

# Evaluation of noncovalent interactions in L-(S)-lysinium L-(S)-mandelate dihydrate crystal: Inputs from Hirshfeld surfaces, PIXEL energy and theoretical charge density

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## Abstract

L-lysine amino acid is cocrystallized with L-mandelic acid by the slow evaporation method. Single crystal X-ray analysis reveals that lysine-mandelic acid crystallized as a dihydrate form. In the crystalline state, the lysine molecule exists in the cationic form in which the backbone and side chain amino groups are protonated and the carboxylic acid is deprotonated. The carboxylic acid proton of the mandelic acid is transferred to the lysine side chain and thus carries a negatively charged ion. The lattice water molecules are located near the amino groups of the lysine. Intermolecular interactions formed between lysinium, mandelate and lattice water molecules are qualitatively analyzed using Hirshfeld surfaces and 2D-fingerprint plots. The energetics of different dimeric complexes is quantitatively analyzed using PIXEL energy analysis. Topological parameters derived from QTAIM framework are used to delineate the nature of different intermolecular interactions formed in the title complex.

## Introduction

The basic building blocks of protein and peptides are 20 genetically encoded amino acids. These amino acids show enormous diversity concerning solubility, hydrophobicity, acidity and solid-state aggregation due to variable side chains.<sup>1</sup> The amino acids also assume a variety of ionization state and it is well-known that the zwitterionic form (protonated  $\alpha$ -amino group and deprotonated  $\alpha$ -carboxylic acid group) is found to be the most stable form in aqueous solution. Some of the amino acids display excellent non-linear optical properties and piezo- or ferroelectricity.<sup>2-5</sup> Crystal structures of 20 genetically encoded amino acids have been studied well to understand the hydrogen bonding, supramolecular self-association and polymorphism.<sup>6-9</sup> To understand the molecular recognition process between protein-inhibitor/drug molecules and protein-protein molecules, structural studies have been carried out for different amino acids complexed with other amino acids or with other cofomers.<sup>10</sup>

Owing to the above, various research groups explored the crystallization of different amino acids (L, D and DL amino acids) in the presence of various carboxylic acids such as mono-, di-, tri- or aromatic carboxylic acids etc. These complexes revealed the most common synthons, variability in the supramolecular assembly, effect of chirality on the ionization state and stoichiometry. The crystal structures of L and DL-lysine complexed with one of the dicarboxylic acids namely adipic acid have been reported and the structures reveals that the

arrangement of molecular ions in the layer is profoundly different.<sup>11</sup> In another study, crystal structures of L/DL-arginine and L/DL-lysine complexed with L/DL-tartaric acid were reported. The result suggests that the L-lysine prefers to form a complex with D-tartrate rather than L-tartrate.<sup>12</sup> We also reported the crystal structure of glycine-phthalic acid (an aromatic dicarboxylic acid) has been studied to delineate hydrogen bonding interactions.<sup>13</sup>

