



Electronic Structure–Driven Hydrogen-Bond Site Selectivity in Ketohexose Crystals: DV- $X\alpha$ Calculations and Full Interaction Maps

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Abstract. Rare sugars are monosaccharides and their derivatives that are found in very small amounts in nature. Single crystals of sugars selectively adopt specific hydrogen-bonding motifs from the vast number of possible patterns derived from their molecular structures. However, the principles governing this selection remain unresolved crystallography. In this study, we investigate the origin of site selectivity in ketohexose crystals using molecular orbital calculations (DV- $X\alpha$ method) combined with Full Interaction Maps (FIMs) analysis. Bond overlap population values ($\sim 10^{-2}$) were used to quantify hydrogen-bond strength. The results show that dominant hydrogen-bonding sites are consistently identified as O2 in fructose- and allulose-type compounds, O3 in sorbose-type compounds, O3–O4 in D-tagatose, and O2–O5 in 1-deoxy-D-tagatose. These sites correspond to regions predicted by FIMs as favorable for hydrogen bonding. These findings demonstrate that hydrogen-bond site selectivity is governed by intrinsic electronic structure and provide a framework for predicting intermolecular interactions in molecular crystals.

Keywords: Computational chemistry, crystal engineering, electronic structure analysis, intermolecular interactions, ketohexose

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1. Introduction

Rare sugars are monosaccharides found in limited quantities in nature and form well-defined molecular crystals with complex hydrogen-bonding networks.

In molecular crystals, numerous hydrogen-bonding configurations are theoretically possible; however, only a limited number of specific hydrogen-bonding motifs are realized in practice. Understanding the principles governing such site selectivity is a fundamental challenge in crystallography and crystal engineering [1-5]. Previous crystallographic studies have suggested that subtle differences in molecular structure led to variations in hydrogen-bonding behavior among ketohexoses [6-8]. However, these studies have primarily focused on structural descriptions, and the mechanism governing hydrogen-bond site selectivity remains unclear. In particular, the role of intrinsic electronic structure in determining preferred hydrogen-bonding sites has not been systematically clarified. Computational approaches, such as molecular orbital calculations, provide a means to quantitatively evaluate intermolecular interactions, while statistical methods like Full Interaction Maps (FIMs) enable visualization of preferred interaction regions based on crystallographic data. However, a unified analysis combining electronic structure calculations with data-driven interaction mapping has not yet been fully explored for ketohexose crystals. Therefore, a key question of this study is: what determines the preferential selection of hydrogen-bonding sites in ketohexose crystals? To address this question, we perform molecular orbital calculations using the DV- $X\alpha$ method and analyze intermolecular interactions using Full Interaction Maps.

2. Methods

By integrating these approaches, we aim to elucidate the relationship between electronic structure and hydrogen-bond site selectivity and to provide a framework for understanding and predicting intermolecular interactions in molecular crystals.

2.1. Molecular orbital calculations

In this study, computational models were constructed using the absolute coordinates of ten ketohexoses and their derivatives. The crystallographic data were obtained from the Cambridge Structural Database (CSD) (β -D-fructose: FRUCTO12, β -D-allulose: OGETAW01, α -L-sorbose: SORBOL01, α -D-tagatose: TAGTOS01, 3-deoxy- β -D-fructose: RUWBIU, 1-deoxy- α -D-sorbose: CERRIB, 1-deoxy- α -D-tagatose: LEQKEY01, 1-deoxy-fructose monohydrate: TICCUE, 4-deoxy-4-fluoro-fructose: CIJHEI, and 6-deoxy-allulofuranose (psicofuranose): RUTQII) [9-16]. To account for intermolecular interactions in the crystal environment, cluster models were constructed by placing neighboring molecules around a central molecule based on the crystallographic coordinates. Neighboring molecules within approximately 3.5 Å of the central molecule, corresponding to the first coordination shell, were included to explicitly represent hydrogen-bonding interactions. This approach enables the evaluation of local intermolecular interactions while maintaining computational efficiency[5,17,24].

