Noncovalent Interactions of π Systems with Sulfur - The Atomic Chameleon of Molecular recognition

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Abstract: The relative strengths of noncovalent interactions of a sulfur atom with a range of π systems have been measured by NMR using designed top pan molecular balances and compared with their oxygen counterparts. The sulfur atom displays a remarkable ability to interact with almost equal facility over the entire range of π systems studied, with the simple alkene emerging as a powerful partner. With the exception of the O(lone pair)···heteroarene interaction, all noncovalent interactions of sulphur with π systems are favoured over oxygen.

Noncovalent interactions involving aromatic systems[1] such as π-stacking,[2] cation[3]/π interactions, and the ability of an arene to act as a hydrogen-bond acceptor[4] are all firmly established as vital control elements in molecular recognition and consequently underpin vast areas of chemistry and molecular biology. More recently, as a consequence of two virtually simultaneous theoretical studies predicting the strength of the related anion/π[5] interaction, this area has witnessed intense research activity[6]. In parallel, following on from the seminal observation of the attractive lp-π interaction in stabilizing the Z-DNA structure[7], this force is also rapidly gaining recognition as a new area of supramolecular chemistry[8].Detailed quantifiable knowledge of the relative strengths of these relatively weak forces is now therefore considered to be essential for the rational design of organocatalysts[9], new drugs and supramolecular materials, as well as the understanding of three-dimensional structure and function in biological systems.

The conformational analysis of designed molecular balances[10] with limited degrees of freedom is a particularly powerful tool for probing the strength, distance and angular dependence of such interactions, and also allows for exploration of all important solvation phenomena[11]. Whilst an increasing number of studies in recent years have focused on measuring the oxygen(lp)···π interaction with electron deficient arenes and heteroarenes [12] we were very surprised to note that quantifiable comparative information using such balances to probe noncovalent interactions involving a sulfur atom with π systems has been almost entirely neglected. The vital role played by sulfur in chemical and biological recognition and in drug development is well recognized[13], and, as summarized in an ongoing series of excellent reviews on the sulfur…arene interaction,[1] is essentially based on extensive database mining of protein crystal structures. In a significant contribution by Dougherty and coworkers[14] the strength of a sulfur-arene interaction in the Dopamine D2 receptor has been probed by progressive modulation of the electrostatic surface of the arene through fluorination. To the best of our knowledge, in spite of the fact that theoretical chemists continue to be intrigued by the noncovalent interactions of a sulfur atom with π systems[15], no quantitative measurements have been reported for either simple alkenes or heteroarenes. In terms of a comparative study of the relative strengths of sulfur versus oxygen···π-arene interactions, we have previously noted a significant preference for sulfur over oxygen in measuring the conformational equilibrium of the dibenzobicyclo[3.2.2]nonane oxathiolane derivative **(1)** (Figure 1).[16a] This bridged bicyclic framework, together with related congeners, has now served as the pivotal element of our top pan molecular balance system for quantifying a wide range of noncovalent functional group interactions with π systems.[16]

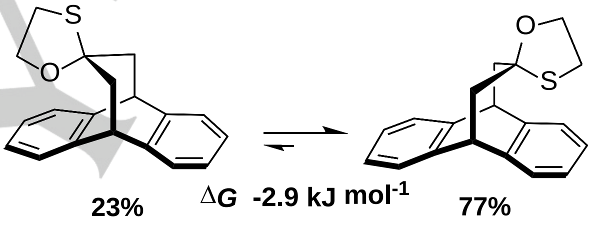

Figure 1. Sulfur versus oxygen···π-arene interactions in oxathiolane **1**.

In a comparison of anisole with thioanisole using a rotameric N-aryl succinimide torsional balance, Cozzi and coworkers[17] have reported a very marginal preference for an O···arene interaction, but indicated that steric interactions may have contributed. The same group have also carried out a beautiful study for the very special case of furan versus thiophene using a cyclophane framework [12c]. Within these extensively conjugated systems, the more aromatic thiophene was found to adopt a sandwich structure, whilst the furan preferred an O···π-arene interaction.

