alysts[15] (0.1 mol) than in their absence, the highest differences being met with in the case of substrates insoluble in the aqueous phase. In the case of esters of primary alcohols, attempts to perform the hydrolysis with 10 M H_2SO_4 failed. This is likely due to the fact that, also under two-phase conditions, acid hydrolysis of *tert*-butyl esters proceeds via unimolecular alkyl–oxygen fission ($A_{AL}1$), whereas in the case of esters of primary alcohols the reactions involve cleavage of the acyl–oxygen bond ($A_{AC}2$), nucleophilic assistance by ions such as Br^- apparently playing an important role.[17]

In the case of alkyl esters the rate strongly depends on the amount of the acid, while in the case of phenolic esters the rate is not affected by the quantity of the acid in the range 0.5–5 mol. This is likely related to the fact that with alkyl esters HBr is consumed during the reaction.

Experimental Section

GC Data were obtained on a Hewlett-Packard Model 5840 A gas chromatograph using a 2-m 3% SE-30 on Chromosorb column acting in the presence of internal standards; conversions were corrected for detector response.

Materials. Mineral acids were reagent grade products. Quaternary onium salts were commercial products. Esters, prepared by standard procedures, assayed by GC showed ≥98% purity: methyl,[18] *n*-butyl,[18] *n*-octyl,[19] and phenyl octanoates,[20] methyl dodecanoate,[21] *n*-octyl benzoate,[22] *n*-dodecyl acetate.[23] *tert*-Butyl esters were prepared from the corresponding acid chlorides and *tert*-butyl alcohol in the presence of *N,N*-dimethyl aniline in anhydrous ethyl ether or benzene according to a described procedure:[24] *tert*-butyl octanoate,[25] *tert*-butyl dodecanoate,[25] *tert*-butyl benzoate.[26]

Typical Procedure for the Hydrolysis of Esters of Primary Alcohols. A mixture of ester (0.1 mol), 55.5 mL of 48% hydrobromic acid (0.5 mol), and the quaternary onium salt (0.01 mol) was heated at 110 °C under magnetic stirring, the process being monitored by GC analysis. At the end of the reaction the layers were separated by adding ethyl ether. The organic phase was washed with water, 5% sodium hydrogen carbonate solution, and water again and then dried. Elimination of the solvent and distillation of the residue afforded the alkyl bromide. By treating the distillation residue with petroleum ether, pure catalyst was recovered in ≥90% yield. Acidification and extraction of the aqueous alkaline phase afforded the carboxylic acid.

In the case of phenolic esters, the carboxylic acid and the phenol were recovered from the organic phase by extraction with 5% sodium hydrogen carbonate and 10% sodium hydroxide, respectively.

Typical Procedure for the Hydrolysis of *tert*-Butyl Esters. A mixture of *tert*-butyl ester (0.1 mol), aqueous acid (0.5 mol; see Table I), and the quaternary onium salt (0.01 mol) was stirred at room temperature, the process being monitored by GC analysis. At the end of the reaction the mixture was worked up as described above to yield the carboxylic acid and the catalyst.

Registry No. *tert*-Butyl octanoate, 5457-66-9; *tert*-butyl dodecanoate, 7143-18-2; *tert*-butyl benzoate, 774-65-2; methyl octanoate, 111-11-5; *n*-butyl octanoate, 589-75-3; *n*-octyl octanoate, 2306-88-9; phenyl octanoate, 5457-78-3; methyl dodecanoate, 111-82-0; octyl benzoate, 94-50-8; dodecyl acetate, 112-66-3; octanoic acid, 124-07-2; dodecanoic acid, 143-07-7; benzoic acid, 65-85-0; *n*-butyl bromide, 109-65-9; *n*-octyl bromide, 111-83-1; phenol, 108-95-2; *n*-dodecyl bromide, 143-15-7.

