Towards quantitative analysis of intermolecular interactions with Hirshfeld surfaces

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Received (in Cambridge, UK) 2nd April 2007, Accepted 2nd May 2007
First published as an Advance Article on the web 14th May 2007
DOI: 10.1039/b704980c

Enhancements to the properties based on Hirshfeld surfaces enable quantitative comparisons between contributions to crystal packing from various types of intermolecular contacts.

Detailed comparison between molecular crystal structures, even structures containing the same molecule, is seldom straightforward, and the rapid growth in the number of published structures has given impetus to the need to rapidly compare and contrast molecular crystal structures and, in so doing, to quantify the similarities and differences. Comparisons of this kind can be performed at a number of levels,[1] but where the aim is understanding of crystal packing, especially for the purposes of crystal design and crystal engineering, an essential prerequisite is a whole-of-molecule approach, stripped of the biases inherent in focusing on a limited number of short atom–atom contacts that are *assumed* to be important. This point was emphasised by Desiraju a decade ago[2] and, almost by way of a challenge, Nangia and Desiraju[3] observed that "Many will appreciate that the structure of, say, naphthalene resembles that of anthracene more than it resembles benzene. Is it possible to quantify such comparisons? If so, such quantification would amount to pattern matching and becomes important because crystals that are structurally similar are also likely to have similar properties".

The Hirshfeld surface[4] is becoming a valuable tool for analysing intermolecular interactions while maintaining a whole-of-molecule approach. It is defined by the 0.5 isosurface of the weight function $w(\mathbf{r})$ (equation 1), the sum of spherical atom electron densities from the molecule of interest (the promolecule) divided by the same sum for the crystal (the procrystal). Inside the Hirshfeld surface the electron density of the promolecule dominates the procrystal. For points on the surface, distances to the nearest atoms outside, d_e, and inside, d_i, are readily defined, and we have used these properties, together with the identity of those atoms, to explore the type (C–H···π, O–H···O, H···H *etc.*) as well as the proximity of intermolecular contacts in a molecular crystal.[5] Here, we describe extensions to the suite of Hirshfeld surface tools with the goal of enabling quantitative comparison between intermolecular interactions in molecular crystals.

$$w(\mathbf{r}) = \rho_{\text{promolecule}}(\mathbf{r}) / \rho_{\text{procrystal}}(\mathbf{r}) = \sum_{A \in \text{molecule}} \rho_A(\mathbf{r}) \Bigg/ \sum_{A \in \text{crystal}} \rho_A(\mathbf{r}) \qquad (1)$$

The distances d_e and d_i mapped on the Hirshfeld surface provide a three-dimensional picture of intermolecular close contacts in a crystal. They are also used to generate a fingerprint plot,[6] a concise two-dimensional summary of intermolecular interactions in the crystal. However, when mapped on the surface d_e and d_i have the limitation that they do not take into account the relative sizes of atoms, so close contacts between large atoms are often not effectively highlighted. To overcome this we define a normalised contact distance, d_{norm} (equation 2), where r^{vdW} is the van der Waals (vdW) radius of the appropriate atom internal or external to the surface. d_{norm} is negative where contacts shorter than vdW separations occur, and positive for contacts greater than vdW separations, and is displayed using a red–white–blue colour scheme, where red highlights shorter contacts, white is used for contacts around the vdW separation, and blue is for longer contacts. Our focus is of course on the shorter contacts, which become brighter and larger red spots as internuclear separations decrease. Moreover, because d_{norm} is symmetric in d_e and d_i, any close intermolecular contact will be characterised by two identical red regions, although not necessarily on the same molecule.

$$d_{\text{norm}} = \frac{d_i - r_i^{\text{vdW}}}{r_i^{\text{vdW}}} + \frac{d_e - r_e^{\text{vdW}}}{r_e^{\text{vdW}}} \qquad (2)$$

