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Interaction geometries and energies of hydrogen bonds to C═O and C═S acceptors: a comparative study

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The occurrence, geometries and energies of hydrogen bonds from N—H and O—H donors to the S acceptors of thiourea derivatives, thioamides and thiones are compared with data for their O analogues – ureas, amides and ketones. Geometrical data derived from the Cambridge Structural Database indicate that hydrogen bonds to the C═S acceptors are much weaker than those to their C═O counterparts: van der Waals normalized hydrogen bonds to O are shorter than those to S by ~ 0.25 Å. Further, the directionality of the approach of the hydrogen bond with respect to S, defined by the C═S···H angle, is in the range 102–109°, much lower than the analogous C═O···H angle which lies in the range 127–140°. *Ab initio* calculations using intermolecular perturbation theory show good agreement with the experimental results: the differences in hydrogen-bond directionality are closely reproduced, and the interaction energies of hydrogen bonds to S are consistently weaker than those to O, by ~ 12 kJ mol^{-1}, for each of the three compound classes. There are no CSD examples of hydrogen bonds to aliphatic thiones, $(Csp^3)_2C{=}S$, consistent with the near-equality of the electronegativities of C and S. Thioureas and thioamides have electron-rich *N* substituents replacing the Csp^3 atoms. Electron delocalization involving C═S and the N lone pairs then induces a significant $>C^{\delta+}{=}S^{\delta-}$ dipole, which enables the formation of the medium-strength C═S···H bonds observed in thioureas and thioamides.

1. Introduction

An earlier paper (Allen *et al.*, 1997) used geometrical information retrieved from the Cambridge Structural Database (CSD; Allen, 2002) to characterize the hydrogen-bond acceptor ability of sulfur in >C═S systems relative to that of oxygen in chemically analogous >C═O systems. In >C═O systems the Pauling (1960) electronegativity difference between C (2.55) and O (3.44) induces the strong dipole $>C^{\delta+}{=}O^{\delta-}$ that makes O such a potent acceptor of hydrogen bonds in *e.g.* carboxylic acids, urea derivatives, amides and ketones. However, the origin of the acceptor ability of S in >C═S systems such as thiourea and thioamides is less obvious, since the Pauling (1960) electronegativities of C (2.55) and S (2.58) are almost equal. However, Allen *et al.* (1997) showed that the effective electronegativity of S in thiourea and thioamides is significantly increased by conjugative interactions between >C═S and the lone pairs on one or more *N* substituents attached to the C atom. Hydrogen bonds in these systems were therefore described as being resonance-induced.

In the earlier study, Allen *et al.* (1997) also showed that hydrogen bonds to the parent thiourea and its derivatives, and

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Table 1
Atomic point charges (q_O, q_S in electrons) on O and S in R_1,R_2C═X (X = O,S) systems calculated using *GAMESS-UK* (Guest *et al.*, 1993) and reported by Allen *et al.* (1997).

R_1	R_2	q_O	q_S
H	H	−0.42	−0.06
NH_2	H	−0.56	−0.27
NH_2	NH_2	−0.63	−0.37

to other appropriately substituted thiones, were analogous to those formed by >C═O groups. However, hydrogen bonds to >C═S:

(i) had a preferred directionality at S defined by a broad peak in the C═S···H angle distribution in the range 100–115° (the analogous C═O···H angle distribution has its peak in the range 115–135°), and

(ii) that the strength of >C═S···H bonds was less than that of analogous >C═O···H bonds.

This latter point was established by comparing experimental hydrogen-bond distance data with the appropriate sums of van der Waals radii: the 'van der Waals normalized' hydrogen-bond distances to C═O were found to be 0.22–0.25 Å shorter than those to C═S, with small variations being due to the donor being either N—H or O—H. This qualitative result was consistent with residual atomic charges (q_O, q_S) calculated using *GAMESS-UK* (Guest *et al.*, 1993) for O and S in different chemical environments R_1,R_2C═X (X = O, S). Table 1 shows that the negative charge on the carbonyl oxygen (q_O) increases by 0.22 e with increasing *N*-substitution at the C atom, whereas the charge on S (q_S) increases by 0.31 e over the same series. Even then, the residual charge on S in thiourea is less negative than that (i) on O in urea by 0.26 e, and (ii) on O in aliphatic ketones (modelled as $H_2C{=}O$) by 0.05 e.