(15) The more efficient catalysts are the more lipophilic ones, tetraoctylammonium bromide and I being the best. The catalytic activity of lipophilic quaternary onium salts as phase-transfer agents of hydrohalogenic acids from their aqueous solutions into low polarity organic media is well established.[8-10,16]

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Communications

Oxidation of Thiols by Nitric Oxide and Nitrogen Dioxide: Synthetic Utility and Toxicological Implications

Summary: Thiols are readily oxidized to disulfides by either nitric oxide or nitrogen dioxide. Reaction conditions are mild, and quantitative yields can be obtained. The reactions are useful for preparative purposes and may have toxicological significance.

Sir: The vital role of thiols and disulfides in living systems has focused attention on their interconversion reactions.[1,2] Although the literature contains reports of many reagents that oxidize thiols to disulfides,[3] it is surprising that the oxides of nitrogen (NO_x) have been virtually ignored in this respect. There are, however, two brief reports. In 1928, Reihlen et al.[4] reported that ethanethiol reacts with NO in the presence of KOH to give a 95% yield of ethyl disulfide and a gas consisting of 90% N_2O and 10% N_2, plus unreacted NO. In 1962, Longhi et al.[5] reported that several thiols are oxidized to disulfides in excellent yields by NO in the presence of sodium methoxide; the nitrogen-containing products were not identified, and the mechanism was not discussed.

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Table I. Oxidation of Thiols by NO at Room Temperature

thiol	solvent	pH[a]	disulfide formed[b]	reaction time[c]	% yield[d]
thiophenol	H_2O, suspension	6	diphenyl disulfide	8 h	100
thiophenol	H_2O/EtOH (1:1)	6	diphenyl disulfide	4 h	100
thiophenol	H_2O/EtOH (1:4)	6	diphenyl disulfide	4 h	100
thiophenol	EtOH	6		18 h	0
thiophenol	EtOH	9-10	diphenyl disulfide	30 min	100
thiophenol	benzene			18 h	0
thiophenol	benzene	alkaline	diphenyl disulfide	20 min	100
thiophenol	hexane	alkaline	diphenyl disulfide	20 min	100
p-nitrothiophenol	EtOH	5	4,4'-dinitrodiphenyl disulfide	6 h	100
p-nitrothiophenol	EtOH	9-10	4,4'-dinitrodiphenyl disulfide	15 min	100
p-chlorothiophenol	EtOH	9-10	4,4'-dichlorodiphenyl disulfide	30 min	>95
$PhCH_2SH$	H_2O/EtOH (1:4)	9-10	dibenzyl disulfide	30 min	>95
heptanethiol	H_2O/EtOH (1:4)	9-10	diheptyl disulfide	35 min	>95
cysteine	H_2O	5-7	cystine	2.5 h	>95[e]
cysteine	H_2O/EtOH (4:1)	5-7	cystine	6 h	>95[e]
cysteine	H_2O	9	cystine	15 min	>95[e]
glutathione	H_2O	4	glutathione disulfide	4 h	0
glutathione	H_2O	7	glutathione disulfide	2 h	90[e]

[a] Alkaline signifies addition of 0.1 mol of sodium ethoxide/mol of thiol. [b] Products were isolated and characterized by physical and spectral properties. [c] Indicated time when uptake of NO stopped, with approximately 5 mM substrate in 50 mL of solvent. [d] Measured by GLC analysis. The column was 50 cm × 1/8 in., was loaded with 5% OV-101, and was programmed for 80-160 °C. [e] Determined by weighing isolated products.

We here report a study of the oxidation of a variety of thiols to disulfides by nitric oxide (NO) or by nitrogen dioxide (NO_2). Both reagents can give quantitative yields of disulfides, free of other products, and are themselves converted to gaseous products that are easy to remove from the reaction mixture. Both can be used in organic solvents or aqueous solutions. Of these two reagents, NO_2 is the more vigorous and does not require catalysis. In contrast, NO is more selective and, in some cases, requires base catalysis.

