Fluorodesulfurization. A New Reaction for the Formation of Carbon–Fluorine Bonds

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The reactions of 2-aminothiols and thiol amino acids in liquid hydrogen fluoride solution with either fluoroxytrifluoromethane, chlorine, *N*-chlorosuccinimide, or a fluorine–helium mixture are described. The cleavage of the carbon–sulfur bond with concomitant formation of a carbon–fluorine bond is observed, affording the synthesis of aminoalkyl fluorides and fluoro amino acids. D-Penicillamine (**1**) was converted to 3-fluoro-D-valine (**2**) in near-quantitative yield while other amino thiols, following more complex pathways, furnish lower yields of the respective fluoro products. The proposed mechanisms involve highly oxidized forms of sulfur such as dihalosulfonium salts or trifluorosulfur dications. These very electropositive sulfur moieties should be very good leaving groups, reacting with hydrogen fluoride, either in a unimolecular sense as in the case of penicillamine, or possibly via a bimolecular mode, as in the case of cysteine. In either case, the solvent appears to be the source of fluorine in the carbon–fluorine bond. Finally, there is described a carbocation-type conversion of some alcohols to thiols which can be effected by reacting the appropriate alcohols with hydrogen sulfide in liquid hydrogen fluoride.

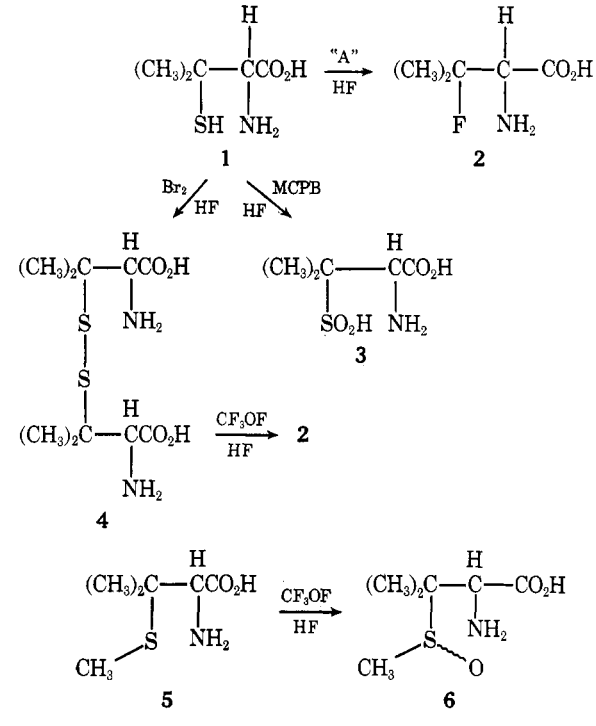
It has been known for a long time that carbon–sulfur bonds of thiols may be cleaved by chlorine[1] or bromine[2] and that a carbon–chlorine or carbon–bromine bond results from such a reaction. We wish to report that fluorine, and in some cases chlorine, *N*-chlorosuccinimide, or fluoroxytrifluoromethane can effect an analogous reaction when these reagents are reacted with amino thiols in liquid hydrogen fluoride. These reactions provide another method for the formation of carbon–fluorine bonds, especially in those molecules containing an amine, which being protonated in the highly acidic medium[3a] is protected from oxidation[3b] by the reagents. It allows the synthesis of certain fluorinated amino acids which, in some cases, would be very difficult to prepare.[4] We propose the name "fluorodesulfurization" for this reaction.

A. Reactions with Fluoroxytrifluoromethane, *N*-Chlorosuccinimide, and Chlorine. Photofluorination[3b] of D-penicillamine (**1**) in liquid HF at −78 °C with fluoroxytrifluoromethane (CF_3OF) afforded not the expected 4-fluoro-D-penicillamine, but rather a high yield of a substance characterized as 3-fluoro-D-valine (**2**). The structural assignment was made on the basis of its elemental analysis, its NMR spectrum, and a comparison (electrophoretic mobility and chromatographic retention time) with a sample of 3-fluorovaline obtained by photofluorination of L-valine.[5] Since $[\alpha]_D$ for **2** was equal to and of opposite sign to the $[\alpha]_D$ of the photofluorination product, it is probable that there is no involvement of C-2 in the reaction.

Subsequently, it was shown that these conversions of penicillamine proceeded equally well in the dark, at −78 or 0 °C, and that the conversion did not require CF_3OF but could also be effected with chlorine (Cl_2) or *N*-chlorosuccinimide (NCS). The stoichiometry was defined using NCS, of which 2 mol were required. However, when **1** was treated with *m*-chloroperbenzoic acid (MCPBA) or with bromine in liquid HF, **2** was not obtained but the products were penicillaminesulfinic acid[6] (**3**) and penicillamine disulfide[7] (**4**), respectively.