To quantitatively evaluate these intermolecular interactions, molecular orbital calculations were performed using the DV- $X\alpha$ method, a first-principles computational approach. Compared to more computationally demanding methods such as density functional theory (DFT), the DV- $X\alpha$ method allows efficient analysis of multiple cluster models while retaining sufficient accuracy for describing hydrogen-bonding interactions. All calculations were carried out using a self-consistent field procedure, and bond overlap population (BOP) values were evaluated from the converged electronic structures. BOP quantitatively represents the overlap of wavefunctions between two atoms, larger values indicate stronger hydrogen bonds. Typically, hydrogen bond BOP values are on the order of 10^{-2} , expressed in units of electrons. It should be noted that the cluster model does not explicitly account for long-range periodic interactions in crystals. However, it is sufficient to capture local hydrogen-bonding interactions, which are the primary focus of this study. For hexoses, carbon positions are numbered according to international conventions, and oxygen atoms bonded to C1 through C6 are labeled O1 through O6,

respectively. In the present study, oxygen atoms are denoted as O1, O2, etc., following this rule[17,19,25].

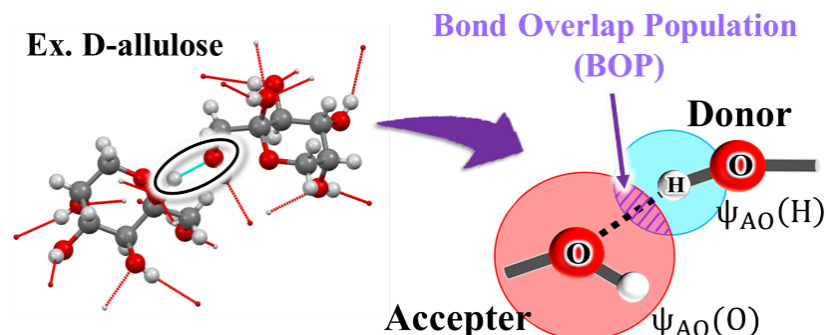


Figure 1. Bond Overlap Population (BOP).

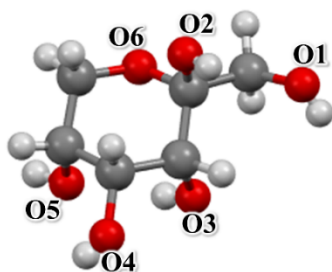


Figure 2. The numbering of Ketohexose.

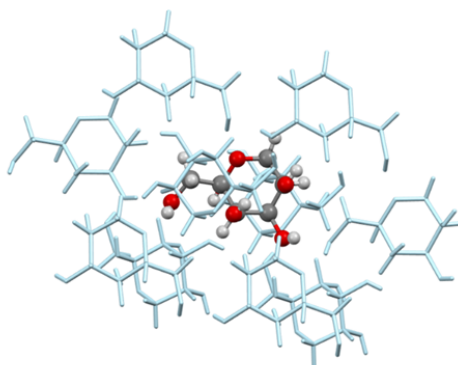


Figure 3. The constructed computational model of D-Allulose.

2.2. Full Interaction Maps (FIMs) analysis

Full Interaction Maps (FIMs) analysis was employed to visualize the preferred intermolecular interactions based on statistical data derived from the Cambridge Structural Database (CSD) [18]. This method enables visualization of the ideal interaction environments around functional groups and facilitates evaluation of molecular packing in crystals. In this study, the correspondence between hydrogen-bonding positions predicted by FIMs and those observed in experimental crystal structures was evaluated. Hydrogen bonds were classified as “ideal” when the donor–acceptor geometry overlapped with high-probability regions identified in the FIMs, and as “non-ideal” otherwise. The evaluation was based on the spatial agreement between experimentally observed hydrogen-bond positions and statistically preferred interaction regions. This combined approach enables a direct comparison between electronic structure–based interaction strength (BOP) and statistically predicted

interaction preferences (FIMs), providing a comprehensive understanding of hydrogen-bonding behavior in ketohexose crystals[20].

