmaceutical Sciences.
[‡] Department of Chemistry.

10.1021/cg800339h CCC: $40.75
Published on Web 07/29/2008

Table 1. Crystallographic Data of Crystal Structures Identified of 2-MPNA

	I	II	III	IV	monohydrate	HCl salt
formula	$C_{13}H_{12}N_2O_2$	$C_{13}H_{12}N_2O_2$	$C_{13}H_{12}N_2O_2$	$C_{13}H_{12}N_2O_2$	$C_{13}H_{12}N_2O_2 \cdot H_2O$	$C_{13}H_{12}N_2O_2 \cdot HCl$
morphology	colorless needle	colorless plate	colorless block	colorless needle	colorless needle	colorless block
melting point (onset) (°C)[a]	133.0	125.0	127.0	129.0	82.0[b]	220.0
space group	*Cc*	$Pca2_1$	*Pc*	$P2_1$	$P2_1/n$	$P2_1/n$
a/Å	11.711(2)	14.3290(2)	13.316(3)	8.6871(7)	7.155(1)	6.896(1)
b/Å	8.644(2)	8.9360(3)	8.841(2)	44.926(4)	7.595(1)	13.5839(3)
c/Å	11.664(2)	26.5210(7)	14.282(3)	14.238(1)	21.868(4)	13.7170(3)
α/°	90	90	90	90	90	90
β/°	104.17(3)	90	91.60(3)	90.113(4)	90.73(1)	102.60(3)
γ/°	90	90	90	90	90	90
Z′	1	3	3	10	1	1
Z	4	12	6	20	4	4
V/Å^3	1144.8(4)	3395.9(2)	1680.7(6)	5556.9(8)	1188.3(3)	1253.9(4)
D_{cal}/g·cm^{-3}	1.324	1.339	1.353	1.364	1.377	1.402
R1	0.0587	0.0539	0.0537	0.0488	0.0388	0.0493
wR2	0.1914	0.1244	0.1060	0.1620	0.1090	0.1485
T/K	90.0(2)	90.0(2)	90.0(2)	90.0(2)	90.0(2)	90.0(2)

[a] Please see Supporting Information for more thermal data of the crystal systems. [b] Strictly speaking, this should be the dehydration temperature.

Table 2. Torsion Angles, *τ*1 (O17−C15−C3−C2), *τ*2 (C3−C2−N7−C8), and *τ*3 (C2−N7−C8−C9/C13), in Forms I−IV, Monohydrate (H), and Salt (S)[a]

	*τ*1	*τ*2	*τ*3
I	±147.1(5)	±36.7(8)	±141.0(6)
II	±145.2(4), ±157.9(4), ±145.6(4)	±31.3(6), ±40.5(6), ±26.7(6)	±140.4(4), ±152.4(4), ±137.5(4)
III	±151.2(4), ±136.9(4), ±148.9(4)	±44.3(6), ±23.5(6), ±36.0(6)	±144.5(4), ±130.8(4), ±144.9(4)
IV	149.1(3), −148.3(3), −135.4(3), 135.2(3), −136.5(3), 136.0(3), 147.9(3), −148.8(3), 156.3(3), −156.1(3),	−36.8(4), 37.2(4), 25.3(5), −25.8(3), 24.9(4), −27.2(4), −36.2(4), 33.5(4), −41.8(4), 40.4(4)	144.5(3), −143.6(3), −132.2(3), 130.7(4), −129.6(3), 133.2(3), 143.7(3), −142.8(3), 151.1(3), −152.2(3)
H	±129.3(1)	±27.9(2)	±128.2(1)
S	±49.2(3)	±30.3(3)	±137.1(2)

[a] A negative value of any angle is of the R enantiomer while a positive is of the S. Unit: degree.