A consideration of related compounds other than thiols led us to react **4** and *S*-methylpenicillamine[8] (**5**) with CF_3OF. From the former, there was obtained a quantitative yield of **2** while from the latter two diastereomeric sulfoxides,[9] **6**, could be isolated. Elemental sulfur[10] is the major by-product (ca. 60% isolated yield) when **1** or **4** was reacted with CF_3OF but sulfur was not found when the reagent was NCS or Cl_2. When **1** was reacted with CF_3OF in trifluoroacetic acid (TFA), as opposed to HF, a number of products were formed but no trace of **2** was observed. Some of these transformations are outlined in Scheme I.

Scheme I. Reactions of Penicillamine and Relatives



"A" = either CF_3OF, NCS, or Cl_2

B. Reactions with a Fluorine–Helium Mixture. It was hoped that the application of this chemistry to the cysteine (**7**) system would provide another route to 3-fluoroalanine (**9**) but none of the latter was found when **7** or cystine (**8**) was reacted with CF_3OF, NCS, or Cl_2 under a variety of conditions. Rather, with these reagents, there was obtained a mixture of cysteinesulfinic acid[11] (**11**) and cystine 1,1-dioxide[12] (**12**). **9** was obtained when F_2/He (1:4 v/v) was used as the reagent in HF/HBF_4 solvent and **7** as the substrate in which case a 33% yield of **9** and a 3% yield of 3,3-difluoroalanine[13] (**10**) were isolated. When **8** was reacted with F_2/He, only **11** was obtained and no **9** or **10** was detected. These transformations are outlined in Scheme II. Table I outlines the results of these reagents with other substrates.

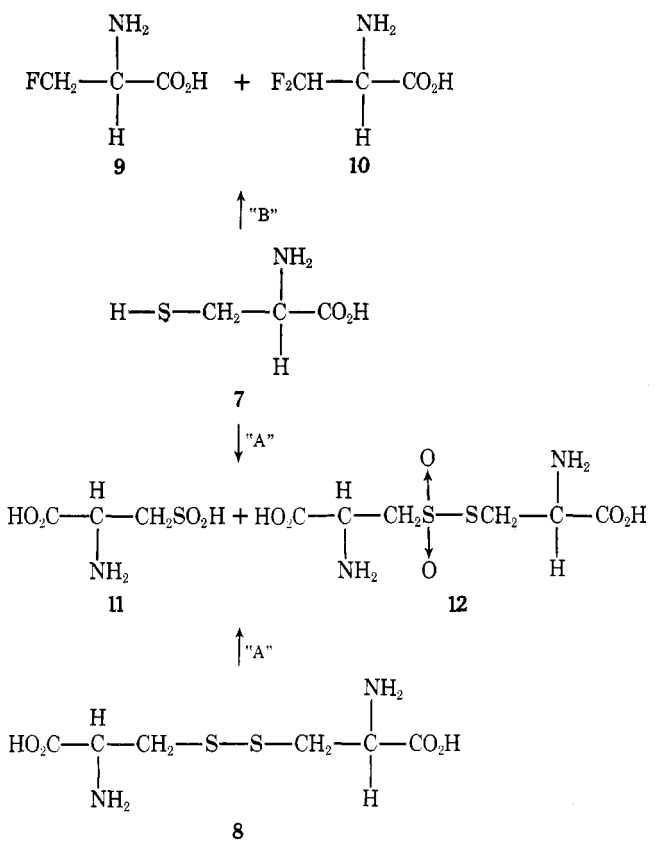
It should be noted that in contrast to the S-substituted compounds **4** and **5**, the 2,2-di-*n*-butyl-1,3-dithiolane[14] (Table I) produced the *gem*-difluoro compound. The next higher substituted compound, 1,1,1-tris(ethylthio)octane[15] (Table

Table I. Reactions of Various Sulfur Compounds in Liquid Hydrogen Fluoride with Fluorodesulfurization Reagents

Substrate	Reagent[a]	Product	Yield,[b] %
D-Penicillamine	A	3-Fluoro-D-valine	94
β-Mercaptophenylalanine	C	β-Fluorophenylalanine[c]	34
L-Cysteine	B	3-Fluoro-L-alanine	33
		3,3-Difluoro-L-alanine[d]	3
L-Cysteine	C	Cysteinesulfinic acid[e]	60
		Cystine 1,1-dioxide[f]	13.7
2-Diethylaminoethanethiol	B	2-Diethylaminoethyl fluoride	25
		2-Diethylamino-1,1-difluoroethane	3
N,α-Dimethyl-β-mercaptophenethylamine	A	N,α-Dimethyl-β-fluorophenethylamine	*g*
Homocysteine lactone	B	Homocystine 1,1-dioxide[h]	30
1,1,1-Tris(ethylthio)octane	A	1,1-Bis(ethylthio)-1-octene	*i*
3-Mercapto-3-methylbutyric acid	A	3,3-Dimethylacrylic acid	80[j]
2-Mercaptosuccinic acid	B	Succinic acid	17
2,2-Dibutyl-1,3-dithiolane	A	5,5-Difluorononane	50[k]

