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Araştırma Makalesi - Research Article

Investigation of Intermolecular Interactions of 2-Acetoxybenzoic Acid with Hirshfeld Surfaces

2-Asetoksibenzoik Asidin Hirshfeld Yüzeyleri ile Ara Moleküler Etkileşimlerinin İncelenmesi

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ABSTRACT

In this study, the crystal structure and intermolecular interactions of acetoxybenzoic acid were analyzed. Through crystal structure analysis, the arrangement of carbon (C), oxygen (O), and hydrogen (H) atoms, along with their chemical bonds, was determined. It was identified that oxygen atoms impart polar character to the molecule and play a significant role in intermolecular interactions, such as hydrogen bonding. Hirshfeld surface analysis, performed using CrystalExplorer software, focused on the interactions of the molecule with solvent molecules. This analysis provided a more comprehensive understanding of molecular interactions and structure. Additionally, properties such as electron density, curvature, and surface shape indices were mapped. The structural and electronic properties of acetoxybenzoic acid were visualized, offering a deeper understanding of its chemical and physical properties. XRD analysis revealed the crystallinity of the molecule and provided detailed insights into the crystal structure through the position of the peaks. This study illuminated the molecular structure and interaction properties of acetoxybenzoic acid, contributing to predictions of reactivity at the molecular level.

Keywords- Acetoxybenzoic Acid, Crystal Structure Analysis, Hirshfeld Surface Analysis, XRD

ÖZ

Bu çalışmada, asetoksibenzoik asidin kristal yapısı ve moleküller arası etkileşimleri analiz edilmiştir. Kristal yapı analizi sonucunda, karbon (C), oksijen (O) ve hidrojen (H) atomlarının düzenlenmesi ve kimyasal bağları belirlenmiştir. Oksijen atomlarının moleküle polar karakter kazandırdığı ve hidrojen bağları gibi moleküller arası etkileşimlerde önemli bir rol üstlendiği tespit edilmiştir. CrystalExplorer yazılımı kullanılarak yapılan Hirshfeld yüzey analizi, molekülün çözücü moleküllerle olan etkileşimlerine odaklanmıştır. Bu analiz sayesinde moleküler etkileşimler ve yapı hakkında daha kapsamlı bir anlayış elde edilmiştir. Ayrıca, molekülün elektron yoğunluğu, eğrilik ve yüzey şekil indeksleri gibi özellikler haritalandırılmıştır. Asetoksibenzoik asidin yapısal ve elektronik özellikleri görselleştirilmiş, bu sayede kimyasal ve fiziksel özelliklerine dair daha derin bir anlayış kazanılmıştır. XRD analizi, molekülün kristalliğini ve tepe noktalarının konumlarıyla kristal yapının detaylarını ortaya koymuştur. Bu çalışma, asetoksibenzoik asidin moleküler yapısını ve etkileşim özelliklerini aydınlatarak moleküler düzeyde tepkime tahminlerine katkı sağlamıştır.

Anahtar Kelimeler- Asetoksibenzoik Asit, Kristal Yapı Analizi, Hirshfeld Yüzey Analizi, XRD

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I. INTRODUCTION

Intermolecular interactions, unlike chemical bonds, is a subject that examines how interactions between molecules affect the properties of matter. These interactions are not related to the formation of chemical bonds between molecules, but are related to Van der Waals forces between molecules, hydrogen bonds, ion-dipole interactions, dipole-induced dipole interactions and solution interactions [1, 2]. The identification of molecules in solution is influenced by many factors such as aromatic interactions, cation-π interactions, CH-O hydrogen bonds, short strong hydrogen bonds, and hydrophobic interactions, which make it difficult to understand the interactions quantitatively [3, 4]. Intermolecular interactions play an important role in the understanding of chemical and biological systems. The behaviour of a molecular system is determined by the free energy. Entropy and enthalpy are useful in understanding the free energy of an intermolecular interaction [4]. Enthalpy and entropy are thermodynamic concepts that are important in intermolecular interactions. During chemical reactions, enthalpy change occurs at the molecular level with the formation or breakage of bonds between molecules [5]. This is important as it determines the energy balance of the reaction. Entropy increase is often associated with the liberalisation of intermolecular interactions or changes that allow for more regulation [6]. Enthalpy and entropy determine the equilibrium state and thermal behaviour of a reaction.

