of **1c** (1.0 g, 3.3 mmol) at 0 °C. After 30 min, the reaction mixture was decomposed by aqueous NH_4Cl solution and extracted with ether. The crude products were chromatographed on silica gel. Elution with 1:5 benzene–hexane gave a mixture of **7o** and **8o** (0.85 g, 2.01 mmol, 61%) in a molar ratio of 56:44. From the second fraction (elution with 1:1 benzene–hexane) was obtained a mixture of 51% **5c** and 49% **6c** (0.25 g, 0.46 mmol, 28%).

Reaction of 8 with (Diphenylmethyl)lithium. To a THF solution (20 mL) of **8w** (0.3 g, 0.65 mmol) was added 3.25 mmol of (diphenylmethyl)lithium in THF at 20 °C. The mixture was kept with stirring at 20 °C for 5 h. Column chromatography on silica gel (elution with 1:1 benzene–hexane) gave **7w** in a yield of 88%. Treatment of **8x–z** with (diphenylmethyl)lithium (5 mol equiv) also gave **7x–z** quantitatively.

Registry No. 1a, 77032-88-3; **1b**, 77032-89-4; **1c**, 72948-51-7; **1d**, 85865-12-9; **1e**, 85865-13-0; **1f**, 77032-93-0; **1g**, 85865-14-1; **2a**-Li, 85865-15-2; **2a**-Na, 85865-16-3; **2b**-Li, 85865-17-4; **2b**-Na, 85865-18-5; **2c**-Li, 85865-19-6; **2c**-Na, 85865-20-9; **2d**-Li, 85865-21-0; **2d**-Na, 85865-22-1; **3c**, 1498-71-1; **3c**-*d*, 85865-23-2; **3d**, 85865-24-3; **4c**-*d*, 85882-55-9; **4d**, 85882-56-0; **5a**, 85922-49-2; **5a′**, 85922-50-5; **5c**, 85922-51-6; **5c′**, 85922-52-7; **5d**, 85882-57-1; **5d′**, 85922-53-8; **6a**, 85922-54-9; **6a′**, 85922-55-0; **6c**, 85922-56-1; **6c′**, 85922-57-2; **6d**, 85882-58-2; **6d′**, 85922-58-3; **7c**, 80503-06-6; **7d**, 85865-25-4; **7h**, 85865-26-5; **7l**, 85865-27-6; **7m**, 85865-28-7; **7n**, 85865-29-8; **7o**, 85865-30-1; **7p**, 85865-31-2; **7r**, 85882-59-3; **7s**, 85865-32-3; **7t**, 85865-33-4; **7u**, 85865-34-5; **7v**, 85865-35-6; **7w**, 85865-36-7; **7x**, 85865-37-8; **7y**, 85865-38-9; **7z**, 85865-39-0; **8c**, 77033-38-6; **8h**, 85882-60-6; **8l**, 85882-61-7; **8m**, 85882-62-8; **8n**, 85882-63-9; **8o**, 85882-64-0; **8p**, 85882-65-1; **8q**, 85882-66-2; **8r**, 85882-67-3; **8s**, 85882-68-4; **8t**, 85882-69-5; **8u**, 85882-70-8; **8v**, 85882-71-9; **8w**, 85882-72-0; **8x**, 85882-73-1; **8y**, 85882-74-2; **8z**, 85882-75-3; $Li^+Naph^{-}\cdot$, 7308-67-0; $Na^+Naph^{-}\cdot$, 3481-12-7; CF_3COOH, 76-05-1; CH_3COOH, 64-19-7; 4-$NO_2C_6H_4OH$, 100-02-7; C_6H_5OH, 108-95-2; CF_3CH_2OH, 75-89-8; H_2O, 7732-18-5; CH_3CH_2OH, 64-17-5; *t*-BuOH, 75-65-0; HMPA, 680-31-9; MeBr, 74-83-9; MeI, 74-88-4; MeOTs, 80-48-8; EtBr, 74-96-4; EtI, 75-03-6; *i*-PrBr, 75-26-3; *i*-PrI, 75-30-9; $PhCH_2Cl$, 100-44-7; $PhCH_2Br$, 100-39-0; $PhCH_2OTs$, 1024-41-5; *p*-$MeOC_6H_4CH_2Cl$, 824-94-2; *m*-$ClC_6H_4CH_2Cl$, 620-20-2; Ph_2CHCl, 90-99-3; Ph_2CHBr, 776-74-9; Ph_2CHLi, 881-42-5; $PhCH_2MgCl$, 6921-34-2; *i*-PrOH, 67-63-0; cyclopentadiene, 542-92-7; indene, 95-13-6.

