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Solvent Effects on the Redox Properties of Thioethers

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The one-electron reduction potential of the radical cations of thioanisole (**1**), benzyl methyl sulfide (**2**) and 2-hydroxyethyl benzyl sulfide (**3**) in water, formamide, acetonitrile, acetone, 1,1,1,3,3,3-hexafluoropropan-2-ol, methanol and 2-propanol was investigated by cyclic voltammetry. For comparison the one-electron reduction potentials in water were also measured using pulse radiolysis. The redox potential is strongly influenced by the nature of the solvent and the solvent sensitivity increases with charge localization. The present results have been used to evaluate solvent effects in view of the Kamlet−Taft relationship. The Kamlet−Taft expression quantitatively describes the solvent effects on the redox properties of **1**−**3** and gives the relative importance of the different solvent properties. The dominating contribution to the solvent effects is the solvent dipolarity/polarizability π^*, whereas α appears to be of minor importance. Furthermore, the relationship between the π^* and reduction potential of radical cations of **1**−**3** appear to be linear. It was also possible to find the same trend between the solvent dipole moment and peak potential of **1**−**3**. These facts indicate that the nature of solvation is mainly nonspecific.

Introduction

Sulfur containing compounds play a central role in the structure and activity of many biological systems.[1−3] The one-electron oxidation of sulfur containing compounds may play an important role for protein oxidation, e.g., in oxidative stress and biological aging.[4,5] Oxidation of even small sulfur containing biomolecules can modify proteins and lead to irreversible damages.[6−8] In addition, sulfide oxidation may present a problem for biotechnology and the pharmaceutical industry.[9,10] Sulfur-centered radicals have recently gained prominence as possible intermediates in redox reactions of biomolecules and it is essential to characterize model systems where physical and chemical properties can be determined. Predicting redox properties for thioethers and understanding how the protein environment regulates the redox properties can be quite important. The effect of the local protein environment on the properties of a redox center can at least partly, be understood in terms of solvent effects. The solvent plays a fundamental role in protein stability.[11] It can induce folding or unfolding of proteins,[12] influence redox processes, for example electron transfer,[13,14] and leads to significant changes of physical properties.[11,15] The natural solvent for proteins is water containing other substances (cosolvents), which can influence the protein properties.[11] In this paper we address the solvent effects on the redox properties of thioether radical cations. Solvent effects on redox properties of radicals and radical ions have been a subject of considerable interest in recent years.[16−18]

Solvent effects on one-electron reduction potentials are a measure of the solvent dependence on the difference in free energy of solvation for a redox couple (eqs 1 and 2).[19]

$$\mathrm{O} + \mathrm{e}^- \rightleftharpoons \mathrm{R} \tag{1}$$

$$E° \approx \mathrm{IP} - \frac{\Delta G^\circ_{\mathrm{solv}}(\mathrm{R}) - \Delta G^\circ_{\mathrm{solv}}(\mathrm{O})}{F} + C \tag{2}$$

IP is the gas-phase ionization potential, C is the absolute potential of the reference electrode in a given solvent, $\Delta G^\circ_{\mathrm{solv}}(\mathrm{R})$ and $\Delta G^\circ_{\mathrm{solv}}(\mathrm{O})$ are the free energies of solvation of the reduced and oxidized forms, respectively, and F is the Faraday constant. In the case of radical cations, the solvent effects are mainly expected to reflect changes in free energy of solvation for the oxidized form.

Properties in solution can be described by free energy relationships or linear solvation energy relationships.[20] The Kamlet−Taft linear solvation energy relationship has been successfully applied to describe solvent effects (eq 3).[21]

$$\mathrm{XYZ} = \mathrm{XYZ}_0 + a\alpha + b\beta + s\pi^* + h\delta_{\mathrm{H}} \tag{3}$$

XYZ is the property of interest, XYZ_0, a, b, s, and h are solvent independent coefficients characteristic of the process, α is the hydrogen bond donor ability of the solvent, β is the hydrogen bond acceptor or electron pair donor ability to form a coordinative bond, π^* is its dipolarity/polarizability parameter and δ_{H} is the Hildebrand solubility parameter, which is a measure of the solvent−solvent interactions.