Reactions with NO. Exposure of stirred aqueous suspensions or aqueous ethanolic solutions of thiophenol to an atmosphere of NO gas results in quantitative formation of diphenyl disulfide. However, thiophenol dissolved in absolute ethanol or common organic solvents does not react with NO. Thiophenol has reported[6] pK_a values of 6.5 (H_2O), 6.8 (H_2O/EtOH, 4:1), 7.8 (H_2O/EtOH, 1:1), and 9.3 (H_2O/EtOH, 1:19). Thus, no reaction occurs when the pK_a of the reactant is greater than about 8, suggesting that the reaction should be susceptible to base catalysis. In agreement with this, the addition of a small amount of alkali (0.1 mol/mol of thiol) promotes the rapid oxidation of thiophenol in ethanol, benzene, and hexane and also greatly increases its rate of oxidation in aqueous ethanol (Table I). *p*-Nitrothiophenol (pK_a = 6.4 in 95% ethanol[6]) is sufficiently acidic to be oxidized by NO in ethanol without the addition of base, although its rate of oxidation is increased in the presence of base.

As indicated in Table I, alkanethiols are only oxidized by NO in the presence of alkali; this is in accordance with their lower acidity (pK_a = 10–12).[6] Cysteine is converted to cystine by NO in aqueous solution at a pH between 5 and 7, and the rate of oxidation is increased at pH 9. Glutathione is oxidized to glutathione disulfide at pH 7. All of the above oxidations were inhibited by addition of sufficient acid to reduce the pH to less than 4.

An important feature of the above reactions, apart from their high yields, is the freedom from side products or products of over oxidation such as sulfoxides, sulfones, etc. that are frequently formed by other oxidants.[3] In addition, the workup of the reaction is extremely easy, since the NO is converted to gaseous N_2O and N_2 (see below). Thus, nitric oxide appears to be a reagent of considerable promise for the synthetic conversion of thiols to disulfides.

The stoichiometry of the reaction of thiophenol with NO in hexane or benzene was examined in a closed system by using gas chromatography for analysis. One mole of NO is used for each mole of PhSH oxidized. Analysis of the residual gas showed that N_2 and N_2O are formed in a ratio of 2.1 ± 0.1 under the conditions studied.[7]

The observation of base catalysis appears to rule out direct H atom abstraction from the thiol by NO, which is energetically unfavorable in any case. Our results are best explained by assuming a nucleophilic addition of the thiol anion to NO, followed by protonation and radical coupling (eq 1–3). The dihydroxyhydrazine produced in eq 3

$$RSH + B:^- \rightleftharpoons RS^- + BH \quad (1)$$

$$RS^- + \cdot NO \rightarrow RS\text{-}\dot{N}\text{-}O^- \xrightleftharpoons{H^+} RS\text{-}\dot{N}\text{-}OH \quad (2)$$

$$2RS\text{-}\dot{N}\text{-}OH \rightarrow RSN(OH)\text{-}N(OH)SR \rightarrow RSSR + HON{=}NOH \quad (3)$$

would be unstable and could eliminate hyponitrous acid to form the disulfide (eq 3).[8] Salts of hyponitrous acid, HON=NOH, are known[9] to decompose N_2 and N_2O, the gaseous products we observe.

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(7) Purified NO was bubbled through a solution of thiophenol that had been deaired with Ar; potassium *tert*-butoxide in methanol was then introduced. In hexane the reaction was over in 1 h and in benzene in 3 h. The gas phase was analyzed for N_2, N_2O, and NO by using gas chromatography and the solution for thiophenol and phenyl disulfide (using an internal standard). One reaction was also run in ethanol/water (30/70) without base catalysis. The reaction was slow and not complete after 18 h, but the gaseous products were shown to include N_2 and N_2O.

