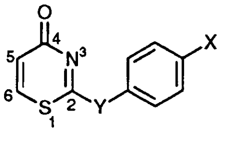
Crystallographic and PM3-COSMO SCF-MO Study of the Structure and Properties of Aryloxy- or Arylthio-thiazinones

Mark Hilton,[a] Peter Fisk,[a] Barbara Odell,[a] Henry S. Rzepa,[b] David J. Williams[b] and ManYin Yi[b]
[a] *Shell Research Centre, Sittingbourne, Kent, UK ME7 8AG*
[b] *Department of Chemistry, Imperial College, London, UK SW7 2AY*

The solid state structures of three *para*-substituted aryloxy- or arylthio-thiazinone derivatives reveal that the conformation of **2** differs from **1** and **3** in the orientation of the Y–aryl bond, due in part to an unusually strong C=O ··· H–C–S intermolecular interaction of $r_{O \cdots H}$ 2.20 Å present in **2**. A search of the Cambridge crystal structure database revealed relatively few other structures with similarly strong O ··· H–C interactions in which the common feature is the H–C–S structural unit. The observed reaction rate for aqueous hydrolysis of this series of compounds *via* attack of water at the C(2) position was found to correlate with the energy of the highest unoccupied orbital corresponding to σ rather than π character, but no feature in the wavefunctions could be found which identified **2** as the most likely to form the strongest O ··· H–C–S hydrogen bonding interaction in this series.

As part of a programme of investigating the properties of cross-conjugated S, N and O heterocyclic ring systems such as the 2-substituted thiazinone derivatives **1**–**3**, we required structural information for correlation with the hydrolytic reactivity of these systems. A search of the Cambridge crystallographic database for this ring system indicated no entries with this type of heterocyclic ring system.[1] We therefore undertook a crystallographic investigation of these structures, together with a theoretical examination at the semi-empirical PM3 level[2] of **1**–**3** in order to help identify the factors that may be responsible for the relative aqueous stabilities and for any unusual structural features identified.



1 X = NO_2, Y = O
2 X = NO_2, Y = S
3 X = OMe, Y = O

Experimental

A solution of 2-chloro-1-thi-3-azin-4-one[3] and 4-nitrophenol in dichloromethane was treated with Et_3N added dropwise, the mixture was stirred overnight and 2-(4-nitrophenoxy)-1-thi-3-azin-4-one collected by filtration; m.p. 225–227 °C (91%) (Found: C, 47.8; H, 2.5; N, 11.4. Calc. for $C_{10}H_6N_2O_4S$: C, 48.0; H, 2.4; N, 11.2%). Similar procedures gave 2-(4-nitrophenylthio)-1-thi-3-azin-4-one, m.p. 179 °C (42%) (Found: C, 45.6; H, 2.3; N, 10.5. Calc. for $C_{10}H_6N_2O_3S_2$: C, 45.1; H, 2.3; N, 10.5%) and 2-(4-methoxyphenoxy)-1-thi-3-azin-4-one, m.p. 136–138 °C (88%) (Found: C, 57.7; H, 4.0; N, 6.0. Calc. for $C_{11}H_9NO_3S$: C, 56.2; H, 3.8; N, 6.0%).

Crystal Data.—**1**: $C_{10}H_6N_2O_4S$, $M = 250.2$, triclinic, $a = 5.547(2)$, $b = 6.383(3)$, $c = 7.976(4)$ Å, $\alpha = 67.60(2)$, $\beta = 87.00(2)$, $\gamma = 81.10(2)°$, $V = 258$ Å^3, space group, $P1$, $Z = 1$, $D_c = 1.61$ g cm^{-3}, Mo radiation, $\lambda = 0.710\,73$ Å, μ(Mo-Kα) = 3.2 cm^{-1}, $F(000) = 128$, crystal dimensions 0.10 × 0.17 × 0.50 mm.

2: $C_{10}H_6N_2O_3S_2$, $M = 266.3$, monoclinic, $a = 14.178(16)$, $b = 6.157(4)$, $c = 25.92(2)$ Å, $\beta = 91.59(2)°$, $V = 2262$ Å^3, space group $P2_1/n$, $Z = 8$ (two crystallographically independent molecules), $D_c = 1.56$ g cm^{-3}, Cu radiation, μ(Cu-Kα) = 43 cm^{-1}, $F(000) = 1088$, crystal dimensions 0.07 × 0.43 × 0.40 mm.

