^{19}F NMR Study of the Reaction of *p*-Fluorobenzenethiol and Disulfide with Periodate and Other Selected Oxidizing Agents

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The products of the reactions of both *p*-fluorobenzenethiol and *p*-fluorobenzene disulfide with a series of oxidants were examined using ^{19}F NMR spectroscopy. Two commonly used mild oxidants (periodate and hydrogen peroxide), a "non-oxygen-transfer" oxidant (tetranitromethane(TNM)) and a strong metal oxidant (Au(III)) were examined in several solvent systems. Under the conditions of our experiments disulfides are not oxidized by periodate, peroxide, or TNM. Au(III) is the only reagent that both oxidizes thiols and cleaves disulfides to sulfonic acids at room temperature. In the periodate oxidation of thiols, the products depend on the solvent and can be best explained if the reaction of periodate with a nucleophilic sulfur atom results in the formation of a complex or mixed anhydride. In aqueous dioxane the products are disulfide and thiosulfonate. The thiosulfonate is formed by the reaction of sulfinic acid with sulfenic acid and not from the oxidation of disulfide. In anhydrous ethanol, the products are ethyl sulfinate and the disulfide. We propose that ethyl sulfinate is formed by the reaction of a sulfinic/iodic acid anhydride with ethanol. The products in aqueous ethanol appear to be a combination of the products observed in aqueous dioxane and anhydrous ethanol. A thiosulfinate/periodate complex may also account for ester formation and other products observed during the oxidation of unsymmetrical thiosulfinates. Even though hydrogen peroxide is the most common oxidant for converting a thiol to disulfide, it appears to be one of the poorer reagents to use, since the reaction yields sulfonic acid as well as disulfide. With TNM a sulfenyl nitrite is formed initially and then either reacts with thiol to give disulfide or isomerizes to a nitrosonium sulfenate to give thiosulfinate and thiosulfonate.

Introduction

The oxidation of thiols to disulfides is a reaction of great importance; however, under some conditions higher oxidation products are also obtained. We felt that there was some question whether the oxy acids and/or oxygenated derivatives of disulfides were formed *directly* from aromatic thiols or were formed via a disulfide intermediate. To answer this question the products of the reactions of both *p*-fluorobenzenethiol and *p*-fluorobenzene disulfide with a series of oxidants were examined using ^{19}F NMR. Many oxidants have been used to oxidize thiols and disulfides. We have carried out numerous mechanistic studies using iodine to oxidize thiols[1] and disulfides[2,3] and have also found that iodine is especially effective in the oxidation of dithiols to cyclic disulfides.[4] In this research two other commonly used mild oxidants (periodate and hydrogen peroxide), a "non-oxygen-transfer" oxidant (tetranitromethane(TNM)) and a strong metal oxidant (Au(III)) were examined in several solvent systems. Although periodate is rarely used for the oxidation of thiols, it was of special interest to us since we were initially directed to the question of the direct oxidation of thiols to the corresponding oxy acids by a statement by Sykes and Todd[5] that disulfides were always a common intermediate in periodate oxidations of thiols. Later reviews reiterate the same statement.[6,7] This idea has never been reexamined for periodate, and subsequently it has been applied to other oxidants as well. Field[8] as well as Ohno and Oae[9] infer that disulfides are always formed when thiols are oxidized and that any oxidized disulfides and oxy acids observed were formed only from the disulfides when a strong oxidant was used for a prolonged period of time.

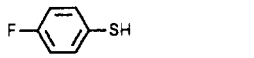
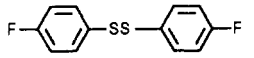
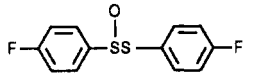
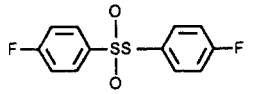
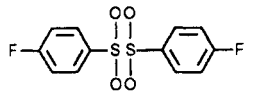
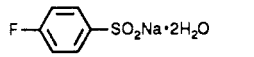
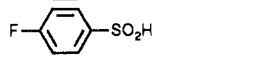
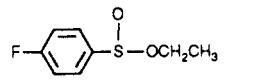
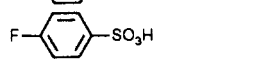
Results and Discussion

The use of *p*-fluorobenzenethiol and it's derivatives to study reactions occurring at the sulfur atom has been successfully used by Chau and Kice,[10] Hogg and Stewart,[11] and Caradonna et al.[12] The ^{19}F probe used requires a concentration of at least 50 mM of fluorinated compound to obtain reasonable spectra in a short period of time. Therefore, almost all reactions were run at this concentration of substrate, normally with a 1:1 mole ratio of substrate to oxidant and then with a 1:5 mole ratio to represent a large excess of oxidant. The fluorine substituent enables the qualitative detection of the reactant and all possible products. The intensities of peaks in the individual ^{19}F NMR spectra are given in the Experimental Section and are relative to the external reference, arbitrarily assigned as 1.0. The external reference was always dissolved in the same solvent system in which the sample was dissolved to determine the chemical shifts more accurately. To confirm the identity of the products, appropriate derivatives were synthesized and purified, and their resonances were determined and compared with those found in the ^{19}F NMR spectrum of a typical reaction mixture. The derivatives were also used to "spike" actual product mixtures to see whether a particular peak or set of peaks was enhanced. A resonance reference guide to the ^{19}F NMR spectra of *p*-fluorothiophenol, *p*-fluorophenyl disulfide, and all the fluorinated oxygenated disulfide and oxyacid derivatives in different solvents is presented in Table I. The reported value of the ^{19}F NMR resonance of the disulfide is quite variable (from δ 107.8 ppm[10] to δ 115.0 ppm[13] in $CDCl_3$ (with reference to standard Freon 11 ($CFCl_3$)). We found a value of δ 114.3 ppm. The thiol

(1) deLeeuw, D. L.; Musker, W. K.; Doi, J. T. *J. Org. Chem.* **1982**, *47*, 4860.
(2) Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1985**, *50*, 1.
(3) Doi, J. T.; Luehr, G. W.; Musker, W. K. *J. Org. Chem.* **1985**, *50*, 5716.
(4) Goodrow, M. H.; Musker, W. K. *Synthesis* **1981**, *6*, 457.
(5) Sykes, P.; Todd, A. R. Committee on Penicillin Synthesis Reports No. 526, 677. Cook, A. H.; Heilbron, I. M. In *The Chemistry of the Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton: New Jersey, 1949; p 927.
(6) Sklarz, B. *Quart. Rev.* **1967**, *21*, 3.
(7) Fatiadi, A. J. In *Synthetic Reagents*; Pizey, J. S., Ed.; Horwood: Chichester, 1981; Vol. 4, Chapter 2.
(8) Field, L. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, 1977; Chapter 7.3.
(9) Ohno, A.; Oae, S. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, 1977; Chapter 4.8.
(10) Chau, M. M.; Kice, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 7711.
(11) Hogg, D. R.; Stewart, J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 436.
(12) Caradonna, J. P.; Harlan, E. W.; Holm, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 7856.
(13) Hergett, S. C.; Peach, M. E. *J. Fluorine Chem.* **1988**, *38*, 367.