In the intervening years, there has been significant activity involving the use of both ureas and thioureas in crystal engineering applications (see *e.g.* Custelcean *et al.*, 2007; Custelcean, 2008, and references therein). Hence, in this paper we extend our earlier work by exploring the bond length–bond strength relationship for hydrogen bonds from D—H (D = N, O) donors to X = O or S acceptors in R_1,R_2C═X systems, using both CSD analysis and *ab initio* calculations carried out using intermolecular perturbation theory (IMPT; Hayes & Stone, 1984).

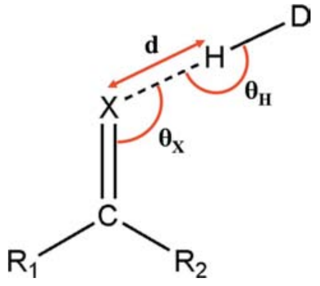

Figure 1
Substructure search fragment and geometrical parameters used to define the hydrogen-bonded interactions.

2. Experimental

2.1. Database analysis

The original searches and geometrical analyses of Allen *et al.* (1997) were carried out using CSD Versions 5.08 and 5.09 of 1994 and 1995 (126 353 and 140 236 structural entries, respectively). These analyses have been repeated and extended for this report with the much expanded CSD Version 5.28 (November 2006: 390 081 entries), using the programs *ConQuest* (Bruno *et al.*, 2002) and *VISTA* (Allen, 2002). The chemical fragment used is depicted in Fig. 1, and the primary intermolecular distance constraint required the O···H and S···H bonds, d_{XH}, to be $\leq v_X + v_H$, where v_X is the van der Waals radius of X (1.52 Å for O, 1.90 Å for S: Bondi, 1964), and v_H = 1.1 Å (Rowland & Taylor, 1996). Additionally, the angle D—H···X, θ_H, was constrained to lie in the range 150–180° to identify the most linear (shortest and strongest) hydrogen bonds in any category. These selection criteria were determined from the outcomes of the previous analysis (Allen *et al.*, 1997). The angle C═X···H, θ_X, at the acceptor was also calculated for each hydrogen-bonded substructure located in the CSD. All calculations were carried out using 'neutron normalized' H-atom positions, *i.e.* the H is moved along the D—H vector to a position that corresponds to the mean D—H distance determined by neutron diffraction (Allen, 1986). For all searches, the following secondary acceptance criteria restricted searches to structures:

(i) having no crystallographic disorder,

(ii) without covalent polymeric (*catena*) bonding,

(iii) having no residual errors following CSD validation procedures,

(iv) determined using single-crystal techniques (no powder diffraction structures),

(v) having $R \leq 0.075$ or ≤ 0.050 (see Table 2), and which were

(vi) organic structures according to CSD definitions (Allen, 2002; Bruno *et al.*, 2002).

2.2. *Ab initio* calculations

The intermolecular perturbation theory (IMPT) of Hayes & Stone (1984) as implemented in the *CADPAC*6.5 program package (Amos *et al.*, 1998) was used to calculate hydrogen-bond interaction energies, using the appropriate >C═X acceptor, as indicated in the sections below, and an O—H donor from a water molecule as the model system. The IMPT methodology yields separate interaction energy components (first order: electrostatic and exchange–repulsion energies; second order: polarization, charge-transfer and dispersion energies) which sum to a total interaction energy (E_t) that is free of basis-set superposition errors (Stone, 1993).

Table 2
Mean values of the interaction geometries for $R_1,R_2C{=}X\cdots H{-}D$ substructures from the CSD.