Supplementary Material Available: Table of physical properties of compounds **7** and **8** (3 pages). Ordering information is given on any current masthead page.

Synergistic Effect of Iodine and Neighboring Amine Groups on Thioester Deacylation

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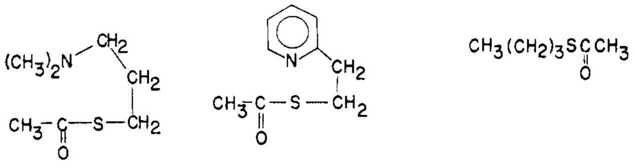
Abstract: The synergistic effect of a Lewis acid (I_2) and an intramolecular Lewis base facilitates the deacylation of thioesters. When iodine is added to an aqueous solution of *S*-3-(dimethylamino)propyl thioacetate (I), deacylation is accelerated by a factor of 10^3–10^4. A severalfold acceleration is observed for *S*-2-(2-pyridyl)ethyl thioacetate (II), and no rate enhancement is observed in the reaction of *S*-*n*-butyl thioacetate (III). The rate of iodine consumption at invariant pH and thioester and iodide concentrations is zero order in iodine when III reacts and first order in iodine when I reacts. Both kinetic orders are observed when II reacts. The effect of pH and iodide ion concentration on the rates of I and II is explained by an intramolecular interaction between an iodine–thioester complex and the neighboring amine. The product of the reaction of the unsubstituted thioester III is the disulfide. However, overoxidation is observed in the reactions of I and II, and the sulfonic acids were the isolated products. The product from the oxidation of I has been confirmed to be $(CH_3)_2{}^+NH(CH_2)_3SO_3{}^-$ (IV) by single-crystal X-ray crystallography.

Introduction

The present examination of the effect of aqueous iodine on the cleavage of thioesters is an extension of our interest in the effect of neighboring groups on thioether oxidation.[1] In view of recent spectroscopic measurements and calculations[2] that show that the thioester carbonyl group resembles a ketone, its –SR fragment may resemble a thioether and coordinate with iodine. In nonaqueous solvents the proton NMR shifts of thioesters are only very slightly affected by I_2.[3] However, a suggestion that a thioester–iodine complex may be involved in a thioester–ester interchange was proposed by Minato et al., who had investigated the reaction of thioesters with halogens.[4] They found that when iodine was added to *S*-phenyl thioacetate in $CDCl_3$ in the presence of 3 equiv of alcohol, transesterification proceeded, yielding the corresponding alkoxy ester, thiophenol, and diphenyl disulfide. No reaction was observed in the absence of alcohol. Some of the most recent studies of the cleavage of thioesters deal with soft metal ion promoted hydrolysis using aqueous solutions at low pH. Patel and Satchell[5] have shown that Cu^{2+}, Ni^{2+}, Pb^{2+}, and Cd^{2+} ions have little or no effect on the hydrolysis rates of thioesters, but soft metal ions like Tl^{3+}, Au^{3+}, Hg^{2+}, $Hg_2{}^{2+}$ and Ag^+ ions are very powerful promoters of thioester hydrolysis in acid solution. The catalysis of thioester deacylation reactions is an important

Chart I



I II III

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[1] Doi, J. Takahashi; Musker, W. K.; deLeeuw, D. L.; Hirschon, A. S. *J. Org. Chem.* **1981**, *46*, 1239.