3: $C_{11}H_9NO_3S$, $M = 253.3$, monoclinic, $a = 8.208(2)$, $b = 11.111(3)$, $c = 11.933(3)$ Å, $\beta = 100.79(2)°$, $V = 1069$ Å^3, space group $P2_1/c$, $Z = 4$, $D_c = 1.46$ g cm^{-3}, Mo radiation, $\lambda = 0.710\,73$ Å, μ(Mo-Kα) = 2.9 cm^{-1}, $F(000) = 488$, crystal dimensions 0.10 × 0.33 × 0.33 mm.

Data for compounds **1** and **3** were measured on a Siemens P4/PC diffractometer with Mo-Kα radiation and for **2** on a P3/PC diffractometer with Cu-Kα radiation using graphite monochromators. Data were measured for $2\theta < 63°$ for **1**, $< 116°$ for **2** and $< 50°$ for **3** using in each case ω-scans. For compounds **1**–**3**, 1578, 2885 and 1887 independent reflections respectively were measured and of these 1414, 2526 and 1193 respectively had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption corrections were applied. The structures were solved by direct methods and the non-hydrogen atoms were refined anisotropically. The positions of all the hydrogen atoms were revealed in ΔF maps. These positions were idealised C–H = 0.96 Å, the atoms assigned isotropic thermal parameters U(H) = 1.2 Ueq(C) and allowed to ride on their parent carbon atoms. Refinement was by full-matrix least squares to give for **1** $R = 0.062$, $R_w = 0.062$ [$w^{-1} = \sigma^2(F) + 0.0007 F^2$], for **2** $R = 0.036$, $R_w = 0.040$, [$w^{-1} = \sigma^2(F) + 0.0005 F^2$], and for **3** $R = 0.055$, $R_w = 0.050$, [$w^{-1} = \sigma^2(F) + 0.0005 F^2$]. The maximum residual electron densities in the final ΔF maps were 0.71, 0.18 and 0.28 e Å^{-3}. Computations were carried out on 386 or 486 PCs using the SHELXTL-PC program system. Atomic coordinates, bond lengths, angles and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.*

Computational Details.—The MOPAC-6 or MOPAC-93[2] programs were used, all geometries being fully optimised. The PM3-COSMO[4] continuum solvation model was used for aqueous modelling, with full geometry optimisation, and selecting a relative permittivity of 78.5. The solute charge distribution was evaluated using atom centred charges, dipole and quadrupole moments, within a cavity defined by the

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* For details of the CCCD deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1994, issue 1.