In this work we have studied solvent effects on the redox properties of three aromatic thioethers by cyclic voltammetry. The observed solvent effects are analyzed in view of the Kamlet−Taft relationship.

Experimental Section

Materials. All compounds were commercially available and used without further purification: thioanisol (**1**) (99% Lancaster), benzyl methyl sulfide (**2**) (>98% TCI), 2-hydroxyethyl

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benzyl sulfide (**3**) (98% Lancaster) and ferrocene (98% Lancaster). The supporting electrolyte tetrabutylammonium tetrafluoroborate (Bu_4NBF_4, Apollo Scientific Ltd.) and Lithium perchlorate ($LiClO_4$, Lancaster). All solvents were of purest spectroscopic grade and used without further purification. Millipore Milli-Q filtred water was used.

General Methods. Cyclic voltammetry was performed with a PAR 263A potentiostat/ galvanostat interfaced to a PC using the EG& G Model 270 software package. The cell was a standard three electrode setup using a glassy carbon or platinum working electrode, a platinum coil counter electrode, and as reference electrode a calomel electrode.

For the measurements in all solvents 0.1 M Bu_4NBF_4 was used as supporting electrolyte except for water and 2-propanol where 0.5 M KCl and 0.1 M $LiClO_4$, respectively, were used. All potentials were measured as the midpoint peak oxidation potential with respect the Fc^+/Fc redox couple. The scan rate in all experiments was 500 mV/s, and the electrodes were polished and cleaned after each cycle.

Pulse radiolysis with optical detection was performed by using a linear accelerator delivering 3 MeV electrons and a computerized optical detection system. The system has been described in detail elsewhere.[22] The pulses were of 5−10 ns duration giving doses of 3−6 Gy. For dosimetry a N_2O-saturated 10^{-2} M KSCN solution was used.[23]

Radiolysis of water results in the formation of $OH^•$, e^-_{aq}, $H^•$, H_2O_2, H_2 and H_3O^+, with $OH^•$ and e^-_{aq} being the major radical species.[24]

N_2O-saturated solutions were used to convert the solvated electrons into hydroxyl radicals. Primary oxidation of the thioethers was carried out by $Br_2^{•-}$.

The primary oxidant was produced in the following way upon irradiation

$$OH^• + Br^- \rightarrow OH^- + Br^• \tag{4}$$

$$Br^• + Br^- \rightarrow Br_2^{•-} \tag{5}$$

The above reactions have the following rate constants $k_{(4)} = 1.1 \times 10^{10}\ M^{-1}\ s^{-1}$ [25] and $k_{(5)} = 1.2 \times 10^{10}\ M^{-1}\ s^{-1}$.[26]

In the present work we have equilibrated the thioether redox couples with a redox couple of well-known reduction potential ($Br_2^{•-}$/ $2Br^-$ $E° = 1.63$ V vs NHE).[27] The one-electron reduction potentials of thioether radical cations were determined by measuring the equilibrium constant for reaction 6, from which the potential difference can be calculated using Nernst's equation ($\Delta E° = 0.0591 \log K$).

$$R_1SR_2 + Br_2^{•-} \rightleftharpoons R_1SR_2^{•+} + 2Br^- \tag{6}$$

The thioether concentration was 1 mM and the Br^- concentration was varied between 0.1 and 0.5 M.

Result and Discussion

The aim of the present study is to characterize the redox properties of thioethers in different solvents. Naturally occurring thioethers are potentially surrounded by a variety of functional groups which have been shown to affect sulfide oxidation.[28−30]

Direct studies of the solvent effect on the naturally occurring thioethers are very difficult due to their low solubility in organic solvents. Therefore, we have focused on compounds that can be used as models for natural systems: thioanisole (**1**), benzyl methyl sulfide (**2**) and 2-hydroxyethyl benzyl sulfide (**3**).

