



Crystal Structure and Hirshfeld Surface Analysis of Diethyl (6-methyl-2-pyridyl)aminoethylenemalonate

Omar Coughlin¹ · Nathan De Bruyn² · David P. A. Kilgour¹ · Sophie L. Benjamin¹

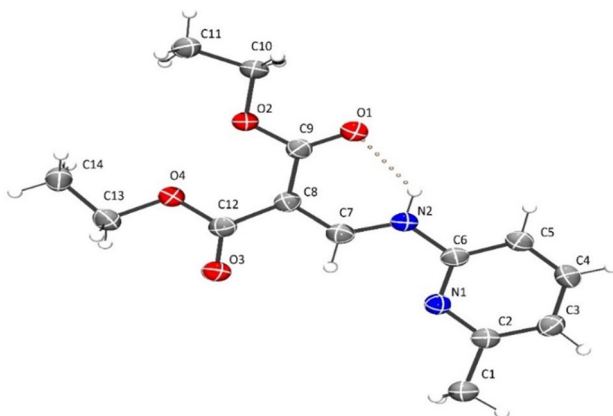
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Abstract

The title compound, diethyl (6-methyl-2-pyridyl)aminoethylenemalonate (**1**), crystallises in the monoclinic space group $P2_1/c$ (No. 14). The unit cell parameters are $a = 10.5657(7)$ Å, $b = 9.1784(5)$ Å, $c = 14.5681(7)$ Å, $\beta = 101.636(6)^\circ$, $Z' = 1$ and $Z = 4$ at 150 K. The extended structure forms approximately orthogonal columns of stacked molecules. All bond lengths and angles are unremarkable. No disorder, twinning or co-crystallised solvent is present in the structure. An intramolecular hydrogen bond exists between the enamine nitrogen and carbonyl oxygen. Hirshfeld surface analysis reveals a short contact between a carbonyl oxygen and neighbouring aryl hydrogen, as well as a carbonyl–carbonyl interaction.

Graphical Abstract

The X-ray structure of diethyl (6-methyl-2-pyridyl)aminoethylenemalonate (**1**), an intermediate in the synthesis of ethyl nalidixate, is reported, and Hirshfeld surface analysis employed to identify intermolecular interactions within the structure.



Keywords Organic structure · Intramolecular hydrogen bonding · Hirshfeld surface analysis · Fingerprint plots · X-ray crystallography

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Introduction

Initially reported in 1962 [1], the title compound diethyl (6-methyl-2-pyridyl)aminoethylenemalonate (**1**) is commonly prepared as an intermediate in the synthesis of ethyl nalidixate in undergraduate medicinal chemistry laboratories. Ethyl nalidixate has since become ubiquitous in medicinal chemistry as a lead compound for the development of quinolone antibiotics [2]. Synthesis of **1** entails

a condensation reaction between 2-aminopicoline and diethyl ethoxymethylenemalonate (Scheme 1). Despite its role as a key characterisation technique for inorganic and organometallic compounds, single crystal X-ray diffraction (SC-XRD) is much less routinely employed for the characterisation of neutral organic compounds, and the solid-state structure of **1** has not been previously reported.

Hirshfeld surface analysis [3] has recently become prevalent for describing interactions within crystals, and provides a method to view molecules as ‘organic wholes’ [4]. It offers a tool for visualising interactions in crystal structures, allowing for comparison between polymorphs and chemically similar structures [5]. By mapping the distance from the nearest external nucleus (d_e) onto the Hirshfeld surface, represented as colour contours on the generated 3D visualisations, we can identify points of intermolecular interaction. Plotting d_e against d_i (the distance to the nearest internal nucleus) gives 2D-fingerprint plots which allow more detailed analysis of these interactions.

