Extensive electron delocalization could occur. In addition, the vacant *d* orbitals on sulfur could participate in a π-bonding scheme involving unshared electron pairs on neighboring atoms. Thus the electron pairs that might normally be considered sites of attack by methyl iodide are delocalized, so that they are no longer available for reaction.

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Dicyclohexylcarbodiimide-Mediated Sulfation of Alkanethiols

New Method for Preparation of Organic Thiosulfates

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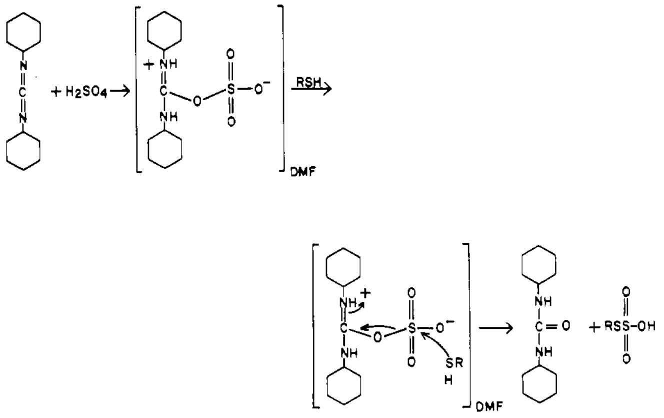
Octyl, dodecyl, hexadecyl, benzyl, and cyclohexyl thiosulfates were synthesized by the reaction of sulfuric acid with alkanethiols and dicyclohexylcarbodiimide in the solvent dimethylformamide. The formation of these organic thiosulfates was highly dependent upon the ratio and concentration of the reactants. The thiosulfates were isolated by ion-exchange chromatography. A mechanism for the reaction is proposed.

ORGANIC THIOSULFATES (Bunte salts) have been studied for many years. Their synthesis and reactions have recently been summarized (*4*). Bunte salts are extensively used in the dye industry and show considerable medicinal potential as antiradiation agents. The isolation of several naturally occurring organic thiosulfates has stimulated biochemical interest (*1, 5, 7, 8*).

Alkyl thiosulfates have been prepared by the reaction of an alkyl halide with thiosulfate ion, the reaction of sulfite or bisulfite ion with a disulfide or hydrodisulfide, and the reaction of chlorosulfonic acid or sulfur trioxide adducts with an alkanethiol. Previously, we reported the radiochemical synthesis of compounds possessing chemical properties of organic thiosulfates (*2*). Further investigation has confirmed the proposed structures and allows us now to report the synthesis of alkyl thiosulfates by this new method, the dicyclohexylcarbodiimide-mediated sulfation of alkanethiols.



EXPERIMENTAL

Material and Methods. The solvents, alkanethiols, and alkyl halides were purified by distillation. Their purity was determined by gas chromatography and thin-layer chromatography (Supelcosil-12B, Supelco, Inc.) (benzene–diethyl ether–ethanol–acetic acid; 50:40:2:0.2, v./v.). The thiosulfates were analyzed by thin-layer chromatography (chloroform-methanol-water; 65:25:4, v./v.) and the plates were stained with iodine and charred with a 20% perchloric acid spray. Infrared spectra were obtained with a Perkin-Elmer 521 spectrophotometer (Nujol). A Bendix Time of Flight mass spectrometer was used for the laser ionization mass spectra of the thiosulfates. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Whatman diethylaminoethylcellulose (DE-11) and Dowex 50W-X8 columns were used as ion exchangers.

General Procedure for Preparation of Sodium Alkyl Thiosulfates by DCC-Mediated Sulfation of Alkanethiol. DCC (21.7 mmoles) was dissolved in 6.68 ml of DMF and added to a solution of 4.0 mmoles of alkanethiol (1-octanethiol, 1-dodecanethiol, 1-hexadecanethiol, α-toluenethiol, 2-naphthalenethiol, and cyclohexanethiol) in 5 ml of DMF. To this swirled solution (0°) was added dropwise 5 ml of DMF containing 4.48 mmoles of concentrated H_2SO_4 (molar ratio of reactants: 5.44:1:1.12, DCC:RSH:H_2SO_4). The reaction mixture was occasionally shaken for 15 minutes and then 4 ml of H_2O was added to convert any unreacted DCC to dicyclohexylurea. The entire mixture was immediately placed on a DEAE-cellulose column (Cl^- form, 5 grams of DEAE-cellulose, 2.6-cm diameter) and eluted with 2 liters of methanol. The unreacted alkanethiol and the relatively insoluble dicyclohexylurea were eluted with the excess methanol. The thiosulfate ester was then eluted from the DEAE-cellulose column with 250 ml of methanolic ammonium hydroxide ($14.8M$ NH_4OH-methanol; 1:9, v./v.) and the eluate was immediately evaporated to dryness under

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reduced pressure. The residue was suspended in 100 ml of methanol and the supernatant liquid decanted. The insoluble material was mostly ammonium chloride. The methanolic solution, containing the ammonium salt of alkyl thiosulfate, was passed through a Dowex-50 column (Na^+ form, 50 grams of Dowex-50, 1.4-cm diameter) and the resulting solution was evaporated under reduced pressure. The residue was suspended in 100 ml of anhydrous acetone and filtered. The insoluble material was mostly sodium chloride. The filtrate was evaporated under reduced pressure, yielding colorless crystalline plates of sodium alkyl thiosulfate. These salts were hygroscopic and thermally unstable, and possessed water of hydration in varying amounts.