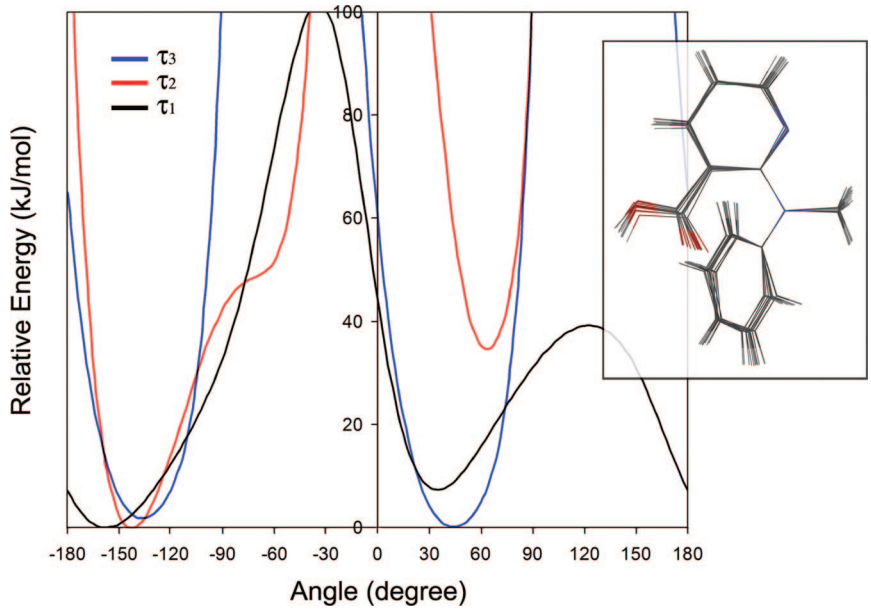


Figure 2. Conformational energy scans by B3LYP/6-311++G(d, p)//B3LYP/6-311G(d, p) of the three torsion angles respectively as the lowest energy of each scan is shifted to zero. The inset is the superimposed 12 *R* enantiomers in forms I−IV.

the acidic proton and participation of water molecules. Moreover, the salt form takes a significant adjustment in the conformation as indicated by *τ*1.

The crystal structures of forms I−IV exhibit the same hydrogen-bonded acid-to-pyridine catemer;[14,15] forms I−III show a C(6) motif and form IV a $C_2^2(12)$ according to the graph-set analysis of hydrogen bonds.[16–18] In form I, molecules with alternating absolute configuration organize themselves as one-dimensional chains perpendicular to the (101) plane (Figure 3a). In form II, the *R*/*S* enantiomers of each conformer form one-dimensional chains along the *a* axis (Figure 3b); similarly, in form III, the one-dimensional chains are along the *c* axis (Figure 3c). In form IV, each enantiomeric pair forms a one-dimensional chain along the *c* axis, resulting in five unique chain packing motifs in the unit cell (Figure 3d). Despite strong similarities among the four crystal structures, these are four distinct polymorphs as demonstrated by the hydrogen-bonding patterns in the crystal structures. Because each 2-MPNA molecule accepts (due to the pyridinyl N1) and donates (due to the hydroxyl O17) protons along every one-dimensional hydrogen-bonding network, the flow direction of protons may be regarded