TABLE 1: One-Electron Reduction Potentials (V vs Fc^+/Fc) for Radical Cations of Compounds 1−3, Measured by Cyclic Voltammetry and Pulse Radiolysis

solvent[a]	**1**[b]	**2**[b]	**3**[b]	Met pH = 2.1	DMS
H_2O	0.906	0.982	0.932	1.04 (34)	0.98 (35)
	0.83[c]	0.86[c]	0.86[c]		
FA	0.996	1.20	1.292		
MeCN	1.016	1.231	1.354		
acetone	1.058	1.294	1.412		
HFP	1.054	1.310	1.514		
MeOH	1.112	1.376	1.692		
2-PrOH	1.344	1.550	1.694	1.694	1.694

[a] The following abbreviations have been used: FA, formamide; MeCN, acetonitrile; HFP, 1,1,1,3,3,3-hexafluoropropan-2-ol; MeOH, methanol; 2-PrOH, 2-propanol; Fc+/Fc, ferrocenium/ferrocene; Met, methionine; DMS, dimethyl sulfide. [b] Peak oxidation potential measured by cyclic voltammetry (uncertainty ±5 mV). [c] Reduction potential determined by pulse radiolysis (uncertainty ±20 mV).

TABLE 2: Kamlet−Taft Solvent Parameters[21,36]

solvent	α	β	π^*	δ_H
MeCN	0.19	0.40	0.75	11.9
MeOH	0.98	0.66	0.60	14.5
HFP	1.96	0	0.65	9.72
H_2O	1.17	0.47	1.09	23.4
acetone	0.08	0.43	0.71	9.9
2-PrOH	0.76	0.84	0.48	11.5
FA	0.71	0.48	0.97	19.2

One-electron oxidation of thioethers initially results in the formation of thioether radical cations. These are highly unstable species that can convert into a series of intermediates and, finally, stable products.[4,31−33] For this reason, only irreversible voltammograms could be obtained. The measured one-electron peak oxidation potential of **1**−**3** radical cations vs Fc^+/Fc are collected in Table 1.

For comparison, a previously reported irreversible potential for methionine and a reversible potential for dimethyl sulfide radical cations in aqueous solution are also given in the Table 1.[34,35]

Because electrochemical oxidation of thioethers is irreversible in all cases, we also measured the reduction potential of the thioether radical cations in aqueous solution by pulse radiolysis. The two methods are complementary and the reversible potentials determined by pulse radiolysis are fairly close to the peak potentials determined by cyclic voltammetry, indicating that the peak potentials do indeed correspond to the formation of radical cations for all three thioethers. Furthermore, the potential for the radical cation of **2** measured by cyclic voltammetry is virtually identical to the reported thermodynamical potential for DMS. In both sets of data, the potentials for **2** and **3** are somewhat higher than for **1**, reflecting the structural difference between benzyl and phenyl thioethers. In conclusion, this suggests that the irreversible potentials measured for **1**−**3** can be used to describe the solvent dependence for these substances, at least qualitatively. It has previously been found that irreversible potentials essentially show the same solvent dependence as reversible potentials; however, the irreversible potentials displayed a somewhat stronger solvent dependence than the corresponding reversible potentials.[16]

In this work we have measured the reduction potential of thioether radical cations in various solvents characterized by different Kamlet−Taft solvent parameters. The Kamlet−Taft parameters for the solvents used in this study are collected in Table 2.

