JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Balancing Polar and Dispersive Forces: Hirshfeld Surface Mapping of the Non-Covalent Interaction Landscape in Crystalline Metronidazole

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Abstract
The crystal structure of metronidazole (CCDC 2380391) was reanalyzed using Hirshfeld surface analysis, fingerprint plots, and contact statistics. O···H/H···O interactions (38.9%) dominate, indicating extensive hydrogen bonding via hydroxyl and nitro groups, while H···H contacts (35.7%) reflect significant dispersion contributions. N···H/H···N interactions (9.5%) form a secondary polar network, with minor C···H, N···C, C···C, O···N, N···N, and O···O contacts providing additional weak stabilization. The packing combines a hydrogen-bonded polar scaffold with densely packed hydrophobic regions, yielding a stable lattice with implications for solubility, thermal stability, and co-crystal design.

Introduction

Metronidazole (1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole) is a nitroimidazole-class antimicrobial widely prescribed for anaerobic bacterial and protozoal infections, including *Trichomonas vaginalis*, *Entamoeba histolytica*, *Giardia lamblia*, and *Helicobacter pylori*.[1–6] Its broad-spectrum activity, oral bioavailability, and favorable safety profile have made it a cornerstone in treating gastrointestinal and genitourinary diseases. Despite decades of clinical use, aspects of its solid-state chemistry—particularly the non-covalent interactions directing molecular packing—remain underexplored. This study addresses that gap by providing an in-depth analysis of the intermolecular interaction network in its crystal structure (CCDC 2380391).[7–9]

While the structure of metronidazole has been determined previously, detailed interpretation from a supramolecular and crystal engineering perspective is lacking.[10–13] Here, the focus shifts from reporting atomic coordinates to dissecting the cohesive forces that organize the lattice. Such analysis is increasingly relevant in pharmaceutical science, as the solid-state architecture of an active pharmaceutical ingredient (API) strongly influences its solubility, stability, polymorphism, and bioavailability.[14–16]

Non-covalent interactions—hydrogen bonding, dipole–dipole forces, van der Waals contacts, and π-interactions—define the supramolecular framework of a crystal and control its morphology, mechanical properties, and reactivity.[17–19] Metronidazole is well suited for such investigation due to its chemically diverse functional groups: a hydroxyl moiety, a nitro group, and a nitrogen-rich imidazole ring, each capable of acting as hydrogen bond donor or acceptor.[20–24] While π–π stacking is unlikely to dominate, secondary forces such as C–H···O and other weak heteroatom contacts merit attention.

This work applies a suite of analytical tools—Hirshfeld surface mapping, fingerprint plots, hydrogen-bond geometry evaluation, and energy framework calculations—to quantify the type, directionality, and energetic significance of each interaction.[25–28] Hirshfeld analysis offers a 3D visualization of close contacts and their

percentage contributions (e.g., H···O, H···H, O···O), while fingerprint plots provide a 2D statistical representation of contact distances.[29–34] Energy framework modeling further separates total lattice energy into electrostatic, dispersion, and polarization components, yielding a complete interaction profile.[35, 36]

Special emphasis is placed on classical and non-classical hydrogen bonds. The hydroxyl group typically participates in strong O–H···O/N linkages, while the nitro substituent can function as an acceptor in both hydrogen bonding and dipolar interactions.[37–40] Weaker contacts, such as C–H···O, though low in individual strength, can cumulatively contribute significantly to lattice stability and influence morphology and mechanical behavior.[41–43]

Understanding these forces has practical pharmaceutical implications. Surface-exposed hydrogen bond donors or acceptors affect wettability and dissolution rates, while the overall packing balance can inform co-crystal design strategies to modulate solubility or mechanical performance.[44–47] From a crystal engineering perspective, identifying recurrent motifs such as $R^{2}_{2}(8)$ and $R^{2}_{1}(6)$ hydrogen-bond ring patterns aids in predicting packing tendencies in related nitroimidazole derivatives.[48–50] Comparative analysis with analogues further clarifies structure–interaction relationships and supramolecular preferences.[51, 52]

By concentrating on interaction analysis rather than structural solution, this study reflects current crystallographic trends that prioritize functional interpretation over primary data acquisition.[53, 54] Leveraging publicly available structural data, it demonstrates how re-analysis with modern computational tools can yield new insights into the stabilization forces, solid-state properties, and potential modification pathways of a well-established API.[55–60]

Result and Discussion

The Hirshfeld-surface contact profile (see Figure 1) obtained for the metronidazole crystal (CCDC 2380391) offers a quantitative map of the intermolecular forces shaping molecular arrangement in the solid state. Because the percentages are normalized to the complete Hirshfeld surface of the reference molecule, they do not enumerate individual hydrogen bonds or discrete contacts, but instead express the proportion of surface area in close approach to specific atom types on neighboring molecules. These values therefore encode both occurrence frequency and proximity: a high percentage signifies either numerous points of contact or particularly short separations.