Red regions on the d_e surface for β-oxalic acid (Fig. 1)† highlight the hydrogen bond acceptor, where d_e is short (the surface is close to the hydrogen nucleus outside the surface), but the hydrogen bond donor is much less prominent (the surface is further from the nucleus of the larger oxygen atom outside the surface). In contrast, the d_{norm} surface (Fig. 1) highlights both donor and acceptor equally (two large red spots), as well as the less-prominent C=O···π contact (a pair of pale-red regions), which is not highlighted at all on the d_e surface. The difference between the d_e and d_{norm} surfaces is more dramatic for α-TTF (tetrathiafulvalene, Fig. 2), where close contacts to sulfur are never highlighted on the d_e surface because of their larger distance relative to contacts to hydrogen. In this case, d_{norm} focuses attention on a single short S···S contact which is not apparent on the d_e surface, while the contacts that were the most prominently highlighted on the d_e surface are less significant.

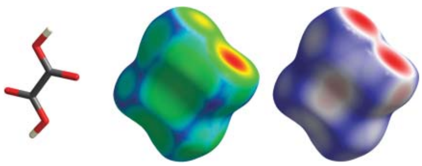

Fig. 1 Hirshfeld surface of β-oxalic acid mapped with d_e (left) and the new d_{norm} property (right).

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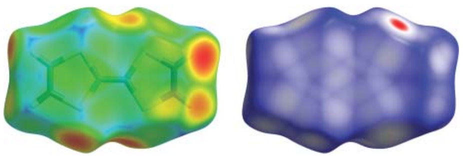

Fig. 2 Hirshfeld surface of α-TTF mapped with d_e (left) and d_{norm} (right).

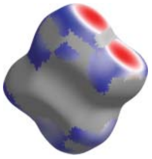

Fig. 3 Selective highlighting of O···H and H···O contacts on the d_{norm} surface of β-oxalic acid.

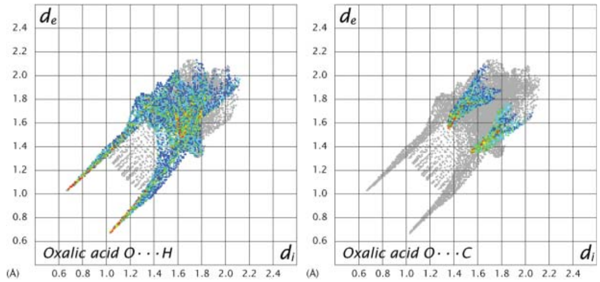

Fig. 4 Fingerprint plots for β-oxalic acid resolved into O···H (left) and O···C contacts (right). The full fingerprint appears beneath each decomposed plot as a grey shadow.

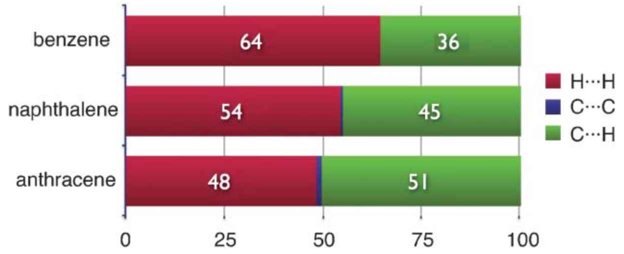

Fig. 5 Relative contributions to the Hirshfeld surface area for the various close intermolecular contacts in benzene, naphthalene and anthracene.

While the Hirshfeld surface and properties defined by it emphasise a whole-of-molecule approach to understanding intermolecular interactions, they can also be used in conjunction with a more direct atom···atom based approach to gain a fuller appreciation of the important interactions in a molecular crystal. In order to display d_{norm} we require for each surface point both the distance and identity of the nearest atoms internal and external to the surface. Using this information it is possible to graphically highlight those regions of the surface involved in a specific type of intermolecular contact. Fig. 3 shows the d_{norm} surface of β-oxalic acid, highlighting only O···H and H···O intermolecular contacts. Only portions of the surface where hydrogen is the closest atom inside the surface, and oxygen the nearest atom outside the surface, or *vice versa*, are coloured. Most importantly, it is now straightforward to sum the area of these highlighted surface patches, to determine that O···H and H···O contacts (*i.e.* hydrogen bonding) comprise 50% of the total Hirshfeld surface area for this molecule.

