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Conformational Polymorphism in a Non-steroidal Anti-inflammatory Drug, Mefenamic Acid

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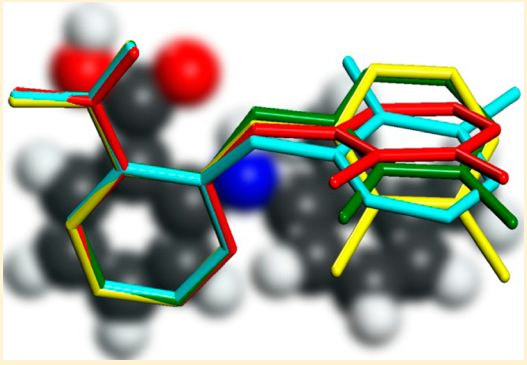
Supporting Information

ABSTRACT: For several years, the non-steroidal anti-inflammatory drug mefenamic acid, **MA**, has been known to exist as dimorphs (**I** and **II**). We report a new metastable polymorph (**III**) of **MA** obtained during attempted co-crystallization experiments and establish its stability relationship with existing forms. At elevated temperatures **I** and **III** convert to **II**, as evident from DSC experiments. On the basis of the lattice energy calculations in conjunction with thermal analysis, the stability order is proposed to be **I** > **II** > **III** at ambient conditions, whereas at elevated temperature the order is **II** > **I** > **III**. In either condition **III** is a metastable form and hence transforms to **I** at ambient conditions and to **II** at higher temperatures. Also we report the structural studies of a DMF solvate and a cytosine complex.



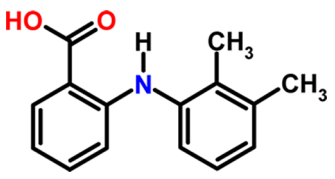
INTRODUCTION

Polymorphism in active pharmaceutical ingredients (APIs) is of topical interest from both the academic and industrial viewpoints. However, a lacuna in the understanding of the mechanism of nucleation and crystal growth at the molecular level makes the control of polymorphic forms a target still to achieve. Consequently, most of the observations on polymorphs are serendipitous and the studies are heuristic in nature. In recent times a wide variety of methods have been employed to control polymorphic behavior in compounds; these include the use of tailor-made additives, heterogeneous crystallization, and epitaxial growth on self-assembled monolayers.[1] Additive-induced crystallization has been adopted since the early days of crystal engineering to control the growth rate, size, and shape of crystals. The research groups of Leiserowitz, Meir Lahav, and a few other pioneers made significant contributions in employing tailor-made additives/selective auxiliaries to control crystal growth and thereby to obtain crystals with definite size and morphology.[2] Such additives are proposed to lessen the free energy barrier to nucleation through favorable interactions between the substrate and prenucleation aggregate and hence provide a strategy to obtain the new forms, otherwise not possible.[3] However, due to the lack of systematic attempts and theoretical backing, such studies are essentially of serendipitous nature.

Co-crystallization provides a potent and promising approach to alter properties such as hydration, tabletability, solubility, and bioavailability of pharmaceuticals.[4] Though considered initially as a remedy to reduce the occurrence of polymorphism, co-crystallization can in fact induce generation of novel polymorphic forms.[5] One of the most debated observations in the recent history of pharmaceutical polymorphism was the discovery of the second form of aspirin, obtained serendipitously by co-crystallizing aspirin with levetiracetam from hot acetonitrile or in the presence of a molar equivalent of acetamide.[6] In a yet another example, Caira et al. reported new polymorphs of nicotinamide and isonicotinamide obtained from their attempted co-crystallization of these coformers with the antitubercular API, isoxyl.[7] Thus, co-crystallization offer an important, though not thoroughly explored, strategy to obtain new solid state forms of pharmaceutically important molecules that cannot be obtained otherwise.