Experimental

NMR spectra were recorded on a JEOL Eclipse 400 MHz NMR spectrometer (399.60 MHz for ^1H and 100.48 MHz for ^{13}C). LC/MS was carried out using a Waters Acquity UPLC (Waters Corp, Milford, MA, USA), coupled to a Waters Xevo G2-XS Q-TOF mass spectrometer (Waters Corp, Milford, MA, USA). Melting point measurements are uncorrected. Yield and spectra were in close agreement with literature values [2].

Synthesis of 1

2-Aminopicoline (2.00 g, 18.49 mmol) and diethyl ethoxymethylenemalonate (4.00 g, 18.49 mmol) were combined and heated at 110 °C for 90 min with stirring. The precipitate formed on cooling was recrystallized from ethanol to afford **1** as a white powder. Yield: 4.11 g, 80%.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 11.04 (1H, d br, $J = 12.58$ Hz, NH), 9.25 (1H, d, $J = 13.04$ Hz, C=C-H), 7.51

(1H, t, $J = 7.78$ Hz, Ar-H), 6.86 (1H, t, $J = 7.55$ Hz, Ar-H), 6.64 (1H, t, Ar-H), 4.27(4H, dq, $J = 19.06$ Hz, 7.08 Hz, OC-H₂), 2.48 (3H, s, Ar-C-H₃), 1.34 (3H, m, C-CH₃).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 14.28 (s), 14.40 (s), 24.29 (s), 60.14 (s), 60.48 (s), 94.99 (s), 108.61 (s), 119.08 (s), 138.68 (s), 149.89 (s), 150.08 (s), 165.69 (s).

LC/MS $[\text{M} + \text{H}]^+$: Calc. for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_4 = 279$; found 279.

Melting point (ethanol): 104–106 °C.

SC-XRD quality crystals were obtained by slow evaporation of a solution of **1** in tetrahydrofuran over 3 days.

X-Ray Crystallography

Crystallographic measurements were performed at 150 K using an Oxford Xcalibur Gemini diffractometer with a Sapphire 3 CCD plate (graphite-monochromated Cu $\text{K}\alpha$ radiation, $\lambda = 1.54184$ Å). A crystal of suitable size and quality was selected, coated with Fomblin® Y oil, and mounted onto a nylon loop. The Numerical absorption correction was based on gaussian integration over a multifaceted crystal model [6]. Empirical absorption correction, using spherical harmonics, implemented in SCALE3. The ABSPACK scaling algorithm was applied for absorption correction [7]. Cell refinement, data collection and data reduction were performed using Rigaku CrysAlisPro 1.171.39.46 [8]. The crystal density was not measured.

Refinement

Using Olex2 [9], the structure was solved with the ShelXT structure solution program using intrinsic phasing and refined with the ShelXL refinement package using Least Squares minimisation [10, 11]. All hydrogen atoms were geometrically placed and refined using the riding model approximation. Methyl groups were refined as a rotating group. Structural and refinement parameters are given in Table 1. Bond lengths, angles and atomic displacement parameters are given in the supplementary information.