3. Results and Discussion

3.1. Molecular orbital calculation

Molecular orbital calculations were performed for ten ketohexoses and their derivatives (β -D-fructose, β -D-allulose, α -L-sorbose, α -D-tagatose, 3-deoxy- β -D-fructose, 1-deoxy- α -D-sorbose, 1-deoxy- α -D-tagatose, 1-deoxy-fructose monohydrate, 4-deoxy-4-fluoro-fructose, and 6-deoxy-allulofuranose) to evaluate the strength of hydrogen bonding. The results are summarized in Table 1.

Table 1. Hydrogen bond strength (BOP values).

O number	BOP						
	b-D-Fructose	b-D-Psicose	a-D-Tagatose	a-L-Sorbose	Deoxy-Fructose	Deoxy-tagatose	Deoxy-sorbose
O1	0.047	0.046	0.034	0.080	0.043	—	—
O2	0.089	0.058	0.037	0.082	0.066	0.118	0.056
O3	0.040	0.034	0.074	0.128	—	0.087	0.084
O4	0.034	0.043	0.065	0.075	0.050	0.091	0.063
O5	0.062	0.043	0.052	0.067	0.041	0.086	0.045
O1	Deoxy-fructose monohydrate		Deoxy-4luoro-fructose		Deoxy-psicofuranose		
O2	—		0.019		0.024		
O3	0.026		0.028		0.015		
O4	0.011		0.028		0.027		
O5	0.028		—		0.010		
O5	0.022		0.031		—		

Although the hydrogen bonds can be categorized into donor-type and acceptor-type, they are crystallographically equivalent; therefore, only donor-type hydrogen bonds are presented here as representative. In the table, notations such as O1 refer to the oxygen atom serving as the origin of the hydrogen bond. The analysis confirmed that most BOP values fall within the order of 10^{-2} , consistent with typical hydrogen-bond magnitudes [21]. Furthermore, the relative differences in BOP values enable identification of dominant hydrogen-bonding sites within each molecule. As shown in Table 1, fructose and allulose, as well as allulose-type compounds, consistently exhibited high BOP values at O2, while sorbose-type compounds showed high BOP values at O3. This localization of high BOP values at specific oxygen sites suggests that hydrogen-bonding preferences are governed by the electronic distribution within each molecule. In contrast, tagatose-type compounds did not exhibit a clear localization of BOP values at a particular site, but instead showed a more delocalized distribution of hydrogen-bonding interactions across multiple hydroxyl groups. This difference indicates that variations in molecular conformation led to distinct electronic distributions, resulting in either localized or distributed hydrogen-bonding behavior. For fructose, allulose, and sorbose, oxygen atoms that consistently showed high BOP values were identified in both chiral and deoxy analogs. Specifically, O2 was dominant in fructose- and allulose-type compounds, whereas O3 was dominant in sorbose-type compounds. These findings indicate that each sugar possesses a characteristic hydrogen-bonding site determined by its intrinsic electronic structure, which directly influences hydrogen bond formation. Further analysis of fructose derivatives revealed that both 1-deoxy-fructose monohydrate and 4-deoxy-4-fluoro- β -D-fructose retained high BOP values at O2, the characteristic hydrogen-bonding site of fructose-type compounds. In contrast, 6-deoxy-allulofuranose exhibited reduced BOP values, indicating a distinct trend. This suggests that minor modifications, such as deoxygenation or fluorination, do not

substantially alter the inherent electronic structure of sugars, whereas major structural changes, such as conversion from a six-membered to a five-membered ring, significantly modify the electronic structure and consequently affect hydrogen-bonding patterns.

3.2. Full Interaction Maps (FIMs) analysis

In this study, the agreement between hydrogen-bonding positions predicted by FIMs and those observed in experimental crystal structures was evaluated. Hydrogen bonds consistent with the high-probability regions in the FIMs were defined as “ideal hydrogen bonds,” while those located outside these regions were classified as “non-ideal hydrogen bonds,” based on spatial overlap with high-probability regions.

