Hirshfeld Surfaces: A New Tool for Visualising and Exploring Molecular Crystals

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Dedicated to the memory of Fred Hirshfeld

Abstract: A remarkable new way of exploring molecular crystals is afforded by isosurface rendering of smooth, nonoverlapping molecular surfaces arising from a partitioning of crystal space based on Hirshfeld's stockholder partitioning scheme. These surfaces reflect the proximity of neighbouring atoms and molecules, and hence intermolecular interactions, in a novel visual manner which offers a hitherto unseen picture of molecular shape in a crystalline environment. This work reports 3D isosurface pictures of these molecular surfaces, which we call Hirshfeld surfaces, as well as a number of quantitative measures of molecular size and global shape, applied to a variety of simple molecular crystals. Implications for the exploration of crystal packing and crystal engineering are discussed.

Keywords: crystal engineering · crystal packing · graphics · molecular surfaces · solid-state structures

Introduction

The structures of molecular crystals continue to attract considerable attention for many reasons, among them the search for materials with desirable physical and chemical properties, which motivates much of modern crystal engineering,[1] the modelling of intermolecular interactions,[2] ab initio crystal structure prediction,[3] and studies of polymorphism.[4] For all these purposes, molecular and crystal structures determined by X-ray and/or neutron diffraction are integral to the research, especially the description and classification of intermolecular interactions in terms of derived interatomic distances and other geometric criteria. We have recently described[5] a scheme for partitioning the volume of a molecular crystal into smooth, nonoverlapping molecular entities (and small intermolecular voids) which reflect the proximity of nearest neighbours, and hence intermolecular interactions, in a novel visual manner and which offer a hitherto unseen picture of molecular shape in a crystalline environment. We now report the first quantitative applications of this partitioning scheme: 3D isosurface pictures of these molecular surfaces, which we call Hirshfeld surfaces, as well as a number of quantitative measures of molecular size and global shape.

Results and Discussion

The molecular Hirshfeld surfaces are constructed by partitioning space in the crystal into regions where the contribution from the electron distribution of a sum of spherical atoms for the molecule (the promolecule) exceeds the contribution from the corresponding sum over the crystal (the procrystal). Following Hirshfeld,[6] a weighting function $w(\mathbf{r})$ can be defined [Eq. (1)], from which it follows that the Hirshfeld

$$\begin{aligned} w(\mathbf{r}) &= \sum_{\mathrm{a} \in \mathit{molecule}} \rho_\mathrm{a}(\mathbf{r}) \Big/ \sum_{\mathrm{a} \in \mathit{crystal}} \rho_\mathrm{a}(\mathbf{r}) \\ &= \rho_\mathrm{promolecule}(\mathbf{r})/\rho_\mathrm{procrystal}(\mathbf{r}) \qquad (1) \\ &\approx \rho_\mathrm{molecule}(\mathbf{r})/\rho_\mathrm{crystal}(\mathbf{r}) \end{aligned}$$

surface for the particular molecule is defined by $w(\mathbf{r}) = 0.5$, and the volume occupied by the molecule in the crystal is that region where $w(\mathbf{r}) \geq 0.5$. Here, $\rho_\mathrm{a}(\mathbf{r})$ is a spherically averaged atomic electron density function[7] centered on nucleus a, and the ratio between promolecule and procrystal electron densities can be regarded as an approximation to the ratio between true molecule and crystal electron densities. For computational purposes the sum over the crystal is truncated to a cluster of molecules within ≈ 10 Å of the molecule of interest. For a given crystal structure and set of atomic electron densities, the isosurface defined by $w(\mathbf{r}) = 0.5$ is unique. Changes in the atomic electron densities (e.g., incorporation of a contracted H atom rather than the ground-state H atom) lead only to very small changes in the resulting surface.

