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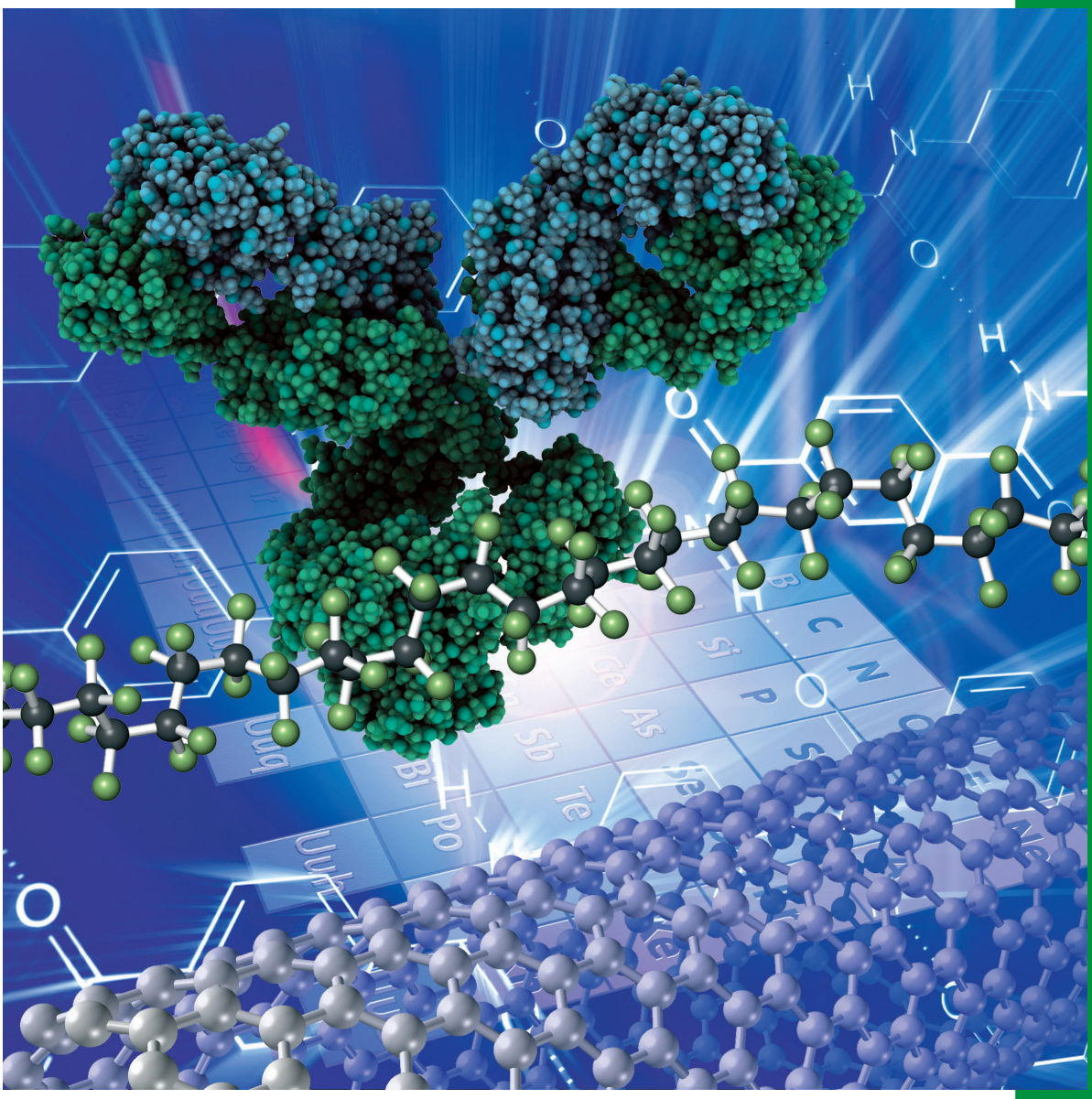

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WILEY-VCH

ChemPubSoc Europe

DOI: 10.1002/slct.201700947

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Organic & Supramolecular Chemistry

Strong Hydrogen Bond Leads to a Fifth Crystalline Form and Polymorphism of Clonixin

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Over 30 years since the discovery of four crystal forms (**I**, **II**, **III** and **IV**) of Clonixin [2-(3-chloro-2-methyl-phenylamino)-nicotinic acid], a fifth form, a dimethylformamide (DMF) solvate, has been obtained by crystal growth in DMF. The new form was characterized by single-crystal X-ray diffraction, FT-IR, and Raman spectroscopy. The crystal structure is stabilized by the strong hydrogen bond between the carboxylic acid OH and the DMF carbonyl whose strength is on par with those of the four solvent-free forms, which are based on either the acid-acid homosynthon or the acid-pyridine heterosynthon, depending on the dihedral angle between the two aromatic rings. This solvate loses DMF to convert into form **I**, as confirmed by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Other aspects of this polymorphic/solvatomorphic system were investigated both experimentally and theoretically. Theoretical studies such as lattice energy calculation, hydrogen-bond strength estimation and Hirshfeld analysis were performed, providing further insight into the polymorphism/solvatomorphism of this system. Based on the analysis of the new form and the whole system, more solvates/cocrystals could be designed and unveiled in due time.

Introduction

2-(2-Methyl-3-chloroanilino)nicotinic acid (Clonixin, a.k.a. CLX) (Figure 1) was initially investigated in a search for agents to treat inflammation in rheumatism, osteoporosis, collagen diseases, bursitis, and gout etc.[1] Later it was found to show beneficial anti-inflammatory and analgesic properties with a much smaller ulcerative effect than other non-steroidal anti-inflammatory drugs (NSAIDs).[2-6] It also exhibited platelet-inhibitory effects[7, 8] and recently it was found to be effective for the treatment of acute migraine.[9, 10] Due to its pharmaceutical stability and bioavailability issues, currently microemulsions[11] and clonixin lysinate are used in clinical formulations.[12]

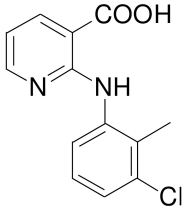

Figure 1. Structure of CLX.

