likely be reintroduced. In any case, there is no theoretical reason for the position of equilibrium to necessarily reflect the position of the transition state in solvolytic studies.

The norbornyl cation appears to be slightly less stable than the *tert*-butyl ion in the solution equilibria. The data agree well with estimates based on heats of solution of the bromides but differ from the mass spectroscopic results in which the norbornyl ion appears to be more stable. Either in solution or in the gas phase, however, it is evident that the norbornyl ion is considerably more stable than an open-chain secondary C_7^+ cation might be expected to be.

The equilibrium results do not address the question of the structure of the norbornyl cation. They are, however, in accord with other indications of ion stability such as obtained from carbonylation equilibria. Thus we estimate the free-energy change in reaction 5 to be +1.6 kcal/mol from the data of Hogeveen, Baardman, and Roobeek.[12]

$$t\text{-}C_4H_9^+ + NCO^+ \rightleftharpoons t\text{-}C_4H_9\overset{+}{C}O + N^+ \qquad (5)$$
$$(N^+ = \text{norbornyl}^+)$$

This is in excellent accord with the values of +0.7 in $AlBr_3/CH_2Cl_2$ and +1.2 in $AlBr_3/SO_2FCl$.

Summary

Four new low-temperature acid systems have been found that can stabilize high concentrations of tertiary alkyl cations. These are $AlBr_3/CH_2Cl_2$, $AlBr_3/CH_2Br_2$, $GaCl_3/CH_2Cl_2$, and $GaCl_3/1,2\text{-}Cl_2C_2H_4$.

Solutions (1 M) of the Lewis acids generally are able to stabilize up to 0.5 M solutions of $t\text{-}C_4H_9^+$ below ca −30 °C. NMR studies indicate that $AlBr_3$ forms an $R^+Al_2Br_6X^-$ salt while $GaCl_3$ appears to form both $R^+Ga_2Cl_7^-$ and $R^+GaCl_4^-$ salts. When RX/acid is >1:2, small amounts of side products tend to form, the least in the mixed halide $AlBr_3/CH_2Cl_2$ system.

The carbonium ions generally participate in intermolecular hydride and halide exchange processes, and the former were studied. Equilibrium measurements with large tertiary hydrocarbons generally show that they ionize more easily than isobutane. The equilibria in solution are usually more thermoneutral than in the vapor phase, and agree well with other estimates that can be made from heats of solution of bromides and equilibrium carbonylation studies.

In some cases the equilibria are widely different from what might be inferred from the kinetics of solvolytic processes. This is not much of a surprise but reinforces the fact that solvolysis rates be used with care in estimating equilibrium properties. The differences found with the *tert*-butyl/adamantyl system are suggested to be due to differences in solvating the open and bridgehead ions and these have been used to establish a scale to measure the ion stabilizing capabilities of superacid media.

Registry No. *i*-C_5, 78-78-4; 2,3-DMC_4, 79-29-8; 2,2,3-TMC_4, 464-06-2; 2,4-DMC_5, 108-08-7; $MCyC_5$, 96-37-7; adamantane, 281-23-2; norbornane, 279-23-2; *tert*-butylcarbonium ion, 14804-25-2; $AlBr_3$, 7727-15-3; CH_2Cl_2, 75-09-2; CH_2Br_2, 74-95-3; $GaCl_3$, 13450-90-3.

(12) H. Hogeveen, F. Baardman, and C. F. Roobeek, *Recl. Trav. Chim. Pays-Bas*, **89**, 227 (1970).

Organic Disulfides and Related Substances. 42. Synthesis and Properties of Some Tertiary Disulfides, Especially Involving Penicillamine[1]

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Five approaches to the synthesis of unsymmetrical tertiary disulfides are illustrated. Penicillamine (**1**) was thioalkylated with acyclic (**2**, **4**) and cyclic (**6**) thiosulfonates to give **3**, **5**, and **7**. 5-(Dimethylamino)-1-naphthyl methoxycarbonyl disulfide hydrochloride (**12**), prepared from the arenesulfonyl chloride (dansyl chloride, **8**) via the thiol (**9**), led to an impure disulfide with *N*-acetylpenicillamine (**13**) but to a pure one (**17**) with a more typical tertiary thiol; the thiol **9** fluoresced more strongly than **8**, but the disulfides less so. In an alternative synthetic approach, **13** was used as its thionitrite (**18**) or thiolsulfonate (**22**) to thioalkylate a typical primary thiol, reactions that may deserve attention for coupling penicillamine derivatives with protein SH. Several tertiary disulfides resist disproportionation for 24 h in water at 100 °C. When R of $RSSCMe_2CH(NH_2)CO_2H$ was $(CH_2)_2NH_3^+Cl^-$, however, disproportionation atypically began much more rapidly (4 h) than for the amide (24 h), and when R was $(CH_2)_4SO_2Na$ more rapidly still (1 h).

The chemistry of organic disulfides has been reviewed recently.[2] In previous studies of organic disulfides,[1a] our attention to unsymmetrical tertiary disulfides has been relatively slight and usually in connection with general interests.[1a,3] Such disulfides are the focus of this paper, with emphasis on disulfides of penicillamine (**1**). Disulfides of **1** are especially interesting representatives of the tertiary class because of the biological and biomedical activities of **1**,[4] as well as because derivatives of **1** are unusual in forming an atypically stable sulfenyl iodide[5] and thionitrite.[6]

(1) (a) Part 41: Field, L.; Grimaldi, Jr., J. A. R.; Hanley, W. S.; Holladay, M. W.; Ravichandran, R.; Schaad, L. J.; Tate, C. E. *J. Med. Chem.* **1977**, *20*, 996. (b) Presented in part at the 28th Southeast Regional Meeting of the American Chemical Society, Gatlinburg, TN, October 1976 (Abstract No. 394). (c) Abstracted from the Ph.D. dissertation of R.R., Vanderbilt University, May 1979, which can be consulted for further detail. (d) This investigation was supported in part by NIH Research Grant AM11685 awarded by the National Institute of Arthritis, Metabolism, and Digestive Diseases, PHS/DHEW, by the Merck Sharp & Dohme Research Laboratories Division of Merck and Co., Inc., and by the Research Council of Vanderbilt University.

(2) Field, L. In "Organic Chemistry of Sulfur"; S. Oae, Ed.; Plenum: New York, 1977; Chapter 7.