Diarylamines, such as mefenamic acid, tolfenamic acid, flufenamic acid, meclofenamic acid, and diclofenac, are well-known non-steroidal anti-inflammatory drugs (NSAIDs), and many of them exhibit polymorphism.[8] Mefenamic acid (2-(2,3-dimethylphenyl)aminobenzoic acid, **MA**) is a potent prostaglandin synthetase inhibitor, commonly used as an analgesic–antipyretic agent (Scheme 1).[9] As per the Biopharmaceutics Classification System (BCS), **MA** belongs to Class II type with low solubility and high permeability. Its poor solubility in water restricts its utility in clinical trials. The higher hydrophobicity and tendency to stick to surfaces impel problems during

Scheme 1. Mefenamic Acid, MA



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granulation and tabletting.[10] Consequently, quite a lot of efforts have been made to modify the compositions and to achieve higher solubility and enhanced bioavailability. The studies on the inclusion complex with cyclodextrin and cobalt(II) complexes in the presence/absence of various N-heterocycles revealed the possibility of alternate approaches to enhance the stability, solubility, and binding propensity of **MA**.[11] For several years, **MA** has been known to exist as dimorphs (**I** and **II**). The crystal structure of **I**, crystallizing from the majority of solvents, was reported in 1976.[12] Although there exist some mentions about the 3D coordinates of **II** in the literature, no such information is available in Cambridge Structural Database (CSD).[16,17] In this article, we report the metastable polymorph, **III**, and the structural studies of **II**, together with a DMF solvate and a molecular complex with cytosine.

EXPERIMENTAL SECTION

The chemicals were purchased from Sigma-Aldrich and used without further purification. The solvents used for crystallization were of analytical grade.

Crystal Preparation. The polymorph **II** and the **MA**-DMF solvate, **4**, were obtained by the slow evaporation of, respectively, $CHCl_3$ (chloroform) and DMF (*N*,*N*-dimethylformamide) solutions. Co-crystallization experiments with adenine in a 1:1 DMF/methanol mixture followed by slow evaporation at room temperature yielded the metastable form **III**. A reaction with cytosine as a coformer yielded the corresponding molecular complex, **5**.

Single Crystal X-ray Diffraction. Single crystals were chosen carefully using an Olympus microscope supported by a rotatable polarizing stage. Single crystal diffraction data for the compounds were collected on an Oxford single-crystal X-ray diffractometer (Micro-source: Mova; Detector: Eos) with a four-circle κ goniometer employing a graphite-monochromatized Mo Kα (λ = 0.71073 Å) radiation. The diffraction intensities were corrected for Lorentz and polarization effects. The data were reduced using CrysAlisRED (programs available with the diffractometer), and an analytical absorption correction (after Clark and Reid) was applied.[13] Structure solution and refinements were performed using SHELX97 using the WinGX suite.[14] The ORTEPs are provided in the Supporting Information (Supplementary Figure S1).

Powder X-ray Diffraction. The phase purity of the bulk sample was evaluated by comparing the experimental PXRD pattern with the simulated one. X-ray powder diffraction data were collected on a Philips X'pert Pro X-ray powder diffractometer equipped with X'cellerator detector. The scan range, step size, and time per step were 2θ = 5° to 30°, 0.02°, and 25 s, respectively.

Thermal Analysis. DSC/TG experiments were carried out using a Mettler Toledo TG/DSC-1 thermal analyzer, with a heating rate of 5 °C/min in the range of 35−250 °C, under N_2 atmosphere.

RESULTS AND DISCUSSION

Polymorphs of Mefenamic Acid. Attempted co-crystallization of **MA** with adenine from a DMF/methanol mixture at ambient conditions led to the serendipitous observation of the third polymorph, **III**. The block-like crystals of **III** were obtained concomitantly with the crystals of adenine trihydrate and the DMF solvate of **MA**. The polymorph **III** crystallizes in the triclinic space group, $P\bar{1}$, with a molecule in the asymmetric unit. The symmetric O−H···O (1.66 Å) hydrogen bonded acid dimer is further stabilized through numerous C−H···π and π···π interactions (Figure 1a). Notably, the crystals obtained from DMF or a 1:1 DMF/methanol turned out to be of **I** and the DMF solvate. Accordingly, it can be inferred that the presence of adenine plays an imperative role in the crystallization of **III**.

