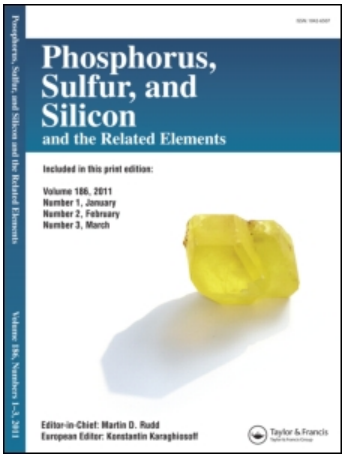

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THERMODYNAMIC AND ELECTROCHEMICAL PROPERTIES OF IMIDAZOLE-2-THIOLS (IMIDAZOLE-2(3*H*)-THIONES)

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THERMODYNAMIC AND ELECTROCHEMICAL PROPERTIES OF IMIDAZOLE-2-THIOLS (IMIDAZOLE-2(3*H*)-THIONES)

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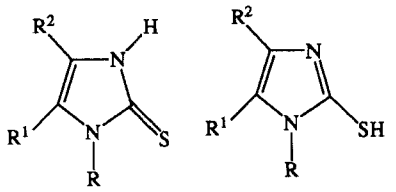
The oxidation and reduction potentials for eight imidazole-2-thiols [imidazole-2-thiol (**1a**), 1-methyl- (**1b**), 4,5-dimethyl- (**1c**), 1,4,5-trimethyl- (**1d**), 4,5-diphenyl- (**1e**), benz- (**1f**), 5-methylbenz- (**1g**), and 5-nitrobenzimidazole-2-thiol (**1h**)] have been determined in ethanenitrile-hydrogen chloride solution. Substituent effects on E(ox) are observed and are discussed. The pK_a's for thiols **1a, 1b**, and **1c** have been determined as a function of pH in buffer solutions at five temperatures and constant ionic strength of 0.10 M using ultraviolet spectroscopy. The ΔH^0 (kJ/mol) and ΔS° (J mol^{-1} K^{-1}) for imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**) are 38.2 and −92.9, 34.1 and −107.5, and 45.2 and −80.3, respectively.

Key words: Imidazole-2-thiol; 1-methylimidazole-2-thiol; 4,5-dimethylimidazole-2-thiol; 1,4,5-trimethylimidazole-2-thiol; 4,5-diphenylimidazole-2-thiol; 1,3-dihydro-2*H*-benzimidazole-2-thiones; benzimidazole-2-thiol; 5-methylbenzimidazole-2-thiol; 5-nitrobenzimidazole-2-thiol; oxidation and reduction potentials; electrochemistry; pK_a's for thiols; equilibrium concentrations of thiols and thiolate anions; ultraviolet spectroscopy; thermodynamic parameters (ΔG^0, ΔH^0, ΔS^0).

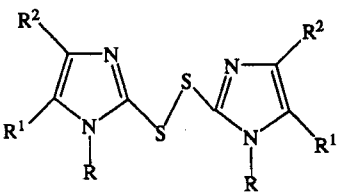
INTRODUCTION

Thionamides such as imidazole-2(3*H*)-thiones (imidazole-2-thiols)[1] and thiouracils[2] have been studied for many years owing to their effective antithyroidal activity. 1-Methylimidazole-2(3*H*)-thione (1-methyl-2-thioimidazole, methimazole, **1b**) is the most commonly used drug to treat hyperthyroidism owing to its effectiveness and low incidence of side effects.[2–5] Imidazole-2-thiols (**1**) that contain electron withdrawing groups are known to have antimicotic activity, and derivatives of imidazole-2-thiols (**1**) are used as antioxidants or inflammation inhibitors in the treatment of arthritis.[1,6] 2,2′-Dithiobis-1*H*-imidazoles (imidazolyl disulfides)[7] and pharmaceutical compositions containing symmetrical imidazole disulfides show activity as schistosomicides[8a] and against sickle cell anemia.[8b]

Recently, the electrochemical synthesis of several 2,2′-dithiobis-1*H*-imidazoles (imidazolyl disulfides, **2**)[7,9] from the corresponding thiols (**1**), the reactions of imidazole-2-thiones (**1**) with diiodine, and the crystal structures of the 1,3-dimethylimidazole-2(3*H*)-thione-diiodine 1:1 charge transfer complex[10] have been