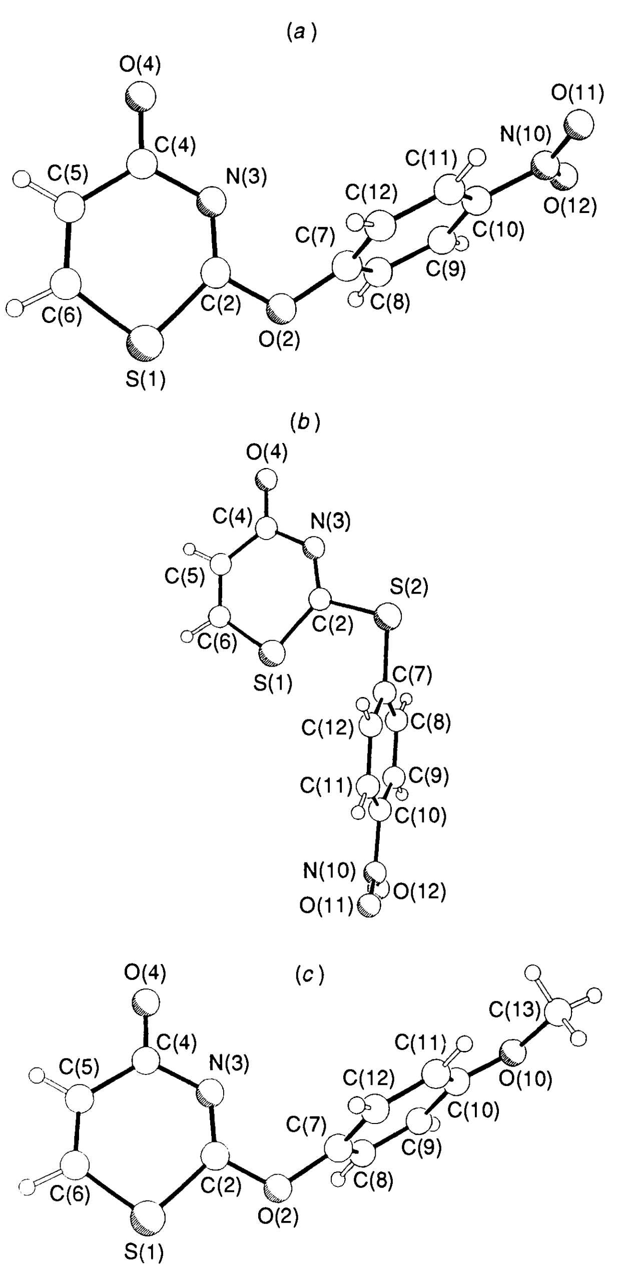


Fig. 1 Molecular structures for (*a*) **1**; (*b*) one of the pair of crystallographically independent molecules in **2**; and (*c*) **3**

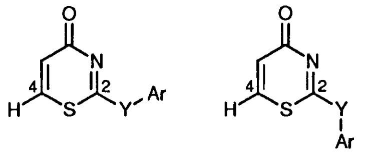
solvent accessible surface area calculated from the van der Waals radii of the atoms.

Results and Discussion

The molecular structures are shown in Fig. 1. Two distinct features are observed in the measured geometries for this series of thiazinone derivatives. Firstly, the *anti*-S–C(2)–Y–R dihedral conformation (*a*) is preferred for **1** and **3**, but the *syn* orientation (*b*) is found for **2** (Fig. 2). Secondly, in each case the aryl and thiazinone rings are essentially orthogonal to each other, with dihedral angles between the aryl and thiazinone rings of 66 and 88° for **1** and **3**, and 80 and 89° for the two crystallographically independent units in **2**. This suggests that no π-mesomeric interaction between the *p*-aryl substituent and the p_π orbital on C(2) is possible and only interaction with the σ-framework can occur. There is a high degree of consistency between the bond lengths and angles for the three molecules, regardless of the nature of the group Y and its conformation, or the substituent on the aryl ring (Table 1).

Table 1 Comparative bond lengths (Å) and angles (°) for compounds **1**–**3** with esds in parentheses

Atom	**1**	**2**		**3**
S(1)–C(2)	1.735(6)	1.740(4)	1.739(4)	1.742(4)
C(2)–Y(2)	1.352(6)	1.758(4)	1.751(4)	1.346(5)
C(2)–N(3)	1.263(7)	1.277(4)	1.284(4)	1.267(5)
N(3)–C(4)	1.402(7)	1.394(4)	1.395(4)	1.394(5)
C(4)–O(4)	1.203(7)	1.220(4)	1.218(4)	1.206(5)
C(4)–C(5)	1.476(9)	1.443(5)	1.443(4)	1.455(6)
C(5)–C(6)	1.329(8)	1.327(5)	1.332(4)	1.319(5)
C(6)–S(1)	1.724(5)	1.704(4)	1.701(4)	1.709(4)
Y(2)–C(7)	1.410(8)	1.771(4)	1.777(4)	1.422(5)
C(2)–S(1)–C(6)	98.6(3)	99.1(2)	99.4(2)	97.9(2)
S(1)–C(2)–Y(2)	107.7(4)	116.6(2)	117.5(2)	107.5(2)
S(1)–C(2)–N(3)	130.5(4)	128.6(2)	127.9(2)	130.0(3)
Y(2)–C(2)–N(3)	121.8(5)	114.8(2)	114.7(2)	122.5(4)
C(2)–N(3)–C(4)	122.4(5)	122.9(3)	123.5(2)	122.5(3)
N(3)–C(4)–C(5)	119.4(4)	119.7(3)	119.8(3)	119.6(3)
N(3)–C(4)–O(4)	119.9(6)	118.5(3)	118.4(3)	119.0(4)
C(5)–C(4)–O(4)	120.7(5)	121.8(3)	121.8(3)	121.4(4)
C(4)–C(5)–C(6)	124.0(5)	124.5(3)	124.1(3)	124.0(4)
C(5)–C(6)–S(1)	124.8(5)	124.9(3)	125.3(2)	125.9(4)
C(2)–Y(2)–C(7)	120.0(4)	102.8(2)	103.0(2)	118.2(3)