Form **II** is generally prepared either by heating crystals of **I** above the transition temperature (165−175 °C) or by the rapid

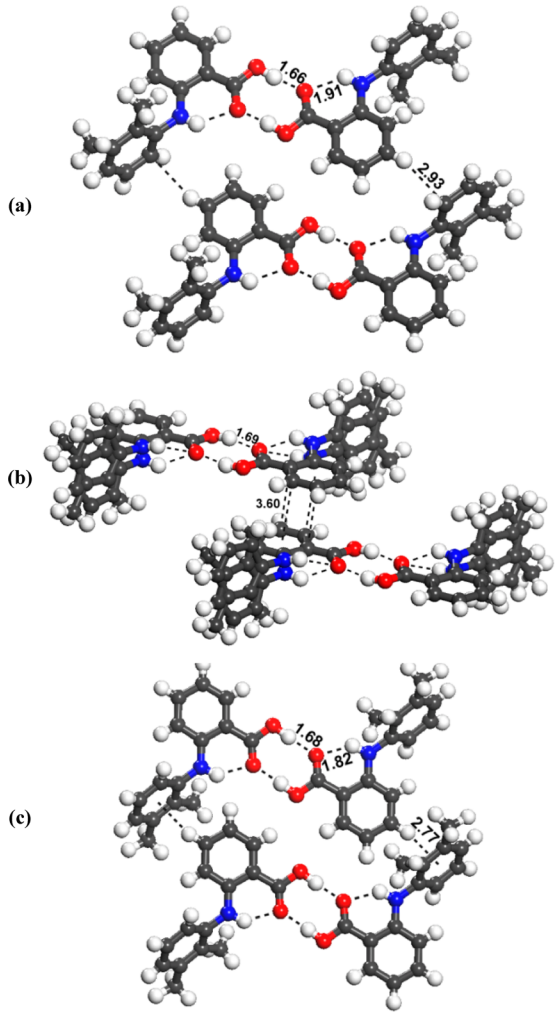

Figure 1. Intermolecular interactions in (a) **III**, (b) **II**, and (c) **I**.

cooling of a supersaturated solution of **MA** in DMF.[15,20b] Nevertheless, none of the aforementioned routes could yield crystals suitable for single crystal diffraction studies. Lee and co-workers reported an additive-induced method, using structurally similar flufenamic acid in ethanol, to obtain the crystals of **II**.[16] Besides, there were reports on the preparation of the polymorphs of **MA** using certain functionalized metallic islands as individual templates to prepare the polymorphs of **MA**.[17] However, owing to the lack of a reliable crystal data for **II**, we performed a large number of crystallizations to explore an alternate pathway to obtain single crystals of **II** by adopting different crystallization conditions and employing numerous solvents or solvent mixtures. The solubility of **MA** being less in the majority of the solvents, the crystallization experiments generally yield **I**. Conversely, slow evaporation of a chloroform solution in a less humid condition yielded single crystals of **II**. In the crystal, the imino bridge and the alkylated phenyl ring are disordered with a population distribution of 55:45. Since the disorder remains even at low temperature (100 K), it could be of static nature. Akin to **III**, carobxylic acid makes symmetric dimers that are further stabilized through various C−H···π and π···π interactions (Figure 1b). The structural features of **I** is comparable to those of **II** and **III**. The phenyl ring with the carboyxylic acid functionality and the imino bridge is coplanar, brought about by a strong intramolecular N−H···O hydrogen bond (H···O, 1.82 Å). The **MA** molecules make symmetric

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dimers, and the adjacent dimers are linked through C−H···π (2.77 Å) interactions involving aromatic C−H and the alkylated phenyl ring (Figure 1c).

Mefanic Acid-DMF Solvate, 4. One molecule each of **MA** and DMF constitute the asymmetric unit and the molecules form asymmetric dimers through O−H···O and C−H···O hydrogen bonds (H···O, 1.62 and 2.41 Å, respectively) (Figure 2; Supplementary Table S1). In three dimensions the molecular