In the present study, we obtained a crystalline complex of L-lysine with L-mandelic acid and the crystal structure has been elucidated. Mandelic acid is one of a number of the aromatic carboxylic acids and is known to be an antiseptic used in the treat of urinary tract infections.<sup>14</sup> It also acts as a chiral intermediate for the synthesis of pharmaceutical agents, such as cephalosporins, vasodilator cyclandelate, hexamine mandelate and antispasmodic mandelic acid benzyl ester.<sup>15</sup> Therefore, structural studies on amino acids with mandelic acid could act as a model system to understand the molecular recognition of a drug by the protein molecules. A Cambridge Structural Database (CSD version 5.40, November 2018) search was conducted for amino acid-mandelic acid complexes. This search indicated that mandelic acid complexed with four different amino acids, such as alanine, cysteine, phenylalanine and methionine. In (*R*)-methionine (*R*)-mandelic acid complex, the methionine exists in the cationic form (a proton transferred from a carboxylic acid of mandelic acid), a neutral mandelic acid and an anionic mandelate.<sup>16</sup> The mandelic molecules are self-assembled *via* O–H...O hydrogen bonding between hydroxy-carboxylate and hydroxy-hydroxy groups. The crystal structures of phenylalanine-mandelic acid complexes ((*R*)-phenylalanine (*R*)-mandelic acid, (*R*)-phenylalanine (*S*)-mandelic acid and (*S*)-phenylalanine (*S*)-mandelic acid) have been reported.<sup>17,18</sup> In all three cases, phenylalanine exists in the zwitterionic form and mandelic acid is in the neutral form. In the (*S*)-alanine (*S*)-mandelic acid complex, the amino acid exists in zwitterionic form and the mandelic acid is in the neutral form.<sup>19</sup> The self-assembly of mandelic acid molecules are mediated by O–H...O hydrogen bonding between hydroxy-carboxylic groups. The crystal structure of the (*S*)-alanine (*R*)-mandelic acid hemihydrate complex has also been reported.<sup>20</sup> The orientation of the O–H group of the carboxylic acid is different in the alanine-mandelic acid complexes. In the cysteine-mandelic acid complexes, the amino acid exists in the zwitterionic form and mandelic acid is in the neutral form.<sup>21</sup>

Herein, the energetics of non-covalent interactions present in the L-(*S*) lysinium-L-(*S*)-mandelate complex is investigated in detail using different theoretical approaches such as Hirshfeld surface,<sup>22</sup> 2D fingerprint plots<sup>23</sup> and Bader’s quantum theory of atoms-in-molecules (QTAIM) framework.<sup>24</sup>

## Methods

### Crystallization and Single crystal X-ray diffraction

Analytical reagent grade L-Lysine (Merck) and L-mandelic acid (Lobachemie) were taken in a stoichiometric proportion (1:1) and dissolved in double distilled water. The resultant solution was filtered and evaporated at room temperature. Transparent needle-shaped single crystals were obtained after a week and used for X-ray diffraction analysis.

A good quality single crystal was chosen for X-ray intensity data collection. The intensity data were collected at room temperature (293 K) on a Bruker Kappa APEX3 CMOS diffractometer equipped with graphite monochromated Mo *K*  $\alpha$  radiation ( $\lambda = 0.71073$  Å) using  $\omega/2\theta$  scan mode. The structure was solved with the SHELXT program.<sup>25</sup> All the non-hydrogen atoms were refined anisotropically using the program SHELXL-2018/3.<sup>26</sup> The positions of H atoms of the ammonium groups and the water molecules were located from a difference Fourier map and the N–H and O–H distances were restrained to 0.85(2) Å. The remaining H atoms were positioned by riding model approach. Since absence of significant anomalous scatterers in the title complex, the absolute configuration was not established. However, the absolute configuration of L-lysine and L-mandelic acid from the starting materials was assumed. The Friedel pairs were merged during the final cycle of the refinement. The refined coordinates belong to (*S*)-lysine and (*S*)-mandelate configurations. The crystal data and refinement parameters of the title complex are presented in Table 1. The thermal ellipsoidal plot and dimeric motifs were produced using the program MERCURY.<sup>27</sup>