SODIUM HEXADECYL THIOSULFATE. 37% yield, recrystallized from H_2O, m.p. 115° (decomp.). Anal. Calcd. for $C_{16}H_{33}S_2O_3Na \cdot \frac{1}{2}H_2O$: C, 52.00; H, 9.27; S, 17.35; Na, 6.22. Found: C, 51.69; H, 9.22; S, 17.30; Na, 6.36. When the amount of H_2SO_4 used was doubled (H_2SO_4:RSH; 2.24:1), the yield of sodium hexadecyl thiosulfate was reduced (15%).

SODIUM BENZYL THIOSULFATE. 55% yield, recrystallized from absolute ethanol, m.p. 170° (decomp.). Anal. Calcd. for $C_7H_7S_2O_3Na$: C, 37.14; H, 3.12; S, 28.34; Na, 10.16. Found: C, 37.34; H, 3.12; S, 28.40; Na, 9.88.

SODIUM OCTYL THIOSULFATE. 28% yield, recrystallized from 95% ethanol, m.p. 170° (decomp.). Anal. Calcd. for $C_8H_{17}S_2O_3Na \cdot H_2O$; C, 36.08; H, 7.19; S, 24.07; Na, 8.63. Found: C, 36.37; H, 6.97; S, 24.30; Na, 9.03. When the amount of H_2SO_4 was doubled (H_2SO_4:RSH; 2.24:1), the yield of thiosulfate was reduced (7%).

SODIUM DODECYL THIOSULFATE. 44% yield, recrystallized from 95% ethanol, m.p. 155° (decomp.). Anal. Calcd. for $C_{12}H_{25}S_2O_3Na \cdot \frac{1}{2}H_2O$; C, 45.98; H, 8.36; S, 20.46; Na, 7.35. Found: C, 45.88; H, 8.53; S, 20.11; Na, 8.01.

SODIUM CYCLOHEXYL THIOSULFATE. 42% yield, recrystallized from 95% ethanol, m.p. 175° (decomp.). Anal. Calcd. for $C_6H_{11}S_2O_3Na \cdot 1\frac{1}{2}H_2O$: C, 29.41; H, 5.47; S, 26.18; Na, 9.39. Found: C, 29.48; H, 5.48; S, 26.25; Na, 8.56.

General Procedure for Preparation of Sodium Alkyl Thiosulfates from Alkyl Halides and Sodium Thiosulfate (*6*). An aqueous solution (11 ml) of sodium thiosulfate (10 mmoles) was added to an ethanol solution (11 ml) containing an alkyl halide (10 mmoles). The mixture was refluxed until it became homogeneous, after which the solvent was evaporated under reduced pressure. The remaining solid was suspended in acetone and the insoluble material removed by filtering. The acetone filtrate was evaporated to dryness under reduced pressure and the residue resuspended in acetone and filtered. Evaporation of the solvent under vacuum gave relatively pure sodium alkyl thiosulfate, which was further recrystallized from the appropriate solvent (ethanol or H_2O).

The sodium salts of hexadecyl thiosulfate (65% yield), benzyl thiosulfate (26% yield), and octyl thiosulfate (7% yield) were prepared in this manner. No sodium cyclohexyl thiosulfate could be prepared from chlorocyclohexane.

RESULTS AND DISCUSSION

Octyl, dodecyl, hexyldecyl, benzyl, and cyclohexyl thiosulfates were synthesized by dicyclohexylcarbodiimide-mediated sulfation of the respective alkanethiol. This procedure is rapid, widely applicable, general in scope, and operative where other procedures may fail. The reaction seems particularly useful for radiochemical synthesis of ^{35}S-labeled thiosulfates because of the readily available and reasonably priced $^{35}SO_4^{2-}$. If only small quantities of thiosulfates are needed, as in the preparation of ^{35}S-labeled intermediates, preparative thin-layer chromatography can be used in place of the ion-exchange columns. The sodium salts of the thiosulfates were produced, in this case, to facilitate the analytical results.

The infrared and mass spectra and the melting points of the alkyl thiosulfates synthesized by the DCC-mediated reaction were compared to the alkyl thiosulfates synthesized by the reaction of thiosulfate ion with an alkyl halide. Cyclohexyl thiosulfate could not be prepared by the alkyl halide method; accordingly, no comparisons were made.

The concentration of the reactants in DMF (*2*) and the molar ratio of sulfuric acid to alkanethiol (1.12:1.0) are critical for optimum yields. No thiosulfates are produced under dilute reaction conditions. Previously 2-naphthalenethiol was shown to form two ^{35}S-labeled products in low yield (7%) and the low yield was reasoned to be owing to the poor nucleophilic strength of the 2-naphthalenethiol (*2*). However, in this investigation no naphthyl thiosulfate was isolated. When the amount of sulfuric acid used was doubled (molar ratio of 2.24:1.0;H_2SO_4:alkanethiol), the yield of thiosulfate was drastically reduced. Evidently, the excess sulfuric acid is competing with the alkanethiol as a nucleophile.

An alternate explanation for the reduced yield of alkyl thiosulfate with increasing sulfuric acid concentrations could be repression of the equilibrium $RSH \rightleftharpoons RS^- + H^+$ which produces the highly nucleophilic thiolate ion. However, this approach does not explain why 2-naphthalenethiol did not react, why the more dilute the reactants the less the yield, and why alcohols react much more readily than alkanethiols. In view of these results and analogous investigations (*2*, *3*), a reasonable mechanism would involve the formation of a solvolyzed protonated DCC-H_2SO_4 intermediate followed by an alkanethiol nucleophilic attack to produce a thiosulfate and dicyclohexyl urea.

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