[2] El Aasar, A. M. M.; Nash, C. P.; Ingraham, L. L *Biochemistry* **1982**, *21*, 1972.

[3] Kingsbury, C. A.; Ebert, G. *Phosphorus Sulfur* **1981**, *9*, 315.

[4] Minato, H.; Takeda, K.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 1095.

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concern in view of their role in biological acetylation.

Recently we demonstrated that an interaction occurs between neighboring amine and thioether groups when 3-(dimethylamino)propyl and 2-(2-pyridyl)ethyl methyl sulfides are oxidized by aqueous I_2.[1] We reasoned that a similar N^+–S^+ dicationic or N^+–S–I sulfurane may form and accelerate the cleavage of substituted thioesters over their usual hydrolytic rate. The compounds selected for the initial investigation of the aqueous I_2 cleavage were the related thioesters *S*-3-(dimethylamino)propyl thioacetate, I (Chart I), and *S*-2-(2-pyridyl)ethyl thioacetate, II. *S*-*n*-Butyl thioacetate, III, an unsubstituted thioether, was chosen as a control substrate.

Experimental Section

Preparation of Materials. *S*-2-(2-Pyridyl)ethyl thioacetate, II, and 2-(2-pyridyl)ethanethiol were synthesized from 2-vinylpyridine and thioacetic acid by the method of Chia et al.[6] *S*-*n*-Butyl thioacetate (Fairfield Chemical Co., Inc., Blythewood, SC) was >99% pure as determined by GC and HPLC. *S*-3-(Dimethylamino)propyl thioacetate was synthesized from 3-(dimethylamino)propanethiol (gift from Evans Chemetics Inc., Darien, CT) and acetic anhydride following the procedure of Schneider,[7] bp 79–80 °C (7 torr). Anal. Calcd for $C_7H_{15}ONS$: C, 52.14; H, 9.38; N, 8.65. Found: C, 52.22; H, 9.28; N, 8.39. ^1H NMR ($CDCl_3$) δ 1.8 (m, 2), 2.2 (s, 6), 2.3 (s and m, 5), 2.9 (t, 2).

Analyses were performed by Microanalytical Laboratories, University of California, Berkeley, CA.

Deionized water was degassed and equilibrated under a N_2 atmosphere.

Gas chromatography was performed by using SE-30 on Chromosorb P (AW, HMDS) in a 6-ft glass column in an Aerograph Model A-90-P3.

HPLC was performed on an MCH-10 column by using 50% aqueous CH_3CN in a Varian 5000 liquid chromatograph.

A radiometer Copenhagen PHM 82 standard pH meter was used alone or in combination with a Model ABU 80 Autoburette and TTT60 titrator.

Hydrolysis. Fresh solutions of I–III were prepared just prior to use in initial concentrations of $(2-4) \times 10^{-4}$ M. Buffers containing 0.06 or 2 M KCl were prepared with 0.20 or 0.058 M total borate. Solutions were thermostated at 26.1 °C and then mixed in equal volumes. The pH of the mixtures was measured both at the time of mixing and at the end of a run. The mixtures were thermostated at 26.1 °C, and 4.0-mL aliquots were taken at appropriate intervals and added to 0.10 mL of 2.5 M aqueous HCl to quench absorbance due to thiolate ion. The disappearance of the thioester absorbance at 233 nm was followed by using a Hewlett-Packard Model 8450A UV–visible spectrophotometer or Beckman DU with a Gilford 2451A attachment.

Rates of Reactions of Thioesters with I_3^-. Fresh solutions of thioester were prepared at a concentration of $(2-4) \times 10^{-3}$ M. To each borate buffer solution was added potassium iodide, potassium chloride, and I_2 so that the initial triiodide concentration would be ca. $(3-6) \times 10^{-4}$ M. For the slower reactions the thermostated solutions were mixed and aliquots taken at suitable times. For the faster reactions the solutions were simultaneously injected into a test tube and then quickly transferred to a 1-mm cell thermostated in the spectrophotometer cell compartment. The I_3^- absorbance at 353 nm was monitored. From these data either the rate of disappearance of triiodide or, from the reaction stoichiometry and the triiodide consumption, the thioester concentration can be calculated at any time.