The results in Table 1 show that the redox properties are sensitive to the nature of the solvent for all investigated thioether

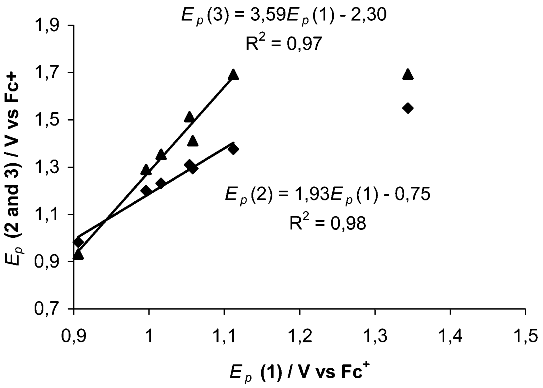

Figure 1. Peak oxidation potential of **2** and **3** plotted against the peak oxidation potential of **1**.

redox couples. In the present series of solvents the reduction potential of the thioether radical cations increases from water to 2-propanol; for the radical cation of **3** the difference between these two solvents is 0.76 V.

The reduction potential in water does not vary much between the three thioether radical cations (0.91–0.98 V); however, for the organic solvents, the difference in reduction potential between the thioether radical cations is more pronounced.

This can be understood in terms of charge localization. The solvation free energy for the radical cation and thereby the solvent sensitivity are expected to increase with increasing charge localization.[16,17] **3** is more sensitive to changes in solvent properties than **1** and **2**. Hence, the positive charge of the radical cation of **3** appear to be more localized than for the other compounds and the radical cation should thereby be more strongly solvated. This can be illustrated when the experimentally determined oxidation potentials of **1**–**3** are compared (Figure 1).

It has previously been shown that, for structurally similar compounds, the higher the gas-phase ionization potential, the more localized is the charge on the radical cation.[17] The gas-phase ionization potential of **1** is 7.94 eV[37] and that of **2** is 8.41 eV,[37] and as expected, the redox properties of **2** display stronger solvent sensitivities than **1**. Unfortunately, the gas-phase ionization potential for **3** is not available. Experimental data on the reduction potentials of the corresponding radical cation indicate a higher ionization potential for **3**. This is also verified by semiempirical quantum chemical calculations.

It should be noted that the potentials for **3** and to some extent also for **2** in 2-PrOH are very close to the maximum potential that can be measured in this solvent using our experimental setup. Therefore, these values are fairly uncertain and can probably only be used as lower limits. This could also explain why the potential for **3** in MeOH is fairly close to the corresponding value in 2-PrOH whereas for the other two thioethers the potentials are significantly higher in 2-PrOH compared to MeOH.

The electrochemical data have been used to evaluate solvent effects on thioether radical cations in view of the Kamlet–Taft relationship. The results are summarized in eqs 7–9.

$$E_p(1) = 0.50 + 0.25\alpha + 1.05\beta + 1.09\pi^* - 0.07\delta_H \qquad R^2 = 0.97 \quad (7)$$

$$E_p(2) = 1.31 + 0.13\alpha + 0.58\beta + 0.15\pi^* - 0.04\delta_H \qquad R^2 = 0.94 \quad (8)$$

$$E_p(3) = 2.11 + 0.09\alpha + 0.41\beta - 1.07\pi^* - 0.01\delta_H \qquad R^2 = 0.91 \quad (9)$$

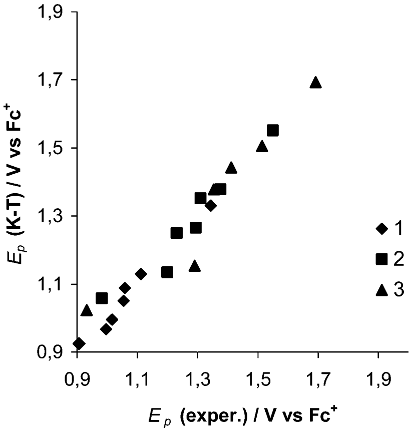

Figure 2. Peak oxidation potentials of **1**–**3** calculated from eqs 7–9 plotted against the corresponding experimental values.