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Table II. Oxidation of Thiols by NO_2 at Room Temperature

thiol	solvent[a]	product	% yield[b]
thiophenol	ethanol	diphenyl disulfide	>90
thiophenol	benzene	diphenyl disulfide	>90
thiophenol	hexane	diphenyl disulfide	100
benzenemethanethiol	benzene	dibenzyl disulfide	>90
$PhCH_2SH$	hexane	dibenzyl disulfide	>95
heptanethiol	hexane	diheptyl disulfide	>95
cysteine	water	cystine	95
glutathione	water	glutathione disulfide	>80

[a] The pH of these solutions was initially neutral, but they became acidic as NO_2 was added. No attempt was made to control pH. [b] By GLC or isolation of crystalline products.

Reactions with NO_2. Thiophenol in ethanol, benzene, or hexane is rapidly oxidized by NO_2 gas. The reaction is exothermic and becomes quite hot if the rate of addition of NO_2 is appreciable. In our work NO_2 was added slowly, and reaction mixtures remained approximately at room temperature. A strong green color develops immediately when the NO_2 comes into contact with the thiophenol solution, intensifies during the reaction, and then fades to pale yellow at the end of the reaction; this color is due to the presence of the *S*-nitroso thiol (see below). The thiophenol–NO_2 initial reaction mixture follows Beer's law and shows absorption maxima at 530 and 568 nm in pentane or ethyl acetate as the solvent. The cysteine reaction mixture in water also shows evidence of the *S*-nitroso thiol intermediate.

The green intermediate is the *S*-nitroso thiol. *S*-Nitroso thiols are known compounds[10-13] that have reasonably long lifetimes; the absorption maxima[13a,b] for *S*-nitroso thiols are reported to be about 550 nm when the thiol is cysteine, GSH, or dithiothreitol and about 590 nm when the thiol is trityl mercaptan[12] or penicillamine. In fact, we find that an independently prepared solution[10] of PhSN=O (from $NaNO_2$ plus acid in ethyl acetate containing a small amount of methanol) has the same spectrum as does a solution of thiophenol in ethyl acetate through which NO_2 has been bubbled.

The results of our oxidation studies using NO_2 are given in Table II. Use of excess of NO_2 must be avoided since NO_2 can further oxidize disulfides to higher oxidation products;[14] however, good yields of disulfides can be obtained, as indicated in Table II.

The stoichiometry of the NO_2–thiophenol reaction was studied by using a closed system in which a solution of thiophenol was mixed with N_2O_4 at low temperatures,[13c] and the evolution of NO was followed by GC. When excess thiophenol in benzene or toluene is allowed to react with NO_2, 2 mol of PhSH disappear for each mole of NO_2 used, and 1 mol of NO appears.

We propose the scheme shown in eq 4–8 as a reasonable

$$RSH + \cdot NO_2 \longrightarrow [RS{-}\overset{\overset{O}{|}}{\underset{\cdot}{N}}{-}OH] \xrightarrow{RSH} RS\overset{\overset{OH}{|}}{N}OH + RS\cdot \quad (4)$$

$$RSN(OH)_2 \rightarrow RSN{=}O + H_2O \quad (5)$$

$$RSN{=}O \rightarrow RS\cdot + NO \quad (6)$$

$$2RS\cdot \rightarrow RSSR \quad (7)$$

$$RS\cdot + RSN{=}O \rightarrow RSSR + NO \quad (8)$$

$$NO + NO_2 \rightarrow N_2O_3 \quad (9)$$

hypothesis to explain our observations. The *S*-nitroso thiol is shown as an intermediate, and NO is the immediate gaseous product that is formed. It could react with excess NO_2 to form N_2O_3, which could oxidize thiols to disulfides, predicting a complex stoichiometry if excess thiol is not used.