Stoichiometry. Studies were carried out for thioesters I and II and 2-(2-pyridyl)ethanethiol to determine the stoichiometry of the iodine reaction. A solution of II was prepard at a concentration of 2.48×10^{-4} M. Potassium iodide (0.499 g) and approximately 0.03 g of iodine were added to 50 mL of the pH 8.5 0.058 M borate buffer. Equal volumes (25 mL each) of the thioester solution and the buffer solution were mixed. Blanks, prepared by substituting distilled water for the thioester solutions, were run simultaneously. Aliquots of the sample solutions and the blanks were diluted with distilled water and quenched with 2.5 M hydrochloric acid, and the absorbance at 353 nm was recorded. The reaction with compound II was complete after 2 mol of iodine had been consumed for each mole of the thioester.

A solution of 9.0×10^{-4} M I was mixed in equal volumes with a solution containing 4.0×10^{-3} M I_2, 0.010 M KI, and 0.99 M KCl in pH 8.5 0.2 M borate buffer. After 15- and 30-min intervals, titration of aliquots of the mixture with $Na_2S_2O_3$ indicated that 2.3 equiv of I_2 had reacted per equivalent of thioester.

A 7.7×10^{-4} M solution of 2-(2-pyridyl)ethanethiol was prepared in pH 9.0 0.2 M borate buffer. The solution was diluted with an equal volume of a solution containing 4.0×10^{-3} M I_2 and 0.010 M KI. Titration of aliquots with $Na_2S_2O_3$ indicated that 2.3 mol of I_2 had reacted per mole of thiol.

Product Run: *S*-*n*-Butyl Thioacetate (III). Compound III (2.6 g, 0.02 mol) was dissolved in 100 mL of CH_3CN. The solution was mixed with 150 mL of 0.67 M pH 9 borate buffer. To this mixture was added 2.1 g of I_2 in CH_3CN in portions over 12 days. After 14 days the brown solution was distilled through a Vigreux column into an ice-cooled receiver under vacuum drawn by an aspirator. The distillate was continuously extracted for 20 h with CH_2Cl_2 and gave a mixture of *S*-*n*-butyl thioacetate and *n*-butyl disulfide, identified by GC retention times. The 25 mL of residue was extracted with CH_2Cl_2. Neither the CH_2Cl_2 extract nor the residue contained organic product.

Product Run: *S*-2-(2-Pyridyl)ethyl Thioacetate (II). A saturated aqueous solution of iodine, 200 mL, was prepared, and 0.19 g of II was added to it. The resulting solution was placed on the pH stat, which kept the reaction solution at a constant pH 9.0 by adding 0.1 N sodium hydroxide as needed. Solid iodine and potassium iodide were added in excess to the solution when the yellow started to fade. The reaction was assumed to have gone to completion when the uptake of base had essentially ceased. The water was removed by using a Buchi rotary evaporator, leaving a solid brown residue. This residue was dissolved in a small amount of water and decolorized with Norite. Hydrochloric acid was added to acidify the solution, and the water was removed leaving a yellow residue. The acid was added so that any acetate ion that was present in solution would be removed as acetic acid when the water was removed. The yellow residue had IR absorbances at 1060 and 1200 cm^{-1}; ^1H NMR (D_2O) δ 3.45 (m, 4, CH_2CH_2), 8.03–8.6 (m, 4, py ring protons). This spectrum of the product was identical with that of 2-(2-pyridyl)ethanesulfonate (Sadtler 5631M).

