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Observation of neutral, ionic and intermediate states in lamotrigine-acid complexes- inference from crystallographic bond geometries

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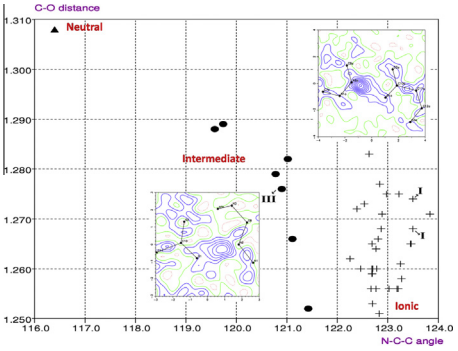
HIGHLIGHTS

- Three novel acid complexes with active pharmaceutical ingredient lamotrigine are reported.
- Geometrical bond descriptors are utilized to differentiate neutral, ionic and intermediate states.
- Complete proton transfer is seen in I and II and only partial proton transfer in III.
- The most favored lamotrigine-acid heterosynthon and lamotrigine-lamotrigine homosynthon are observed.
- The observation of intermediate state can have a direct impact to the pharmaceutical industry.

GRAPHICAL ABSTRACT

The anticonvulsant and antiepileptic drug lamotrigine was crystallized with three aromatic acids viz., 2, 5-dihydroxybenzoic acid, para-toluenesulfonic acid and 4-bromobenzoic acid (**III**), with the objective of understanding the formation of a salt or co-crystal in the solid state. The triazine bond angles of lamotrigine and bond distances of carboxylic acid are found to be the best descriptors for distinguishing all three ionization states, whereas, the bond angles of carboxylic acid have to failed to distinguish intermediate state from ionic.



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ABSTRACT

The anticonvulsant and antiepileptic drug lamotrigine was crystallized with three aromatic acids viz., 2,5-dihydroxybenzoic acid (**I**), para-toluenesulfonic acid (**II**) and 4-bromobenzoic acid (**III**), with the objective of understanding the formation of a salt or co-crystal in the solid state. Single crystal X-ray diffraction and FT-infrared spectroscopic measurements were carried out for all of them. The asymmetric units of **I** and **II** contain two lamotriginium cations and two anions (2,5-dihydroxybenzoate in **I** and *para*-toluenesulfonate in **II**), respectively, and additionally **II** contains one water molecule. The asymmetric unit of **III** comprises one lamotriginium cation, one 4-bromobenzoate anion and one dimethylformamide (DMF) solvate. In all three complexes the protonation occurs at the N2 atom of the triazine ring. In **I** and **II**, the complete proton transfer is observed. However in **III**, only partial proton transfer is inferred from O to N because of the acidic H atom disorder. The protonation of lamotrigine is also confirmed by the unambiguous location of H atom from the difference Fourier map and as well as from the geometrical bond analysis. Further, various lamotrigine-acid complexes from the CSD were analyzed to establish a correlation between different ionization states (neutral, intermediate and ionic) and changes in the geometrical parameters. The bond angles of triazine ring in lamotrigine and bond distances of carboxylic acid are found to be the best descriptors for distinguishing all three ionization states, whereas, the bond angles of carboxylic acid have to failed to distinguish intermediate state from ionic. From hydrogen

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bonding point of view, only the lamotrigine-acid heterosynthon is observed in **I** and **II**, whereas in **III**, both lamotrigine-lamotrigine homosynthon and lamotrigine-acid heterosynthon are observed. In **I**, the cation–anion and anion–anion interactions form a supramolecular two-dimension hydrogen-bonded square grid network, while the water molecule of **II** cross-link the two-dimensional cation–anion hydrogen-bonded layers. In **III**, a pseudo-quadruple hydrogen bonding is formed with aid of DMF solvate.

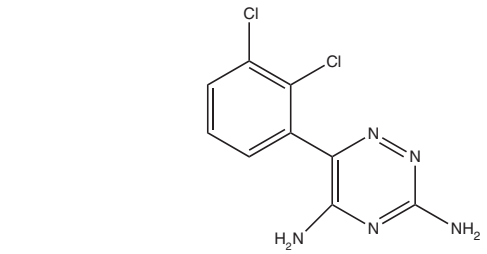
Introduction

Lamotrigine [6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine] is used as an anticonvulsant and an antiepileptic drug. Lamotrigine is chemically unrelated to other anticonvulsant or mood regulating medicines with relatively benign side effects [1]. One study showed that lamotrigine is also beneficial in the treatment of specific cluster headaches and migraines [2]. Lamotrigine within its molecular frame work can acts as donor as well as acceptor in the hydrogen bonding interactions and is a potential target for both co-crystal and salt formations. The CSD's 500,000th (half-a-million) structure is the crystal structure of Lamotrigine published by us in Acta Crystallographica in 2009 [3]. The latest version of the Cambridge Structural Database (CSD Version 5.35 with November 2013 updates [4]) indicates 60 structures (excluding the parent one), which are categorized into salts (44 structures, 73%), co-crystals (6 structures, 10%) and solvates/hydrates (10 structures, 17%). Although these different solids can be placed under a single umbrella of "multi-component crystalline systems", the distinction arises from the nature of interactions that exist in their respective crystalline states. Salts are stabilized primarily by ionic interactions, whereas co-crystals and solvates/hydrates are stabilized by neutral interactions such as hydrogen bonding, C—H···O, pi···pi stacking and van der walls interactions [5]. Solvates/hydrates are sometimes considered as a separate class from co-crystals because the second component is liquid in the former and but is a solid in the latter. Because these solids contain distinct intermolecular interactions, unique physico-chemical properties are expected from one another [6].

