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Interactions of Arenes and Thioethers Resulting in Facilitated Oxidation

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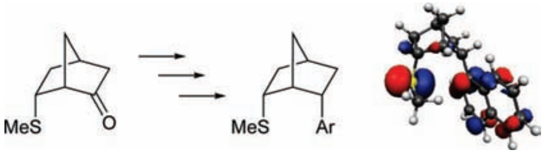
ABSTRACT



Synthesis of 6-endo and 6-exomethylthio-2-endoarylbicyclo[2.2.1]heptanes was accomplished stereoselectively. The ionization energies, determined by photoelectron spectroscopy, and electrochemical oxidation potentials, determined by cyclic voltammetry, were lower for the 6-endomethylthio compounds than for their 6-exomethylthio analogues. Calculations supported the notion that facilitation of electron transfer in the 6-endomethylthio compounds results from through-space S···π interaction.

Little is known about the consequences of through-space interaction on the redox chemistry of thioethers and π-systems but such interaction has been hypothesized to be of biological importance. In particular, would juxtaposed thioethers and π-systems undergo oxidation at less positive potentials than either one alone? It was hypothesized that alternating S−π interactions are involved in conducting electrons in proteins.[1] A thioether moiety modulates the reduction potential of flavin in a model receptor.[2] The effect was ascribed to a favorable electrostatic interaction between sulfur and the oxidized flavin.[2,3] Interaction between aromatic rings and the rubredoxin active site mediated by sulfur has been suggested as the basis for shifts in reduction potentials.[4] Stabilization of thioether radical cations by arenes has been reported[5] based on EPR and time-resolved fluorescence-detected magnetic resonance spectroscopy. It has also been postulated[6] that amyloid β-peptide aggregates produce reactive oxygen species by reducing metal ions using Met-35 as the reducing agent in the pathogenesis of Alzheimer's disease. Furthermore, it has been suggested that the conformation of these peptides results in Met-35 positioned over Phe-19[7] and this promotes electron-transfer. It has also been speculated that the aromatic ring of Phe-20 mediates electron transfer from Met-35 to peptide bound Cu(II)[8] but this role has been questioned.[9] In addition, ESR spectroscopic evidence has been interpreted to suggest one-electron oxidation of Met-35 by Tyr-10 tyrosyl radical in Aβ−42.[10]

We now report that juxtaposition of an aromatic ring and a thioether moiety in **1** results in substantial lowering of the HOMO ionization energy and electrochemical oxidation

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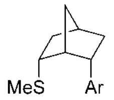
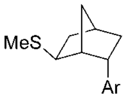
potential compared with **2** in which through-space interaction is precluded.



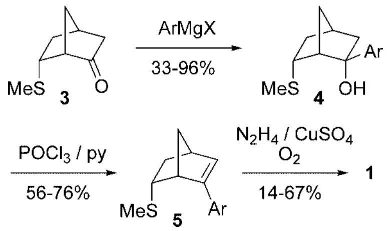
1a, Ar = 1-Nphth
b, Ar = Ph
c, Ar = p-MeOC$_6$H$_4$
d, Ar = p-HOC$_6$H$_4$
e, Ar = 2-Nphth
f, Ar = m-MeOC$_6$H$_4$



2a, Ar = 1-Nphth
b, Ar = Ph
c, Ar = p-MeOC$_6$H$_4$
d, Ar = 2-Nphth
e, Ar = m-MeOC$_6$H$_4$

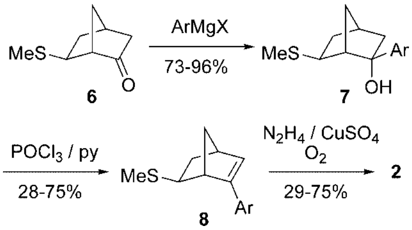
Compounds **1a**−**f** were synthesized as shown in Scheme 1 from the known[11] ketosulfide **3**. Reaction of **1** with aryl Grignard reagents[12] gave alcohols **4** in 33−96% yields. Dehydration with POCl$_3$/py provided alkenes **5** in 56−76% yields without any competing rearrangements. Stereoselective reduction of **5** from the less hindered exodirection with diimide generated by copper (II) catalyzed oxidation of hydrazine afforded **1** in 14−67% yields.