Product Run: *S*-3-(Dimethylamino)propyl Thioacetate (I). Compound I (0.86 g, 5.3×10^{-3} mol) and iodine (2.72 g, 10.7×10^{-3} mol) were added in portions to 40 mL of 0.03 M KI. The solution was maintained at pH 8.5 by using the pH stat. When the addition was complete, the mixture was stirred for 30 min, acidified to pH <5 with aqueous HCl, and evaporated to 8–10 mL. The salts were removed by passing the residue through 50 g of Dowex ion-retardation resin. The organic product was in the first 55 mL of eluent and had an R_f value of 0.13 on Merck silica gel plates with 4:1:1 butanol–glacial acetic acid–H_2O. The solvent was evaporated to give a waxy residue that had IR absorbances at 1625, 1605, 1200, and 1060 cm^{-1} (neat). The acetate was removed by dissolving the residue in pH 3 aqueous HCl and evaporating the solution to dryness. The residue was dissolved in pH 6 aqueous solution and put through the 50 g ion-retardation resin again. The organic residue found in the 16th–25th mL of eluent was a viscous liquid that could be converted to a paste by adding a few milliliters of absolute ethanol and evaporating twice. The paste solidified after triturating five times with small volumes of diethyl ether. This solid had an R_f value of 0.13. Crystallization from 1:1 ether–methanol yielded pure $(CH_3)_2{}^+$-$NH(CH_2)_3SO_3{}^-$ (IV): ^1H NMR (D_2O) δ 2.95 (m, br, overlaps a singlet at δ 2.65; total of 10 protons), 1.90 (m, 2); IR (KBr) 1200, 1060 cm^{-1}. These crystals quickly decompose when isolated yielding a mixture of liquid and solid. The structure of $(CH_3)_2{}^+NH(CH_2)_3SO_3{}^-$ (IV) was determined by single-crystal X-ray crystallography.

3-(Dimethylamino)propanesulfonic Acid (IV): X-ray Data Collection. Crystals of $C_5H_{13}NSO_3$, M_r 167.23, form as colorless needles from methanol–diethyl ether. The crystal selected for data collection had dimensions $0.25 \times 0.37 \times 0.50$ mm and was coated with epoxy to prevent uptake of water. It was mounted in the cold stream (T = 140 K) of a Syntex $P2_1$ diffractometer with the long dimension parallel to ϕ. Crystal data (at 140 K) are a = 11.005 (2) Å, b = 11.384 (2) Å, c = 12.435 (2) Å, V = 1560.7 (4) $Å^3$, space group *Pbca* (No. 61) based on the following conditions: $h0l$, $l = 2n$, $0kl$, $k = 2n$; $hk0$, $h = 2n$. The measured (at 298 K) and calculated (at 140 K) densities are 1.44 and 1.42 g cm^{-3}, respectively; $Z = 8$, μ(Mo Kα) = 3.51 cm^{-1}. Radiation used was graphite-monochromated Mo Kα (λ 0.71069 Å). Data were collected to a $2\theta_{max}$ of 55°. The intensities of two check reflections exhibited only random fluctuations. A total of 1802 unique reflections were measured.

Solution and Refinement of the Structure. All computations were carried out by using the SHELXTL, version 3 (July 1981) crystallographic programs installed on a Data General Eclipse computer. Corrections for Lorentz and polarization effects were applied to the data.

No correction was considered necessary for absorption since computed absorption correction factors were 1.16–1.25. Scattering factors used were from Vol. IV of the "International Tables". Of the original data, 1484 with $F > 3\sigma(F)$ were retained for solution and refinement of the

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[6] (a) Chia, P. S. K.; Livingston, S. E.; Lockyer, T. N. *Aust. J. Chem.* **1966**, *19*, 1835. (b) deLeeuw, D. L.; Doi, J. T.; Musker, W. K. *J. Org. Chem.* **1982**, *47*, 4860.

[7] Schneider, F. *Hoppe*-Seyler's *Z. Physiol. Chem.* **1967**, *348*, 1034.