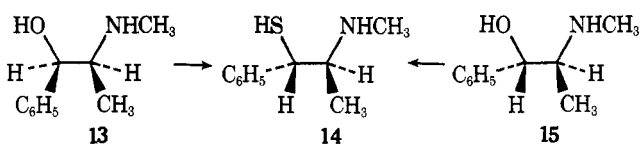
[a] Reagent A = CF_3OF; reagent B = F_2/He (1:4 v/v); reagent C = Cl_2 or NCS. [b] Unless otherwise stated, yields are isolated ones. [c] NMR and Spinco-Beckman amino acid analysis indicate one isomer. [d] Reference 13. [e] Reference 11. [f] Reference 12. [g] Could not be isolated analytically pure. [h] Identified by elemental analysis and NMR. [i] Identified by mass spectrum and NMR. [j] NMR yield. [k] Elemental analysis indicates 90% purity. Structural assignment made by mass spectral and NMR analysis.

Scheme II. Reactions of Cysteine and Cystine



I), afforded the ketene mercaptal, a result which may be caused by the fact that the starting material does not dissolve in liquid HF. Nitrogen heterocycles containing a thiol functionality are a readily available structural type, and thus 4-methyl-2-mercaptothiazole, 1-methyl-2-mercaptoimidazole, and 2-mercapto-6-hydroxypurine were subjected to a variety of fluorodesulfurization conditions. However, in no case was a carbon–fluorine bond formed. Finally when **5** was reacted with F_2/He, several products were obtained including a 40% yield of **2** (cf. CF_3OF reaction with **5**).

C. Thiolation in Liquid HF. Useful methods require readily available starting materials and therefore a thiolation method was developed which allows select alcohols to be transformed into thiols. It involves reacting the alcohol, dissolved in liquid HF, with hydrogen sulfide and has furnished DL-penicillamine (yield 60% by amino acid analysis) from DL-3-hydroxyvaline, and DL-β-mercaptophenylalanine (34% yield) from *threo*-DL-phenylserine. The stereochemistry of the reaction was defined by the isolation of *threo*-(+)-phenyl-2-methylaminopropanethiol[16] (**14**) from both (−)-ephedrine and (+)-pseudoephedrine (**15**):



13 **14** **15**

The reaction also gave 7 mol % of bis(1-phenyl-2-methylaminopropyl) sulfide.[17]

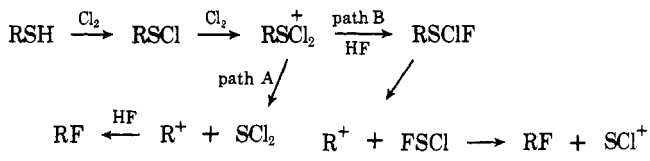
Discussion

The chlorinolytic cleavage of carbon–sulfur (C–S) bonds is well documented and a C–S bond rupture effected by bromine has been suggested but no carbon–fluorine bonds have been made by this route. Compounds in the cysteine–cystine system have been converted to their 3-chloroalanine analogues.[1b,c] These reactions were carried out with suspensions of hydrochlorides in methylene chloride and their mechanistic relevance to the reactions presented here is questionable.

Reactions with CF_3OF, NCS, Cl_2. We have arbitrarily divided our mechanistic considerations into two types: those reactions which *require* F_2/He and those which may be effected by CF_3OF, Cl_2, or NCS, reagents of lower oxidizing potential. It is probable that the reactions with the latter group of reagents have similar pathways and that they involve a heterolytic rupture of the C–S bond. Such an ionic, as opposed to a radical, pathway may be inferred by a consideration of the redox potentials of the species involved. That is, if a radical mechanism obtained, then at some point a fluoride ion would have to be oxidized to a fluorine atom and this is not possible with these reagents (e.g., Cl_2). Based on dielectric constant correlations, Norcross and Martin[1c] suggested ionic intermediates in the chlorinolysis of cysteine and cystine esters. That the intermediates are carbocations may be inferred from the successful fluorodesulfurization of tertiary and benzylic types and the failure of heterocyclic thiols to undergo this reaction.

