Table VII. Representative Rate Data for 3-Bromopropyldimethylamine (1)[a]

Initial concn, M		$k_{obsd} \times 10^5$/
1	$LiNO_3$	s^{-1} [b]
0.02	...	5.0
0.02	0.40	6.0
0.10	...	5.7
0.50	...	7.2
1.01	...	11.1

[a] Solvent methanol, 25 °C. [b] Apparent first-order rate constant.

at about 0.8 ppm lower field than the triplet for the polymer, and the separation permits an analysis for the amount of cyclic products. The difference is smaller for the C-6 compound.

Registry No.—3-Dimethylaminopropanol, 3179-63-3.

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Effect of Hexadecyltrimethylammonium Bromide on the Thiolysis of *p*-Nitrophenyl Acetate

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Micelles of hexadecyltrimethylammonium bromide produce a rate increase of ca. 50-fold in the thiolysis of *p*-nitrophenyl acetate by thiophenoxide anions. The distribution constants between the water and the micellar phase, determined spectrophotometrically, of *p*-Cl, *p*-CH_3, *p*-CH_3O, and thiophenoxide anions were 20×10^3, 8.2×10^3, 2.7×10^3, and 4.8×10^3 M^{-1}, respectively. The calculated distribution constants of all four undissociated thiophenols were of the order of 1×10^3 M^{-1}. The apparent pKs of the thiophenols were lowered upon incorporation into the micellar phase. The entire rate increase produced by hexadecyltrimethylammonium bromide in the thiolysis of *p*-nitrophenyl acetate by thiophenoxides can be explained on the basis of concentration of the reagents on the micellar phase.

Only a limited number of nucleophiles have been unequivocally demonstrated to participate in covalent catalysis by enzymes.[1] Among these, the SH group of cysteine residues shows an unusually high reactivity when situated in the active site of "SH enzymes" such as papain,[2] ficin,[3] bromelin,[4] or glyceraldehyde-3-phosphate dehydrogenase.[5] The nucleophilic reactivity of SH groups in proteins can range from those which are extremely reactive to those which are nonreactive or "masked".[6,7] Although the details are far from clear, there is general agreement that this wide range of reactivities can be attributed to differing microenvironments of the potentially reactive SH group. Unusually high SH reactivities are also found with low molecular weight compounds such as coenzyme A (CoASH) and glutathion (GSH), which participate covalently as coenzymes in a number of enzyme-catalyzed reactions.[6,7] Since the reactivities of the SH groups of GSH or CoASH are entirely within the expected range[8] (on the basis of comparison with other mercaptans), the SH group of both GSH and CoASH must be "activated" by the apoenzyme, much in the same manner as active site SH groups.

Since micelles serve as models of the (possible) role of charged and/or neutral interphases on nucleophilic reactivity (for recent reviews on micelles see 9–12) the study of micellar effects on SH reactivity has relevance to the question of the reactivity differences found in biological systems. There is indeed evidence that micelles affect, markedly in some cases, the rates of different SH reactions:[8,13–16] (1) The rate of reaction of *N*-dodecanoyl-*dl*-cysteine (DCS) with chloroacetamide, iodoacetamide, and *p*-nitrophenyl acetate (NPA) is increased by 5–7-, 60–100-, and 100–200-fold, respectively, upon addition of hexadecyltrimethylammonium bromide (CTAB).[13] On the other hand, incorporation of DCS into negative micelles leads to a decrease of the apparent reactivity of the SH group.[13] (2) The rate of reaction of alkyl mercaptans

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with NPA is accelerated by up to 10^4-fold upon addition of alkyl trimethylammonium bromide detergents.[14] (3) The formation of mixed micelles of thiols (like β-mercaptoethylammonium) and oleic acid has been proposed to explain the thiol-catalyzed cis–trans isomerization of oleic acid.[15] (4) CTAB increases 3×10^3-fold the reaction rate of thiophenoxide anion with 2,4-dinitrofluorobenzene.[16] (5) The rate of thiolysis of NPA by GSH and CoASH is accelerated by CTAB micelles by factors of 100 and 300, respectively.[8]

The rate increase observed for many reactions upon addition of detergents above the critical micelle concentration (CMC) can often be explained on the basis of concentration of the reagents in the micellar phase and changes in the apparent pK of a nucleophile, without requiring the postulation of changes in the intrinsic reactivity of the attacking nucleophile.[17] Before attributing the observed rate effect of micelles to changes in nucleophile reactivity (a pertinent analysis can be found in ref 18) it is thus necessary to correct these rates for concentration effects and distribution of the ionic species between the aqueous and micellar phases.