CLX is a diarylamine with two aromatic rings (one pyridine, and the other benzene) bridged by a secondary amine. Conformational flexibility is to be expected, leading to the possibility that it could crystallize in multiple forms, *i.e.*, as conformational polymorphs. Indeed, polymorphism, *i.e.*, the existence of more than one crystal form, of CLX was reported in 1982 when Takasuma *et al.* described four forms (dubbed **I**-**IV**).[13] Nowadays, polymorphism is known to be widely observed in chemistry and it is of particular importance in pharmaceuticals since it may affect kinetic, thermodynamic, surface, mechanical, and packaging properties, and thus its clinical formulation and eventual bioavailability.[14] In the 1982 study, the authors investigated the hydrogen bonds and dihedral angle between the two aromatic rings in the four forms with IR, X-ray analysis and UV. Form **I** was found to be monoclinic, space group $P2_1/c$. The dihedral angle between the two aromatic rings is 70.8 (1)°, and the molecules are associated through the acid-pyridine heterosynthon.[15] Form **II** is orthorhombic, space group $Pca2_1$, with a dihedral angle of 40.2(4)°, and due to the proton transfer between the carboxylic acid and pyridine N, the molecules are connected through the $-COO^-$ and pyridinium NH. Both forms **III** and **IV** are triclinic,

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.201700947

space group $P\bar{1}$, but with different unit cell parameters and dihedral angles (**III**: 21.2(2)°, and **IV**: 1.7(1)°), and the molecules are connected through the acid-acid homosynthon.[15] The study represents a useful start, but is lacking many of the details required by modern standards. Later, theoretical studies were performed for this polymorphic system. In two studies, the geometry of CLX was studied in both gas phase and solid state.[16, 17] Another study investigated the conformational aspect of the polymorphism of CLX, and even predicted a new form for CLX.[18] Recently, Kumar and Nangia attempted to compare the solubility of neutral and zwitterionic forms in a variety of polymorphic systems and CLX was included since it has one zwitterionic polymorph. In the study, a combination of spectroscopic and spectrometric methods and theoretical approaches was applied to study the polymorphic system of CLX.[19]

Our lab has been studying the polymorphism of CLX and its analogs to understand the causative effects of their polymorphic behavior. We synthesized a series of CLX analogs and investigated their polymorphism both experimentally and theoretically. Some of the compounds, such as 2-PNA [2-(phenylamino)nicotinic acid] and 2-MPNA (2-[methyl(phenyl)amino]nicotinic acid) are highly polymorphic, with each showing at least four forms.[20, 21] These two systems together with other related systems[22, 23] seemed to indicate that 2-PNA falls into the category of polymorphophore which is a structural element that, when incorporated into a molecule, favors the formation of polymorphic crystal forms, as proposed by Matzger and Price.[24, 25] We also took a look at these systems from the aspect of synthon and realized the controlled formation of either the acid-acid homosynthon or the acid-pyridine heterosynthon.[26-29]

The carboxylic acid and pyridine functional groups on CLX are good hydrogen bond formers. Other than the well-known acid-acid homosynthon and acid-pyridine heterosynthon observed in CLX, it could also form hydrogen bonds with other compounds, forming solvates or cocrystals depending on the state (liquid or solid) of the chemical involved. Solvates and cocrystals of pharmaceuticals have been proven to be promising alternate formulating approaches.[14,30-36] In this study, we applied a variety of protic solvents (as both hydrogen bond donor and acceptor) and polar aprotic solvents (as hydrogen bond acceptor) prone for hydrogen bond formation for the crystal growth of CLX with the aim of obtaining potential solvates. Here we report the discovery and characterization of a fifth form of CLX, a DMF solvate, and relate investigation of this solvate to the polymorphic system of pure CLX, complimentary to the Nangia study. The new form was fully characterized by single-crystal X-ray diffraction, FT-IR, Raman spectroscopy, and its phase behavior was investigated by DSC, TGA, and PXRD. New observations about the polymorphic system were added to the existing data. Moreover, we also calculated the hydrogen bond strength of each form and the lattice energy for the solvent-free forms and performed Hirshfeld analysis for the polymorphic/solvatomorphic system. The insight gained from the computation should shed light on the formation of the fifth form as well as the relative stability of the polymorphs. The discovery of the new form could provide clues to the design of more solvates and cocrystals of CLX.

Results and Discussion

Crystal Structures

Four known polymorphic forms and a new solvated form (**I**, **II**, **III**, **IV**, and **S**) were obtained for CLX (Figure 2). Form **I** crystals were obtained as colorless blocks from methanol, water, DMSO and sometimes concomitantly with other forms from other solvents; form **II** crystals were grown as pale yellow needles from acetic acid, and sometimes concomitantly with other forms from ethyl acetate, ethanol, and acetonitrile; crystals of form **III** were harvested as light yellow plates from acetone and methanol, and sometimes concomitantly with other forms from ethanol, acetonitrile, ether and benzene; form **IV** grew as yellow rods from benzene and concomitantly with other forms from ethyl acetate, ethanol, dichloromethane; and **S** crystallized as colorless blocks from DMF. In the 1982 paper, the four solvent-free forms **I-IV** were grown from ethyl acetate, methanol, ethanol, and acetone, respectively. Our crystallization experiments, as well as those from Nangia, did not show solvent selectivity: the same solvent readily gave different (including concomitant) crystal forms. CLX gave similar UV-Vis curves in ethyl acetate, ethanol and methanol, indicating similar distribution of the various conformers (both twisted and planar), while the UV-Vis curve in acetone suggested the predominant conformers might be conformationally flat (Figure 3). The unit cell parameters are similar to the reported values except for a slight shortening in axis length due to the effect of thermal contraction. The solvate **S** is triclinic, space group $P\bar{1}$ ($Z = 2$). Crystallographic data of all the forms are listed in Table 1; for complete CIF files, see the Supporting Information. There is one formula unit in the asymmetric unit for each crystal form. These crystallographically independent molecules are conformers as suggested by the dihedral angle between the two aromatic rings in the molecules (68.22 (5)°, 40.00(5)°, 20.14(4)°, 0.40(6)°, 66.51(5)° for **I**, **II**, **III**, **IV** and **S**, respectively) (Table 2) and the superposition of the five molecules (Figure 4).