The simplest view of the C–F bond forming step would involve discharge of the carbocation, formed in the penultimate step, by fluoride ion (path A, Scheme III). However, one can

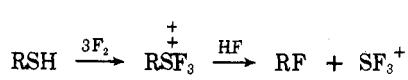
Scheme III. Possible Mechanistic Pathways for the Fluorodesulfurization Reaction



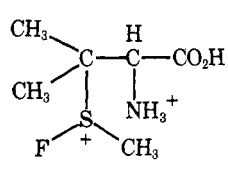
also envision a fluorine species being transferred from sulfur in an SNi process (path B).

Our preference is for path A since (1) it is probable that the carbon-bound fluorine originates in the HF solvent, a view supported by the finding that **2** is not formed when **1** is reacted with CF_3OF in trifluoroacetic acid, and (2) path B would require a fluorine–chlorine ligand interchange at sulfur when chlorine is the reagent. Although supporting evidence is not available, such an interchange seems unlikely considering the nature of some of the by-products: thus, no elemental sulfur was observed when chlorine was the reagent. This is consistent with the formation of sulfur dichloride, a stable molecule. Sulfur dichloride was identified by Norcross and Martin[1b] as a by-product. Sulfur difluoride, on the other hand, is known to rapidly disproportionate to sulfur and sulfur tetrafluoride,[18] thus accounting for the presence of sulfur in the CF_3OF reaction. The chemistry of mixed or complex sulfur halides or oxyhalides has not yet been established and the definitive statement about this mechanistic aspect will come when the by-products are identified in situ.

Reactions with F_2/He. The requirement of primary thiols such as cysteine for the more powerful oxidizer, F_2/He, may reflect the need of such systems for more potent leaving groups. Oxidation to the dihalosulfonium species by Cl_2, NCS, or CF_3OF affords only a singly positive ion, whose sulfur moiety may not be a good enough leaving group to compensate for the higher energy of an incipient primary carbocation. On the other hand, F_2/He could oxidize the sulfur to a dispositive species whose greatly enhanced leaving tendency could give rise to a primary carbocation or suffer ready bimolecular displacement by a fluoride ion:



Such a process would lead to an SF_3^+ ion, whose existence in liquid HF has been demonstrated.[19] Further support for the critical electropositive nature of the leaving group comes from the results of reactions of *S*-methylpenicillamine (**5**). Its failure to be converted to **2** by CF_3OF indicates that the inductive effect of the methyl group in an intermediate such as **16** is enough to vitiate the reaction, whereas an intermediate



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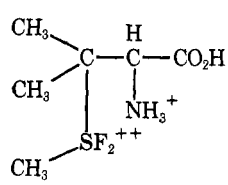

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such as **17** formed in the F_2/He reaction can overcome these difficulties. The difluorinated compounds such as **10** can be explained by an elimination of HF followed by addition of fluoride to carbon forming an α-fluorosulfenyl fluoride which reacts further.

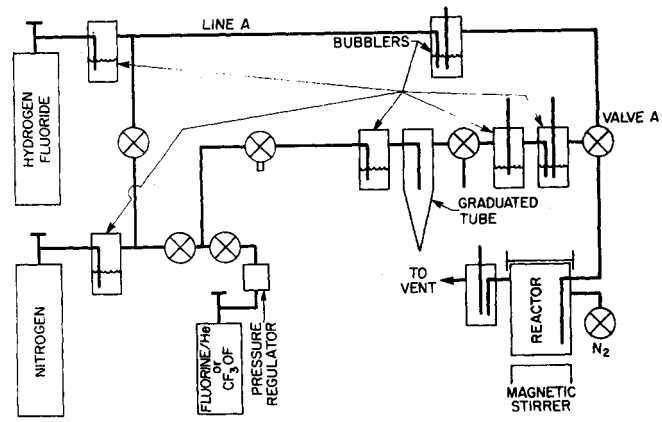
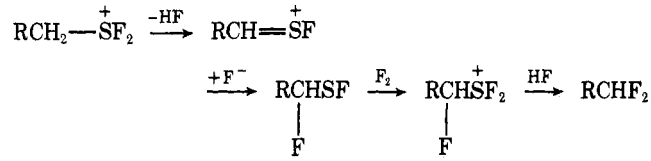


Figure 1.



This type of transformation has analogies in the reaction of *n*-butyl disulfide with silver difluoride yielding 1-fluorobutyl sulfur trifluoride[20a] and also in the chemistry of chlorosulfonium salts.[20b]

The Thiolation Reaction. It seems fairly clear that the thiolation reaction involves a carbocation mechanism. This is supported by a consideration of the structural types that undergo the reaction (e.g., tertiary and benzylic alcohols) and the stereochemical results (in which diastereomeric alcohols afford the same product). Additionally, the structural types which do not react are those which would afford less stable carbocations on C–OH cleavage. Thus threonine was recovered unchanged from the usual reaction conditions. The synthesis of the tertiary sulfide, felinine,[21] probably follows a similar mechanistic pathway.