Scheme 1 Synthesis and molecular structure of **1**

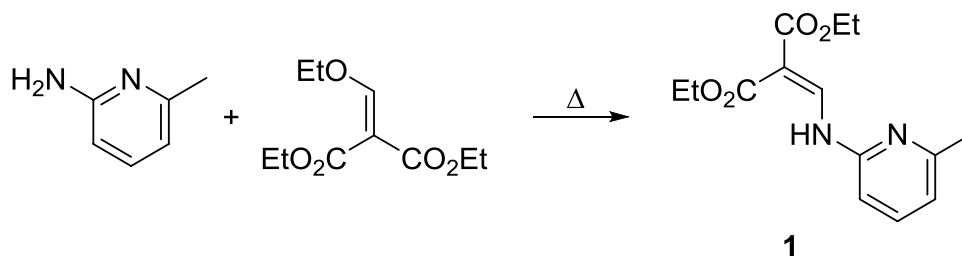


Table 1 Crystal data and structure refinement of **1**

CCDC deposition number	1877868
Empirical formula	C ₁₄ H ₁₈ N ₂ O ₄
Formula weight	278.30
Temperature/K	150.01(10)
Crystal system	Monoclinic
Space group	P2 ₁ /c
a/Å	10.5657(7)
b/Å	9.1784(5)
c/Å	14.5681(7)
α/°	90
β/°	101.636(6)
γ/°	90
Volume/Å ³	1383.73(14)
Z	4
ρ _{calc} g/cm ³	1.336
μ/mm ⁻¹	0.819
F(000)	592.0
Crystal size/mm	0.413 × 0.214 × 0.122
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	8.544 to 133.168
Index ranges	−11 ≤ h ≤ 12, −6 ≤ k ≤ 10, −12 ≤ l ≤ 17
Reflections collected	3693
Independent reflections	2407 [R _{int} = 0.0293, R _{sigma} = 0.0523]
Data/restraints/parameters	2407/0/184
Goodness-of-fit on F ²	1.098
Final R indexes [I >= 2σ(I)]	R ₁ = 0.0726, wR ₂ = 0.1949
Final R indexes [all data]	R ₁ = 0.0902, wR ₂ = 0.2121
Largest diff. peak/hole/e Å ⁻³	0.37/−0.26

Structural Analysis

Bond parameters were measured using Mercury 3.10 [12–14]. Hirshfeld surface analysis was performed using CrystalExplorer [15]. The Hirshfeld surface was mapped using an isovalue of 0.5. Red contours indicate a contact less than the sum of the Van Der Waals radii of the respective elements. Blue and white contours indicate that the nearest external atom is at a distance greater than or equal to the sum of the Van Der Waals radii respectively from the atomic co-ordinate. As hydrogen atoms have been placed geometrically, e.s.d. are not included in quoted bond lengths.

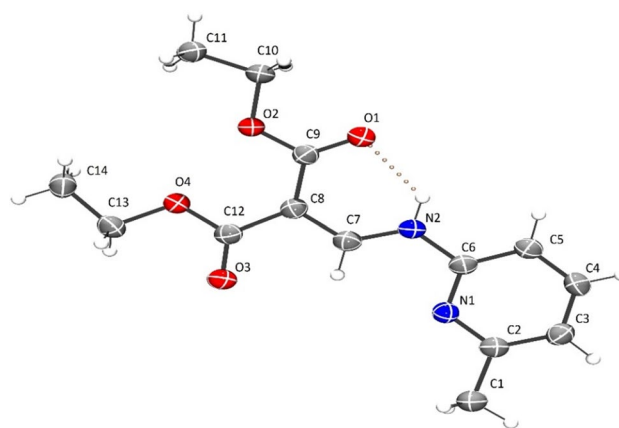


Fig. 1 Representation of the solid-state structure of **1**. Thermal ellipsoids are shown at 50% probability. Hydrogen atom labels are omitted for clarity. The O1–N2 hydrogen bond is shown as a tan dashed line

Results and Discussion

Asymmetric Unit

1 Crystallises in the monoclinic space group P2₁/c (No. 14). The asymmetric unit consists of one molecule of **1** (Fig. 1) and the unit cell consists of four molecules of **1**.

The molecular configuration of **1** is essentially planar in the solid state, with C4 and C14 having the largest deviation from the plane at 0.117 Å and 0.129 Å respectively. This planarity is supported by a hydrogen bonding interaction between O1 and N2, which forms a six-membered ring (O1–C9–C8–C7–N2–H2) and locks the conformation of the ester groups. The strongly downfield shift of the enamine proton in the ¹H NMR spectrum (11.04 ppm) suggests that this hydrogen bonding interaction is maintained in solution. No disorder, twinning or co-crystallised solvent is present in the structure. All bond lengths and angles are unremarkable. The bond lengths and angles in the heterocyclic component of **1** are similar to pyridine [16].