Scheme 1



Similarly, compounds **2a**−**e** were synthesized from the known[11b,13] ketosulfide **6** as shown in Scheme 2. All of the compounds in Schemes 1 and 2 were isolated in pure form and characterized spectroscopically. In addition, preliminary X-ray crystallographic analysis of **1d** further supported the structural assignments.

Scheme 2



Photoelectron spectroscopy has proven to be a powerful tool for identifying proximity effects in organic chemistry.[14] Consequently, the He I and He II photoelectron spectra were measured for compounds **1a**, **1b**, and **2a**. The spectra for **1a** are shown in Figure 1 and that for the other compounds are shown in the Supporting Information. Table 1 lists the ionization energies for **1a**, **1b**, and **2a** obtained by fitting the photoelectron spectra for the ionization energies below 10 eV and the He I/He II relative intensities. It is known[15] that the intensity of ionizations from a sulfur p-type orbital decreases 60−70% relative to ionizations from a carbon π−MO on changing the ionizing source from He I to He II. In addition, it has been shown[15] that comparison of such photoelectron spectra is a reliable way to determine the sulfur 3p and carbon π-orbital composition of molecular orbitals. Comparison of the ionizations of **1a** with those of **2a** support the notion of interaction between the naphthyl and sulfur

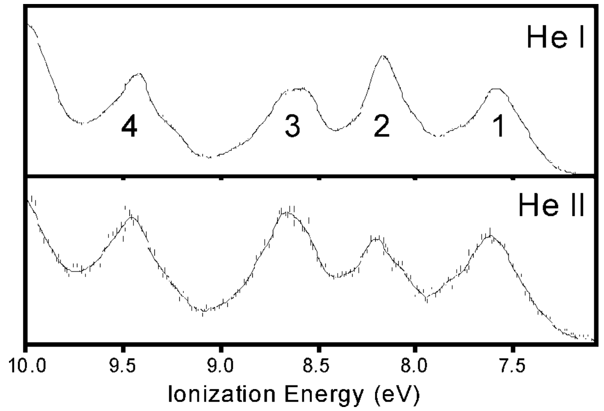


Figure 1. He I and He II gas-phase photoelectron spectra of the first four valence ionizations of **1a**.

Table 1. Lowest Ionization Energies for **1a**, **1b**, and **2a** from Photoelectron Spectroscopy and He I/He II Relative Intensities[a]

compd	Ar	ionization energies, eV
1a	1-Nphth	7.61 (0.78), 8.18 (0.60), 8.57 (1), 9.43 (0.93)
2a	1-Nphth	7.81[b] (1.07), 8.24 (0.53), 8.73 (1), 9.51 (0.75)
1b	Ph	7.96 (0.76), 8.41 (0.76), 8.67 (1.02), 8.98 (1)

[a] He I/He II relative intensities are in parenthesis. [b] A band also appears at 7.97 eV which is assigned to vibrational fine structure of the ionization at 7.81 eV in analogy with that reported for naphthalene.[16,17]

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[12] In the Grignard reagent used for the preparation of **1**, Ar = p-HOC$_6$H$_4$, the phenolic OH group was protected with a t-butyl dimethylsilyl moiety which was removed on workup.