The molecule in the asymmetric unit of form **I** is highly twisted as suggested by the dihedral angle of 68.22 (5)° between the pyridine ring and the benzene ring. Due to the nonplanarity of the molecule, the crystals are colorless and the energetically more favorable hydrogen bond between the carboxylic acid and pyridine N is observed (C(6) in graph-set notation).[37, 38] This is in agreement with the general rule established in our recent study regarding the formation of either the acid-acid homosynthon or the acid-pyridine heterosynthon in 2-PNA analogs, *i.e.*, if the dihedral angle between the pyridine ring and the benzene ring is higher than 30°, the acid-pyridine heterosynthon will be observed, otherwise the acid-acid homosynthon will be formed.[29] The hydrogen bond parameters are 1.871 Å for the bond length and 173.61° for the bond angle. Other than the intermolecular hydrogen bonds, there is also an intramolecular hydrogen bond in each molecule

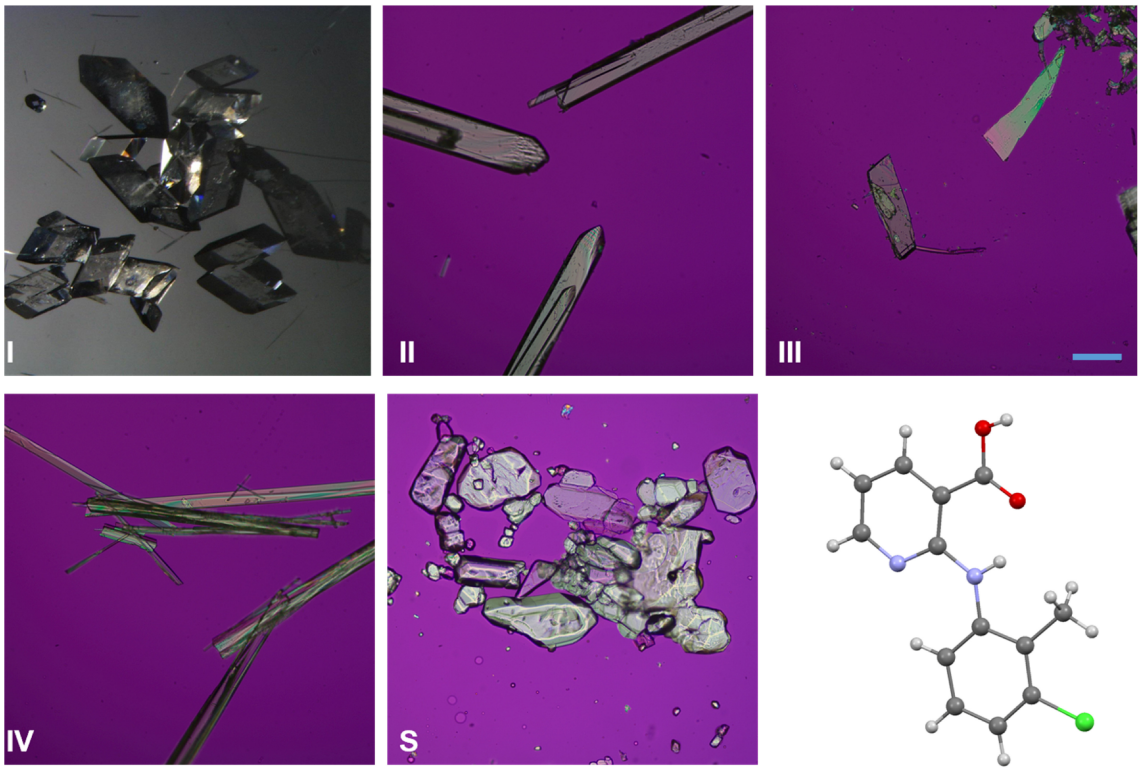

Figure 2. Crystals of the four anhydrates and one solvate of Clonixin. Scale bar 0.2 mm.

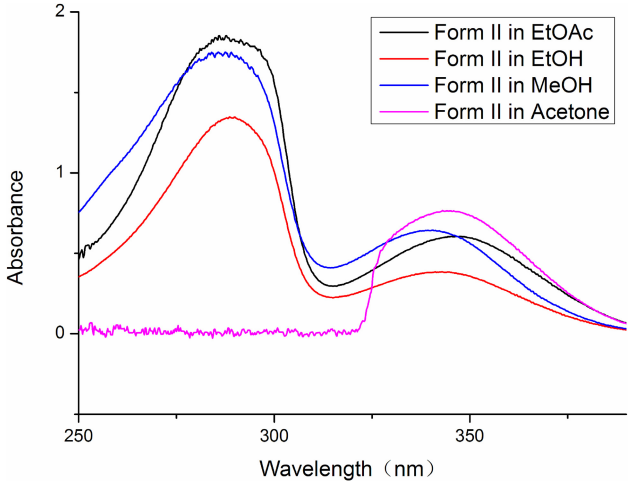

Figure 3. UV-Vis spectrum of Clonixin in different solvents.

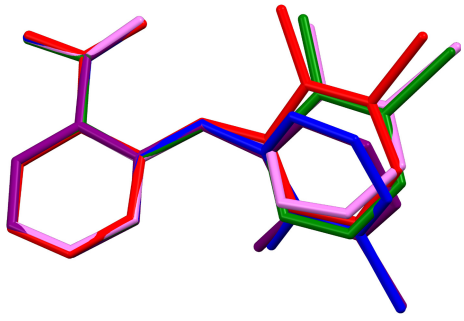

Figure 4. Superposition of five conformations in the asymmetric units of forms **I, II, III** and **IV**, and solvate (**I**, blue; **II**, red; **III**, green; **IV**, violet; and **S**, purple).

between the NH that bridges the two aromatic rings and the carbonyl O of the carboxylic acid (S6), with a bond length of 1.940 Å and bond angle of 135.29°(Figure 5). Different from the literature structure, disorder is observed for the aniline part, but the degree of disorder could be ignored since the minor portion is only 5.5%. It is possible that disorder was present in the literature structure, but not modeled due to the very low minor component fraction.