The parameters d (Å) and θ_X (°) are defined in Fig. 1, R_{max} is the R factor cut-off applied in the CSD search, Δ_X (Å) is the difference between d and the relevant sum of van der Waals radii (see text), and $\Delta_O - \Delta_S$ (Å) is the difference between the van der Waals normalized hydrogen-bond distances for O and S acceptors for the relevant N—H or O—H donor indicated in the table. The use of different R factor limits for the selection of substructures from the CSD represents a balance between structural precision and the need to retrieve acceptable numbers of fragments for analysis. Despite this, the lack of data points for S acceptors prevents calculation of these quantities for certain substitution patterns, as indicated in the footnotes.

X	R_1	R_2	D	R_{max}	N	d	Δ_X	$\Delta_O - \Delta_S$	θ_X
S	N	N	N—H	0.075	1010	2.451 (3)	−0.449		107.0 (3)
O	N	N	N—H	0.075	1601	1.928 (3)	−0.692	−0.243	127.2 (4)
S	N	N	O—H	0.075	86	2.341 (12)	−0.559		101.8 (12)
O	N	N	O—H	0.075	536	1.794 (6)	−0.826	−0.267	131.6 (6)
S	N	C_{any}	N—H	0.075	155	2.455 (9)	−0.439		107.7 (7)
O	N	C_{any}	N—H	0.050	3617	1.937 (2)	−0.683	−0.244	136.2 (3)
S	N	C_{any}	O—H	0.075	19	2.335 (20)	−0.549		103.9 (23)
O	N	C_{any}	O—H	0.050	2027	1.793 (3)	−0.827	−0.278	132.0 (3)
S	N	Csp^3	N—H	0.075	55	2.448 (14)	−0.452		108.5 (12)
O	N	Csp^3	N—H	0.050	2195	1.948 (3)	−0.672	−0.220	137.8 (4)
S	N	Csp^3	O—H	0.075	†	†	†	†	†
O	N	Csp^3	O—H	0.050	1131	1.793 (3)	−0.827	†	132.5 (5)
O	C_{any}	C_{any}	N—H	0.050	448	1.937 (7)	−0.683	†	139.0 (8)
O	C_{any}	C_{any}	O—H	0.050	1259	1.835 (3)	−0.785	†	131.7 (4)
O	Csp^3	Csp^3	N—H	0.075	122	2.028 (12)	−0.592	‡	139.6 (13)
O	Csp^3	Csp^3	O—H	0.075	621	1.875 (4)	−0.745	‡	132.5 (5)

† Insufficient (< 10) data points for X = S acceptors. ‡ No data points for X = S acceptors.

3. Results and discussion

3.1. Database analysis

Mean values for the interaction geometries of the $R_1,R_2C{=}X\cdots H{-}D$ substructures of Fig. 1 as obtained from the CSD are presented in Table 2 in groups that correspond to R_1,R_2 = *N*,*N*-, *N*,*C*- and *C*,*C*-disubstitution, respectively. Within these substitution groups, data are given for both N—H and O—H donors, but data points are either sparse (<10 observations) or non-existent for the C=S acceptors indicated in the table footnotes. In each case, where sufficient data are available, the quantity $\Delta_X = d - (v_X + v_H)$ is calculated using the van der Waals radii cited above so as to normalize the hydrogen-bond lengths to take account of the different van der Waals radii of the acceptor O and S atoms. The quantity $\Delta_O - \Delta_S$ (in Å) then provides a distance-based qualitative indication of the relative strengths of hydrogen-bonds formed to O acceptors compared with those formed by S acceptors.

