

Reaction Chemistry of the Iron–Sulfur Protein Site Analogues $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$. Sequential Thiolate Ligand Substitution Reactions with Electrophiles

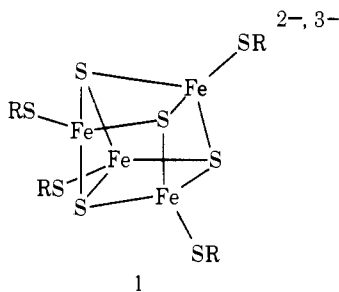
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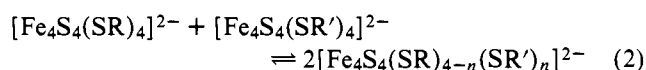
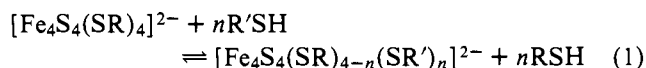
Abstract: In further development of the reaction chemistry of the iron–sulfur protein site analogues $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$, these clusters (R = Ph, *p*-tolyl, CH₂Ph, *t*-Bu) are shown to react with a variety of electrophiles YX in aprotic solvents to yield the species $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{X}_n]^{2-}$ and YSR. Reactions were monitored by electronic spectroscopy, differential pulse polarography, and ¹H NMR spectroscopy. With CH₃COCl and (CH₃CO)₂O the complete series of species ($n = 1-4$, X = Cl, OAc) was generated, including the first oxygen-ligated tetramer $[\text{Fe}_4\text{S}_4(\text{OAc})_4]^{2-}$, with no observable decomposition. Other reagents such as (CF₃CO)₂O, (CF₃SO₂)₂O, and CF₃SO₃CH₃ afford the corresponding $n = 1$ species (X = CF₃CO₂, CF₃SO₃). Identical species are formed by an acid and its anhydride. All species with $n = 1-4$ can be reconstituted to the original tetramer dianion $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ by reaction with excess RSH and Et₃N. All such species with any ligand X are characterized by decreased visible absorbance and positive 2–/3– potential shifts compared to the $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ precursors. Successive 2–/3– potential differences in a given series are usually ca. 100 mV, indicating a nearly linear dependence of potential on n . Ligands X are more labile than thiolate, as illustrated by the binding of several isonitriles to $n = 1, 2$ species (X = Cl, OAc) but not to $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$. The reaction rate of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{3-}$ with (CH₃CO)₂O is much faster than that of the corresponding dianion, indicating that reduction activates the cluster to electrophilic attack. Some possible biological implications of mixed ligand clusters in proteins are considered.

Introduction

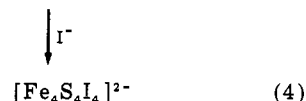
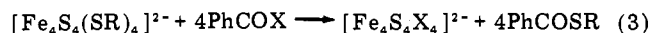
Since the initial synthesis of the tetranuclear dianions $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ and, more recently, their one-electron reduction products $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{3-}$, an extensive body of structural, spectroscopic, and magnetic evidence has been collected in order to demonstrate that these species are viable synthetic analogues of the 4-Fe clusters in oxidized and reduced ferredoxin (Fd) proteins, respectively. These anions possess the structure **1**^{3,4,7} containing a cubane-type Fe₄S₄ core. An



integral part of our investigations of the cluster complexes **1** is a continuing development of reactions which effect thiolate ligand substitution with retention of core structure. Earlier work has demonstrated the facile stepwise substitution reaction **1**^{4,8,9} and the ligand redistribution reaction **2**.⁸



Reaction **1** has been the more thoroughly investigated, including a mechanistic study,⁹ and forms the basis for the core extrusion reaction of iron–sulfur proteins.^{10,11} More recent experimentation¹² has resulted in demonstration of reaction **3**, whereby $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ species are converted to fully substituted halide tetramers (X = Cl, Br) which in turn may be metathesized to the iodo complex (reaction **4**). An x-ray diffraction study of (Et₄N)₂[Fe₄S₄Cl₄] has shown retention of core structure with unimportant changes in metrical features compared to thiolate tetramer precursors.¹³



The only other studies of the reactivity properties of synthetic tetramers **1** (excluding electron transfer) are those of acid–base equilibria, solvolysis, and hydrolysis by Bruce and co-workers^{14,15} and isonitrile/thioformimidate conversions (RNC → R'SCH=NR) by Schwartz and van Tamelen.¹⁶ The latter are described as catalytic in a reduced form of **1** (considered to be $[\text{Fe}_4\text{S}_4(\text{SR}')_4]^{4-}$) in the presence of excess thiol. As such these are the only catalytic reactions of the tetramers **1** thus far reported.

Insofar as is known the principal biological function of protein 4-Fe sites is electron transfer, without catalysis of substrate transformation at such sites. However, it is highly probable that the reactions of hydrogenases¹⁷—dihydrogen uptake and evolution and H/D exchange—occur as a consequence of substrate activation and catalysis involving one or more 4-Fe clusters. Three such clusters in clostridial hydrogenase have been identified by the core extrusion technique.^{10,18} Extrusion and spectroscopic studies of nitrogenase FeMo proteins²⁰⁻²² indicate the presence of 4-Fe clusters. While molybdenum has been considered by many workers to be a likely component of the nitrogen-reducing catalytic center(s), the composition of such center(s) in nitrogenase which are responsible for dihydrogen evolution and other substrate reduction remains undefined.²⁰ We have become interested in exploring the possible stoichiometric and catalytic reactions of 4-Fe clusters with biologically significant substrates. Noting that the extrusion technique¹⁰ identifies the Fe₄S₄ core structure but not necessarily its terminal ligands, we have begun investigation of complexes with this core structure but without the exclusive thiolate ligation found in the $[\text{Fe}_4\text{S}_4(\text{S-Cys})_4]$ redox centers of Fd proteins. Reported in this paper are means of generating and identifying the sequentially formed species $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{X}_n]^{2-}$ ($n = 1-4$). In these species ligand X is more labile than thiolate, allowing subsequent exploration of possible displacement of X by substrate with concomitant

Table I. Peak Potentials for the Couples $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{X}_n]^{z,z-1}$ in NMP Solution