Molecular structure is one of the key factors determining the chemical and physical properties of a compound. These structural properties can be better understood by detailed analysis of the crystal structure [7]. The study of crystal structure is critical in understanding intermolecular interactions and stability. The crystal structure of acetoxybenzoic acid, when analysed in terms of the arrangement of atoms and chemical bonds, provides valuable information about the stability and reactivity of the molecule.

Hirshfeld surface analysis is a powerful tool for the detailed study of molecular interactions in crystallography and materials science. This technique allows us to visualise intermolecular distances, electron densities and surface properties [8, 9]. Hirshfeld surface analysis on acetoxybenzoic acid molecule reveals how the molecule interacts with solvent molecules and how these interactions contribute to the properties of the molecule.

In this study, it is aimed to understand the interactions of the acetoxybenzoic acid molecule in the identification of molecules in different solutions. The pharmacological activity of this molecule is closely related to its molecular structure and intermolecular interactions. Therefore, a detailed study of the acetoxybenzoic acid molecule can provide a better understanding of this compound and expand its potential application areas.

II. MATERIALS AND METHODS

A. Crystal Structure

In the crystal structure of acetoxybenzoic acid molecule, the bonds between molecules and the arrangement of atoms determine the characteristic properties of the molecule. The crystal structure of acetoxybenzoic acid molecule is shown in Figure 1. In Figure 1, brown spheres represent carbon (C) atoms, red spheres represent oxygen (O) atoms and pink spheres represent hydrogen (H) atoms. The lines between atoms in this structure indicate chemical bonds. C atoms form the main skeleton of the molecule, providing most of the molecular structure and stability. O atoms give the molecule a polar character and play a role in intermolecular interactions such as hydrogen bonds. Table 1 presents the key bond lengths and angles in the optimized structures.

Table 1. Key Bond Lengths and Angles in Optimized Structures

Parameter	2-Acetoxybenzoic Acid	K-Doped	Na-Doped
C=O (carboxyl)	1.23 Å	1.25 Å	1.24 Å
C-O (acetoxy)	1.35 Å	1.37 Å	1.36 Å
K-O (carboxyl oxygen)	-	2.80 Å	-
K-O (acetoxy oxygen)	-	2.85 Å	-
Na-O (carboxyl oxygen)	-	-	2.30 Å
Na-O (acetoxy oxygen)	-	-	2.35 Å
C-C (benzene ring)	1.39 Å	1.38-1.40 Å	1.37-1.39 Å
O-C=O (angle)	124.3°	125.6°	125.1°

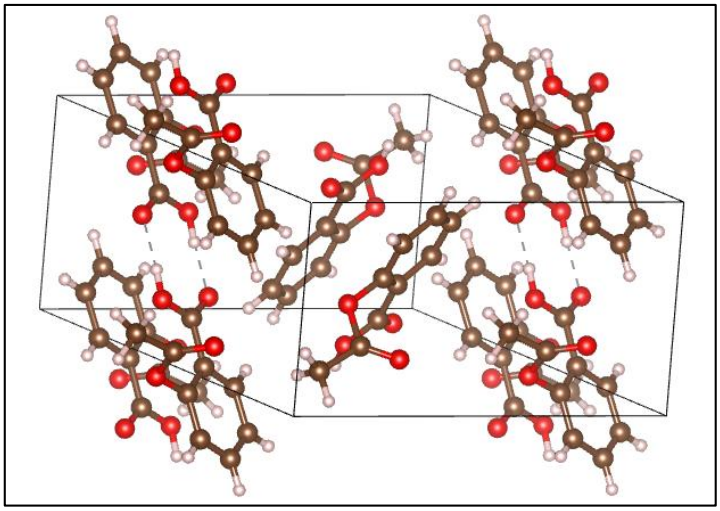

Figure 1. Crystal structure of acetoxybenzoic acid molecule

B. Method

Hirshfeld surface analysis was performed using the CrystalExplorer programme [14]. This analysis helps to better understand molecular interactions and structure. The properties of the molecule, such as electron density, curvature, and surface shape indices, have been mapped to investigate the molecular structures and interactions. Hirshfeld surface analysis was performed on the interactions of 2-acetoxybenzoic acid molecule with solvent molecules.