Table 2 confirms and extends the results of Allen *et al.* (1997), *viz*:

(i) based on van der Waals normalized distances, hydrogen bonds to O acceptors are relatively shorter (stronger) than those to S acceptors, with $\Delta_O - \Delta_S$ in the range −0.220 to −0.278 Å (in agreement with the significant differences in the atomic point charges q_O and q_S for each substituent group given in Table 1),

(ii) there is an indication that hydrogen bonds involving O—H donors to both acceptors are slightly shorter (stronger) than those involving N—H donors,

(iii) hydrogen bonds to C=S in the *C*,*C*-substituent group do not occur, as expected from the relevant q_S value (−0.06 e) in Table 1,

(iv) there are no statistically discernable differences in the hydrogen-bond lengths observed for each acceptor in their *N*,*N*- and *N*,*C*-substituent groups, for which differences in the relevant q_O and q_S values are small, of the order of 0.08–0.10 e, and

(v) the mean θ_X values for hydrogen-bond directionality at S acceptors are in the range 101.8 (12)–108.5 (12)°, while those for O acceptors are in the range 127.2 (4)–139.6 (13)°. This directionality difference is clearly illustrated in the contoured *IsoStar* plots (Bruno *et al.*, 1997) presented in Fig. 2 for the distribution of donor-H from O—H and N—H groups around (*a*) ureas and (*b*) thioureas as determined from the CSD.

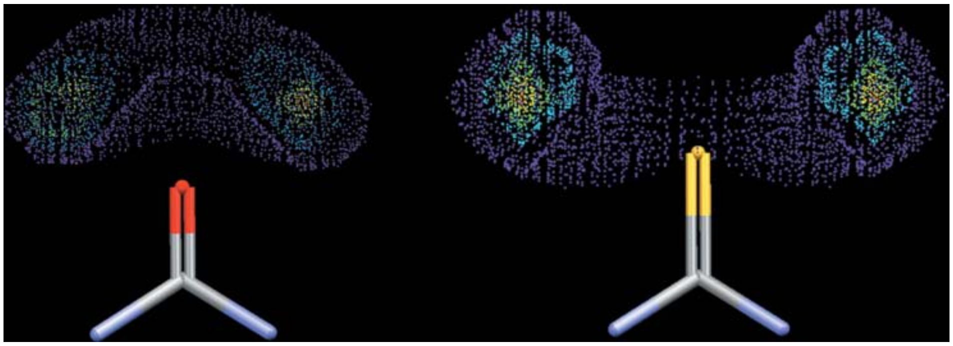

Figure 2
IsoStar plots (Bruno *et al.*, 1997) for N—H and O—H donors around (*a*) O acceptors in ureas and (*b*) S acceptors in thioureas. Contours are based on the positions of the H atoms of the donor groups.

Table 3
Values of the total interaction energy, E_t (kJ mol^{-1}) for O—H$\cdots X$=C hydrogen bonds in *N*,*N*-disubstituted ureas and thioureas (see Fig. 3*a*), computed for different values of the hydrogen-bond distance *d* (Å) and the H$\cdots X$=C angle θ_X (°).

d (Å)	θ_X = 125°	θ_X = 130°	θ_X = 135°	θ_X = 140°	θ_X = 145°
X = O					
1.6	−17.9	−23.6	−25.1	−24.9	−24.0
1.7	−23.7	−28.9	−30.3	−30.1	−29.2
1.8	−26.7	−31.2	−32.5	−32.2	−31.5
1.9	−27.9	−31.8	−32.8	−32.5	−31.8
2.0	−27.8	−31.1	−31.9	−31.6	−31.0
2.1	−27.0	−29.8	−30.4	−30.1	−29.5

d (Å)	θ_X = 105°	θ_X = 110°	θ_X = 115°	θ_X = 120°	θ_X = 125°
X = S					
2.3	−9.8	−16.3	−17.2	−16.0	−14.1
2.4	−13.2	−18.7	−19.3	−18.1	−16.4
2.5	−15.3	−20.0	−20.4	−19.2	−17.6
2.6	−16.6	−20.4	−20.6	−19.5	−18.0
2.7	−17.1	−20.3	−20.3	−19.2	−17.8
2.8	−17.2	−19.7	−19.6	−18.6	−17.4

