ELECTRONIC SUPPLEMENTARY INFORMATION

S···O Chalcogen Bonding in Sulfa Drugs: Insights from Multipole Charge Density and X-ray Wavefunction of Acetazolamide

Sajesh P. Thomas, Dylan Jayatilaka and T. N. Guru Row

1. Intermolecular interaction energy estimation from *CrystalExplorer*

The interaction energy estimates from *CrystalExplorer* uses the unperturbed gas phase molecular wavefunction calculated at B3LYP/6-31G(d,p) level (Figure S1 and Table S1). The method applies space group symmetry operations on the density matrix corresponding to this molecular wave function to generate symmetry related neighbors and calculate the interaction energy. Further, the electrostatic terms are appended by terms to obtain the total interaction energy. Scale factors were obtained for the electrostatic, repulsion, dispersion, and polarization terms separately from a fitting the interaction energy values to large number of accurate interaction energy values reported in the literature (for more details of the calculation, see: M. J. Turner, S. Grabowsky, D. Jayatilaka and M. A. Spackman, *J. Phys. Chem. Lett.*, 2014, **5**, 4249). These interaction energy values were used to generate the energy frameworks (Figure S2), which represent the topology of intermolecular interactions in terms of their relative strengths (for details of energy frameworks, see: M. J. Turner, S. P. Thomas, M. W. Shi, D. Jayatilaka and M. A. Spackman, *Chem Commun*, 2015, **51**, 3735).
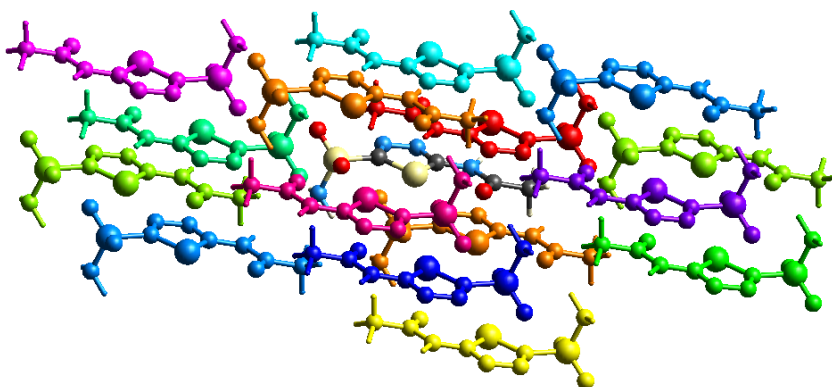

Figure S1. Colour coding based on the interaction energies of various neighbors around a central molecule.

Table S1. The interaction energies (kJ/mol) of various neighbors around a central molecule, and the scale factors used.

	Symop	Dist.	Wavefunc.	Coul.	Polariz.	Disp.	Repul.	Total
	-x, -y, -z	6.85	B3LYP/6-31G(d,p)	-125.0	-29.7	-26.3	140.3	-94.1
	x, y, z	5.28	B3LYP/6-31G(d,p)	-6.9	-5.1	-29.2	22.4	-22.5
	-x, -y, -z	8.06	B3LYP/6-31G(d,p)	6.5	-0.8	-2.7	0.0	4.1
	x, y, z	11.46	B3LYP/6-31G(d,p)	-4.5	-1.2	-5.3	2.3	-8.8
	-x, -y, -z	13.16	B3LYP/6-31G(d,p)	2.6	-0.9	-6.4	6.0	0.3
	-x, -y, -z	7.85	B3LYP/6-31G(d,p)	-61.3	-13.0	-16.9	48.7	-60.3
	-x, -y, -z	4.60	B3LYP/6-31G(d,p)	-40.5	-8.6	-38.5	27.0	-66.0
	x, y, z	9.35	B3LYP/6-31G(d,p)	13.1	-2.9	-9.7	4.8	6.3
	-x, -y, -z	4.81	B3LYP/6-31G(d,p)	-94.0	-19.7	-34.9	91.3	-90.0
	-x, -y, -z	10.74	B3LYP/6-31G(d,p)	-13.9	-1.9	-6.9	5.4	-18.8
	-x, -y, -z	10.37	B3LYP/6-31G(d,p)	10.1	-1.4	-2.6	0.7	7.9
	-x, -y, -z	6.09	B3LYP/6-31G(d,p)	6.4	-2.0	-7.7	3.1	0.7

Scale Factor Key:
Ke = electrostatic energy
Kp = polarization energy
Kd = dispersion energy
Kr = repulsion energy

