

# T4. Introduction to CrystalExplorer and Hirshfeld surface analysis

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# Outline

1. The *crystal structure* versus the *molecular* structure
2. Why consider the crystal/lattice structure?
3. What is *Crystal Engineering*?
4. Introduction to *CrystalExplorer*
5. Practice with structure analysis using *CrystalExplorer*

# 1. The *crystal structure* versus the *molecular* structure

# All too typical figure from a chemistry journal article

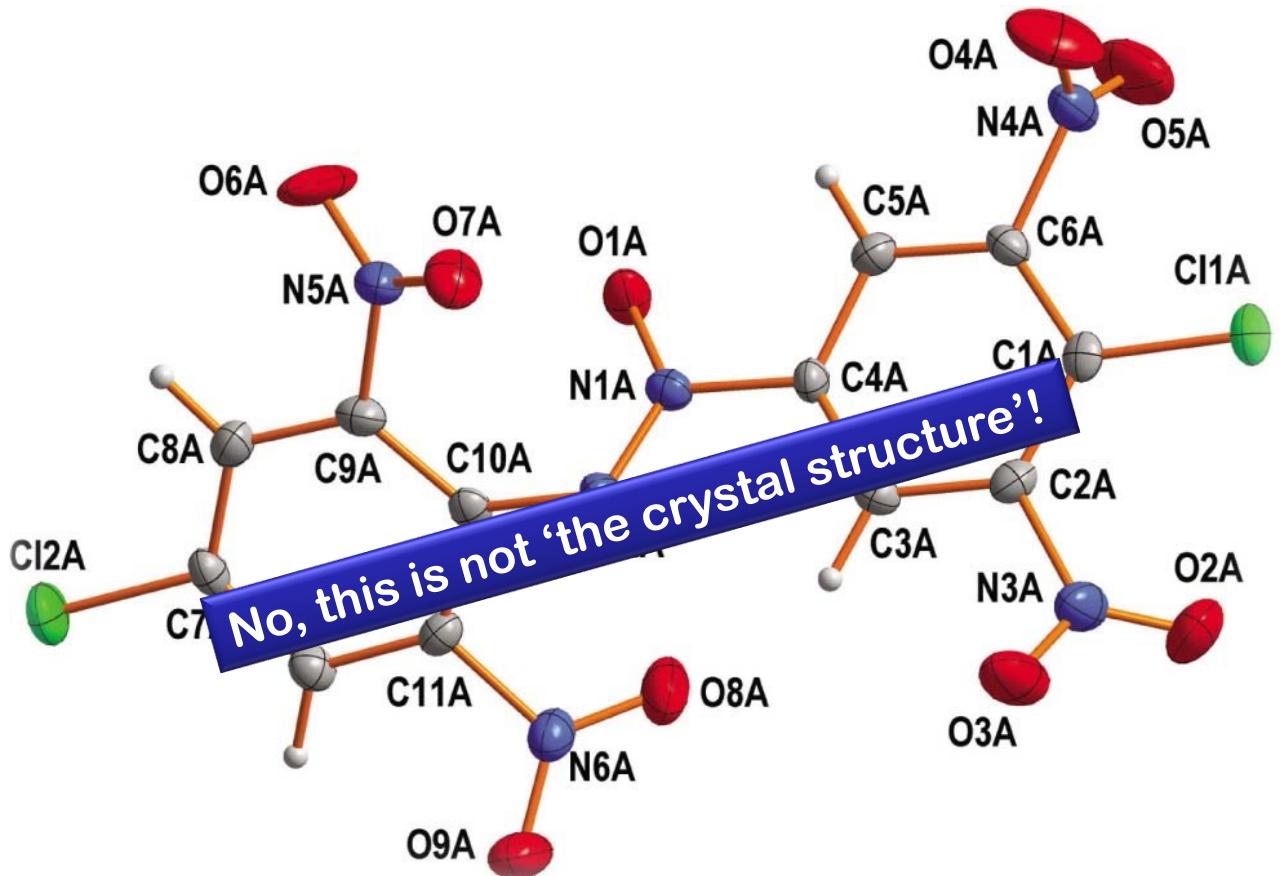


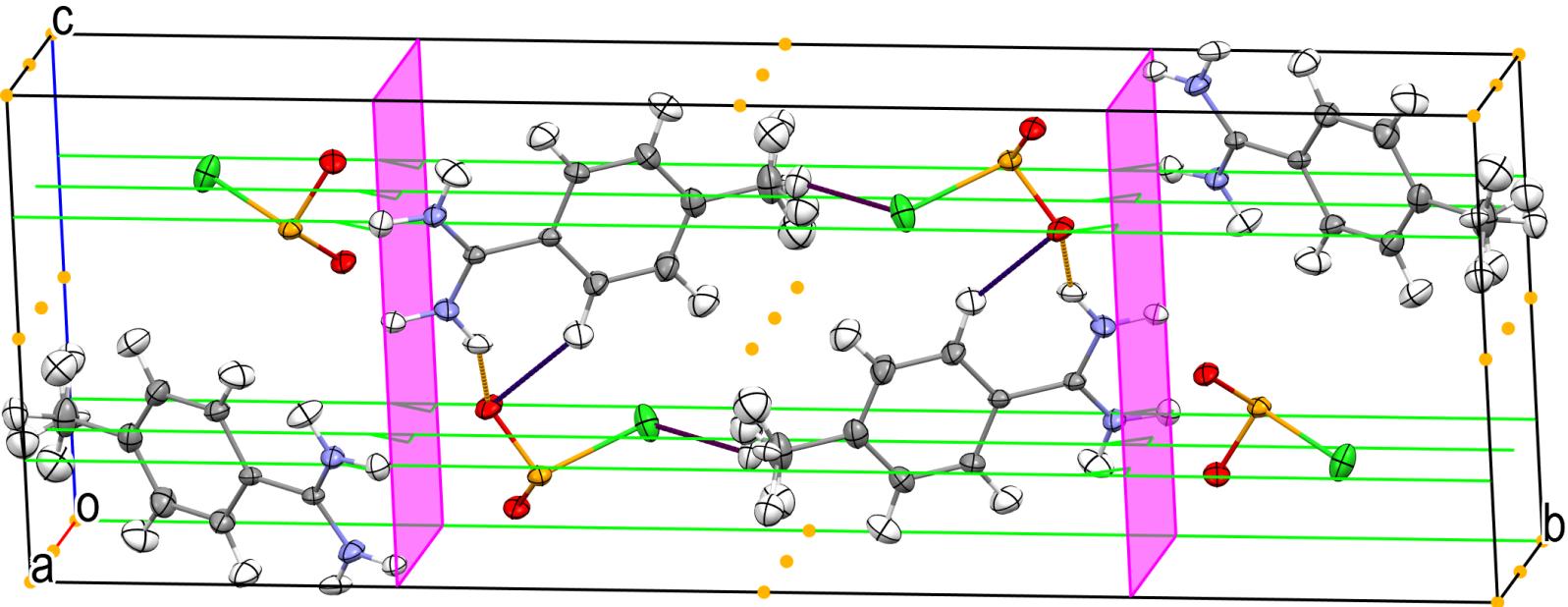
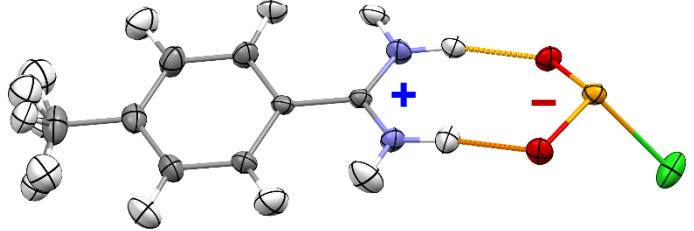
Figure 1. The crystal structure of 2-(4-chloro-2,6-dinitrophenyl)-1-(4-chloro-3,5-dinitrophenyl)diazene

One *could* correctly write:

Figure 1. Displacement ellipsoids plot showing the molecular structure of 2-(4-chloro-2,6-dinitrophenyl)-1-(4-chloro-3,5-dinitrophenyl)diazene as determined from a crystal structure.

So what is the difference?  
Even if your goal is to know the *molecular structure* of some compound you have made, that structure is determined within a crystal lattice *and is affected by that lattice!*

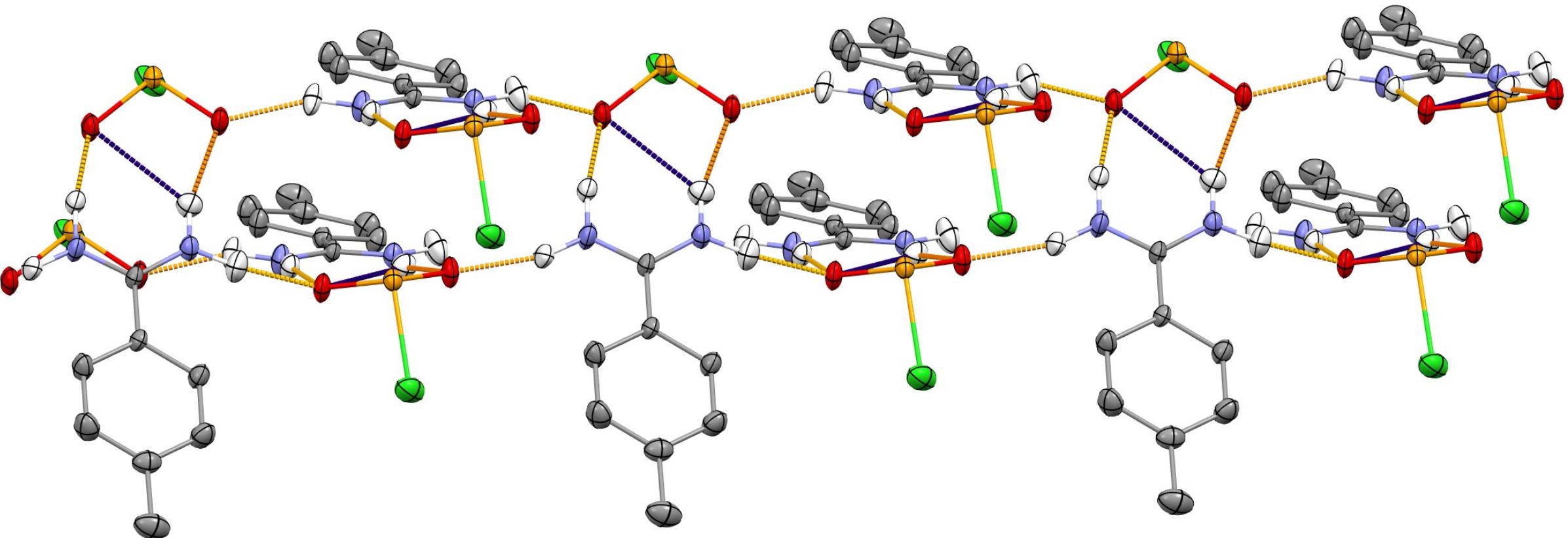
# Considering the ‘whole’ crystal lattice