In the same manner we can decompose fingerprint plots to highlight particular close contacts. Fig. 4 illustrates this for β-oxalic acid, highlighting separately the C···O and O···H intermolecular contacts; to provide context, the outline of the full fingerprint is shown in grey. This decomposition enables separation of contributions from different interaction types, which commonly overlap in the full fingerprint. It also facilitates rapid comparison between related molecules in the same or different crystals, and as an example we return to the question raised by Nangia and Desiraju concerning benzene, naphthalene and anthracene. Fig. 5 shows the relative contributions to the Hirshfeld surface area due to C···H (*i.e.* C–H···π), H···H and C···C (*i.e.* π···π) close contacts for benzene, naphthalene and anthracene. From this simple analysis, it immediately emerges that naphthalene (45% C···H area, small C···C area) is more similar to anthracene (51% C···H area, small C···C area) than it is to benzene (36% C···H area, no C···C area). The visual comparison between these three structures is even more convincing. Fig. 6 shows fingerprints of only the C···H contacts in these three molecular crystals. It is clear that the *natures* of the C···H contacts in naphthalene and anthracene are strikingly similar to each other, while the pattern of C···H contacts in benzene is distinctly different. Fig. 6 also reveals that the C–H···π contact becomes progressively shorter across the series, and the changing shape of the shortest region of the contact reflects the changing nature of the shortest C–H···π contact in these systems.[7]

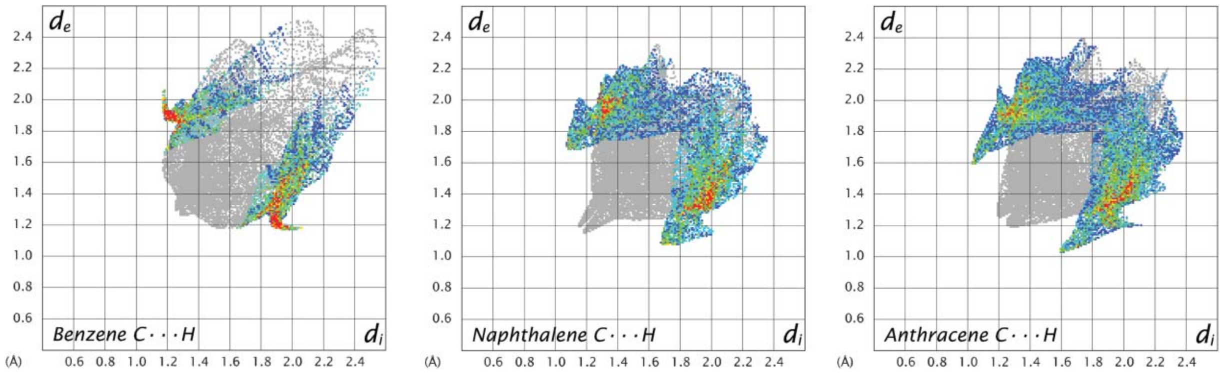

Fig. 6 Fingerprint plots for benzene, naphthalene and anthracene resolved into C···H contacts. The full fingerprint appears beneath each decomposed plot as a grey shadow.

Fig. 7 Relative contributions to the Hirshfeld surface for the major intermolecular contacts in forms I and II of paracetamol.

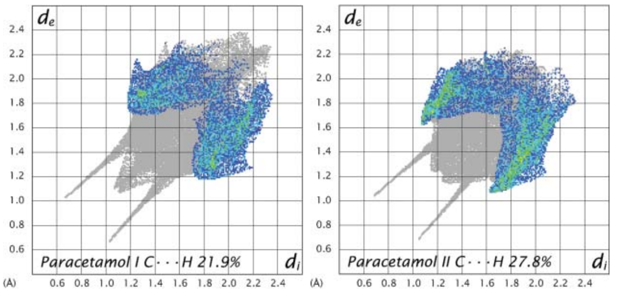

Fig. 8 Decomposed fingerprints of the C···H contacts in paracetamol.