In the evaluation of the solvent effects on **3**, the potential in 2-PrOH was not included for reasons stated above. For compound **2**, the potential in 2-PrOH was included. However, it should be noted that the resulting Kamlet–Taft expression for compound **2** did not change dramatically when the potential in 2-PrOH was excluded. This was not the case for compound **3** for which the potential in 2-PrOH has a significant influence.

In Figure 2, we have plotted the one-electron reduction potential of radical cations of **1**–**3**, predicted from eqs 7–9 against the corresponding experimental values.

As can be seen, the solvent effects on the redox properties of **1**–**3** can be quantitatively described by the Kamlet–Taft relationship. Due to the fairly limited set of data (number of solvents) the uncertainty in the coefficients is significant, ranging from 30 to >100%.

To extract physicochemical information from the obtained Kamlet–Taft relationships, the relative importance of the different solvent properties must be evaluated. This can be done from so-called beta coefficients derived according to eq 10, where x' (x' denotes a', b', s' or h') is the partial regression coefficient (or "beta coefficient"), $|x|$ is the absolute value of the regression coefficient ($|a|$, $|b|$, $|s|$ or $|h|$), y_i is the Kamlet–Taft parameter (α_i, β_i, π_i^* or δ_{H_i}) of a given solvent (i), $\bar{y}$ is the average value of this quantity ($\bar{\alpha}$, $\bar{\beta}$, $\bar{\pi}^*$ or $\bar{\delta}_H$) in a given set of solvents, E_i^0 is the potential measured in a given solvent and $\bar{E}^\circ$ is the average value of the potentials in a given set of solvents.[38]

$$x' = |x|\sqrt{\frac{\sum_{i=1}^{n}(y_i - \bar{y})^2}{\sum_{i=1}^{n}(E_i^0 - \bar{E}^0)^2}} \qquad (10)$$

The relative importance of a given parameter can be calculated from the beta coefficients using eq 11. This equation

$$\bar{a} = \frac{a'}{a' + b' + s' + h'} \qquad (11)$$

gives the relative importance of α, the hydrogen bond donor ability of the solvent. The relative importance of β, π^* and δ_H can be calculated in the same way. The relative importance of the Kamlet–Taft solvent parameters for the thioethers are summarized in Table 3.

TABLE 3: Relative Importance of Solvent Parameters

	α (%)	β (%)	π* (%)	δ_H (%)
1	13.31	22.17	38.46	26.06
2	15.10	28.00	21.33	35.59
3	15.15	21.80	49.69	12.96

As can be seen, the relative importance of the dipolarity/polarizability is highest for compounds **1** and **3** where it is the most significant parameter. However, for compound **2** the dipolarity/polarizability has a lower relative importance. By analyzing the actual coefficients, we see that *s* changes from +1.09 to −1.07 when compounds **1** and **3** are compared. For compound **2** the coefficient is +0.15. Because the analysis only accounts for the absolute number (not the sign), the relative importance of the dipolarity/polarizability is lower for compound **2**. Nevertheless, it is interesting to note that the coefficient changes from a fairly high positive number to a fairly high negative number as charge localization is increased. This reflects the increasing impact of solvent dipolarity/polarizability on the stabilization of the radical cation as the charge becomes more localized to the heteroatom. Indeed, this also indicates that the nature of solvation is largely nonspecific for these compounds.

Considering that one-electron oxidation of organic sulfides leads to formation of radical cations, which show a strong tendency to stabilize by coordination with a free electron pair from another heteroatom, we would expect a stronger effect of the solvent electron pair donor ability, β. Indeed, this parameter is more important than the hydrogen bond donor ability, α, and the coefficient becomes less positive with increasing charge localization, as expected. However, this specific interaction is not the dominating solvent effect.

For other classes of radical cations the most important solvent parameter was the hydrogen bond donor ability, α, of the solvent.[16] As has been pointed out before, this shows that it is not possible to generalize solvation too much.