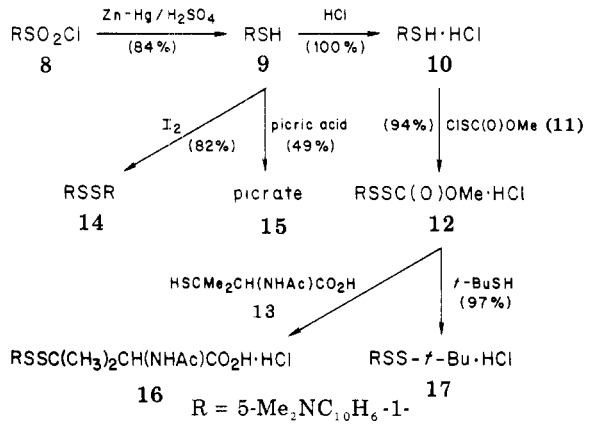
(3) (a) Field, L.; Owen, T. C.; Crenshaw, R. R.; Bryan, A. W. *J. Am. Chem. Soc.* **1961**, *83*, 4414. (b) Field, L.; Härle, H.; Owen, T. C.; Ferretti, A. *J. Org. Chem.* **1964**, *29*, 1632. (c) Parsons, T. F.; Buckman, J. D.; Pearson, D. E.; Field, L. *Ibid.* **1965**, *30*, 1923. (d) Field, L.; Buckman, J. D. *Ibid.* **1968**, *33*, 3865. (e) Field, L.; Giles, Jr., P. M. *Ibid*, **1971**, *36*, 309. (f) Field, L.; Hanley, W. S.; McVeigh, I.; Evans, Z. *J. Med. Chem.* **1971**, *14*, 202.

(4) For leading references, see: Dilbeck, G. A.; Field, L.; Gallo, A. A.; Gargiulo, R. J. *J. Org. Chem.* **1978**, *43*, 4593.

(5) (a) Field, L.; White, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 328. (b) Field, L.; White, J. E. *Int. J. Sulfur Chem.* **1976**, *8*, 539.

0022-3263/79/1944-2624$01.00/0

Scheme I



Synthesis of the tertiary disulfides could be achieved by either of two broad approaches. In the first, an acyclic or cyclic thiolsulfonate or an alkoxycarbonyl disulfide thioalkylated the tertiary thiol. In the second, a reverse of the first, the tertiary thiol as its thionitrite or thiolsulfonate thioalkylated another thiol.

In the alkylation by an acyclic thiolsulfonate, the acetamidoethyl thiolsulfonate **2** thioalkylated **1**, without the use of base, to give the disulfide **3** in 76% yield (eq 1).

$$\underset{\mathbf{1}}{Me_2C(SH)C(NH_2)HCO_2H} + RSO_2SR \rightarrow Me_2C(SSR)C(NH_2)HCO_2H \quad (1)$$

2, R = $(CH_2)_2NHAc$
4, R = $(CH_2)_2NH_3^+Cl^-$
6, R, R = $(CH_2)_4$
3, R = $(CH_2)_2NHAc$
5, R = $(CH_2)_2NH_3^+Cl^-$
7, R = $(CH_2)_4SO_2Na$

Attempts were made beforehand to use **1** with 2 equiv of alkali, in order to form the thiolate and carboxylate ions of **1**, followed after reaction by acidification with 2 equiv of HCl; pure **3** could not be obtained. A similar use of alkali in the conversion of **1** by the aminoethyl thiolsulfonate salt **4** to the disulfide **5** also proved unpromising (eq 1). Fortunately, with **4** alkali again was found to be unnecessary, and reaction of **1** with **4** alone led to **5** in 52% yield. In the conversion of **1** with the cyclic thiolsulfonate **6** to the disulfide sulfinate **7** (eq 1), initial attempts using 2 equiv of sodium methoxide led to considerable disproportionation of the product (**7**) as did too long a reaction time with 1 equiv of methoxide. However, use of only 1 equiv of methoxide with a 15-min reaction period gave **7** in 73% yield; 2 equiv of the cyclic thiolsulfonate **6** were used to trap a maximum of thiol and thus minimize the effect of thiol in inducing disproportionation, since the excess of **6** could be removed readily by washing the product with acetone. The importance of avoiding unnecessarily basic conditions in the preparation of **3**, **5**, and **7** probably finds its explanation in the fact that free aminoalkyl disulfides are less stable to disproportionation than the hydrochloride salts, which in turn are less stable than the amides,[7] so that a free α-amino group led to complications.

In the elegant route of Brois, Pilot, and Barnum for thioalkylating thiols with alkoxycarbonyl disulfides (eq 2),

$$R^1SH + R^2SSC(O)OMe \rightarrow R^1SSR^2 + COS + MeOH \quad (2)$$

a fragmentation reaction produces the desired unsymmetrical disulfide.[8] Carbon oxysulfide and methanol are the only additional products.[8] For the applications with tertiary thiols shown in Scheme I, R was the 5-(dimethylamino)-1-naphthyl moiety. Such combinations illustrate tertiary disulfides containing a type of aryl group and substituent we have not heretofore studied. Of special interest, however, was determination of whether presence of the (dimethylamino)naphthyl moiety might lead to useful fluorescence of disulfides such as **16** and **17** of Scheme I. Since 5-(dimethylamino)-1-naphthalenesulfonyl chloride (**8**; dansyl chloride) is a well-known fluorescent reagent used for labeling amino acids and proteins,[9] an answer to the question of whether or not the corresponding disulfides would fluoresce seemed both theoretically and practically significant. For example, fluorescence might point to the possible use of **12** both for fluorimetric analysis of **1** and for introducing a biochemically valuable fluorescent probe onto thiol groups of amino acids and proteins.[10]

Reduction of dansyl chloride (**8**) gave the thiol **9**, the identity of which was confirmed by oxidation to the disulfide **14** and conversion to the picrate **15**. The thiol **9** then was converted through the thiol hydrochloride **10** to the methoxycarbonyl disulfide **12**, the desired thioalkylating agent (about 10% excess of the sulfenyl chloride **11** proved desirable). Early efforts to bypass the formation of **10** by reaction of the aminothiol **9** directly with the sulfenyl chloride **11** were quite unpromising because the aminothiol **9** competed with the free base of the product **12** for HCl, and the resulting hydrochloride of **9** (i.e., **10**) could not be separated from the desired disulfide hydrochloride **12**; efforts to remove the **9** by using alkali led to considerable disproportionation of the disulfide **12**. TLC using three solvents showed only a single spot for the unsymmetrical disulfide **12**, and NMR integrals also were consistent with absence of symmetrical disulfides.