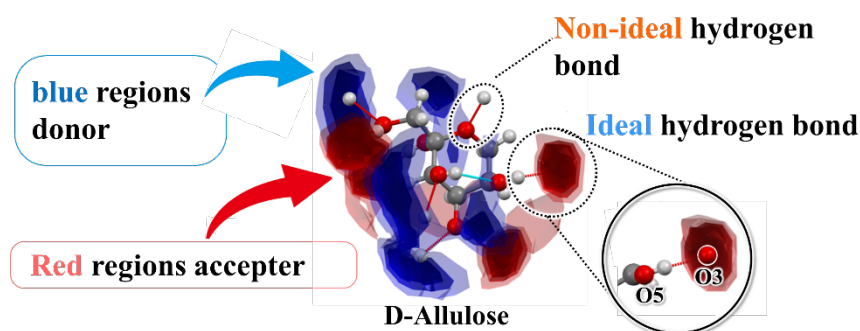


Figure 4. Full Interaction Maps (FIMs) analysis of D-Allulose.

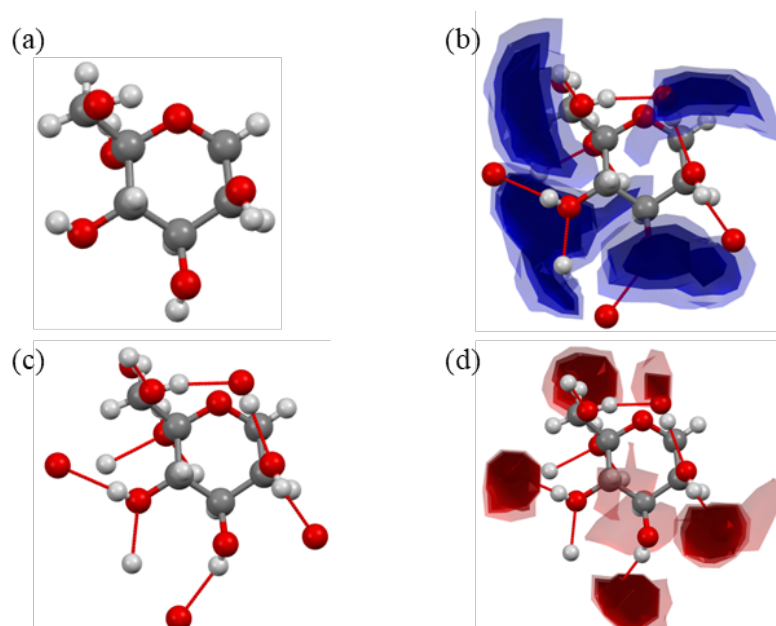


Figure 5. Results of FIMs analysis for β-D-fructose. (a) Molecular structure. (b) Full interaction maps (map of donor-type hydrogen bonds). (c) Intermolecular hydrogen bonds. (d) Full interaction maps (map of acceptor-type hydrogen bonds).

The FIMs analysis predicted regions corresponding to preferred hydrogen-bonding sites. Hydrogen bond pairs are presented in the order donor...acceptor. It was found that hydrogen bond pairs exhibiting the highest BOP values generally correspond to ideal hydrogen bonds predicted by FIMs. This strong correspondence indicates that electronic structure-based interaction strength (BOP) is closely aligned with statistically preferred interaction regions derived from crystallographic data [22]. Therefore, for the ketohexoses examined, hydrogen bonds with high BOP values coincided with the regions identified by FIMs as favorable for hydrogen bonding. These results indicate that such hydrogen bonds play a

central role in crystal formation. This agreement suggests that BOP can serve as a quantitative descriptor for predicting hydrogen-bonding preferences in molecular crystals.