Given the importance of the solvent dipolarity/polarizability, we also analyzed the correlation between the reduction potential of the thioether radical cations and π* alone.

The trend is illustrated in Figure 3. It should be noted that the potential for compound **3** in 2-PrOH is estimated from the Kamlet−Taft relationship because the experimental value was found to be unreliable for reasons stated above.

As can be seen, the solvent dipolarity/polarizability can be used to qualitatively describe the solvent effects. The empirical π* parameter represents a measure of the nonspecific electrostatic interaction.[39]

The environment of the protein matrix surrounding the redox center can at least partly be compared with the solvent surrounding simple solute ions.[40,41] The orientation of dipolar solvent molecules around the solute molecule in absence of specific solute−solvent interaction is largely determined by the dipole moment.[42]

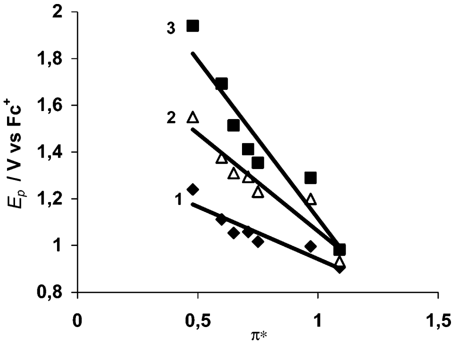

Figure 3. Peak oxidation potentials of **1**−**3** (V vs Fc$^+$/Fc) plotted against the solvent parameter π*.

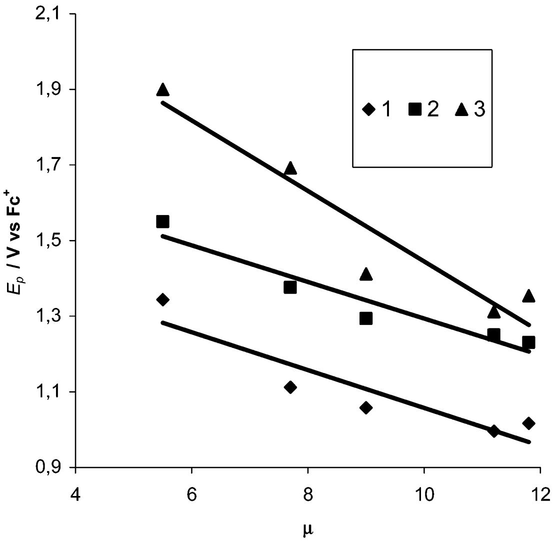

Figure 4. Peak oxidation potentials of **1**−**3** (V vs Fc$^+$/Fc) plotted against the solvent dipole moment.

It has been reported previously that nonspecific electrostatic interaction strongly influences the relative stability of the oxidation state of metal proteins.[43,44] Therefore, we have also plotted the measured peak potentials against the dipole moment (μ) of the solvent (Figure 4) for all thioether radical cations including all solvents except water and 1,1,1,3,3,3-hexafluoropropan-2-ol. It has been noted that interactions between water and thioether radical cation have more than electrostatic character. Solvation in water is much stronger than in other solvents. Also, it has previously been suggested that the radical cation of thioether can form a three-electron bond with water.[1] Hence, solvation is expected to be more specific. The potentials measured in 1,1,1,3,3,3-hexafluoropropan-2-ol are excluded from the plot simply because we were not able to find a literature value for the dipole moment of this solvent.

As can be seen, the solvent dipole moment also roughly describes the solvent effects for this limited set of solvents. However, it should be noted that the observed trend could very well be coincidental.

Conclusion

The redox properties of thioether radical cations display strong solvent sensitivity where the most important solvent property appears to be the solvent dipolarity/polarizability. The Kamlet−Taft relationship based on four solvent parameters can be used to describe the solvent effects. Qualitative estimations of the solvent effects can be performed using the solvent dipolarity/polarizability, π*, or the solvent dipole moment, μ, alone.

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