In light of the above, there is a very clear need for a detailed energy landscape map to provide a comparative data set for both oxygen and especially sulfur noncovalent interactions over a range of differing π systems. We have accordingly prepared the series of oxathiolanes **(1)** – **(8)**, dithioketals **(9)** – **(12)**, and ketals **(13)** and **(14)** and measured their conformational preferences in a

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range of solvents using our previously established NMR methods. The results of this study are collected in Table 1 and, even by simple visual inspection of the preferred conformer from a qualitative standpoint, reveal several features of interest.

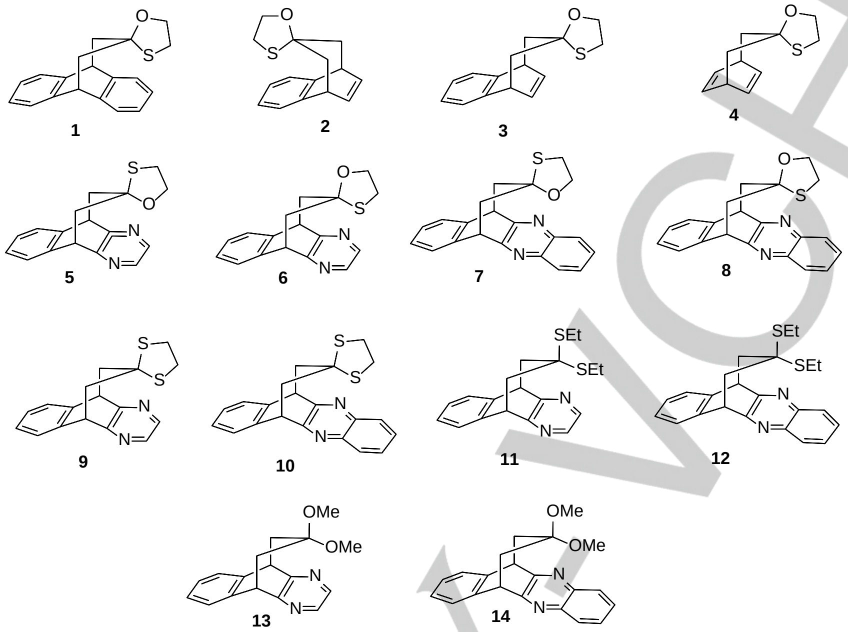

Figure 2. Molecular balances **(1)** – **(14)**. The structure of the preferred conformer is shown.

Table 1. Populations of the preferred conformers (in %) in molecular balances **(1)**-**(14)** shown in Figure 2.[a] For **(1)** and **(5)**-**(12)**, boundaries are changed to 1.10/7.31 (measured for **(12)** in CD_3OD at -40 °C).

Solvent	**1**	**2**	**3**	**4**
$CDCl_3$	76.7	86.8	88.2	92.3
C_6D_6	64.1	82.3	85.9	
CD_3CN	70.0	89.6	80.9	
CD_3OD	69.2	85.1	86.6	
Py-d_5	64.6	81.5	86.5	
DMSO-d_6	72.0	86.4	89.3	
	5	**6**	**7**	**8**
$CDCl_3$	77.1	77.5	71.3	83.7
C_6D_6	83.4	75.2	68.0	90.5
CD_3CN	76.7	76.8	72.5	85.8
CD_3OD	87.0	80.8	79.1	91.0
Py-d_5	82.9	75.7	70.5	89.0
DMSO-d_6	77.8	81.5	77.3	82.1
	9	**10**	**11**	**12**
$CDCl_3$	64.4	58.6	90.7	94.2
C_6D_6	72.0	67.1	90.3	93.7
CD_3CN	68.8	65.2	90.2	94.0
CD_3OD	77.1	76.8	93.4	97.1
Py-d_5	72.8	68.8	90.2	93.6
DMSO-d_6	72.1	73.8	88.9	95.2
	13	**14**		
$CDCl_3$	90.1	97.0		
C_6D_6	91.6	97.0		
CD_3CN	90.0	97.0		
CD_3OD	94.3	100.0		
Py-d_5	90.9	97.1		
DMSO-d_6	88.4	93.9		