Reaction of **12** was studied with *N*-acetylpenicillamine (**13**) instead of with penicillamine (**1**) to obviate possible complications with the amino group of **1**. The reaction of **12** with **13** could be followed in methanol-d_4 by using NMR by decrease of the OCH_3 singlet of **12** relative to the arene protons. Decrease of this ratio from 1:2 to 0.06:2 after 59 h (~25 °C) signified nearly quantitative conversion of **13** to **16**. Unfortunately, the disulfide **16** produced could not be purified to the point of an acceptable elemental analysis, although NMR spectra were consistent with structure **16** essentially free of the starting materials **12** and **13** (but probably not of the two symmetrical disproportionated disulfides). Use of triethylamine as a catalyst led mainly to **14**. Reactions of **12** nevertheless should be satisfactory for more typical tertiary thiols, although poor adaptability of the naphthyl moiety to separations is likely to impede purification. Thus with 2-methyl-2-propanethiol, where excess (volatile) thiol could be used to force conversion of the **12**, the OCH_3 singlet disappeared after 5 days (~25 °C), and **17** was isolated in a fairly pure state in 97% yield (reduced, not unexpectedly, to 46% by rigorous purification); TLC (three solvents), spectra, and analysis were consistent with structure **17** and with absence of symmetrical disulfides. Parenthetically, NMR showed that **12** reacted quantitatively with thioacetic acid after only 1 h; ill-adapted physical properties precluded rigorous

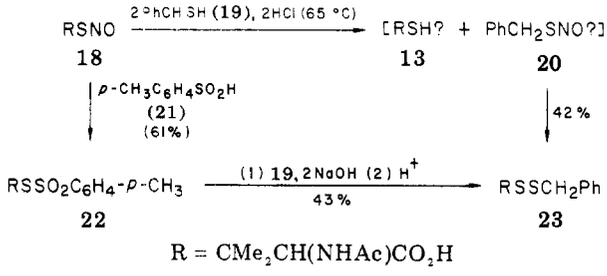
(6) Field, L.; Dilts, R. V.; Ravichandran, R.; Lenhert, P. G.; Carnahan, G. E. *J. Chem. Soc., Chem. Commun.* **1978**, 249.
(7) Bellas, M.; Tuleen, D. L.; Field, L. *J. Org. Chem.* **1967**, *32*, 2591.
(8) Brois, S. J.; Pilot, J. F.; Barnum, H. W. *J. Am. Chem. Soc.* **1970**, *92*, 7629.
(9) Cf., for example: "The Merck Index", 9th ed.; Windholz, M., Ed.; Merck and Co.: Rahway, NJ, 1976; p 2806.
(10) For leading citations on fluorescent probes for SH and their biochemical value, see ref 1c.

Table I. Disproportionation of Unsymmetrical Tertiary Disulfides at 100 °C[a]

compd	structure	approx time for disproportn, h: onset	approx time for disproportn, h: no further change
b	$Me_2NC(S)SS$-t-Bu[b]	72 (2-3%)[b]	
c	$Cl^-H_3N^+(CH_2)_2SS$-t-Bu[c]	>20[c]	
23	$PhCH_2SSCMe_2CH(NHAc)CO_2H$	40	48
3	$AcNH(CH_2)_2SSCMe_2CH(NH_2)CO_2H$	24	25[d]
5	$Cl^-H_3N^+(CH_2)_2SSCMe_2CH(NH_2)CO_2H$	4	6[d]
7	$NaO_2S(CH_2)_4SSCMe_2CH(NH_2)CO_2H$	1	1.7[d]

[a] In the dark with H_2O as solvent, unless otherwise specified. [b] Previous work; see ref 3d. Dioxane as solvent. [c] Previous work; see ref. 3a. Ambient light. Results based on no $(t\text{-BuS})_2$ after 20 h. [d] Apparently equilibrium was established with the H_2O-soluble symmetrical disulfides.

Scheme II



R = $CMe_2CH(NHAc)CO_2H$

purification of the unsymmetrical disulfide produced.

The thiol **9** fluoresced comparably to dansyl chloride (**8**) under a hand UV lamp but more strongly than **8** in a spectrophotofluorometer (excitation 330 nm, emission 442 nm). Fluorescence of the disulfides **12** and **16** was considerably weaker than of **8** but might still suffice to make such structures feasible as fluorescent probes, if solvents for **12** such as methanol can be used. Evidently the disulfide linkage quenches fluorescence, presumably because an interaction between the naphthyl ring and the SS linkage facilitates vibrational dissipation of the excitation energy, with the SS linkage acting as an "energy sink";[11b] several instances of quenching of fluorescence by SS linkages have been reported with systems of biochemical interest.[11] Efforts to use **12** as a fluorescent probe with protein thiols were thwarted by the colloidal nature of aqueous solutions of **12** (Tyndall effect observed). Although **12** forms clear solutions in methanol, with 2:3 MeOH–H_2O the UV spectrum begins to change and, unfortunately, addition of even this amount of methanol led to incipient clouding of aqueous solutions of ovalbumin, our intended substrate. Hence one may conclude that although the alkoxycarbonyl disulfide **12** may be useful for replacing H of SH with a fluorescent probe, disadvantages are that solvents must be largely organic, that reaction rates are slow, and that the products probably will not fluoresce strongly. A more suitable analytical procedure might be measure of the fluorescent thiol **9** after expulsion from its disulfide **14** by an attacking thiol of interest.