1a R = R^1 = R^2 = H
1b R = CH_3; R^1 = R^2 = H
1c R = H; R^1 = R^2 = CH_3
1d R = R^1 = R^2 = CH_3
1e R = H; R^1 = R^2 = C_6H_5
1f R = H; R^1-R^2 = (-CH=CH-)$_2$
1g R = H; R^1 = -C(CH_3)=CH-; R^2 = -CH=CH-
1h R = H; R^1 = -C(NO_2)=CH-; R^2 = -CH=CH-



2a R = R^1 = R^2 = H
2b R = CH_3; R^1 = R^2 = H
2c R = H; R^1= R^2 = C_6H_5
2d R = H; R^1- R^2 = -(CH=CH)$_2$
2e R = H; R^1 = -C(CH_3)=CH-; R^2= -CH=CH-

reported. In this paper, we report the electrochemical properties of several imidazole-2-thiol (**1**)-imidazolyl disulfide (**2**) systems and the pK_a values of imidazole-2-thiols **1a, 1b,** and **1c** as a function of temperature in buffered aqueous solutions of constant ionic strength. Thermodynamic parameters(ΔG^0, ΔH^0, ΔS^0) are also reported for imidazole-2-thiols **1a, 1b,** and **1c**.

RESULTS AND DISCUSSION

Ultraviolet Spectra of Imidazole-2-thiols (**1**)

The ultraviolet spectra of imidazole-2-thiols **1a, 1b,** and **1c** in aqueous solution were obtained as a function of pH and at constant temperature (Figures 1 and 2, Table I). In Figures 1 and 2, the ultraviolet spectra of thiols **1a, 1b,** and **1c** at pH 10.80 and 12.5 are compared. The absorption maximum not only is shifted but also becomes less intense when the pH of the solution in increased. Thiols **1a** and **1b** are found to be blue shifted (4 nm) whereas **1c** is red shifted (6 nm) when the solution is basic.

pK_a Values of Imidazole-2-thiols (**1**)

We have determined the acid-base equilibrium constants, pK_a, for imidazole-2-thiols **1a, 1b,** and, **1c** from their ultraviolet absorption spectra in aqueous solution of 0.10 M ionic strength as a function of pH in buffered (phosphate or borate) solutions from pH 6.0 to pH 12.5 at several temperatures.

Figure 3 shows the calculated absorbance and experimental absorbance versus pH plots at 25 °C for thiols **1a, 1b,** and **1c.** The following equations (1 and 2) were derived to determine the pK_a's of the thiols and to theoretically fit the experimental absorbance-pH data obtained. The theoretical fits are represented by the solid lines in Fig. 3

$$[RS^-]_e = \frac{[RSH]_i\,(K_a/[H^+])}{(1 + (K_a/[H^+])} \quad (1)$$

$$A_t = (\varepsilon_{RS^-} - \varepsilon_{RSH})\,[RS^-]_e + \varepsilon_{RSH}\,[RSH]_i \quad (2)$$

where $[RS^-]_e$ and $[RSH]_i$ are the equilibrium thiolate anion and initial thiol concentration and A_t is the observed absorbance at each pH. The molar absorptivities of the thiol and thiolate anions are represented by their appropriate ε symbol.

From the absorbance and the molar absorptivity values obtained, the equilibrium concentrations of the thiols and thiolate ions at each pH were calculated at 25°C from Equation 2 and are shown for all three thiols **1a, 1b,** and **1c** in Figure 4.