(*a*) (*b*)

Fig. 2

To investigate the origins of the differing conformational behaviour, we inspected each structure for close intermolecular contacts. For **2**, we found a strong (2.20 Å) hydrogen bonding interaction between a carbonyl oxygen atom of one monomer, and a H–C(6) bond of another unit (labelled a Fig. 3), with coplanarity between the two adjacent thiazinone ring systems. These features are found in both crystallographically independent units, with the length of the bond derived from each being identical. There are in addition, interlayer O ··· H–C hydrogen bonds (labelled b in Fig. 3) that are distinctly weaker but also present in both independent units (2.40, 2.46 Å). The orientation of this interaction disfavours the aryl–Y bond from adopting conformation (*b*), and appears to favour the *syn* orientation (*a*) shown in Fig. 2. A much weaker (2.43 Å) O ··· H–C(6) interaction is also present in **1** (Fig. 4), but here the hydrogen bond is stepped and the coplanarity of the adjacent linked molecules is no longer present, as a means of avoiding unfavourable intermolecular steric repulsions in orientation (*a*) (Fig. 2). Such O ··· H–C interactions are increasingly recognised as forming important intermolecular contacts in a variety of systems.[5] A search of the Cambridge crystallographic data base[1] based on the sub-structure O ··· H–C–S in which the O to H distance is < 2.35 Å suggests that this specific interaction is also well established (Table 2), although only two other examples reveal a shorter interaction than in **2**. In the instance of thiamine picrate,[6] the short (2.21 Å) O ··· H–C–S hydrogen bond can be directly related to the high kinetic acidity of the C(2) proton, which suggests that H–C(6) in **2** might also show similar behaviour.

To investigate whether this structural feature is related to the rate of hydrolysis of these derivatives, which involves nucleophilic attack of water at the C(2) position of **1**–**3**, we initially performed PM3 semiempirical calculations at the isolated molecule SCF-MO level for comparison with the crystal structures. In all cases, optimisation converged to the same

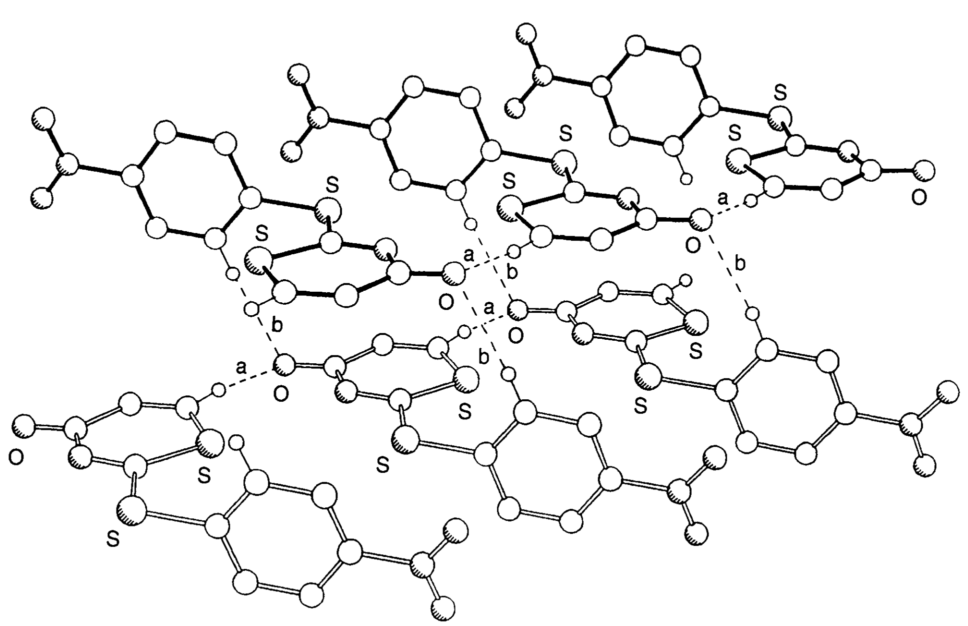


Fig. 3 Intermolecular contacts in **2**, showing the close approach between the C=O group of one molecule and the H–C(6) of another labelled as a and the weaker carbonyl to aryl ring interlayer O • • • H–C contact labelled b