As Scheme II shows, the role of the tertiary thiol could be reversed to that of the thioalkylating species, at least in effect, by reaction of the thionitrite **18** or thiolsulfonate **22** with a typical primary thiol (α-toluenethiol, **19**). With the thionitrite **18** (and acidic catalysis) excess thiol (**19**) was used, since the excess was easily removable. The acidic catalysis may favor loss of HNO in a direct attack of **19** on **18**.[12] However, three points suggest that the bracketed intermediates of Scheme II may be involved: (1) Under *neutral* conditions, **18** (green) and **19** give **20** (red) and **13**.[6] (2) In the reaction of **18** with **19**, the color changed from green to red (despite acidic catalysis). (3) Attack of **13** on **20** presumably is considerably faster than of **19** on the neopentyl-type thionitrite **18**. Oae et al., in reporting that thionitrites thioalkylate thiols, formulated only direct attack by the thiol.[12]

The thiolsulfonate **22** was best prepared by reaction of the thionitrite **18** with three molar proportions of *p*-toluenesulfinic acid (**21**) at ~25 °C (see Experimental Section). Since the salt of **21** gave poor results, **21** probably serves both as an acidic catalyst and a reactant. Oae et al. have prepared thiolsulfonates from aryl and primary alkyl thionitrites by using 1–1.5 proportions of sulfinic acids.[12] Treatment of **22** with **19**, in the presence of enough base to convert each to the mono salt, followed by acidification, gave disulfide **23** identical with that from **18**. This thioalkylation, like that by **18**, conceivably could involve a preliminary transfer of the tosyl group to **19**, followed by attack of the thiol **13** thus engendered. Whatever the mechanism, however, reactions of **18** and **22** afford promising means of forming unsymmetrical disulfides of penicillamine derivatives; with easily removed acyl groups such as *tert*-butoxycarbonyl, for example, they may be useful in preparing protein-coupled penicillamine derivatives needed for engendering antibodies for immunoassays.

Evidence that the unsymmetrical disulfides **3**, **5**, **7**, **12**, **17**, and **23** were not merely mixtures of the two symmetrical ones was provided by the fact that each met all of the criteria 1–6 outlined earlier (except that disproportionation of **12** and **17** could not be studied; vide infra).[1a]

Physical properties and/or limited quantity precluded the quantitative study of disproportionation of the unsymmetrical disulfides we usually have made. However, Table I shows estimates from TLC, in order of decreasing resistance, that afford practical guides as to about when one may expect thermally induced disproportionation in the dark to begin and end. Several conclusions are possible: (1) As a class, tertiary disulfides resist disproportionation quite well. Thus Table I shows that solutions of the first four disulfides are little changed after 24 h at 100 °C. (2) As noted earlier,[7] an acetamidoethyl disulfide (**3**) is far more resistant than the amine salt (**5**), which disproportionates with atypical ease. (3) As also noted before,[13] a sulfinate (**7**) disproportionates readily, presumably because of a neighboring-group effect of SO_2Na on the S–S bond.[13] Efforts to obtain information about the disproportionation of the methoxycarbonyl naphthyl disulfide **12** were unavailing because similarity of the disulfides precluded analysis by TLC, NMR, or extraction; volatilization of methoxycarbonyl disulfide also gave poor results. With the *tert*-butyl disulfide **17**, very limited solubility and turbid solutions in water precluded definite

(11) (a) Cowgill, R. W. *Biochim. Biophys. Acta* **1970**, *207*, 556. (b) *Ibid.* **1967**, *140*, 37.

(12) Oae, S.; Kim, Y. H.; Fukushima, D.; Shinhama, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 913.

(13) (a) Srivastava, P. K.; Field, L. *J. Org. Chem.* **1972**, *37*, 4196. (b) Khim, Y. H.; Field, L. *Ibid.* **1972**, *37*, 2714.

conclusions; however, it is worth adding that the free base in methylene chloride was unchanged after 72 h in the dark, while ambient light led to disproportionation in 12–15 h.

Experimental Section

General procedures were as described earlier.[4] Reported procedures were used for preparing 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**2**),[14] 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (**4**),[15] 1,2-dithiane 1,1-dioxide (**6**),[16] and DL-2-(acetylamino)-2-carboxy-1,1-dimethylethyl thionitrite (**18**).[6] *p*-Toluenesulfinic acid (**21**) was made by acidifying the commercial salt. D-Penicillamine and DL-*N*-acetylpenicillamine were commercial products, as were other materials for which no source is stated.

D-2-Amino-3-methyl-3-[(2-acetamidoethyl)dithio]butanoic Acid (3). A solution of **2** (3.59 g, 13.4 mmol) in 25 mL of EtOH was added to finely ground D-**1** (2.00 g, 13.4 mmol) suspended in 60 mL of EtOH over 10 min with vigorous stirring. During the addition, the D-**1** dissolved, and after the addition the solution was clear. The solution was stirred for 12 h. Ether (1000 mL) was added to produce a gummy solid, which was recrystallized from EtOH–ether to give 2.70 g (76%) of white **3**; mp 167–169 °C. Recrystallization to constant melting point from EtOH–ether gave 2.03 g (57%) of **3**: mp 177–177.5 °C; TLC showed only one spot (R_f 0.33, EtOH); IR (KBr pellet) 3250, 3000, 1600, 1540, 1380 (doublet), 1340, 1300 cm^{-1}; NMR (D_2O) δ 1.35 and 1.55 [s, 6 H, $(H_3C)_2$], 2.0 (s, 3 H, $COCH_3$), 2.9 and 3.5 [t, 4 H, $(CH_2)_2$], 3.8 (s, 1 H, CH).

Anal. Calcd for $C_9H_{18}N_2O_3S_2$: C, 40.57; H, 6.82; N, 10.52; S, 24.07; neut. equiv 266. Found: C, 40.62; H, 6.82; N, 10.47; S, 24.14; neut. equiv (by formol titration)[17] 272.

D-2-Amino-3-methyl-3-[[2-aminoethyl]dithio]butanoic Acid Hydrochloride Sesquihydrate (5). A solution of **4** (5.17 g, 20.1 mmol) in 50 mL of H_2O was added during 8 min to a vigorously stirred suspension of finely ground D-**1** (3.00 g, 20.1 mmol) in 100 mL of absolute EtOH. The mixture at first contained considerable insoluble material but became clear 5 min after completion of the addition. After 7 h more of stirring, the clear solution was heated to gentle boiling, and ether was added until the solution became cloudy. A semisolid precipitated upon chilling at 0 °C overnight. This semisolid was recrystallized from EtOH–ether to leave 3.02 g (52%) of white **5**, mp 151–153 °C dec, which on further recrystallization left 2.57 g (44%) of crystalline **5** with a constant melting point of 153–155 °C dec: TLC showed only one spot (R_f 0.25, 1:1 EtOH–H_2O); IR (KBr pellet) 3350, 3200–2800 (b), 1600, 1480, 1360, 1340, 1100 cm^{-1}; NMR (D_2O) δ 1.35 and 1.50 [s, 6 H, $(CH_3)_2C$], 3.0 and 3.3 [t, 4 H, $(CH_2)_2$], 3.8 (s, 1 H, CH).