[a] Based on the accuracy of NMR *J* coupling measurements (±0.05 Hz, see Supporting Information), the uncertainty in p_D values is estimated to be within ±0.9%.

Thus, within the subset of 1,3-oxathiolanes **(1)** – **(8)** there is a distinct preference in six of these molecules to place the larger sulfur atom (van der Waal's radii: O, 1.52 Å; S, 1.80 Å) over the π system in preference to the counterbalancing oxygen atom. Remarkably, this preference is displayed irrespective of whether the noncovalent interaction of the sulfur atom is with an aromatic ring [as in **(1)** and **(2)**], a simple alkene [as in **(3)** and **(4)**], or a heteroarene [as in **(6)** and **(8)**]. For the remaining pyrazine **(5)** and its congeneric quinoxaline derivative **(7)**, the noncovalent interaction of the oxygen atom with the π-deficient aromatic heterocycles clearly dominates over the counterbalancing S···π-arene interaction. The strength of this O(lp)···N(heteroarene) interaction (vide infra) can also be seen in the ketals **(13)** and **(14)**. Within the series of four dithioketals **(9) – (12)** the S···heteroarene interaction is also preferred over a competing S···π-arene interaction. This preliminary overview clearly indicates that, whilst the most favoured interaction of an oxygen atom is with the π-acidic heterocycles, the sulfur atom can interact with an entire range of π systems of very differing electronic character. Steric effects are certainly of little consequence.

At a more detailed level, a quantitative comparative estimate of these subtle energy differences can be obtained through consideration of the free energy differences (Δ*G*°) and the derived ΔΔ*G*° values from pairwise comparison of similar groups of derivatives. Thus, as illustrated for the family of oxathiolanes, **(1)**-**(8)**, it is possible to construct an internally consistent comparative energy level diagram (Figure 3 and Table 2) which reveals the relative energies for the entire set of noncovalent interactions of π systems with both oxygen and sulfur atoms.

The first and most surprising feature of this diagram is that, whilst the interactions of the oxygen atom span almost 8 kJ mol^{-1}, those involving sulfur are concentrated in a much narrower energy band (1.5-2.0 kJ mol^{-1}).The sulfur atom can, in essence, be described as an “atomic chameleon“, which is capable of blending and participating in noncovalent interactions with almost equal facility irrespective of whether an electron rich arene or a π-acidic heteroarene partner is involved. Of equal surprise is the fact that the isolated alkene unit provides the most favourable π interaction for a sulfur atom and the most unfavourable interaction with an oxygen atom. Thus, the S···arene and S···pyrazine interactions differ by only 0.2 kJ mol^{-1} in favour of the pyrazine, which stands in sharp contrast to the attractive O(lp)···pyrazine interaction which is favoured by 5.9 kJ mol^{-1} over the O···arene counterpart. We have previously measured the strength of this O(lp)···heteroarene interaction for the hydroxyl group[16d] and a similar value has also been recorded by Gung [12b] for the noncovalent interaction of an oxygen atom in a 9-benzyl triptycene unit with a highly fluorinated arene. The simplest explanation for the overall pattern displayed by the oxygen atom is that it essentially involves electrostatic interactions, whilst the behaviour of the sulfur atom is dominated by its much greater polarisabilty (nearly five times larger than that of oxygen)[18] and the presence of vacant orbitals for further interaction.