Intermolecular Interactions

Molecules are stacked in a head-to-tail fashion (Fig. 2). The interplanar distance between molecules is 3.396 Å. Stacked molecules are fully co-planar, with an angle of 0.00° between them. These planes are offset by 2.84 Å. The

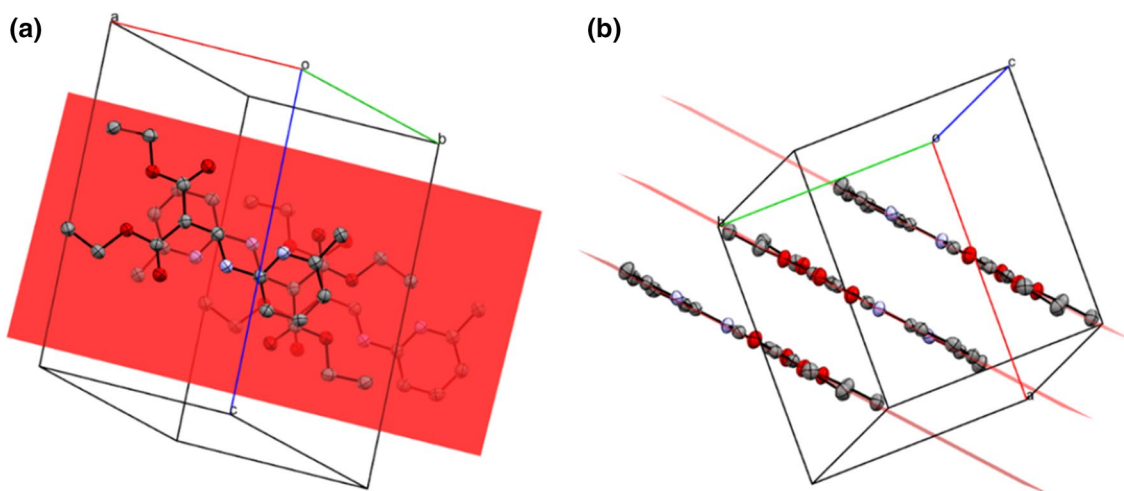


Fig. 2 **a** Parallel view of the asymmetric unit of **1** with stacked molecule above and below it. **b** Perpendicular view of the asymmetric unit of **1** with stacked molecule above and below it. The molecule planes and cell axes are shown. Atom labels and hydrogen atoms omitted for clarity

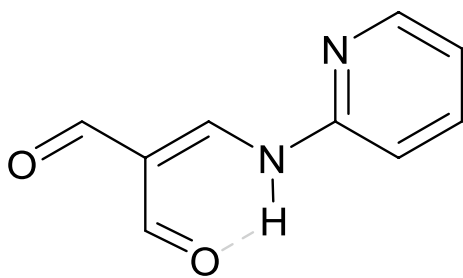


Fig. 3 Structure of 2-(N-(2,2-diformylethenyl)amino)pyridine (CCDC:297480), showing the intramolecular hydrogen bond in grey

resulting columns of stacked molecules are approximately orthogonal to one another with an angle of 86° between them.