Two contact categories dominate this profile: O···H (38.9%) and H···H (35.7%). The prominence of oxygen–hydrogen approaches is chemically reasonable for metronidazole, which contains multiple oxygen centers (nitro and hydroxyl groups) acting as strong acceptors, along with hydrogens capable of donation (from the alcohol and possibly an imidazole N–H depending on tautomeric form). This large fraction indicates that the lattice is strongly influenced by hydrogen bonds in which oxygen atoms align near hydrogen-bearing sites of adjacent molecules. In practice, such contributions usually comprise a combination of classic O–H···O/N motifs (e.g., an OH group donating to a nitro oxygen or ring nitrogen) and numerous weaker C–H···O contacts common in organic crystals, which nevertheless measurably reinforce packing. On fingerprint plots, O···H contacts generally manifest as sharp, symmetric spikes at low d_e/d_i values, typical of directional hydrogen bonding.

The equally substantial H···H proportion points to extensive hydrophobic, van der Waals interactions between hydrogen-rich surfaces. These contacts exemplify dispersion forces—individually weak, isotropic, and widespread wherever C–H groups face each other. That they nearly match the O···H fraction underscores the cooperative nature of the packing: specific polar hydrogen bonds work in tandem with widespread close approaches between nonpolar fragments to generate overall cohesion. Energetically, such a large H···H share signals the cumulative effect of London dispersion, where many small contributions together rival the strength of fewer but stronger hydrogen bonds.