In this work, we demonstrate that the rate increase produced by CTAB on the reaction between thiophenoxide and NPA can be explained entirely on the basis of concentration of the reagents in the micellar phase; consequently, intrinsic effects of the micellar phase on reactivity must be of little or no importance in this system.

Experimental Section

CTAB (E. Merck, Darmstadt pro Analysis grade Lot 252534) was extracted with ether and recrystallized three times from acetone–ethanol. Thiophenol (Eastman Kodak Co.) was vacuum distilled. p-Methoxythiophenol (Aldrich Chem. Co.) was used as received. p-Methyl- and p-chlorothiophenol were recrystallized from ethanol–water. Thiophenyl acetate was prepared from acetic anhydride and thiophenol and purified by vacuum distillation (bp 110 °C (13 mmHg)).[19]

p-Nitrophenyl acetate (Sigma Chem. Co.) and 5,5′-dithiobis(p-nitrobenzoic acid) (BDH Biochemicals) were used without further purification. All other reagents were analytical grade. Water which had been deionized and twice distilled in glass was used throughout.

Methods. The CTAB concentration of stock solutions was determined by bromide titration.[20] Thiophenol concentrations in stock solutions in deareated ethanol were determined by measuring the free SH content.[21]

Kinetics. The thiolysis of NPA was followed by measuring the appearance of p-nitrophenoxide (405 nm) in a Gilford recording spectrophotometer equipped with a thermostated cell compartment (Forma Scientific Circulating Bath) maintained at 30 ± 0.2 °C. The reaction mixture was temperature equilibrated in the cell compartment and reaction was initiated by adding (0.01 mL) a stock solution of NPA ($1–2 \times 10^{-3}$ M) in CH_3CN. The total organic solvent in the reaction never exceeded 0.8% (v/v). All solutions were deareated under vacuum and flushed with N_2.

Apparent first-order rate constants (thiophenol/NPA:10/1) were obtained from log ($DO_\infty - DO_t$) vs. time plots (Hewlett Packard Model 10 simple linear regression program), which were linear for (at least) 4 half-lives. Second-order rate constants were obtained from

$$k_2 = \frac{k_\psi - k_w}{|\mathrm{RSH}|_T} \tag{1}$$

where k_ψ is the observed apparent first-order rate constant in the presence of thiophenol and k_w is the observed first-order rate constant for the spontaneous hydrolysis of NPA under the same conditions (pH, CTAB) in the absence of the thiophenol. $|\mathrm{RSH}|_T$ is the total concentration of added thiophenol, which, under the conditions employed (vide infra), is totally dissociated.

These results were confirmed (Figures 1A and 1B) by measuring the variation of the observed rate constant with thiophenol concentration, both in the absence (Figure 1A) and in the presence (Figure 1B) of CTAB.

Determination of pK of Thiophenols. The effect of CTAB on the apparent pK of the thiophenols was determined at a single (saturating) CTAB concentration. Spectral data obtained for thiophenol and thiophenoxide anion both in the presence and absence of CTAB were utilized in the following equation:

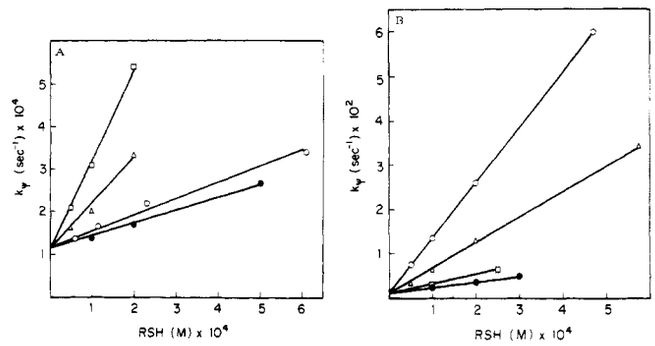

Figure 1. Effect of the variation of thiophenol concentration on the rate of thiolysis of NPA. All reactions were done in 0.02 M borate buffer pH 8.5 with ca. 5×10^{-6} M NPA. A: (●) p-chlorothiophenol; (○) thiophenol; (△) p-methylthiophenol; (□) p-methoxythiophenol. B (all reactions contained 4×10^{-3} M CTAB): (●) p-chlorothiophenol; (□) thiophenol; (△) p-methylthiophenol; (○) p-methoxythiophenol.

$$K = \frac{[H^+](1 - (E_{AH}/E_\psi))}{(E_{A^-}/E_\psi) - 1} \tag{2}$$

where E_ψ is the observed extinction coeficient ($A_\psi/(\mathrm{RSH})_T$) at particular H^+ concentration and wavelength and E_{AH} and E_{A^-} are the extinction coefficients of the thiophenol and thiophenoxide anions at the same wavelength. Appropriate controls assured that Lambert–Beer law was obeyed at the CTAB (4×10^{-3} M) and thiophenol (ca. 2×10^{-5} M) concentrations used.

Determination of Distribution Constants between the Water and Micellar Phases. According to the phase-separation model,[17,18] the distribution constant (K_a) for the thiophenoxide anions can be defined as

$$K_a \simeq \frac{C_m}{C_w}\overline{V} \tag{3}$$

where C_m and C_w are the concentrations of the anion in the micellar and aqueous phases, respectively, and $\overline{V}$ is the molar volume of the micellized detergent. Using this model and assuming that the volume of the micellar "phase" is small compared to the total volume of the solution, it can be shown that

$$C_T = C_m C_D \overline{V} + C_w \tag{4}$$

where C_D is the concentration of micellized detergent and C_T is the total anion concentration.

From eq 3 and 4, it can be shown that

$$E_\psi = \frac{K_a C_D}{(1 + K_a C_D)} \times E_m + \left(1 - \frac{K_a C_D}{(1 + K_a C_D)}\right) \times E_w \tag{5}$$

where E_ψ is the observed extinction coefficient at a particular wavelength and detergent concentration and E_m and E_w are the extinction coefficients of the anion in the micellar and aqueous phases, respectively.

Rearranging eq 5, one obtains a linearized form of this equation that permits the determination of K_a.

$$\frac{1}{E_\psi - E_w} = \frac{1}{K_a(E_M - E_w)} \times \frac{1}{C_D} + \frac{1}{(E_m - E_w)} \tag{6}$$

Typical results, showing the effect of CTAB on the spectra of thiophenoxides and plots of eq 6, are presented in Figures 2A and 2B. The distribution constants for the undissociated thiophenols were calculated as described by Berezin and co-workers from the K_a and the effect of CTAB on pK.[22]

Results

We have previously shown that CTAB exerts a marked effect on the UV spectra of thiophenoxide anion.[16] These spectral changes were used to calculate both distribution constants and apparent pK shifts of the thiophenols (Experimental Section). The relevant spectral data are presented in Table I.

Table II summarizes the results for the effect of CTAB on

Table I. Effect of CTAB on the Spectra of Thiophenols

Compd	Registry no.	RSH[a] λ_{max}, nm	RSH[a] E, M^{-1} cm^{-1}	R_S^-[b] λ_{max}, nm	R_S^-[b] E, M^{-1} cm^{-1}	RSH + CTAB[c] λ_{max}, nm	RSH + CTAB[c] E, M^{-1} cm^{-1}	R_S^- + CTAB[d] λ_{max}, nm	R_S^- + CTAB[d] E, M^{-1} cm^{-1}
Thiophenol	108-98-5	237.8	271	262.5	12600	238.0	252	275.0	9468
p-Methoxythiophenol	696-63-9	239.0	753	262.5	14097	241.0	650	270.0	16632
p-Chlorothiophenol	106-54-7	245.0	1041	270.0	15143	247.0	1650	285.0	15500
p-Methylthiophenol	106-45-6	238.0	511	265.0	12634	240.0	522	276.0	12426

[a] In 0.01 M HCl. [b] Borate buffer, 0.02 pH 8.5. [c] In 0.01 M HCl containing 4×10^{-3} M CTAB. [d] In 0.02 M borate buffer pH 8.5 containing 4×10^{-3} M CTAB.

