International Journal of Creative and Open Research in Engineering and Management
ISSN: **3108-1754 (Online)**
Volume 02 Issue 07 July-2026 | Impact Factor: 3.5

Comparative Hirshfeld Surface Analysis of the Enol and Diketo Tautomers of Curcumin: Insights into Crystal Packing and Intermolecular Interactions

Sumit Kumar

Assistant Professor, PG Department of Chemistry, Magadh University, Bodh-Gaya 824234

Email: sumitkrmgr@gmail.com

How to Cite this Article:

Kumar, S. (2026). Comparative Hirshfeld Surface Analysis of the Enol and Diketo Tautomers of Curcumin: Insights into Crystal Packing and Intermolecular Interactions. International Journal of Creative and Open Research in Engineering and Management, 02(7). https://doi.org/10.55041/ijcope.v2i7.018

https://doi.org/ 10.55041/ijcope.v2i7.018

Abstract

Curcumin has two main tautomeric forms: enol and diketone, which lead to different crystal packing and intermolecular interactions. A comparative Hirshfeld surface analysis was conducted using the crystal structures of enol (CCDC 636155) and diketone (CCDC 1111255) to compare intermolecular interactions forming crystal stability. In the enol form, H···H (41.1%), C···H (25.3%), and O···H (25.2%) interactions predominantly stabilize the crystal, while C···C (51.4%) and O···C (29.9%) interactions stabilize the crystal of the diketone form. This shows that keto-enol tautomerism plays a significant role in intermolecular interactions and crystal packing in curcumin. The results also show the impact on the relationship of the molecular structure of curcumin on the solid state and its polymorphic behavior.

Introduction

Curcumin undergoes keto-enol tautomerism: two structurally different tautomers, enol and diketo (keto) exist in the equilibrium.[1-3] The environment (pH, temperature, solid state, solvent polarity) alters the equilibrium of either tautomer.[4-6] Crystalline tautomers will have different molecular conformations and packing, thus, different intermolecular interactions which define their stability and their tauto-derivative physicochemical properties.[7-10] The enol tautomer is stabilized by an intramolecular hydrogen bond and extends the conjugation throughout the crystal lattice.[11-13] The lack of internal hydrogen bond in the uncovered diketo tautomer forces stability to rely on intermolecular interactions.

Hirshfeld surface analysis adds a new dimension to crystallography by enabling the investigator to visualize and evaluate the strength and type of intermolecular contacts present in the crystal. It utilizes the crystal electron density partitioned by fingerprint plots to estimate the contributions of atom…atom contacts to the crystal

packing. This could include H…H, C…O, C…C, O…O, and many other contacts. The results show the major forces involved in the packing of the molecules and allows the investigator to make comparisons between different crystal forms.

In this study, Hirshfeld surface fingerprint plots were used to study and compare the different intermolecular interactions of the enol (CCDC 636155) and diketo (CCDC 1111255) forms of curcumin.[14] The results showed the major intermolecular interactions and the interaction contributions which helped to identify the contacts that are responsible for the stability of the two forms. Comparing these patterns of interaction helped to visualize the effect that tautomerism has on intermolecular packing, molecular recognition, and the contribution of different interactions. This can provide the information needed to relate the solid-state characteristics of curcumin with its potential pharmaceutical activity and polymorphism and with its solid-state stability.