Table I. Atom Coordinates ($\times 10^4$) for $(CH_3)_2{}^+NHCH_2CH_2CH_2SO_3{}^-$

S	5347 (1)	521 (1)	−2101 (1)
O(1)	5804 (2)	729 (1)	−3181 (1)
O(2)	6242 (1)	−10 (1)	−1397 (1)
O(3)	4798 (1)	1572 (1)	−1632 (1)
N	1983 (2)	−2314 (2)	−489 (2)
C(1)	4154 (2)	−521 (2)	−2260 (2)
C(2)	3588 (2)	−915 (2)	−1207 (2)
C(3)	2607 (2)	−1807 (2)	−1461 (2)
C(4)	1302 (2)	−1418 (2)	144 (2)
C(5)	2826 (2)	−2996 (2)	215 (2)
H(1A)	4504 (22)	−1191 (22)	−2601 (20)
H(1B)	3572 (22)	−155 (21)	−2704 (19)
H(2A)	3328 (23)	−251 (23)	−823 (21)
H(2B)	4249 (22)	−1276 (21)	−756 (19)
H(3A)	2000 (23)	−1480 (22)	−1878 (19)
H(3B)	2953 (21)	−2488 (22)	−1832 (18)
H(4A)	1896 (20)	−948 (20)	520 (18)
H(4B)	870 (22)	−1849 (21)	695 (19)
H(4C)	789 (22)	−967 (22)	−336 (19)
H(5A)	3281 (22)	−3496 (23)	−204 (20)
H(5B)	2326 (20)	−3413 (20)	726 (17)
H(5C)	3370 (20)	−2437 (21)	602 (18)
H	1409 (23)	−2812 (22)	−770 (20)

Table II. Effect of Thioester Concentration on the Rate Constants of the Reaction of *S*-3-(Dimethylamino)propyl Thioacetate, I, with I_3^- in Aqueous Base[a,b]

$[(CH_3)_2N(CH_2)_3SCOCH_3]_0$, M	rate constant for first-order reaction of triiodide (10^4 k), s^{-1}
0.62×10^{-3}	87 ± 7
0.93×10^{-3}	145
1.24×10^{-3}	188 ± 4
1.86×10^{-3}	266 ± 4

[a] pH 9.0, 0.10 M borate buffer; 0.25 M KI, 0.75 M KCl, 26.1 °C. [b] log [I] vs. log k_{obsd}: slope = 1.01, correlation coefficient = 0.995.

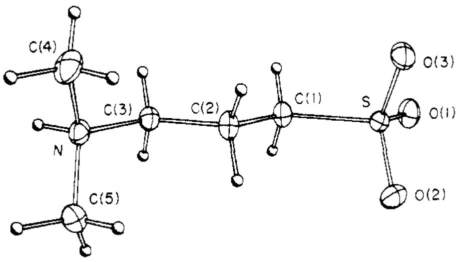

Figure 1. 3-(Dimethylamino)propanesulfonic acid zwitterion.

structure. The structure was solved by direct methods. All atoms were located on difference Fourier maps. Non-hydrogen atoms were assigned anisotropic thermal parameters. Hydrogen atoms were allowed to refine with isotropic thermal parameters. Blocked-cascade least-squares refinement converged with $R = 0.043$ and $R_w = 0.041$ with $w = 1/[\sigma^2(F) + 0.00017F^2]$. In the last cycle of refinement the mean shift/estimated standard deviation was 0.007. No features of chemical significance could be found on a final difference map. A list of final atomic coordinates is presented in Table I. Thermal parameters have been deposited as supplementary material.

Results

Kinetics. *S*-3-(Dimethylamino)propyl Thioacetate (I). In the presence of I_3^- and buffer, the pseudo-first-order rate constants for triiodide decrease were determined over 2 half-lives and had correlation coefficients of >0.999. The initial I_3^- concentration was ca. 10^{-4} M. In the kinetic runs summarized in Table II the thioester concentration was varied, and the first-order rate constant was found to be directly proportional to the thioester concentration. A plot of log [I] vs. log k_{obsd} had a slope of 1.01 and a correlation coefficient of 0.995.