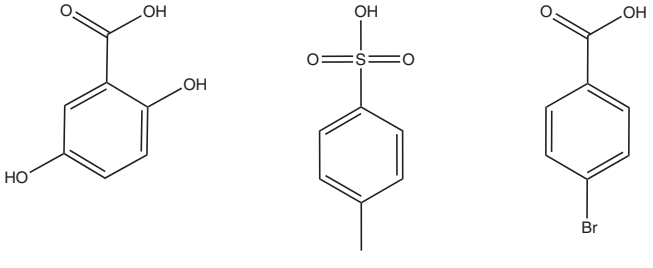
In the solution state, the salt formation is usually guided by the acid-base strengths and also by the solvent used [7]. The propensity of an acid to give up a proton is represented by its pK_a values. For acids of varying strength, the pK_a ranges are <0 (very strong), 0–4.5 (strong), 4.5–9.5 (weak), 9.5–14 (very weak), >14 (extremely weak) and similarly for bases of varying strengths, pK_a > 14 (very strong), 9.5–14 (strong), 4.5–9.5 (weak), 0–4.5 (very weak), <0 (extremely weak) [8]. The extent of proton transfer can be figured out from the difference pK_a value between the acid and the base [ΔpK_a = (pK_a(base) − pK_a(acid)]. A ΔpK_a value of 2 or 3 was traditionally used as selection criteria for choosing the counter ions for salt preparation [8]. It must be remembered that, although the pK_a value represents an equilibrium phenomenon in the solution state, the ΔpK_a rule was quite successful and without a doubt became a widely accepted rule for predicting salts in the solid state [9]. Over the years, the ΔpK_a rule was also extended to anticipate the co-crystal formation in the solid state (no proton transfer and must lead to a neutral complex). Nangia and coworkers [10] based on the analysis of several cocrystals and salts, concluded that the carboxylic acid–pyridine O—H···N interaction will be neutral when $\Delta pK_a < 0$ and the interaction will be ionic N^+—H···O^- when $\Delta pK_a > 3.75$. However, in the transition range $0 < \Delta pK_a < 3.75$, an intermediate H bond character, O—H···N and/or N^+—H···O^- are seen. Similar observation was noted by Childs et al. [7] in their analysis of theophylline-acid complexes. Co-crystals are formed for $\Delta pK_a < 0$ and salts for $\Delta pK_a > 2.5$. In the range of $0 < \Delta pK_a < 2.5$, salts, co-crystals and mixed ionizations states are noted and hence this zone was referred as salt–cocrystal continuum. The exact ionization state is difficult to predict and it was commented that the molecular environment in each crystal structure is unique and can affect the amount of proton transfer. For example, pyridine and formic acid form a co-crystal in 1:1 ratio, while it forms a salt in 1:4 ratio [11]. Recently, Cruz-Cabeza [9] has suggested a modified pK_a rule, analyzed from 6465 crystalline complexes from the CSD and figured out that the ionized acid-base complexes are observed exclusively for $\Delta pK_a > 4$ and non-ionized-base complexes are observed exclusively for $\Delta pK_a < -1$, and salt–co-crystal continuum in the ΔpK_a range −1 and 4.

Very recently USFDA suggested guidelines for Industry on the classification of pharmaceutical co-crystal that when "ΔpK_a (pK_a(base) − pK_a(acid)) ⩾ 1, there will be substantial proton transfer resulting in ionization and formation of salt as opposed to a co-crystal. On the other hand, if the API and its excipient(s) have a ΔpK_a (pK_a(base) − pK_a(acid)) < 1, there will be less than substantial proton transfer. If this criterion is met, the active ingredient-excipient complex should be classified as co-crystal". The USFDA treats co-crystals as API-excipient complex, and hence API is used for drug and the excipient is used to represent the co-former selected for co-crystallization. By following the definition, many proven salts in the literature may have to be reclassified as co-crystals. Under these circumstances, the analysis of other crystallographic parameters, such as bond distances, angles, H atom location in the Fourier map, should be utilized to investigate and establish correct ionization state and the classification must be based on the actual experimental results, but not on the empirical rules.

In continuation of our structural characterization of lamotrigine [12–16] the present study reports the three lamotrigine acid complexes (Scheme 1), namely, lamotriginium 2,5-dihydroxybenzoate (**I**), bis(lamotriginium *para*-toluenesulfonate) hydrate (**II**) and lamotriginium 4-bromobenzoate dimethylformamide (**III**). The objective is to distinguish ionic/neutral/intermediate states of



Lamotrigine



I II III

Scheme 1.