R	X	$z/(z-1)$	E_p , V vs. SCE ^a				
			$n = 0$	1	2	3	4
<i>t</i> -Bu	Cl ^b	2-/3-	-1.42	-1.32	-1.18	-1.00	-0.85
	OAc ^c	2-/3-	-1.42	-1.29	-1.16	-1.05	-0.93
CH ₂ Ph	Cl	2-/3-	-1.25	-1.16	-1.07	-0.98	-0.88
	OAc	2-/3-	-1.25	-1.17	-1.09	-1.00	-0.92
	OAc	3-/4-	-1.95	-1.84	-1.76	-1.67	-1.62
Ph	OAc	2-/3-	-1.04				-0.94
	OAc	3-/4-	-1.75	<i>d</i>	<i>d</i>	<i>d</i>	-1.65
	CF ₃ CO ₂ ^f	2-/3-	-1.04	-0.94	<i>e</i>	<i>e</i>	<i>e</i>
	CF ₃ SO ₃ ^g	2-/3-	-1.04	-0.93			

^a All measurements made at ~25 °C. Reagents: ^b CH₃COCl; ^c (CH₃CO)₂O. ^d Potentials unspecified because peak potential separations of $n = 1-3$ species too small to measure accurately. ^e Decomposition observed upon addition of >1 equiv of reagents: ^f (CF₃CO)₂O; ^g (CF₃SO₂)₂O.

binding to and activation toward reductive transformation by the Fe₄S₄ core in the appropriate oxidation state.

Experimental Section

Materials. (Et₄N)₂[Fe₄S₄(SCH₂Ph)₄],³ (Et₄N)₂[Fe₄S₄(SPh)₄],²³ (Et₄N)₂[Fe₄S₄(S-*t*-Bu)₄], and (Me₄N)₂[Fe₄S₄(SC₆H₄-*p*-CH₃)₄]²⁴ were prepared by the method of direct tetramer synthesis.³ (Et₄N)₃[Fe₄S₄(SPh)₄] was synthesized by reduction of the corresponding dianion salt.⁶ *n*-Butyl and *tert*-butyl isonitrile were prepared by standard procedures.²⁵ Phenyl thioacetate (bp 73 °C, 1.5 mm) and *p*-tolyl thioacetate (bp 120 °C, 1 mm) were synthesized by reaction²⁶ of the thiol with excess acetyl chloride in refluxing benzene containing 3 drops of pyridine. Phenyl thiotrifluoroacetate (bp 45 °C, 6 mm) was obtained by reaction of benzenethiol with trifluoroacetic anhydride in diethyl ether. The three thioesters, required for gas chromatographic or NMR identification of reaction products of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ (vide infra), are previously reported compounds and were purified by distillation and identified by NMR and infrared spectra. Trifluoromethanesulfonic acid (3 M), trifluoromethanesulfonic anhydride, methyl trifluoromethanesulfonate, benzylthiol, thioanisole, and *tert*-butylthiol were commercial samples and were used as received. The following reagents and solvents were purified by distillation in a dinitrogen or argon atmosphere and were stored under anaerobic conditions: acetyl chloride, triethylamine (from sodium hydroxide); acetic and trifluoroacetic anhydride (from P₂O₅); benzenethiol (bp 80 °C, 20 mm); acetonitrile (from calcium hydride); *N,N*-dimethylformamide (DMF), bp 60 °C (18 mm); and *N*-methyl-2-pyrrolidinone (NMP, Aldrich), bp 60 °C (1.5 mm) (from calcium hydride and then barium oxide). All reagents were transferred by syringe to solutions of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ under anaerobic conditions.

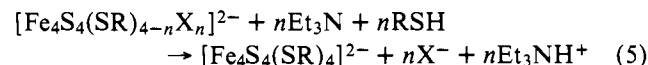
Physical Measurements. All measurements were performed under anaerobic conditions. Conventional dc and differential pulse polarograms were recorded for solutions containing 50 mM (*n*-Bu₄N)(BF₄) supporting electrolyte, ~2 mM $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$, and specified reagents at a scan rate of 5 mV/s using a Princeton Applied Research Model 170 electrochemistry system. The working electrode was a dropping mercury electrode. Potentials are reported vs. a saturated calomel electrode (SCE). Electronic spectra were obtained with a Cary Model 17 spectrophotometer using an anaerobic cell with serum cap adapters for injection of reagents. Infrared spectra were recorded on a Perkin-Elmer Model 621, 337, or 597 grating spectrophotometer. ¹H NMR spectra were obtained with a Varian XL-100-15 spectrometer equipped with a deuterium lock and a Varian 4412 probe with a 5-mm insert. Data collection and processing were done by a Nicolet Model 1180 Fourier transform computer with a TT 1010A pulser unit and a Diablo Model 31 magnetic disc storage system. Chemical shifts downfield of Me₄Si internal reference are designated as negative. Gas chromatography was performed with a Varian 3700 chromatograph utilizing a flame ionization detector and a 1-ft 5% OV 101 on Chromosorb G column.

Results

The reactions of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ (1, R = Ph, *p*-tolyl, CH₂Ph, *t*-Bu) with electrophilic reagents (acetyl chloride, anhydrides, acids) have been examined in aprotic solvents and monitored by electrochemistry, electronic spectroscopy, and

¹H NMR spectroscopy. The selection of complexes includes those with aryl- and alkylthiolate substituents and encompasses the near extremes of potentials of the $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$,³⁻ couple in aprotic solvents ($E_{1/2} = -1.42$ V (R = *t*-Bu), -1.04 V (R = Ph) in DMF vs. SCE²³). Electrochemical,^{6,23,27} electronic spectral,^{23,27} and ¹H NMR spectral^{24,28} properties of these dianions in the same or similar media have been described previously. Because of the small potential differences involved for 2-/3- couples, differential pulse (DP) polarography was found to be the most effective electrochemical method of detection of the species $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{X}_n]^{2-}$ ($1 \leq n \leq 4$) resulting from the reaction of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ with electrophiles. Peak potentials (E_p) vs. SCE are reported. Of the solvents employed, acetonitrile, DMF, and NMP, the stabilities of reaction products are in general most favorable in NMP and nearly all reported results were obtained in this solvent.