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The marching cubes algorithm[8] was used to locate and triangulate the Hirshfeld surfaces for a variety of molecular crystals for visual display, also enabling rapid computation of molecular volume (V_H), surface area (S_H) and packing ratio ($P_H = \sum_{cell} V_H/V_{cell}$). Two other descriptors of global shape[9] were also computed: globularity (G) and asphericity (Ω). Globularity[10] is a measure of the degree to which the surface area differs from that of a sphere of the same volume; $G = (36\pi V_H^2)^{1/3}/S_H$, and will be 1.0 for a sphere, and progressively less than one as the molecular surface becomes more structured. Asphericity[11] is a measure of anisotropy, and when applied to the positions of atoms in molecules is defined by Equation (2), where λ_i are the three principal moments of inertia of the molecule.

$$\Omega = ½\{\sum_{i \neq j} (\lambda_i - \lambda_j)^2\}\{\sum_{i \neq j} \lambda_i\}^{-2} \tag{2}$$

We have applied this descriptor to the Hirshfeld surfaces by allocating each surface point unit mass, and summing over all points on the surface to determine Ω. Ω assumes a value of zero for an isotropic object (e.g., a sphere, tetrahedron or octahedron where all principal values are identical), 1.0 for a prolate object, and 0.25 for an oblate object. We have found $\sqrt{\Omega}$ to be a more useful measure, as it transforms the range to 0.0 (isotropic), 0.5 (oblate) and 1.0 (prolate). The combination of G and $\sqrt{\Omega}$ can divulge shape information that each alone would not and, although it must be acknowledged that both are crude global descriptors, along with surface area and volume they can potentially provide significant information about the shapes of molecules in crystals. For integration over the Hirshfeld surfaces, optimum balance between accuracy and time was achieved with a resolution of 0.1 au for the marching cubes grid, which corresponds to a typical distance between surface points of ≈0.08 au. At this resolution (which, for example, represents 51 530 points for urea and 71 430 for benzene) all derived quantities (Table 1) are within 1% or less of the converged result.

Table 1. Quantitative measures of Hirshfeld surfaces for some molecular crystals.

Name	V_H [Å^3]	S_H [Å^2]	G	$\sqrt{\Omega}$	P_H
acetylene	53.1	73.5	0.931	0.238	0.939
benzene	113.0	128.7	0.878	0.242	0.959
alloxan	115.3	134.4	0.853	0.283	0.968
uracil	111.7	127.8	0.878	0.269	0.964
urea	69.1	91.1	0.894	0.196	0.946
α-oxalic acid	74.9	99.1	0.867	0.290	0.958
β-oxalic acid	74.9	97.9	0.877	0.236	0.954
α-1,4-dichlorobenzene	148.6	160.4	0.846	0.387	0.969
β-1,4-dichlorobenzene	148.7	160.1	0.848	0.387	0.969
γ-1,4-dichlorobenzene	148.0	161.0	0.840	0.384	0.969
phosphorylethanolamine	142.9	157.7	0.841	0.317	0.954

Before presenting and discussing detailed examples of Hirshfeld surfaces and exploring what physical insight they might reveal, it is worthwhile discussing what they are not. Unlike other molecular volumes and surfaces (e.g., fused-sphere van der Waals volumes, solvent-accessible surfaces, solvent-excluded surfaces[12]), Hirshfeld surfaces are not a simple function of the molecular geometry; they are only defined within the crystal,[13] and hence necessarily reflect the interplay between different atomic sizes and intermolecular contacts in the crystal: intermolecular interactions. Whether they do this in a quantitative or qualitative manner remains to be seen. From Table 1 we also see that Hirshfeld surfaces and volumes are much larger than conventional ones—they generally fill at least 95% of the crystal volume, compared with more conventional packing coefficients of between 0.65 and 0.80.[14] Finally, they obviously pack very tightly in the crystal but, quite unlike any other partitioning or packing scheme, they leave small intermolecular voids, which can be regarded as regions where the crystalline electron density is not dominated by any single molecule.

