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COMMENTARY

What is Alanine Hippurate, In Fact?

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Abstract
In this critical comment, we prove that a recently published paper titled, "Fabrication, Characterization and Optical Investigation of Semi-organic Nonlinear Alanine Hippurate Single Crystals" (Akilandeswari et al J Clust Sci 33, 439–448, 2022) is completely erroneous. A so-called "alanine hippurate" is, in fact, hippuric acid.

Keywords Alanine hippurate · Hippuric acid · Dubious crystal · Crystal structure

Introduction

We became aware of a recently published article [1] in Journal of Cluster Science reporting on the fabrication of a so-called nonlinear optical "alanine hippurate" crystal. In view of our long-standing research interest in the area of amino acid-based materials [2–9], we perused the paper due to the unusual name *viz*. alanine hippurate. As we have published several critical comments [4–9] in the area of amino acid crystals especially L-alanine based compounds (for a list of our critiques on L-alanine based crystals see [8]), we could easily infer that the claims of fabrication of alanine hippurate single crystals are incorrect. In the following commentary, we prove that the title paper is completely erroneous.

Comments

The problem of this paper begins in the title with the name of the crystal. The term alanine can refer to L-alanine or D-alanine or DL-alanine or β-alanine. Hence it is not clear what the authors mean by "alanine hippurate". As "hippurate" refers to the mono anion of hippuric acid (also known as *N*-benzoylglycine) the correct name of a hippurate containing crystal should be, for example, L-alaninium hippurate.

The abstract begins with the statement, "…*a single crystal of alanine and hippuric acid was prepared through the slow growth dynamics of sample evaporation*". It is not clear, if "alanine and hippuric acid" is same as "alanine hippurate" and what authors means by sample evaporation especially when the sample is supposed to be stable up to 290 °C. The title crystal's name becomes more confusing in the statement "… *the various functional groups of alanine with hippuric acid were investigated* …."

The first sentence of introduction is inappropriate, because nonlinear optical crystals must be noncentrosymmetric, but not necessarily polar, while ferroelectrics must be polar. Although authors mention, "*Alanine is a unique collagen-abundant amino acid characterized by the pyrrolidine ring which gives its rigidity* …." alanine does not contain any pyrrolidine ring.

Under the heading "Experimental methods" authors reported "…. *Briefly, alanine and hippuric acid with stoichiometric ratio of 1:2 were dissolved in ethanol."* It is not clear why from a 1:2 mol ratio a so-called "alanine hippurate" can form. Authors attempt to substantiate the reaction scheme in *Fig. 1*, which does not represent 1:2 mol ratio of reagents. The discovery that "hippurate is cation" based on pKa arguments is not only incorrect but also unacceptable because hippurate by definition is an anion.

In "Results and Discussion" authors reported "*X-ray diffraction data revealed that, compound AH single crystals crystallized in the orthorhombic space* $P2_12_12_1$ *with*

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molecular formula $C_9H_9NO_3$ in the unit cell as shown in Fig. S1. The lattice parameters of AH single crystals were a = 8.8978 Å, b = 9.1486 Å, c = 10.5943 Å, α = 90.14°, β = 90.02°, γ = 90.17°, volume = 862.40 Å^3, atomic number Z = 4 and the calculated density was 1.380 Mg/m^3". In fact, *Fig. S1* does not depict any structure. For the orthorhombic system α, β, γ angles must be 90.00°, otherwise it will be the triclinic system. It is not clear what is atomic number Z = 4.

The discussion of single crystal X-ray diffraction ends with the following claim, "*The intermolecular hydrogen bond … our results were examined and compared with the literature [34–39] and matched the reported semi-organic nonlinear single crystals*." Unfortunately, two of the four citations *[34–37, 39]* pertain to Zn-thiourea compounds and one to Ca-thiourea compound, while *[38]* on L-alanine acetate is also incorrect because L-alanine acetate has been proved to be L-alanine (see [2]).