Experimental Section

^1H NMR spectra (60 and 100 MHz) were obtained on Varian T-60 and HA-100 spectrometers, respectively, using tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. ^{19}F NMR spectra were obtained on either a Varian T-60 fitted with a 56.4-MHz transmitter and receiver or a JEOL C60HL spectrometer. In either case, trifluoroacetic acid or $CFCl_3$ was used as an internal standard and trifluoroacetic acid assumes the value $\phi = 77.0$. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. F_2/He (1:4 v/v) was obtained from Matheson Gas Products, East Rutherford, N.J.; fluoroxytrifluoromethane from PCR, Gainesville, Fla.

Caution: The herein described technique for handling hydrogen fluoride is relatively safe as it does *not* involve transfer of *liquid* HF. A well-ventilated hood is indispensable for this type of work. The operator should wear face shield as well as rubber gloves. With these precautions, handling of HF, F/He, and CF_3OF proved in our laboratory to be routine and safe. Instructions of suppliers for safe handling of these reagents should be observed. First aid treatment of HF burns has been described.[23]

Fluorodesulfurization. General Procedure. The flow diagram of the apparatus is illustrated in Figure 1. (The design of this equipment and its modus operandi is in essence the same as described in ref 3a, with some improvements in details.) The reactor[3a] and bubblers are constructed from polychlorotrifluoroethylene (Kel-F); the valves are of polytetrafluoroethylene (Hamilton Co., P.O. Box 307, Whittier, Calif. 90608) (Teflon) and the connecting tubes were constructed of Teflon, polyethylene, and glass. The bubbler liquid was Halocarbon Oil (a blend of completely halogenated chlorofluorocarbons, Halocarbon Products Corp., Hackensack, N.J.). The glass graduated tube had to be replaced after four to five runs when CF_3OF was used.

Substrates were sealed in the reactor which was purged with N_2 throughout the reaction. The reactor was immersed in a −78 °C bath

(dry ice–acetone) and hydrogen fluoride gas was introduced via line A. After the requisite amount of liquid had been condensed, line A was purged with N_2 to avoid condensation of the remaining HF. Valve A was then closed to line A. F_2/He or CF_3OF was then introduced into the reactor either directly by reading the pressure drop on a regulator, or by condensation (with CF_3OF only) with a liquid N_2 bath in the graduated tube and measuring the liquid volume. When Cl_2 was used, it was condensed and measured using a −78 °C bath. Addition of NCS was accomplished by opening the top of the reactor under a vigorous stream of N_2 and adding in one portion.

After completion of the reaction, N_2 was introduced via the train until all the HF was removed from the reactor. The residue was generally dissolved in hydrochloric acid (ca. 2.5 N) and concentrated in a rotary evaporator. At this point, the desired analytical measurements (e.g., NMR, amino acid analysis) were made. The residues were then chromatographed, generally on Dowex 50X8 cation exchange resin (200–400 mesh), by applying the residue to the column and eluting with water until no fluoride ion could be detected in the effluent with fluoride ion test paper (Macherey, Nagel & Co.). Elution was continued by increasing the concentration of HCl in the eluent from 0.2 N to 4 N. A Teflon bellows pump was used and 15–20-ml fractions were collected. Concentration of fractions containing ninhydrin-positive materials was effected in vacuo (bath temperature <40 °C).

3-Fluoro-D-valine. D-penicillamine (1.49 g, 10 mmol) was sealed into the reactor, a slight nitrogen pressure applied, placed in a −78 °C bath, and 35 ml of liquid hydrogen fluoride was condensed resulting in the dissolution of the amino acid. The −78 °C bath was replaced with an ice bath, and approximately 30 mmol of fluoroxytrifluoromethane (85% purity) (the amount ascertained by a pressure drop on a gauge) was introduced through the inductor tube.

After the completion of the addition, an aliquot revealed the absence of starting material and only had NMR resonances corresponding to 3-fluorovaline. The HF was evaporated in a stream of nitrogen and the residue was taken up in concentrated HCl and concentrated in vacuo to yield 1.62 g of 3-fluoro-D-valine hydrochloride (94%).