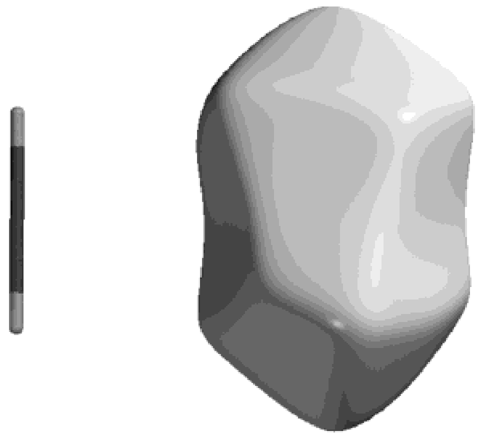

Figure 1. Tube model of acetylene with Hirshfeld surface at the same orientation; note the almost completely convex nature of the surface.

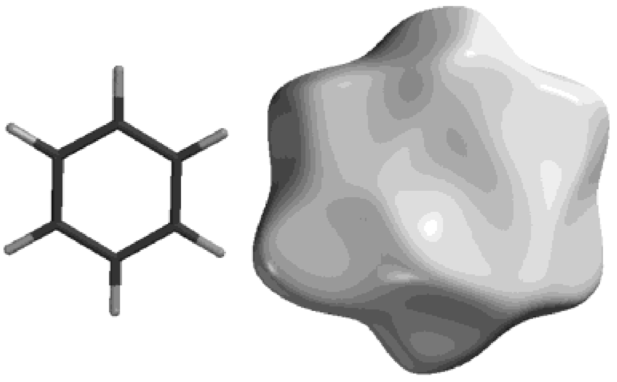

Figure 2. Tube model of benzene with Hirshfeld surface at the same orientation; the indentation in the surface above the ring results from the close C–H⋯π interaction between nearest neighbours.

Hirshfeld surfaces for acetylene (Figure 1) and benzene (Figure 2) reflect the weak and largely nondirectional intermolecular forces at play in these crystals,[15] and act as a benchmark for subsequent comparison. The curvature of the surfaces varies smoothly, and the edge-to-face C–H⋯π interaction in benzene shows up as the broad depression in the surface above the ring plane. Although anisotropy values are almost identical for the two molecules, G clearly discriminates between the two with acetylene having a much higher value (0.931) than benzene (0.878) (in fact the highest of all those in Table 1), a result of the almost completely convex nature of the surface in this case. We have observed that water molecules also display similarly large globularities, and they too show largely convex surfaces. Packing diagrams of unit cells for acetylene and benzene (Figure 3) illustrate the potential for the use of these surfaces to convey crystal packing arrangements in a rather novel manner, namely, as packing of vesicles deformed by close contact with their neighbours, the extent of the deformation depending intimately on the strength of the interaction and the types of atoms involved. In Figure 3 the depression above the benzene ring is much more obvious, and the interlocking of neighbouring molecules by the C–H$\cdots\pi$ interaction is evident. The packing motifs for acetylene and benzene depicted in this figure are remarkably similar; both can be described rather simply as pseudo-fcc, and the smaller packing ratio for acetylene (Table 1) is evident in the slightly greater distance between molecules along the vertical cell edge.

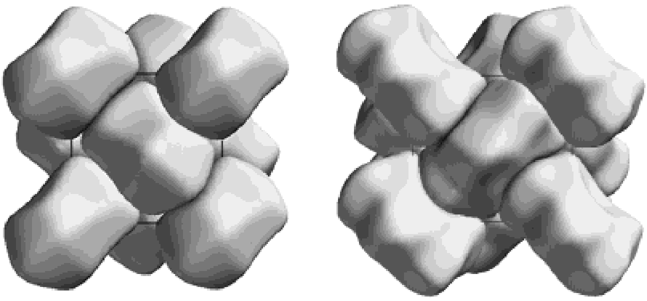

Figure 3. Unit cell packing diagrams of Hirshfeld surfaces of acetylene (left, viewed down the crystal *a* axis) and benzene (right, viewed down the crystal *b* axis); cell edges are also indicated. The two cells are not drawn on the same scale, but they emphasise the similar packing motifs for these two crystals.