Reactions with Acetyl Chloride. Treatment of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$, $[\text{Fe}_4\text{S}_4(\text{S-}p\text{-tolyl})_4]^{2-}$, $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$, and $[\text{Fe}_4\text{S}_4(\text{S-}t\text{-Bu})_4]^{2-}$ with successive equivalents of acetyl chloride in NMP solution resulted in smooth changes in the visible spectra. The prominent maxima at ca. 420–460 nm are progressively decreased in intensity until, with 5.0 equiv of reagent, the spectrum of $[\text{Fe}_4\text{S}_4\text{Cl}_4]^{2-}$ (λ_{max} 690 nm), previously obtained by reaction 3 and isolated as its Et₄N⁺ salt,¹² is achieved. With ~5 mM dianion concentrations the reactions are essentially instantaneous, and the concomitant formation of thioester CH₃COSR was demonstrated by gas chromatography. At any point during the reaction the initial $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ species could be regenerated in nearly quantitative amounts by the reconstitution reaction



(X = Cl) employing a slight excess of thiol and amine in equimolar amounts. Reconstitution in this and other cases was not observed or was not quantitative in the absence of base.

The formation of the species $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{Cl}_n]^{2-}$ responsible for the visible spectral changes was demonstrated by two techniques. Addition of successive equivalents of acetyl chloride to $[\text{Fe}_4\text{S}_4(\text{S-}t\text{-Bu})_4]^{2-}$ or $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$ in NMP resulted in the appearance of new peaks in DP polarograms at potentials positive to that for the 2-/3- couple of the initial complex. Potentials for the various $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{Cl}_n]^{2-}$,³⁻ couples are collected in Table I and DP polarograms for the R = CH₂Ph reaction system are shown in Figure 1. Successive potential differences are 100–180 and 90–100 mV for the R = *t*-Bu and CH₂Ph systems, respectively. The final peak observed after the addition of 4.0 equiv of reagent corresponds to the couple $[\text{Fe}_4\text{S}_4\text{Cl}_4]^{2-}$,³⁻ with a potential which is the same as that for an authentic sample measured under the same conditions.²⁹ Also evident from the

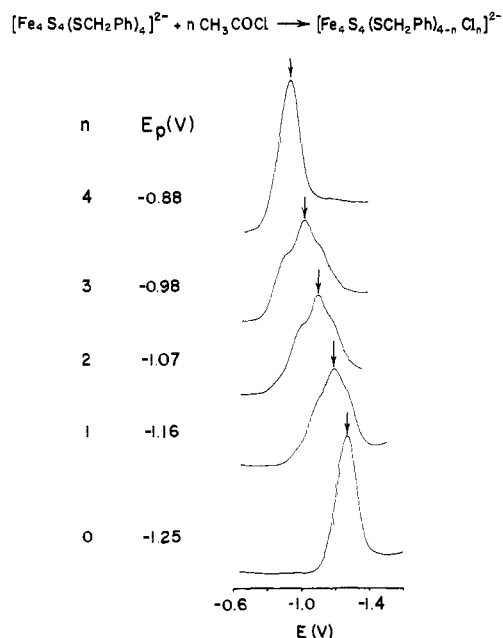


Figure 1. Differential pulse polarograms for the reaction of 2.0 mM $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$ with 1–4 equiv of CH_3COCl in NMP (scan rate 5 mV/s). Arrows designate peaks whose potentials vs. SCE are given.

polarograms of Figure 1 is a distribution of $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}\text{Cl}_n]^{2-}$ species upon addition of 1–3 equiv of acetyl chloride. Although peaks are too closely spaced to permit measurement of relative areas, line shapes suggest an approximately statistical distribution (1:2:1) with the dominant species having an n value equal to the number of equivalents of added reagent. Similar experiments with $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ yielded unresolved peaks which progressively shifted toward a final value of -0.88 V. The lack of resolution arises from the small (160 mV) separation between potentials of initial and final species. In all cases the reconstitution reaction 5 yielded solutions whose polarograms contained as the only peak that of the initial $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ couple.

The ^1H NMR spectrum of $[\text{Fe}_4\text{S}_4(\text{S-}i\text{-p-tolyl})_4]^{2-}$ in $\text{DMF-}d_7$ at 23 °C contains a contact-shifted ring methyl resonance²⁴ at -3.96 ppm. Successive additions of 1.0 equiv of acetyl chloride reduced the intensity of this signal and resulted in the sequential growth and decline of three new downfield singlets at -4.02 , -4.08 , and -4.14 ppm, which are correlated with $n = 1, 2$, and 3 mixed ligand complexes, respectively. Addition of 5.0 equiv of reagent abolished all contact-shifted methyl resonances. Peaks arising from p -tolyl thioacetate were observed to increase in intensity as acetyl chloride was added. Methyl signals of the mixed ligand complexes could not be accurately integrated because of small chemical shift separations, but their relative intensities are similar to the features of the DP polarograms assigned to the same predominant species.

Reactions with Anhydrides. Reactions of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$, $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$, and $[\text{Fe}_4\text{S}_4(\text{S-}i\text{-Bu})_4]^{2-}$ with acetic anhydride are much slower than with acetyl chloride and rates increase in the order $\text{R} = i\text{-Bu} < \text{CH}_2\text{Ph} < \text{Ph}$. Most spectral and electrochemical measurements were made 30–60 min after the addition of reagent in order to be sure that equilibrium had been reached. Reactions of these three dianions with the anhydride in NMP solutions resulted in progressive diminution in visible spectral intensity, generation of the appropriate thioester, and near-quantitative reconstitution of the original complex by reaction 5 ($\text{X} = \text{OAc}$) using excess thiolate. Spectral results for the $\text{R} = \text{Ph}$ system in the 400–700-nm region are illustrated in Figure 2. Successive additions of 0.25