Energy Model	Ke	Kp	Kd	Kr
HF/3-21G	0.882	0.593	0.852	0.681
MP2/6-31G(d,p)	1.027	0.722	0.842	0.605
B3LYP/6-31G(d,p)	1.063	0.756	0.843	0.595

| | View down *a* axis | View down *b* axis | View down *c* axis |

Electrostatic term
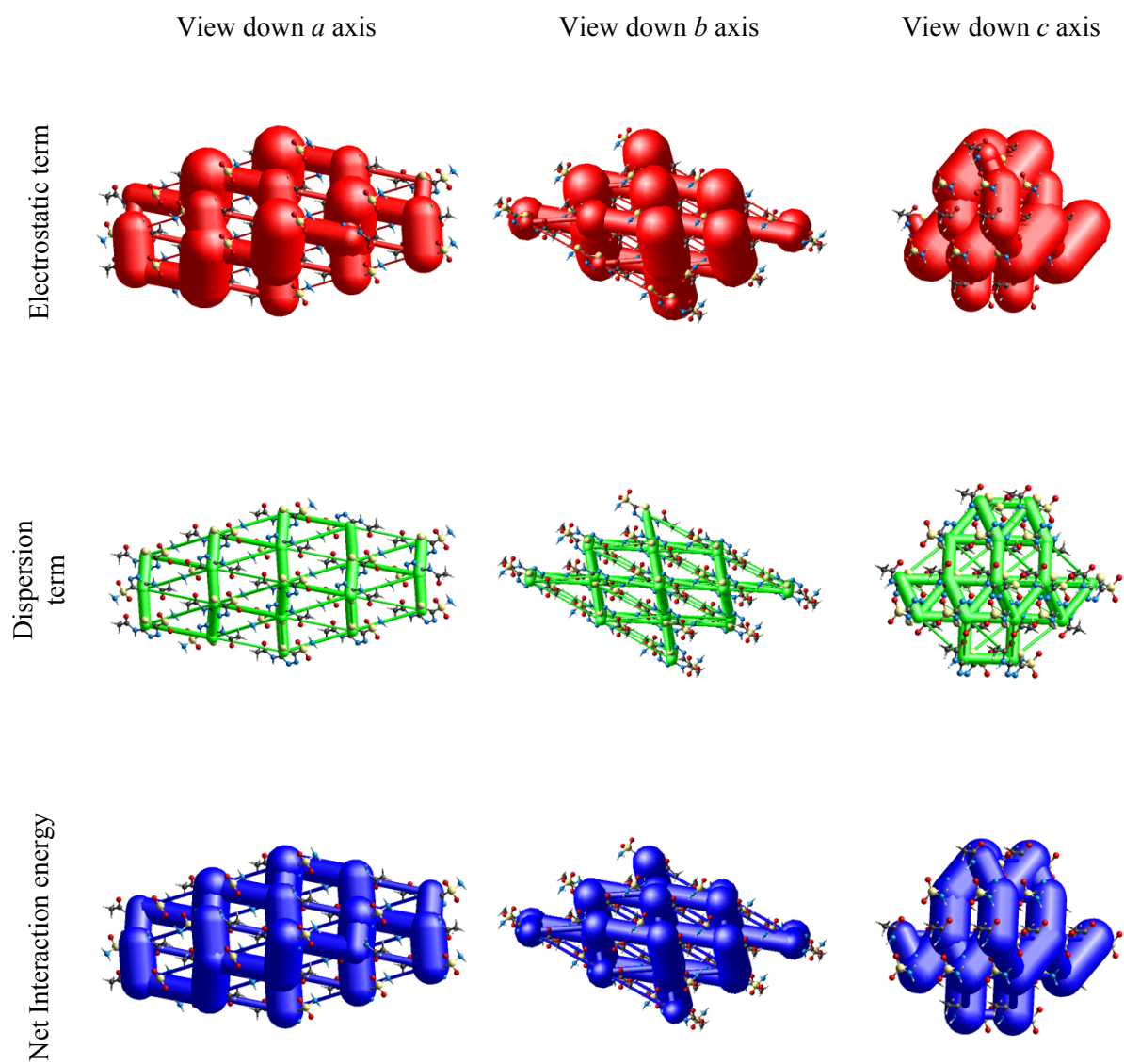
Dispersion term

Net Interaction energy

Figure S2. Energy framework based on electrostatic (red) and dispersion (green) components and net interaction energies (blue) viewed down different directions.
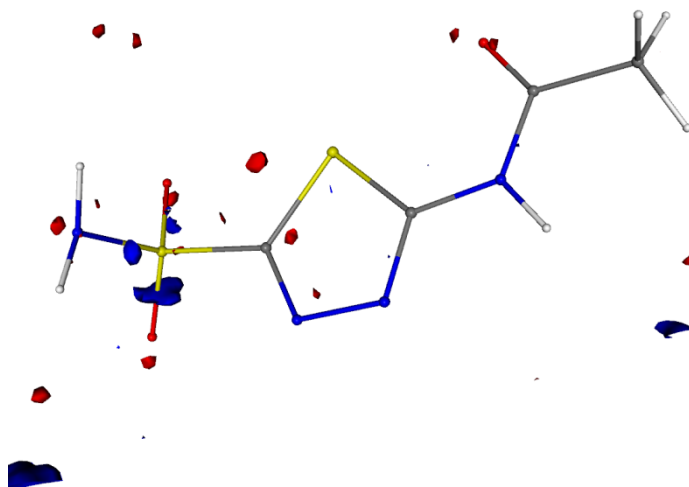
Figure S3. 3D residual density maps generated from XWR, isosurfaces plotted at +/- 0.1 eÅ⁻³(blue for peaks and red for holes).