C. Intermolecular Hirshfeld Surface Analysis

Hirshfeld surface analysis provides an understanding of molecular interactions in crystallography and materials science, allowing us to better understand the structural properties and interactions of molecules [10]. The Hirshfeld surface is defined to contain a certain fraction of the electron density of a molecule to visualise the interactions of the molecule with neighbouring molecules [11-13]. On the Hirshfeld surface, a wide range of properties can be visualised, including the external, de, and internal, di, distances of atoms to the surface. The intermolecular distance information on the surface can be condensed into a two-dimensional histogram of de and di, a so-called fingerprint plot, which is a unique identifier for molecules in a crystal structure [3].

Hirshfeld surface analysis visualises the relationship between the characteristic properties of the acetoxybenzoic acid molecule and its interactions with solvent molecules and how the whole molecule interacts with its environment. The Hirshfeld surface maps showing the surfaces mapped on curvedness, de, di, dnorm and shape-index, which were analysed to explain the intermolecular interactions, is shown in Figure 2.

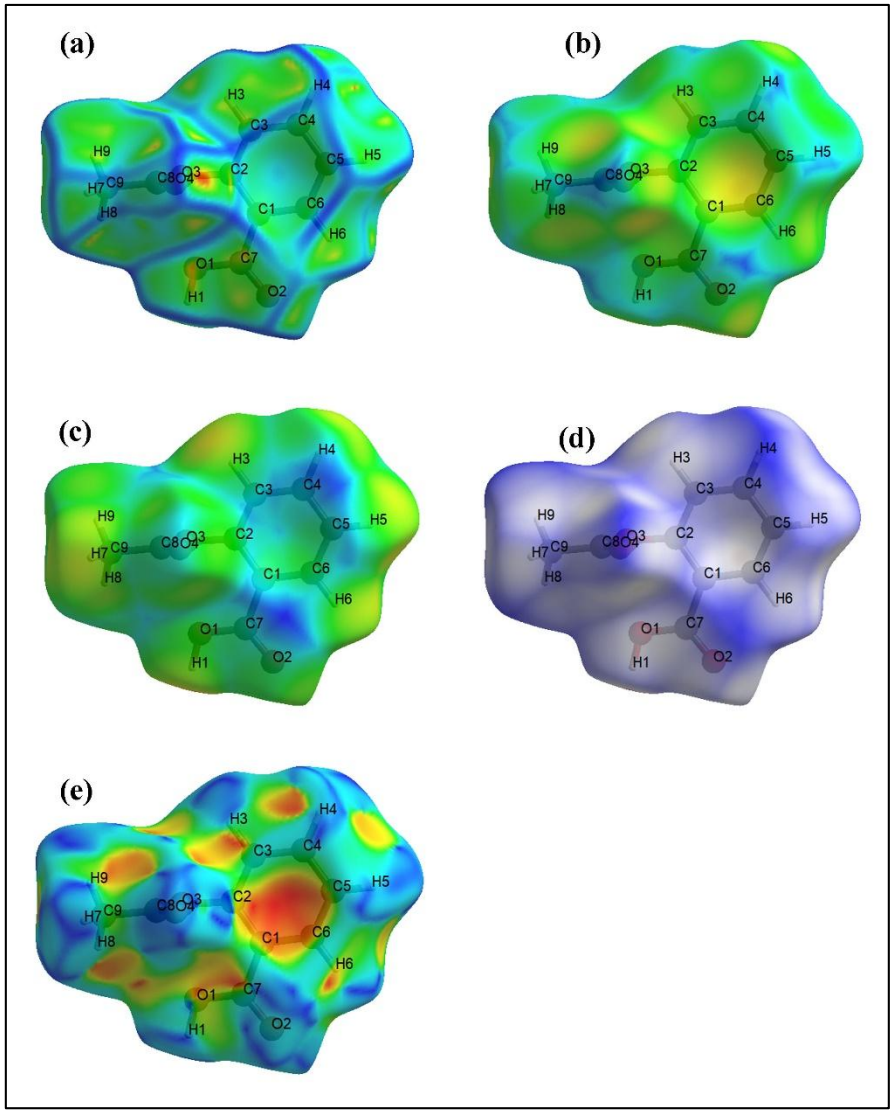

Figure 2. Hirshfeld surfaces mapped with **(a)** curvedness **(b)** de **(c)** di **(d)** dnorm and **(e)** shape-index for for the molecule investigated