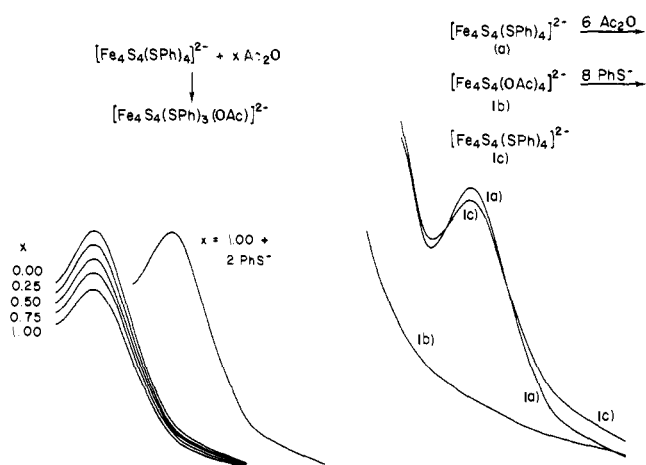


Figure 2. Electronic spectra (400–700 nm) for the reaction of 5.0 mM $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ and $(\text{CH}_3\text{CO})_2\text{O}$ in NMP. Left: successive additions of 0.25 equiv of anhydride at 30-min intervals, followed by reconstitution of the 1.0 equiv solution. Right: spectra of (a) $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$; (b) reaction product of (a) with 4.0 equiv of anhydride after 4 h; (c) reconstitution of (b) with 8.0 equiv each of Et_3N and PhSH .

equiv of anhydride reduced the intensity of the prominent 459-nm peak. The spectrum after addition of 1.0 equiv is predominantly that of the monosubstituted species $[\text{Fe}_4\text{S}_4(\text{SPh})_3(\text{OAc})]^{2-}$, which can be quantitatively reconstituted to $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ by 2.0 equiv of benzenethiolate. Addition of 6.0 equiv of anhydride abolished any trace of the visible peak of the initial tetramer, which may be $\geq 90\%$ reconstituted by treatment with 8.0 equiv of benzenethiolate. On the basis of the reconstitution reaction the featureless spectrum with absorbance rapidly rising into the ultraviolet is assigned to the previously unknown tetramer $[\text{Fe}_4\text{S}_4(\text{OAc})_4]^{2-}$. Quantitative gas chromatographic analysis of reaction products gave 0.95 and 3.9 equiv of phenyl thioacetate after the addition of 1.0 and 6.0 equiv, respectively, of anhydride to $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$.

DP polarograms of the reactions of the preceding three dianions with acetic anhydride in NMP show changes similar to those in Figure 1. Depicted in Figure 3 are polarograms for the 2–/3– and 3–/4– couples of the reaction products of $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$ with anhydride. Positive 2–/3– potential shifts and multiple species are again observed after addition of 1–4 equiv of reagent. Unlike the acetyl chloride reaction system substitution is not complete after 4 equiv inasmuch as the peak at -1.00 V for the $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})(\text{OAc})_3]^{2-}$ couple is still observable. Positive shifts of the 3–/4– couples are evident against the increasing background current at potentials more negative than ca. -1.6 V. Addition of 8.0 equiv of benzylthiolate after stepwise introduction of 4.0 equiv of anhydride resulted in reconstitution of $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$, as seen by the presence of the peak for its 2–/3– couple. The 3–/4– peak of this complex is obscured by background current.

The reaction of $[\text{Fe}_4\text{S}_4(\text{S-}i\text{-p-tolyl})_4]^{2-}$ with acetic anhydride in $\text{DMF-}d_7$ was monitored by ^1H NMR spectroscopy. The spectral changes were consistent with those found in the acetyl chloride reaction system. Contact-shifted methyl signals were observed for $n = 1, 2$, and 3 species at -4.04 , -4.13 , and -4.22 ppm, respectively, upon successive additions of 1.0 equiv of reagent, and signals from p -tolyl thioacetate progressively increased in intensity.

Reactions of acetic anhydride with $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ complexes are decidedly slower than those of acetyl chloride. This behavior is illustrated in Figure 4 by the time course of the reaction between $[\text{Fe}_4\text{S}_4(\text{S-}i\text{-Bu})_4]^{2-}$ and 1.0 equiv of the

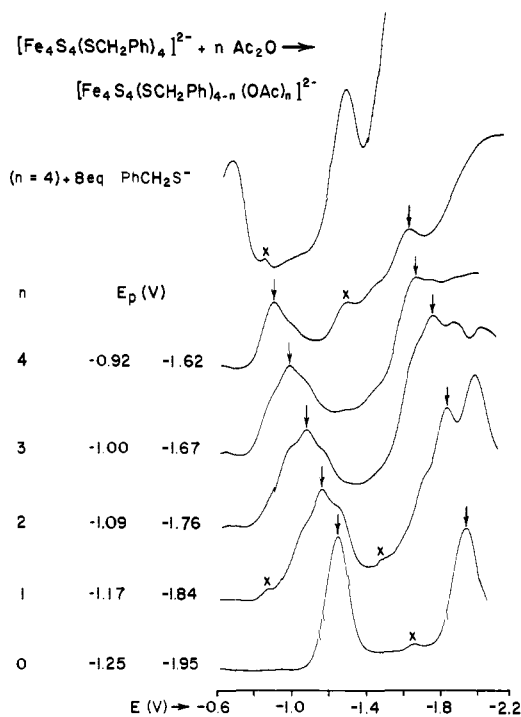


Figure 3. Differential pulse polarograms for the reaction of 2.0 mM $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$ with 1–4 equiv of $(\text{CH}_3\text{CO})_2\text{O}$ in NMP (scan rate 5 mV/s). Arrows designate peaks whose potentials vs. SCE are given. Polarograms were recorded 45 min after each addition of anhydride. The top polarogram corresponds to reconstitution by addition of 8.0 equiv each of Et_3N and PhCH_2SH after the final addition of anhydride. Peaks marked with X are unidentifiable; that at -1.3 V is much reduced in intensity if 4.0 equiv of reagent is added in one portion rather than in increments of 1.0 equiv. The peak at -0.65 V in the top polarogram is due to oxidation of excess thiolate.