Table S2. Topological parameters for intramolecular covalent bonds obtained from experimental multipole model (MM), X-ray wavefunction refinement (XWR), and gas phase calculations at BLYP/def2TZVP level.

		Electron density at BCP, ρ(eÅ⁻³)			Laplacian $\nabla^2\rho$ (eÅ⁻⁵)		
		MM	**XWR**	**Gas phase**	**MM**	**XWR**	**Gas phase**
1	S(1)−C(1)	1.376	1.464	1.423	-4.916	-2.924	- 2.456
2	S(1)−C(2)	1.444	1.434	1.444	-6.374	-2.630	-2.631
3	S(2)−O(2)	2.304	2.14	2.121	-2.084	5.270	5.463
4	S(2)−O(3)	2.392	2.13	2.117	-1.973	5.470	5.297
5	S(2)−N(1)	1.866	1.77	1.729	-16.781	-2.702	-2.023
6	S(2)−C(1)	1.412	1.458	1.448	-7.927	-3.016	-2.870
7	O(1)−C(3)	2.846	2.74	2.756	-26.754	-3.000	-3.448
8	N(1)−H(1N)	2.123	2.286	2.293	-29.780	-11.22	-10.266
9	N(1)−H(2N)	2.311	2.33	2.341	-31.858	-11.70	-10.995
10	N(2)−N(3)	2.359	2.444	2.423	-4.469	-4.716	-4.417
11	N(2)−C(1)	2.616	2.562	2.562	-27.898	-8.526	-7.382
12	N(3)−C(2)	2.544	2.508	2.509	-26.760	-8.524	-7.325
13	N(4)−C(2)	2.250	2.21	2.176	-19.620	-6.484	-6.205
14	N(4)−C(3)	2.223	2.196	2.174	-25.824	-6.722	-6.110
15	N(4)−H(4N)	2.109	2.168	2.178	-27.310	-10.788	-9.410
16	C(3)−C(4)	1.822	1.788	1.780	-14.308	-4.228	-4.124
17	C(4)−H(4A)	1.771	1.914	1.921	-14.592	-5.924	-5.958
18	C(4)−H(4B)	1.793	1.878	1.887	-16.382	-5.724	-5.713

| 19 | C(4)−H(4C) | 1.776 | 1.856 | 1.844 | -15.860 | -5.620 | -5.477 |

Table S3. Roby bond indices and populations obtained from XWR, for various bonds in AZM.

Atom_a	Atom_b	n_a	n_b	n_ab	s_ab	Bond Index	% Covalency
S1	O1	16.946195	9.367678	26.274396	0.039476	0.205785	100.000000
C4	C3	9.056835	8.250822	15.855564	1.452093	1.184160	92.385258
N2	C1	8.775620	8.506082	15.397128	1.884574	1.738339	99.433827
N3	C2	8.854447	8.435623	15.525990	1.764081	1.609201	98.645582
N3	N2	8.854447	8.775620	16.205594	1.424473	1.361051	99.910951
N4	C2	9.201806	8.435623	16.109547	1.527883	1.354834	91.916695
N4	C3	9.201806	8.250822	15.948798	1.503831	1.409426	89.880724
O1	C3	9.367678	8.250822	15.834204	1.784295	1.812352	90.573513
S1	C1	16.946195	8.506082	24.141269	1.311008	1.226545	98.770384
S1	C2	16.946195	8.435623	24.028350	1.353468	1.273806	98.499784
S2	N1	16.524878	9.271885	24.776219	1.020545	1.015312	89.052946
S2	O2	16.524878	9.384754	24.702533	1.207098	1.310722	90.831467
S2	O3	16.524878	9.399119	24.719858	1.204139	1.308932	90.331693
H1N	N1	1.428112	9.271885	9.406806	1.293192	0.951850	87.530083
H2N	N1	1.424591	9.271885	9.410688	1.285789	0.951491	87.675217
H4A	C3	1.595832	8.250822	9.804439	0.042215	0.104576	50.187547
H4A	C4	1.595832	9.056835	9.238139	1.414528	0.947780	95.629512
H4B	C4	1.614619	9.056835	9.241046	1.430408	0.946300	96.113780
H4C	C4	1.594069	9.056835	9.224355	1.426549	0.948823	95.401846
H4N	C2	1.394739	8.435623	9.780486	0.049876	0.154613	24.226672
H4N	C3	1.394739	8.250822	9.599515	0.046046	0.161260	20.957587
H4N	N4	1.394739	9.201806	9.370506	1.226039	0.934561	85.731724