{insert Table 1}

## Details of theoretical calculations

The crystal structure geometry was taken after normalizing the distances involving H atoms to their typical neutron values (C–H= 1.083, N–H = 1.009 and O–H = 0.983 Å). The normalized model was used for Hirshfeld surface analysis<sup>29</sup> and PIXEL energy calculation.<sup>30-32</sup> The Hirshfeld surface analysis was performed with CrystalExplorer program<sup>33</sup> to qualitatively analyze the intermolecular interactions. Further, the intermolecular interaction energy ( $E_{\text{tot}}$ ) was calculated for various dimers using the PIXEL method. The  $E_{\text{tot}}$  value decomposed into the Coulombic ( $E_{\text{coul}}$ ), polarization ( $E_{\text{pol}}$ ), dispersion ( $E_{\text{disp}}$ ), and repulsion ( $E_{\text{rep}}$ ) contributions. The PIXEL code handles up to two-component system, but the title complex is a four-component system (lysine, mandelate and two water molecules) which cannot be handled by PIXEL code. Therefore, the title complex was separated into different combinations of two-component system which yielded five different pairs. These pairs were: pair1: L-lysine-L-mandelate, pair2: L-lysine-water1, pair3: L-lysine-water2, pair4: L-mandelate-water1 and pair5: L-mandelate-water2. We followed this procedure as suggested for the dihydropyrimidinium hydrochloride derivatives in the literature.<sup>34</sup> For each pair, the electron densities have been obtained using the program GAUSSIAN 09<sup>35</sup> at MP2/6-31G\*\* level of theory. The intermolecular interaction energies ( $E_{\text{tot}}$ ) of different dimers were computed by the PIXEL method were further compared with those of dimeric energies ( $\Delta E_{\text{cp}}$ ) computed using the M06-2X/6-311++G(d,p) level of theory with Grimme’s empirical dispersion D3.<sup>36</sup> Further, the value of  $\Delta E_{\text{cp}}$  was corrected for basis set superposition error (BSSE) using the counterpoise method.<sup>37</sup>

The topological analysis within the framework of Bader’s QTAIM approach was performed for different dimers identified in the title complex to characterize the nature of bonding. To obtain wave function, single point energy calculation (with the normalized X-ray structure geometry) was carried out for these dimers at M06-2X-D3/6-311++G(d,p) level of theory. From the calculation, we computed topological properties like electron density  $\rho(r)$ , Laplacian of the electron density  $[\nabla^2\rho(r)]$ , potential energy density  $V(r)$ , kinetic energy density  $G(r)$  and total energy density  $H(r)$  for intermolecular interactions at their bond critical points (BCPs) using the AIMALL package.<sup>38</sup> Further, the bond dissociation energies ( $D_e = \frac{-V(r)}{2}$ ) for all the intermolecular interactions were calculated using the relationship of Espinosa *et al.*<sup>39</sup>

## Results and Discussion

The title complex crystallized in the triclinic system with the  $P1$  space group. The unit cell comprises one lysine, one mandelic and two water molecules (Figure 1). The lysine exists in the cationic form in which backbone (N1) and side chain (N2) amino groups are protonated and carboxylic acid group is deprotonated. The mandelic acid carries a negative charge due to the loss of proton from the carboxylic acid moiety. This proton is transferred to the lysine side chain amino group (N2). In the crystal, lysine in the cationic form and mandelic acid in the anionic form and thus charge neutrality was achieved.

{insert Figure 1}

### Molecular dimers in the complex

We performed PIXEL energy calculation to obtain intermolecular interactions energies for different molecular dimers formed in the crystal structure (Table 2). These dimers are held together by various intermolecular interactions. It should be noted that both stabilizing and destabilizing molecular pairs are existed in the dihydrated complex.

The stabilizing molecular dimers are formed between different charged-charged and charged-uncharged species such as cation...anion [+1...-1], cation...H<sub>2</sub>O [+1...0] and anion...H<sub>2</sub>O [-1...0] pairs. Among stabilizing dimers, the dimers (motifs D1-D4, Table 2) formed by lysine...mandelate ions are strong. The other stabilizing pairs (motifs D5-D9) formed by cation-water and anion-water components are relatively weaker dimers.

{insert Table 2}

The destabilizing molecular pairs (motifs D10-D11) are formed through the same charged ions (lysini-

um...lysiniium and mandelate...mandelate). The intermolecular interactions present in the stabilizing and destabilizing molecular pairs are discussed below.