anhydride as followed by DP polarography. The initial peak at -1.42 V, due to the couple $[\text{Fe}_4\text{S}_4(\text{S}-t\text{-Bu})_4]^{2-}$, slowly decreases in intensity as the species $[\text{Fe}_4\text{S}_4(\text{S}-t\text{-Bu})_{4-n}(\text{OAc})_n]^{2-}$ are formed. The $n = 1$ species becomes evident after 25 min and gives rise to a well-defined peak at -1.29 V after 100 min. At longer times this feature continues to increase in intensity as does a shoulder at -1.16 V, which is assigned to the $n = 2$ complex. No further changes were observed after 700 min. Addition at that time of 8.0 equiv of *tert*-butylthiolate resulted in reconstitution which, however, may not be complete as judged by the larger peak half-width as compared to the initial polarogram. In other experiments introduction of larger quantities of anhydride led to detection of $n = 1$ – 4 species. Potentials for the various $[\text{Fe}_4\text{S}_4(\text{SR})_{4-n}(\text{OAc})_n]^{2-}$ and $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_{4-n}(\text{OAc})_n]^{2-}$ couples are set out in Table I. Separations of successive 2–/3– potentials are 110–130 (R = *t*-Bu) and 80–90 mV (R = CH_2Ph); for the 3–/4– couples these separations are less uniform (50–110 mV).

Reactions of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ with more electrophilic anhydrides were also examined but not as comprehensively as the preceding cases. Treatment of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ with 1.0 equiv of $(\text{CF}_3\text{CO})_2\text{O}$ or $(\text{CF}_3\text{SO}_2)_2\text{O}$ resulted in visible absorbance decreases similar to that in Figure 2. Peaks for the 2–/3– couples of $n = 1$ species were detected by DP polarography (Table I). In the reaction of trifluoroacetic anhydride in acetonitrile phenyl trifluoroacetate was detected as a product by gas chromatography and the initial dianion could be fully reconstituted. Addition of further equivalents of either anhydride resulted in some decomposition. Reactions of the R = CH_2Ph and *t*-Bu dianions with either anhydride appeared to give decomposition. Treatment of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ with 1.0 equiv of $\text{CF}_3\text{SO}_3\text{CH}_3$ also lowered the visible absorbance, yielded

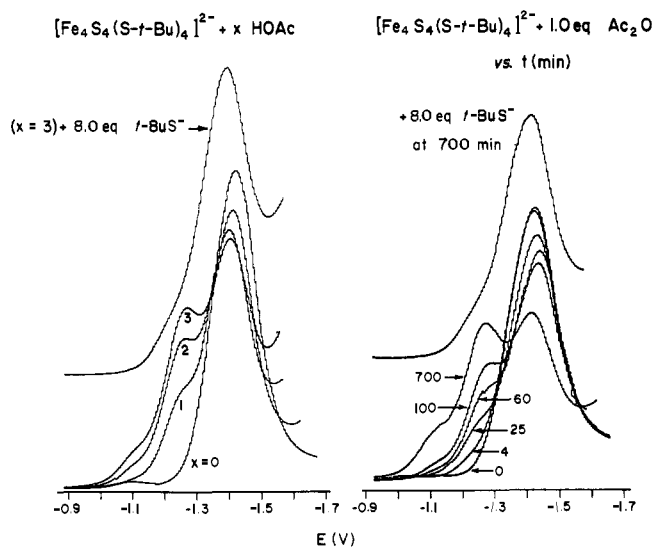


Figure 4. Differential pulse polarograms for the reactions of 2.0 mM $[\text{Fe}_4\text{S}_4(\text{S}-t\text{-Bu})_4]^{2-}$ with HOAc and $(\text{CH}_3\text{CO})_2\text{O}$ in NMP solution (scan rate 5 mV/s). Left: addition of 1.0–3.0 equiv of acid. Right: addition of 1.0 equiv of anhydride with polarograms recorded up to 700 min reaction time. Both systems were reconstituted by addition of 8.0 equiv each of Et_3N and *t*-BuSH.

thioanisole (detected by gas chromatography) as a reaction product, and generated a polarographic peak whose potential is the same as that for the $n = 1$ species formed from $(\text{CF}_3\text{SO}_2)_2\text{O}$.

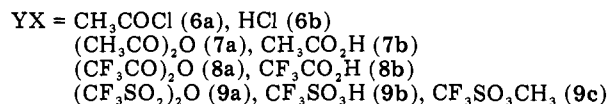
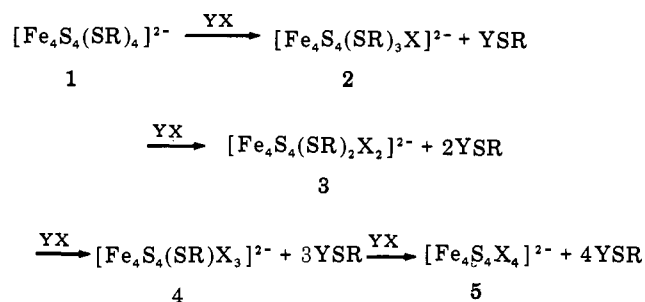
Reactions with Acids. Reduction in visible absorbance was also observed upon the addition of acid to NMP solutions of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ (R = Ph, CH_2Ph , *t*-Bu), the amount being dependent on the acid employed. All dianions exhibited reactions with 0.2 equiv of $\text{CF}_3\text{CO}_2\text{H}$ and $\text{CF}_3\text{SO}_3\text{H}$, and decomposition became significant at 0.5 equiv of acid. DP polarographic examination of the reaction products of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ with the two acids in the absence of significant decomposition revealed the same peaks as for $n = 1$ species generated by reaction with the corresponding anhydride (Table I). Careful treatment of NMP solutions of $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$ and $[\text{Fe}_4\text{S}_4(\text{S}-t\text{-Bu})_4]^{2-}$ with a solution of anhydrous HCl in acetonitrile produced, along with some decomposition, the spectrum of $[\text{Fe}_4\text{S}_4\text{Cl}_4]^{2-}$. When followed by DP polarography the same peaks were observed as in the sequential addition of acetyl chloride to these dianions.