**Table 2.** Hydrogen bonds and inter-anion contacts in the crystal structure of **2**.

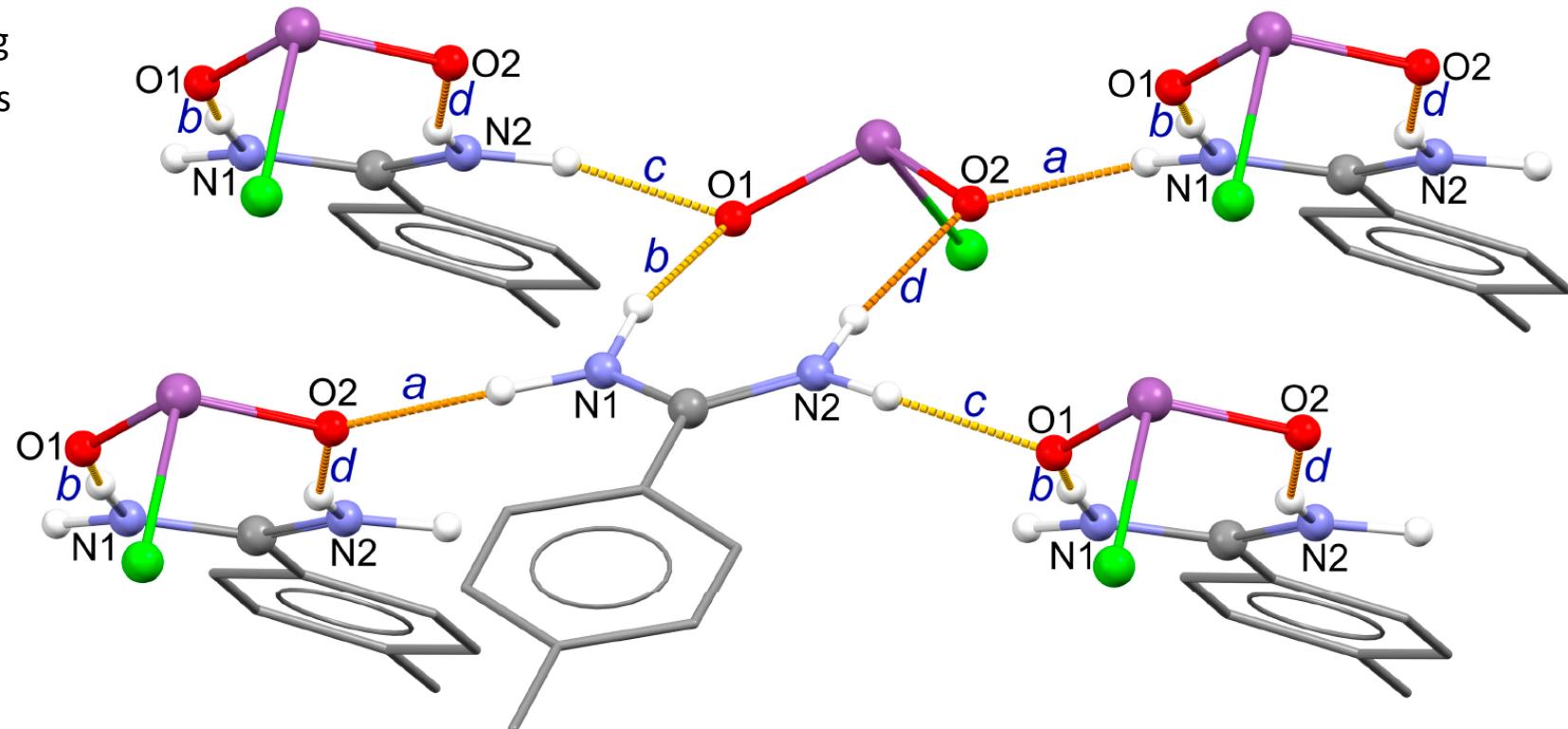
D(-H)	:A	$d(D-H)/\text{\AA}$	$d(H \cdots A)/\text{\AA}$	$d - \sum r_{vdW}$	$d(D \cdots A)/\text{\AA}$	Angle/ $^\circ$
Hydrogen-bonds						
N1-H1a	O2 <sup>1</sup>	1.045(17)	1.90(3)	-0.82	2.852(3)	150(3)
N1-H1b	O1	1.051(18)	1.843(19)	-0.877	2.880(4)	168(3)
N2-H2a	O1 <sup>2</sup>	1.030(17)	1.83(3)	-0.89	2.792(3)	153(4)
N2-H2b	O2	1.039(18)	1.95(2)	-0.77	2.948(3)	160(3)

# Alternative approach: follow the interactions



# Classification: Etter Notation

- o Margaret Etter () developed graph set analysis for H-bonding
- o This is now built into Mercury as an analysis tool



**Figure 3.** Hydrogen bond network in the crystal lattice of **2**. The Etter notation for the lower-level nets are indicated in the blue lettering:  $D_1^1(2)$   $a$ ;  $D_1^1(2)$   $b$ ;  $D_1^1(2)$   $c$ ;  $D_1^1(2)$   $d$ ;  $C_2^2(6) > a < b$ ;  $C_2^2(8) > a < c$ ;  $C_2^1(6) > a < d$ ;  $C_2^1(6) > b < c$ ;  $R_2^2(8) > b < d$ ;  $C_2^2(6) > c < d$ . The relative H-bond strengths are color-coded, with yellow being stronger than orange.

# Hydrogen Bond Classification (Jeffrey)

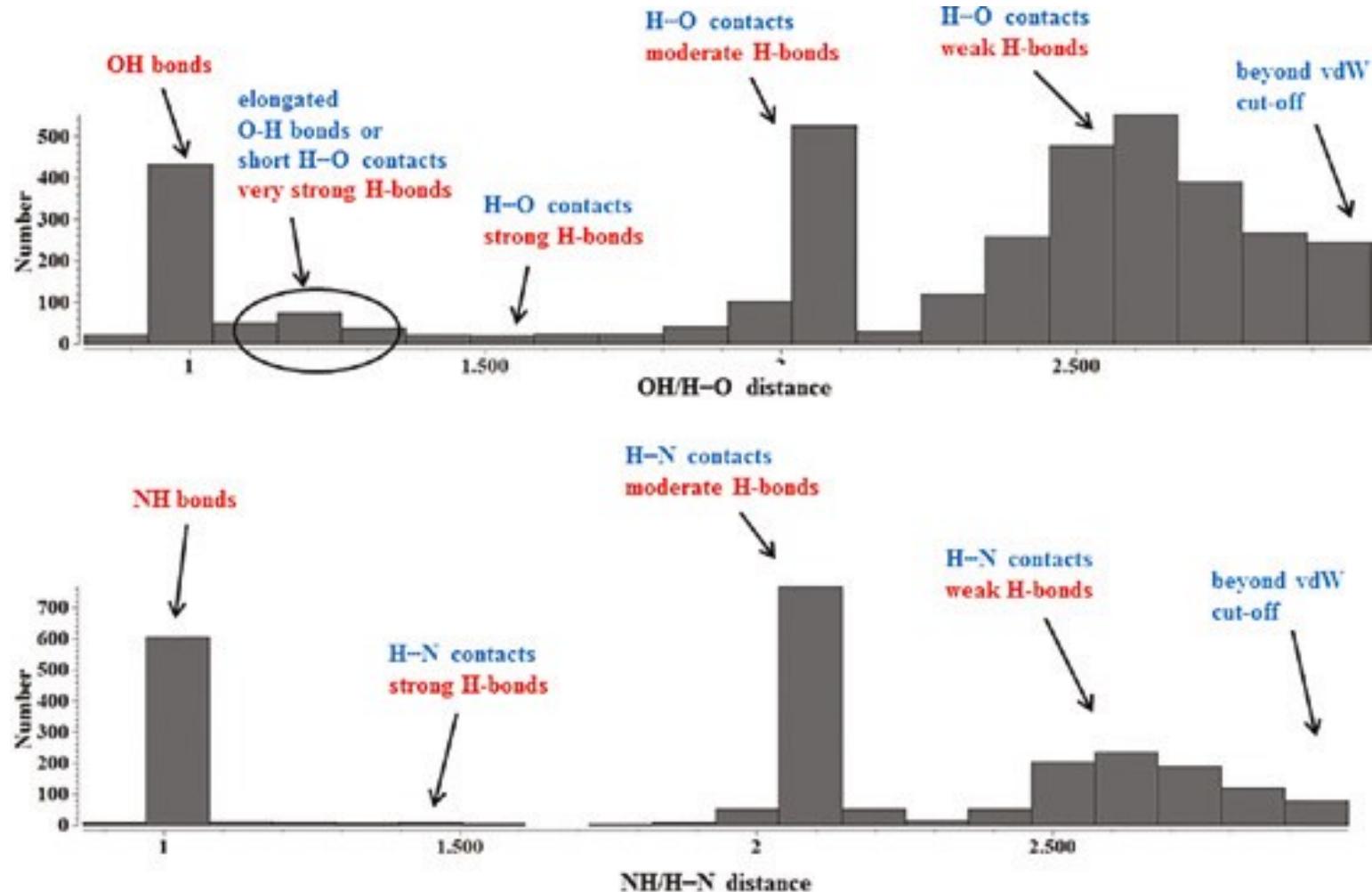
**Table A1.** Ranking of Hydrogen Bond Strengths and Properties Adapted from Jeffrey \*.