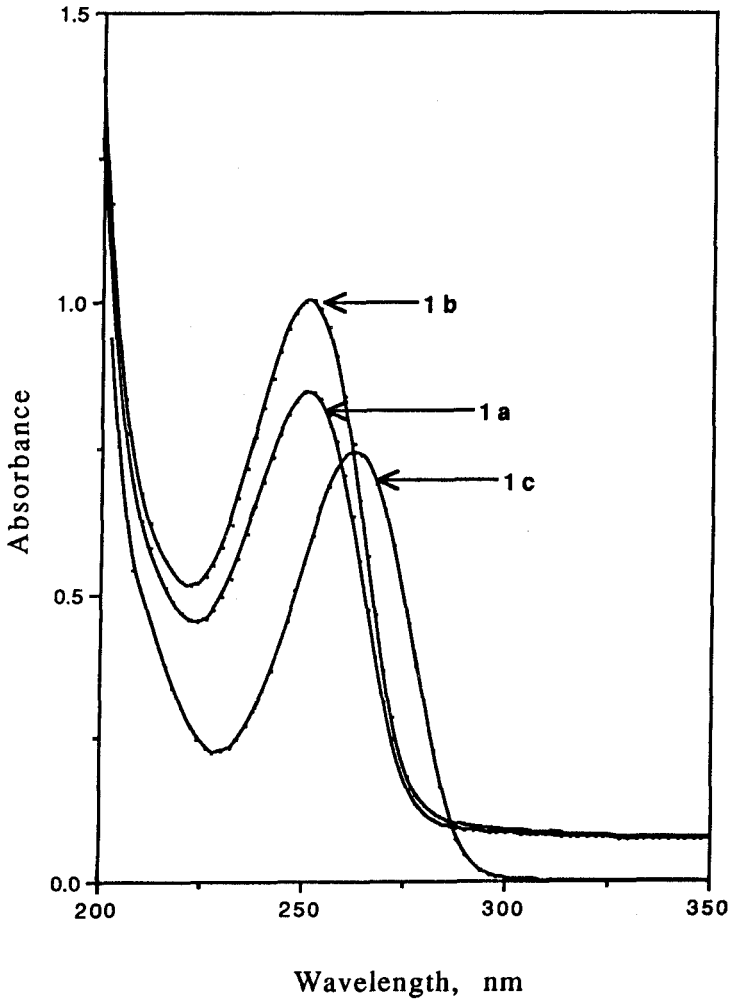


FIGURE 1 Ultraviolet spectra of imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**) in pH 10.80 borate buffer solution at 25.0°C; [**1a**] = [**1c**] = 5.59×10^{-5} M, [**1b**] = 5.63×10^{-5} M, $[Na_2B_4O_7] = 1.83 \times 10^{-2}$ M, $[H_3BO_3] = 3.17 \times 10^{-2}$ M, $[NaClO_4] = 2.67 \times 10^{-2}$ M, μ = ionic strength = 0.10 M.

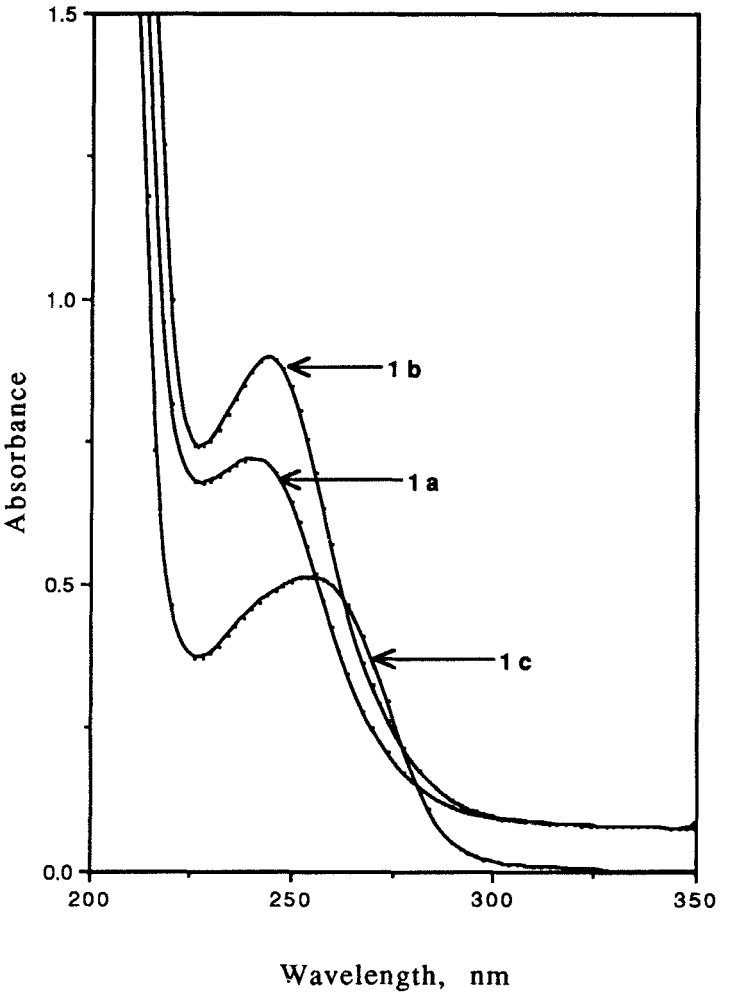


FIGURE 2 Ultraviolet spectra of imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**), pH 12.5 phosphate buffer solution at 25.0°C. [**1a**] = [**1c**] = 5.59×10^{-5} M, [**1b**] = 5.83×10^{-5} M, $[Na_2HPO_4] = 4.77 \times 10^{-3}$ M, $[Na_3PO_4 \cdot 12H_2O] = 2.29 \times 10^{-4}$ M, $[NaClO_4] = 8.43 \times 10^{-2}$ M, $\mu = 0.10$ M.