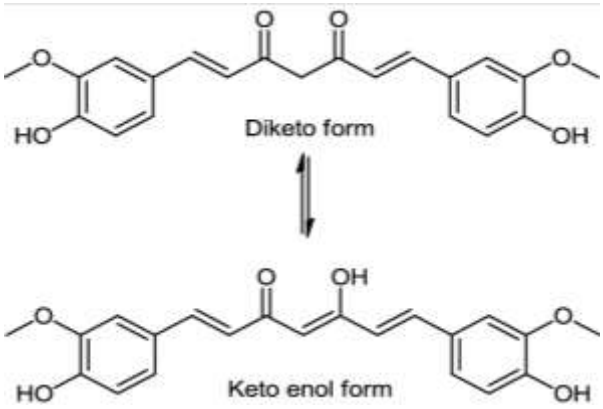

Figure 01: Keto-Enol forms of Curcumin

Materials and Methods

The enol and diketo crystal structures of curcumin were accessed through the CSD with CCDC deposit numbers 636155 (enol) and 1111255 (diketo). Hirshfeld surface analysis and two (2) dimensional fingerprint plots were produced and analyzed using the CrystalExplorer software.[15] The Hirshfeld surfaces were mapped over normalized contact distance (d_{norm}) to depict the significant intermolecular interactions within a crystal structure.[16, 17] The corresponding 2D fingerprint plots were examined to determine the percentage of various intermolecular contacts such as H···H, C···H/H···C, O···H/H···O, C···C, O···C/C···O, and O···O interactions.[18-20] These contacts were analyzed and compared between the two forms of curcumin to determine the effect of the keto-enol tautomerism on crystal packing and the nature and pattern of intermolecular interactions.[21-23]

Result and Discussion

The differences in the molecular packing and intermolecular interactions of curcumin's enol vs diketo (keto) polymorphs are illustrated in the contributions of the Hirshfeld surface fingerprints (Figure 01). The differences result from the variations in the hydrogen bonding and the conformational flexibility of the two tautomers. The enol (CCDC 636155) form has an intramolecular O–H···O hydrogen bond that results in a molecular structure that is almost planar. The diketo (keto) form (CCDC 1111255) does not have this bond and relies on intermolecular hydrogen bonds to stabilize the structure of the crystal. The Hirshfeld surface analysis of the two forms reflects different molecular packing of the two crystals by showing different distributions of the intermolecular interactions.

The enol form shown in Figure 02 has the largest proportion of the Hirshfeld surface (41.1%) due to H···H interactions, suggesting that van der Waals interactions of hydrogen atoms dominate the crystal packing. The