Parameter	Strong	Moderate	Weak
Interaction type:	strongly covalent	mostly electrostatic	electrostatic/ dispersion
$d(\text{H}\cdots\text{A})$ , Å #	1.2–1.5	1.5–2.2	>2.2
$d(\text{D}\cdots\text{A})$ , Å #	2.2–2.5	2.5–3.2	>3.2
lengthening of D–H	0.08–0.25	0.02–0.08	<0.02
D–H versus H…A	$\text{D–H} \approx \text{H}\cdots\text{A}$	$\text{D–H} < \text{H}\cdots\text{A}$	$\text{D–H} \ll \text{H}\cdots\text{A}$
Directionality: $\angle \text{D–H}\cdots\text{A}$ , °	Strong 170–180	moderate >130	weak >90
Bond energy, kJ mol <sup>-1</sup>	60–160	16–60	<16
IR shift $\Delta\bar{\nu}_{DH}$ , cm <sup>-1</sup>	25%	10–25%	<10%
<sup>1</sup> H downfield shift, ppm	14–22	<14	

\* Jeffrey, G. A. *An introduction to hydrogen bonding*. Oxford University Press: New York, 1997, Volume 12, pp. 330 [79]. # For a given donor type, the hydrogen-bond distance typically increases by over 0.5 Å from 2nd to 3rd period, 0.15 Å from 4th to 5th period, and 0.25 Å from 5th to 6th period acceptors [80].

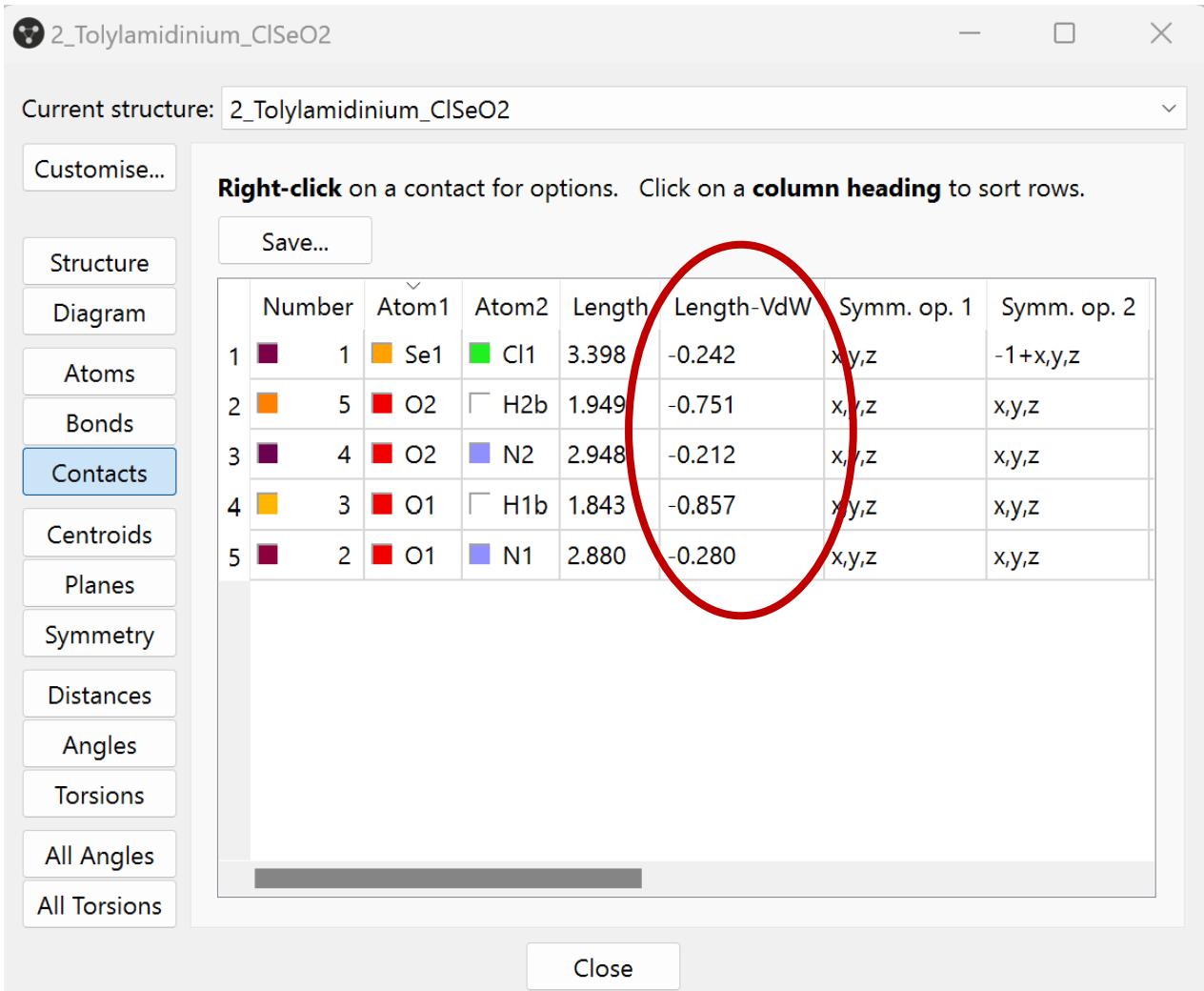
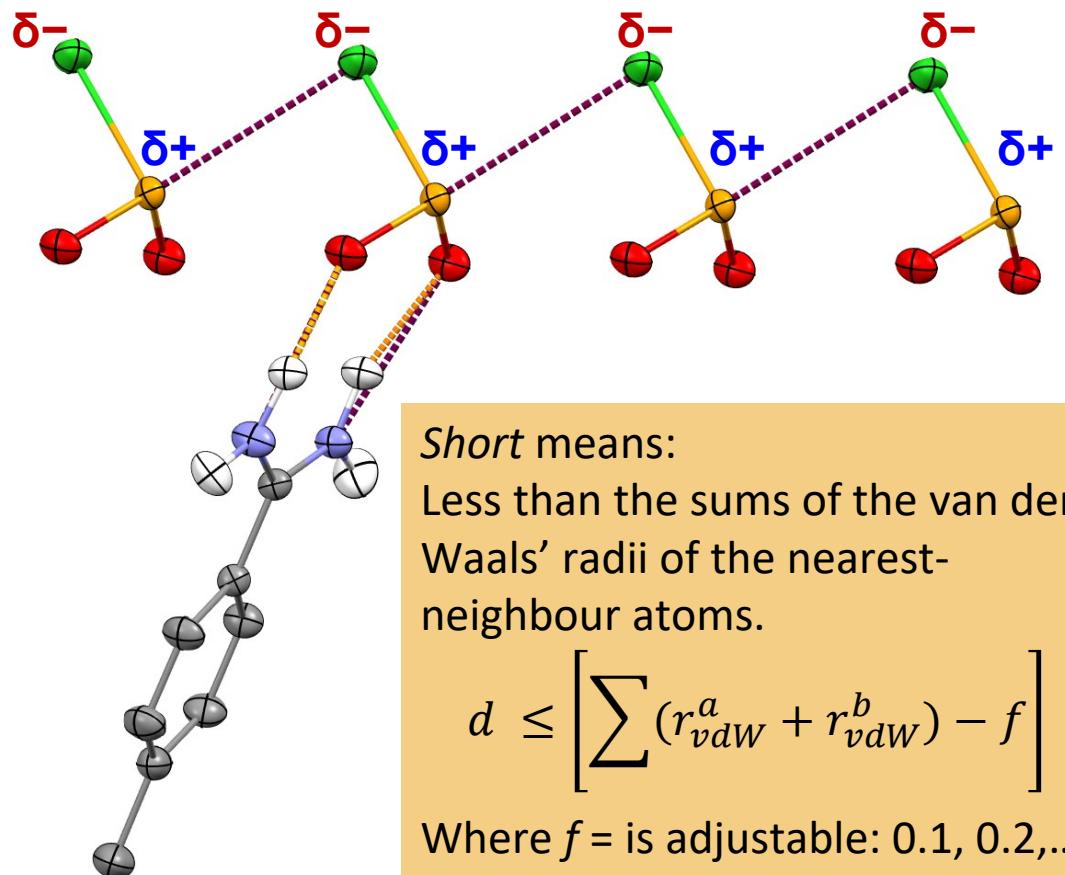
# Categories of H-bonds - Graphical

- o Categorize by *strength* →
  - Very strong H-bonds
  - Strong H-bonds
  - Weak H-bonds (sometimes called non-classical H-bonds)
- o Categorize by *type*:
  - Types of H-bonds
  - Intermolecular...
  - Intramolecular...
  - Resonance-assisted (RAHB)
  - Charge-assisted (CAHB)
- o Categorize by *orientation*:
- o Linear H-bonds
- o Bifurcated H-bonds



# Short Intermolecular Contacts

- Beyond the CAHBs, we should consider other prominent *intermolecular short contacts*:



## 2. Why consider the crystal lattice?

# Contributions (+/-) of the Lattice

- o At root, there is only *one* issue: **energy**
- o The interaction between ‘entities’ that leads to the formation of a crystal is an *energy minimization*
- o Which means energy is released during lattice formation
- o That energy can be highly beneficial (giving the drug polymorph of choice so medicines are safe....)
- o That energy can also cause confusion (by e.g. changing bond distances, bond angles and especially, torsional angles)
- o Why?      **Because gaining a large lattice energy can override a smaller geometry change.**
- o Thus, the ‘lattice energy’ may significantly change the molecular structure from that in the TELP.
- o Similarly, understanding the source of the lattice energies may help us *direct* the formation of favourable solid architectures.
- o There are profound benefits to undertaking such design in many aspects of chemical sciences.
- o Collectively, those have become known as *crystal engineering*.

### 3. What is *Crystal Engineering*?

# Briefest introduction to a vast enterprise...

- o One example is the role of hydrogen bonds in molecular recognition patterns (“supramolecular synthons”), and the use of suitably robust motifs for the construction of crystalline architectures with desired properties (“crystal engineering”).
- o The term “crystal engineering” was coined by Gerhard Schmidt at the Weizmann Institute of Science. He worked on the construction of crystal packing schemes with the aim of aligning reactive groups in crystals in such a way that they are ready for topochemical reactions.