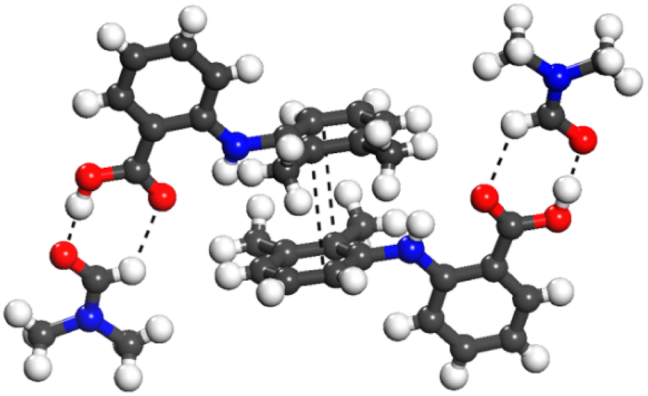

Figure 2. Interactions in the solvate, **4**.

units make a close packed structure, stabilized through several C−H···π and π···π interactions. Upon removing from the mother liquor the crystals effloresce rapidly to yield **I**, as is evident from a PXRD analysis (Supplementary Figure S4).

Mefenamic Acid-Cytosine Complex, 5. Crystallization of **MA** with cytosine from a DMF/methanol mixture yielded a 1:2 molecular complex, **5**, along with the crystals of **4**. The carboxylic acid of **MA** is deprotonated, while one of the cytosine units is protonated. Symmetry-independent cytosine molecules form dimers through N−H···O/N^+−H···N interactions (H···O, 1.74 and H···N, 1.84 Å, respectively), which extends as a molecular tape, as shown in Figure 3a. The carboxylate functionality of **MA** make N−H···O^- (H···O^-, 1.59 Å) interactions with the adjacent tapes and hence act as clips that bind the tapes (Figure 3b).

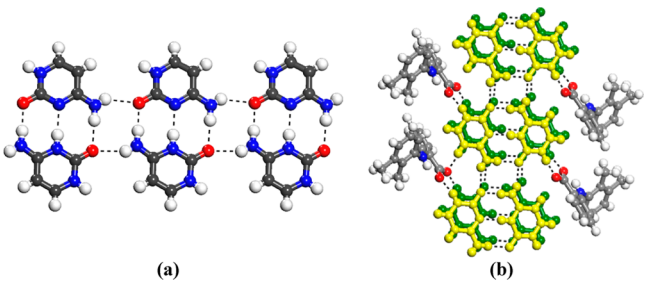

Figure 3. Crystal structure of **5**. (a) Cytosine tapes. (b) Interactions between cytosine and acid units.

All three polymorphs (**I**−**III**) of **MA** crystallize in the triclinic space group ($P\bar{1}$) with a molecule in the asymmetric unit (Table 1); such an observation is relatively rare, wherein all the polymorphic forms consist of $Z' = 1$. The simulated PXRD patterns of the polymorphs are given in Figure 4. Although the polymorphs exhibit significant variations in the unit cell dimensions, the hydrogen bonds in the polymorphs are comparable; the carboxylic acid makes a symmetric O−H···O synthon, and additional C−H···π and π···π interactions complement the structure formation.

Analysis of Torsion Angles. The polymorphic forms exhibit major differences in the torsion angles, as evident from an overlay of the molecules (Figure 5a). The conformational polymorphism in **MA** is determined by three torsion angles (Figure 5b): twisting of the carboxylic group with respect to the axis $\tau_1(O_{72}-C_7-C_1-C_2)$, rotation of the phenyl ring along the axis $\tau_2(C_1-C_2-N_2-C_8)$, and flipping of the 2,3-dimethylphenyl ring along the axis $\tau_3(C_2-N_2-C_8-C_9)$. The observed torsional shift is tabulated in Table 2. While the crystal forms exhibit comparable values for τ_1 and τ_2, the conformational variation is dictated by τ_3. Though the intramolecular N−H···O interaction restricts the free rotation of the carboxylic acid containing aromatic ring, one can anticipate that the presence of an imino bridge makes the rotation of the dimethyl-substituted phenyl ring energetically less demanding.