Some assignments of IR and Raman spectral bands (claimed to be both active and inactive) are rather contradictory. For example, it is reported "*C–H stretching mode (Raman inactive) appeared at 3071.78 cm^{-1}*" and authors also claimed "*C–H stretching (Raman active) shown at 691.97 cm^{-1}*". A strong band at 1751 cm^{-1} and a weak signal at 1735 cm^{-1} are not interpreted. Authors report "*Final outcomes were examined and compared with the literature [41, 42] which had Raman analysis of pure and L-serine with ammonium dihydrogen phosphate single crystals*" instead of comparing with the spectra of alanine and hippuric acid.

In the discussion of SEM analysis authors claim, "*… the prepared crystals were capped into the cavity (red square), and after cavity magnification, irregular spherical and rod-shaped crystals were obtained, this shape is known as the anisotropic shape*". It is not clear what authors mean by anisotropic shape.

The statement, "*The effects of 8 MeV electron radiations on the optical properties of the crystals were experimentally-investigated and discussed with a comparison in the obtaind data and with related studies [37, 44–46]*" in the UV–VIS-NIR spectral discussion is meaningless and the citations *[44–46]* have nothing to do with either alanine or hippuric acid.

In Thermal Study the authors report "*The sample had stability up to 210 °C, then decomposition started at 210 °C and ended at 290 °C*" and contradict by stating "*DSC curve of the synthesized AH single crystals revealed that, the sharp endothermic peak at 190.6 °C was due to the melting point*". One finds it unusual that a crystal can be stable up to 290 °C after melting at 190.6 °C.

In the discussion of Nonlinear Optical Studies, authors mention, "*The results are shown in Fig. 6 and Table 3*". Despite the caption "*The second harmonic generation (SHG) efficiency of the synthesized AH single crystals*" *Fig.* 6 displays the transmittances of KDP and "1.0 mol.% alanine Hippurate (AH) single crystal" in UV–Vis–NIR region, while in Table 3 under the column heading "Dopants in potassium dihydrogen phosphate (KDP), results pertaining to the SHG efficiency of pure KDP, (0.1 mol.%) pure Alanine, (0.2 mol.%) pure Hippuric acid and (1.0 mol.%) Alanine Hippurate (AH) single crystal" are listed. It is unfortunate that the SHG efficiency of pure KDP could be determined to be equal to 0.85 times of KDP.

In a case study of salts of amino acids [2] it was demonstrated that the most common mistake is that the authors wishful thinking of formation of a certain product (for example alanine hippurate in this case) does not take place but instead one of the reactants fractionally crystallizes due to no chemical reaction (for example see [9]). To know about this, it is sufficient to compare the IR spectra or unit cell parameters of the obtained product and initial reagents. The authors determined the structure of the obtained crystal, but did not understand that one of the components, namely, hippuric acid, was actually formed (see *Fig.* 2 in [1] where only four molecules of hippuric acid are present in the unit cell). The formula $C_{12}H_{16}N_2O_5$ in *Table* 1 is fake, but in the discussion of Single Crystal X-Ray Diffraction, $C_9H_9NO_3$ (*vide supra*) is provided as the formula of the obtained crystal, which is actually the molecular formula of hippuric acid, whose structure was first reported in 1971 [10]. The original CIF file submitted by S. Akilandeswari, L. Jothi, Kaushik Pal, M. A. Elkodous, G. S. El-Sayyad to the CSD on the so-called alanine hippurate is archived under the Refcode HIPPAC09. The name of the compound for this entry in CSD (CCDC 1887963) is *N*-(benzenecarbonyl)glycine which unambiguously shows that the crystal under study is hippuric acid or *N*-benzoylglycine or *N*-(benzenecarbonyl)glycine, and not alanine hippurate.

In summary, the so-called "alanine Hippurate" in fact, is hippuric acid and the paper [1] is completely erroneous. The authors were offered the opportunity to retract their original paper (https://doi.org/10.1007/s10876-020-01825-4), but they declined.

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