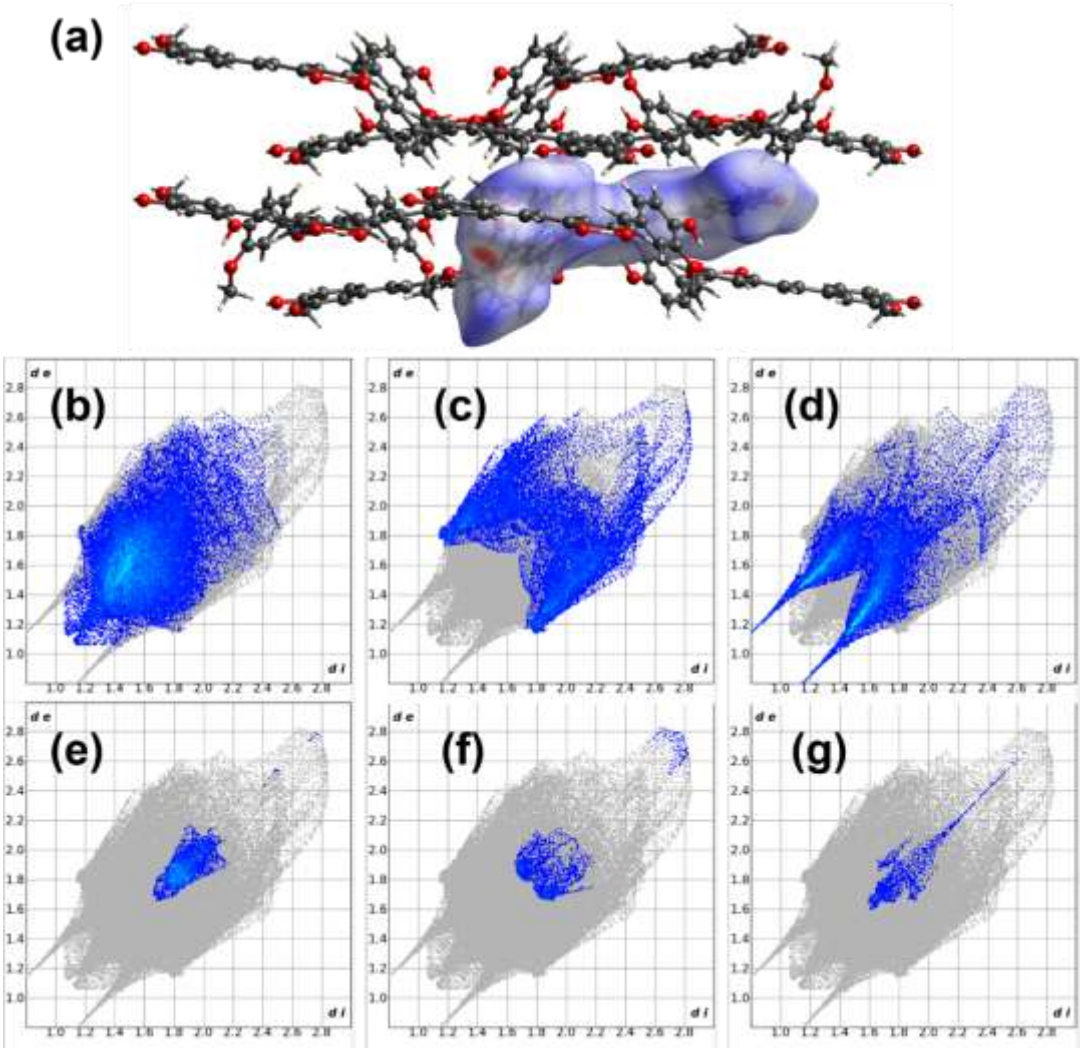

Figure 02: Comparative Hirshfeld surface analysis of the **enol** (CCDC **636155**) and **keto** (CCDC **1111255**) polymorphs. (a) and (h) Hirshfeld surfaces of the enol and keto forms, respectively; corresponding two-dimensional fingerprint plots showing the percentage contributions of intermolecular contacts for the **enol** form: (b) H···H (41.1%), (c) C···H/H···C (25.3%), (d) O···H/H···O (25.2%), (e) C···C (5.2%), (f) O···C/C···O (2.0%), and (g) O···O (1.2%) intermolecular interactions.

The second and third largest contributions in the enol form are almost equally attributed to C···H (25.3%) and O···H (25.2%) interactions. Though C···H contribution is majorly attributed to C–H···π and weak hydrogen bonding of curcumin's aromatic rings, it is important in stabilizing the adjacent aromatic rings of curcumin in the presence of hydrogen and electron-rich carbon. The O···H also shows that the oxygen of the hydroxyl, methoxy, and carbonyl groups are weakly and hydrogen bonded with other molecules. Since one hydroxyl proton is bonded with an intramolecular and strong O–H···O hydrogen bond of the enol form, the intramolecular O···H hydrogen bond and C···H contact contributions are balanced.

The enol form shows a limited interaction of C···C (5.2%) indicating a limited π···π stacking between neighboring aromatic rings. The enol form also has a planar and conjugated backbone that could be favorable for π stacking. Given the current offsets in the arrangements, the crystal packing of curcumin also prefers dispersion and less engagement of the aromatic rings. C···O (2.0%) and O···O (1.2%) interactions also suggest that direct contact with oxygen are scarce and weak and form the least stabilizing interactions in the crystal structure. O···O interactions are also limited due to the electrostatic repulsion of the O-rich structures.

The Hirshfeld function for the diketo form gives different interactions, seen in Figure 03. The largest contribution is C···C interactions, which cover 51.4% of the Hirshfeld surface. This is a large fraction, showing that carbon-based interactions, and more specifically, the π···π interactions of the carbon frameworks and aromatic rings, are the main stabilizing features of the crystal structure. Because of the missing stabilizing intramolecular hydrogen bond of the enol form, molecules in this form pack more closely and allow for greater flexibility of the entire structure and more aromatic systems, which increases the intensity of the carbon-based intermolecular interactions. The intensity of the C···C interactions clearly shows that there is extended aromatic stacking and an optimal overlap of the molecular systems.