Thermal Analysis and Phase Stability. In order to obtain an understanding of the relative stability relationships between different solid phases of **MA**, thermal analyses (both DSC and TG) were carried out. As known from the earlier studies, **I** exhibit an endothermic peak in the temperature range of 178−180 °C that corresponds to the enantiotropic phase transition to **II**.[15a,18] The melting endotherm is observed with an onset temperature of 229 °C (Figure 6b). Similar characteristic endothermic phase transition is observed for **III**, in the temperature range of 175−178 °C followed by a melting endotherm at 227 °C. However, no such events are observed for **II**, prior to the melting (onset temperature: 229 °C). At high temperature **I** and **III** convert to **II**. However, at ambient conditions, over a period of time, **II** and **III** revert to **I**. Thus, while **II** is stable at elevated temperature, **I** is the stable form at ambient conditions. Slurry experiments at ambient conditions also corroborate the stable nature of **I**. Under ambient conditions no transformation relating **II** and **III** is observed. Though **II** was obtained from $CHCl_3$, solvent drop grinding of **MA** with $CHCl_3$ or crystallization in humid conditions yielded only **I**, as evident from PXRD analysis (Supplementary Figure S2).

Better solubility of **MA** in $CHCl_3$ provides an opportunity to the molecules to assemble/reassemble to yield the high temperature form **II**; however, in humid conditions the experiments preferentially yielded **I**. Thus, it may be assumed that under humid conditions the rate of transformation of **II** → **I** could be higher than the rate of formation of **II**, making it difficult to obtain **II**. Thermogravimetry together with PXRD analysis of **4** confirms the desolvation, with onset at 45 °C, followed by its transformation to **I** (Supplementary Figures S3 and S4).

Lattice Energy Calculations. Lattice energy of **I** and **III** were calculated using the Forcite module of Material Studio 4.4 with COMPASS27 force field.[19] **I** and **III** are energetically close; **III** being less stable by 0.56 kcal/mol. The disorder in **II** restricts from obtaining a reliable quantity for the lattice energy. However, calculation of the crystal lattice energies based on the sublimation and solution calorimetric experiments, **II** is apparently more stable than **I**.[20] Thus, as per the lattice energy calculation, the stability of the polymorphic forms are in the order **II** > **I** > **III**. This observed order of stability can be correlated with the conformational energy.[21] Among the three, the conformational arrangement of **III** is the least stable, with 8.867 kJ/mol less stable, as compared to **I**. For **II**, two different orientations are possible due to the disorder and the

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Table 1. Crystallographic Information of Various Solid-State Forms of MA

	I[a]	II	III	4	5
formula	$C_{15}H_{15}NO_2$	$C_{15}H_{15}NO_2$	$C_{15}H_{15}NO_2$	$C_{15}H_{15}NO_2$, C_3H_7NO	$C_{15}H_{14}NO_2$, $(C_4H_6N_3O)$ $(C_4H_5N_3O)$
CCDC no.		848899	846433	848900	848901
formula wt	241.28	241.28	241.28	314.38	463.50
crystal system	triclinic	triclinic	triclinic	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	14.556	7.7584(5)	7.723(2)	7.4730(10)	6.966(5)
b(Å)	6.811	9.2772(6)	7.9340(10)	9.559(2)	7.321(5)
c (Å)	7.657	9.3991(4)	11.2320(10)	13.306(2)	23.801(9)
α (deg)	119.57	106.308(5)	83.590(10)	105.070(3)	86.950(9)
β (deg)	103.93	91.847(4)	80.940(10)	103.780(3)	83.940(8)
γ (deg)	91.3	101.856(5)	67.510(10)	103.410(3)	67.850(8)
V (Å^3)	631.766	632.52(6)	626.96(19)	846.5(2)	1117.8(12)
Z	2	2	2	2	2
D_{calc} (g cm^{-3})		1.267	1.278	1.233	1.377
T (K)		298(2)	298(2)	298(2)	298(2)
μ (mm-1)		0.084	0.085	0.084	0.098
2θ range (deg)		50.48	50.48	49.98	50.50
total reflns		12155	12135	8036	9014
unique reflns, R_{int}		2294	2287	2969	4017
reflns used		1942	1460	1990	2892
no. of parameters		250	169	220	333
GOF on F^2		1.162	1.037	1.005	1.146
final $R1$, $wR2$		0.089, 0.302	0.042, 0.109	0.045, 0.124	0.072, 0.149

[a]Literature values for **I** (Refcode XYANAC).