Alloxan packs in a herringbone pattern similar to that in benzene, with unusually short O=C$\cdots$O intermolecular distances and an absence of conventional hydrogen bonds, despite the presence of only C=O and N–H groups.[16] Its Hirshfeld surface (Figure 4) is visually quite different from that of benzene, with slightly larger volume and surface area, smaller G (hence less spherical and more structured) and larger $\sqrt{\Omega}$ (hence more oblate). In particular, the deeper indentation in the surface above the molecular plane is quite different from benzene, and it accommodates the large bulbous region around O(6) (bottom left of Figure 4). This is a direct result of the short O=C$\cdots$O contact, and the difference between these two surface features for benzene and alloxan (and the absence of such a feature in uracil, below) suggests a means of readily discriminating between interactions on a visual basis, but also hints at the possibility of using the Hirshfeld surfaces in a more direct and quantitative way.

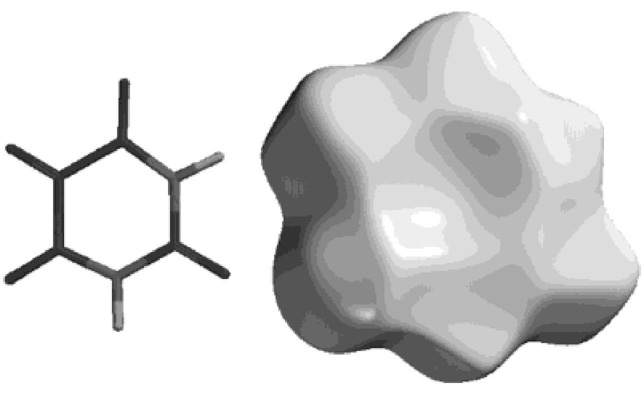

Figure 4. Tube model of alloxan with Hirshfeld surface at the same orientation; the indentation above the ring, which results from close O$\cdots$C=O interactions, is quantitatively different from that in benzene (Figure 2).

Uracil provides yet another type of surface for a six-membered ring molecule (Figure 5). Here the Hirshfeld surface is largely flat above and below the ring plane, with no evidence of interactions out of the molecular plane. Instead we see a surface which is highly deformed perpendicular to the plane, with abrupt flat regions at the extensions of, and perpendicular to, the N–H bonds, and regions around the carbonyl oxygens pinched in on each side of the C=O bond (contrast the area around the C=O at top right of Figure 5 with that at bottom left of Figure 4). These features, which are also evident in a number of structures we discuss later, appear to characterise strong hydrogen bonds, offering a ready visual diagnostic for the presence of hydrogen bonding. The shape of the Hirshfeld surface for uracil suggests strong intermolecular interactions between molecules in a plane, but weaker and nondirectional interactions between planes. This is precisely the packing displayed by uracil,[17] and Figure 6 illustrates this for a planar cluster.

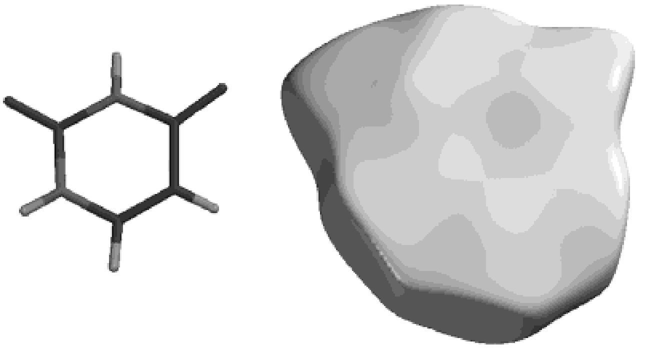

Figure 5. Tube model of uracil with Hirshfeld surface at the same orientation; the surface is virtually flat above and below the ring, but has abrupt faces perpendicular to the molecular plane and characteristic of strong hydrogen bonds.