Table 2. The free energy differences ($\Delta G°$, in kJ mol^{-1}) and the derived $\Delta\Delta G°$ values (in kJ mol^{-1}) from pairwise comparison of similar groups of derivatives in $CDCl_3$.

Compa-rison	Free energy difference	Definition	Value, kJ mol^{-1}
S vs O	ΔG_1	$\Delta G_{\mathrm{SAr}} - \Delta G_{\mathrm{OAr}}$	-2.9
	ΔG_2	$\Delta G_{\mathrm{SAr}} - \Delta G_{\mathrm{O}\pi}$	-4.7
	ΔG_3	$\Delta G_{\mathrm{S}\pi} - \Delta G_{\mathrm{OAr}}$	-5.0
	ΔG_4	$\Delta G_{\mathrm{S}\pi} - \Delta G_{\mathrm{O}\pi}$	-6.2
	ΔG_5	$\Delta G_{\mathrm{OPy}} - \Delta G_{\mathrm{SAr}}$	-3.0
	ΔG_6	$\Delta G_{\mathrm{SPy}} - \Delta G_{\mathrm{OAr}}$	-3.1
	ΔG_7	$\Delta G_{\mathrm{OQuin}} - \Delta G_{\mathrm{SAr}}$	-2.3
	ΔG_8	$\Delta G_{\mathrm{SQuin}} - \Delta G_{\mathrm{OAr}}$	-4.1
O	$\Delta(\Delta G_2 - \Delta G_1)$	$\Delta G_{\mathrm{OAr}} - \Delta G_{\mathrm{O}\pi}$	-1.8
	$\Delta(\Delta G_4 - \Delta G_3)$	$\Delta G_{\mathrm{OAr}} - \Delta G_{\mathrm{O}\pi}$	-1.2
	$\Delta(\Delta G_5 - (-\Delta G_1))$	$\Delta G_{\mathrm{OPy}} - \Delta G_{\mathrm{OAr}}$	-5.9
	$\Delta(\Delta G_7 - (-\Delta G_1))$	$\Delta G_{\mathrm{OQuin}} - \Delta G_{\mathrm{OAr}}$	-5.2
	$\Delta(\Delta G_2 - (-\Delta G_5))$	$\Delta G_{\mathrm{OPy}} - \Delta G_{\mathrm{O}\pi}$	-7.7
	$\Delta(\Delta G_7 - (-\Delta G_2))$	$\Delta G_{\mathrm{OQuin}} - \Delta G_{\mathrm{O}\pi}$	-7.0
S	$\Delta(\Delta G_3 - \Delta G_1)$	$\Delta G_{\mathrm{S}\pi} - \Delta G_{\mathrm{SAr}}$	-2.1
	$\Delta(\Delta G_4 - \Delta G_2)$	$\Delta G_{\mathrm{S}\pi} - \Delta G_{\mathrm{SAr}}$	-1.5
	$\Delta(\Delta G_6 - \Delta G_1)$	$\Delta G_{\mathrm{Spy}} - \Delta G_{\mathrm{SAr}}$	-0.2
	$\Delta(\Delta G_8 - \Delta G_1)$	$\Delta G_{\mathrm{SQuin}} - \Delta G_{\mathrm{SAr}}$	-1.2
	$\Delta(\Delta G_3 - \Delta G_6)$	$\Delta G_{\mathrm{S}\pi} - \Delta G_{\mathrm{SPy}}$	-1.9
	$\Delta(\Delta G_3 - \Delta G_8)$	$\Delta G_{\mathrm{S}\pi} - \Delta G_{\mathrm{SQuin}}$	-0.9