Anal. Calcd for $C_7H_{17}ClN_2O_2S_2 \cdot 1.5H_2O$: C, 29.21; H, 7.02; S, 22.27; H_2O, 9.38. Found: C, 29.51; H, 7.27; S, 22.70; H_2O, 7.64 (after drying for 171 h, until decomposition appeared to begin, at 100 °C (0.5 torr)).

Preparation of **5**, as the aminoethyl base in solution, has been reported, but with no details either of isolation or of characterization.[18]

Sodium 4-[(D-1,1-Dimethyl-2-amino-2-carboxyethyl)dithio]butanesulfinate (7). The NaOMe from 0.09 g (3.9 mmol) of Na in 10 mL of absolute MeOH was added dropwise during 10 min to a solution of 1,2-dithiane 1,1-dioxide (**6**) (1.16 g, 7.6 mmol) and D-**1** (0.57 g, 3.8 mmol) in 30 mL of MeOH at 0–2 °C. The mixture was stirred for 5 min more at ~25 °C, and 100 mL of ether then was added. A semisolid that precipitated was separated by decanting solvent and turned into white powder when rubbed with ether. The solid was separated by centrifugation, repeatedly washed with acetone (to remove unreacted **6**), and dried at ~2 torr overnight at ~80 °C: yield of **7**, 0.90 g (73%); mp 199–201 °C dec; TLC showed only one spot (R_f 0.51, MeOH); IR (KBr pellet) 3350, 2850, 2600, 1580, 1539, 1361 (doublet), 1340, 970, 941 cm^{-1}; NMR (D_2O) δ 1.4 and 1.5 [s, 6 H, $(CH_3)_2C$], 1.8 [m, 4 H, $CH_2(CH_2)_2CH_2SO_2Na$], 2.4 and 2.9 (t, 4 H, CH_2), 3.8 (s, 1 H, CH).

Anal. Calcd for $C_9H_{18}NNaO_4S_3$: C, 33.42; H, 5.62; S, 29.74. Found: C, 33.51; H, 5.70; S, 29.59.

Preparation and Reactions of 5-(Dimethylamino)-1-naphthyl Methoxycarbonyl Disulfide Hydrochloride (12). A. (Dimethylamino)-1-naphthalenethiol (9). As described,[19] zinc dust (15.46 g, 0.24 g-atom, Fisher Scientific Co.) was amalgamated using 3.09 g of $HgCl_2$ in 1.55 mL of concentrated HCl and 46 mL of H_2O by stirring for 15 min and then washing with 75 mL of H_2O containing 5 mL of 10% HCl, with EtOH, and with ether. It was used before all of the ether evaporated to ensure minimum contact with air.

In a procedure based on one for 1,5-naphthalenedisulfonyl chloride,[19] concentrated H_2SO_4 (31.9 g, ~315 mmol) was added to 60.83 g of water. Finely pulverized dansyl chloride (**8**; 5.00 g, 18.54 mmol; purified[20] by precipitation from acetone with H_2O) then was added with vigorous stirring, and immediately the zinc amalgam was added over ~2 min to the resulting solution. The mixture then was heated with vigorous stirring under reflux for 6 h, cooled to ~25 °C, and let stand for 3 h. Saturated aqueous $NaHCO_3$ was added (to pH 5), and the mixture was extracted with 5 × 25 mL of ether. The pale yellow fluorescent ether layer was dried and evaporated to leave 3.57 g (95%) of crude **9** as yellow oil. Distillation with a 5-cm column led to 3.16 g (84%) of **9**: bp 124–126 °C (0.45 torr); n^{25}_D 1.6698; TLC ($CHCl_3$, MeOH, or EtOAc) showed only one spot (R_f, respectively, 0.67, 0.69, and 0.71); IR (neat) 3050, 3000, 2950, 2875, 2850, 2800, 2554, 1610, 1580, 1500, 1480, 1460, 1400, 1320, 1300, 1220, 1200, 1180, 1140, 1085, 1050, 940, 780, 760, 730 cm^{-1}; NMR ($CHCl_3$-*d*) δ 2.8 [s, 6 H, $(CH_3)_2$], 3.5 (s, 1 H, SH), 7.0–8.1 (m, 6 H, arene H).

Anal. Calcd for $C_{12}H_{13}NS$: C, 70.88; H, 6.46; S, 15.77. Found: C, 71.05; H, 6.33; S, 15.81.

For reasons that are unclear, yields were only ~50% when 10 g of **8** was reduced.

The thiol **9** was converted to **bis[5-(dimethylamino)-1-naphthyl] disulfide (14)** by adding 0.62 g of I_2 (2.44 mmol) in 10 mL of absolute EtOH dropwise with stirring to 1.00 g (4.92 mmol) of **9** in 10 mL of absolute EtOH. A bulky yellow precipitate appeared, but the iodine color persisted. The solid was removed by filtration to give 1.36 g (84%) of the disulfide dihydroiodide; mp 190–192° C dec. An ether solution of this salt was shaken with 5 × 20 mL portions of 5% aqueous NaOH (to remove HI and any unreacted thiol), washed with H_2O, dried, and evaporated to leave 0.81 g (82%) of crude **14**; mp 124–126 °C. This **14**, recrystallized twice from H_2O–EtOH, gave 0.55 g (56%) of pale yellow **14**, having a constant melting point of 128–129 °C: TLC showed only one spot ($CHCl_3$, R_f 0.62); IR (KBr pellet) 3075, 2950, 2825, 1580, 1500, 1475, 1450, 1380, 1300, 1220, 1180, 1140, 1080, 1060, 1040, 940, 780, 740 cm^{-1}; NMR ($CHCl_3$-*d*) δ 2.8 [s, 12 H, $(CH_3)_2N$], 7.0–8.2 (m, 12 H, arene H).

Anal. Calcd for $C_{24}H_{24}N_2S_2$: C, 71.24; H, 5.99; S, 15.85. Found: C, 71.44; H, 6.07; S, 15.77.