Urea (Figure 7) was chosen as an example of a strongly hydrogen-bonded system with interactions in the molecular plane as well as above and below it.[18] As expected from uracil, there are abrupt changes in curvature on the surface, leading to nearly flat regions perpendicular to both of the N–H bonds, as well as evidence of a pinched nature on four sides of the C=O bond. From its Hirshfeld surface urea is clearly revealed as a molecule which packs with strong interactions in two perpendicular directions; this packing motif is displayed in the cluster shown in Figure 8, which highlights the columns of head-to-tail interacting molecules,

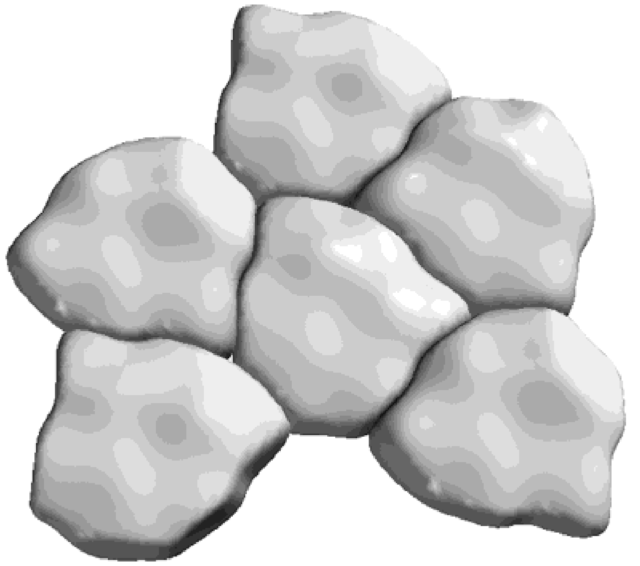

Figure 6. A planar cluster of Hirshfeld surfaces for uracil, highlighting the close packing of molecules in the (001) plane.

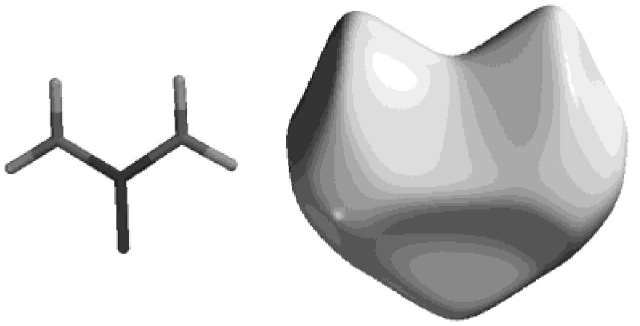

Figure 7. Tube model of urea with Hirshfeld surface at the same orientation; abrupt faces characteristic of hydrogen bonding are evident near the N–H bonds, as is pinching in of the surface around the carbonyl oxygen.

each column directly interacting with adjacent columns directed antiparallel and rotated by 90°. The relatively large value of G and small value of $\sqrt{\Omega}$ suggest a highly regular shape, in keeping with the highly symmetric packing in the crystal.

Equipped with the rudimentary appreciation of the nature of Hirshfeld surfaces gathered so far, we now discuss an example of polymorphism: anhydrous α- and β-oxalic acid (Figure 9). Hirshfeld surfaces for these two polymorphs are dramatically different, showing quite effectively the difference between packing modes utilised in the two structures.[19] α-oxalic acid crystallises with a strong three-dimensional network of hydrogen bonds and close intermolecular contacts, essentially a pseudo-fcc packing arrangement in *Pbca*, very similar to that observed in benzene, and these interactions are clearly reflected in the Hirshfeld surface. The Hirshfeld surface for the β polymorph shows evidence of strong O–H$\cdots$O hydrogen bonds to form linear chains (see top and bottom of the surface in Figure 9), the chains then packing in parallel and nearly at right angles to one another (Figure 10) in a manner analogous to urea. Interestingly, from Table 1 the only significant difference between descriptors for these two