Examination of the results for the ketals **(13)** and **(14)** and the dithioketals **(9) – (12)** are also highly informative. In the first instance, they serve to confirm the measurements made for the oxathiolanes in terms of the dominance of the O(lp)···heteroarene interaction. The greater number of degrees of conformational freedom in the acyclic ketals allows for the optimal orientation of the oxygen lone pair towards the π-acidic pyrazine or quinoxaline ring and an even greater measured preference for the O(lp)···heteroarene interaction over the O···π-arene interaction. Intriguingly, the measured conformational populations for the acyclic dithioketals **(11)** and **(12)** are virtually identical with their oxygen congeners, whereas the more conformationally restricted 1,3-dithiolanes **(9)** and **(10)** display a less marked preference for the sulfur atom to interact with the heteroarene as opposed to an arene. It is vitally important to recognize however that the electronic character of the heteroatoms in these systems is strongly influenced by their environment and that quantitative comparisons can only be made within the same subset of compounds. This is readily appreciated by comparison of electrostatic potential (ESP) derived atomic charges for the three 1,1-dimethyl model systems shown in Figure 4.

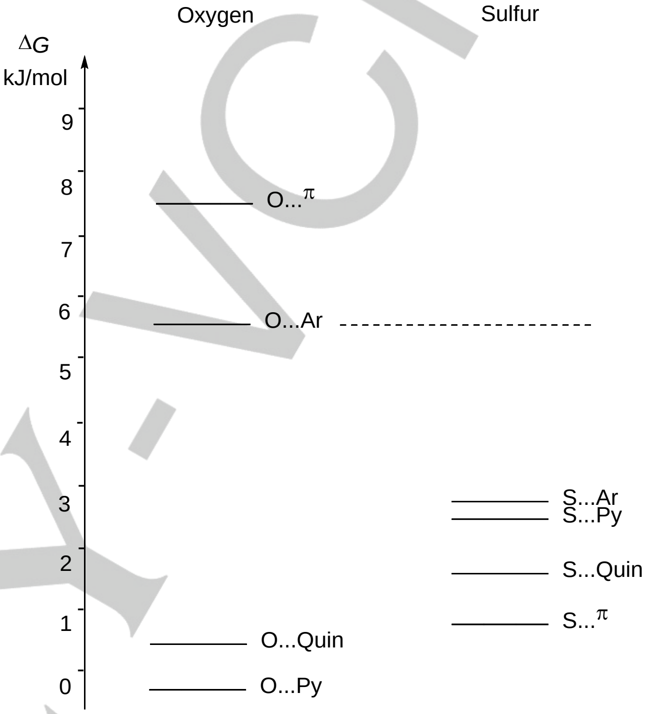

Figure 3. Comparative energy level diagram showing the relative energies for noncovalent interactions of π systems with oxygen and sulfur atoms **in** 1-3 oxathiolanes.

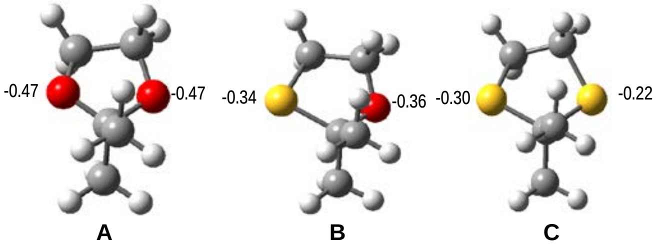

Figure 4. Atomic charges based on calculated electrostatic potentials (ESP) at the HF/cc-pVTZ level of theory.

Thus, the negative potential on the oxygen atom of the 1,3-dioxolane **A** is clearly reduced in moving to the 1,3-oxathiolane **B**, and, in similar fashion, the negative charge on the sulfur atom of **B** is further reduced in the 1,3-dithiolane **C** which exhibits two distinct sulfur atoms as a consequence of its non-planar structure. In global terms, whilst the decrease in the negative potential of the heteroatom in moving from sulfur to oxygen may be a contributing factor in the overall preference for a sulfur atom to interact with a range of π systems, it is even more significant to note that the negative potentials on the two heteroatoms of the 1,3-oxathiolane **B** are virtually identical. With the exception of the O(lp)···heteroarene interaction, the consistent preference for sulfur noted within the oxathiolane subset cannot therefore be attributed solely to electrostatic interactions, but must arise as a consequence of dispersive effects related to the presence of vacant orbitals on the polarizable sulfur atom.