The molecule in the asymmetric unit of form **II** also has a twisted conformation, as the dihedral angle between the two aromatic rings is 40.00(5)°, which is above our previously established threshold of 30°. Moreover, the carboxylic acid H is transferred to the pyridine N, rendering the molecule zwitterionic. Accordingly, the molecules form one-dimensional chains based on the interaction between the carboxylate and pyridinium NH. The corresponding parameters are 1.908 Å for the bond length and 150.45° for the bond angle. The intramolecular hydrogen bonding between the carbonyl O of the carboxylate and the secondary N has slightly different parameters, 1.820 Å and 140.86° (Figure 5). Again, disorder exists on the methyl group on the benzene ring. But this is not reported

Table 1. Crystallographic data of four polymorphs and one solvate of Clonixin

	I	II	III	IV	S
formula	$C_{13}H_{11}ClN_2O_2$	$C_{13}H_{11}ClN_2O_2$	$C_{13}H_{11}ClN_2O_2$	$C_{13}H_{11}ClN_2O_2$	$C_{16}H_{18}ClN_3O_3$
formula weight	262.69	262.69	262.69	262.69	335.78
crystal size (mm)	0.20 x 0.20 x 0.12	0.25 x 0.25 x 0.05	0.32 x 0.18 x 0.13	0.25 x 0.20 x 0.10	0.30 x 0.20 x 0.10
crystal system	monoclinic	orthorhombic	triclinic	triclinic	triclinic
space group	$P2_1/c$	$Pca2(1)$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a/Å	7.4792(1)	23.5464(4)	3.7849(1)	7.1074(2)	8.4308(2)
b/Å	14.1615(2)	3.9351(1)	10.8927 (2)	7.6026(2)	9.1449(2)
c/Å	11.5824(2)	12.2358(2)	13.7953 (2)	10.7885(3)	11.1425(2)
α/°	90.00	90.00	94.4324(6)	78.5665(10)	103.6358(8)
β/°	101.5499(8)	90.00	95.2653(7)	80.1915(11)	93.1393(8)
γ/°	90.00	90.00	96.1085(6)	87.9426(11)	107.8451(9)
Z, Z'	4, 1	4, 1	2, 1	2,1	2,1
V/Å^3	1201.93(4)	1133.74 (4)	560.95 (2)	563.03 (3)	787.17(3)
D_{cal}/g·cm^{-3}	1.452	1.539	1.555	1.549	1.417
T/K	90.0 (2)	90.0 (2)	90.0 (2)	90.0 (2)	90(2)
abs coeff (mm^{-1})	0.312	0.331	0.335	0.333	0.262
F(000)	544	544	272	272	352
2θ range(deg)	2.30-27.50	1.73-27.50	1.49-27.49	1.95-27.47	1.90-27.49
limiting indices	$-9 \le h \le 9$	$-30 \le h \le 30$	$-4 \le k \le 4$	$-9 \le h \le 9$	$-10 \le h \le 10$
	$-18 \le k \le 18$	$-5 \le k \le 5$	$-14 \le l \le 14$	$-9 \le k \le 9$	$-11 \le k \le 11$
	$-15 \le l \le 15$	$-15 \le l \le 15$	$-17 \le l \le 17$	$-13 \le l \le 13$	$-14 \le l \le 14$
completeness to 2θ	99.9%	92.0%	99.9%	99.7%	99.9%
Unique reflections	2264	2401	2164	1805	2845
$R_1[I > 2\sigma(I)]$	4.60	2.91	3.40	4.42	4.02
wR_2 (all data)	0.1198	0.0712	0.0892	0.1113	0.1039

Table 2. Values of the dihedral angle of the molecules in crystal structures of all five forms. Unit: degree.

I	II	III	IV	S
68.22(5)	40.00(5)	20.14(4)	0.40(6)	66.51(5)

for the literature structure, and could be a result of low temperature.

For form **III**, the molecule is slightly twisted and the aforementioned dihedral angle is 20.14(4)°. Since the dihedral angle is less than 30°, not surprisingly the molecules are connected through the acid-acid homosynthon ($R_2^2(8)$). The hydrogen bond parameters are 1.807 Å and 174.22°. The intramolecular hydrogen bond has parameters of 1.958 Å and 139.20°(Figure 5).

Unlike the other molecule**s**, the molecule in the asymmetric unit of form **IV** is almost flat [dihedral angle 0.40(6)°]. As expected, the molecules pair up through the acid-acid homosynthon. The intramolecular hydrogen bond is persistent. The parameters of the hydrogen bond are 1.849 Å and 174.44° (intermolecular) and 1.926 Å and 140.39° (intramolecular) (Figure 5). In the reported structure (BIXGIY03), the carboxylic acid H is missing.

The CLX molecule in the solvate **S** is also highly twisted, as demonstrated by the dihedral angle of 66.51(5)°. Accordingly, the crystals are colorless, as in form **I**. Due to the presence of DMF, neither of the two synthons, *i.e.,* acid-acid homosynthon and acid-pyridine heterosynthon, is observed in the new crystal structure. Instead, the hydrogen bond is between the carboxylic OH and the carbonyl O of DMF (Figure 5). This hydrogen bond should be stronger than or at least on par with the other two types considering the shorter bond distance of 1.77 Å and the near linear alignment of the three atoms (178.22° bond angle) and intramolecular hydrogen bond has the following parameters: 1.955 Å and 134.36°. Other than the hydrogen bond, the short contact between Cl and carboxylic acid O likely provides additional stability for the crystal. Based on the role of DMF, *i.e.*, providing a strong hydrogen-bond acceptor, there is a good reason to believe similar compounds, particularly dimethylacetamide (DMA), could also form solvates or cocrystals (if the compound is solid) with CLX.