0022-3263/90/1955-2337$02.50/0

Table I. Resonances (ppm) of Fluorinated Aryl Sulfur Compounds Relative to Trifluorotoluene[a]

		solvents[b]				
no.	compound	50% EtOH–H_2O	50% dioxane–H_2O	EtOH	$CHCl_3$	10% aqueous NaOH
1		119.08	–	119.22	117.33	124.89
2		115.04	114.69	115.13	114.26	114.09
3		108.12 110.18[c]	108.77 110.41[c]	108.77 110.74[c]	107.84 109.84[c]	*e*
4		103.32 108.14[c]	103.54 108.24[c]	104.56 108.89[c]	103.32 107.65[c]	*e*
10		97.82	–	–	98.32	–
8		113.42	–	114.70	107.61[d]	111.04
9		110.87	–	109.64	106.05[d]	111.98
11		107.63	–	107.89	–	–
7		111.43	111.51	112.79	108.31[d]	109.71

[a] Extremal reference, C_6H_5–CF_3, set at 63.72 ppm relative to $CFCl_3$. [b] All solvents purified by literature methods. Water is triple deionized. [c] Equal heights. [d] Partially soluble. [e] Alkaline hydrolysis producing $ArSO_2^-$ (111.82 ppm) and ArSSAr (114.35 ppm, insoluble).

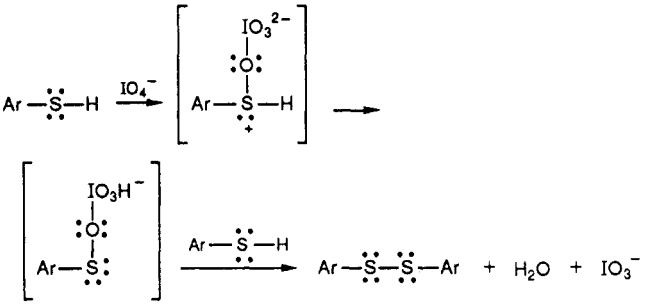
and the disulfide have limited solubility in aqueous solvents, but they dissolve sufficiently to observe an intense signal. The more oxidized products are more soluble and can be detected readily in all solvents used. These experiments were not designed to improve the synthesis of organosulfur compounds since none of the products were isolated. However, one should be able to use this information to realize the potential side reactions that could occur under synthetic conditions.

Oxidations

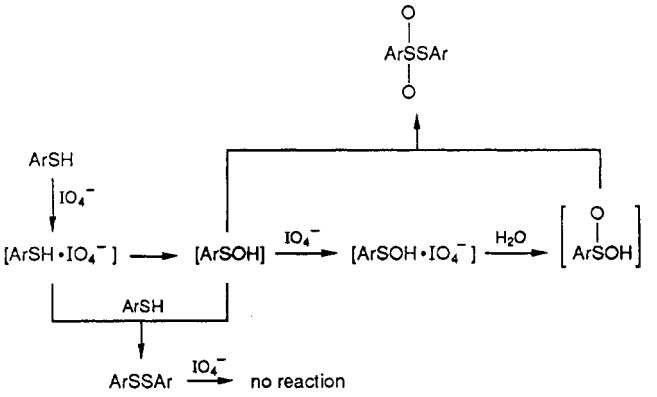
A. Sodium Periodate. 1. 50% Aqueous Dioxane. When the thiol is treated with 5 equiv of periodate in 50% aqueous dioxane at ambient temperature, the major product is the disulfide and the minor product is the thiosulfonate. No reaction occurs when the disulfide is treated with periodate under the same conditions, although when the appropriate are of the NMR is expanded, a trace of thiosulfinate and sulfonic acid are also observed. However, the amounts are so small that their formation can be neglected.

Since periodate is an electrophilic reagent, we believe that the first step is the formation of a mixed anhydride (Scheme I), and the anhydride reacts either with thiol to give disulfide or rearranges to give sulfenic acid (Scheme II). In most discussions of the mechanism of periodate oxidations of sulfur compounds, a direct transfer of oxygen from periodate to sulfur is proposed,[14] but there is one example where a complex between the sulfur atom and the iodine of periodate has also been invoked.[15] To our knowledge a mixed anhydride, where an oxygen atom of periodate is bound to sulfur, has not been proposed before as an intermediate in organosulfur chemistry. We feel that it is necessary to propose the formation of a mixed anhydride to account for many periodate oxidations in a systematic way (vide infra). Periodate complexes are well

Scheme I. Formation of a Sulfenic–Iodic Anhydride and Its Reaction with Thiols

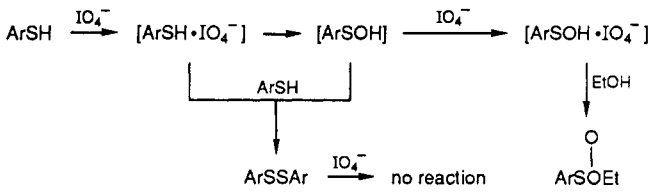


Scheme II. Proposed Mechanistic Scheme for the Reaction of ArSH with Periodate in 50% Aqueous Dioxane



(14) Ruff, F.; Kucsman, Á, *J. Chem. Soc., Perkin Trans. 2*, **1985**, 683.
(15) (a) Oae, S. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1988; Vol. 1, pp 304–335. (b) A complex between the sulfur atom and the iodine of periodate was ruled out since the oxidation of 1,5-dithiacyclooctane with $NaIO_4$ is not accelerated to the same extent as the oxidation with iodine. Evans, B. J.; Doi, J. T.; Musker, W. K. *J. Org. Chem.*, in press.

Scheme III. Proposed Mechanistic Scheme for the Reaction of ArSH with $(n\text{-Bu})_4NIO_4$ in Anhydrous Ethanol



known in the oxidative cleavage of diols.[7]

A sulfenic/iodic acid anhydride or the sulfenic acid can react with unreacted thiol to form disulfide[16] or the sulfenic acid can be oxidized with periodate to give sulfinic acid. Since no sulfinic acid is found, it must react completely with sulfenic acid to form thiosulfonate[16,17] as shown in Scheme II. The oxidation of sulfenic acid to sulfinic acid occurs more rapidly than dimerization[18] to thiosulfinate since the concentration of sulfenic acid is much lower than the concentration of periodate. It has been reported that sulfinic acids react with disulfides to form thiosulfonates,[16] but we found that p-fluorobenzenesulfinic acid does not react with disulfide under our conditions.

2. Anhydrous Ethanol. Because sodium and potassium periodate are insoluble in ethanol, $(n\text{-Bu})_4NIO_4$ was used as the source of periodate. When the thiol is treated with 1 or more equiv of $(n\text{-Bu})_4NIO_4$, the major product is disulfide and the minor product is ethyl p-fluorobenzenesulfinate. When the disulfide is treated with $(n\text{-Bu})_4NIO_4$, no reaction occurs.