For preparation of **5-(dimethylamino)-1-naphthalenethiol picrate (15)**, picric acid (0.34 g, 1.48 mmol) in 5 mL of EtOH was added to 0.30 g (1.48 mmol) of the thiol **9** in 5 mL of EtOH. Gentle warming gave a solution, which when cooled deposited the yellow crystalline picrate **15**; yield 0.31 g (49%). Three recrystallizations from EtOH led to **15** with a constant melting point of 153–155 °C: TLC (MeOH, R_f 0.73) showed only one spot; IR (KBr pellet) 3400 (br), 3050 (doublet), 2950 (br), 2700, 1620, 1600, 1540, 1500, 1460, 1420, 1360, 1310, 1260, 1160, 1140, 1070, 900, 770, 700 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}N_4O_7S$: C, 49.99; H, 3.74; N, 12.97. Found: C, 49.79; H, 3.78; N, 12.80.

B. (Methoxycarbonyl)sulfenyl Chloride (11). Details of this preparation, based on a communication by Brois, Pilot, and Barnum,[8] were kindly provided by Dr. Brois and are included here with his concurrence.

(14) Prepared by W. S. Hanley of these laboratories;[3a] recrystallized to a constant melting point of 95–96 °C (lit.[3a] mp 95–96 °C).

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(Chlorocarbonyl)sulfenyl chloride, ClSC(O)Cl, was first prepared by placing concentrated H_2SO_4 (56.7 mL) in a three-necked, 250-mL round-bottom flask equipped with a mechanical stirrer, condenser, and addition funnel. Water (4.84 g, 269 mmol) was added dropwise with stirring. The addition funnel was replaced by a thermometer, and the solution was cooled to 20 °C. Trichloromethanesulfenyl chloride (50.00 g, 269 mmol) was added to the mixture at 20 °C over 10 min with vigorous stirring. The resulting yellow emulsion was stirred vigorously, and the temperature was slowly raised during ~30 min to 45–50 °C; rapid heating or poor stirring reportedly lead sometimes to uncontrollable frothing. Evolution of HCl was evident, and the emulsion gradually changed from yellow to amber. The mixture was stirred at 45–50 °C for a total of 2 h and then was cooled. The pale amber upper phase of (chlorocarbonyl)sulfenyl chloride (26.21 g, 74% yield) was purified by simple distillation at aspirator pressure to yield 21.47 g (61%) of the chloride as yellow-brown liquid: bp 30–31 °C (aspirator pressure); $n^{26.5}{}_D$ 1.5156 ($n^{20.5}{}_D$ found by Brois, Pilot, and Barnum 1.5158).

The sulfenyl chloride was esterified to give **11** by adding MeOH (5.24 g, 164.06 mmol) in 12 mL of ether dropwise to a solution of the sulfenyl chloride (21.47 g, 164.02 mmol) in 60 mL of ether over 1 h at ~25 °C. The mixture was stirred at ~25 °C for 23 h and then concentrated. The crude **11** was purified by simple distillation to give the pure ester **11**: yield 17.86 g (86%); bp 67–68 °C (74 torr); $n^{27}{}_D$ 1.4801 (lit.[21] $n^{21}{}_D$ 1.4827); IR (neat, salt plates) 2975, 1760 (b), 1720, 1440, 1320, 1300, 1220–1120 (b), 940, 820, 660 cm^{-1}; NMR ($CHCl_3$-*d*) showed a singlet for the CH_3 group at δ 3.9. The pure sulfenyl chloride **11** is stable for ~1 month at 0 °C (no change in refractive index); after ca. 1 month, the refractive index slowly began to rise, but distillation returned the index to a proper value. Despite negligible changes in index, however, freshly prepared samples of **11** gave best results in the preparation of **12**; older or redistilled samples gave lower yields of less pure **12**.

C. 5-(Dimethylamino)-1-naphthyl Methoxycarbonyl Disulfide Hydrochloride (12). Anhydrous HCl was bubbled through a solution of 730.2 mg (3.59 mmol) of thiol **9** in 20 mL of ether until no more white hydrochloride (**10**) precipitated. The ether was evaporated, and the resulting dry salt (**10**) was dissolved in 20 mL of CH_2Cl_2 and added dropwise over 15 min to a solution of **11** (506.1 mg, 4.00 mmol) in 20 mL of CH_2Cl_2 at 0–5 °C. The mixture then was stirred for 1 h more at the same temperature. Dark oily droplets in the solution were removed by filtration, and the CH_2Cl_2 was removed under reduced pressure. The resulting solid was washed repeatedly with ether to leave 1.110 g (94%) of pale yellow crystalline **12**; mp 208–210 °C dec. Two recrystallizations from EtOAc–hexane gave **12** having a constant melting point of 208–210 °C dec: TLC showed a single spot (EtOAc, R_f 0.68; $ClCH_2CH_2Cl$, R_f 0.57; $CHCl_3$, R_f 0.64); IR (KBr pellet) 3400 (b), 2600–2400 (b), 1740, 1460, 1430, 1380, 1140, 980, 900, 790 cm^{-1}; NMR ($CHCl_3$-*d*) δ 3.4 [s, 6 H, $(CH_3)_2N$], 3.8 (s, 3 H, OCH_3), 7.6–9.1 (m, 6 H, arene H).

Anal. Calcd for $C_{14}H_{16}ClNO_2S_2$: C, 50.97; H, 4.90; N, 4.25; S, 19.44. Found: C, 51.30; H, 5.11; N, 4.54; S, 19.50.

D. Reaction of 12 with D,L-*N*-Acetylpenicillamine. A solution of D,L-*N*-acetylpenicillamine (**13**; 123.0 mg, 0.64 mmol) in 5 mL of MeOH was added dropwise over 5 min to a solution of **12** (212.1 mg, 0.64 mmol) in 5 mL of MeOH at ~25 °C. The mixture was stirred for 60 h at ~25 °C (NMR of a similar mixture in MeOH-d_4 had shown no further change after 59 h). Evaporation of MeOH then left 270.7 mg (98%) of crude **16**: mp 145–150 °C dec; NMR (MeOH-d_4; integrals based on arene H) δ 1.4 [d, 4.8 H $(CH_3)_2C$], 1.9 (s, 2.3 H, CH_3CO), 3.5 [s, 5.5 H, $N(CH_3)_2$], 4.7 (s, 0.8 H, CH), 7.7–8.7 (m, 6 H, arene H); only a trace of the OCH_3 protons of **12** at δ 3.8 remained (integral, 0.1 H), and no other peaks were present. Attempted purification, to prepare analytically pure **16**, failed when recrystallization, preparative TLC, or short-column chromatography was used.