Thermal Properties

DSC was conducted to investigate the thermal properties of the five forms. For the solvent-free forms, our results match with those of Nangia and won't be discussed here. The DSC thermogram of the solvate is shown in Figure 6. It shows two main thermal events: the first one with an onset temperature of 46.5 °C and heat of fusion of 78.4 J/g corresponds to the loss of the solvent DMF and transformation into form **I**, and the second one with an onset temperature of 231.2 °C and heat of fusion of 81.0 J/g matches the melting of form **I**. The spikes on the DSC curve could be due to the accumulation of DMF since it is a solvent with high boiling point. The desolvation was also confirmed by the TGA study, as suggested by a weight loss of ~23.0% (theoretical value should be 21.8%) (*i.e.*, essentially 1:1 CLX:DMF) (Figure 7). In addition, the 1:1 ratio of DMF and CLX is also verified by a ^{1}H NMR study as indicated by the 1:1 ratio of the integers of CH_3 (chemical shift 2.32 ppm) from CLX and CH_3 (chemical shift 2.89 ppm and 2.73 ppm) from DMF (Supporting Information). The phase transition from the solvate

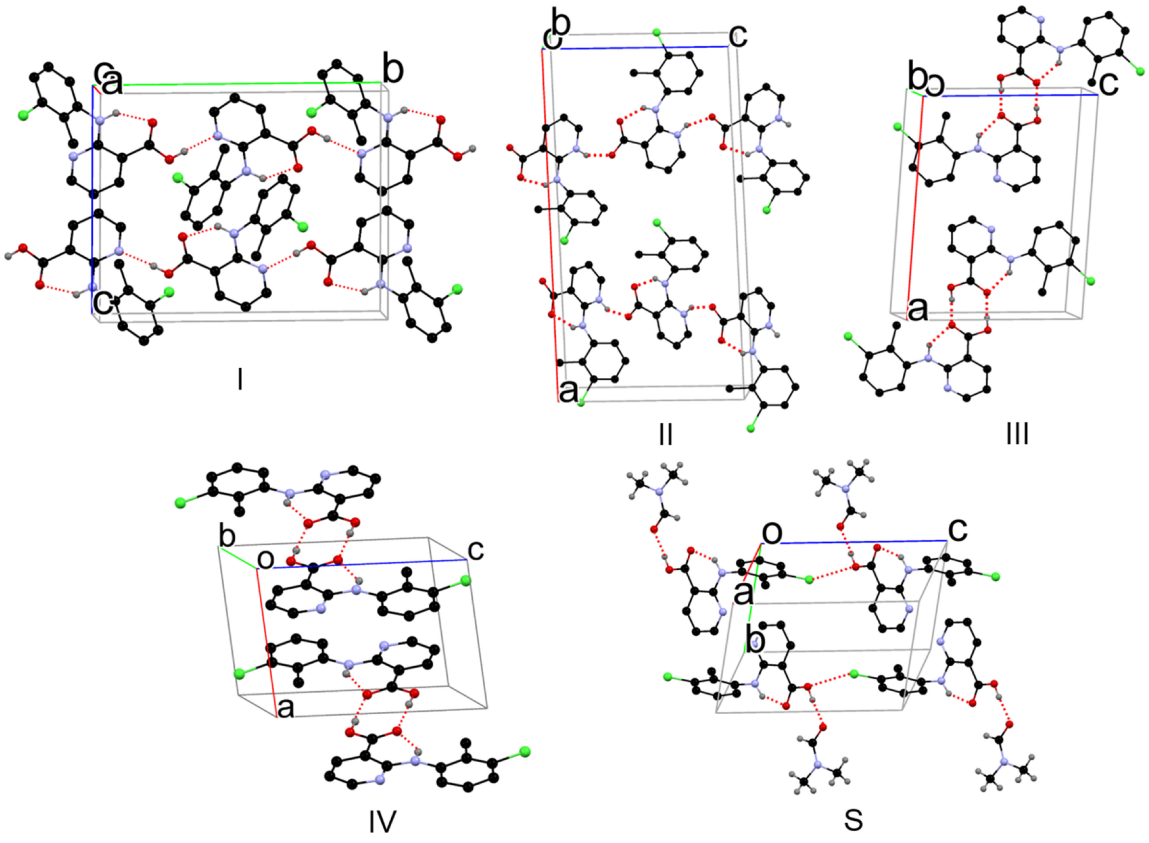

Figure 5. Crystal packing of anhydrates **I, II, III**, and **IV**; and solvate **S** (for clarity, hydrogens not involved in hydrogen bonding were omitted).

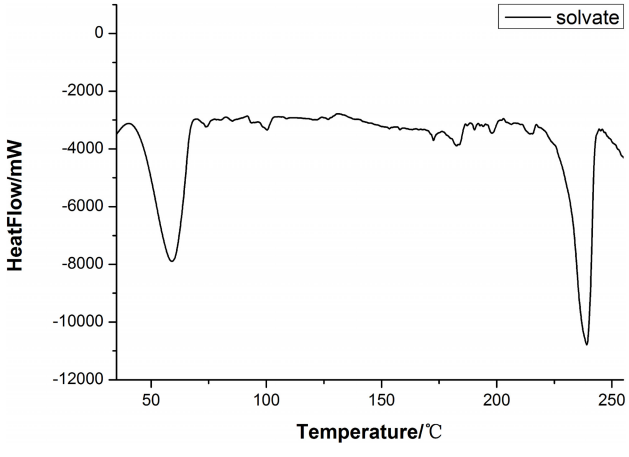

Figure 6. DSC thermogram of Clonixin solvate.

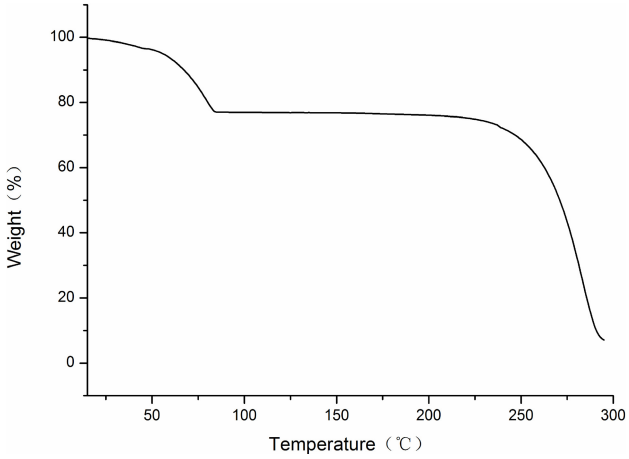

Figure 7. TGA thermogram of Clonixin solvate.

to form **I** is also confirmed by PXRD. When the solvate was heated to 60 °C for two hours, the resulting colorless sample showed a PXRD pattern matching that of form **I** (Figure 8).