To confirm the identity of ethyl p-fluorobenzenesulfinate, the compound was synthesized by treatment of p-fluorobenzenesulfinic acid with ethyl chlorocarbonate in pyridine instead of ethanolysis of p-fluorobenzenesulfinyl chloride. Although the isomeric ethyl sulfone can be formed as a possible impurity, the former method was preferred as the least cumbersome and quickest route to the ethyl ester. The ^{19}F NMR spectrum of the product of the reaction, in either ethanol or 50% aqueous ethanol, showed only one peak, δ 107.89 and 107.63 ppm, respectively. The single peak in this region eliminates the presence of sulfinic acid or any oxy acid or oxidized disulfide (Table I). However, this peak could be due to either the structural isomer, p-fluorophenylsulfone, or ethyl sulfonate which could have formed on atmospheric oxidation of the sulfinate during workup. To rule out these possibilities, the product was hydrolyzed in acid (observed by ^{19}F NMR). Although some ethyl ester remained and a trace of sulfonic acid formed, the major product is sulfinic acid. This is good evidence for the sulfinate ester since sulfones do not hydrolyze and the sulfonate ester would hydrolyze to sulfonic acid. The infrared absorption spectrum was also useful to differentiate the sulfinate ester from the sulfone and sulfonate ester.[19] As shown in 1964,[20] the ^1H NMR data of sulfinate esters provides some interesting structural characteristics due to the prochiral sulfur, but today, using high-field NMR methods, the chemical shifts and coupling constants of sulfinate esters can be determined with great accuracy.[21]

In anhydrous ethanol, the most surprising result is the absence of thiosulfonate (which forms in the periodate oxidation of the thiol in both aqueous ethanol and aqueous dioxane) and the presence of ethyl p-fluorobenzenesulfinate. The first step in the oxidation is the formation of a sulfenic/iodic acid anhydride followed by a reaction with thiol to give disulfide or rearrangement to the sulfenic acid. The sulfenic acid reacts with $(n\text{-Bu})_4NIO_4$ to give the sulfinic/iodic acid anhydride, as shown in Scheme III. The sulfinic/iodic acid anhydride then reacts with ethanol to give the sulfinate ester. It is the formation of the sulfinate ester that required us to invoke mixed anhydrides in these reactions. A rapid reaction of sulfenic acid with ethanol to give ethyl sulfenate, followed by subsequent oxidation to ethyl sulfinate, seems unlikely because esterification of a weak acid (estimated pK_a is 9 for sulfenic acid)[22] would not occur rapidly in the absence of a strong acid catalyst. A mechanism which involves direct oxygen atom transfer from $(n\text{-Bu})_4NIO_4$ to the sulfenic acid to give sulfinic acid followed by rapid reaction with ethanol to give ethyl sulfinate does not occur because dissolution of the sulfinic acid in anhydrous ethanol does not result in ester formation. In addition, we have found that the sulfinate ester is not formed on oxidation of the thiol with a known oxygen transfer reagent, hydrogen peroxide, in ethanol (vide infra.).

Sulfinate esters are also formed by oxidation of aromatic disulfides with lead tetraacetate.[23] Although several mechanisms were proposed, it is possible that a sulfinate/acetate anhydride intermediate is formed and reacts with ethanol to give the ester. Perhaps mixed anhydrides are often formed during the oxidation of thiols and their derivatives to oxy acids. We have evidence for the formation of cyclic mixed anhydrides during anchimerically assisted disulfide oxidation.[3]

3. 50% Aqueous Ethanol. Treatment of the thiol with 1 equiv of periodate in 50% aqueous ethanol gives disulfide and a small amount of thiosulfonate and ethyl p-fluorobenzenesulfinate. We were surprised by the formation of the ester in the presence of water; however, the composition of the reaction mixture in aqueous ethanol appears to be a combination of the products observed in aqueous dioxane and anhydrous ethanol (Schemes I and II). As before, we believe that the ester is formed by reaction of ethanol on the sulfinic/iodic acid anhydride. In aqueous ethanol other paths are possible involving oxy acids and thiosulfonate precursors; however, dissolution of sulfinic acid or thiosulfonate in 50% aqueous ethanol does not give the ester. Although thiosulfinates have been shown to thermally disproportionate to thiosulfonate and disulfide,[16] when p-fluorobenzenethiosulfinate is warmed under our reaction conditions, only trace amounts of disproportionation products are formed.

(16) Kice, J. L. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, K., Eds.; Academic: New York, 1980; Vol. 17, pp 65–181 and references therein.

(17) Allan, R. D.; Barton, D. H. R.; Girijavallabhan, M.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1456.

(18) Davis, F. A.; Friedman, A. J.; Nadir, U. K. *J. Am. Chem. Soc.* **1978**, *100*, 2844 and references therein.

(19) The S–O stretching vibration of ethyl p-chlorobenzenesulfinate occurs at 1136 cm^{-1}. Likewise the p-CH_3, p-CH_3O, p-Br, and p-NO_2 homologues all absorb between 1126 and 1138 cm^{-1} (Kobayashi, M.; Nobuko, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1788). Sulfonate esters are characterized by absorptions at 1350, 1175, and between 1000 and 750 cm^{-1} while sulfones are characterized by absorptions at 1150 and 1300 cm^{-1}. The product has strong absorption bands at 1136 and 1012 cm^{-1} which support the structure of the sulfinate ester.

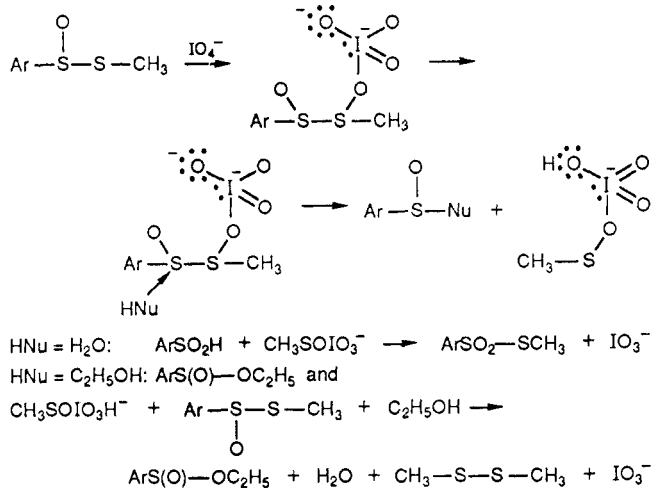
(20) Wilt, J. W.; Wagner, W. J. *Chem. Ind. (London)* **1964**, 1389.

(21) The triplet at 1.29 ppm due to the methyl group is actually two overlapping doublets with equal coupling constants. The two multiplets at 3.75 and 4.12 ppm are assigned to the two protons on the methylene carbon which are diastereotopic and thus inequivalent even though they are two atoms away from the prochiral sulfur.[13] The complete spectrum of ethyl p-fluorobenzenesulfinate and a detailed portion from 3.7 to 4.2 ppm are given as supplementary material.

(22) Hogg, D. R. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon: Oxford, 1979; Vol. 3, Chapter 11.16, and references therein.

(23) Field, L.; Hoelzel, C. B.; Locke, J. M. *J. Am. Chem. Soc.* **1962**, *84*, 847.