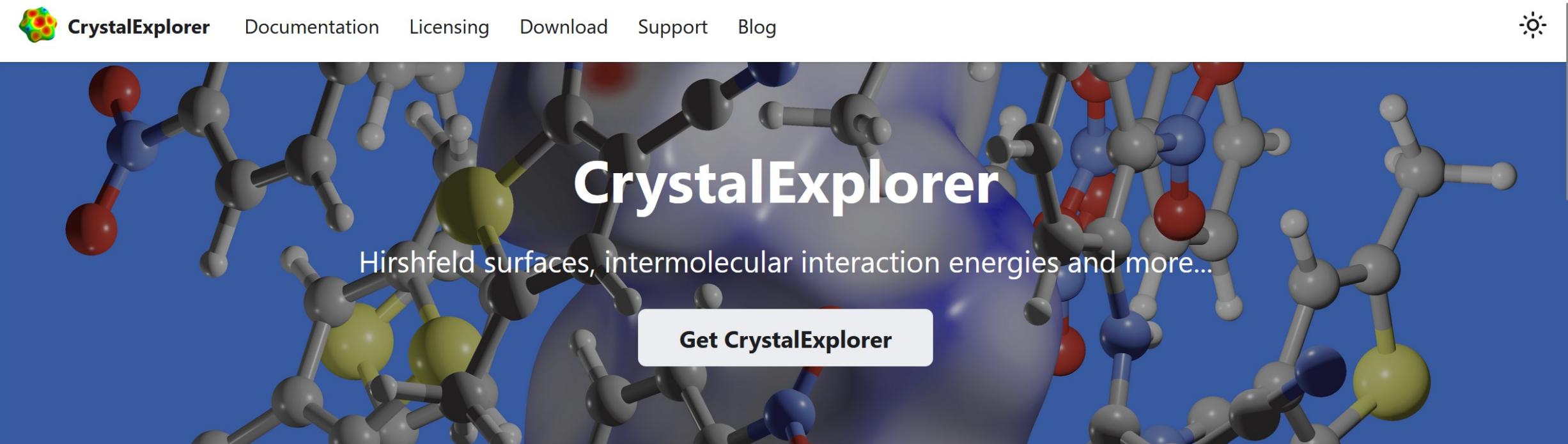
**G. R. Desiraju, *Crystal Engineering. The Design of Organic Solids*, Elsevier, Amsterdam, 1989.**

- o Desiraju and Steiner note, “There is a growing need to simultaneously assess different interactions and to establish their hierarchy”.
- o It was to this purpose that Spackman, McKinnon and others developed the program *CrystalExplorer* using a built-in general computational software called TONTO .
- o It runs simple Hartree-Fock and Density Functional Theory calculations, the latter compensated by Grimme’s (2002) D2 dispersion correction.

## 4. Introduction to *CrystalExplorer*

# CrystalExplorer

- o CrystalExplorer is a software that aims to systematize and quantify intermolecular interactions involved in crystal engineering.
- o Found at: <https://crystalexplorer.net/>



CrystalExplorer

Hirshfeld surfaces, intermolecular interaction energies and more...

Get CrystalExplorer

- o Download at: <https://crystalexplorer.net/download> (Windows 10+, MacOS 10.13+, Ubuntu 20.04 LTS, CentOS 7.6)

# Information on the Program

- o Download your version of choice
- o I have tried 17 & 21 and see no difference in performance, and have only tested the Windows version.
- o You *still need* the license code (that they provide)

## License key for older versions

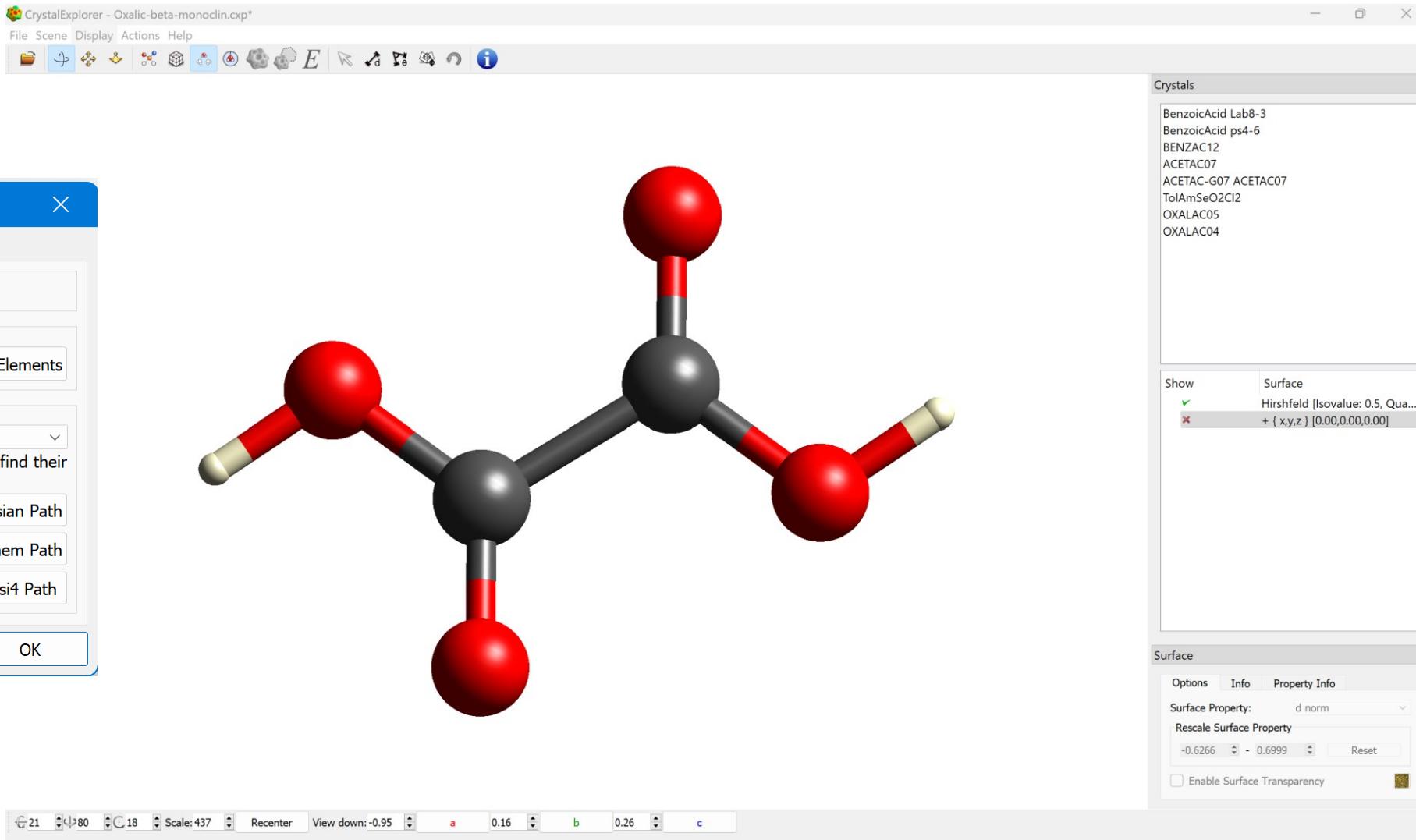
For older versions of CrystalExplorer, feel free to use the following license key:

User name	Key
user	1066-24A2-0114-24C3

- o Windows version graphics are sensitive to specific computers (high-resolution video drivers and also “older IntelHD integrated graphics chipsets”!)

- o CrystalExplorer 21
- o 64 bit
- o Built in TONTO computational software (free)
- o Built-in support for using **Gaussian** as a quantum chemistry backend – implemented on my laptop
- o Built-in support for using **NWChem** as a quantum chemistry backend
- o No support for ORCA
  
- o CrystalExplorer17
- o 32 bit
- o Built in TONTO computational software (free)
- o Built-in support for using **Gaussian** as a quantum chemistry backend – implemented on my laptop

# The main window: structure from a CIF



A Hirshfeld surface is defined by the density weight function of the specific molecule of interest (i.e. the promolecule) over the same sum of density of its nearest neighbour (i.e. the pro-crystal), thereby resulting in a 0.5 arbitrary units isosurface, which is similar to that of a van der Waals surface but, unlike the latter, takes into consideration neighbouring molecules and hence provides information about intermolecular interactions (McKinnon et al., 2007; Spackman & Jayatilaka, 2009).

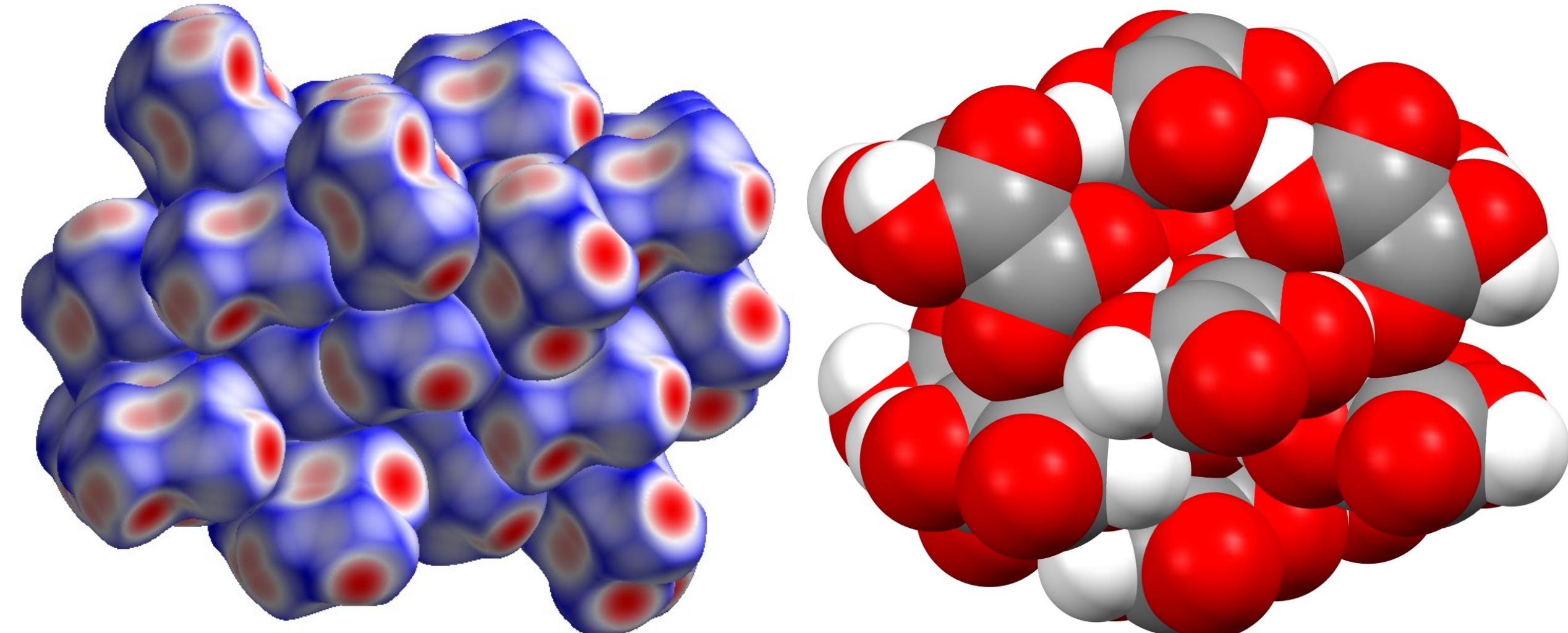
**Table 1**

Available surface properties in *CrystalExplorer*.