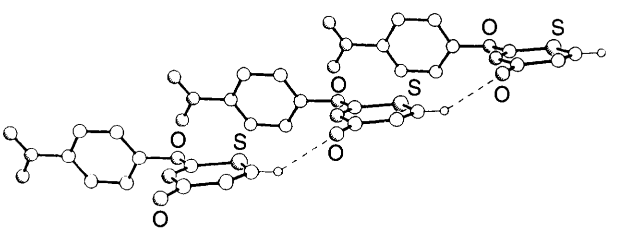


Fig. 4 Intermolecular contacts in **1**, showing the noticeably weaker O • • • H–C interaction and the stepping of adjacent thiazinone rings, compared with **2**

Table 2 Entries in the Cambridge Crystallographic Database for short intermolecular O • • •H–C–S contacts

Cambridge Refcode[1]	$r_{O\cdots H\text{–}CS}$/Å	Type of oxygen atom involved in the interaction
BAGSAD	2.26	Hydroxy
BAGSEA	2.32	Water
BCXDTH	2.29	Ketone
DENHIN	2.35	Ester
EAMTHZ	2.24	Ester
FEXSUW	2.29	Amide
FUBRAV	2.01	Amide
IPTHBZ	2.32	Ester
JIYVIW	2.34	Ketone
JOYHOU	2.38	Ketone
KASSOM01	2.32	Ester
KITZIW	2.34	Ketone
KUDTOS	2.26	Amide
KUGZAN	2.30	Ketone
SOXWIL	2.34	Ketone
VAPMUU	2.31	Ketone

orthogonal orientations as determined in the crystal structures. For **2** however, orientation (*a*) is preferred to (*b*) by 3 kcal mol^{-1},† providing some measure of support for the orientation in the crystal lattice of **2** being brought about by intermolecular interactions. Inspection of the calculated isolated molecule charge on the hydrogen attached to C(6) and the H–C σ* orbital energy indicated that compound **1** has a slightly more positive charge on the hydrogen atom (0.146) and the lower energy H–C σ* orbital energy (2.29 eV) compared with **2** (0.145, 2.38 eV). There is therefore little evidence from these calculations that this hydrogen atom is particularly acidic for compound **2**, and the reasons for the formation of this particular hydrogen bond remain to be established.

We have established from kinetic measurements that the hydrolytic half lives at pH 9 are *ca.* **1** (2 h), **2** (< 1 h) and **3** (30 h), in each case the products corresponding to attack by water at the C(2) position and subsequent elimination of phenoxide or thiophenoxide. The PM3 calculations were repeated at the PM3/COSMO level in order to provide a more realistic model for the electronic structure of the substrates in aqueous solution, since it has been noted by Katritzky and Karelson[7] that orbital energies may be significantly influenced by the effect of a surrounding polar medium such as water. The lowest unoccupied orbital in all four systems is found to be a σ* orbital delocalised over the C(6)–S–C(2)–Y framework, and extending into the σ system of the aryl ring. This orbital will therefore play a crucial role in accepting electrons from a nucleophile such as water. A direct correlation was found with the energy of this orbital and the hydrolytic half-life of **1**–**3** at pH 9 (Table 3), with **2** showing the lowest σ-acceptor energy, and **3** the highest. The interactions with the σ system are clearly only possible with the aryl groups in the orthogonal orientation as found in the crystal lattice, which implies therefore that the role of the aryl substituent propagates largely through this σ system, rather than acting in any π-mesomeric sense.

Conclusions

The orientation of the Y-aryl bond in the series of compounds **1**–**3** is established by X-ray crystallography as corresponding to an orthogonal orientation with respect to the thiazinone ring system. This results in σ rather than π-conjugation with the bonds associated with C(2), and a direct correlation of the calculated σ* orbital energies with the rate of hydrolysis of this type of system. The factors which promote O • • • H–C(6) intermolecular hydrogen bonding for **2** only remain obscure.

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† 1 cal = 4.184 J.

Table 3 PM3 SCF and COSMO calculated properties of **1**–**3**

	ΔH(SCF)/ kcal mol^{-1}	ΔH(COSMO)/ kcal mol^{-1}	σ-LUMO/ eV[a]	Orbital coeff.[b]
1	−0.4	−36.3	−1.40	0.40
2	36.1	1.6	−1.76	0.45
3	−30.2	−49.9	−1.23	0.55

[a] Energy of σ-type unoccupied orbital. [b] Defined as $[\Sigma(c)^2]^{0.5}$.

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