Scheme IV. Formation of a Periodate/Thiosulfinate Complex and Its Reaction with Nucleophiles



HNu = H_2O: $ArSO_2H + CH_3SOIO_3^- \rightarrow ArSO_2{-}SCH_3 + IO_3^-$

HNu = C_2H_5OH: $ArS(O){-}OC_2H_5$ and

$CH_3SOIO_3H^- + Ar{-}S(O){-}S{-}CH_3 + C_2H_5OH \rightarrow$

$ArS(O){-}OC_2H_5 + H_2O + CH_3{-}S{-}S{-}CH_3 + IO_3^-$

The products of our reaction are similar to those reported by Ciuffarin et al.[24] who found that when methyl toluene-*p*-sulfenate in dioxane is treated with an acid catalyst and a trace of water, the products are the corresponding methyl sulfinate ester and disulfide (eq 1), whereas in solutions containing larger amounts of H_2O, the products are thiosulfonate and disulfide (eq 2). The

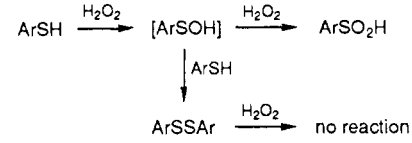
$$3ArSOMe + H_2O \xrightarrow{H^+} ArS(O)OMe + ArSSAr + 2MeOH \quad (1)$$

$$4ArSOMe + 2H_2O \xrightarrow{H^+} ArS(O)_2SAr + ArSSAr + 4MeOH \quad (2)$$

functional groups that form in the "absence" and presence of H_2O in acidic dioxane are similar to the functional groups we observed in anhydrous ethanol and in aqueous ethanol, with the exception of a trace of thiosulfinate they observed in the presence of water. Acid is essential for the rapid hydrolysis reactions (eqs 1 and 2) since displacement occurs on the protonated methyl sulfenates. Since no acid is present in our reactions the products which we obtain cannot come from the disproportionation of ethyl *p*-fluorobenzenesulfenate.

There is one other example of the formation of a sulfinate ester in the presence of aqueous periodate in aqueous alcohol.[25] The treatment of an unsymmetrical thiosulfinate, $ArS(O)SCH_3$, with periodate in aqueous ethanol for 5–9 h gives an unsymmetrical thiosulfonate, $ArS(O)_2SCH_3$, and only one sulfinate ester, $ArS(O)OC_2H_5$. This reaction is much slower than thiol oxidation by periodate, so it could not account for our products. Oae et al.[25] uses periodate as a nucleophile to account for these "anomalous" oxidation products, but we feel that it is more consistent to keep periodate in its electrophilic capacity[14] and propose that periodate reacts with the sulfenyl sulfur to give a thiosulfinate/periodate complex (Scheme IV). When ethanol attacks the adjacent sulfinyl sulfur, the sulfur–sulfur bond is cleaved and the sulfinate ester, $ArS(O)OC_2H_5$, and methanesulfenic/iodic acid anhydride are formed. Attack by water on the thiosulfinate/periodate complex gives sulfinic acid and the methanesulfenic/iodic acid anhydride, and these two compounds react together to give the unsymmetrical thiosulfonate and iodate. Thus, the asymmetry of the thiosulfinate/periodate complex accounts for the "anomalous" oxidation of unsymmetrical thiosulfinates with periodate to give the unsymmetrical thiosulfonates. Attack of water on the thiosulfinate/periodate complex as described above would give the thiosulfonate without scrambled products. In contrast, peracid oxidants which also attack the sulfenyl sulfur form an α-disulfoxide which rearranges rapidly to give scrambled thiosulfonates.[10,16,26-28] α-Disulfoxides have been observed as intermediates by ^{13}C NMR spectroscopy when sulfinyl chlorides were treated with lithium tributyltin.[29]

Scheme V. Proposed Mechanistic Scheme for the Treatment of ArSH with H_2O_2 in 50% Ethanol–Water



4. Chloroform. The major product of the reaction of $(n\text{-}Bu)_4NIO_4$ with thiol in chloroform is disulfide with only a trace of thiosulfonate and sulfonic acid. In this nonnucleophilic solvent the sulfenic/iodic acid anhydride is predominantly cleaved by thiol to give disulfide, but, since water is a product of this reaction, small amounts of sulfenic acid are also formed. Thus the trace of higher oxidized products undoubtedly results from further oxidation of sulfenic acid as discussed earlier.

B. Hydrogen Peroxide. 1. 50% Aqueous Ethanol. Use of hydrogen peroxide instead of periodate in 50% aqueous ethanol gives dramatically different results. When 1 equiv of hydrogen peroxide is used most of the thiol remains unreacted, but a small amount of disulfide and trace of sulfinic acid had formed. When the solution is heated, more disulfide and traces of both sulfinic and sulfonic acid are formed. When the disulfide is treated with hydrogen peroxide under the same conditions, no reaction occurs even when the solution is warmed. We were surprised that the disulfide was inert to hydrogen peroxide since thiosulfinates or thiosulfonates are known to be formed using this reagent.[30] Perhaps these products would have been detected if the reaction was observed for a much longer period of time.

These results are different from periodate oxidations in that neither thiosulfonate nor sulfinate ester is formed. If there is a slow oxidation of thiol to sulfenic acid, such that the sulfenic acid concentration never builds up to any appreciable amount, the sulfenic acid can either react with unreacted thiol (which is always present in high concentration since the reaction does not go to completion) to form disulfide or oxidize to sulfinic acid, as shown in Scheme V. The sulfinic acid does not further oxidize to sulfonic acid unless the solution is warmed. Even with excess hydrogen peroxide the reaction does not proceed to completion at room temperature. However when the solution is heated, the amount of disulfide and sulfonic acid increases and only a small amount of thiol remains.

It appears that disulfides are more easily oxidized with MCPBA in chloroform at 0 °C than with hydrogen peroxide in aqueous ethanol since we used this method to prepare our standards in less than 1 h. We also examined

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the reaction of the disulfide with excess MCPBA in $CHCl_3$ by ^{19}F NMR spectroscopy and found that many of the peaks which developed were different from those we had observed before. The peaks that could be assigned were those of the thiosulfonate and the α-disulfone but the major peak was a singlet at 36.74 ppm and the next most intense peak was another singlet at 41.15 ppm. Since we were unable to synthesize known compounds which absorbed at these resonances we are unable to make an assignment. Possible species could be the sulfonic acid anhydride and mixed anhydrides between sulfur oxy acids and aromatic acids. It is unlikely that an α-disulfoxide would be detectable since they are observed only at low temperature.[28,29]

2. Anhydrous Ethanol. When the thiol is treated with 5 equiv of hydrogen peroxide in anhydrous ethanol the major component is unreacted thiol and the minor component is disulfide. No sulfinate ester is formed. When the solution is warmed the amount of disulfide, sulfinic acid, and sulfonic acid increases. When the disulfide is oxidized under identical conditions, no reaction occurs, even after warming. Since the oxidation products in anhydrous ethanol are similar to those observed in aqueous ethanol (Scheme V) the paths must be similar.

3. In 10% Aqueous NaOH. Since both the thiol and disulfide are sparingly soluble in H_2O, we decided to examine the reaction under basic conditions where the thiol would be more soluble. When 1 equiv of thiolate is treated with 1 equiv of hydrogen peroxide in 10% aqueous NaOH, the same products are formed as found in neutral solution. When the thiolate is treated with excess hydrogen peroxide, sulfinate is the major product along with disulfide, sulfonate, and unreacted thiolate. When the solution is warmed for 15 min all the thiolate reacts, and the major product is sulfonate with minor amounts of disulfide and sulfinate. Oxidation of thiol by air in aqueous NaOH did not occur in an hour in the absence of any oxidizing agent. The potential products, thiosulfinate and thiosulfonate, are not stable in base,[31,32] but since they do not form with neutral peroxide, there is no reason to think that they are formed and then hydrolyzed in base.