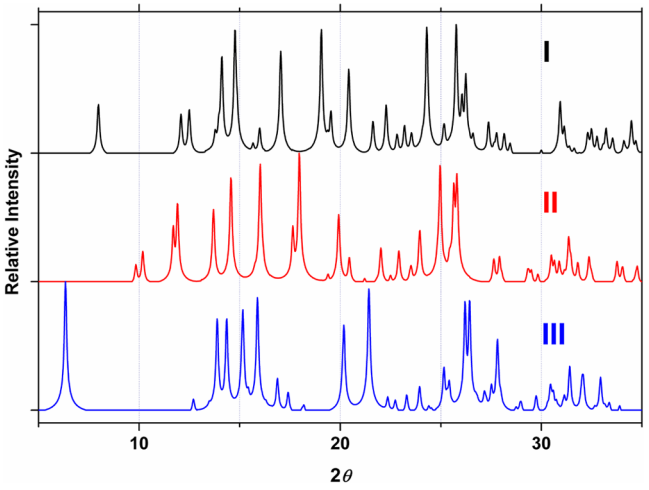

Figure 4. PXRD patterns (simulated) of the polymorphs of **MA**.

stabilization energy is intermediate to **I** and **III**. The conformational energy is provided in Table 3.

Table 2. Torsion Angle Values (deg) of Various Forms of MA

			II		
angle		I	a[a]	b[a]	III
τ_1	$\angle O_{72}-C_7-C_1-C_2$	178.60	−177.43	−177.43	−177.38
τ_2	$\angle C_1-C_2-N_2-C_8$	−179.34	176.32	−179.57	−179.55
τ_3	$\angle C_2-N_2-C_8-C_9$	−119.99	68.20	−81.03	−80.82

[a]**MA** molecules of **II** with (a) 55% occupancy and (b) 45% occupancy.

Polymorph **II** is known to exhibit higher solubility than **I** in several solvents and hence preferable for pharmaceutical formulations.[20a,22] However, our results together with some earlier reports confirm that **II** is metastable at ambient conditions and transforms to **I**. The rate of transformation is sensitive to relative humidity (RH) and the solvent systems (faster in the least polar mixtures).[23] This metastable nature negates the utility of **II** in pharmaceutical formulations. The present study, through the crystallization in different solvents, solvent drop grinding and slurry experiments, confirms that at ambient conditions the order of stability is **I** > **II** > **III**. At

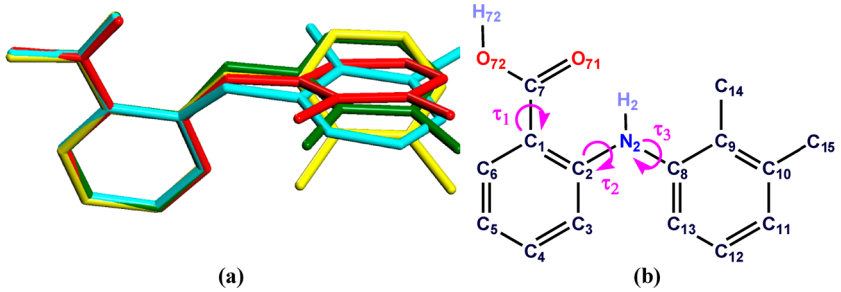

Figure 5. (a) Overlay of the molecules of **I** (red), **II** (55% occupancy, blue; 45% occupancy, green), and **III** (yellow). (b) Numbering scheme used for the analysis of torsion angles.

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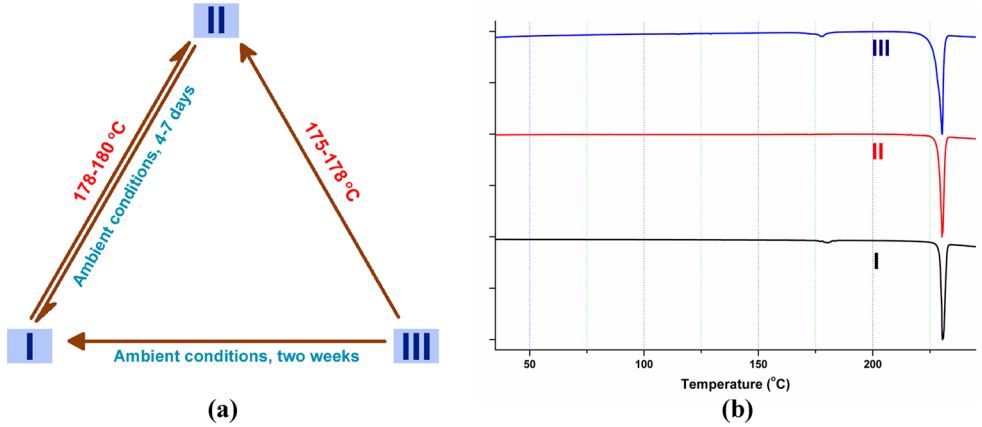

Figure 6. Polymorphs of **MA**: (a) phase transformation and (b) DSC plots.