Table II. Distribution Constants of Thiophenols between Water and CTAB and Effect of CTAB on the Apparent pK of Thiophenols

Compd	$K_{a(SH)} \times 10^{-3}$ [a]	$K_a \times 10^{-3}$ [b]	pK[c]	pK_m[d]
p-Chlorothiophenol	1	20 ± 5	6.5	5.3
Thiophenol	1	4.7 ± 0.8	6.8	6.2
p-Methylthiophenol	1	8.2 ± 0.5	7.1	6.3
p-Methoxythiophenol	0.93	2.7 ± 0.4	7.0	6.6

[a] Calculated according to ref 22. [b] Calculated from eq 6. [c] pK in the water see ref 29 for independent measurements. [d] Apparent pK in the presence of 4×10^{-3} M CTAB, calculated from eq 2.

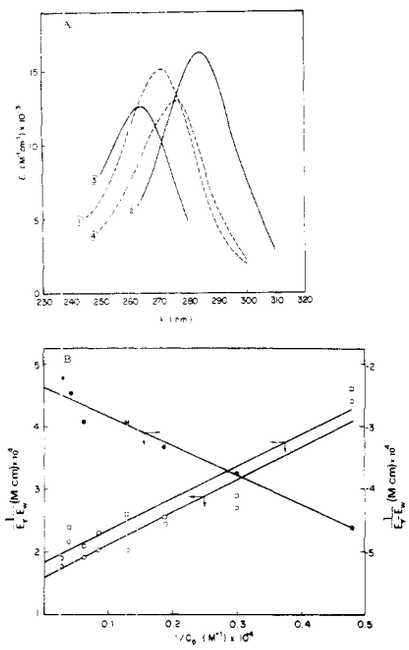

Figure 2. Effect of CTAB on the spectra of thiophenoxide anions. All spectra were obtained in 2×10^{-2} borate buffer pH 8.5. A: (1) *p*-chlorothiophenol; (2) *p*-chlorothiophenol, with added 4×10^{-3} M CTAB; (3) *p*-methylthiophenol; (4) *p*-methylthiophenol, with added 4×10^{-3} M CTAB. B (determination of K_a of thiophenoxide according to eq 6): (●) 250 nm; (○) 285 nm; (□) 275 nm.

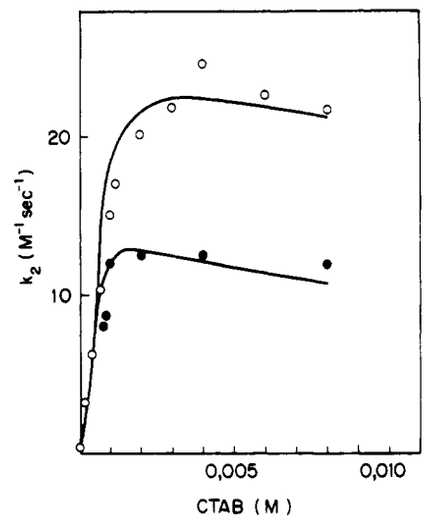

Figure 3. Effect of CTAB on the thiolysis of NPA: (●) *p*-chlorothiophenol in 2×10^{-2} M borate buffer pH 8.5; (○) thiophenol in phosphate buffer 4.5×10^{-2} M pH 7.8. The curves were calculated using eq 7 (see text). The concentration of NPA used was usually 5×10^{-6} M and the thiophenols 5×10^{-5} M.