$r_I^{\text{vdw}}$  is the van der Waals radius of the nearest atom  $I$  closest to and inside the HS, while  $r_E^{\text{vdw}}$  is the van der Waals radius of the nearest atom  $E$  closest to and outside the HS. Curvedness and shape index were defined by Koenderink (1990) and Koenderink & Van Doorn (1992).

Property	Description
$d_i$	Distance from HS to the nearest atom $I$ internal to the surface
$d_e$	Distance from HS to the nearest atom $E$ external to the surface
$d_{\text{norm}}$	Normalized sum of $d_e$ and $d_i$ , i.e. $(d_i - r_I^{\text{vdw}})/r_I^{\text{vdw}} + (d_e - r_E^{\text{vdw}})/r_E^{\text{vdw}}$
$\rho_{\text{promol}}$	Promolecule electron density
$V_{\text{elec}}$	Electrostatic potential
$\rho$	Electron density
$ \phi ^2$	Probability density of a given molecular orbital
$\rho_{\text{def}}$	Deformation density, i.e. $\rho - \rho_{\text{promol}}$
Fragment patch	Unique (coloured) region based on atoms external to the HS designed to indicate the nearest-neighbouring molecule
Curvedness	Function depending on the HS concavity or convexity
Shape index	Function depending on the HS flatness or curvature

# Hirshfeld vs. van der Waals' surfaces

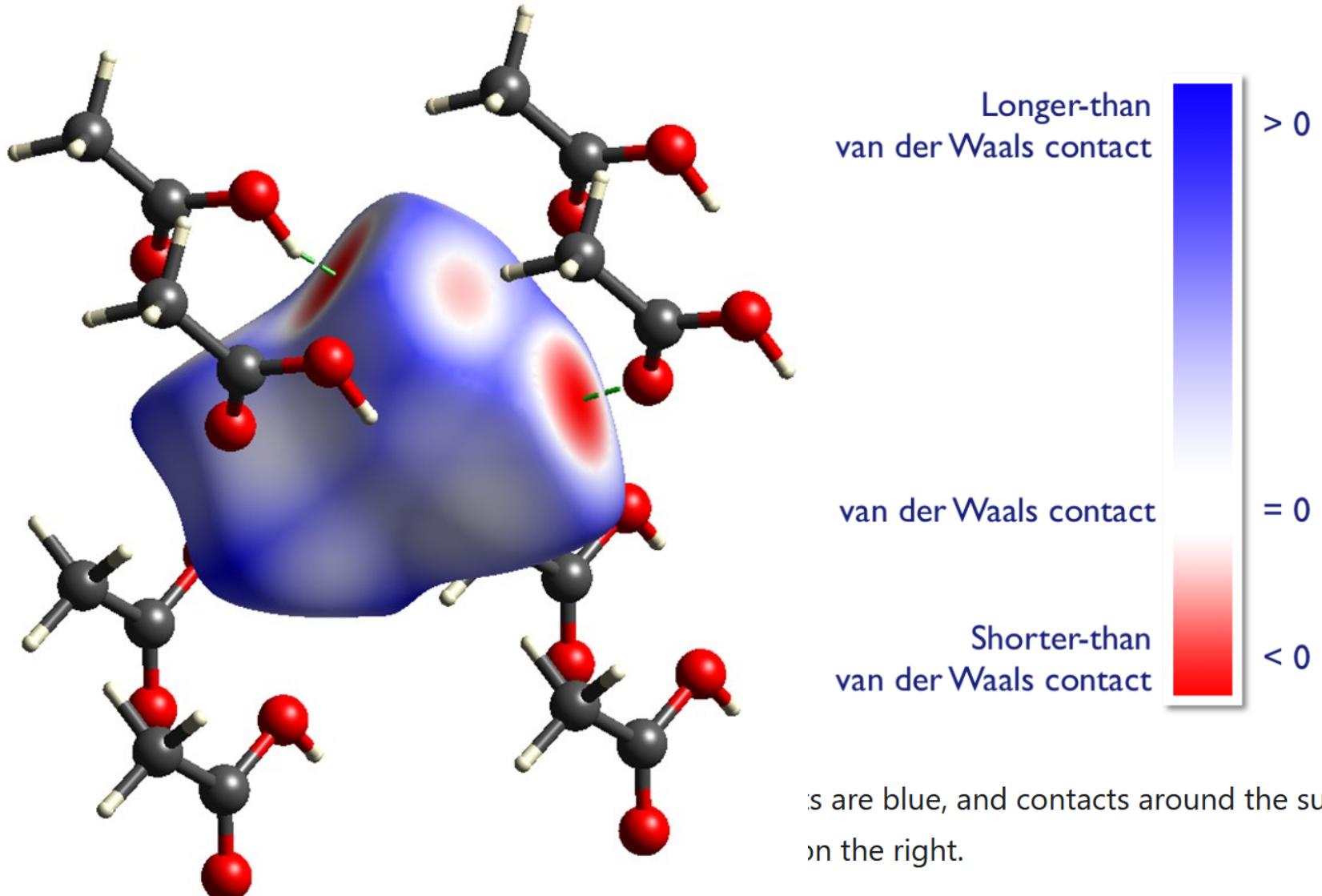


# 5. Practice with structure analysis using CrystalExplorer

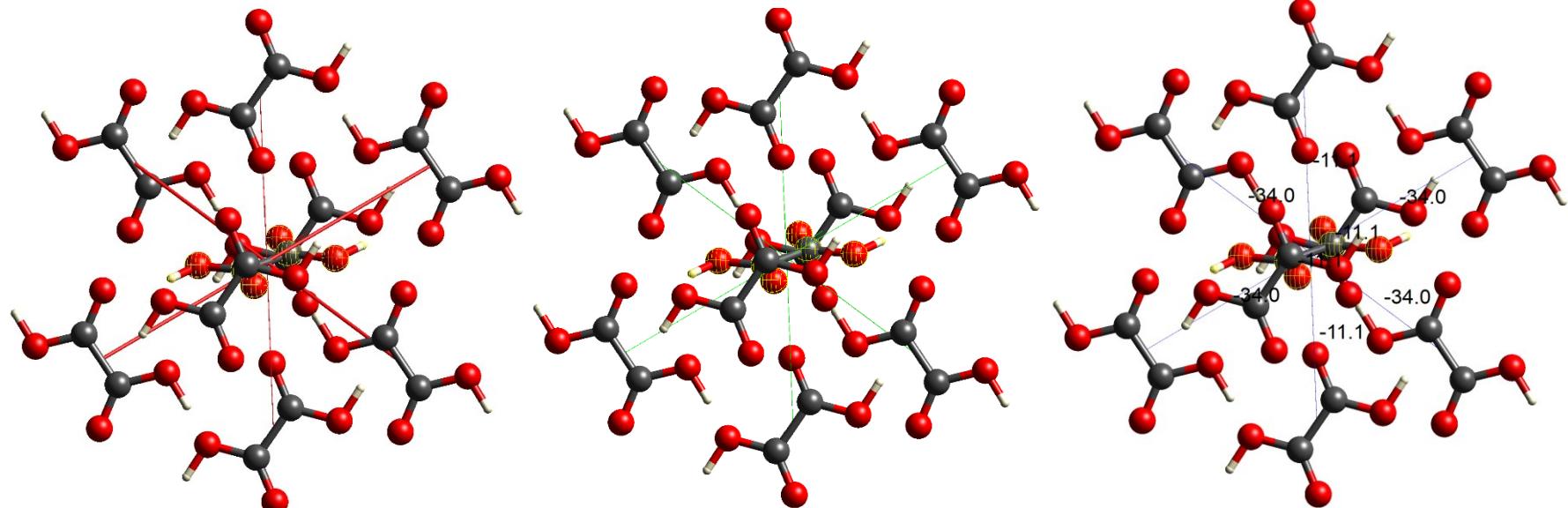
## Definition and reading of the $d_{\text{norm}}$ surface

**Acetic Acid**  
cluster in its  
unit cell.  
The central  
molecule's  
Hirshfeld  
surface is  
surrounded  
by 8 nearest  
neighbours.  
Of these, two  
participate in  
H-bonds (as  
shown by the  
dashed  
green lines)

**$d_{\text{norm}}$**



# Energy of Interaction – $\alpha$ & $\beta$ oxalic acid



Crystal Atoms Surface Energies

Interaction Energies (kJ/mol)

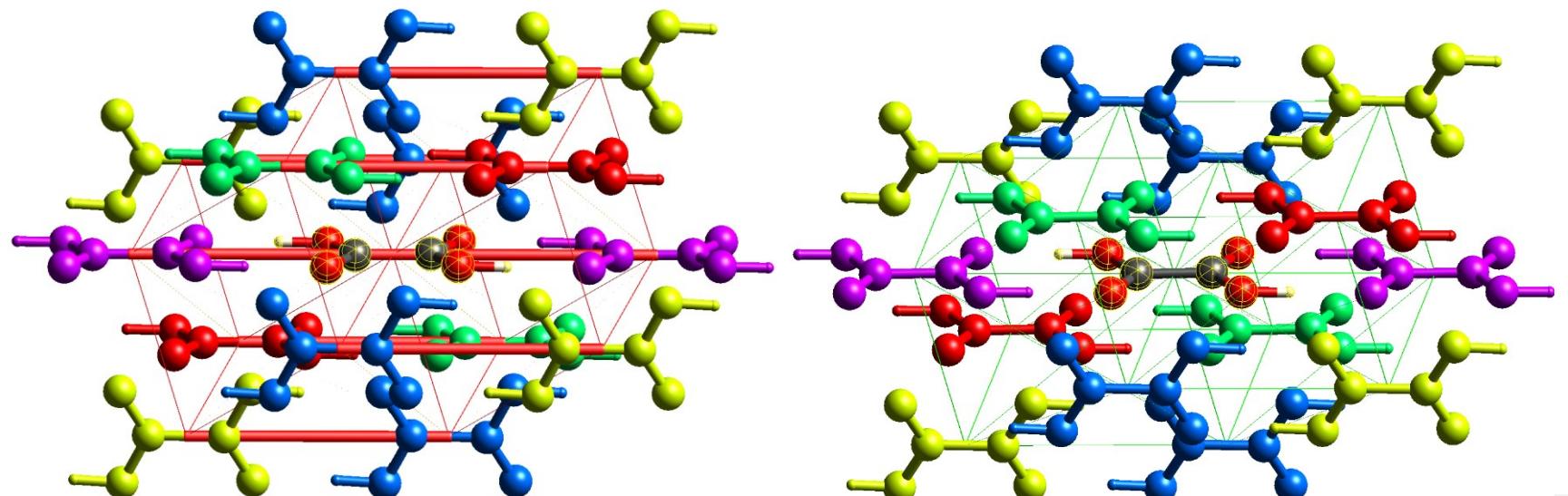
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
4	x+1/2, -y+1/2, -z	4.44	B3LYP/6-31G(d,p)	-10.0	-2.5	-9.0	14.7	-11.1
4	-x, y+1/2, -z+1/2	4.94	B3LYP/6-31G(d,p)	-44.6	-9.6	-10.2	47.2	-34.0