3.2. *Ab initio* calculations

IMPT calculations were carried out using the model systems illustrated in Fig. 3. In the case of the $NHCH_3$ substituents, the methyl group and the O—H$\cdots X$ interaction were placed in a *cis* arrangement with respect to the C=*X* bond, thus avoiding any possible interference from the N—H of the model molecule with the O—H$\cdots X$ bond under study. The internal geometries of the model molecules were optimized using a 6-31G** basis set in each case. For the sulfur-containing model system, further calculations were performed to test the effect of increasing the basis set on the S atom from 6-31G** to 6-31G(3df), but it was found that the results were not significantly changed, so the data reported here are based on the former set of results.

IMPT calculations were then carried out varying the $X\cdots$H distance (*d*) and the C=$X\cdots$H angle (θ_X) to find the maximum absolute interaction energy E_t for each acceptor in the *N*,*N*-disubstituted urea and thiourea models of Fig. 3(*a*). Results in the vicinity of these minima for both O and S acceptors are shown in Table 3. The extended potential energy landscapes in *d*, θ_X space are illustrated in Figs. 4(*a*) and (*b*). They reveal broad minima which are in good agreement with the crystal structure data of Table 2 in showing that the angle of approach of O—H to the C=*X* bond, θ_X, is significantly lower for S acceptors, at *ca* 110–115°, than for O acceptors at 130–135°. The hypersurfaces (Table 3, Fig. 4) show E_t minima at *d* = 1.9 Å, θ_X = 135° for O acceptors, and at *d* = 2.6 Å, θ_X = 115° for S acceptors which, in terms of the van der Waals normalizations used in Table 2, correspond to values of Δ_O = −0.72 and Δ_S = −0.30 Å. The resultant value for $\Delta_O - \Delta_S$ is −0.42 Å, somewhat larger than the values obtained from the experimental data (Table 2). Although both potential energy minima are broad and shallow, Fig. 4 does show that the descent into the minimum is steeper and better defined for the S acceptor. This is reflected in the narrower distribution of θ_S observed in the crystal structure data when compared with θ_O (Allen *et al.*, 1997).

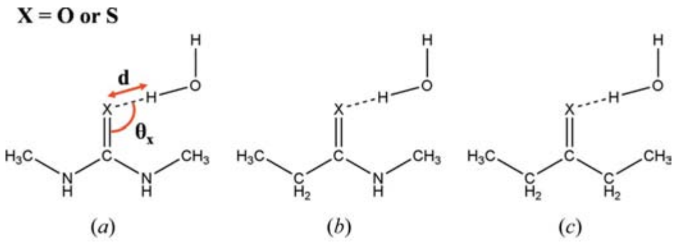

Figure 3
Model molecule pairs used in the IMPT calculations.

Single-point IMPT calculations were then carried out for the *C*,*N*- and *C*,*C*-disubstituted models of Figs. 3(*b*) and (*c*), using *d* and θ_X values fixed at the minima determined for the *N*,*N*-species, as described above. The full IMPT results, *i.e.* E_t and its five components, for these models are compared with the corresponding data for the *N*,*N*-species in Table 4, which