The results demonstrate that hydrogen-bond site selectivity in ketohexose crystals is governed by the intrinsic electronic structure of each molecule. The localization of electronic density at specific oxygen atoms enhances their ability to form strong hydrogen bonds, leading to preferential selection of these sites during crystal formation. A comparison across different ketohexose types reveals that small structural differences, such as the orientation of hydroxyl groups, significantly influence electronic distribution and consequently hydrogen-bonding behavior. This explains why structurally similar sugars exhibit distinct hydrogen-bonding patterns. The strong agreement between BOP and FIMs analyses further indicates that hydrogen-bonding preferences can be predicted by combining electronic structure calculations with statistical interaction mapping. This integrated approach provides a framework for understanding and predicting intermolecular interactions in molecular crystals. However, it should be noted that the present study is based on cluster models and does not explicitly account for long-range periodic effects in crystals. In addition, the comparison between BOP and FIMs is based on qualitative agreement rather than rigorous statistical validation. Despite these limitations, the present findings provide important insights into the predictability of hydrogen-bonding patterns and contribute to the development of design principles in crystal engineering and structure–property relationships [23].

Table 2. Results of FIMs analysis. Ideal hydrogen-bond pairs are shown in blue, while non-ideal hydrogen-bond pairs are shown in red.

compound	Hydrogen bond pairs	
	H Donor	H Acceptor
α -L-Sorbose	O1-O3	O3-O1
	O2-O5	O5-O2
	O3-O4	O4-O3
	O4-O6	O6-O4
	O5-O2	O2-O5
	O5-O3	O3-O5
α -D-tagatose	O1-O5	O5-O1
	O2-O5	O5-O2
	O3-O4	O4-O3
	O4-O6	O6-O4
	O5-O2	O2-O5
β -D-Fructose	O1-O3	O3-O1
	O2-O1	O1-O2
	O3-O5	O5-O3
	O3-O6	O6-O3
	O4-O2	O2-O4
	O5-O2	O2-O5
compound	Hydrogen bond pairs	
	H Donor	H Acceptor
β -D-Allulose	O1-O6	O6-O1
	O2-O4	O4-O2
	O3-O2	O2-O3
	O4-O1	O1-O4
	O5-O3	O3-O5
	O5-O4	O4-O5
1-Deoxy- α -D-sorbose	O2-O5	O5-O2
	O3-O4	O4-O3
	O4-O6	O6-O4
	O5-O2	O2-O5
	O5-O3	O3-O5
1-Deoxy- α -D-tagatose	O2-O5	O5-O2
	O3-O4	O4-O3
	O4-O6	O6-O4
	O5-O2	O2-O5
3-Deoxy- β -D-Fructose	O1-O6	O6-O1
	O2-O5	O5-O2
	O4-O1	O1-O4
	O5-O4	O4-O5
compound	Hydrogen bond pairs	
	H Donor	H Acceptor
Deoxy-fructose monohydrate	O2-H ₂ O	H ₂ O-O2
	O3-O4	O4-O3
	O3-O5	O5-O3
	O4-O6	O6-O4
	O5-O3	O3-O5
4-Deoxy-4-fluoro- β -D-fructose	O1-O3	O3-O1
	O2-O1	O1-O2
	O3-O5	O5-O3
	O3-O6	O6-O3
	O5-O2	O2-O5
6-deoxy- α -L-allulofuranose	O1-O5	O5-O1
	O2-O1	O1-O2
	O3-O2	O2-O3
	O4-O3	O3-O4
	O4-O4	O4-O4

4. Conclusion

In this study, detailed investigations of intermolecular interactions were conducted using molecular orbital calculations and Full Interaction Maps (FIMs) analysis. The results demonstrate that hydrogen-bond site selectivity is governed by the intrinsic electronic structure of each molecule, where specific oxygen atoms with favorable electronic distributions preferentially form strong hydrogen bonds. Furthermore, the strong correspondence between bond overlap population (BOP) values and FIMs predictions indicates that electronic structure–based interaction strength is consistent with statistically preferred interaction regions in molecular crystals. These findings provide a unified framework for

understanding hydrogen-bond formation, extending beyond ketohexoses to general molecular crystals. In particular, the integration of electronic structure analysis with data-driven interaction mapping offers a promising approach for predicting intermolecular interactions and guiding molecular design in crystal engineering.

While the present study is based on cluster models and qualitative comparison between BOP and FIMs, future work incorporating periodic calculations and quantitative statistical validation will further enhance the predictive capability of this approach.

Declaration of AI and AI assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to improve the English language, readability, and clarity of the manuscript. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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