Again, the theoretical fits are represented by the solid lines which are calculated by using Equations 1 and 2. The pK_a value for each thione is obtained from the midpoint of the graph. Listed in Table II are the temperature dependence pK_a values determined for the thiols. The effect of a methyl substituent on the pK_a is small since the bigger sulfur atom has a p orbital which overlaps less effectively with the ring π orbital. The methyl substituent also causes a small shift of pK_a to higher value [(11.53) (**1a**), 11.56 (**1b**), 12.19 (**1c**)] suggesting that the electron donating substituent destabilizes the thiolate anion and thus forming a weaker acid. Therefore, the order of acidity of the thiols studied is **1a** > **1b** > **1c**.

From the slopes of pK_a versus 1/T plots, the ΔH^0's were obtained. The values of ΔG^0 and ΔS^0 were calculated from the following equations at 25°C.

$$\Delta G^0 = -RT \ln K_a \quad (3)$$

$$\Delta S^0 = (\Delta H^0 - \Delta G^0)/T \quad (4)$$

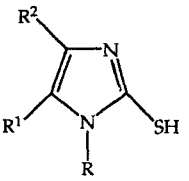
Listed in Table III are the thermodynamic parameters obtained in this study for the three thiols. The ΔG^0 values are comparable for the thiols and range from 65.9 to 69.1 kJ/mole. Compounds **1a** and **1b** have smaller $\Delta H°$ than **1c**. However, the $\Delta S°$ for **1c**, as expected, is much more positive than either **1a** or **1b**. This is due to the methyl substituents at C4 and C5. Nonetheless, methyl substituent at the N position does not significantly change the ΔS^0 value.

*Electrochemistry of Imidazole-2-thiols (**1**)*

The electrochemistry of the imidazole-2-thiol/imidazolyl disulfide systems has been performed in ethanenitrile-hydrochloric acid solution and the results are listed in Table IV. Figure 5a shows a typical cyclic voltammogram of 1-methylimidazole-2-thiol (**1b**) scanned in the negative potential direction, reversed at -0.15 volt and at $+0.8$ volt to the starting potential. Only an oxidation peak at $+0.5$ volt was observed. However, both the oxidation and the reduction peaks were observed when the scan was initiated from the positive potential direction and reversed at $+0.8$ volt to the negative potential region (Figure 5b). The peak separation of the imidazole-2-thiol (**1**)-imidazolyl disulfide (**2**) systems that were studied is usually

TABLE I

Ultraviolet absorption characteristics of imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**)[a].



thiol	pH	buffer	λ_{max} nm	log ε
1a	7.04	phosphate	252	4.20
1b	7.06	phosphate	252	4.26
1c	7.04	phosphate	262	4.14
1a	10.85	borate	250	4.27
1b	10.85	borate	251	4.26
1c	10.85	borate	264	4.11
1a	12.50	phosphate	242	3.94
1b	12.50	phosphate	246	4.12
1c	12.50	phosphate	270	3.74

a) Ionic strength = 0.10 M ($NaClO_4$); T = 25.0 °C.