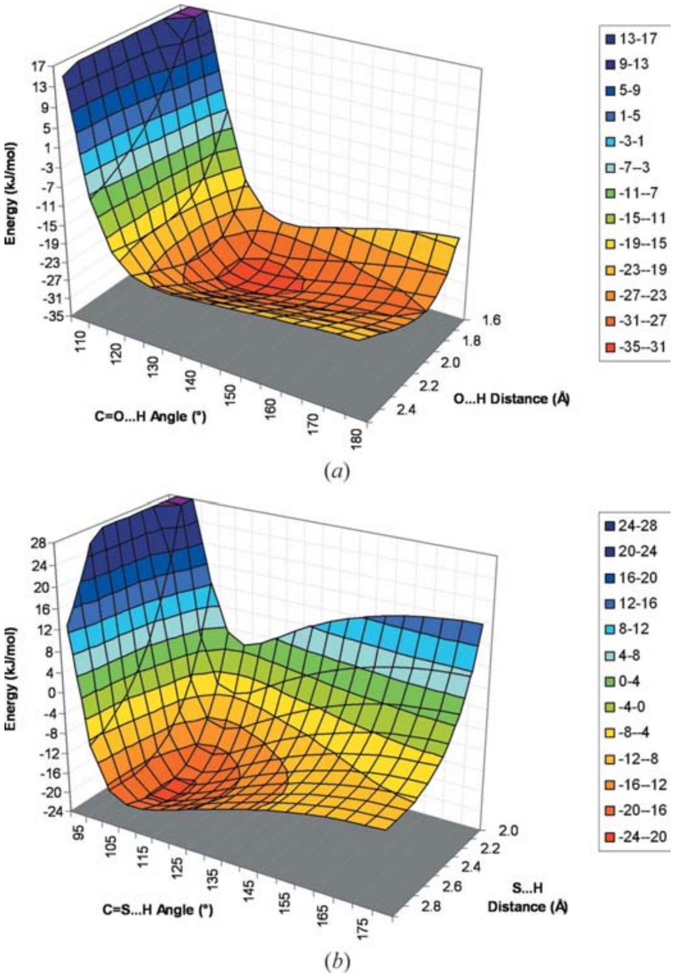

Figure 4
Potential energy landscapes computed using the IMPT software (Amos *et al.*, 1998) in *d*, θ_X space for N,N—C=$X\cdots$H—O hydrogen bonds for (*a*) *X* = O (modelling urea) and (*b*) *X* = S (modelling thiourea).

Table 4
Comparison of the IMPT energies (kJ mol^{-1}) calculated for the *N*,*N*-, *N*,*C*- and *C*,*C*-disubstituted models of Fig. 3.

The total interaction energy E_t is given together with its IMPT components: electrostatic (E_{es}), repulsion (E_r), polarization (E_{pol}), charge-transfer (E_{ct}) and dispersion (E_{disp}). The d and θ_X values used in these calculations were fixed as described in the text.

Substituent	E_{es}	E_r	E_{pol}	E_{ct}	E_{disp}	E_t
(*a*) Disubstituted C=O						
N,*N*	−45.4	31.3	−4.8	−4.7	−9.2	−32.8
N,*C*	−41.5	31.3	−4.4	−4.5	−9.1	−28.2
C,*C*	−39.1	34.7	−4.1	−4.4	−10.0	−22.9
(*b*) Disubstituted C=S						
N,*N*	−27.8	16.7	−1.9	−2.4	−5.3	−20.6
N,*C*	−25.0	16.9	−1.8	−2.2	−5.3	−17.4
C,*C*	−21.7	19.6	−1.7	−2.2	−6.1	−12.0

shows good synergy between the *ab initio* calculated energies and:

(i) the inferences about relative hydrogen-bond strengths that could be made on the basis of the analysis of experimental data in the CSD (Table 2), and

(ii) the residual charges on each acceptor (Table 1) as calculated by the Mulliken population analysis.

Thus, the strongest hydrogen bonds for both O and S acceptors are formed by the *N*,*N*-disubstituted species – modelling urea or thiourea – for which the electron delocalization involving the C=*X* double bonds and the *N*,*N* lone pairs induces the largest residual negative charge on *X*. Replacement of one of the *N* substituents by C (modelling amides and thioamides) reduces that negative charge slightly, and this is reflected in a concomitant reduction in the absolute E_t values for hydrogen bonds to both C=O and C=S. However, this effect is small, in the range 3–4 kJ mol^{-1}, and is not reflected in the mean geometries determined from experimental data (Table 2). Finally, elimination of the delocalization effect in the *C*,*C*-disubstituted species (modelling aliphatic ketones and thiones) reduces the residual negative charge still further (Table 1), and yields further reductions in E_t for both acceptors.