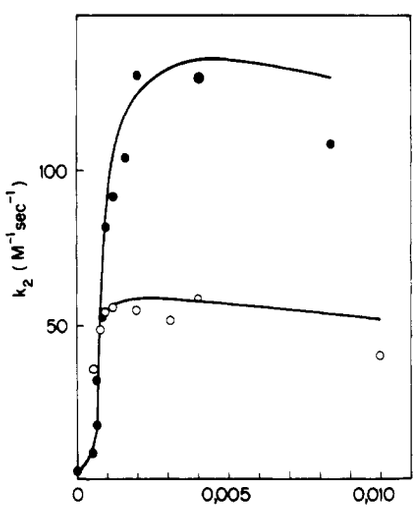

Figure 4. Effect of CTAB on the thiolysis of NPA: (○) *p*-methylthiophenol; (●) *p*-methoxythiophenol. Reactions were done in 2×10^{-2} M borate buffer pH 8.5; curves were calculated using eq 7 (see text). The concentration of NPA used was usually 5×10^{-6} M and the thiophenols 5×10^{-5} M.

the apparent pK of substituted thiophenols and the corresponding distribution constants between the aqueous and micellar phases of both the protonated and unprotonated forms of the thiophenols. From the pK values it is evident that all of the thiophenols should be completely dissociated under our kinetic conditions (pH >7.8), especially in the presence of CTAB. Thus, the second-order rate constants for thiolysis of NPA represent those for the reaction between the thiophenoxide anions and NPA.

The addition of CTAB causes ca. a 50-fold increase in the rate of thiolysis of NPA by the thiophenoxide anions (Figures 3 and 4, Table III). The products of these reactions are, in all cases, *p*-nitrophenoxide and the corresponding thiophenyl acetate. On the basis of known reaction rates for hydrolysis of thiol esters,[1,8,23] it can be anticipated that the resulting thioesters should be stable under our reaction conditions.

Table III. Effect of CTAB on the Thiolysis of NPA by Thiophenoxides

Compd	Registry no.	k_{2w}, M^{-1} s^{-1} [a]	k_{2max}, M^{-1} s^{-1} [b]	k_{2M}, M^{-1} s^{-1} [c]	K_a, M^{-1} [d]
p-Chlorothiophenoxide	35337-68-9	0.30	12.7	0.19	15000
Thiophenoxide	13133-62-5	0.36	25.0	0.39	3900
p-Methylthiophenoxide	26330-85-8	1.08	59.4	0.91	7700
p-Methoxythiophenoxide	26971-83-5	2.29	130.0	2.18	2300

[a] Second-order rate constant in the aqueous phase. [b] Observed maximum second-order rate constant in the presence of CTAB (see Figures 3 and 4). [c] Calculated values for the second-order rate constant in the CTAB phase (eq 7 see text). [d] Best fit value for the distribution constant (eq 7 see text).

Conclusive evidence for such stability was obtained by demonstrating a quantitative correspondence between the decrease of the free SH content and the production of p-nitrophenoxide, both in the presence (4×10^{-3} M) and absence of CTAB, and the stability of thiophenyl acetate under all reaction conditions described in this work.

The second-order rate constants increase sharply at CTAB concentrations above 5×10^{-4} M. Independent conductimetric data confirm that, under our kinetic conditions, the CMC of CTAB is, in fact, lowered from 9×10^{-4} M[11] to 5×10^{-4} M.

The effect of CTAB on the rate of thiolysis was quantitatively analyzed using a phase-separation model[17]

$$k_2 = \frac{(k_{2M}/\overline{V})K_aK_bC_D + k_{2w}}{(1 + K_aC_D)(1 + K_bC_D)} \quad (7)$$

where k_2 is the observed second-order rate constant, k_{2M} and k_{2w} are the second-order rate constants in the micellar and aqueous phases, respectively, and K_a and K_b are the distribution constants of the thiophenoxide and NPA, respectively.