Reactions of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ with the weaker acid, acetic acid, were also examined. As judged by visible absorbance decreases and/or the heights of polarographic peaks, reactivity varied in the order R = *t*-Bu > CH_2Ph > Ph with the first two dianions exhibiting reaction at 1.0 equiv of added acid and the last being only slightly affected by 5.0 equiv of acid. Shown in Figure 4 are DP polarograms resulting from the addition of 1–3 equiv of acid to an NMP solution of $[\text{Fe}_4\text{S}_4(\text{S}-t\text{-Bu})_4]^{2-}$. Formation of the $n = 1$ species at the same potential (-1.29 V) as that for the reaction with $(\text{CH}_3\text{CO})_2\text{O}$ is evident, as is a small extent of $n = 2$ species formation of higher levels of added acid. Reconstitution of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ /HOAc reaction systems could be achieved by the addition of triethylamine alone, except for the R = *t*-Bu case, where excess thiol proved necessary.

Discussion

The results of reactions of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$ with electrophilic reagents Y–X are describable by the generalized Scheme I involving sequential replacement of thiolate ligands. Reagents investigated which should provide a common X ligand according to this scheme are appropriately grouped. Table I

Scheme I



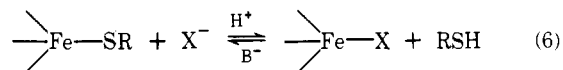
serves as a summary of the various [Fe₄S₄(SR)_{4-n}X_n]²⁻ species 2-5 which have been detected by DP polarography. In addition the mixed ligand complexes 2-4 having R = *p*-tolyl and X = Cl, OAc were identified by ¹H NMR spectroscopy. The earlier work¹² which had established reaction 3 and led to the isolation of (Et₄N)₂[Fe₄S₄Cl₄] did not include attempts to detect intermediate mixed ligand species.

The following experimental results are summarized in support of Scheme I for the reactions of [Fe₄S₄(SR)₄]²⁻ (1, R = Ph, *p*-tolyl, CH₂Ph, *t*-Bu) with reagents Y-X: (1) identification by DP polarography and electronic spectroscopy of the previously characterized tetramer [Fe₄S₄Cl₄]²⁻¹² as the terminal reaction product with reagents 6; (2) detection by polarographic and ¹H NMR measurements of only *three* intermediate species (2, 3, 4; X = Cl, OAc) in reactions with reagents 6 and 7a; (3) formation of identical species (peak potential criterion) upon reaction of reagents 6 (2-5, X = Cl), 7 (2, 3; X = OAc), 8 (2, X = CF₃CO₂), and 9 (2, X = CF₃SO₂) with the previously specified dianions 1; (4) identification (where sought) by gas chromatography and ¹H NMR spectroscopy of the appropriate thioester or thioether, YSR, as the reaction product of displaced thiolate; (5) ≥90% reconstitution of any species 2-5 upon addition of excess thiolate (reaction 5, polarographic and electronic spectral criteria), indicating retention of Fe₄S₄ core structure throughout the thiolate ligand substitution sequence. Neither Scheme I nor these results are meant to indicate that all reagents 6-9 when utilized under our experimental conditions effect the complete (or even partial) sequence of reactions culminating in the formation of the fully substituted dianions 5. While this matter has not been exhaustively investigated, we have found that in NMP solutions only two of the reagents tested, acetyl chloride and acetic anhydride, lead to formation of all complexes 2-5 without observable decomposition. As already noted addition of (CF₃CO)₂O and (CF₃SO₂)₂O past the amount required to generate appreciable amounts of the complexes 2 (R = Ph) produced some decomposition, treatment of 1 (R = CH₂Ph, *t*-Bu) with either anhydride resulted in decomposition, and these two dianions but not [Fe₄S₄(SPh)₄]²⁻ reacted with 1.0 equiv of acetic acid to yield 2.

Several experimental regularities were observed in the course of executing the reactions of Scheme I, primarily with acetyl chloride and acetic anhydride as reagents. ¹H NMR spectral and polarographic results (Figures 1 and 3) show that individual mixed ligand complexes [Fe₄S₄(SR)_{4-n}X_n]²⁻ (2-4) are the major but not the exclusive reaction products formed with *n* equiv of reagent. Similar behavior was found in ¹H NMR studies of reaction 1.⁸ The roughly statistical distribution of species presumably precludes isolation of a pure salt of any one such species. Reactions with acetyl chloride were uniformly fast and stoichiometric whereas reactions with acetic

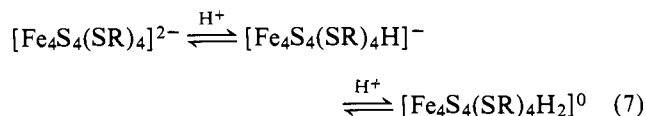
anhydride were slow and required excess reagent to achieve complete conversion to 5. This behavior probably reflects the weaker acylating strength of the anhydride. Reaction of any tetramer dianion with any reagent 6-9 results in a decrease in the intense visible absorption bands at 420-460 nm. This behavior provides further evidence that the visible spectral features of [Fe₄S₄(SR)₄]²⁻ arise from RS → core(Fe) charge transfer transitions³⁰ and is diagnostic of thiolate ligand substitution. The spectra of the fully substituted complexes [Fe₄S₄Cl₄]²⁻¹² and [Fe₄S₄(OAc)₄]²⁻ are quite different from those of their [Fe₄S₄(SR)₄]²⁻ precursors. Indeed, [Fe₄S₄(OAc)₄]²⁻, the first example of exclusive oxygen ligation to an Fe₄S₄ core, displays no band maxima in the visible region (Figure 2). At parity of R substituent potentials of 2-/3-couples of species 2-4 containing ligands X derived from any reagent 6-9 are shifted to less negative values compared to [Fe₄S₄(SR)₄]²⁻ potentials (Table I). The trend continues to [Fe₄S₄Cl₄]²⁻¹² and [Fe₄S₄(OAc)₄]²⁻¹² potentials. These shifts, which signify increasing ease of reduction, are presumably the consequence of introduction of ligands with lesser electron-releasing tendencies, thereby increasing the effective electron affinity of the core. From the nearly constant separation of potentials of successively substituted species and the approximately statistical distribution of such species, we conclude that ligands RS and X function nearly independently such that the properties of a given tetramer vary as the sum of the effects imparted by the individual ligands. Lastly, by assuming a linear variation of potential with substitution and using the ~100 mV separation observed for the R = Ph systems (Table I), we estimate the [Fe₄S₄X₄]²⁻³⁻ potentials for X = CF₃CO₂ and CF₃SO₂ to be -0.6 V. Given the generally poor binding properties of the trifluoromethanesulfonate ion in particular, this potential may be an approximate upper limit for that of the "naked" (solvated) core, i.e., "[Fe₄S₄]^{2+.1+}".