Database Survey

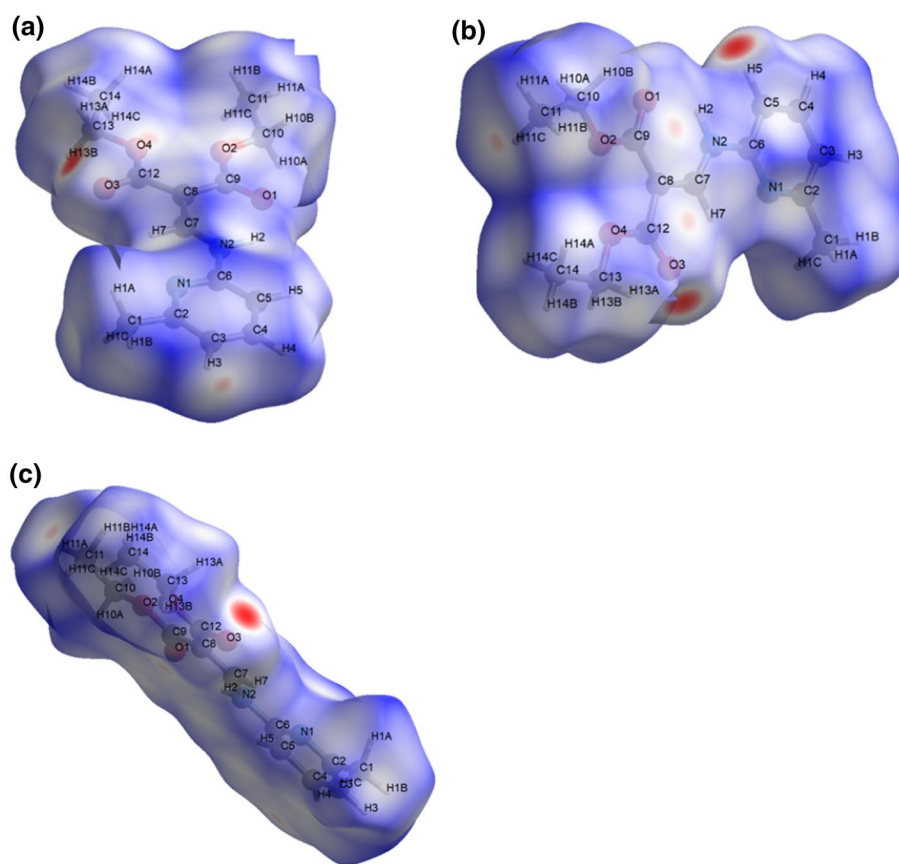
Eleven crystal structures possessing a 2-(2,2-dicarbalkoxyvinylamino)-pyridine substructure exist

in the Cambridge Structural Database (CSD, Version 5.39, November 2017). The most comparable to **1** is 2-(N-(2,2-diformylethenyl)amino)pyridine (CCDC:297480, Fig. 3). Similarly to **1**, a hydrogen bond interaction exists between the enamine N and a carbonyl O. The supramolecular structure is similar to **1**, in that the molecule is planar, with a shorter intermolecular stacking distance (3.389 \AA).

Hirshfeld Surface Analysis

The Hirshfeld analysis reveals a short contact between O3 and H5 of a neighbouring molecule of 2.402 \AA , demonstrated by red contours on the Hirshfeld surface at these atoms (Fig. 4). A fairly short contact is also identified between C9 and C12 (3.444 \AA). This is likely the result of a carbonyl–carbonyl stacking interaction. Such interactions have been found in other small molecules and the secondary structures of proteins, and are the result of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ interactions [17]. There is also a short contact between H3 and C11 (2.817 \AA).

Fig. 4 Hirshfeld surface of **1**. **a** View down a axis, **b** view down b axis, **c** view down c axis



The fingerprint plots (Fig. 5) show that the predominant intermolecular interaction is H–H interactions; these account for 60% of the Hirshfeld surface (Fig. 5c). These interactions are presumed to be primarily the result of attractive dispersion forces [18]. C–C interactions, primarily the result of stacking interactions, also contribute to the Hirshfeld surface (Fig. 5b).

Conclusions

Here, we have presented the solid-state structural analysis of a common organic small molecule. Intramolecular H-bonding is present in the structure, and Hirshfeld surface analysis has been used to reveal intermolecular interactions that would otherwise have been difficult to elucidate.