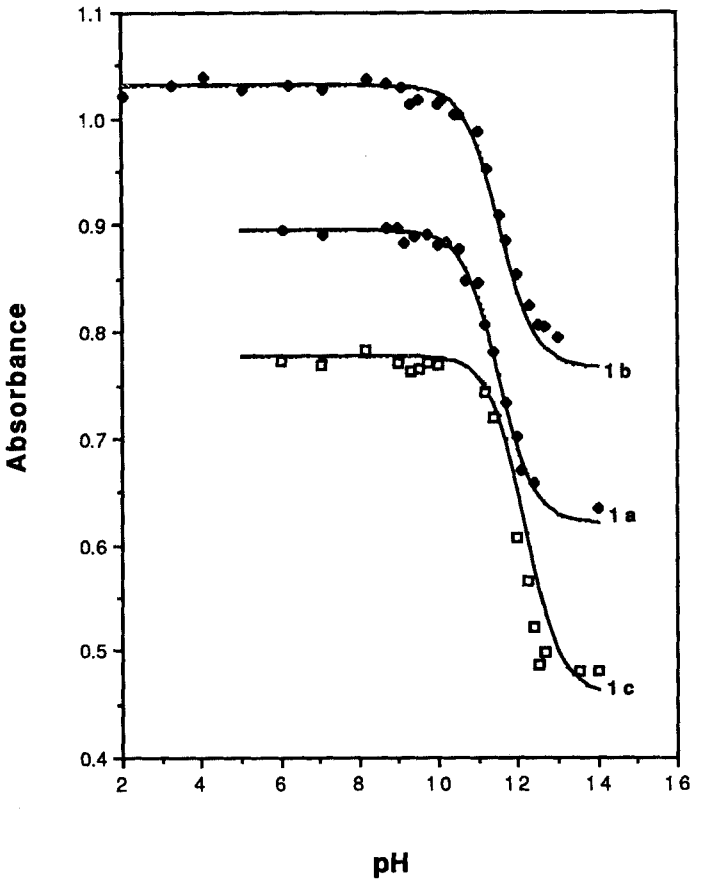


FIGURE 3 Calculated and observed absorbance versus pH at 25°C for imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**). Solid lines are calculated fits of the experimental points using Equations 1 and 2.

much greater than 60 mv, which is an indication that these systems undergo irreversible electron-transfer reaction. From Table IV, it is evidenced that methyl groups at the N or C-4 and C-5 positions tend to produce smaller increases in E(ox), from 0.03 to 0.10 volt, whereas phenyl group and benzyl group at the C-4 and C-5 positions increase the E(ox) from 0.16 to 0.23 volt. This suggests that electron withdrawing substituents decrease the electron density on the sulfur atom and make the thiol more difficult to oxidize. For the benzimidazole-2(3*H*)-thiol system, substitution at the 5-position on the benzyl group does not appear to substantially alter the E(ox). This could mean that the electronic effect is localized on the six-membered ring. Correlation of the substituent effect against E(red) is, however, not possible in the present study. All of the redox couples, except the **1h** system, are irreversible. With the 5-nitrobenzimidazole-2(3*H*)-thiol (**1h**) system, the ΔE separation (90 mv) approaches 60 mv at 200 mv/sec. This indicates that it is possible for the **1h** redox couple to be reversible at higher scan rate. Cyclic voltammetry was also done on 5-nitrobenzimidazole, and it was observed to be