Figure 2(a) shows the curvedness map of the aspirin molecule. This map expresses the geometrical features of the surface of the molecule under investigation and visualises waviness or roughness on the surface of the molecule in colours to understand the chemical and physical properties of the molecule. The curvature map provides information about how open regions are to molecular interactions. The different levels of curvature around regions such as carboxyl acid (C7, O1) and ester group (C7, O2) are striking. Low curvature levels are coloured "blue" on the map. The blue areas show areas where the molecule is relatively flat on its surface and less rough parts. At the same time, these regions may be less active for molecular interactions and form stable molecular structures. Regarding molecular dynamics, these areas may undergo less deformation or play a lesser role in environmental interactions. Regions showing moderate curvature are represented by the colours "Green" and "Yellow". These regions of the molecule represent regions where the molecule is potentially more open to interaction for certain chemical interactions. Reactive regions of the molecule may be marked by these colours. In Figure 2(a), the red areas are regions of high curvature. They are the roughest and most wavy areas on the surface of the molecule and are potentially active sites for molecular interactions and reactions, and may be regions where the molecule can interact with surrounding molecules. High curvature regions can be reactive sites in molecular dynamics simulations. It provides important information to determine the potential of the molecule to participate in various reaction mechanisms.

Figure 2(b) shows the electron density map of the molecule. This map provides information about the electronic structure of the molecule. The electron densities of each atom and their bonds with each other are visualised and described in colours. The atoms in the molecule and the hydrogen atoms bonded to their carbon and oxygen atoms have density regions in various colours. The colours represent the electron density in different regions of the molecule; usually blue indicates low-density areas, green medium-density areas and yellow or red high-density areas. The electron densities of carbon (C1, C2, C3, C4, C5, C5, C6, C7, C8, C9) atoms are usually

green to yellow, which means medium to high density. Oxygen (O1, O2, O3) atoms are usually represented by reddish or yellow colours because of their high electron density. Because oxygen is an electronegative element, it attracts electrons from the hydrogen atoms to which it is bonded, thus causing the density regions to be more pronounced. These regions are generally more reactive areas. But blue regions where the electron density is relatively low are more reactive areas.

The di map of the Hirshfeld surface is shown in Figure 2(c). di map gives the fraction of the electron density from the molecule at a point in the molecule. The blue and green areas on the map are the less reactive parts of the molecule and indicate the regions where the electron density is low. These regions can be said to be more electronically stable and inert. Yellow regions on the map are areas with high electron density. The interactions between carbon and oxygen atoms can be seen in this density map. Oxygen atoms (O1, O2, O3) generally have high electron density due to their electron-withdrawing properties, which makes them effective in attracting electrons from the surrounding atoms.

Figure 2(d) shows the dnorm (normalised distance) map of the molecule. In the dnorm map, the potential surrounding the surface of the molecule, the Van der Waals volume and the distance to its nearest neighbours are expressed in colours. In the blue and purple regions, the molecule has minimal interaction with neighbouring molecules. Darker colours (grey or black tones) represent densely packed regions where the molecule interacts more tightly with neighbouring molecules. On norm surfaces, large circular depressions indicate hydrogen bond contacts, while other visible spots are due to H-H contacts.

Figure 2(e) shows the shape index on the surface of the molecule as a coloured map. The hollow regions on the surface of the molecule are shown in blue. The less reactive parts of the molecule show flat areas and are represented by the green colour. The red regions represent raised areas and are where the molecule interacts strongly with other molecules around it.

D. Fingerprint Plots

It helps to fingerprint the types and frequencies of intermolecular interactions in the crystal and simplifies the complex chemical information of the structures and helps to present them numerically or graphically. In addition, it is possible to make comparisons by comparing the similarities and differences of different molecules. For each molecule, a characteristic shape is produced [3]. Fingerprint graphs are unique for any molecule and their size is independent of atoms in the molecule. The fingerprint graph indicating the important intermolecular interactions in the molecule of interest is shown in Figure 3.