The solid-solid phase transition from forms **II**, **III**, and **IV** to **I** was further studied under a hot-stage microscope. A solid-to-solid phase transition from form **II** single crystals to form **I** captured was presented as an example. As shown in Figure 9, single crystals of form **II** convert into form **I** at around 155 °C.

Phase transitions were also studied with the solvent drop grinding method.[39] When CLX form **II** was ground in MeOH alone or together with form **I**, no phase transition was observed (Figure 10). This is in agreement with the slurry experiment performed by Nangia & Kumar.[19] When form **III** was ground in MeOH, it converted into form **I** over time (Figure 10). Slurry experiment also confirmed the phase transition. When form **IV** was ground in MeOH alone, the phase transition into form **I**

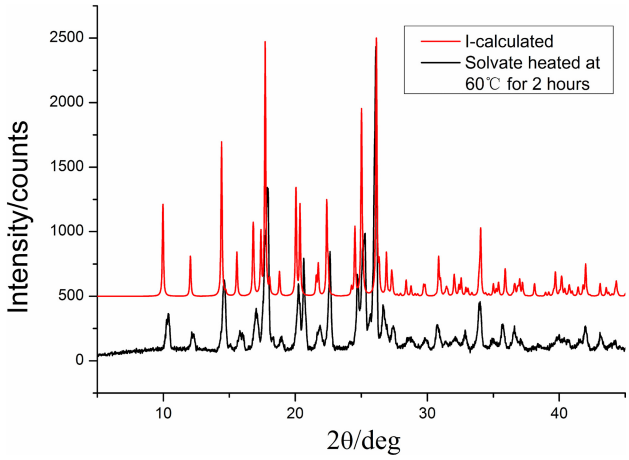

Figure 8. Phase transition from the solvate to form **I**.

was not obvious, but when forms **IV** and **I** were ground together in MeOH, the phase transition was immediately observed (Figure 10).

Figure 11 shows the powder X-ray diffraction pattern of the solvate collected at room temperature, along with PXRD patterns calculated from the single-crystal structure determined at 90 K as well as the calculated PXRD pattern of form **I**. It can be inferred that during the process of sample preparation, the solvate of CLX loses DMF and converts into form **I**. The experimental PXRD of the other forms are included in the supporting information.

FT-IR and Raman

Vibrational spectroscopy methods such as IR and Raman can provide structural information regarding polymorphs under investigation in a convenient manner. FT-IR and Raman spectra of the four solvent-free forms were collected by Nangia, *et al.* Here the spectra of CLX solvate were laid side-by-side with the corresponding literature spectra. The spectra of the solvate showed clear differences from the four solvent-free forms. The data are displayed in Figures S4 and S5 in the supporting information.

Computational Results

Lattice energy

For forms **I**, **II**, **III**, and **IV**, the calculated lattice energies based on the empirically augmented DFT method were -32.2, -28.9, -34.0 and -34.5 KCal mol^{-1}, respectively. The results suggest the stability order to be **IV** > **III** > **I** > **II** with form **IV** being the most stable, an observation at odds with the fact that forms **II**, **III**, and **IV** all convert into form **I** when heated. The same lattice energies were calculated with QE to be -34.8, -37.2, -35.7, and

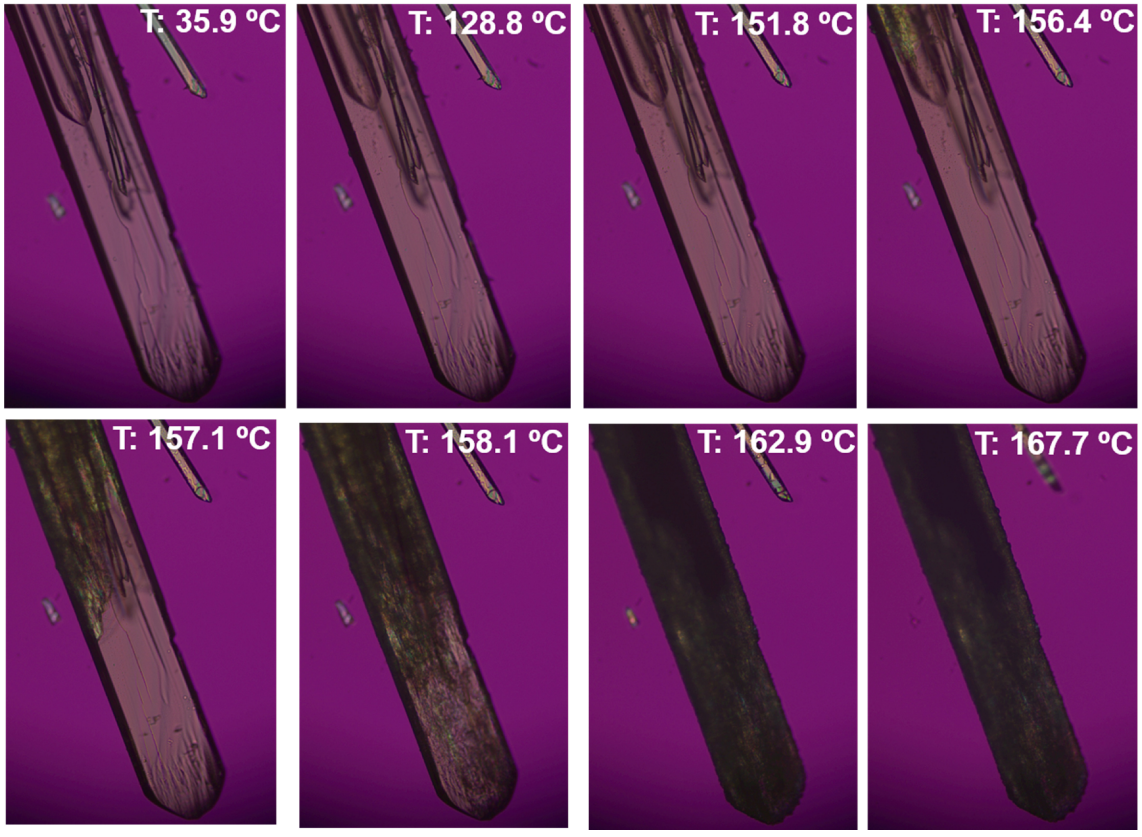

Figure 9. Solid-to-solid phase transition from form **II** to form **I** observed under hot-stage microscope.