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moieties on ionization. The lowest ionization energy for **1a** is 0.20 eV lower than that for **2a**.[18], Furthermore, the He I/He II intensities for the two lowest ionization energies of **1a** show that they result from orbitals that have both sulfur and arene character; whereas those for **2a** reveal that the lowest ionization at 7.81 eV has only arene character[23] and at 8.24 eV has predominantly sulfur character.[24] Interaction of the sulfur and arene can occur through-bond or through-space.[25]

Through-bond interactions of sulfur lone pairs have been reported for 1,4-dithiane[26] and, more recently, silicon and tin-substituted mesocyclic dithioethers.[27] Consequently, to gain more insight into the interaction, DFT calculations on **1a** were performed at the MPWB1K/6−31+G** level[28] for comparison to the experimental results. The lowest energy conformer has the sulfur p-type lone pair oriented for maximum through-space interaction with the naphthyl π system. The computational results show that there is mixing of sulfur p-type lone pair and naphthalene π−MO character for the HOMO,[29] as seen for the lowest energy conformer in Figure 2, as well as HOMO-1, and two essentially naphthalene-based π−MOs at higher ionization energy accounting for the four ionizations of lowest energy listed in Table 1. Although there is some mixing of the sulfur p-type lone pair orbital and the π-symmetry combination of σ C(6)−H and C(6)−C(1) orbitals in the HOMO of **1a**, the predominant interaction between sulfur and naphthalene appears to be mediated through-space. In HOMO-1 of **1a** there is no apparent through-bond interaction either; the interaction seems to be through space. The ionization energies for **1b** show that, although there is mixing of the sulfur p-type lone pair and phenyl π-molecular orbitals,[31] it is less than the sulfur p-type lone pair and naphthalene π−molecular orbital mixing. This is expected because the energy of the sulfur p-type lone pair orbital is better matched with naphthalene than phenyl π-molecular orbitals.[33] Furthermore, the calculations show that the HOMO for **1b** is predominantly sulfur lone-pair character while HOMO-1 is predominantly phenyl π-character. In both HOMO and HOMO-1, there is more π-like σ C(6)−H and C(6)−C(1) orbital contribution than for **1a**.[34] Consequently, through-bond as well as through-space interaction may be possible in **1b**. The relative importance of through-bond and through-space interaction in **1b** is under further study.

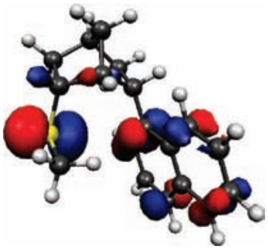

Figure 2. Highest occupied molecular orbital (±0.05 cutoff) for the lowest energy conformation of **1a**.

These interactions are also manifested in the oxidation potentials of these compounds. Their electrochemistry was studied in acetonitrile using the technique of cyclic voltammetry. All of the compounds showed irreversible oxidations and the first anodic peak potentials are given in Table 2.

Table 2. First Oxidation Peak Potentials[a] for **1a**−**f** and **2a**−**d** Determined by Cyclic Voltammetry

compd	Ar	E_p
1a	1-Nphth	0.74
b	Ph	0.96
c	*p*-MeOC$_6$H$_4$	0.76
d	*p*-HOC$_6$H$_4$	0.75
e	2-Nphth	0.73
f	*m*-MeOC$_6$H$_4$	0.74
2a	1-Nphth	1.16
b	Ph	1.27
c	*p*-MeOC$_6$H$_4$	1.27
d	2-Nphth	1.20

[a] Peak potentials of the oxidation peaks determined at a Pt electrode, 0.1 V/s scan rate and measured in CH_3CN, 0.1 M of $NaClO_4$ versus Ag/0.1 M $AgNO_3$ in CH_3CN reference electrode.

Comparison of the E_p for oxidation of **1a** with **2a**, **1b** with **2b**, **1c** with **2c**, and **1e** with **2d** shows that the oxidation potentials in the case where neighboring arene participation is possible (**1a**−**c**, **e**) are 0.31 V - 0.47 V less positive than in those cases where it is not possible (**2a**−**d**). Similarly, **1d** and **1f** are more easily oxidized than expected in the absence of neighboring group participation. For the totally irreversible case the peak potential, E_p, at constant scan rate will depend

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(18) This ionization energy is lower than that of typical sulfides (8.1−8.7 eV),[19,20] naphthalene (8.09,[16] 8.13,[17] 8.15[21] eV) and 1-methyl-naphthalene (7.85,[21] 7.95[22] eV).