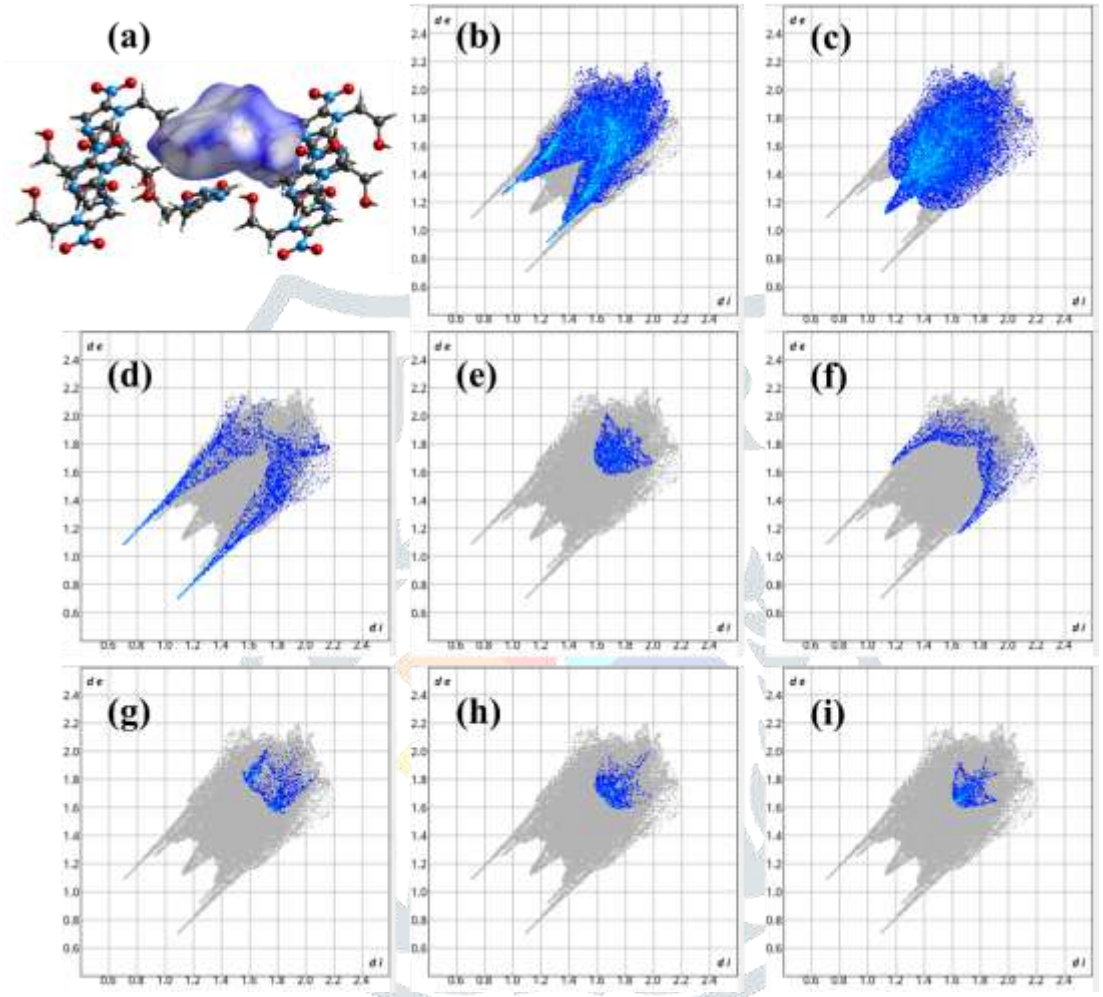

Figure 1: Hirshfeld surface analysis of metronidazole crystal. (a) overall Hirshfeld surface mapped to highlight close contact regions. Specific intermolecular interactions corresponding to distinct element pairs are shown: (b) O···H/H···O, (c) H···H, (d) N···H/H···N, (e) N···C/C···N, (f) C···H/H···C, (g) O···N/N···O, (h) N···N, and (i) C···C.

The next most significant polar contact, N···H (9.5%), complements the oxygen-based interactions. Nitrogen atoms of the imidazole ring can act as acceptors or, when unsubstituted, donors. This percentage likely reflects N–H···O, N–H···N, and C–H···N contacts. Such interactions help fix ring orientations and join molecular chains or sheets. Their smaller share compared with O···H indicates that nitrogen-based bonding supports, rather than dominates, the polar framework.

Intermediate and minor contributions—N···C (3.4%), C···H (3.1%), C···C (2.3%), N···N (2.4%), O···N (2.6%), O···C (1.7%), O···O (0.5%)—add further subtleties. The modest C···C value argues against strong π–π stacking, consistent with the presence of a small heteroaromatic ring rather than extended aromatic planes. Detectable C···H and N···C contacts indicate weaker C–H···π or C–H···N interactions and close heteroatom–carbon approaches that complement the dominant hydrogen bonds. The extremely small O···O fraction reflects electrostatic avoidance of direct oxygen–oxygen proximity, favoring interactions with hydrogen donors instead.

The near-100% total (subject to rounding) confirms that the dataset fully accounts for all close approaches. Overall, the metronidazole lattice emerges as a hybrid architecture: a polar scaffold of O···H and N···H linkages arranged into chains, layers, or networks, embedded within a dense shell of H···H and other dispersion-rich contacts that promote space filling and van der Waals cohesion. This organizational scheme—directional polar "connectors" within a nonpolar packing matrix—is typical of small, multifunctional organic compounds combining hydrophilic and hydrophobic domains.

Table 1: Close contacts from elements in Metronidazole Crystal.

Inside	Outside	percentage
O	O	0.5
O	N	2.6
O	C	1.7
O	H	38.9
N	N	2.4
N	C	3.4
N	H	9.5
C	C	2.3
C	H	3.1
H	H	35.7

From a materials standpoint, such a contact distribution has clear implications. A surface dominated by oxygen-centered hydrogen bonding often leads to anisotropic cohesion, elevated melting temperatures, and reduced mobility in the solid. At the same time, a large hydrophobic-contact fraction favors efficient packing, mechanical resilience, and low volatility. In pharmaceuticals, the interplay of polar and nonpolar surfaces influences solubility: extensive internal hydrogen bonding can raise lattice energy and limit dissolution, while hydrophobic regions affect wetting and dissolution rates. Thus, the observed contact balance explains metronidazole's notable stability and provides insight into its behavior during formulation.

Finally, the percentages suggest logical follow-up studies. Close inspection of the fingerprint plots could separate short, directional O···H and N···H bonds (sharp spikes) from broader distributions corresponding to weaker C–H···O or C–H···N interactions. Mapping the Hirshfeld surface with d_{norm} would pinpoint the exact surface patches forming the closest approaches, clarifying the hydrogen-bond motifs present. Energy-framework analysis could then partition the total lattice energy into electrostatic, polarization, and dispersion components, quantifying the relative role of cumulative H···H contacts. Together, these analyses confirm that metronidazole's packing is maintained through an orchestrated combination of strong, oxygen-centered hydrogen bonds and pervasive dispersion contacts—an equilibrium that defines its solid-state properties.

Conclusion

Hirshfeld surface analysis of the metronidazole crystal (CCDC 2380391) shows that its packing is governed by a synergy of directional hydrogen bonding and extensive dispersion contacts. O···H interactions (38.9%) serve as primary stabilizers, with N···H contacts (9.5%) reinforcing the polar network. H···H contacts (35.7%) highlight the role of London dispersion in dense packing, while minor C···H, N···C, and C···C contributions indicate weaker interactions such as C–H···π contacts that fine-tune lattice geometry. The negligible O···O fraction reflects a preference for heteroatom–hydrogen over heteroatom–heteroatom contacts. This interplay between polar order and dispersive space filling underpins the crystal's stability, mechanical robustness, and pharmaceutical relevance, informing solubility, dissolution, and co-crystal design strategies.

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