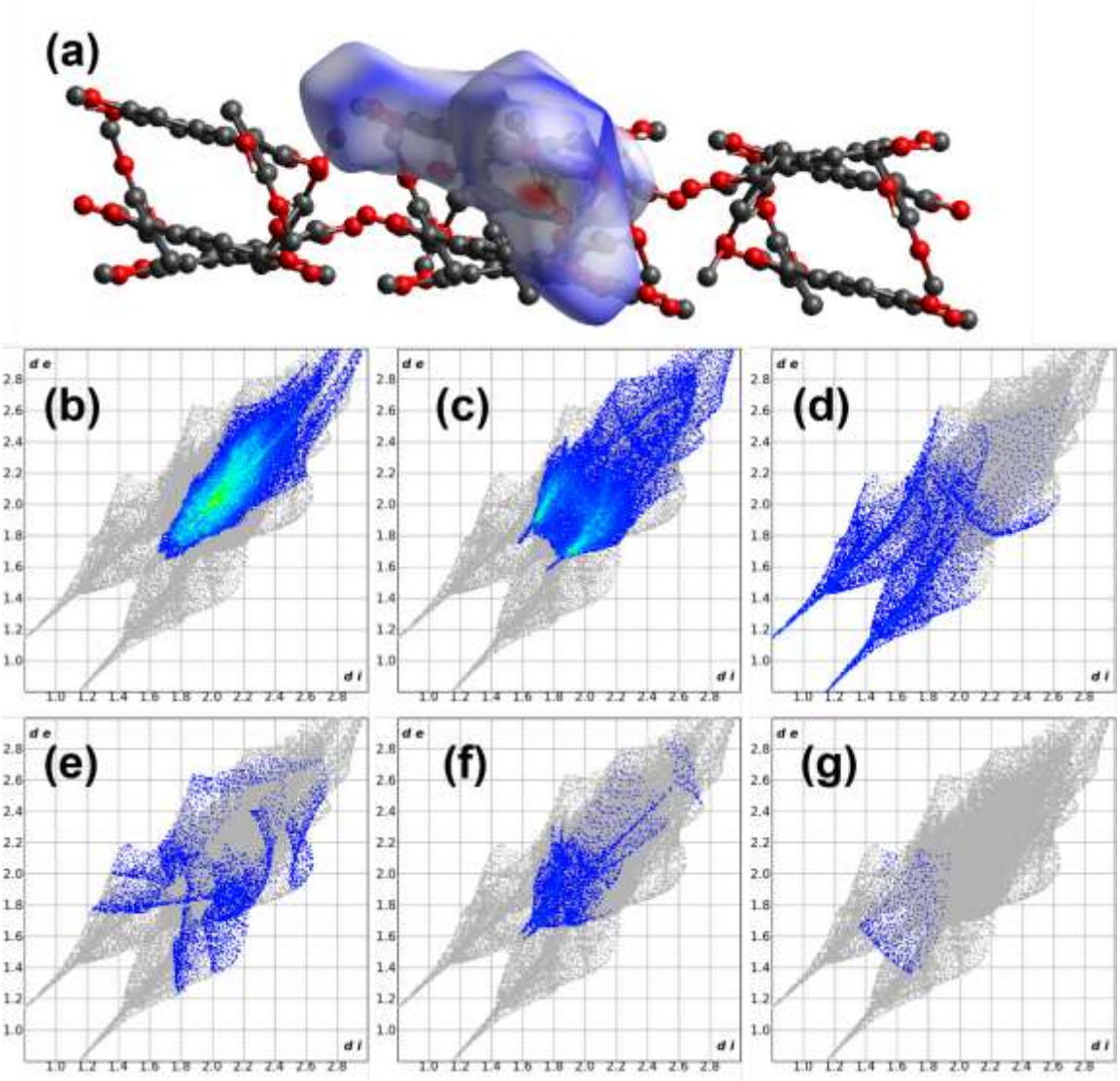

Figure 03: Hirshfeld surface analysis of the **keto** crystal structure (**CCDC 1111255**): (a) Hirshfeld surface showing the intermolecular contacts; corresponding two-dimensional fingerprint plots depicting the percentage

contributions from (b) C···C (51.4%), (c) O···C/C···O (29.9%), (d) O···H/H···O (9.4%), (e) C···H/H···C (4.7%), (f) O···O (4.0%), and (g) H···H (0.4%) intermolecular interactions.