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(23) In addition, this ionization energy is comparable to that of the lowest ionization energy of 1-methylnaphthalene (7.85,[21] 7.95[22] eV).

(24) Furthermore, this ionization energy is in the range reported for the lowest ionization energies of dialkylsulfides (8.1−8.7 eV).[19,20]

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(28) MPWB1K/6−31+G** has been shown to well describe through-space interactions:Zhao, Y.; Truhlar, D. G *Phys. Chem. Chem. Phys.* **2005**, *7*, 2701–2705.

(29) It is well known[30] that sulfur-arene interactions are overall stabilizing. Thus, even though the HOMO of **1a** is raised in energy, other factors likely compensate for this orbital destabilization resulting in overall stabilization of **1a**.

primarily on $E^{\circ\prime}$, the formal potential, and k°, the heterogeneous electron transfer rate constant.[35] We have previously established that ionization energy differences track E_p differences when peak potentials are measured at the same scan rate for a related series of sulfides.[19,36] This suggests that the k° values and the solvation energy changes may be relatively constant for the first one-electron oxidation step and that $E^{\circ\prime}$ is the dominant factor in defining E_p. Therefore, the lowest ionization energies and lowest oxidation potentials track each other for **1a**, **2a**, and **1b**. Furthermore, the structure of the radical cation formed on oxidation, which differs from that formed in the nonadiabatic photoelectron spectroscopic measurement in that geometric reorganization can occur, is under study. It is anticipated that, in analogy with our previous studies[15b] on oxidations of compounds with transannular S−S interactions, the stabilization of the radical cation accounts for the facilitated electrochemical oxidation.

In summary, electrochemistry, photoelectron spectroscopy, and theoretical calculations all support the notion that interaction between sulfur and arenes lowers their ionization energies and oxidation potentials. Molecular orbital plots suggest that the predominant basis for this interaction is through-space. This result may be of relevance to redox chemistry in biological systems in which aromatic rings and sulfur moieties can adopt the requisite geometrical orientations.

Acknowledgment. This paper is dedicated with best wishes to Professor E. J. Corey in celebration of his 80th birthday. We thank the National Science Foundation for financial support of this research (CHE-0455575), Chris Ceccarelli of Oxford Diffraction for collecting the X-ray crystallographic data for **1d** at Virginia Tech University and solving the structure, and Ms. Olga Lobanova (Department of Chemistry, University of Arizona) for measuring the photoelectron spectra of **1b** and **2a**.

Supporting Information Available: Experimental procedures, spectral data, X-ray crystallographic parameters and molecular structure of **1d**, He I and He II photoelectron spectra of **1b** and **2a**, computational results and MO plots for **1a** and **b** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The ionization energy of toluene is 8.78,[16] 8.8222 eV and that of isopropylbenzene (cumene) is 8.75 eV.[32] Consequently, the lowest ionization energy of **1b** is less than that of either R_2S or phenyl alone, that is, without interaction.

(32) Shudo, K.; Kobayashi, T.; Utsunomiya, C. *Tetrahedron* **1977**, *33*, 1721–1724.

(33) As shown by the lower first ionization potential for 1-methylnaphthalene (7.85,[21] 7.95[22] eV) than that of toluene (8.78,[16] 8.82[22] eV).

(34) The lowered first ionization energy for **1b** (as well as **1a**) cannot be ascribed to its endo-position and not $S\cdot\cdot\pi$ interaction because other endo-methylthiobicyclo[2.2.1]heptanes in which there is no neighboring group have ionization energies in the range 8.29−8.55 eV.[19]

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