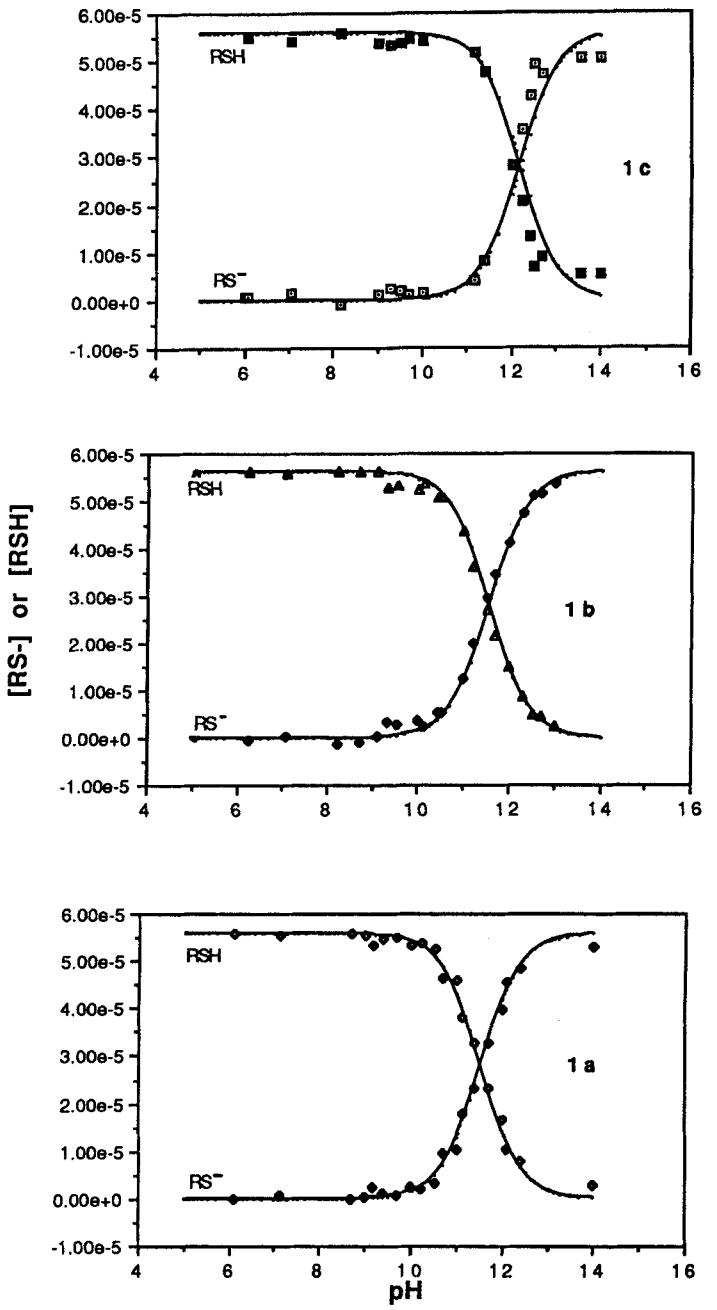


FIGURE 4 Equilibrium concentration of $[RSH]_e$ and $[RS^-]_e$ versus pH at 25°C for imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**). The experimental points are calculated from absorbance data using Equation 2 whereas the solid lines are the calculated fits using Equations 1 and 2.

TABLE II

pK_a values for imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol(**1c**)[a].

thiol	pK_a	temp °C
1a	11.65	20.0
	11.53	25.0
	11.31	35.4
	11.61[b]	21 ± 1[b]
1b	11.76	16.4
	11.56	24.9
	11.46	30.2
	11.44	35.3
	11.90[b]	21 ± 1[b]
1c	12.35	15.0
	12.22	20.1
	12.19	25.0
	11.87	32.0

a) 0.10 M Ionic strength ($NaClO_4$), borate or phosphate buffer range 6.00 to 12.85, [RSH] = 5.59×10^{-5} to 5.63×10^{-5} M.

b) References 11 and 12.

TABLE III

Thermodynamic parameters for imidazole-2-thiol (**1a**), 1-methylimidazole-2-thiol (**1b**), and 4,5-dimethylimidazole-2-thiol (**1c**)[a].

Thione	ΔH° kJ/mol	ΔG ° kJ/mol	ΔS° J mol^{-1} K^{-1}
1a	38.2	65.9	-92.9
1b	34.1	66.1	-107.5
1c	45.2	69.1	-80.3

a) Temp. = 25.0 °C, ionic strength 0.10 M ($NaClO_4$), borate and phosphate buffer from pH 6.00 to 12.85.

electrochemically inactive under these experimental conditions. A mechanistic scheme (Equation 5) can be proposed to account for the electrochemical redox process of the thiol/imidazolyl disulfide.

The proposed mechanistic scheme shows that 2 moles of thiol are electrochemically oxidized to the disulfide. This could involve an electron abstraction step with free radicals formed which rapidly dimerize to the disulfide. The thione-thiol tautomerism[13] step is proposed to account for the tautomeric form and also the thiolate anion oxidation pathway.

For the controlled-potential experiment, we have used uv-vis spectrometry to monitor the absorption spectrum of benzimidazole-2-thiol (1,3-dihydro-2*H*-ben-

TABLE IV

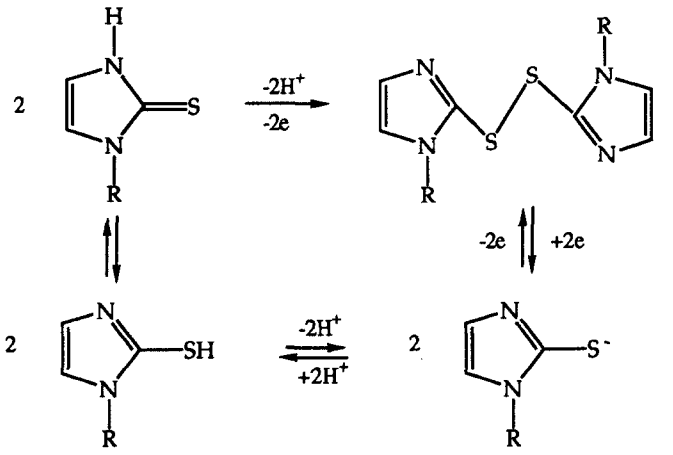
Oxidation and reduction and potentials of the imidazole-2-thiol (**1**)/imidazolyl disulfide (**2**) systems[a].