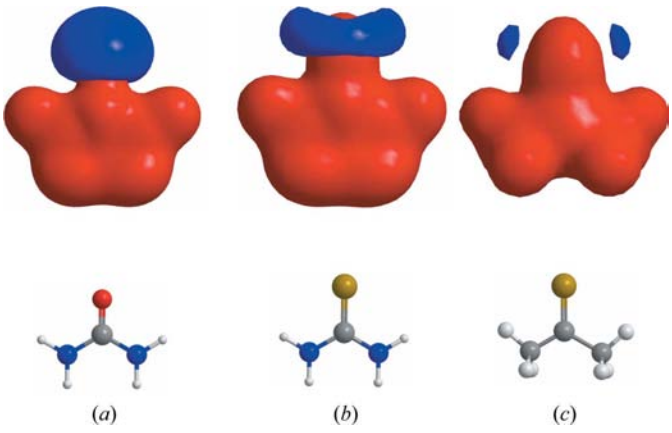

Figure 5
Molecular electrostatic potential surfaces for (*a*) urea, (*b*) thiourea and (*c*) thioacetone, calculated using *GAUSSIAN*03 (Frisch *et al.*, 2004), as described in the text.

Comparison of the calculated energy data for the O and S acceptors (Table 4) also follows the trend expected from the CSD analysis of Table 2. Absolute E_t values for the C=O···H—O hydrogen bonds for each of the three disubstituted series are consistently larger, by 10–12 kJ mol^{-1}, than for the corresponding C=S···H—O hydrogen bonds. Given that C=O···H—O bonds in urea derivatives can be regarded as strong hydrogen bonds in molecular systems with E_t = −32.8 kJ mol^{-1}, it is clear that the corresponding bonds in thiourea derivatives can only be classed as being of medium strength. Indeed, as indicated by the residual charge calculations of Table 1, hydrogen bonds to keto-O atoms in C,C—C=O systems (E_t = −22.9 kJ mol^{-1}) are actually stronger than their counterparts in thiourea and its derivatives (N,N—C=S···H—O, E_t = −20.6 kJ mol^{-1}).

Table 4 shows that the largest contribution to the attractive IMPT interaction energy (E_t) comes from the electrostatic contribution (E_{es}), and calculations of the electrostatic potential surface have been made using *GAUSSIAN*03 (Frisch *et al.*, 2004) at the MP2/6-31G** level of theory. The results are shown in Fig. 5 for (*a*) urea, (*b*) thiourea and (*c*) thioacetone. An isopotential of 1.5 a.u. was used to compute surfaces (*a*) and (*b*), while this was reduced to 1.3 a.u. to generate surface (*c*). Figs. 5(*a*) and (*b*) should be compared with the *IsoStar* plots of Fig. 2. Fig. 5(*a*) shows the expected negative potential capping the O in urea, but Fig. 5(*b*) shows an annulus of negative potential surrounding the S in thiourea, and an area of positive potential facing outwards along the C=S bond. Incoming hydrogen-donor atoms will naturally interact with this annulus at a C=S···H angle in the range indicated by the crystallographic analysis and the IMPT calculations (Tables 3 and 4, and Fig. 4). Figs. 5(*a*) and (*b*) are very similar in form to the electrostatic potential maps for the *N*,*N*-dimethyl derivatives of urea and thiourea presented by Custelcean (2008). The dramatic fall-off in negative charge density around S in thioacetone is illustrated in Fig. 5(*c*), and accounts for the lack of hydrogen bonds to S in crystal structures containing this functionality.

In conclusion, this work shows that the use of parent urea and thiourea and their derivatives in crystal engineering applications should be informed:

(*a*) by the relative energetic considerations, and

(*b*) by the fact that these S acceptors have very different directional properties with respect to incoming hydrogen bonds than their O analogues, as discussed and illustrated by Custelcean (2008).

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