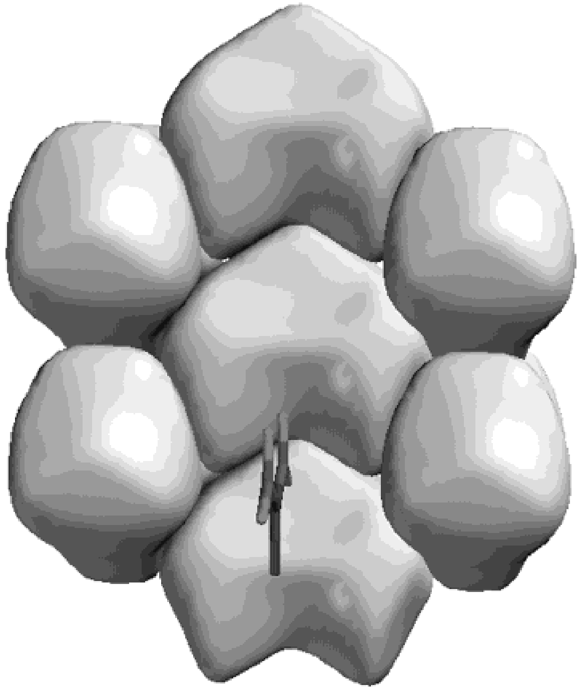

Figure 8. A cluster of Hirshfeld surfaces for urea showing the head-to-tail packing arrangement in columns along the c axis, and the antiparallel packing of columns perpendicular to one another.

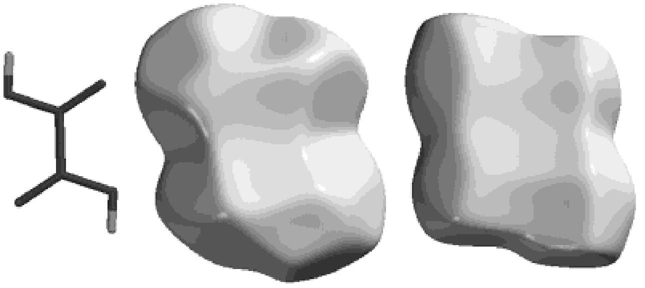

Figure 9. Tube model of oxalic acid with Hirshfeld surfaces at the same orientation for molecules in the α and β (right) anhydrous polymorphs; note the quite different surfaces for molecules in these polymorphs.

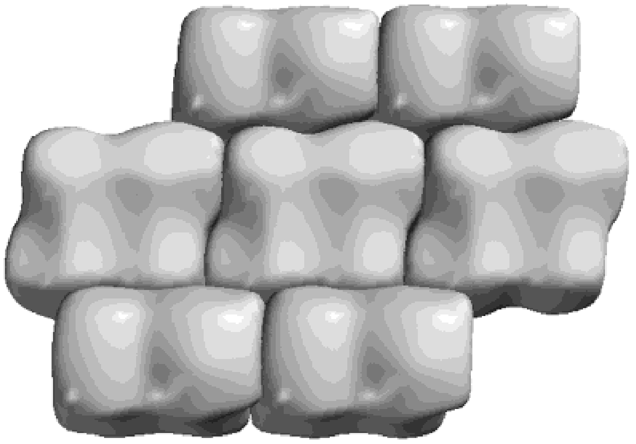

Figure 10. A cluster of Hirshfeld surfaces for β-oxalic acid showing the arrangement in rows along the a axis (left to right), and the packing of rows almost perpendicular to one another (compare this arrangement with that in Figure 8).

polymorphs occurs for the anisotropy, with the α form being far more anisotropic than the β form (the difference between the two values is in fact remarkably similar to the difference between anisotropies for benzene and urea, whose packing arrangements they echo). With polymorphs such as these it is tempting to correlate surface descriptors with relative lattice stabilities. We note that the best estimates of sublimation enthalpies[20] indicate the α form is more stable than β by 6 $\mathrm{kJ\,mol^{-1}}$ but, recognising the crudeness of the present global descriptors, such small energy differences are unlikely to be reflected in the Hirshfeld surfaces, even if we could quantitatively relate surface structure to lattice energy.