The second largest contribution in the diketo form is O···C interactions, which are larger than those previously mentioned for the enol structure. These interactions are the result of the available carbonyl oxygen atoms making close contacts with aromatic or carbon-containing systems that are highly accessible in the diketo form. In the diketo form, the carbonyl oxygen atoms are free and do not participate in an intramolecular hydrogen bond, and are thus available to form a large number of intermolecular interactions. The O···C interactions further indicate that the carbonyl groups have dipolar interactions, and this is an important feature of the diketo form.

The amount of O…H contribution goes from a very high percentage of 25.2% for enols to only about 9.4% for diketo so that classical hydrogen bonding between oxygen atoms plays a very small role in stabilizing the diketo crystal. There are not as many hydrogen bonds between the two molecule crystals, which indicate that the stability of the diketo crystal and the molecules in it are mostly determined by phenyl stacking and other molecular interactions with carbonyls. The contribution of C...H to the diketo crystal is also much smaller, at 4.7%, than with the enol form. Therefore, weak C-H…π interactions have been replaced by the stronger C…C and the carbon-carbon interaction patterns that make up the diketo crystal than by those in the enol crystal. These reductions of hydrogen mediated interactions correspond with the abundance of conjugated carbon connections present in the diketo form and therefore validates that hydrogen mediated interactions between the two molecule crystals have greatly decreased in the diketo crystal as compared to in the enol.

The contribution from O…O increases from 1.2% in the enol form, to 4.0% in the diketo form, which shows that there are more frequent occurrences of close O…O approaches. Despite being small, the increase in this interaction is presumably due to the presence of two exposed carbonyl oxygens in the diketo tautomer that contribute to the overall packing arrangement of the molecules, despite O…O interactions being inherently electrostatically repulsive. In contrast, the number of H…H contacts decrease significantly from 41.1% in the enol form to just 0.4% in the diketo form, showing that hydrogen-hydrogen dispersive interactions have negligible contribution to the crystal stability of diketo. Such significant differences in number illustrate the fundamentally different packing mechanisms of the two tautomers.

Curcumin exhibits disparate intermolecular interaction profiles based on the nature of its enol and diketone forms, as demonstrated by the Hirshfeld surface analyses. In the enol polymorph, van der Waals type H/ H interactions are the strongest and are complemented by balanced C…H and O…H interactions; therefore, there are many dispersive interactions and moderate hydrogen bonding among a rigid, intramolecularly hydrogen bonded framework. In contrast, the diketogenic form has largely C…C and O…C interactions, indicating that aromatic stacking and multiple carbonyl interactions accommodate the majority of crystalline packing. Thus, the difference in intermolecular contacts between the two tautomers will greatly impact their intermolecular interactions, packing efficiency within the crystal lattice and, consequently, the solid-state stability and physical/chemical properties of curcumin due to their different intermolecular interactions. The Hirshfeld surface conclusion clearly indicates that the chemical basis for the stabilisation of the enol analogue arises predominantly from dispersion and hydrogen bonding and that the stabilisation of the diketone form arises principally from π-stacking and multiple carbonyl-type intermolecular contacts.

Conclusion

The Hirshfeld surface analyses of the two tautomeric forms of curcumin show that keto-enol tautomerism has a major impact on the intermolecular interactions and crystal packing. For the enol (CCDC 636155), the predominant intermolecular interactions involve H...H, C...H, and O...H contacts, indicating that van der Waals forces and hydrogen bonding play important roles in stabilizing the enol form of curcumin. Conversely, for the diketo form (CCDC 1111255), the main stabilizing intermolecular interactions involve C...C and O...C contacts, indicating a greater amount of π-π stacking and interactions that involve carbonyl moieties in this tautomeric form of curcumin. The data demonstrate that tautomerism is critical in determining curcumin's solid-state structure and stability, providing a framework for further studies of curcumin crystal engineering and potential pharmaceutical usage.