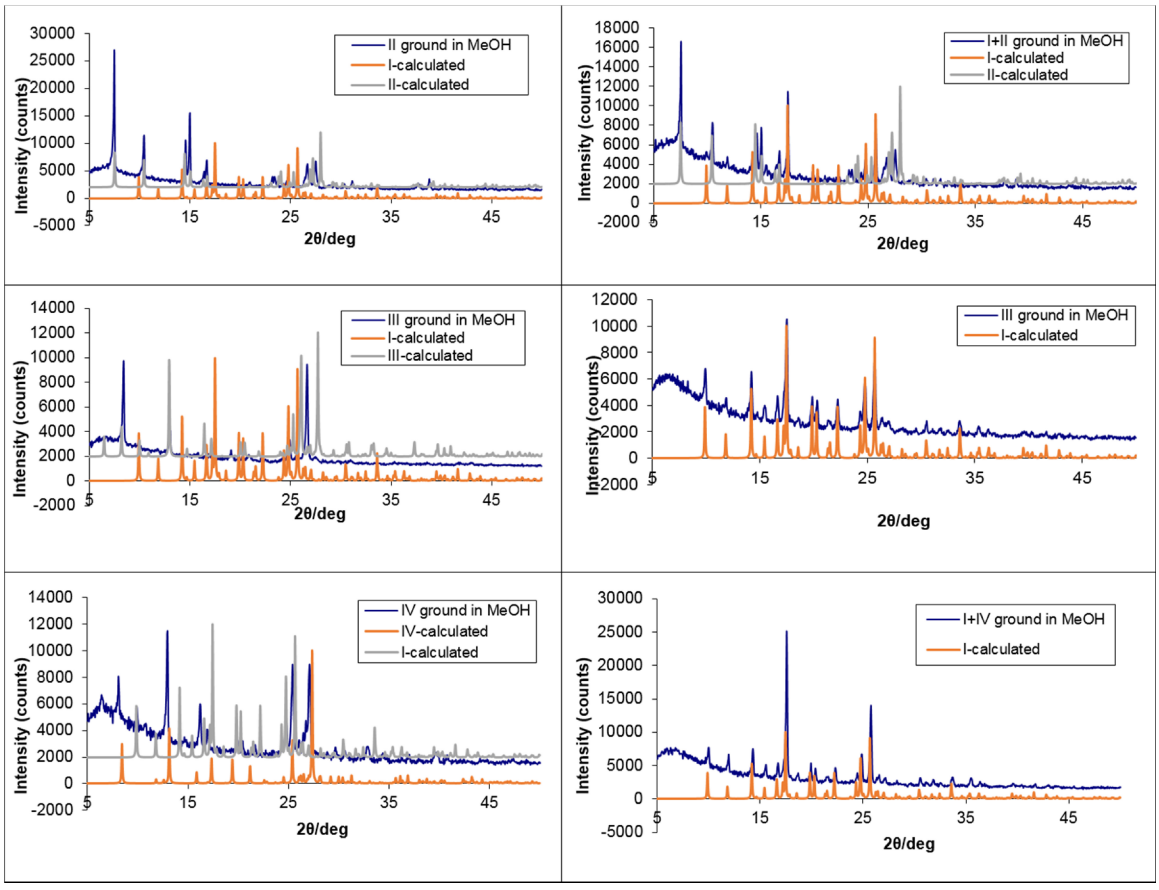

Figure 10. Grinding experiments.

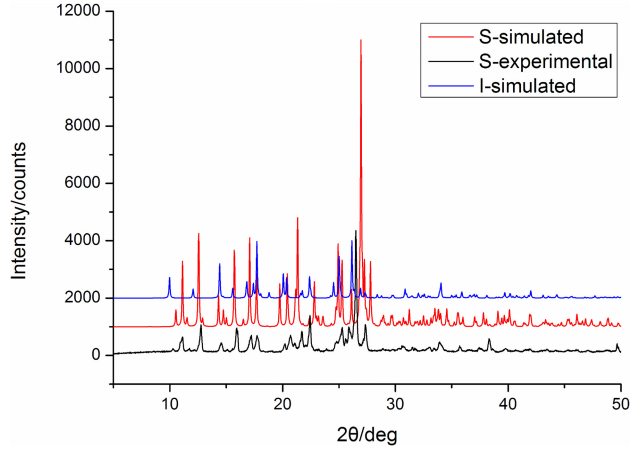

Figure 11. Experimental and calculated powder X-ray diffraction patterns of Clonixin solvate.

-36.2 KCal mol^{-1} for the four forms, which indicates a stability ranking of **II** > **IV** > **III** > **I**. Density values indicate a ranking order of forms **III** > **IV** > **II** > **I** with form **III** being the most dense (Table 2). Forms **III** and **IV** have almost the same calculated densities at 90 K, which explains their near identical calculated lattice energies. While form **II** has a higher density than that of form **I**, its lattice energy is higher than that of form **I** indicated by Crystal14 calculations, but not suggested by QE. Nevertheless, no assessment of the accuracy of the two methods is inferred here. Moreover, due to the uncertainty limit associated with the computation methods (depending on the basis set used, it can range from a few KJ/mol to a few KCal/mol or even higher), the small energy difference between the forms should not be regarded as absolute evidence of their relative stability. Also since the computation was implicitly conducted assuming 0 K, and the densities are calculated for the structures solved at 90 K, and the DSC experiments were performed at elevated temperatures, some discrepancy is not unexpected.