The free amino acid was isolated by dissolving 1.52 g of the hydrochloride in 7 ml of water, decolorizing with 100 mg of Darco G-60, and filtering through Celite. The filtrate was cooled, treated with 0.7 ml of pyridine, and diluted with 20 ml of 2-propanol. There was obtained 560 mg of 3-fluoro-D-valine (44% overall) as white plates. An analytical sample was obtained by recrystallization from water–2-propanol: 60-MHz NMR (D_2O–DCl) δ 1.53 (d, 3 H, J = 22.5 Hz), 1.68 (d, 3 H, J = 24 Hz), 4.38 (d, 1 H, J = 14 Hz); $[\alpha]D$ −6.1° (*c* 2.5, 1 N HCl); ^{19}F NMR (D_2O–DCl) 14 lines centered at ϕ 143.5. Anal. Calcd for $C_5H_{10}NFO_2$: C, 44.44; H, 7.41; N, 10.35; F, 14.07. Found: C, 43.93; H, 7.30; N, 9.95; F, 14.31.

(+)-*threo*-1-Phenyl-2-methylaminopropanethiol Hydrochloride. A. From (−)-Ephedrine. The reactor was charged with 16.5 g of (−)-ephedrine (100 mmol), sealed under N_2, and after cooling to −78 °C was dissolved in 200 ml of liquid HF. Then H_2S was passed through the solution for 2 h at −78 °C and at 0 °C for 1 h. The HF was evaporated in a stream of nitrogen overnight and the residue was dissolved in concentrated HCl.

The solution was evaporated to 20 g of a semisolid which was dissolved in 30 ml of H_2O and basified with 70 ml of 2.5 N NaOH. The mixture was extracted with 100 ml of ether, and the aqueous layer was acidified with 11 ml of concentrated HCl and concentrated to dryness. The residue was extracted with hot ethanol and on addition of ether, 8.67 g of (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride (40%), mp 175–177 °C dec, was obtained. For analysis it was recrystallized from acetonitrile: mp 178–180 °C dec; 60-MHz NMR (D_2O) δ 1.25 (d, 3 H, J = 6.2 Hz), 2.90 (s, 3 H), 3.78 (m, 1 H), 4.23 (d, 1 H, J = 10 Hz), 7.50 (s, 5 H); $[\alpha]D$ +88.9° (*c* 1.45 ethanol). Anal. Calcd for $C_{10}H_{16}NSCl$: C, 55.17; H, 7.36; N, 6.44; S, 14.71. Found: C, 55.41; H, 7.24; N, 6.21; S, 14.91.

The above ether extract was saturated with gaseous HCl at 0 °C, and the precipitate was slurried with acetonitrile to afford 2.9 g of the bis(1-phenyl-2-methylaminopropyl) sulfide dihydrochloride, mp 236–238 °C dec. An analytical sample was prepared by recrystallization from ethanol–ether: mp 236–237 °C dec; 60-MHz NMR (D_2O–DCl) δ 1.10 (broad doublet, 6 H, J = 5.6 Hz), 2.57 (s, 6 H) 3.80 (m, 4 H), 7.53 (s, 10 H). Anal. Calcd for $C_{20}H_{30}N_2SCl_2$: C, 59.85; H, 7.48; N, 6.98; S, 7.90; Cl, 17.71. Found: C, 60.02; H, 7.45; N, 6.14; S, 7.71; Cl, 18.02.

B. From Pseudoephedrine. (+)-Pseudoephedrine (1.65 g, 10 mmol) was dissolved in 20 ml of liquid HF in the usual reactor and H_2S bubbled through the solution at −78 °C for 1 h and at 0 °C for 2 h. The HF was evaporated in a stream of nitrogen, and the residue taken up in concentrated HCl, concentrated to dryness, and triturated with acetonitrile, affording 500 mg of (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride, mp 177.5–179.5 °C dec, $[\alpha]D$ +86.9° (*c* 1.85, ethanol). Addition of ether to the acetonitrile supernatant yielded a second crop of 500 mg, mp 173–175 °C dec. The combined yield (1 g) was 46% of theory.

β-Mercapto-DL-phenylalanine. The reactor was charged with 15 g of DL-*threo*-phenylserine (83 mmol) which was then dissolved in 150 ml of liquid hydrogen fluoride at −78 °C. The solution was saturated with H_2S continuously for 1.5 h at −78 °C and for an additional 3 h at 0 °C. The HF and H_2S were removed in a stream of nitrogen at room temperature (overnight). The residue was dissolved in 75 ml of H_2O and after cooling in an ice bath was saturated with gaseous HCl. The precipitate which was formed was collected, redissolved in 50 ml of H_2O, and again saturated with HCl at 0 °C. The precipitate was filtered, washed with ether, and dried, affording 6.5 g of β-mercapto-DL-phenylalanine hydrochloride (34%) which showed a single peak on amino acid analysis and a single spot on electrophoresis (10% acetic acid buffer). Analytically pure material was prepared as follows: a 2-g sample was covered with 15 ml of concentrated HCl, warmed, and dissolved with addition of about 15 ml of methanol. After filtering the solution there was added an additional 15 ml of concentrated HCl, causing 1.18 g of analytically pure β-mercaptophenylalanine hydrochloride, mp 222–223 °C dec, to crystallize. Anal. Calcd for $C_9H_{12}NO_2SCl$: C, 46.25; H, 5.14; N, 5.97; S, 13.71. Found: C, 46.58; H, 5.44; N, 5.93; S, 13.30.