compound number	Thiol	E(ox), v	E(red),v
1a	imidazole-2-thiol	0.48	0.05
1b	1-methylimidazole-2-thiol	0.51	0.09
1c	4,5-dimethylimidazole-2-thiol	0.58	-0.015
1d	1,4,5-trimethylimidazole-2-thiol	0.55	0.01
1e	4,5-diphenylimidazole-2-thiol	0.64	----
1f	benzimidazole-2-thiol	0.71	0.14
1g	5-methylbenzimidazole-2-thiol	0.68	-0.01
1h	5-nitrobenzimidazole-2-thiol	0.63	0.54

[a] Potentials measured versus Ag/AgCl reference electrode; T = 26.0 °C.

zimidazole-2-thione, **1f**) in ethanolic HCl solution to observe the formation of disulfide (**2d**). The spectra of the initial and the final electrolyzed solutions are shown in Figure 6. The absorption maxima of the thiol at 308 and 248 nm were replaced by a more intense band at 206 nm. Visually, we have also observed the electrolytic solution changing from clear to an intense yellow color during the electrolysis.

Moreover, we have reported the preparation of several imidazolyl disulfides by controlled-potential electrolysis.[7] Malik and coworkers [14] have reported the electrooxidation products of 2-thioxanthine in the pH range 2-10 at a pyrolytic graphite electrode and concluded that the purine ring is oxidized prior to the $-SH$ group. The final products of the electrooxidation of the 2-thioxanthine are urea and the disulfide of 2-thio-4,5,6-trioxopyrimidine. However, ring oxidation can be excluded from the present thione electrooxidation since each voltammogram shows a single oxidation peak at around $+0.5$ to $+0.6$ volt.



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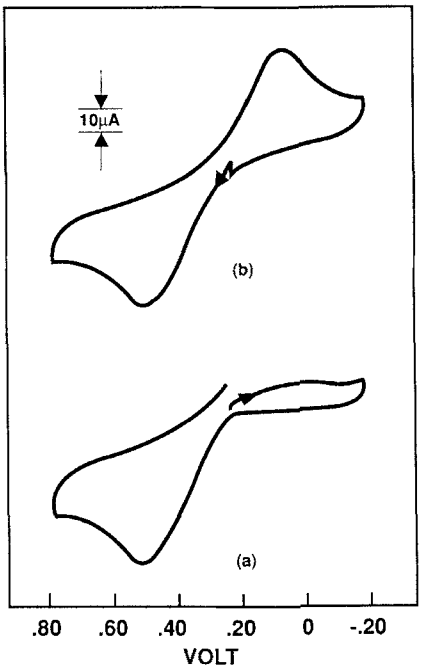

FIGURE 5 Cyclic voltammograms of 1-methylimidazole-2-thiol (**1b**). Scan rate = 200 mV/sec; [thiol] = 1 mM. Ag/AgCl reference electrode. (a) Scan initiated toward negative potential direction; (b) scan initiated toward positive potential.

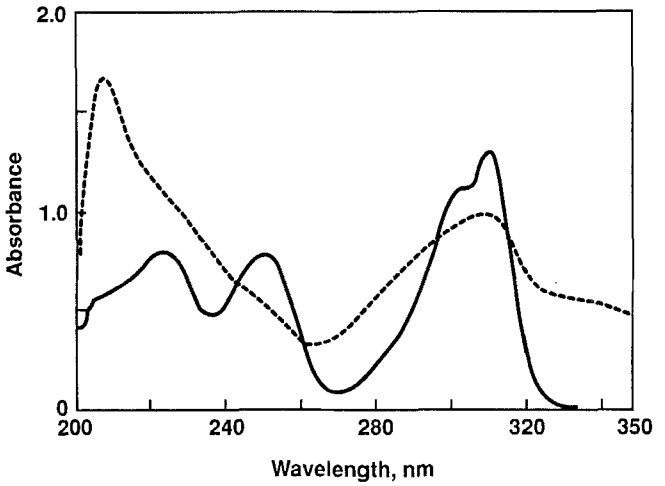

FIGURE 6 Ultraviolet specta of benzimidazole-2-thiol **1f** (solid line) and bisbenzimidazolyl disulfide **2d** (dashed line) during controlled-potential electrolysis.