C. Tetranitromethane in Anhydrous Ethanol. Tetranitromethane (TNM) is a rather strong oxidant which has been used in the oxidation of cysteine.[33]

When 1 equiv of thiol in anhydrous ethanol is treated with 1 equiv of TNM, a clear, pale yellow solution forms which contains mostly unreacted thiol, disulfide, and a small amount of thiosulfinate. The solution becomes dark yellow when it is warmed for 15 min, and the mixture consists mainly of disulfide with small amounts of thiosulfinate and thiosulfonate. The dark yellow color imparted to the solution is due to the formation of nitroformate anion $[C(NO_2)_3]^-$. Under the same conditions, the disulfide does not react.

The mechanism of the formation of thiosulfinate and thiosulfonate presumably involves the formation of sulfenyl nitrite as the active intermediate (eq 3). The sulfenyl nitrite predominantly reacts with thiol to form disulfide, the major product, with the loss of nitrous acid (eq 4).[33,34] However, we believe that both thiosulfinate and thiosulfonate are formed via a nitro–nitrite isomerization (eq 5).

$$RSH + C(NO_2)_4 \rightarrow RSNO_2 + HC(NO_2)_3 \quad (3)$$

$$RSNO_2 + RSH \rightarrow RSSR + H^+ + NO_2^- \quad (4)$$

$$RSNO_2 \rightarrow RSONO \quad (5)$$

Nitro–nitrite isomerizations are well known[35] in carbon chemistry and could occur in sulfur chemistry as a sulfenyl nitrite ($ArSNO_2$)–nitrosonium sulfenate (ArSONO) isomerization. The nitrosonium sulfenate (ArSONO) could then react with thiol to give thiosulfinate and nitrous acid or homolytically cleave to give the sulfenyl radical. The dimerization of sulfenyl radicals has often been proposed to give thiosulfonate.[16]

D. Au(III) in 50% Aqueous Dioxane. Since it was reported that Au(III) oxidizes cystine, homocystine, and penicillamine disulfide to the sulfonic acids in aqueous solution,[36] it was of interest to determine if sulfonic acid is the only oxidation product when an aromatic thiol is treated with Au(III). When thiol is treated with $HAuCl_4 \cdot 3H_2O$ in 50% aqueous dioxane at ambient temperature both sulfonic acid and thiosulfonate are formed. When the disulfide is treated with $HAuCl_4 \cdot 3H_2O$ under the same conditions, the results were identical to those observed for the thiol. This is the first case where the disulfide is readily oxidized by the oxidant.

We suggest that when the thiol is treated with Au(III), an ArSH/Au(III) complex is formed which is attacked by thiol to give the disulfide, Au(I), and two protons or by water to give sulfenic acid, Au(I), and two protons. Further oxidation of sulfenic acid gives sulfinic acid and sulfonic acid. When the disulfide is treated with Au(III) it gives an ArSSAr/Au(III) complex which can be attacked by water to give sulfenic acid and an ArSH/Au(III) complex. The thiosulfonate may be produced either by direct oxidation of the disulfide or from the reaction of sulfenic acid with sulfinic acid. The Au(I) which is formed probably disproportionates to Au(III) and Au(0) (eq 6) since colloidal gold is observed during the reaction.[37]

$$3Au^+(aq) \rightarrow Au^{3+} + 2Au(s) \qquad K \approx 10^{10} \quad (6)$$

An alternate path[38] involves the transfer of "positive" chlorine from $AuCl_4^-$ to the sulfur atom of either the thiol to form the sulfenyl chloride, ArSCl, or the disulfide to form $ArSSAr \cdot Cl^+$, followed by hydrolysis to give the observed products. There is a two-electron oxidation of sulfur and reduction of $AuCl_4^-$ to $AuCl_3^{2-}$.

Conclusion

Au(III) is the only reagent that both oxidizes thiols and cleaves disulfides at room temperature and thus is the only oxidant for which the disulfide could be the common intermediate. With periodate in anhydrous ethanol, we propose that a sulfinic–iodic acid anhydride forms which reacts with ethanol to give ethyl sulfinate. The composition of the products of the reaction of thiol with periodate in aqueous ethanol appears to be a combination of the products observed in aqueous dioxane and anhydrous ethanol. The thiosulfonate is formed by the reaction of sulfinic acid with sulfenic acid and not by the oxidation of disulfide. A thiosulfinate/periodate complex may also

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account for ester formation during the oxidation of unsymmetrical thiosulfinates. The intermediate which accounts for the products of thiol oxidation with peroxide is sulfenic acid which reacts with thiol to give disulfide or with peroxide to give sulfinic acid. Even though hydrogen peroxide is the most common oxidant for converting a thiol to disulfide,[39-44] it appears to be one of the poorer reagents to use, since the reaction yields sulfonic acid as well as disulfide. With TNM in anhydrous ethanol, the sulfenyl nitrate appears to be the active intermediate which reacts with thiol to give disulfide or isomerizes to a nitrosonium sulfenate in order to obtain thiosulfinate and thiosulfonate. Under the conditions of our experiments, periodate, peroxide, and TNM do not oxidize disulfides, and thus the disulfide cannot be a common intermediate.

Experimental Section

Melting points were obtained on a Thomas-Hoover Uni Melt capillary melting point apparatus and/or on a Nalge Polarized Hot-Stage microscopic melting point apparatus and are uncorrected. Thin-layer chromatograms were obtained using either Eastman Kodak siliga gel F_{254} TLC sheets or DC-Plastikfolien Kieselgel 60 F_{254} (0.2 mm thickness).

Spectral Data. Ultraviolet–visible spectra were recorded on a Hewlett-Packard Model 8450A UV–vis spectrophotometer. Solution spectra were obtained using 1-mm matched quartz cells purchased from Helma Optics. Solvents used were of HPLC quality. Infrared spectra were obtained on an IBM FTIR-32 spectrometer continuously purged with N_2 and absorption values are given in cm^{-1}. Low-field ^1H NMR were recorded on a Varian EM-390 90-MHz continuous wave spectrometer. High-field ^1H were recorded on a General Electric QE-300 FT spectrometer at 300 MHz with a 7.0 T superconducting magnet. All resonance values are listed in ppm referenced downfield to internal tetramethylsilane in the indicated deuterated solvent. Coupling constants, J, are given in hertz with aryl protons ortho to S or $S(O)_n$ designated as H_a and $H_{a'}$, and aryl protons ortho to fluorine designated as H_b and $H_{b'}$. Computerized spectrum simulations were performed using a Nicolet NMC-1280 software program entering in the required number of spins, nucleus identifiers, spectrometer frequency, display width and offset, resonances, coupling constants, and Lorentzian line width. ^{19}F NMR spectroscopy were recorded on a Nicolet NT-200 FT spectrometer operating at 188.234 MHz using a 4.7 T superconducting magnet and a ^{19}F, 12-mm probe. Recordings were done at ambient temperature, were nonspinning, and were proton coupled. Line fits varied from 3 to 24 Hz depending on the compound, solvent system, and magnet shimming, and thus F–H coupling was not seen. Line fits for the external reference, α,α,α-trifluorotoluene (TFT), averaged around 3–9 Hz while the fluorinated sulfur containing sample was higher, often around 20 Hz. Only a singlet with a wide base (usually about 10 Hz) and narrow upper peak was observed for each fluorine resonance. 8 K data points were used to represent a 12.195-kHz sweep width. Unless otherwise stated, all resonance values are listed in ppm and were continuously referenced (to avoid drifting) to external TFT diluted in the same solvent system as the sample. TFT was referenced at −63.72 ppm relative to the commonly used $CFCl_3$ (Freon 11) at 0.00 ppm.[45] By convention, peaks appearing upfield of a specific reference are reported as positive and those appearing downfield of the reference are reported as negative. High- and low-resolution gas chromatographed mass spectra were obtained on a Hewett-Packard gas chromatograph using a DB 1 column, flow rate of about 35 cm/s, and a vacuum gauge mass spectrometer.