Scale factors for benchmarked energy models

See Mackenzie et al. IUCrJ (2017)



Energy Model k\_ele k\_pol k\_disp k\_rep

CE-HF ... HF/3-21G electron densities 1.019 0.651 0.901 0.811

CE-B3LYP ... B3LYP/6-31G(d,p) electron densities 1.057 0.740 0.871 0.618

Crystal Atoms Surface Energies

Interaction Energies (kJ/mol)

R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
2	x, y, z	5.72	B3LYP/6-31G(d,p)	-5.2	-0.5	-3.4	1.1	-8.2
4	-x, y+1/2, -z+1/2	5.68	B3LYP/6-31G(d,p)	0.3	-1.1	-5.1	2.0	-3.7
2	x, y, z	5.44	B3LYP/6-31G(d,p)	2.0	-0.7	-2.7	0.4	-0.5
4	-x, y+1/2, -z+1/2	4.05	B3LYP/6-31G(d,p)	-8.4	-3.0	-11.6	12.3	-13.6
2	x, y, z	5.33	B3LYP/6-31G(d,p)	-110.9	-27.4	-11.8	131.1	-66.8

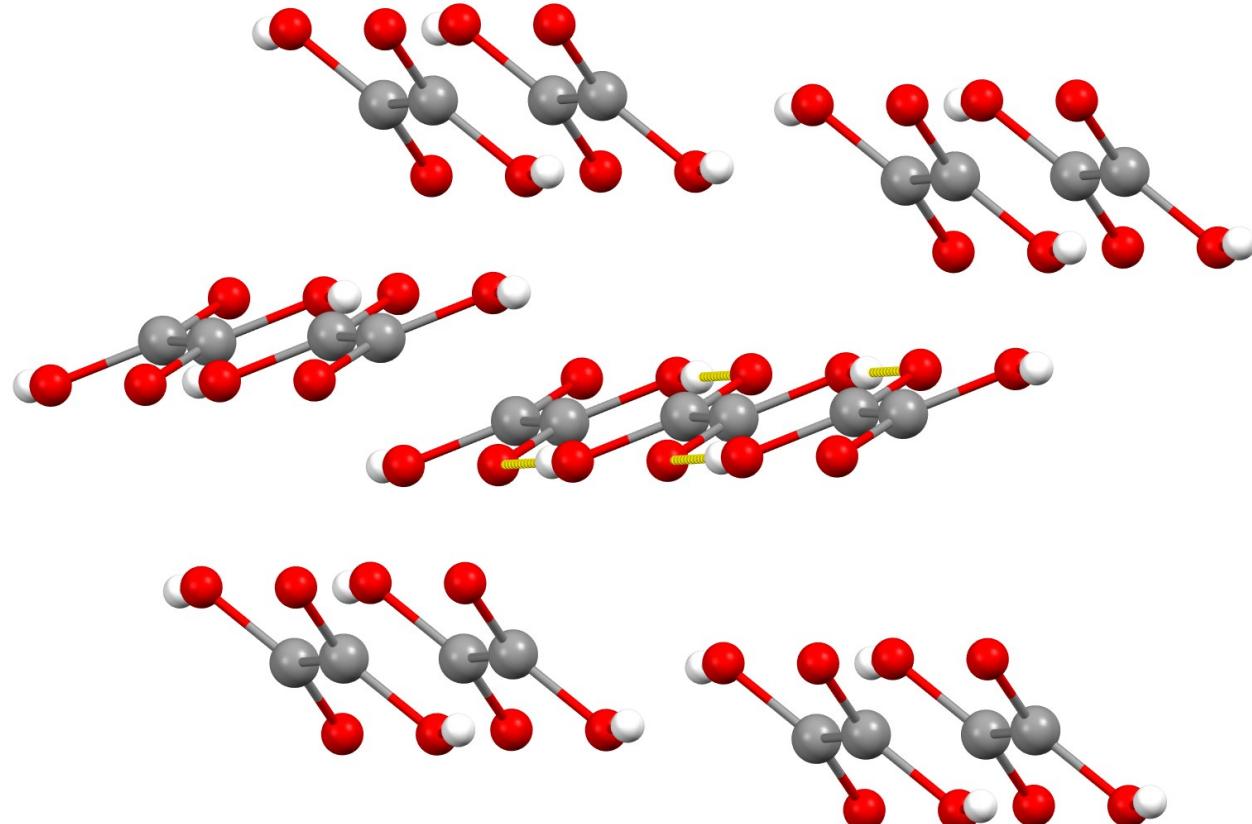
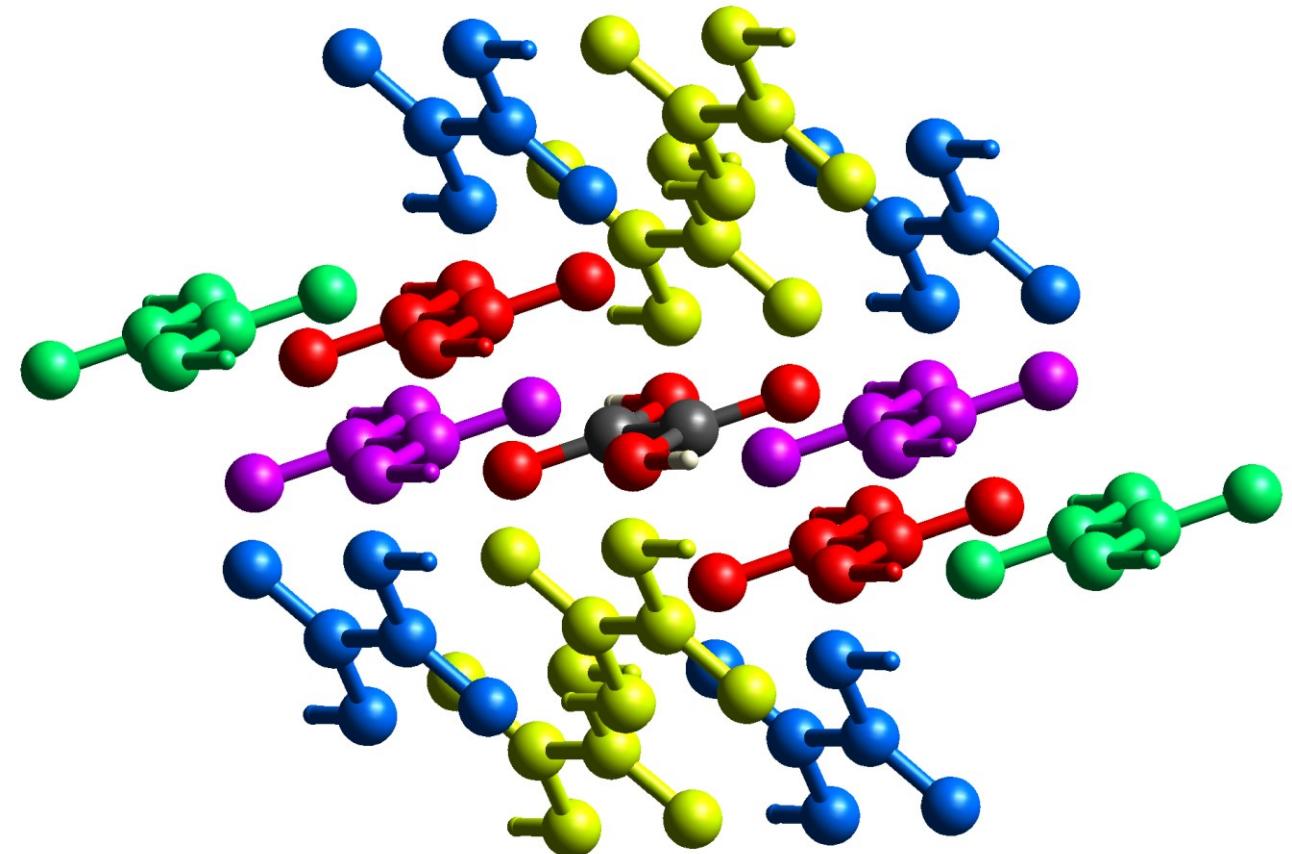
Scale factors for benchmarked energy models