### Stabilizing molecular pairs

The intermolecular interaction energies for the stabilizing molecular pairs formed by cation and anion species of the type  $[+1\cdots-1]$  ranging from -462.8 to -250.4 kJ mol<sup>-1</sup>. These molecular pairs are depicted in Fig. 2. The molecular dimer D1 is stabilized by three intermolecular interactions (N-H...O, C-H...O and C-H...C( $\pi$ )). The lysinium acts as donors for N-H...O and C-H...C( $\pi$ ) interactions, whereas mandelate anion is involved as a donor for the C-H...O interaction and one of the oxygens (O4) of the carboxylate group of lysinium cation acts as an acceptor for this interaction. The D2 dimer is formed by N-H...O (involving side chain N2 of the cation and hydroxy group of the anion) and C-H...C( $\pi$ ) interactions. The D1 dimer is flanked on the both sides molecules formed by the motif D2. Motifs D1 and D2 are combined to form a layer which runs parallel to the crystallographic *b* axis. In this layer, lysinium and mandelate ions are alternately arranged and forming the -D2-D1-D2-D1- sequence as shown in Fig. 2. Dimer D3 is generated by three-centered intermolecular interactions (C-H...O and a short *Csp*<sup>3</sup>-H...H-*Csp*<sup>2</sup> contact formed between cation and anion with a distance of 1.98 Å). The least stabilizing dimer D4 which belongs to  $[+1\cdots-1]$  type is formed by intermolecular N-H...O (involving backbone amino group of the lysinium and carboxylate group of the anion), O-H...O (involving hydroxy of the anion and carboxylate of the cation). It should be noted that there is a short contact formed between C1...O3 which provides additional stability to the dimer D4. Further, the adjacent layers of -D2-D1-D2-D1- supramolecular motifs are interconnected by the motif D4 as shown in Fig. 2.

### {Insert Figure 2}

As mentioned earlier, relatively weak stabilizing molecular dimers are formed between cation-water and anion-water dimeric complexes in the solid state. Both water molecules (O1W and O2W) interact with lysinium and mandelate ions forming  $[0\cdots-1]$  and  $[0\cdots+1]$  molecular species with stabilizing in nature. There are five such molecular types observed in which cation-water complex makes four molecular dimers (motifs D5, D7-9 and  $[0\cdots+1]$  type) and anion-water complex forms only one dimer (motif D6 and  $[0\cdots-1]$  type).

As shown in Fig. 3, water molecules bridge the adjacent cations and adjacent anion in the solid state. We note that the lysinium side chain amino group (*via* H2A) interacts with water molecule (O2W) through N-H...O interaction and found to be stronger dimer (motif D5,  $E_{\text{tot}}$ : -86.4 kJ mol<sup>-1</sup>) among four  $[0\cdots+1]$  type molecular dimers. The backbone amino group (*via* H1B) also interacts with the water molecule (O1W) through intermolecular N-H...O interaction (motif D9,  $E_{\text{tot}}$ : -21.4 kJ mol<sup>-1</sup>). This dimer is relatively weaker than that of the dimers formed by water molecules and oxygens of the carboxylate group of the lysinium (motif D7,  $E_{\text{tot}}$ : -32.8 kJ mol<sup>-1</sup> and motif D8,  $E_{\text{tot}}$ : -22.4 kJ mol<sup>-1</sup>). The water molecule (O2W) interacts with carboxylate group of the anion forming a molecular dimer D6. The strength of this dimer ( $E_{\text{tot}}$ : -51.4 kJ mol<sup>-1</sup>) is found to be stronger than the dimer formed by intermolecular N-H...O interaction involving backbone nitrogen and water molecule (motif D9). From the energetic point of view, one can see that water molecules in the complex make stronger interactions with side chain N of the cation and carboxylate group of the anion.

### {Insert Figure 3}

### Destabilizing molecular pairs

There are three pairs identified as destabilizing molecular dimers (motifs D10-D12) in the title complex. These dimers exist between cation-cation, anion-anion and water-anion pairs. Among them, the anion-water complex has a weak nature of destabilization with the  $E_{\text{tot}}$  value being 3.4 kJ mol<sup>-1</sup>. We note that the destabilization nature is remarkably higher (almost 2-fold) in the case of anion-anion complex as compared to the cation-cation complex. As depicted in Fig. 4, the adjacent anions are self-assembled *via* intermolecular C-H...O interaction (motif D12, Table 2) which produces 1D chain that has a graph-set motif of *C*(6).<sup>40</sup> It should be emphasized that the hydroxy is not participated in the self-assembly of mandelate anions as

observed in other amino acids-mandelic acid complexes.