Crystal structure and intermolecular interactions in the polymorphic *p*-dichlorobenzene crystals have long been of some interest,[21] and are worth attention here because they are an example of polymorphism without hydrogen bonds, and in addition they contain short-range Cl$\cdots$Cl contacts which have been the focus of recent attention.[22] Hirshfeld surfaces for the α, β and γ crystalline forms (Figure 11) reveal the great similarity between molecular shapes for the α and β forms, and the distinctly different packing evinced by the surface of the γ form. Although subtle differences between α and β are noticeable in the figure (e.g., the region between adjacent H and Cl atoms at the top right of both surfaces), the two molecular surfaces are extremely similar both visually and from the measures in Table 1, and suggest that these two polymorphs can be considered as different packing arrangements of flexible vesicles deformed in much the same manner as one another, and hence readily interchangeable.[23] The γ polymorph is quite obviously different (again, both from the figure and the table), with an indentation above the benzene ring which closely resembles that in benzene itself (Figure 2), suggesting a close intermolecular approach to the C atoms of the ring. This is indeed the case (C–H$\cdots$C contacts of 2.82, 2.88 and 2.91 Å, compared with contacts of 2.79, 2.89 and 2.85 Å in benzene), although curiously this feature of the structure of the γ phase appears to have received little attention. The anisotropic nature of Cl$\cdots$Cl intermolecular contacts also appears to correlate with the structure of the Hirshfeld surface around chlorine atoms. The surface is clearly flattened along the direction of the C–Cl bond in all three polymorphs, hinting at the polar flattening described by Nyburg and Faerman.[24]

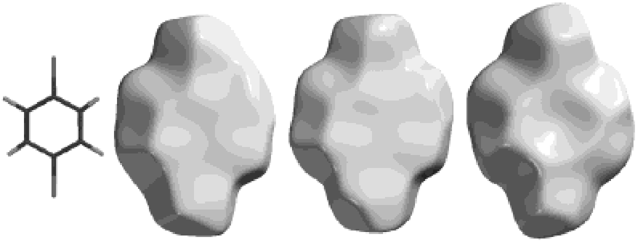

Figure 11. Tube model of *p*-dichlorobenzene with Hirshfeld surfaces at the same orientation for molecules in the α (left), β (center) and γ (right) polymorphs; note the great similarity of surfaces for the α and β forms, and the obvious indentation above the benzene ring for the γ form, characteristic of C–H$\cdots\pi$ interactions (compare with Figure 2).

Our last example is another strongly hydrogen-bonded system, the zwitterionic phosphorylethanolamine (PEA), which contains the phosphate monoester and ethanolamine groups commonly found in biological systems, and which has been shown to contain a molecular arrangement similar to the packing of PEA groups in a phospholipid crystal.[25] The Hirshfeld surface for PEA (Figure 12) exhibits extremely flat regions at each end of the molecule corresponding to the N–H$\cdots$O=P contacts, and these interactions link molecules in the planar group parallel to (001) (Figure 13). The protrusion on the Hirshfeld surface near the center of the molecule (Figure 12) corresponds to a methylene group which is not involved in any close intermolecular contacts, pointing towards the other methylene group in an adjacent molecule: hydrophobic regions in neighbouring molecules face one another rather than one of the highly charged ends of the molecule.

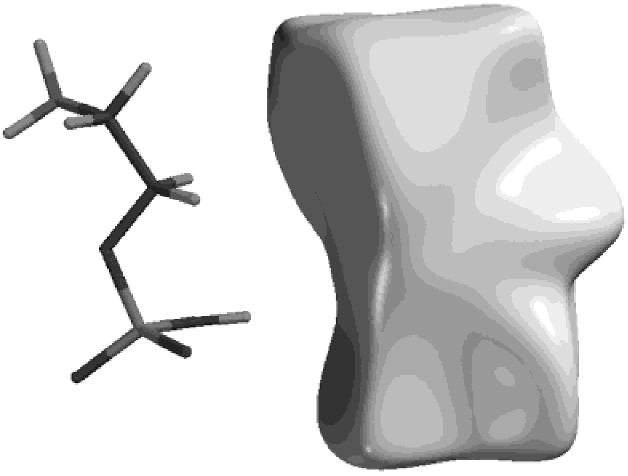

Figure 12. Tube model of phosphorylethanolamine with Hirshfeld surface at the same orientation; note the flat ends of the molecular surface, which result from hydrogen bonding, and the protuberance on the right arising from the methylene C–H hydrogen atoms, which form no close intermolecular contacts and face a hydrophobic cavity in the structure.