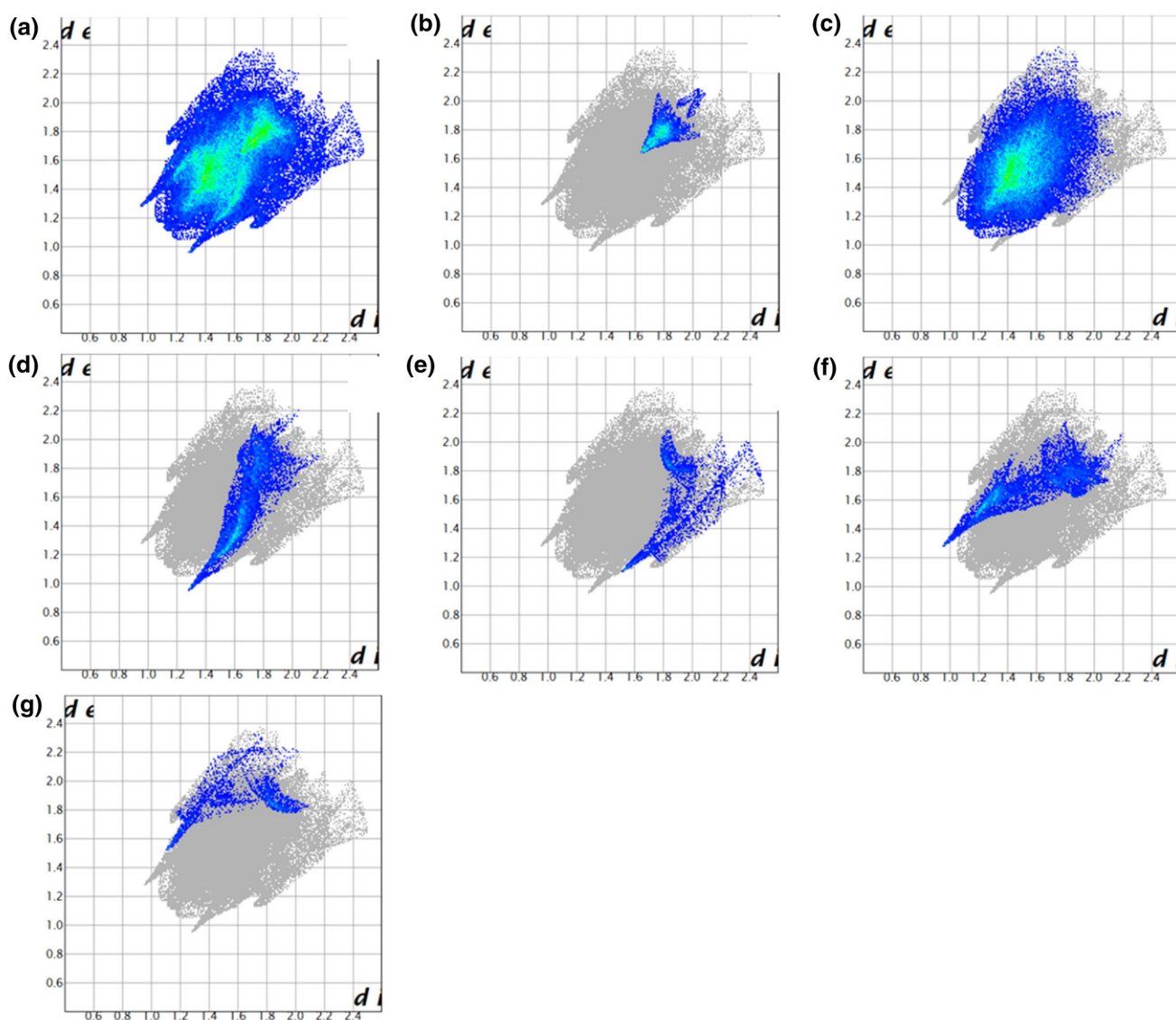


Fig. 5 Hirshfeld fingerprint plots for **a** all intermolecular interactions. **b** C–C interactions. **c** H–H interactions. **d** O(inside)–All(outside) interactions. **e** N(inside)–All(outside). **f** All(inside)–O(outside). **g** All(inside)–N(outside)

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