Table 3. Conformational Energies of I–III

	hartree	kcal/mol	kJ/mol
I	−786.0826765	0	0
II[a]	−786.0810805	1.001	4.192
II[b]	−786.0793395	2.094	8.761
III	−786.0792989	2.119	8.867

[a]**MA** molecules of **II** with 55% occupancy. [b]**MA** molecules of **II** with 45% occupancy.

higher temperatures through enantiotropic transformation, the order is changed to **II** > **I** > **III**. In either conditions **III** is a metastable form and hence transform to **I** at ambient conditions whereas to **II** at higher temperatures.

Hirshfeld Surface Analysis. Hirshfeld surface (HS) analysis allows the fast identification of the shortest intermolecular contacts and subsequently their quantification.[24] Hirshfeld surfaces and fingerprint plots (FP) were generated for the polymorphs and exhibited significant divergence confirming the distinction in the polymorphic forms. In all of the three forms the types of interactions available are similar, although their contribution to the structure stabilization varies. While the contribution of the carboxylic acid dimer in **III** is 14.7%, it is 12.9% and 14.9% for **I** and **II**, respectively. This O–H···O intermolecular interactions appear as a pair of sharp spikes of equal lengths in the 2D fingerprint plots. In all the forms, the contribution of the H···H contacts is higher than 50%. The flat regions of HS depict parts of the molecule involved in $\pi\cdots\pi$ stacking. The contribution of $\pi\cdots\pi$ interactions in the stabilization of **II** and **III** is approximately 100% more as compared to **I**. This is consistent with the twisted conformation adopted by **I**, which can significantly hinder the possible $\pi\cdots\pi$ stacking. In **I** the angle between the two planar grouping (the ring containing carboxylic acid and 2,3-dimethylphenyl) is 62°, whereas for **II** and **III** it is almost perpendicular (80°). This angular shift (see Figure 7) is having profound influence in the nature of weak interactions (C–H···π and $\pi\cdots\pi$) present in these forms. In **I** there is fairly significant C–H···π contacts stabilizing the dimers, whereas in **II** and **III** such contacts are weaker. However the contribution from $\pi\cdots\pi$ interactions follow the opposite trend. To be precise, the percentage of C–H···π and $\pi\cdots\pi$ interactions are 25.4% and 2.1% in **I**; 21.18% and 5.04% in **II**; and 20.3% and 4.7% in **III**, respectively (Figure 8).

CONCLUSION

A new metastable polymorph (**III**) of mefanamic acid has been obtained during attempted co-crystallization experiments. Together with the structural studies, we established the stability relationship of **III** with respect to the existing polymorphs. Crystallization experiments in different solvents, solvent drop grinding, and slurry experiments confirm that at ambient conditions the order of stability is **I** > **II** > **III**. At higher temperatures, through enantiotropic transformation, the order is changed to **II** > **I** > **III**. In either condition **III** is a metastable form and hence transforms to **I** at ambient conditions and to **II** at higher temperatures. Thus it can be inferred that co-crystallization of an API with suitable coformers could lead to a new polymorph of either API or the coformer. Indeed, these occur serendipitously, though the methods could be considered for the generation of new polymorphic forms of a drug molecule. The induction of the polymorphic modification appears as a consequence of the well understood morphological control of crystallization; however, the specific control on the use of solvent combinations needs to be clearly worked out.