β-Fluoro-DL-phenylalanine. The reactor was charged with 1.167 g of β-mercapto-DL-phenylalanine (5 mmol), and dissolved in 20 ml of liquid HF at −78 °C. When solution was complete, 1.468 g of *N*-chlorosuccinimide (11 mmol) was added in one portion. The resultant solution was stirred at −78 °C for 10 min and at 0 °C for an additional 15 min; 5 ml was removed and quenched on ice for an alternate workup. The remainder of the HF solution was rapidly evaporated in a stream of nitrogen at 0 °C and the residue was taken up in a small quantity of H_2O and applied to a 100-ml Dowex 50X8 (200–400 mesh) column. The column was eluted with H_2O (300 ml), 0.5 N HCl (300 ml), and then continuously with 1 N HCl.

Fractions 119–135 afforded 300 mg of β-fluoro-DL-phenylalanine hydrochloride (34%): 60-MHz NMR (D_2O–DCl) δ 4.75 (d of d, 1 H, J = 26, 4 Hz), 6.33 (d of d, 1 H, J = 45, 5 Hz), 7.53 (s, 5 H). Anal. Calcd for $C_9H_{11}NO_2FCl$: C, 49.25; H, 5.01; N, 6.37; F, 8.65. Found: C, 48.76; H, 5.31; N, 6.35; F, 8.30.

The free amino acid was obtained by dissolving 30 mg of the hydrochloride in about 0.1 ml of H_2O, cooling, adding 0.011 ml of pyridine, and washing with H_2O–2-propanol (1:1). β-Fluoro-DL-phenylalanine (13 mg) was obtained, mp 173–174 °C. Anal. Calcd for $C_9H_{10}NO_2F$: C, 59.10; H, 5.46; N, 7.56; F, 10.37. Found: C, 58.36; H, 5.42; N, 7.52; F, 10.26.

Reaction of Cysteine with Fluorine–Helium. 3-Fluoro-L-alanine and 3,3-Difluoro-L-alanine. The reactor was charged with 1.50 g of anhydrous L-cysteine hydrochloride (9.5 mmol), cooled to −78 °C, and 50 ml of liquid hydrogen fluoride condensed into the reactor. This was evaporated at room temperature in a stream of nitrogen to remove HCl. The residue was redissolved the same way in 50 ml of HF and the solution was saturated at −78 °C with gaseous boron trifluoride. After the −78 °C bath was exchanged for an ice bath, a fluorine/helium mixture (1:4 v/v) was bubbled through the solution (ca. 2 bubbles/s) for 3 h.

The solution was evaporated with a stream of nitrogen and one-half of the residue was chromatographed on 100 ml of Dowex 50X8 cation exchange resin column (200–400 mesh) eluting with water and then with 0.5 N HCl. Concentration of fractions 65–77 afforded 230 mg of 3-fluoro-L-alanine hydrochloride (33%). Paper electrophoresis (10% aqueous acetic acid) showed it to be one substance. Its NMR spectrum was identical with that of an authentic sample. This 230 mg was dissolved in 1 ml of H_2O, cooled, and treated with 0.127 ml of pyridine and 3 ml of 2-propanol affording 139 mg of 3-fluoro-L-alanine[22] (81% recovery from the hydrochloride), $[\alpha]D$ +9.9° (*c* 3, 1 N HCl). Anal. Calcd for $C_3H_6NO_2F$: C, 33.65; H, 5.65; N, 13.08; F, 17.74. Found: C, 33.28; H, 5.90; N, 12.88; F, 17.63.

Fractions 54–56 were concentrated to give 20 mg of 3,3-difluoro-L-alanine hydrochloride (3%), a substance previously prepared in these laboratories:[13] 60-MHz NMR (D_2O–DCl) δ 4.77 (4 lines, 1, J_{HF} = 24.6, J_{HH} = 2 Hz), 6.56 (t of d, 1, J_{HF} = 52 Hz); ^{19}F NMR ϕ_A 125.5 (m, J_{FF} = 285 Hz), ϕ_B 129.9.