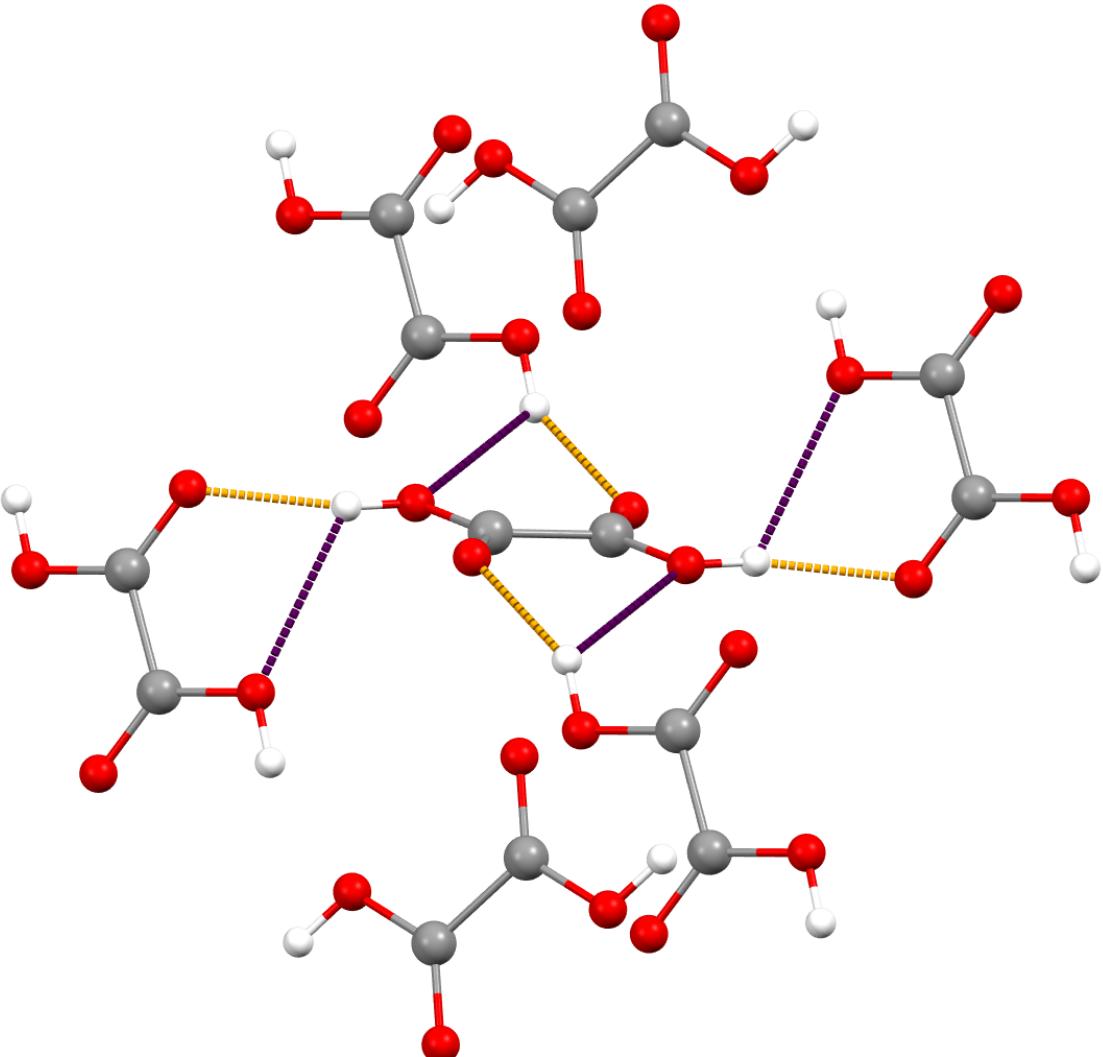
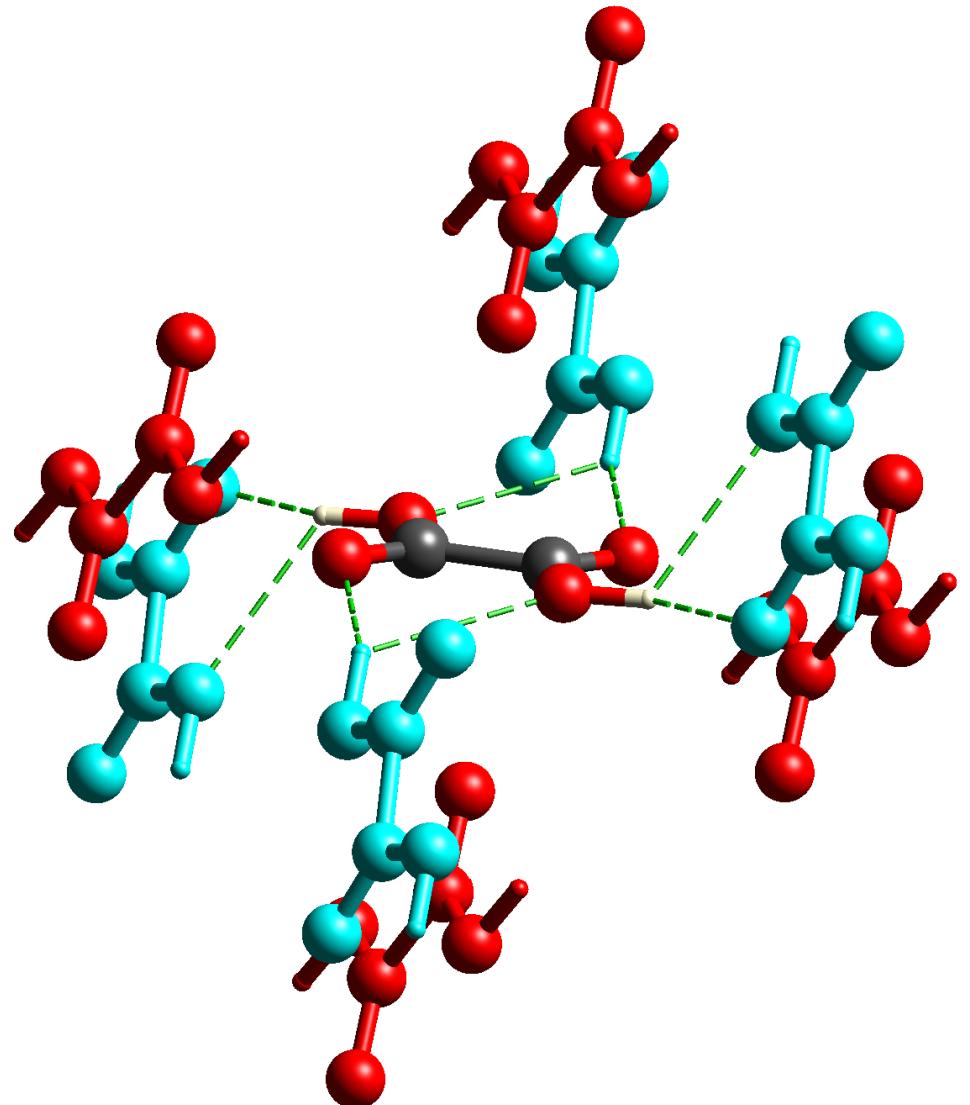
See Mackenzie et al. IUCrJ (2017)

Energy Model k\_ele k\_pol k\_disp k\_rep

CE-HF ... HF/3-21G electron densities 1.019 0.651 0.901 0.811

CE-B3LYP ... B3LYP/6-31G(d,p) electron densities 1.057 0.740 0.871 0.618

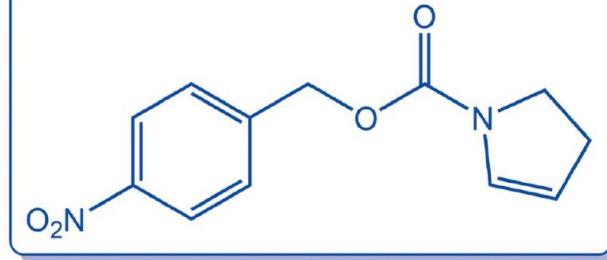
Beta Oxalic Acid –  $P2_1/c$ 

Alpha Oxalic Acid – *Pbca*

## 6. Second example with CrystalExplorer

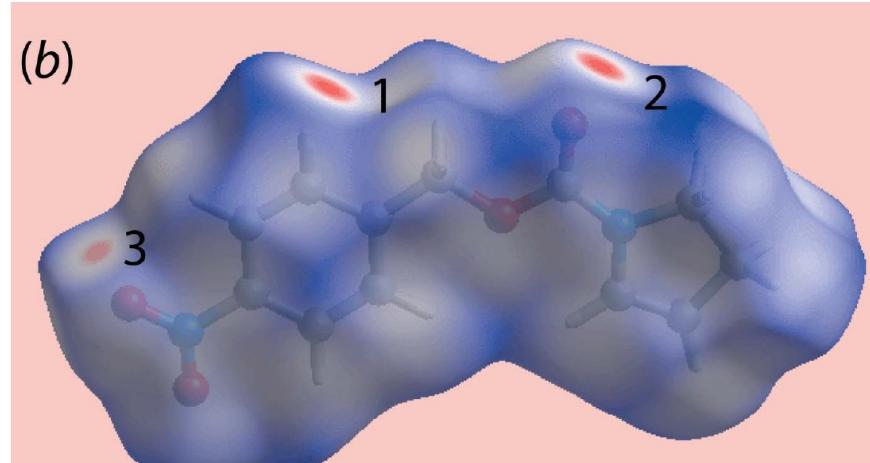
Acta Cryst. (2019). E75, 308–318. <https://doi.org/10.1107/S2056989019001129>

(a)

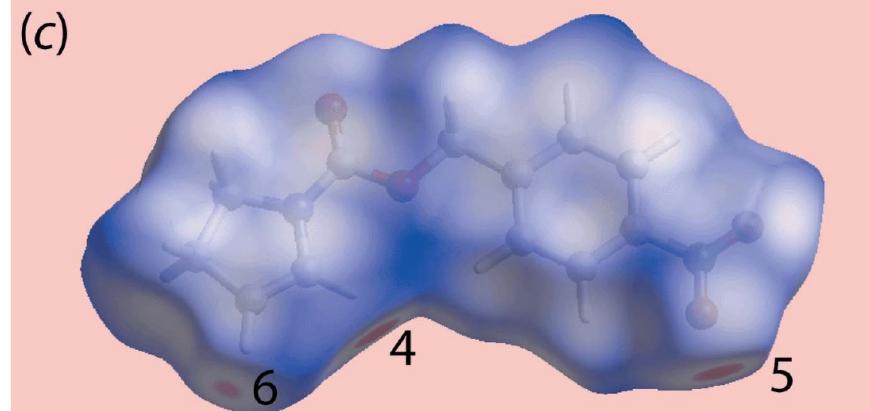


(a) Chemical diagram for (I).  
(4-nitrophenyl)methyl-2,3-dihydro-1H-pyrrole-1-carboxylate

(b)