The previous findings that the rates of solvolysis and hydrolysis^{14,15} and ligand substitution by added thiol^{9,15} of the clusters 1 increase with increasing acidity and the need for base in cluster reconstitution led us to examine protonation as a pathway for ligand substitution. Confirmation of reaction 6 follows from the results of treating [Fe₄S₄(SR)₄]²⁻ with the acid reagents 6b-9b, especially anhydrous HCl. In contrast



to acylation and alkylation reactions, which appear to be irreversible under our conditions, protonation reactions should be reversible and subject to equilibrium control. Reconstitution of the original complex with triethylamine alone is indicative of these properties as is the reactivity order R = *t*-Bu > CH₂Ph > Ph when [Fe₄S₄(SR)₄]²⁻ complexes are treated with equal equivalents of acetic acid. This order is the same as that of thiolate basicity in aqueous solution.³¹

The results of this investigation allow us to make several observations concerning the mechanistic proposals of Bruce and co-workers, who have examined the reactions of [Fe₄S₄(SR)₄]²⁻ and the isoelectronic complex [Fe₄S₄(SCH₂CH₂CO₂)₄]⁶⁻ in mixed aqueous and pure aqueous media,^{14,15,32} respectively. One proposal is that the mechanisms for cluster solvolysis (ligand substitution by lyate species) and hydrolysis (irreversible core destruction) involve as initial steps the acid-base equilibria

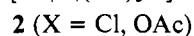
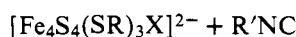


in which clusters are suggested to be protonated on core faces. In support of this proposal are the reported determinations of

$\text{p}K_a = 3.9$ for $[\text{Fe}_4\text{S}_4(\text{S-}i\text{-Bu})_4]^{2-}$ ¹⁴ and 7.4 for $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{CH}_2\text{CO}_2)_4]^{6-}$ ¹⁵ derived from pH vs. absorbance plots which suggest a >60% drop in absorbance upon monoprotonation. In addition these investigators conclude that solvolysis by OH^- occurs at high pH values where excess thiol slows the hydrolysis process but not by water at pH values below ~ 6 where excess thiol has little effect on rates or $\text{p}K_a$ measurements. While protonic equilibria are certainly involved, our results, especially with anhydrous HCl, suggest that in NMP solutions ligand substitution occurs at all pH values. The observed absorbance decrease ascribed to monoprotonation is much larger than we find at 300–700 nm for monosubstitution of a thiolate ligand but is not inconsistent with tetrasubstitution by an oxygen-binding ligand (Figure 2). Because the ligands function independently, the presence of one equilibrium constant but hydrolysis rate expressions up to fourth order in thiolate concentration is not unexpected,³³ and both have been observed by Bruice et al.^{14,15} The effect of excess thiol vs. solution pH clearly depends on $\text{p}K_a$ of the thiol because only when the pH is sufficiently high to form thiolate will competitive substitution affect the rates and equilibria. Other differences found under reported aqueous solvolysis conditions¹⁵ are an increase in absorbance during reaction and the development of a single product wave at -0.99 V, which is 160 mV more negative than the $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{CH}_2\text{CO}_2)_4]^{6-}$ ⁷ potential and has been assigned to solvolyzed cluster.³⁴ Here we find for any species 2–5 generated from reagents 6–9 in NMP solutions absorbance decreases and positive potential shifts consequent to thiolate substitution.

Other than these differences, which may in part result from the aqueous vs. nonaqueous solvent media employed, our results tend to support several aspects of the chemistry of cluster complexes 1 initially proposed by Bruice et al.^{14,15} clusters do undergo solvolytic-type reactions in protic media; thiolate can be replaced by chloride; hydrolysis of the Fe_4S_4 core proceeds by initial protonation of core sulfide inasmuch as thiolate protonation leads to substitution. In other work³⁵ we have confirmed their observation¹⁵ that excess thiolate stabilizes clusters in aqueous solution.

Scheme I places at our disposal various reactions for replacing thiolate by assorted ligands which are more labile. Evidence that thiolate substitution promotes binding with other ligands is found in the occurrence of reaction 8. Solutions

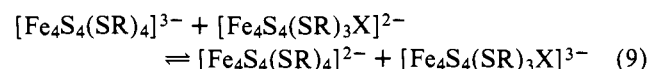


of 8 mM $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ in acetonitrile containing 2–5 equiv of *n*-butyl isonitrile or *tert*-butyl isonitrile exhibited single $\text{N}\equiv\text{C}$ stretching frequencies at 2149 and 2136 cm^{-1} , identical with those of the isonitriles in the absence of the cluster dianions. Generation of species 2 (R = Ph) followed by isonitrile addition (1–2 equiv) produced new bands at 2169 (R' = *n*-Bu) and 2161 cm^{-1} (R' = *t*-Bu). The former band was also observed in solutions containing 2 (R = CH_2Ph , *t*-Bu) or $[\text{Fe}_4\text{S}_4\text{Cl}_4]^{2-}$ and 1–3 equiv of *n*-butyl isonitrile. The visible spectrum underwent only minor changes when *n*-butyl isonitrile was added to $[\text{Fe}_4\text{S}_4(\text{SPh})_3\text{X}]^{2-}$. Addition of *n*-butyl isonitrile to $[\text{Fe}_4\text{S}_4\text{Cl}_4]^{2-}$ gave a new DP polarographic peak at -0.98 V, ascribed to the couple $[\text{Fe}_4\text{S}_4\text{Cl}_3(\text{CN-}i\text{-Bu})]^{1-}$ ²⁻; linear extrapolation leads to ca. -1.28 V for the (hypothetical) $[\text{Fe}_4\text{S}_4(\text{CN-}i\text{-Bu})_4]^{2+,1+}$ couple. The latter value is close to that for the $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_4]^{2-}$ ³⁻ couple (-1.25 V), and accounts for the fact that addition of isonitrile to solutions of $[\text{Fe}_4\text{S}_4(\text{SCH}_2\text{Ph})_3\text{Cl}]^{2-}$ diminishes the peak height near -1.16 V and increases it near -1.25 V. Increases in NC stretching frequencies upon coordination enjoy precedent³⁶ and are generally associated with metals in normal oxidation states

stabilized by weak field ligands. In such cases isonitriles are susceptible to attack at carbon by nucleophiles³⁶ whereas species containing low-valent metals with decreased NC frequencies^{36,37} are often reactive toward electrophiles at nitrogen.³⁶ The present results show that the mixed ligand clusters 2 are more reactive than 1 to binding isonitrile, a result of possible interest in connection with the role of methyl isonitrile as a nitrogenase substrate.