Equation 7 was fitted to the experimental data (Figures 3 and 4) in the following manner. Taking $K_b = 27$ M^{-1},[18] CMC $= 5 \times 10^{-4}$ M (vide supra), and $\overline{V} = 0.37$ M^{-1} [18] and using the corresponding experimental values for k_{2w} (Table III), the best values for K_a and k_{2M} were obtained by successive iterations. The initial value for K_a was obtained from the results presented in Table II. An initial estimate of k_{2M} can be obtained by an examination of the maximum catalytic enhancement in the following manner. From eq 7 it can be shown that:[17]

$$\left|\frac{k_{2max}}{k_{2w}}\right| = \frac{k_{2M}}{k_{2w}\overline{V}} \times \frac{K_a \times K_b}{(K_a^{1/2} + K_b^{1/2})^2} \quad (8)$$

where k_{2max} is the maximum second-order rate constant obtained by addition of detergent. When $K_a \gg K_b$ eq 8 reduces to

$$\lim_{K_a \gg K_b} \left|\frac{k_{2max}}{k_{2w}}\right| = \frac{k_{2M}}{k_{2w}} \times \frac{K_b}{\overline{V}} \quad (9)$$

For $K_b = 27$ M^{-1} and $\overline{V} = 0.37$ M^{-1}

$$\lim_{K_a \gg K_b} \left|\frac{k_{2max}}{k_{2w}}\right| = \frac{k_{2M}}{k_{2w}} \times 77 \quad (10)$$

which predicts a maximum rate enhancement of 77 if $k_{2M} = k_{2w}$. Since the maximum rate enhancements found are no larger than 50, an initial value of $k_{2M} = k_{2w}$ is fully justified. The best fit values of k_{2M} and K_a are presented in Table III. It should be noted that the latter are within experimental error of the values of K_a obtained from the absorption data. Moreover, the second-order rate constants in the micellar phase (k_{2M}) (with the exception of p-chlorothiophenoxide) are essentially equal to those in the aqueous phase (k_{2w}).

Discussion

The interpretation of micellar effects on reactions between hydrophobic nucleophiles and micelle-incorporated substrates has been greatly facilitated by an analysis, due to Berezin and co-workers,[17] in which the concentration of substrates in the micellar phase can be explicitly taken into account. It can be shown[24] that this treatment may be applied rigorously (that is, micelles can be considered as a separate pseudophase) when the concentration of the substrates is not sufficient to saturate the micellar phase and the substrates partition independently of each other.

The analysis of the effect of CTAB on the thiolysis of NPA demonstrates unequivocally that the rate acceleration can be attributed exclusively to concentration of the substrates in the micellar phase. The calculated second-order rate constants for thiolysis of NPA by thiophenoxide, p-methylthiophenoxide, and p-methoxythiophenoxide in the micellar phase are, within experimental error, identical to the second-order rate constants measured in the absence of CTAB. The calculated second-order rate constant for the thiolysis of NPA by p-chlorothiophenoxide is lower in the micellar phase than in water. Even in this case a net acceleration is observed, since this decrease in rate is outweighed by the concentration of NPA and p-chlorothiophenoxide in the micellar phase.

The distribution constants for the thiophenoxide anions increase in the order

$$p\text{-MeO} < p\text{-H} < p\text{-Me} < p\text{-Cl}$$

On the other hand, the distribution constants for the undissociated thiophenols are smaller than those for the corresponding anions and have a constant value of ca. 1×10^3 M^{-1}. This difference between the distribution constants for the protonated and unprotonated forms of the thiophenols indicates that the association of the thiophenoxides with the micelle has a strong electrostatic component. Furthermore, the association of the thiophenoxides with CTAB exhibits a dependence on the para substituent; analogous substituent effects have been observed in other studies of the incorporation of negatively charged aromatic derivatives in CTAB.[25,26]

In conjunction with the substituent effects on K_a there is a corresponding shift in the apparent pKs of the thiophenols in the order

$$p\text{-MeO} < p\text{-H} < p\text{-Me} < p\text{-Cl}$$

In view of the lack of micellar effects on reactivity, this pK shift can be attributed to the increased solubilization of the thiophenoxide anions as compared to the thiophenols.