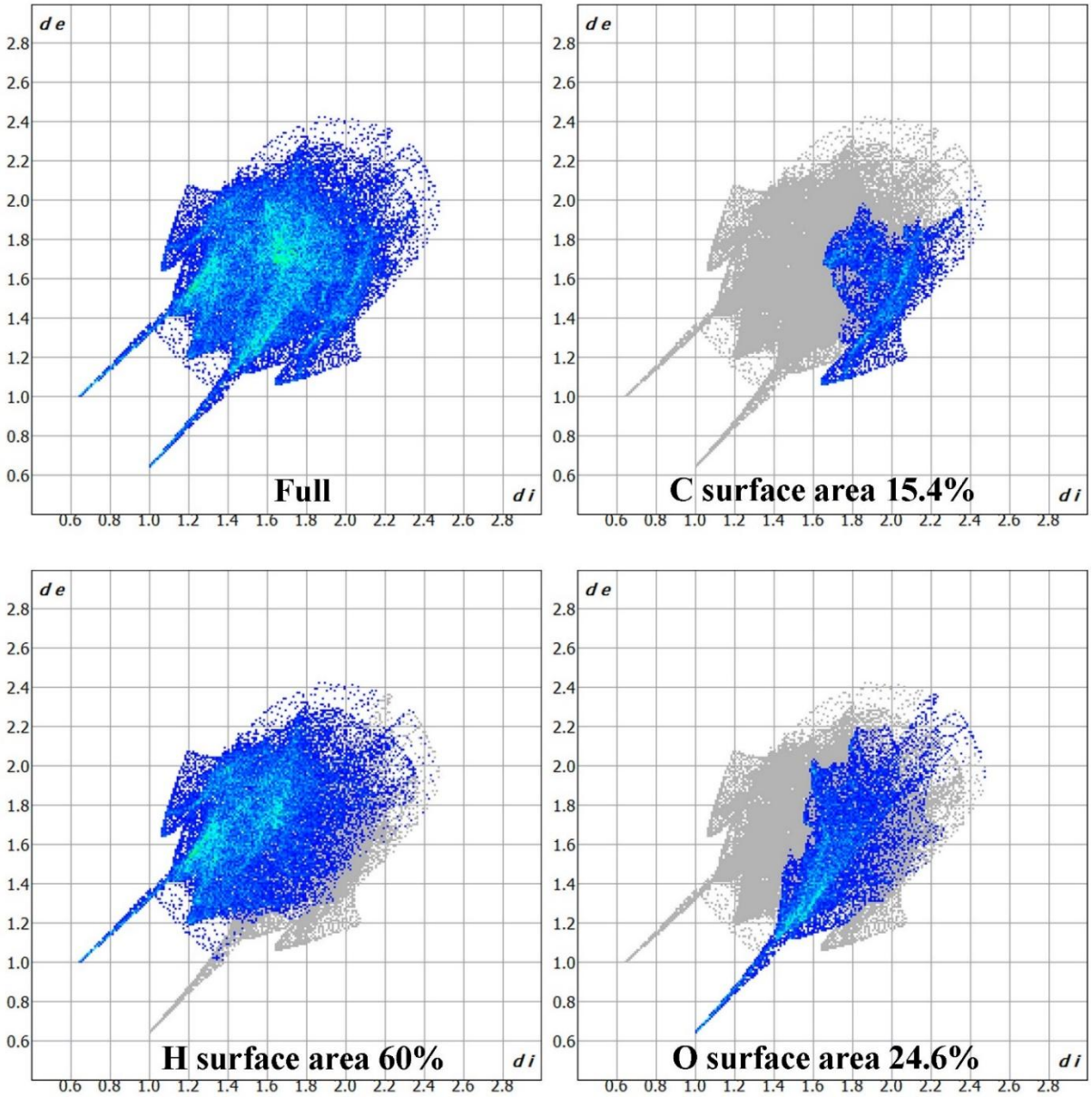

Figure 3. Fingerprint graphics

In the fingerprint graphs shown in Figure 3, each graph visualises a different aspect of the molecule. The first graph (top left) represents the entire molecule. Areas of high density in the molecule are coloured blue. These areas indicate that the interactions between the atoms that make up the molecule are high. The relatively less dense areas are painted in a less blue and grey tone. The Carbon (C) Surface Area graph (top right) shows the three-dimensional structural distribution and density of carbon atoms in the molecule and shows that 15.4% of the molecule consists of carbon atoms. The areas occupied by C atoms in the molecule are shown in grey. In the hydrogen (H) surface area graph, hydrogen atoms (60%) in the molecule cover a large area. It indicates that the effect of hydrogen on the molecule is more than other atoms.

Oxygen (O) surface area constitutes 24.6% of the surface area of the molecule. Therefore, considering the structural properties of oxygen, it states they can have a great effect on the chemical reactivity and polarity of the molecule. Oxygen increases electronegativity and polarity in molecules.