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Madison, NJ 07940.

Ultraviolet spectra were obtained on Hewlett Packard 8451A diode array spectrometer equipped

with themostatted water bath to maintain constant cell temperature in the spectrometer. An Orion Research EA 940 pH meter equipped with ATC (automatic temperature compensation) was used to measure the pH.

Electrochemistry. These experiments, cyclic voltammetry and controlled-potentials electrolysis, were carried out in a three-electrode system using a Princeton Applied Research Model 173 Potentiostat Model 179 Digital coulometer and Model 178 probe. The three-electrode system consists of a silver/silver chloride reference electrode, a platinum disk, or a gauze electrode, and a platinum foil counter electrode. The counter electrode is placed in a glass tube sealed at the end with porous fritted disk containing the electrolyte solution. For the cyclic voltammetry experiment, the thione (1 mM) was dissolved in ethanenitrile solution (1 mL of 12 M HCl in 80 mL of ethanenitrile). Argon gas was passed through the solution prior to the cyclic voltammetric scan. The scan rate was usually kept at 200 mV/sec.

Chemicals. Imidazole-2-(3*H*)-thione (**1a**) was prepared from aminoethanal and potassium thiocyanate as previously decribed[15,16]: mp 226–228°C dec (lit.[15] mp 226–228°C). 4,5-Dimethylimidazole-2(3*H*)-thione (**1c**) was prepared from 3-hydroxy-2-butanone and ammonium thiocyanate as previously described[17,18]: mp > 300°C (lit.[17] mp > 300 °C). 1,4,5-Trimethylimidazole-2(3*H*)-thione (**1d**) was prepared from 3-hydroxy-2-butanone and N-methylthiourea as previously described[17]: mp 214–217°C (lit.[18] mp 217–218°C). 1-Methylimidazole-2(3*H*)-thione (**1b**) (mp 144–147°C, lit.[19] mp 143–144°C), 4,5-diphenylimidazole-2(3*H*)-thione (**1e**) (mp > 300°C, lit.[20] mp 321°C)), 1,3-dihydro-2*H*-benzimidazole-2-thione (**1f**) (mp 301–305°C, lit.[21] mp 303–304°C), 5-methylbenzimidazole-2-thiol (**1g**) (mp 290–293°C, lit.[22] mp > 295°C), and 5-nitrobenzimidazole-2-thiol (**1h**) (mp 271–275°C, lit.[23] mp 280–281°C) are commercially available.[24]

Analytical reagent grade dichloromethane was purifed by drying over CaH_2 followed by fractional distillation from CaH_2. Ethanenitrile was "glass-distilled" grade from Burdick and Jackson (American Hospital Supply Corp.) and was used as obtained.

Buffer Solutions. Phosphate buffer: (pH = 2.00 to 2.85) $[Na_2HPO_4 \cdot H_2O] = 3.5 \times 10^{-3}$ M, $[H_3PO_4] = 4.65 \times 10^{-2}$ M, $[NaClO_4] = 5.00 \times 10^{-2}$ M; acetate buffer: (pH = 3.00 to 5.85) $[NaOAc \cdot 3H_2O] = 7.43 \times 10^{-3}$ M, $[HOAc] = 4.26 \times 10^{-2}$ M, $[NaClO_4] = 5.00 \times 10^{-2}$ M; phosphate buffer: (pH = 6.00 to 8.80) $[NaH_2PO_4] = 4.70 \times 10^{-2}$ M, $[Na_2HPO_4] = 2.98 \times 10^{-2}$ M, $[NaClO_4] = 4.40 \times 10^{-2}$ M; borate buffer: (pH = 9.00 to 10.85) $[Na_2B_4O_7] = 1.83 \times 10^{-2}$ M, $[H_3BO_3] = 3.17 \times 10^{-2}$ M, $[NaClO_4] = 2.67 \times 10^{-2}$ M; phosphate buffer: (pH = 11.00 to 12.85) $[Na_2HPO_4] = 4.77 \times 10^{-3}$ M, $[Na_3PO_4 \cdot 12H_2O] = 2.29 \times 10^{-4}$ M, $[NaClO_4] = 8.43 \times 10^{-2}$ M.

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