References:

[1] V. Bertolasi, V. Ferretti, P. Gilli, X. Yao, C.J. Li, New Journal of Chemistry 32 (2008) 694. https://doi.org/10.1039/b714708b
[2] P. Chatterjee, S. Dutta, T. Chakraborty, The Journal of Physical Chemistry A 126 (2022) 1591. https://doi.org/10.1021/acs.jpca.1c08612
[3] S. Anjomshoa, M. Namazian, M. Noorbala, Journal of Solution Chemistry 45 (2016) 1021. https://doi.org/10.1007/s10953-016-0481-y
[4] A. Hu, S.Y. Lin, S.C. Cheng, T.L. Shih, Microchemical Journal 220 (2025) 116375. https://doi.org/10.1016/j.microc.2025.116375
[5] P. Anand, A. Kunnumakkara, R. Newman, B. Aggarwal, Molecular Pharmaceutics 4 (2007) 807. https://doi.org/10.1021/mp700113r
[6] S. Hewlings, D. Kalman, Foods 6 (2017) 92. https://doi.org/10.3390/foods6100092
[7] B. Aggarwal, A. Kumar, A. Bharti, PubMed 23 (2003) 363.
[8] R. Maheshwari, A. Singh, J. Gaddipati, R.C. Srimal, Life Sciences 78 (2006) 2081. https://doi.org/10.1016/j.lfs.2005.12.007
[9] B. Aggarwal, C. Sundaram, N. Malani, H. Ichikawa, Advances in experimental medicine and biology 595 (2007) 1. https://doi.org/10.1007/978-0-387-46401-5_1
[10] K. Priyadarsini, Molecules 19 (2014) 20091. https://doi.org/10.3390/molecules191220091
[11] S. Moghadamtousi, H. Kadir, P. Hassandarvish, H. Tajik, S. AbuBakar, K. Zandi, BioMed Research International 2014 (2014) 1. https://doi.org/10.1155/2014/186864
[12] A. Giordano, G. Tommonaro, Nutrients 11 (2019) 2376. https://doi.org/10.3390/nu11102376
[13] H. Zhou, C. Beevers, S. Huang, Current Drug Targets 12 (2011) 332. https://doi.org/10.2174/138945011794815356
[14] C.R. Groom, I.J. Bruno, M.P. Lightfoot, S.C. Ward, Structural Science 72 (2016) 171.
[15] M. Spackman, D. Jayatilaka, CrystEngComm 11 (2008) 19. https://doi.org/10.1039/b818330a
[16] P. Spackman, M. Turner, J. McKinnon, S. Wolff, D. Grimwood, D. Jayatilaka, M. Spackman, Journal of Applied Crystallography 54 (2021) 1006. https://doi.org/10.1107/s1600576721002910
[17] J. McKinnon, D. Jayatilaka, M. Spackman, Chemical Communications (2007) 3814. https://doi.org/10.1039/b704980c
[18] C. Jelsch, K. Ejsmont, L. Huder, IUCrJ 1 (2014) 119. https://doi.org/10.1107/s2052252514003327
[19] H. Clausen, M. Chevallier, M. Spackman, B. Iversen, New Journal of Chemistry 34 (2009) 193. https://doi.org/10.1039/b9nj00463g
[20] J. McKinnon, F.P.A. Fabbiani, M. Spackman, Crystal Growth & Design 7 (2007) 755. https://doi.org/10.1021/cg060773k

[21] S. Seth, G. Maity, T. Kar, Journal of Molecular Structure 1000 (2011) 120. https://doi.org/10.1016/j.molstruc.2011.06.003

[22] A. Martin, K. Hartlieb, A. Sobolev, C. Raston, Crystal Growth & Design 10 (2010) 5302. https://doi.org/10.1021/cg1011605

[23] K. Priyadarsini, Current Pharmaceutical Design 19 (2013) 2093. https://doi.org/10.2174/1381612811319110010