These reactions of NO and NO_2 with thiols may have important toxicological implications. Sources rich in NO_x could inactivate thiol-containing enzymes, leading to biological damage. For example, cigarette smoke contains up to 880 ppm of NO_x; most of the nitrogen oxide in fresh mainstream smoke consists of NO, but the NO is slowly oxidized to NO_2 in aged mainstream and sidestream smoke.[15] An unidentified factor in smoke destroys thiols,[16] and smoke inactivates glucose 6-phosphate dehydrogenase and other thiol-containing enzymes.[17] Externally added thiols protect against this inactivation.[17c] The total NO_x content of smoke correlates with its cytotoxicity, whereas its tar or nicotine content do not.[18] Our results suggest that NO and NO_2 should be potent inhibitors of thiol-dependent enzymes, and we suggest that the enzyme-inhibitory effects of cigarette smoke may well be due to these species. This work also provides an explanation for results such as those of Green,[17c] showing that cysteine and glutathione protect macrophages against cigarette smoke; this could be due to the sacrificial oxidation of the external thiols by NO or NO_2 in smoke.

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Registry No. Thiophenol, 108-98-5; benzyl thiol, 100-53-8; heptyl thiol, 1639-09-4; cystein, 4371-52-2; glutathione, 70-18-8; diphenyl disulfide, 882-33-7; dibenzyl disulfide, 150-60-7; diheptyl disulfide, 10496-16-9; cystine, 24645-67-8; glutathione disulfide, 27025-41-8; *p*-nitrothiophenol, 1849-36-1; *p*-chlorothiophenol, 106-54-7; 4,4′-dinitrodiphenyl disulfide, 100-32-3; 4,4′-dichlorodiphenyl disulfide,

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1142-19-4; NO, 10102-43-9; NO_2, 10102-44-0.

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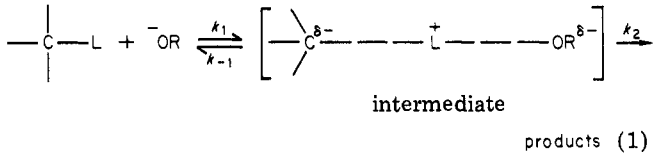
Evidence for Proton Tunneling in Strong Base Promoted (Stepwise) β-Elimination Reactions

Summary: In the case of a single-step, strong base promoted β elimination, tunneling is recognized by a temperature-dependent isotope effect in which $[\Delta E_a]_D^H \gg [\Delta E_0]_D^H$ and $A_H/A_D \ll 0.7$. In a multistep, ElcB-like reaction of methyl 2-methyl-2-bromo-3-phenylpropionate with $NaOCH_3$ it is found that k_H/k_D is temperature independent over a nearly 70 °C range ($[\Delta E_a]_D^H \approx 0$, $A_H/A_D = 1.197$). An appropriate computer program was applied to model the overall mechanism based on a scheme resembling that devised by Streitweiser and further developed by Koch and Dahlberg. The activation parameters computed from the best solution fit to the experimental isotope effect data are consistent with a mechanism of elimination in which the first step is reversible H tunneling through a narrow reaction barrier into the narrow potential well of a hydrogen-bonded intermediate complex. The reaction TS*, arising from this intermediate and having a potential well of nearly the same dimensions as that for the initial complex of base and substrate, accounts for $[\Delta E_a]_D^H \approx 0$. The α secondary deuterium isotope effect measured for the analogous substrate **3** (where CH_3 in **2** has been replaced by deuterium) shows $(k_H/k_D)_\alpha = 1.08$. This result is interpreted to indicate a reactant-like TS*.