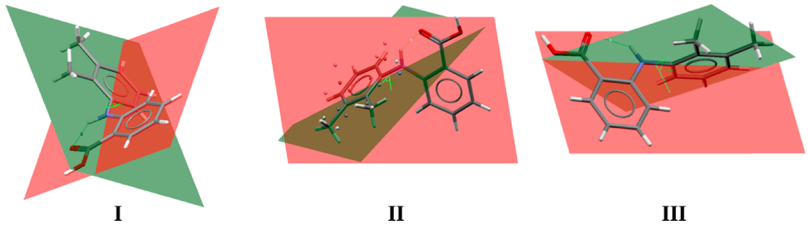

Figure 7. Angle between the planar grouping consisting of phenyl rings bearing the carboxyl group (red) and 2,3-dimethylphenyl group (green): **I** (62°); **II** (80°), and **III** (80°).

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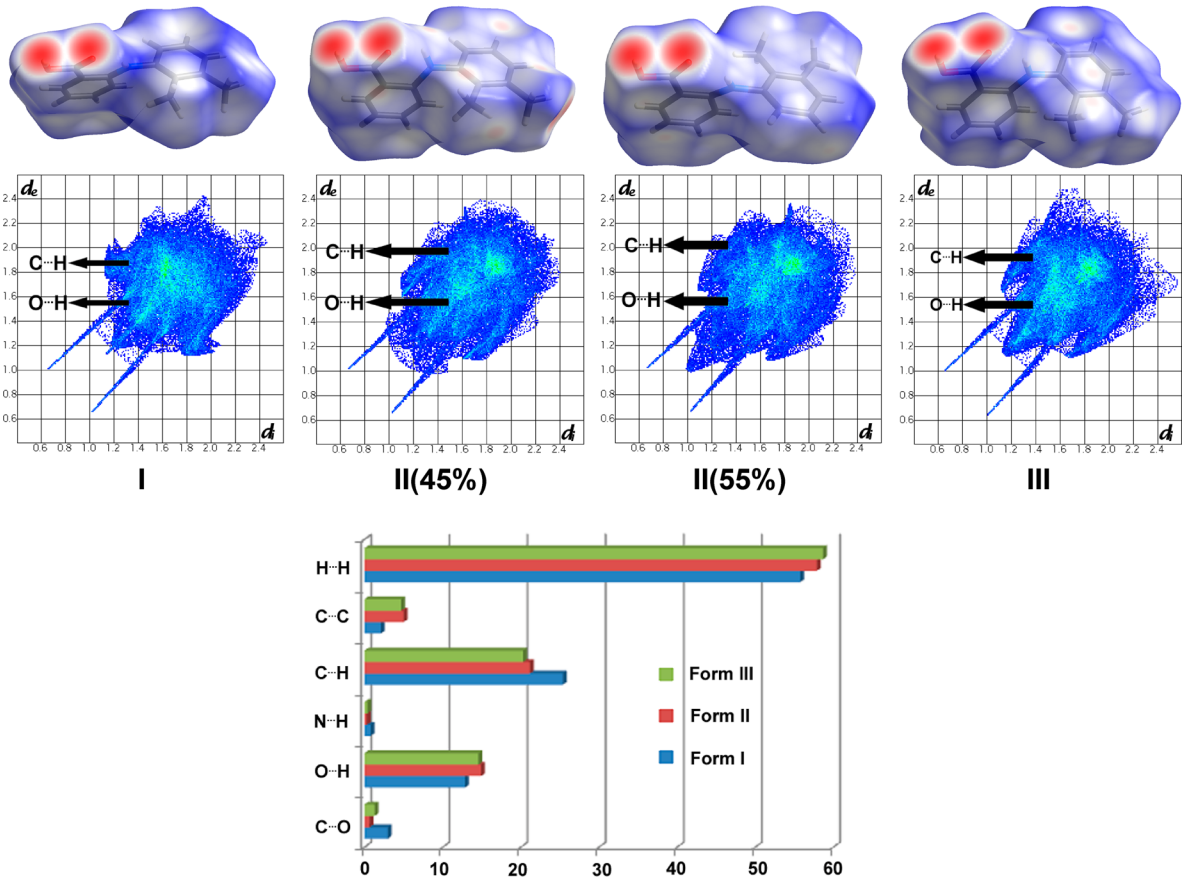

Figure 8. Hirshfeld surfaces, fingerprint plots (labels showing regions of important interactions), and contribution of interactions in the polymorphs of **MA**.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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