Chemicals. Except as noted below, all commercial solvents used were analytical reagent grade and used without further purification. All commercially obtained reagents and starting materials were of reagent grade or better and were used without further purification. p-Fluorobenzenethiol was commercially available. p-Fluorophenyl disulfide, S-p-fluorophenyl p-fluorobenzenethiosulfinate and S-p-fluorophenyl p-fluorobenzenethiosulfonate were prepared by the method of Chau and Kice.[10] p-Fluorophenyl α-disulfone was prepared by a modification of Denzer et al.[46] and Kice and Kasperek.[47] p-Fluorobenzenesulfonyl chloride and sodium p-fluorobenzenesulfonate dihydrate were prepared by the method of Dumont and Rumpf.[48] p-Fluorobenzenesulfonic acid was prepared by a modification of the method of Olah and Pavlath.[49] Tetra-n-butylammonium periodate was prepared by a modification of the method of Santaniello et al.[50]

Ethyl p-fluorobenzenesulfinate was prepared using a modification of the method of Kobayashi and Terao.[51] Ethyl chloroformate (2.50 g, 2.30×10^{-2} mol) was slowly added dropwise to an ice-cooled, stirring mixture of p-fluorobenzenesulfinic acid (3.07 g, 1.92×10^{-2} mol) in 20 mL of pyridine. HCl and CO_2 evolution occurred immediately. Toward the end of the addition, the mixture became homogeneous and a fine brown solid precipitated. The mixture was stirred for 30 min, mixed with 25 mL of H_2O, and extracted two times with 20 mL of petroleum ether, and the aqueous layer was discarded. The petroleum ether layer was washed two times with 25 mL of 1 M HCl and then two times with 20 mL of H_2O. The aqueous layer was checked by TLC for residual ester and found to contain none. The petroleum ether layer was then dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to yield 12% (0.432 g) of the ester as a pale yellow oil: TLC R_f = 0.72 (5% EtOH in $CHCl_3$); FTIR (neat on NaCl) 2984 (w), 1590 (s), 1492 (s), 1230 (m), 1136 (s), 1012 (m), 884 (m), 838 (m), 717 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, line fit = 0.72 Hz) δ 7.723 (m, 2 H, $J^o(H_a-H_b)$ = 8.5 $J^m(H_a-F)$ = 5.0 $J^m(H_a-H_{a'})$ = 3.0, $J^p(H_a-H_{b'})$ = 0.3) and 7.224 (m, 2 H, $J^o(H_b-H_a)$ = 8.5, $J^o(H_b-F)$ = 8.5, $J^m(H_b-H_{b'})$ = 3.0, $J^p(H_b-H_{a'})$ = 0.3) AA'BB'X spin system, 4.120 (overlapping qd, 1 H, H_aCH synclinal to sulfur and nearer the side of the sulfinyl oxygen, $J(H_{gem})$ = 10.0, $J(H-CH_3)$ = 7.1), 3.743 (overlapping qd, 1 H, HCH_b synclinal to sulfur and nearest the side of aryl group, $J(H_{gem})$ = 10.0, $J(H-CH_3)$ = 7.1), 1.294 (dd, 3 H, $J(CH_3-H_a)$ = 4.5, $J(CH_3-H_b)$ = 4.5, CH_3); computor simulation of aryl protons using a line fit of 0.72 Hz at 300 MHz frequency yielded the exact same line pattern entering δ H_a 7.723 (m, $J^o(H_a-H_b)$ = 8.5, $J^m(H_a-F)$ = 5.0, $J^m(H_a-H_{a'})$ = 3.0, $J^p(H_a-H_{b'})$ = 0.3) and d H_b 7.224 (m, $J^o(H_b-H_a)$ = 8.5, $J^o(H_b-F)$ = 8.5, $J^m(H_b-H_b)$ = 3.0, $J^p(H_b-H_{a'})$ = 0.3) AA'BB'X spin system; ^{19}F NMR (EtOH) δ 107.89 (a trace of $ArSO_2SAr$, δ 103.86 and 108.17 was detected, most likely an impurity from the $ArSO_2H$ starting material) (aqueous EtOH) δ 107.63; high-resolution gas chromatographed mass spectrum m/e (relative intensity) for $C_8H_9FO_2S$ 188.02975 (49.0, M^+, calculated 188.03072), 159.99742 (52.7, $FC_6H_4SO_2$ + H), 143.99762 (13.9, FC_6H_4SO + H), 127.00275 (7.6, FC_6H_4S), 96.03708 (96.0, FC_6H_4 + H), 83.94832 (100, FSS + H).

Acidic Hydrolysis of Ethyl p-Fluorobenzenesulfinate. Heating ethyl p-fluorobenzenesulfinate for 1 h at 60 °C in 4.0 mL of aqueous ethanol with 1 equiv of HCl (0.20 mL of 1.0 M HCl) resulted in no change in the ^{19}F NMR spectrum of the solution (δ 107.67). To the same sample, after adding 0.20 mL of 6 M HCl and heating for 45 min at 65 °C, the ^{19}F NMR spectrum of the solution contained signals at δ 107.54 (unhydrolyzed ArS(O)OEt), 109.32 ($ArSO_2H$), and 111.01 ($ArSO_3H$). The peak at δ 109.32 was shown to be due to $ArSO_2H$ in aqueous acid by mixing 4.0 mL of 50 mM $ArSO_2H$ (δ 111.24) with 0.40 mL of 1 M HCl and

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observing that the peak shifted to δ 109.63 (also forming a trace of $ArSO_3H$ (δ 111.02)).

General Procedure for the Determination of the ^{19}F NMR Resonances of Fluorinated Aryl Sulfur Compounds. The ^{19}F NMR spectra were obtained in each of the following solvent systems: 50% (unless otherwise stated) aqueous ethanol, anhydrous ethanol, 50% aqueous dioxane and 10% aqueous NaOH (see Table I). All solvents were purified by standard procedures. The ^{19}F NMR shift values of thiosulfinate and thiosulfonate were not determined in 10% aqueous NaOH because alkaline hydrolysis produces the corresponding sulfinate and disulfide.[31,32] Neither the α-disulfone nor the sulfinate ester were determined in 10% aqueous NaOH because of the potential for alkaline induced hydrolysis (the α-disulfone forms sulfinate and sulfonate and the sulfinate ester hydrolyzes to sulfinate and ethanol). Typically, an unmeasured quantity in an excess of 1×10^{-4} mol of sample was added to 4.0 mL of solvent, mixed and/or gently warmed to maximize dissolution if not fully dissolved. An external reference of TFT in the same solvent as the sample was always referenced at −63.72 ppm to avoid any spectrometer drift.