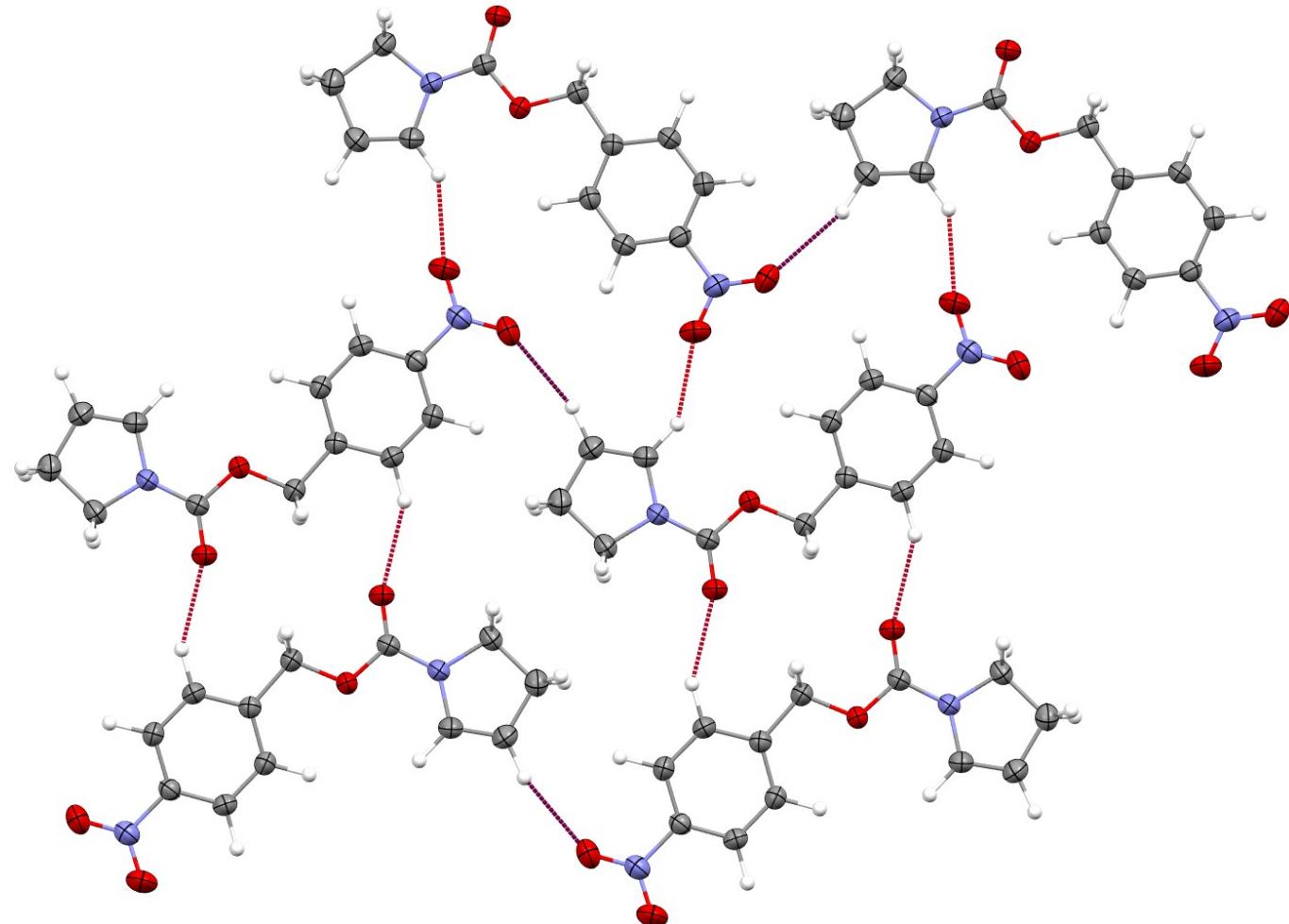
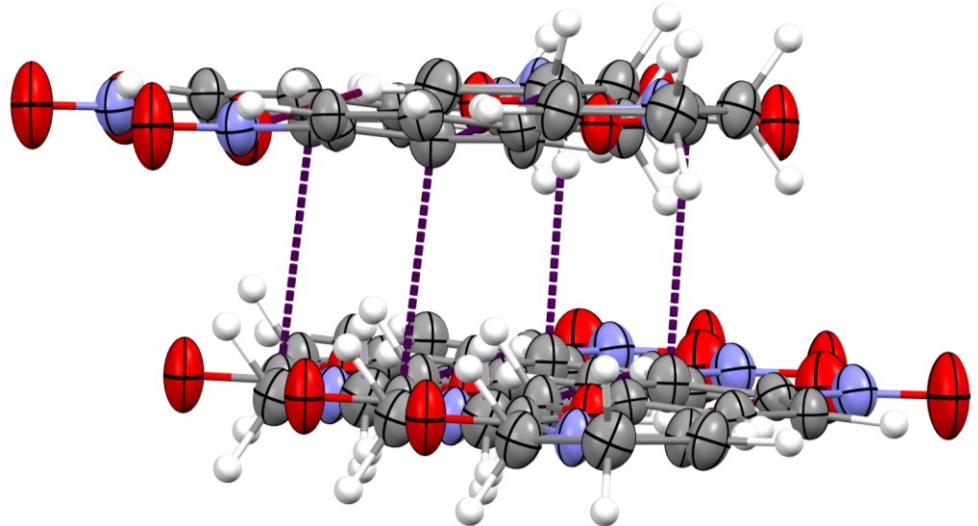


(c)

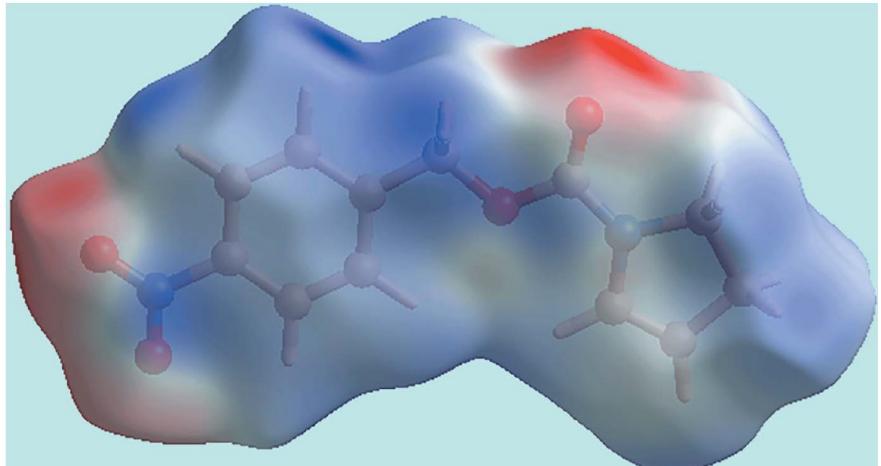


(a) Chemical diagram for (I), two views of the Hirshfeld surface mapped over  $d_{\text{norm}}$  for (I) over the ranges (b) 0.255 to +1.393 and (c) 0.055 to +1.393 arbitrary units; the numbers 4–6 indicate points of contact derived from different intermolecular interactions than those indicated in (b).

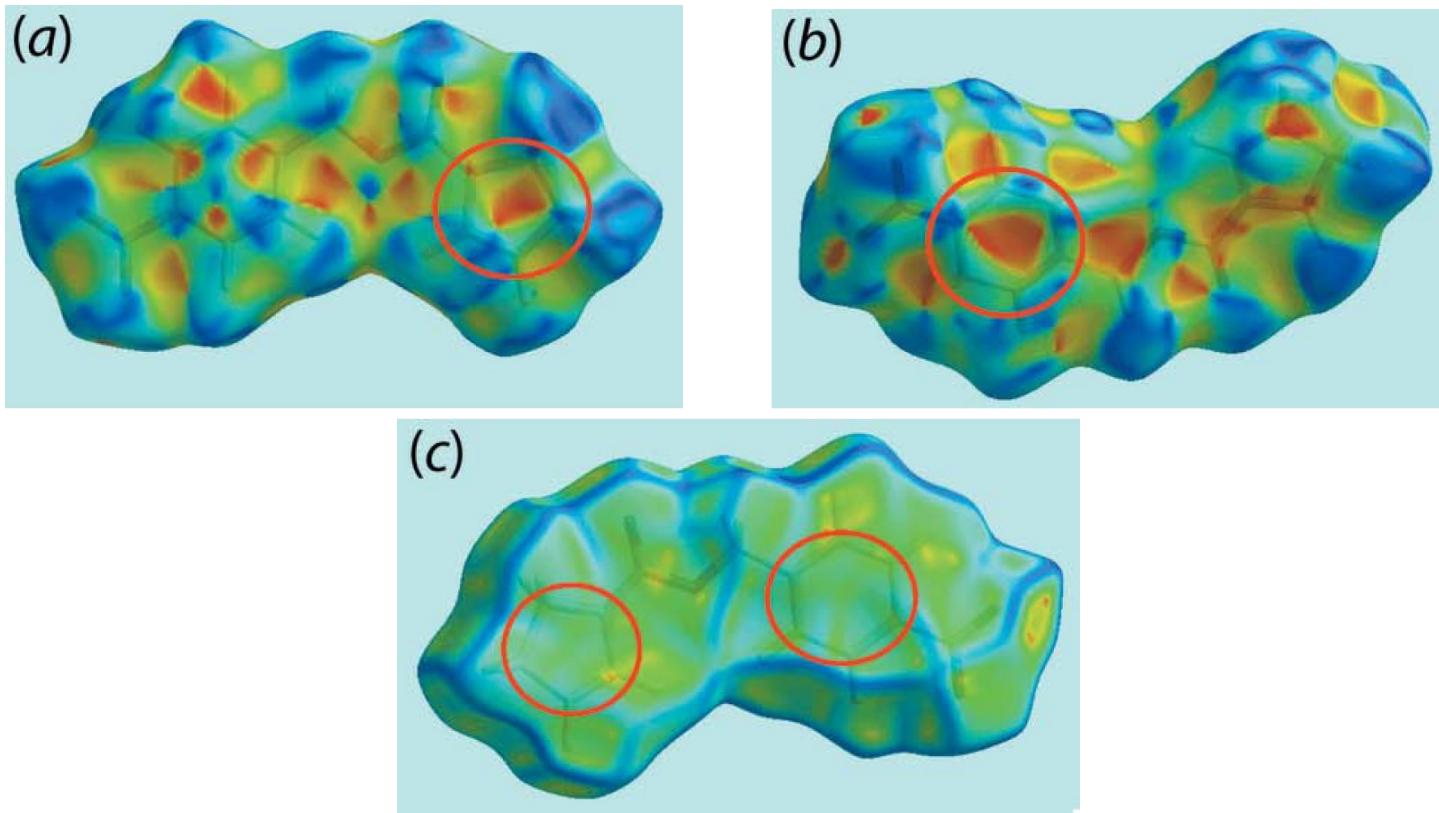
# Stacking and in-plane short contacts



# Practice with more surface types



(A view of the Hirshfeld surface for (I) mapped over the calculated electrostatic potential in the range 0.077 to +0.056 atomic units (the red and blue regions represent negative and positive electrostatic potentials, respectively).



(a) Views of the Hirshfeld surface for (I) mapped over the shape-index property highlighting blue regions about bright-red spots within the (a) pyrrolyl and (b) benzene rings, and (c) the Hirshfeld surface mapped over curvedness indicating flat regions around the pyrrolyl and benzene rings. The respective rings are highlighted by the red circles.