E. X-Ray Diffraction Analysis (XRD)

XRD analysis is often used to determine the crystal structure of a substance. The XRD spectrum of the crystal structure of the molecule is given in Figure 4. Due to the regular and repeated structure of aspirin crystals, sharp peaks with pronounced intensity are observed in the spectrum. These peaks indicate substantial crystallinity. The molecule has a highly ordered crystal structure, indicating that the sample largely consists of a uniform

crystalline phase. The background level and other peaks with low intensity in the spectrum can give information about the purity of the sample, small amounts of impurities or multiple phases. The position of the peaks at 2 Theta indicates the spacing and orientation of the planes in the crystal structure. Significant increases in 2 Theta values of 10°, 20°, 30° are usually observed. These are characteristic reflections of the crystal structure of the molecule and are used to determine the crystal cell parameters.

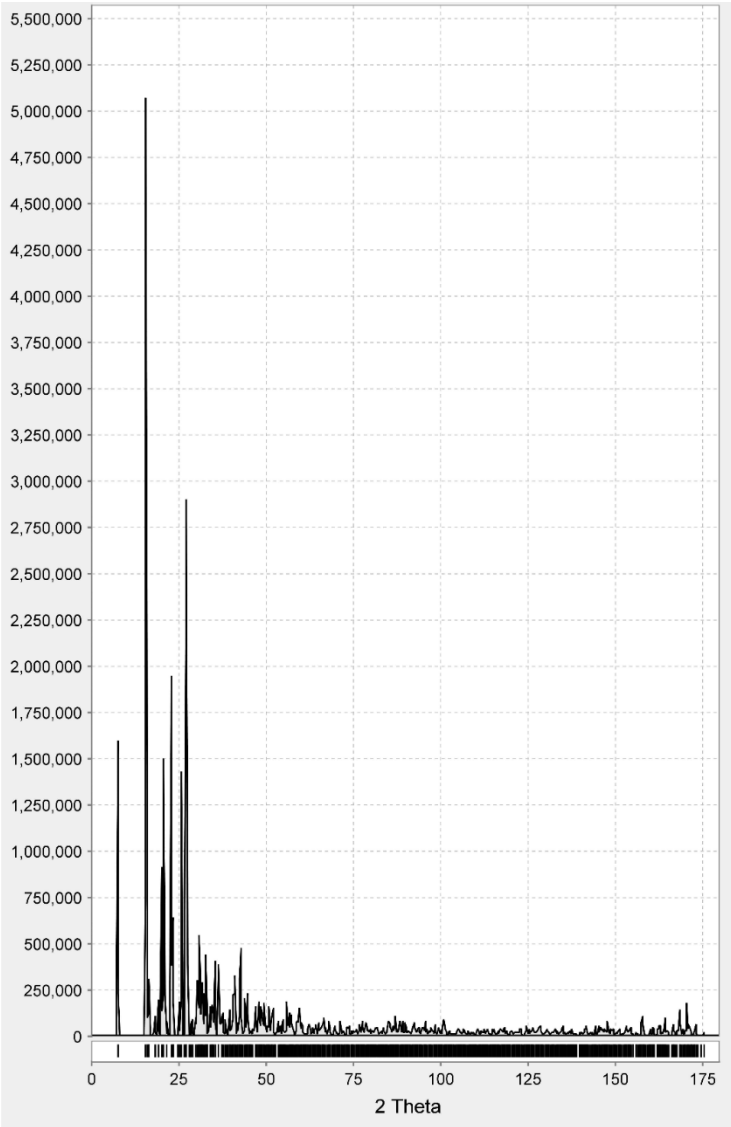

Figure 4. XRD spectrum of the molecule

III. CONCLUSIONS

In this work, we have studied the complex molecular interactions and crystal structure of 2-acetoxybenzoic acid along with its chemical and physical properties. Using advanced analytical techniques such as XRD and Hirshfeld surface analysis, the arrangement of atoms was detailed and the molecular interactions underpinning the stability and reactivity of the molecule were visualized. We found that oxygen atoms play the critical role of forming polar features and hydrogen bonds, which facilitate the molecule's interaction with its environment. Hirshfeld surface analysis has provided a deeper understanding of how these interactions affect the behavior of the molecule in different solvent conditions, which is vital for predicting its reactivity and pharmacological potential. Detailed mapping of the electron density, curvature and surface shape indices not only confirmed the high crystallinity of 2-acetoxybenzoic acid, but also illuminated potential sites of chemical activity and interactions. These insights are valuable for theoretical and computational modeling of similar molecular systems and can guide practical applications in materials science and pharmaceuticals.

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