E. 5-(Dimethylamino)-1-naphthyl *tert*-Butyl Disulfide Hydrochloride (17). 2-Methyl-2-propanethiol (0.31 mL, 248.0 mg, 2.75 mmol) was added dropwise to a stirred solution of 225.8 mg (0.68 mmol) of **12** in 2 mL of MeOH-d_4. The NMR spectrum of a portion of the reaction mixture was scanned periodically. After 5 days, disappearance of the OCH_3 singlet at δ 3.8 showed the reaction to be complete. Concentration under reduced pressure then left 216.9 mg (97%) of crude **17**; mp 184–186 °C dec. Two recrystallizations from CH_2Cl_2–ether gave 103.2 mg (46%) of **17** having a constant melting point of 186–188 °C dec: TLC showed single spots (EtOAc, R_f 0.67; $CHCl_3$, R_f 0.68; benzene, R_f 0.53); IR (KBr pellet) 3500–3400 (br), 2950, 2850, 2400 (br), 1500, 1440, 1420, 1380–1360 (doublet), 1170, 1150, 1090, 980, 890, 780 cm^{-1}; NMR ($CHCl_3$-*d*) δ 1.3 [s, 9 H, $C(CH_3)_3$], 3.4 [s, 6 H, $N(CH_3)_2$], 7.7–9.1 (m, 6 H, arene H).

Anal. Calcd for $C_{16}H_{22}ClNS_2$: C, 58.59; H, 6.78; N, 4.27; S, 19.55. Found: C, 58.40; H, 6.69; N, 4.19; S, 19.36.

F. Fluorescence. Qualitatively (hand UV unit, UVSL 25, Ultraviolet Products Inc.), the thiol **9** in MeOH showed strong bluish fluorescence roughly comparable in intensity to the more greenish fluorescence of a similar amount of dansyl chloride (**8**). The HCl salt of **9** (**10**) seemed to fluoresce somewhat less than **8**. Solutions in MeOH of all the disulfides (**14**, the methoxycarbonyl disulfide **12**, the crude penicillamine derivative **16**, or the *tert*-butyl disulfide **17**) showed little or no fluorescence.

With an Aminco-Bowman spectrophotofluorometer, 10^{-5} M solutions in MeOH of **8**, **9**, **12**, and crude **16** all showed greatest fluorescence excitation maxima at 330 nm. Emission maxima were at 472, 442, 450, and 445 nm, respectively. Relative intensities were 57 for the thiol **9**, 8 for dansyl chloride (**8**) as a standard, and 1 for the disulfides **12** and **16**.

Weaker fluorescence was seen for **9**, **12**, and crude **16** at other wavelengths. Values in nanometers for excitation and emission (in parentheses) were as follows: for **9**, 232 (440); for **12**, 253 (456); for crude **16**, 246 (455).

D,L-2-Acetamido-3-methyl-3-(benzyldithio)butanoic Acid (23). A. Via the Thionitrite 18. A solution of 1.5 mL of 6 N HCl (9 mmol) in 5 mL of H_2O was added to the thionitrite **18** (1.00 g, 4.5 mmol) in 5 mL of DMF with stirring. α-Toluenethiol (**19**; 1.13 g, 9.1 mmol) was added. The green solution immediately became red. The resulting solution was heated to 65 °C; after 4 h at 65 °C the red color disappeared. Water (50 mL) was added, and the solution was kept at ~0 °C overnight. Solid **23** that separated was repeatedly washed with ether to remove dibenzyl disulfide: yield of crude **23** 0.60 g (42%); mp 150–152 °C. Recrystallization from EtOH–H_2O left 0.40 g (28%) of **23** with a constant melting point of 153–154 °C: TLC showed only one spot (R_f 0.64, MeOH); IR (KBr pellet) 3400, 3000, 2900, 1720, 1610, 1540, 1440, 1380, 1360, 1240, 840, 700 cm^{-1}; NMR (MeOH-d_4) δ 1.3 and 1.4 [s, 6 H, $(CH_3)_2$], 2.0 (s, 3 H, CH_3CO), 3.9 (s, 2 H, CH_2Ph), 4.7 (b, 1 H, CH), 7.2 (broad s, 5 H, Ph).

Anal. Calcd for $C_{14}H_{19}NO_3S_2$: C, 53.64; H, 6.12; S, 20.45. Found: C, 53.76; H, 6.17; S, 20.30.

B. Via the Thiolsulfonate 22. (a) D,L-2-Acetamido-3-methyl-3-(*p*-toluenesulfonylthio)butanoic Acid (22). A solution of *p*-toluenesulfinic acid (**21**; 9.80 g, 62.8 mmol) in 25 mL of DMF was added to one of the thionitrite **18** (4.50 g, 20.4 mmol) in 15 mL of DMF with stirring over ~5 min. (DMF was considered the solvent of choice because **18** decomposes only very slowly in it at ~25 °C). After 48 h of stirring, the green color disappeared. Upon addition of 200 mL of water and cooling at ~0 °C overnight, white solid that resulted was removed and repeatedly washed with ether to remove any sulfinic or sulfonic acid impurities: yield of **22** 4.30 g (61%); mp 148–150 ° C. Recrystallization from EtOH–H_2O left 4.00 g (57%) of white crystalline **22**: mp 166–167 °C; TLC showed only one spot (R_f 0.63, MeOH); IR (KBr pellet) 3400, 2950, 1720–1700, 1620, 1520, 1360, 1340, 1240, 1140, 1080, 840, 820 cm^{-1}; NMR (MeOH-d_4) δ 1.50 and 1.60 [s, 6 H, $(CH_3)_2$], 1.95 (s, 3 H, CH_3CO), 2.5 (s, 3 H, H_3CPh), 7.4–7.9 (d of d, 4 H, Ph); NMR in acetone-d_6 revealed the broad CH peak at δ 4.80, which had been buried under the HDO peak in MeOH-d_4.

Anal. Calcd for $C_{14}H_{19}NO_5S_2$: C, 48.67; H, 5.55; N, 4.06; S, 18.56. Found: C, 48.57; H, 5.65; N, 4.00; S, 18.38.

The thiolsulfonate is unchanged so far (~12 months) as indicated by NMR, TLC, melting point, and mixture melting point.