In polymorphic crystals understanding the differences between the chemical environments of identical molecules is a key to understanding the structure as a whole. This task can be made considerably more difficult by the fact that the structural differences being investigated are often quite subtle. Alternatively, where structural differences are more substantial, direct comparisons of particular intermolecular interactions are less meaningful. As an example, we apply the new tools to polymorphism in paracetamol (*p*-hydroxyacetanilide), for which a detailed comparison between the crystal structures of forms I and II has been reported,[8] and limit discussion to the additional insight that may be gained using the new Hirshfeld surface tools. Fig. 7 shows the contribution to the Hirshfeld surface area for each type of intermolecular contact for both polymorphs. H···C contacts comprise 28% of the surface area in form II, and only 22% of the surface in form I. This breakdown gives information about the quantity of the H···C contacts in the two polymorphs, and suggests differing importance of this interaction to the crystal packing in each case. More can be learned, however, from inspecting the decomposed fingerprint plots for the two polymorphs (Fig. 8), which reveal that form II features significantly shorter C···H contacts. In fact in form II C(phenyl)–H···C contacts occur on both sides of the benzene ring, at 2.70 Å and 2.74 Å, while form I features a single C(methyl)–H···C contact at 2.93 Å. Finally, Fig. 9 presents d_{norm} surfaces of the two forms of paracetamol with O···H contacts highlighted, along with the surrounding molecules involved in hydrogen bonding. This clearly shows that despite significantly different crystal packing arrangements, the paracetamol molecule engages in the same pattern of hydrogen bonding contacts – both donor and acceptor – in the two crystalline forms.

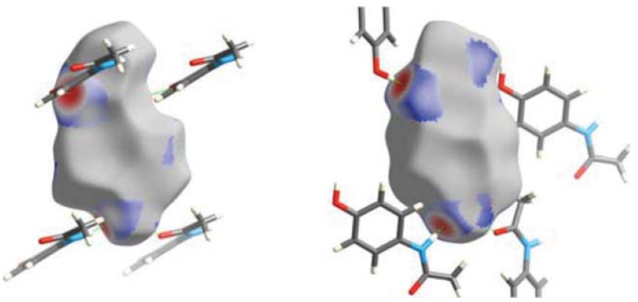

Fig. 9 d_{norm} surfaces of paracetamol molecules in forms I (left) and II (right), highlighting the hydrogen bonding motifs. The molecules within the surfaces have the same orientation.

We conclude by observing that although some of the structural insights described in this communication could have been obtained by more conventional means, many could not. The new d_{norm} surface and the breakdown of fingerprint plots that we have documented here greatly enhance the existing techniques and tools based on the Hirshfeld surface, and already incorporated in *CrystalExplorer*.[9] Together they constitute a powerful resource for visualising, exploring, analysing, and now quantifying intermolecular interactions in molecular crystals with unprecedented ease, rapidity and immediacy.

We thank Dr Francesca Fabbiani for many helpful discussions, and for her valuable comments on the manuscript. This research was supported by the Australian Research Council.

Notes and references

† *Hirshfeld surfaces*. CSD refcodes for structures: β-oxalic acid: OXALAC04; α-TTF: BDTOLE10; benzene: BENZEN07; naphthalene: NAPHTA16; anthracene: ANTCEN10; paracetamol: HXACAN06 (form I), HXACAN21 (form II). For the generation of surfaces and properties all bond lengths to hydrogen atoms were set to typical neutron values (C–H = 1.083 Å, O–H = 0.983 Å, N–H = 1.009 Å),[10] and vdW radii from Bondi[11] were used. The methods described in this work have been implemented in *CrystalExplorer*.[9]

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