{insert Figure 4}

### Qualitative analysis of intermolecular interactions: Hirshfeld surface and 2D fingerprint plots

Hirshfeld surface (HS) has widely been used as a qualitative tool to analyze the intermolecular contacts present in the title complex. The 2D-fingerprint plots (2D-FP) were obtained for the individual component of the complex from the HS analysis (Fig. 5). For the lysinium cation, the intermolecular H...H interactions (with the contribution of 45.9%) are appeared as a single spike ( $d_i + d_e = 2.0 \text{ \AA}$ ;  $d_i$  and  $d_e$  are the distances from the surface to the nearest nucleus internal and external to the surface, respectively) which confirms the existence of C6-H6B...H14-C14 contact (motif D3). The next contribution comes from the intermolecular H...O interactions and shown as double spikes with the shortest  $d_i + d_e$  distance of 1.8  $\text{\AA}$ . It should be noted that the intermolecular H...C contacts (sum of  $d_i$  and  $d_e$  distance is being 2.8  $\text{\AA}$ ) are contributing 11% to the total HS area of the cation. The entire contribution emanated from the donor molecules ( $d_e > d_i$ ) for these interactions. The C=O<sub>lp</sub>...C <sub>$\pi$</sub>  contacts contribute about 0.8% to the total HS area.

For mandelate anion, the H...H contacts are also shown as a single spike on the FP with the shortest contact at 2.0  $\text{\AA}$ . In the case of H...O contacts, there is a remarkable difference noticed on the FP as compared to the lysinium ion. The contribution from donor molecules ( $d_e > d_i$ ) is reduced by ca. 2.5% that of the acceptor molecules ( $d_e < d_i$ ) of the anion. Similarly, the acceptor molecules contributing more to the H...C contacts from the anion as compared to the cation in which the contribution of donor molecules is more towards crystal packing. Furthermore, the contributions of H...H and H...O also varied between water molecules.

{insert Figure 5}

### Topological analysis of intermolecular interactions

The intermolecular interactions present in the title complex were quantitatively analyzed using topological parameters. These parameters for the intermolecular interactions at the BCPs are summarized in Table 3 and the molecular graphs of various dimeric motifs are depicted in the supporting information (Fig. S1). The molecular graphs in the title complex, six intermolecular N-H...O hydrogen bonding interactions are observed in which three of them are N-H<sup>+</sup>...O<sup>-</sup> type HB (involving protonated side chain/backbone N atoms and deprotonated carboxylate groups of lysine and mandelate) and the remaining three of them are N-H<sup>+</sup>...O type HB (involving oxygens of water and hydroxy groups).

{insert Table 3}

The electron densities ( $\rho(r)$ ) and Laplacian of the electron densities ( $[?]^2\rho(r)$ ) of the H<sup>+</sup>...O<sup>-</sup> interactions (involving ammonium and carboxylate groups) are 0.215 to 0.277 e  $\text{\AA}^{-3}$  and 2.610 to 3.041 e  $\text{\AA}^{-5}$ . The corresponding values for H<sup>+</sup>...O interactions are ranging from 0.114 to 0.227 e  $\text{\AA}^{-3}$  and 1.79 to 2.796 e  $\text{\AA}^{-5}$ . The  $\rho(r)$  and  $[?]^2\rho(r)$  values are slightly lower for N-H<sup>+</sup>...O<sub>water</sub> interactions as compared to other N-H<sup>+</sup>...O/O<sup>-</sup> interactions. The theoretical  $\rho(r)$  and  $[?]^2\rho(r)$  values for these interactions are comparable to those of values obtained from experimental charge densities studies.<sup>41</sup> Moreover, both  $\rho(r)$  and  $[?]^2\rho(r)$  values for the intermolecular N-H<sup>+</sup>...O/O<sup>-</sup> hydrogen bonding interactions show exponential decay trend with the magnitude of bond path ( $R_{ij}$ ) values ( $R^2=0.993$  for  $\rho(r)$  and  $R^2=0.938$  for  $[?]^2\rho(r)$ ). However, there is a linear correlation between  $R_{ij}$  values and the bond dissociation energies ( $D_e$ ) with the  $R^2$  value of 0.975. For different HBs, these types of correlations have been found in previous work.<sup>42,43</sup> Among the above six interactions, four interactions (N2-H2C...O1, N1-H1C...O3, N2-H2A...O2W and N1-H1B...O1W) satisfy the conditions i.e.  $|\frac{V(r)}{G(r)}| < 1$ ;  $H(r) > 0$  and  $[?]^2\rho(r) > 0$ ) and these interactions are categorized as closed shell interactions and the remaining two interactions (N2-H2B...O2 and N1-H1A...O5) have intermediate ( $|\frac{V(r)}{G(r)}| > 1$ ;  $H(r) < 0$  and  $[?]^2\rho(r) > 0$ ) values between closed and shared shell interactions.<sup>44</sup> The Laplacian of the electron density and the total electronic energy density for these two interactions are shown in Fig. 6.