General Procedure for the ^{19}F NMR Reactions of p-Fluorobenzenethiol and p-Fluorophenyl Disulfide. Because oxidations were run in different solvents with various oxidants, reaction conditions varied such that an experimental description is required for all of the different reactions. Unless otherwise stated, reaction mixtures consisted of 4.0 mL of solutions which were 50 mM in ArSH (0.025 g) or 50 mM in ArSSAr (0.049 g) which were placed in the NMR tube and to which were then added one of the following oxidants: $(n\text{-Bu})_4NIO_4$, $NaIO_4$, H_2O_2, MCPBA, tetranitromethane, or chloroauric acid trihydrate such that the final solution was 50 or 250 mM in the oxidant. Intensities of peaks are given in parenthesis and are relative to the external reference arbitrarily assigned as 1.0. This only provides relative peak height information for each *individual* spectrum. Reactions were warmed by placing the capped NMR tube in a warmed water bath at the given temperature and for the stated length of times, but most reactions were carried out at ambient temperature.

1. $NaIO_4$ or $(n\text{-Bu})_4NIO_4$. (a) In 50% Aqueous Dioxane. The thiol was dissolved in 2.0 mL of dioxane and mixed with a solution containing 5 equiv of $NaIO_4$ in 2.0 mL of H_2O. The resulting orange solution which contained a yellow precipitate was diluted by adding 4.0 mL of dioxane followed by 4.0 mL of H_2O. The solution was centrifuged, and the clear orange solution exhibited the following ^{19}F NMR signals: δ 114.54 (11.8, ArSSAr) and 103.30 and 108.00 (4.6 each, $ArSO_2SAr$). When the disulfide was mixed with 5 equiv of $NaIO_4$ in the same manner as above, no reaction occurred.

(b) In 50% Aqueous Ethanol. The thiol plus 1 equiv of $NaIO_4$ yielded a yellow suspension to which 4.0 mL more solvent was added. The resulting solution which was cloudy exhibited the following ^{19}F NMR signals: δ 114.77 (2.3, ArSSAr), 103.04 and 107.62 (0.12 each, $ArSO_2SAr$), 107.80 (0.34, ArS(O)OEt). With 5 equiv of periodate the suspension (diluted by adding an additional 4.0 mL of 50% aqueous ethanol) was centrifuged, and the clear orange solution exhibited the following ^{19}F NMR signals: δ 114.88 (7.4, ArSSAr), 103.18 and 108.01 (1.3 and 1.6, $ArSO_2SAr$), 107.75 (2.5, ArS(O)OEt) and 111 (trace, $ArSO_3H$).

When the disulfide was mixed with 1 equiv of periodate in 50% aqueous ethanol, no reaction occurred. When heated for 45 min at 60 °C, the solution became pale yellow in color and exhibited the following ^{19}F NMR signals: δ 114.90 (17.6, ArSSAr), 108.17 and 110.23 (1.6 and 1.2, ArS(O)SAr), 103.37 and 107.91 (0.40 each, $ArSO_2SAr$).

(c) In Anhydrous Ethanol. The thiol was mixed with 1 equiv of $(n\text{-Bu})_4NIO_4$ to give a clear solution which exhibited the following ^{19}F NMR signals: δ 115.25 (3.5, ArSSAr) and 108.68 (0.97, ArS(O)OEt). When 5 equiv of periodate were used and the mixture was heated for 30 min at 55–60 °C the same products were formed. The disulfide did not react, even when the mixture was warmed for 15 min at 60 °C.

(d) In $CHCl_3$. The thiol was mixed with 1 equiv of $(n\text{-Bu})_4NIO_4$ to give a clear yellow solution which exhibited the following ^{19}F NMR signals: δ 117.43 (0.6, ArSH), 114.31 (1.7, ArSSAr), and 112.72 (0.07, $ArSO_3H$). Upon warming for 30 min at 60 °C, the clear orange solution exhibited the following ^{19}F NMR signals: δ 114.30 (2.1, ArSSAr), 112.75 (0.12, $ArSO_3H$), and 103.18 and 107.54 (0.21 and 0.17, $ArSO_2SAr$). When the disulfide was mixed with 1 or 5 equiv of $(n\text{-Bu})_4NIO_4$, a clear, pale yellow solution was obtained but no reaction occurred, even on heating.

2. H_2O_2. (a) In Aqueous Ethanol. One equivalent of hydrogen peroxide was mixed with the thiol. The resulting slightly cloudy white suspension exhibited the following ^{19}F NMR signals: δ 118.96 (7.3, ArSH), 114.79 (1.3, ArSSAr), and 112.80 (0.09, $ArSO_2H$ which increased when spiked with sulfinic acid). When a sample was heated for 15 min at 60 °C the following ^{19}F NMR signals were observed: δ 119.11 (4.8, ArSH), 114.90 (2.7, ArSSAr), 113.01 (0.17, $ArSO_2H$), and 111.68 (0.17, $ArSO_3H$) which increased when spiked with sulfonic acid.

The disulfide was mixed with 1 equiv of hydrogen peroxide and further diluted with 8.0 mL of aqueous ethanol to produce a clear solution and an oily residual disulfide layer. No compound, other than the disulfide, was found in the solution. No reaction occurred when the solution was heated for 20 min at 60 °C.

(b) In Anhydrous Ethanol. The thiol was mixed with 5 equiv of hydrogen peroxide to give a solution which exhibited the following ^{19}F NMR signals: δ 119.20 (11.0, ArSH) and 115.04 (1.9, ArSSAr). When heated for 15 min at 60 °C, the solution exhibited the following ^{19}F NMR signals: δ 119.18 (3.3, ArSH), 115.03 (4.4, ArSSAr), 112.88 (1.3, $ArSO_3H$), and 110.11 (0.44, $ArSO_2H$), which increased when spiked with a small amount of sulfinic acid. Both solutions were clear, colorless, and homogeneous.

The disulfide gave no reaction when mixed with five equivalents of peroxide. No change was observed when the clear, colorless solution was heated for 15 min at 60 °C.

(c) In 10% Aqueous NaOH. A 50 mM solution of the thiol in 4.0 mL of 10% aqueous NaOH gave a cloudy white suspension which showed only the resonance of the thiolate anion, ArSNa (δ 123.32). An external capillary reference of TFT in D_2O was used for this solvent system, and this same reference was used for all 10% aqueous NaOH experiments. Since the external reference was so large relative to the peaks observed in the sample, each reference peak was plotted at a height of 39.9 cm, and the relative peak heights are multipled by 10^3.

Hydrogen peroxide (1 equiv) was mixed with the thiol to give a cloudy white suspension which exhibited the following ^{19}F NMR signals: δ 123.63 (6.26, ArSNa), 113.20 (4.5, ArSSAr, which increased when spiked with disulfide), and 111.05 (1.5, $ArSO_2Na$, which increased when spiked with sulfinic acid). When 5 equiv of peroxide were used similar results were obtained except for a new peak at 108.87 (4.8, $ArSO_3Na$).