Sir: The occurrence of proton tunneling in the course of some E-2 (one step) elimination reactions has been demonstrated by Shiner and Smith.[1] This conclusion stems from their determination of the isotopic activation parameters for the reaction of 1-bromo-2-phenylpropane (**1**): $[\Delta E_0]_D^H \ll [\Delta E_a]_D^H \approx 1.79$ kcal/mol and $A_H/A_D \approx 0.44$; i.e., $k_H/k_D = 0.44 \exp(1790/RT)$, a temperature dependent isotope effect which is the usual means of recognizing tunneling in a single-step, linear H-transfer process.[2] The question to be addressed here is concerned with the identification of tunneling in a *multistep* process in which H transfer is less than fully completed in the transition state (TS*). The KIE values in a somewhat similar processes have been suggested by Streitwieser[3] to be anomalous and attributable to internal return. Recently Koch and Dahlberg[4,5] have discussed a computer-modeling technique for evaluating the various activation parameters involved in such ElcB-like, β-elimination processes promoted by alkoxide bases which can be characterized by the two-step mechanism expressed by eq 1, where L = H or D. We have applied a very similar approach for estimating the isotopic activation parameters prevailing in the methoxide-promoted β-elimination reaction of a substrate, $C_6H_5CHD–C(CH_3)Br–COOCH_3$ (**2**), somewhat analogous to **1** and under reaction conditions for which Shiner[1] has identified tunneling.



(1)

In choosing **2** as the substrate, we reasoned that the $COOCH_3$ substituent would tend to promote an ElcB mechanism, while the benzylic hydrogen would be enhanced compared to that in **1** in its susceptibility to tunneling via strong base abstraction. The $COOCH_3$ was also intended to suppress the possibility for ion-pair development at the α-carbon which might foster a competing $E2_{ip}$ mechanism.[6]

Table I. Primary KIE in the Dehydrobromination of $C_6H_5CHD-(CH_3)Br-COOCH_3$ (2) with $NaOCH_3$ in CH_3OH Solution[a]

temp ± 0.05 °C	exptl[b] k_H/k_D	calcd[c] k_H/k_D	% difference[d]	variance[e] × 10^6
66.3	1.221 ± 0.001	1.226	0.163	4
79.0	1.237 ± 0.003	1.227	0.081	1
89.7	1.225 ± 0.001	1.227	0.081	1
101.5	1.233 ± 0.001	1.227	0.081	1
110.7	1.227 ± 0.004	1.227	0.081	1
121.1	1.229 ± 0.003	1.227	0.081	1
133.5	1.227 ± 0.006	1.227	0.081	1

[a] Sum of variances = 1.0×10^{-5}. The k_H/k_D experimental mean value = 1.228 ± 0.005 for 140 000 determinations. Runs were made by using equimolar (0.01 M) solutions of $NaOCH_3$ and **2** in methanol in serum-capped pressure bottles. The small quantity of pure **2** was rapidly injected under stirring after the base solution had equilibrated in the thermostat to ensure that the temperature of reaction was constant and uniformly maintained throughout the run. The product consisting principally of a mixture of deuterated and undeuterated cinnamate ester was worked up after drowning the reaction in ice-water, extraction with pentane, drying, stripping the solvent, and isolation by a preparative GLC procedure. [b] The D content of each sample was determined by the mass spectroscopic procedure previously described.[11] The parent peaks of the substrates analyzed were scanned 20 000 times per sample to yield a mean value of the M_{176}/M_{177} amu ratio. For methyl α-methylcinnamate the M_{H+1}/M_H amu ratio is 0.207. For methyl β-deuterio-α-methylcinnamate the M_{D-1}/M_D amu ratio is 0.238. The correction made for the measured isotope ratio M_{176}/M_{177} is given by

$$M_D/M_H = 0.212(4.831 - M_{176}/M_{177})/(M_{176}/M_{177} - 0.238)$$

$$k_H/k_D = M_D/M_H$$

[c] A DBASIC program on the B-770 computer was employed to determine the (k_H/k_D) calculated values. Numerous iterations were performed by using the kinetic expressions derived previously[4,5] until the solution with the lowest sum of variances was reached. The parameters listed beneath Figure 1 were arrived at simultaneously. [d] Percent difference = difference/1.197 × 100. [e] Variance = (difference)².

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