Use of equimolar proportions of sodium *p*-toluenesulfinate with the thionitrite **18** under otherwise similar conditions led to an intractable mixture. When the molar proportion of sulfinic acid

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21 was reduced from 3 to 1.5, the yield of **22** dropped from 64 to 40% (and to 35% at 60 °C). When the proportion was increased to 6, the yield was 20%. Generation of the somewhat unstable sulfinic acid in situ from three proportions of the salt with equivalent concentrated HCl, with reaction at 60 °C, gave **22** in 35% yield.

(b) Preparation of 23 from 22. Solutions were prepared by adding 0.90 mL of 1 N NaOH (0.9 mmol), and then 5 mL of EtOH, to 0.31 g (0.90 mmol) of **22** and also to 0.11 g (0.89 mmol) of α-toluenethiol (**19**). The solution of the resulting thiolate of **19** then was added to that (cloudy) of **22**. The solution, which then became clear, was stirred at ~25 °C for 2 h more and then was acidified with 10% aqueous HCl to pH 1. When the cloudy solution was kept at ~0 °C for 2 h, 0.12 g of the disulfide **23** precipitated: yield 43%; mp 152–153 °C. The melting point, mixture melting point, TLC, IR spectrum, and NMR spectrum were identical with those of **23** prepared from **18**.

Disproportionation. Aqueous solutions (having the millimolarity parenthetically stated) of **3** (38 mM), **5** (174 mM), **7** (62 mM), and **23** (6 mM) were stirred and heated under reflux in the dark (foil wrapped) at 100 ± 0.1 °C in an oil bath. Minute portions of the solutions were removed periodically and spotted on 3 × 10 cm glass slides coated with Brinkmann silica gel G, eluted (EtOH for **3**, EtOH–H_2O for **5**, MeOH for **7**, $CHCl_3$ for **23**), and subsequently developed in I_2 vapor. The "onset" of disproportionation (Table I) was taken as the time when a single spot in each case, corresponding to the unsymmetrical disulfide initially, first gave rise to three spots; the two new spots corresponded to the two symmetrical counterparts, which were run simultaneously on the plate, as was the original disulfide. "No further change" (Table I) was taken as the time when the two new spots and the initial spot no longer appeared to change in intensity or area. For study of the free base of **17**, a solution of 10 mg of **17** in 2 mL of CH_2Cl_2 was shaken with saturated aqueous $NaHCO_3$, washed with H_2O, and dried ($MgSO_4$). TLC (benzene) on one portion of the solution kept at ~25 °C in the dark still showed only one spot after 72 h. Another portion kept in ambient light at ~25 °C first showed spots corresponding to **14** and di-*tert*-butyl disulfide after ~12 h and no apparent further change in these three spots after ~15 h.

Registry No. D-**1**, 52-67-5; **2**, 38695-52-2; D-**3**, 70527-76-3; **4**, 10027-70-0; D-**5**, 70561-52-3; **6**, 18321-15-8; D-**7**, 70527-77-4; **8**, 605-65-2; **9**, 67101-61-5; **10**, 70527-78-5; **11**, 26555-40-8; **12**, 70527-79-6; D,L-**13**, 59-53-0; **14**, 70527-80-9; **14** 2HI, 70527-81-0; **15** picrate, 70527-82-1; D,L-**16**, 70527-83-2; **17**, 70527-84-3; **17** free base, 70527-87-6; D,L-**18**, 67776-06-1; **19**, 100-53-8; **21**, 536-57-2; D,L-**22**, 70527-85-4; D,L-**23**, 70527-86-5; (chlorocarbonyl)sulfenyl chloride, 24768-49-8; 2-methyl-2-propanethiol, 75-66-1; sodium *p*-toluenesulfinate, 824-79-3; trichloromethanesulfenyl chloride, 25004-95-9.

A Macrocyclic Tetradisulfide from Tetrafluoro-1,4-benzenedithiol

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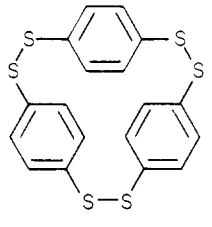
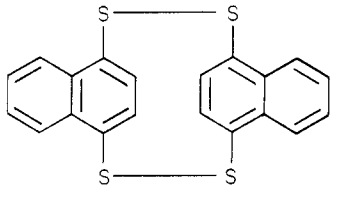
A macrocyclic tetradisulfide (**4**) has been obtained in 95% yield by the oxidation of tetrafluoro-1,4-benzenedithiol with dimethyl sulfoxide. The compound forms complexes with *N,N'*-dimethyldihydrophenazine and 1,3-diphenylisobenzofuran. Conformational changes take place in solution with changes in temperature.

Oxidation of aromatic 1,4-dithiols has been the subject of a number of studies. 1,4-Benzenedithiol is reported to give polymeric disulfides.[2-4] However, by carrying out the oxidation with iodine at high dilution, Wong and Marvel obtained the three-unit macrocycle **1** in 30% yield.[5]

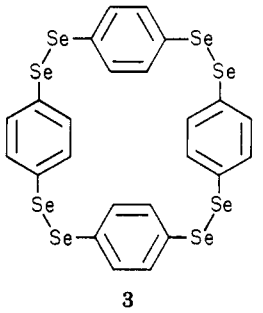


1

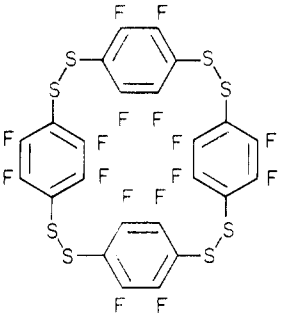


2

Marschalk recorded the formation of **2**, supported by molecular weight data, in unspecified yield from oxidation of 1,4-naphthalenedithiol with alkaline ferricyanide.[6] Air oxidation of 1,4-benzenediselenol gives the four-unit macrocycle **3** quantitatively.[7]



3



4

Synthesis and Properties of 4. In the present work, tetrafluoro-1,4-benzenedithiol has been oxidized with dimethyl sulfoxide.[8] When the dithiol is placed in dimethyl sulfoxide, it quickly dissolves with formation of a deep orange solution, the solution becomes warm, and the crystalline, four-unit macrocycle **4** soon precipitates in 95% yield while the color fades. This facile synthesis of **4** is a peculiarity of tetrafluoro-1,4-benzenedithiol, as 1,4-benzenedithiol, 2,5-dimethoxy-1,4-benzenedithiol, and tetramethyl-1,4-benzenedithiol formed polymers under the

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