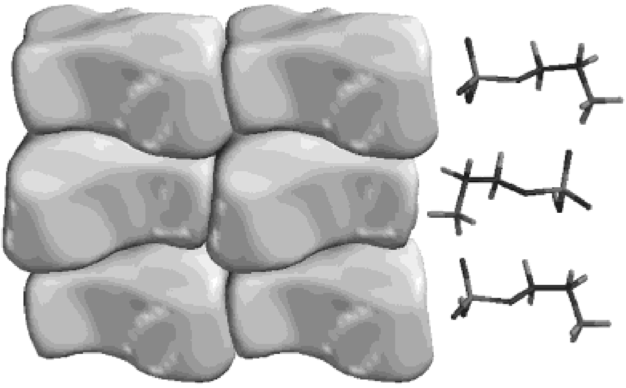

Figure 13. Cluster of Hirshfeld surfaces for phosphorylethanolamine with tube models of molecules on the right to indicate the relative molecular orientations within each row. The cluster is part of a sheet of hydrogen-bonded zwitterions parallel to (001), and the Hirshfeld surfaces highlight the close packing arrangement which forms the sheet.

Conclusion

This brief presentation of a limited number of crystal structure types illustrates some of the potential applications of the Hirshfeld surface to the discussion of packing arrangements and intermolecular interactions in molecular crystals. However, we anticipate that the applications of such surfaces will not be restricted to the 3D isosurfaces and quantitative measures we have presented here. The Hirshfeld surface is such a simple concept, yet it implicitly contains information on relative atomic sizes and intermolecular contacts in crystals, and offers a novel and potentially rich source of additional insight into molecular crystals. The 3D isosurfaces and packing diagrams presented here are unfortunately static; real-time rotation of these on a screen is really the only way to properly appreciate their beauty and three-dimensional nature, and to adequately explore their properties. Through this simple exercise we have learned that crude global measures of size and shape (Table 1) are inadequate for many purposes,[26] and we are currently pursuing a number of local properties mapped onto the Hirshfeld surface. Among these will be curvature, which has been shown to play an important role in condensed matter physics, chemistry and biology,[27] and properties such as the electrostatic potential, which when mapped onto molecular electron density surfaces has been used to predict and explain a number of bulk properties.[28]

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[13] This is not a necessary restriction. We can readily envisage a generalisation to any condensed phase; for example, snapshots from a liquid simulation would yield Hirshfeld surfaces, but different ones for each molecule. Likewise, the partitioning scheme can be readily applied to extended covalent networks like diamond, or even ionic solids; in these cases atomic (or ionic) surfaces would be obtained.

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[25] H.-P. Weber, R. K. McMullan, S. Swaminathan, B. M. Craven, *Acta Crystallogr. Sect. B* **1984**, *40*, 506–511; S. Swaminathan, B. M. Craven, *Acta Crystallogr. Sect. B* **1984**, *40*, 511–518.

[26] For example, we originally thought that the fraction of void space in the crystal, $1 - P_H$, might reveal different packing efficiencies, but it is clear from Table 1 and other examples that Hirshfeld surfaces exclude between 6 % and less than 1 % of the crystal volume as void space, and this very small fraction is determined largely by the complexity of the molecule.

[27] S. Hyde, S. Andersson, K. Larsson, Z. Blum, T. Landh, S. Lidin, B. W. Ninham, *The Language of Shape*, Elsevier, Amsterdam, **1997**.

[28] See, for example, P. Politzer, J. S. Murray, M. E. Grice, M. DeSalvo, E. Miller, *Mol. Phys.* **1997**, *91*, 923–928; J. S. Murray, T. Brinck, P. Politzer, *Chem. Phys.* **1996**, *204*, 289–299.

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