Hydrogen Bond Strength

The hydrogen bond strength was calculated by Crystal14 to be -12.21 Kcal/mol, -23.23 Kcal/mol, -14.47 Kcal/mol, -14.70 Kcal/mol, -12.24 Kcal/mol, and by QE to be -18.41 Kcal/mol, -24.24 Kcal/mol, -21.66 Kcal/mol, -20.64 Kcal/mol, -16.86 Kcal/mol for forms **I**, **II**, **III**, **IV** and **S**, respectively. In both methods, the strongest is the carboxylate-pyridinium interaction, and the hydrogen bond between CLX and DMF is nearly on par with that of the form **I**, which together with other interactions, combine to explain the formation of the solvate.

Hirshfeld Analysis

The Hirshfeld analysis results are shown in Figure 12. It is evident that in all thirteen potential molecular contacts, hydrogen-hydrogen contacts predominate, contributing to about 40% of the Hirshfeld surface in any of the five forms. The other significant interactions vary for the different forms: for example, in form **I**, C···H (21.70%), H···Cl (11.50%), H···O (10.50%), and H···N (6.4%); in form **II**, H···O (18.60%), H···Cl (14.40%), C···H (11.50%), C···C (8.90%); in form **III**, H···Cl (12.10%), C···H (11.10%), C···C(10.00%), H···O (9.8%); in form **IV**, C···H (15.10%), H···Cl (13.90%), C···C (10.00%), H···O (9.70%); in S, H···O (17.30%), C···H (15.40%), H···Cl (11.80%). Taken together, the crystal structures are stabilized by a variety of interactions.

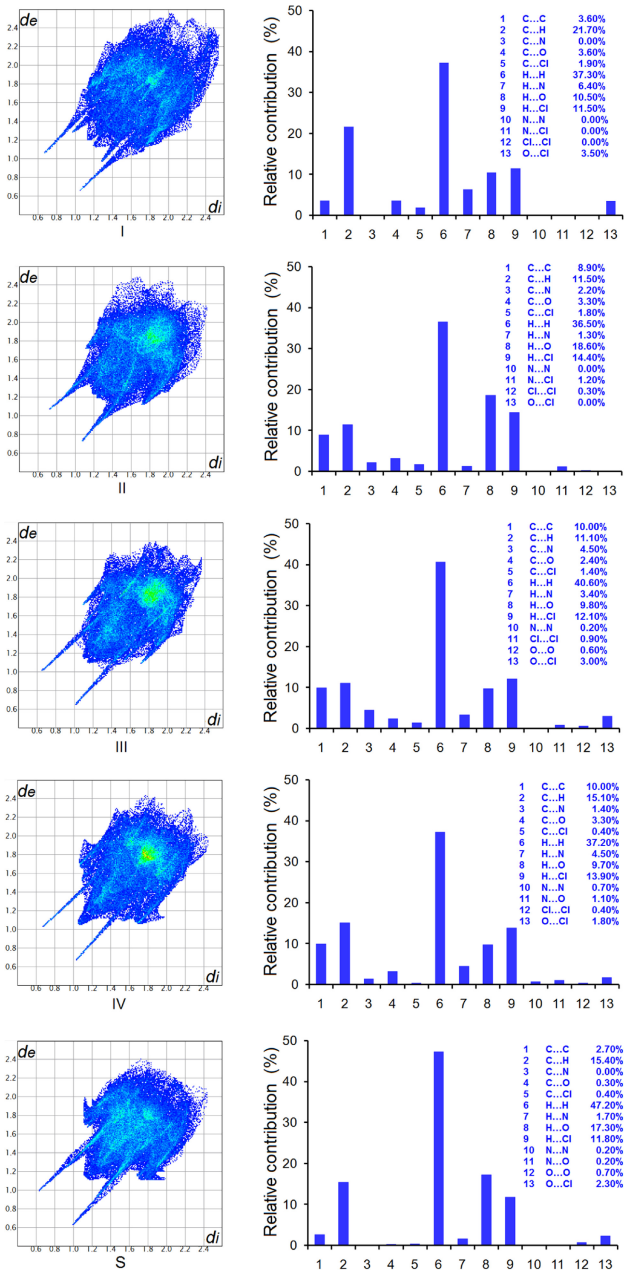

Figure 12. 2D fingerprint plots (left) for five forms (**I, II, III, IV**, and **S**) and relative contributions to the Hirshfeld surface (right) by the various intermolecular contacts in the five forms.

Conclusions

CLX was synthesized through an SNAr reaction and a fifth crystalline form was obtained as a DMF solvate upon crystal growth in DMF. The new form was fully characterized by SCXD, PXRD, ^{1}H NMR, FT-IR and Raman. The crystal structure of the new form is sustained on the hydrogen bond between the carboxylic acid OH and the DMF carbonyl, which is different from the acid-acid homosynthon or the acid-pyridine heterosynthon in the four known solvent-free forms, depending on the dihedral angle between the two aromatic rings. Thermal study of the solvate by DSC and TGA revealed the solvent loss and conversion into form **I**. Phase transition study of the solvent-free forms by HSM confirmed the solid-solid phase transition from forms **II**, **III**, **IV** to form **I**. Lattice energy calculations provide insight into the relative stability of the solvent-free forms, and the Hirshfeld analysis further delineates the contribution of individual interactions to the overall stability of each form. The hydrogen bond strength in the solvate is as strong as that of the three neutral polymorphs, which explains its existence/stability. Using compounds structurally similar to DMF, *i.e.*, good hydrogen bond donors as coformers, there is a good reason to believe new solvates and cocrystals could be discovered for CLX, and this work is underway.

Supporting Information Summary

The synthesis of the compound, crystal growth and structure determination, thermal analysis, spectroscopic studies, computation details, and crystal structures of the four polymorphs and the solvate in the form of crystallographic information file (CIF) are provided as supporting information.

Accession Codes: All five structures are deposited in CCDC with accession codes 1519174, 1519175, 1519177, 1519178, and 1545935. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data request/cif, or by emailing data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Acknowledgment

SL thanks Natural Science Foundation of Hubei Province for financial support (2014CFB787). PPZ acknowledges the financial support by the National Natural Science Foundation of China (Grant No. 21403097) and the Fundamental Research Funds for the Central Universities (lzujbky-2014-182). TL is grateful to NSF for supporting the work (DMR1006364).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Clonixin · conformation · hydrogen bond · polymorphs · solvate · theoretical studies

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Submitted: May 4, 2017
Accepted: June 1, 2017