In terms of solvation effects, there were no dramatic differences over the range of solvents studied, with the acyclic dithioketals **(11)** and **(12)** and ketals **(13)** and **(14)** being effectively solvent independent. Nevertheless, it was of interest to note that, throughout the entire range of cyclic oxathiolanes and dithianes possessing both an aromatic and a heteroaromatic ring, the observed percentage of the already dominant conformer tended to increase with more polar solvents and especially methanol. Curiously, this effect is slightly more marked in those compounds with a sulfur atom exposed to solvent, as in **(5), (7),** and especially **(9)** and **(10),** as opposed to an oxygen atom as in **(6)** and **(8)**. Further detailed scrutiny of these more subtle solvation effects, especially in terms of the contribution of dispersive forces,[19] will certainly be of interest.

Throughout our studies, single crystal X-Ray Diffraction has always provided additional insights. In the present instance, ~~five~~ six structures, **(2),** **(5)**, **(6)**, **(9)**, **(10)** and **(~~13~~14)** have been determined and, in each of these derivatives, the preferred conformer in solution is also observed in the solid state, thus providing some additional support for the strength of these noncovalent interactions. For the dimethyl ketal **(~~13~~14)**, and the 1,3-oxathiolane **(5)**, both of which feature the O(lp)···heteroarene interaction, the distances from the oxygen atom to the centroid of the heteroaromatic ring are 3.~~118~~ 113 Å and 3.~~111~~ 106 Å respectively and lie within the sum of the van der Waal's radii (3.22 Å). In similar fashion, for the oxathiolane **(2), the oxathiolane** diastereoisomer **(6)**, and the two dithiolane derivatives **(9)** and **(10)**, the respective values of 3.236 Å, 3.~~209~~ 210 Å, 3.223 Å, and 3.~~327~~ 322 Å are all less than 3.50 Å, the sum of the van der Waal's radii for sulfur and carbon.

In conclusion, the quantitative data reported above provide clear evidence that, with the exception of the extremely powerful O(lp)···heteroarene interaction, the sulfur atom is favoured over oxygen in noncovalent interactions both with simple alkenes and with arenes. Remarkably, and in stark contrast to the oxygen atom, the sulfur atom can engage, with almost equal facility, in its noncovalent interactions with partners ranging from electron rich alkenes and arenes through to electron deficient heteroarenes. Surprisingly, the strength of the noncovalent interaction between a simple alkene and a sulphur atom is of comparable magnitude to that found for the O(lp)···heteroarene interaction.

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Keywords: Conformational analysis · Molecular balances · NMR spectroscopy · Non-covalent interactions · Lone pair · π-interactions

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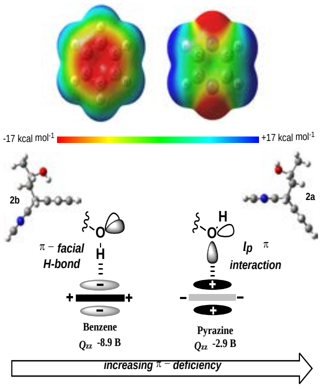
COMMUNICATION

A comparative study shows that the noncovalent interaction of a hydroxyl group with pyrazines and quinoxalines involves a lone pair···heteroarene attraction which is stronger and solvent independent when measured relative to the π-facial hydrogen bond to a benzene ring. Organic fluorides also prefer the heteroarene ring over benzene. The attraction between a quinoxaline and a terminal alkyne is stronger than the intramolecular OH···arene bond.



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Noncovalent Interactions of Heteroarenes with Lone Pairs, the Hydroxyl Group, Fluorine and a Terminal Alkyne.