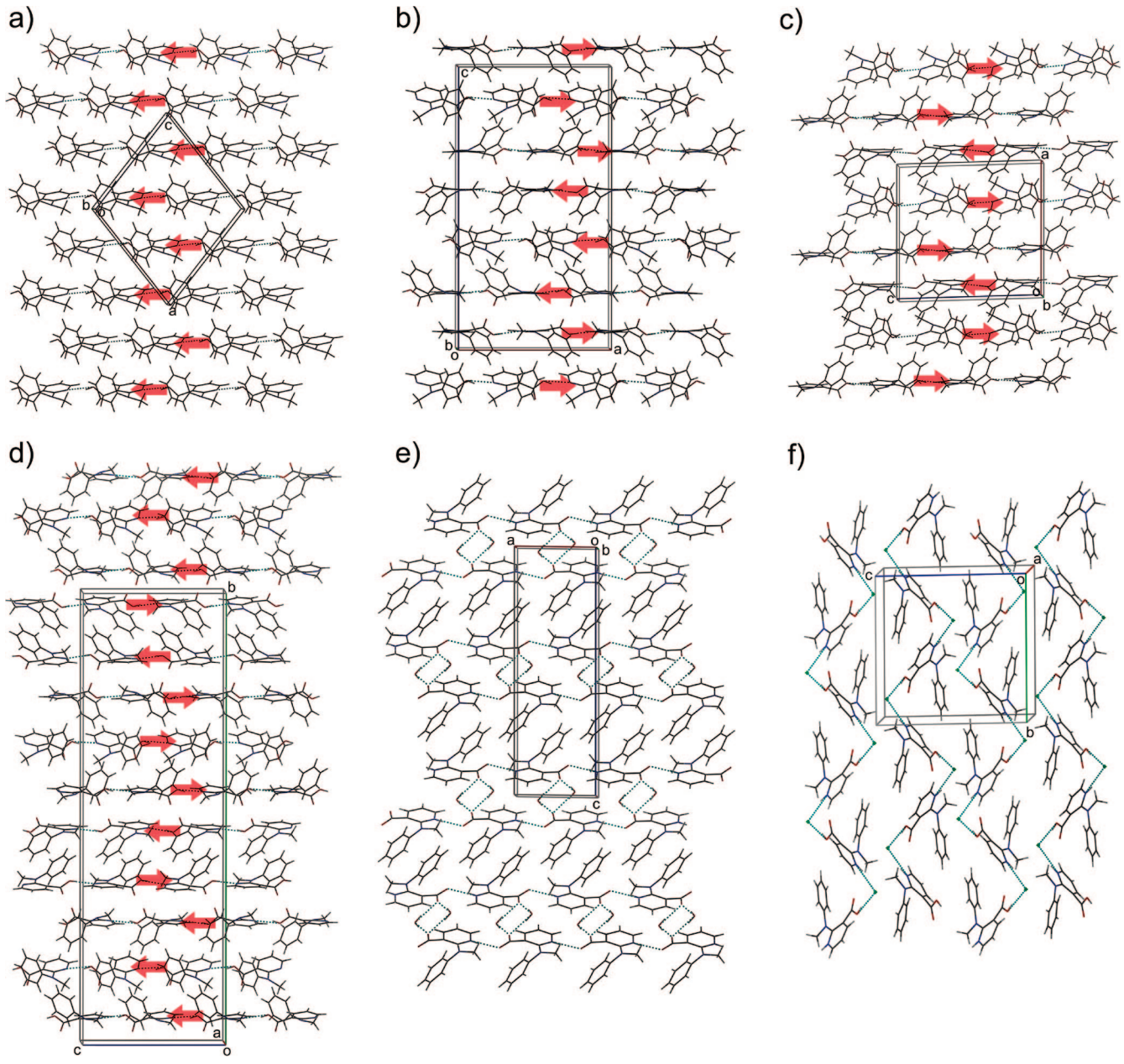


Figure 3. Crystal packing of forms I (a), II (b), III (c), IV (d), monohydrate (e), and salt (f). Arrows indicate the hydrogen-bonding directions.

as the directionality of the chain (a similar concept was mentioned earlier[19]). In form I, all chains have the same directionality, pointing to the left in Figure 3a (marked by red arrows). In form II as shown in Figure 3b, the directions of hydrogen-bonding chains become "right, right, right, left, left, left," and so on. In form III, the directions change to "right, right, left, right, right, left," and so on. And in form IV, the repeating pattern is "left, left, left, right, left, right, right, right, left, and right." In the monohydrate, 2-MPNA is zwitterionic with complete acidic proton (H17) transfer to the pyridinyl N1. The molecules form a one-dimensional chain based on a C(6) NH···O hydrogen bonding motif. Two water molecules act as linkers hydrogen-bonding pairs of molecules from adjacent chains *via* the two carboxyl O atoms, forming an $R_4^2(8)$ hydrogen bonding motif leading to one-dimensional columns along the *a* axis of the crystal structure (Figure 3e). There also exists a $D_3^3(11)$ and a D(2) hydrogen-bond motif. In the salt form, the pyridinyl N1 is protonated, and the common one-dimensional chains as seen in structures I−IV are replaced with ones along the *b* axis in which 2-MPNA molecules are hydrogen bonded by Cl *via* pyridinyl -NH and carboxyl -OH (Figure 3f).