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Registry No.—D-Penicillamine, 52-67-5; hydrogen fluoride, 7664-39-3; fluoroxytrifluoromethane, 373-91-1; 3-fluoro-D-valine hydrochloride, 59752-73-7; 3-fluoro-D-valine, 59752-74-8; (−)-ephedrine, 299-42-3; (+)-*threo*-1-phenyl-2-methylaminopropanethiol hydrochloride, 59752-75-9; bis(1-phenyl-2-methylaminopropyl) sulfide dihydrochloride, 59738-51-1; (+)-pseudoephedrine, 90-82-4; DL-*threo*-phenylserine, 2584-75-0; β-mercapto-DL-phenylalanine hydrochloride, 59779-79-2; *N*-chlorosuccinimide, 128-09-6; β-fluoro-DL-phenylalanine hydrochloride, 59729-21-4; β-fluoro-DL-phenylalanine, 57362-93-3; L-cysteine hydrochloride, 52-89-1; 3-fluoro-L-alanine hydrochloride, 59729-22-5; 3-fluoro-L-alanine, 35455-21-1; 3,3-difluoro-L-alanine, 59729-23-6; 2-diethylaminoethanethiol, 100-38-9; *N*,α-dimethyl-β-mercaptophenethylamine, 4389-42-8; homocysteine lactone, 2338-04-7; 3-mercapto-3-methylbutyric acid, 59729-24-7; 2-mercaptosuccinic acid, 70-49-5; 2,2-dibutyl-1,3-dithiolane, 59729-25-8; cysteinesulfinic acid, 1115-65-7; cystine 1,1-dioxide, 30452-69-8; 2-diethylaminoethyl fluoride, 369-60-8; 2-diethylamino-1,1-difluoroethane, 59729-26-9; *N*,α-dimethyl-β-fluorophenethylamine, 59729-27-0; homocystine 1,1-dioxide, 59729-28-1; 1,1-bis(ethylthio)-1-octene, 13880-01-8; 3,3-dimethylacrylic acid, 541-47-9; succinic acid, 110-15-6; 5,5-difluorononane, 59729-29-2.

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Effect of Hydrogen Bonding and Solvent on the Conformational Preferences of Some 4-Hydroxythioxanthene *S*-Oxides

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For a series of 4-hydroxythioxanthene *S*-oxides, it is shown by ^{1}H NMR spectroscopy that these molecules preferentially exist in conformations in which the sulfinyl oxygen is pseudoequatorial (e′) in chloroform but pseudoaxial (a′) in dimethyl sulfoxide solutions. Intra- vs. intermolecular hydrogen bonding is used to explain these observations. This is the first observation where the equilibrium between two possible conformations of a thioxanthene *S*-oxide type molecule has been altered such that either conformation can be preferred. The temperature dependence in the ^{1}H NMR spectrum was also examined.

The solution conformational preferences of thioxanthene *S*-oxide and its various substituted derivatives have been the subject of recent interest.[1-4] A number of conclusions have been made concerning the conformational dispositions of these molecules in solution.[5] The sulfinyl oxygen prefers to be in a pseudoequatorial position (10e′) (in a rapid conformational equilibrium) in thioxanthene *S*-oxide[3] (II, R = H). However, when a substituent (e.g., R = chloro, methyl) is placed in the 4 position peri to the sulfinyl moiety, the sulfinyl oxygen prefers the 10a′ position[3] (I). This is a result of steric repulsive interactions and demonstrates the larger steric requirement of sulfinyl oxygen vs. the sulfur lone pair. Thus, "the efficacy of peri substituents in altering the conformation of these (and related) systems"[3] was concluded.

Proton magnetic resonance (^{1}H NMR) spectroscopy has been the primary tool in making conformational assignments in these systems and several ^{1}H NMR parameters have become definitive in assigning preferred conformations in the thioxanthene *S*-oxide systems. When the 10e′ position (II) is preferred, the 9-H_a′ absorption appears upfield and broadened[2,3] relative to the 9-H_e′ absorption. It is broadened owing to long-range coupling to the peri (1,8) protons[2,3] as substantiated by decoupling experiments. Alternatively, when the 10a′ position (I) is preferred, the 9-H_a′ absorption appears downfield and broadened relative to the 9-H_e′ absorption. It appears downfield owing to the large deshielding effect of the 10a′ sulfinyl group. In addition, these criteria and the conformational preferences do not appear to depend significantly upon solvent, e.g., benzene, chloroform, or dimethyl sulfoxide (Me_2SO).[2,4]

In our search for new polymer additives, we began an investigation of some 4-hydroxythioxanthene *S*-oxide compounds. In the course of characterizing these compounds, we have shown (1) that a hydroxy group at C-4 does not necessarily drive the sulfinyl oxygen into the 10a′ position, (2) that solvent is sufficient for changing the conformational prefer-