3. MCPBA. (a) Chloroform. The disulfide was mixed with 4 equiv of MCPBA to give a clear, colorless solution which exhibited the following ^{19}F NMR signals: δ 107.66 and 103.33 (0.08 each, $ArSO_2SAr$), 104.87 (0.43, unidentified), 101.48 (0.08, unidentified), 100.47 (0.93, unidentified), and 98.20 (0.22, $ArSO_2SO_2Ar$).

4. $C(NO_2)_4$. (a) Anhydrous Ethanol. The thiol was mixed with 1 equiv of $C(NO_2)_4$ to give a clear, pale yellow solution which exhibited the following ^{19}F NMR signals: δ 118.55 (1.0, ArSH), 114.43 (0.27, ArSSAr), and 108.04 and 110.07 (0.15 and 0.13, ArS(O)SAr). Upon heating for 15 min at 55 °C, the solution became dark yellow and exhibited the following ^{19}F NMR signals: δ 114.40 (1.0, ArSSAr), 108.12 and 110.06 (0.32 and 0.26, ArS(O)SAr), and 103.80 and 107.87 (0.22 each, $ArSO_2SAr$).

The disulfide did not react even after heating for 15 min at 60 °C.

5. $HAuCl_4 \cdot 3H_2O$. (a) In 50% Aqueous Dioxane. $HAuCl_4 \cdot 3H_2O$ (3.3 equiv) was weighed out in a N_2 dry box, dissolved in 2.0 mL of H_2O, and mixed with 1 equiv of thiol dissolved in 2.0 mL of dioxane. After sitting for 17 h at room temperature in the dark, the clear, golden colored solution contained a trace of purple precipitate and exhibited the following ^{19}F NMR signals: δ 111.18 (13.2, $ArSO_3H$), and 103.35 and 108.11 (4.7 each, $ArSO_2SAr$).

The disulfide was dissolved in 3.0 mL of dioxane and mixed with 3.3 equiv of $HAuCl_4 \cdot 3H_2O$ dissolved in 2.0 mL of H_2O to give a pale, golden-colored solution after 17 h at room temperature in the dark. The solution exhibited the following ^{19}F NMR signals: δ 111.83 (8.9, $ArSO_3H$) and 103.74 and 108.39 (10.6 each, $ArSO_2SAr$).

6. Other Reactions of p-Fluorophenyl Disulfide S-p-Fluorophenyl p-Fluorobenzenethiosulfinate or p-Fluoro-

benzenesulfinic Acid. In Aqueous Ethanol. (a) Treatment of ArSSAr with $ArSO_2H$. A 50 mM (36 μL, 0.04905 g) solution of *p*-fluorophenyl disulfide in 2.0 mL of EtOH was mixed with 2.0 mL of H_2O. The disulfide was only partially soluble as most of the oil settled to the bottom of the tube. To this was added 50 mM (0.23050 g) *p*-fluorobenzenesulfinic acid. No reaction occurred.

(b) Stability of ArS(O)SAr to Disproportionation. A sample of *S*-*p*-fluorophenyl *p*-fluorobenzenethiosulfinate was dissolved in 4.0 mL of aqueous ethanol to give a solution which exhibited the following ^{19}F NMR signals: δ 114.72 (0.06, ArSSAr), 107.92 and 109.95 (2.4 each, ArS(O)SAr), and 103.03 and 107.90 (0.04 each, $ArSO_2SAr$). After heating at 60 °C for 30 min, there was very little change: δ 114.76 (0.2, ArSSAr), 107.99 and 110.04 (2.6 each, ArS(O)SAr), and 103.10 (0.11 each, $ArSO_2SAr$).

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Supplementary Material Available: ^1H NMR spectra of ethyl *p*-fluorobenzenesulfinate (2 pages). Ordering information is given on any current masthead page.

Effects of Mass Transfer and Extraction of Quaternary Salts on a Substitution Reaction by Phase-Transfer Catalysis

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The substitution reaction of hexachlorocyclotriphosphazene with 2,2,2-trifluoroethanol using quaternary ammonium salts as the phase-transfer catalysts in an organic solvent/alkaline solution has been investigated. The pseudo-first-order reaction rate constant of the two-phase reaction and the rate constant ratios of the sequential substitution reaction in the organic phase were obtained. The hydration number of the catalyst, $QOCH_2CF_3$, is determined from the experimental data. The reaction reactivity is influenced by the content of the acids, which include water and alcohol in the aqueous phase. For an extraction mechanism, the reactivities of all kinds of catalysts in the organic phase with the same kind of solvent are the same. The effects of mass transfer and the extraction of quaternary ammonium salts on the conversion are used to explain the experimental data. The obtained results can be used as a reference for selecting the appropriate solvent and catalyst as well as for determining the appropriate content in the aqueous phase. Meanwhile, the desired distributed products, including the intermediate and final products, can be obtained by the appropriate choice of reaction conditions.

Introduction

The problems of two-phase reactions were not solved until Jarrouse[1] discovered the catalyzing effect of quaternary ammonium salt in the aqueous–organic phase reaction system. The quaternary ammonium salt, which served as a phase-transfer catalyst in the two-phase reaction system, was then studied by many chemists.[2-4] At this time, it has been extensively applied to the synthesis of special organic chemicals by displacement, alkylation, arylation, elimination, condensation, oxidation, reduction, and free-radical polymerization. The most advantageous uses of phase-transfer catalysis to synthesize organic chemicals are fast reaction rate, high selectivity of product, moderate operating temperature, and applicability to industrial-scale production.

In recent years, scientists have paid great attention to the development of inorganic cyclic compounds and high polymers for material applications.[5-8] In the past, poly(trifluoroethoxycyclotriphosphazene) was synthesized by reacting metallic sodium (or sodium hydride) with phosphazene.[9] Unfortunately the yield was too low even though the experiment was carried out at a high temperature for a long time.[10] Allcock[11] used tetra-*n*-butylammonium chloride as a phase-transfer catalyst to study the substitution of mono-$OC_6H_{14}NO_2$-P from chloride in chloropentaphenoxylcyclotriphosphazene. Further, Carr and Nichols[12] synthesized phosphazene esters by using phase-transfer catalysis. However, the effects of mass transfer and extraction of catalyst in the organic phase during conversion were not investigated.

In general, there are three main topics which need to be clarified in studying the phase-transfer catalytic reaction, i.e., the selection of an appropriate catalyst, and solvent, and the determination of an appropriate content in the aqueous phase. In the present study, the effects of mass transfer and extraction of quaternary ammonium salts on the substitution reaction of hexachlorocyclotriphosphazene with 2,2,2-trifluoroethanol by phase-transfer catalysis (PTC) are studied in detail. The objective of this paper is to employ the experimental data in studying the effects of mass transfer and extraction of quaternary ammonium salts on the conversion in order to give a reasonable explanation of the phenomenon.

Experimental Section

Materials. Hexachlorocyclotriphosphazene, $(NPCl_2)_3$; 2,2,2-trifluoroethanol ($HOCH_2CF_3$; ROH); tetra-*n*-butylammonium

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