The data presented above strongly suggest that the lack of micellar effects on the second-order rate constants is related to the position of the thiophenoxide ions in the CTAB micelle. The relative orders and magnitudes of the association constants for the thiophenoxide anions and the thiophenols suggest, as has been previously shown for cases of other negatively charged aromatics,[11] that the principal interaction involved in the association of the thiophenoxide(s) with the micelle is that between the positive surfactant head group and the aromatic ring. Such an interaction would tend to restrict the environment of the negatively charged sulfur to the aqueous limit of the Stern layer. This environment, and the

fact that nucleophilic attack of the thiophenoxide anions is probably not rate limiting in this case,[27] would minimize the effect of the interface on the reaction rate.

We emphasize, however, that the absence of significant intrinsic rate effects on the thiolysis of NPA by thiophenoxides in CTAB cannot be taken as general phenomenon, i.e., the lack of an effect of charged interfaces on the reactivity of SH groups. Indeed preliminary investigations[14] of the thiolysis of NPA by long-chain alkyl mercaptans, which is not limited by the same restrictions, show that the catalytic factors are much higher than those predicted on the basis of eq 9 with $k_{2M} = k_{2w}$.

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Registry No.—CTAB, 57-09-0; NPA, 830-03-5.

References and Notes

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Addition of Organocopper(I) Reagents to α,β-Acetylenic Sulfoxides[1a]

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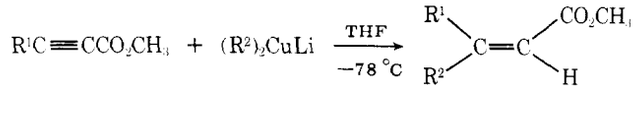
α,β-Acetylenic sulfoxides (**2**) reacted readily with monoalkylcopper reagents (**1**) at −78 °C in tetrahydrofuran to afford high yields of β-alkylated α,β-ethylenic sulfoxides (**3**). As in the analogous reaction with α,β-acetylenic esters, the addition was highly stereoselective, giving the product of a cis addition to the triple bond almost exclusively. The product sulfoxides were oxidized almost quantitatively with *m*-chloroperbenzoic acid to produce the corresponding sulfones (**12**) stereospecifically, thus providing a highly stereoselective synthesis of isomeric α,β-ethylenic sulfones. The structures of these compounds, and thus the cis nature of the addition reaction, were established on the basis of their ^{1}H NMR spectra, and in the case of (*Z*)- and (*E*)-1-(ethanesulfonyl)-2-methyl-1-hexene (**14a** and **14b**) were confirmed unambiguously by an alternate stereospecific synthesis of each isomer. The reaction of (*E*)-2-iodo-1-(ethanesulfonyl)-1-hexene (**21**) with methylcopper bis(diisopropyl sulfide) gave **14a**, while (*E*)-2-iodo-1-(ethanesulfonyl)propene (**20**) and the corresponding *n*-butylcopper complex gave **14b**. In contrast to the clean addition of monoalkylcopper reagents to acetylenic sulfoxides, lithium di-*n*-butylcuprate reacted with **2a** and **2b** to also give ethyl *n*-butyl sulfoxide. This cleavage product presumably resulted from attack at the sulfoxide sulfur rather than additive attack on the triple bond.

The chemistry of organocopper(I) reagents represents an ever-expanding topic of investigation that has received a great deal of attention in recent years.[2] In particular, the conjugate addition reactions of organocopper(I) reagents with α,β-unsaturated carbonyl compounds and related substances have been actively investigated since 1966, when it was demonstrated that such species were the reactive intermediates in the copper-catalyzed conjugate additions of Grignard reagents to α,β-unsaturated ketones.[3] α,β-Acetylenic esters also undergo a facile conjugate addition reaction with lithium diorganocuprates,[4] with cis addition taking place exclusively.



In contrast, an investigation of the reaction of lithium dialkylcuprates with a number of α,β-ethylenic sulfur compounds[5] has shown that with these substrates conjugate addition, if it occurs at all, is more difficult than with α,β-ethylenic carbonyl compounds, and that competing side reactions are more prevalent.

At the time this work was initiated, no additions of organocopper(I) reagents to α,β-acetylenic sulfur compounds had

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