The recent isolation of the reduced clusters $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{3-}$ (R = Ph, CH_2Ph),^{5,6} which are analogues of the 4-Fe sites of Fd_{red} proteins,^{5,7} has allowed us to initiate a corresponding study of their ligand substitution reactions. Cluster trianions are stable in rigorously anaerobic aprotic solvents. Addition of 1.0–2.0 equiv of acetyl chloride or acetic anhydride to a solution of $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{3-}$ resulted in an immediate decrease in visible absorbance and formation of phenyl thioacetate. Reconstitution under the conditions of reaction 5 largely restored the original spectrum⁶ but with ca. 15% oxidation to $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$, which we have not been able to suppress. The rapid rate of reaction with the anhydride, compared to the considerably slower reaction of the dianion, provides evidence that reduction activates the cluster toward substitution by electrophilic reagents³⁸ and suggests that any further substitution of X in, e.g., $[\text{Fe}_4\text{S}_4(\text{SR})_3\text{X}]^{3-}$ may be more facile than in the oxidized species 2.

The biological implications of mixed ligand clusters in proteins are numerous; several which are suggested by observations in this work are noted here. Thiolate ligand lability in a $[\text{Fe}_4\text{S}_4(\text{S-Cys})_4]$ cluster might be achieved by aqueous protonation coupled with protein conformational change. Demonstration of acetate binding to clusters together with its substitutional lability presents the possibility of protein 4-Fe sites with Glu-CO_2^- or Asp-CO_2^- side chains coordinated, a variation which would not necessarily be detected by core extrusion experiments or qualitative electronic spectra (Figure 2). By such means a site for substrate binding could be opened, and the modified cluster might then be capable of catalyzing reductive transformations. Taking monosubstituted clusters as an example, those with any ligand X in Table I will cause the reaction



to proceed to the right by virtue of the driving force generated by the positive potential shifts of the $[\text{Fe}_4\text{S}_4(\text{SR})_3\text{X}]^{2-,3-}$ couples. In this case any reducible substrate substituted for X in the oxidized cluster and capable of effecting a positive potential shift, or substituted for X in the reduced cluster, becomes potentially activated toward reduction by electron transfer and concomitant protonation. In a second example, not involving substrate transformation, ligand substitution, which results in a negative potential shift, if occurring at a reduced cluster, would cause reaction 9 to proceed to the left. This possibility, previously recognized by Job and Bruice,¹⁵ provides a means of pumping an electron to a lower potential, thereby increasing the reducing power of $[\text{Fe}_4\text{S}_4(\text{S-Cys})_4]$ redox centers. Experiments designed to explore stoichiometric and catalytic conversions of biologically significant substrates using mixed ligand species of the type $[\text{Fe}_4\text{S}_4(\text{SR})_3\text{X}]^{2-,3-}$ in the presence of $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{3-}$ as a reducing agent are underway.³³

Acknowledgments. This research was supported by National Science Foundation Grant CHE 77-04397. We thank A. Schwartz for a gift of isonitriles, Dr. J. Renaud and J. G. Reynolds for experimental assistance, and the Stanford Magnetic Resonance Laboratory for the use of NMR facilities.

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Photooxidation of Dichloro- and Trichlorocuprate(I) Ions in Acid Solution^{1a}

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Abstract: Photooxidation of the dichloro- and trichlorocuprate(I) ions in aqueous acidic media produces chlorocuprate(II) ions and hydrogen with quantum yields approaching unity. The photolysis of $CuCl_3^{2-}$ at 274 nm shows a linear dependence for the reaction $Cu(I) + H^+ \rightarrow Cu(II) + \frac{1}{2}H_2(g)$ on the square root of scavenger (H^+) concentration within a range of scavenger concentrations greater than 10^{-2} M and less than 2 M. The square-root dependence as well as the response at high and low scavenger concentrations is explained by invoking a Noyes-geminate-pair scavenging mechanism. The charge transfer to solvent (CTTS) character of the transition, and the dependencies of ϕ on $[H^+]$, ionic strength, temperature, and on the presence of acetone as an electron scavenger, are used as evidence for the production of an electron in the primary step. In addition, laser flash photolysis experiments at 265 nm have confirmed the production of the hydrated electron in a neutral solution of di- and trichlorocuprate ion, containing no known efficient electron scavengers. An unusual dependence of ϕ on chloride ion concentration was observed, and this is explained in terms of a salt effect. In the absence of efficient scavengers the hydrated electron is the primary product. The equilibrium constant for the reaction $CuCl_2^- + Cl^- = CuCl_3^{2-}$ and the resolved spectra for the two complexes were measured at 3 M ionic strength. The association constant obtained was 1.1 ± 0.1 . $CuCl_3^{2-}$ exhibits a band at 274 nm, believed to be CTTS because of its behavior in different solvents, while $CuCl_2^-$ is transparent at this wavelength. Both complexes absorb at 230 nm, but the nature of this band is unclear. An overall mechanism is proposed and the implications of this system for solar energy conversion are discussed.

In spite of the fact that copper(I) chloride has been used for a great number of photocatalyzed organic reactions, the photochemical behavior of copper(I) complexes in solution has

been given very little attention. Recently it has been reported by Hurst et al.² and by McMillin et al.³ that excitation of metal-ligand charge transfer bands of Cu(I) complexes results