{Insert Figure 6}

The magnitude of the  $\rho(r)$  and  $[\rho]^2(r)$  values for the five intermolecular O–H...O interactions fall in the range ( $0.013 < \rho(r) \text{ e } \text{Å}^{-3} < 0.236$ ;  $0.580 < [\rho]^2(r) \text{ e } \text{Å}^{-5} < 3.355$ ) proposed by Koch-Popelier for hydrogen bonds.<sup>45</sup> Further, these interactions are found to be closed shell in nature. It is of interest to note that  $R_{ij}$  and  $D_e$  values for the O–H...O interactions follow the exponential decay trend ( $R^2=0.972$ ) rather than linear correlation ( $R^2=0.844$ ). The title complex also stabilized by three intermolecular C–H...O interactions. As can be seen from the table 3, the  $\rho(r)$  values for these interactions lie within the suggested limit of Koch-Popelier. However, only one interaction (C10–H10...O2) which is involving in the self-assembly of mandelate anions satisfying the suggested limit of the Laplacian.

In addition to N–H<sup>+</sup>...O/O<sup>-</sup>, O–H...O and C–H...O interactions, some of the motifs are additionally stabilized by intermolecular C–H...C( $\pi$ ),  $C_{sp^3}$ –H...H– $C_{sp^2}$  type dihydrogen bonding and  $C_{\pi}$ ...O<sub>lp</sub> interactions. These three interactions are of closed shell in nature as revealed by the topological parameters. It should be noted that the  $C_{sp^3}$ –H...H– $C_{sp^2}$  type dihydrogen bonding interaction is found to be strongest based on the values of  $D_e$  and  $H(r)$  as compared to C–H...C( $\pi$ ) interactions.

## Conclusions

The lysine amino acid was cocrystallized with an important antiseptic agent mandelic acid. Single crystal X-ray analysis revealed that there was a proton transfer from the carboxylic acid group of mandelic acid to the lysine side chain and lysine also exhibits a zwitterionic form due to the proton transfer from the carboxylic acid of lysine to the backbone amino group. The inclusion of water molecules in the crystal lattice facilitates the formation of intermolecular N–H...O and O–H...O interactions. The strength and stabilizing/destabilizing nature of different dimeric complexes were evaluated by the PIXEL energy analysis. The relative contribution of different inter-contacts was qualitatively analyzed using Hirshfeld surface analysis and 2D fingerprint plots. Topological analysis suggested that N–H<sup>+</sup>...O<sup>-</sup> interactions which emanated from proton transfer between the side chain N2 of lysine and the carboxylate of the mandelate and between atom backbone N1 and the carboxylate group of lysine showed intermediate bonding character between closed and shared shell interactions. Other interactions that exist in the title complex are closed shell in nature.

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**Keywords:** lysine . mandelic acid . QTAIM . PIXEL . Hirshfeld surface

## Conflict of interests

The authors declare no potential conflict of interest.

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