To conclude, four polymorphs, one monohydrate, and one salt of 2-MPNA have been crystallized from solution under different conditions. The system demonstrates a large number of crystallographically independent enantiomeric conformers with varying yet similar torsion angles as shown in Table 2. Despite the similar yet different conformations, the polymorphism of the system stems from the packing of molecules and, particularly, the directionality of hydrogen-bonding chains. The one-dimensional chains stack themselves in a similar fashion in the four anhydrate forms; even the crystallographic data of the forms II and III (Table 1) may ostensibly suggest a possibility of being the same crystal system due to their similar lattice parameters (the *a* and *b* in form II are close to the *c* and *b* in form III, respectively, and the *c* in form II is almost twice as long as the *a* in form III. Also see the simulated powder X-ray diffraction patterns in Supporting Information). Nonetheless, as illustrated in Figure 3, it is truly the alternating patterns of the directionalities of hydrogen-bonding chains that govern the polymorphism. How the growth condition regulates the tessellation of hydrogen-bonding chains as well as the molecular conformation deserves further investigation.

Acknowledgment. T.L. and S.L. are grateful to NSF for the financial support of this study (DMR-0449633).

Supporting Information Available: Experimental details of synthesis and characterization of 2-MPNA (including powder X-ray diffraction and differential scanning calorimetry), crystal growth, crystal structure determination, and conformational search; crystal structures of the four polymorphs, monohydrate, and salt in the form of the Crystallographic Information File (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) McCrone, W. C. In *Physics and Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds. Interscience Publishers: New York, 1965; Vol. 2, pp 725−767.
(2) Allen, F. H. *Acta Crystallogr. B* **2002**, *58*, 380–388.
(3) Brittain, H. G., Ed. *Polymorphism in Pharmaceutical Solids*; Marcel Dekker: New York, 1999.
(4) Byrn, S. R.; Pfeiffer, R. R.; Stowell, J. G. *Solid State Chemistry of Drugs*, 2nd ed.; SSCI, Inc.: West Lafayette, IN, 1999.
(5) Bernstein, J. *Polymorphism in Molecular Crystals*; Clarendon Press: Oxford, UK, 2002.
(6) Hilfiker, R., Ed. *Polymorphism: in the Pharmaceutical Industry*; Wiley-VCH: Weinheim, 2006.
(7) Murthy, H. M. K.; Bhat, T. N.; Vijayan, M. *Acta Crystallogr. B* **1982**, *38*, 315–317.
(8) Takasuka, M.; Nakai, H.; Shiro, M. *J. Chem. Soc. Perk. Trans. 2* **1982**, 1061–1067.
(9) Andersen, K. V.; Larsen, S.; Alhede, B.; Gelting, N.; Buchardt, O. *J. Chem. Soc. Perk. Trans. 2* **1989**, 1443–1447.
(10) Chen, S.; Guzei, I. A.; Yu, L. *J. Am. Chem. Soc.* **2005**, *127*, 9881–9885.
(11) Nangia, A. Acc. Chem. Res. 2008, *41*, ASAP.
(12) Steed, J. W. *CrystEngComm* **2003**, *5*, 169–179.
(13) The refcodes of 20 organics are FEXCAN, OPDDTE01, ZZZONS, WIMTOB, WODCOH, ABUDAD02, GEKLOX01, GENLAN, GENLAN01, HEYHUO02, LANXOO02, LEZQUD, QAJDAG, TRIMES10, BIPCOS01, CHOEST01, CHOLES03, PUBMUU21, HUGDOC, BEWZEI; the refcodes of 10 organometallics are GAVPEY, ASAPEP, QQQGGJ, NABUOX, LANBOS, NIKZUC, PUTKOE, HUVLAL, IDOSID, TMESNH.
(14) Hagler, A. T.; Dauber, P.; Lifson, S. *J. Am. Chem. Soc.* **1979**, *101*, 5131–5141.
(15) Beyer, T.; Price, S. L. *J. Phys. Chem. B* **2000**, *104*, 2647–2655.
(16) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.
(17) Etter, M. C.; Macdonald, J. C.; Bernstein, J. *Acta Crystallogr. B* **1990**, *46*, 256–262.
(18) Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1555–1573.
(19) Grell, J.; Bernstein, J.; Tinhofer, G. *Acta Crystallogr. B.* **1999**, *55*, 1030–1043.

CG800339H