Table III contains the values of k_{obsd} determined over a range of pH values in solutions in which [KI] = [KCl] = 0.5 M; total borate = 0.100 M. The slope of the plot of log k_{obsd} vs. pH as shown in Figure 2 decreases with increasing pH. Also nonlinear was a plot of log k_{obsd} vs. log $(K_a/([H^+] + K_a))$. The latter function is the fraction of I in the form of free amine at a given pH. However, a two-term combination of these functions gives eq 1 which was used to draw the solid line in Figure 2:

Table III. Effect of pH on the Rate Constants of the Reaction of *S*-3-(Dimethylamino)propyl Thioacetate, I, in Aqueous Base, with and without Added I_2

pH	A: rate constant for first-order oxidation of I with I_3^- (10^4k), s^{-1} [a]	pH	B: rate constant for first-order hydrolysis of I (10^6k), s^{-1} [b]
8.16	8.9 ± 0.5	8.16	2.47 ± 0.01
8.54	28.1 ± 0.6	8.54	4.72 ± 0.06
8.84	54 ± 3	8.72	8.00 ± 0.17
9.15	139 ± 6	9.00	11.4 ± 1.0
9.66	464 ± 8	9.32	25.4 ± 0.1
9.81	590 ± 30	9.65	33.9 ± 1.9
10.16	1020 ± 80	9.95	52 ± 2

[a] $[I_3^-]_0 \simeq 6 \times 10^{-5}$ M; [thioester] = 9.10×10^{-4} M; [KI] = [KCl] = 0.50 M; 0.100 M borate buffer. [b] [KCl] = 1.00 M; 0.100 M borate buffer; [thioester] = $(4-20) \times 10^{-4}$ M; 26.7 °C.

Table IV. Effect of KI Concentration on the Rate Constants of the Reaction of *S*-3-(Dimethylamino)propyl Thioacetate, I, with I_3^- in Aqueous Base (0.10 M Borate Buffer)

[KI], M	[KCl], M	pH 8.16[a] (10^4k), s^{-1}	pH 9.14[b] (10^4k), s^{-1}	pH 10.1[c] (10^4k), s^{-1}
1.00			24 ± 2	172 ± 14
0.50	0.50	9.7 ± 0.8	70 ± 3	487 ± 13
0.25	0.75	24.5 ± 0.5	210 ± 10	1035 ± 5
0.125	0.875	61.8 ± 1.0	479	2260 ± 10

[a] [Thioester] = 1.12×10^{-3} M. [b] [Thioester] = 9.60×10^{-4} M. [c] [Thioester] = 9.10×10^{-4} M.

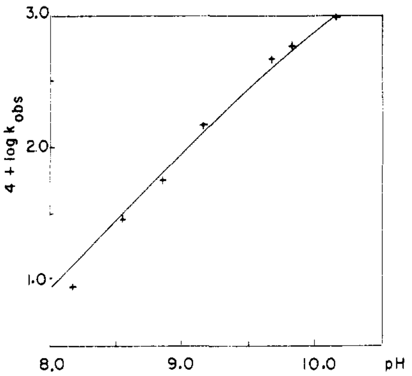

Figure 2. pH dependence of the I_2 reaction of I when [I] = 9.10×10^{-4} M; [KI] = [KCl] = 0.50 M; total borate = 0.10 M; k is in inverse seconds. The solid curve has been drawn from eq 1.

$$k_{obsd} = \frac{K_a}{[H^+] + K_a}(0.0353 + (7.05 \times 10^2)[OH^-])\ s^{-1} \quad (1)$$

where $pK_a = 9.6$ (the value obtained by titration of I[8]).

The effect of added KI on the rates is shown in Table IV for solutions buffered at pHs of 8.16, 9.14, and 10.1. At the two lower pHs, the data gave linear plots of $k_{obsd}[I^-]$ vs. $(0.5 + [I^-])^{-1}$ and the coefficient of correlation was 0.993 in each case. At these pHs, the first term in eq 1 is dominant. At pH 10.1, however, both terms of the equation must be considered, and the iodide dependence was observed to follow eq 2 when [I] = 9.10×10^{-4}

$$k_{obsd} = \frac{0.0065}{[I^-](0.5 + [I^-])} + \frac{1.29 \times 10^2[OH^-]}{[I^-]}\ s^{-1} \quad (2)$$

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[8] Angelici, R. J. "Synthesis and Technique in Inorganic Chemistry"; W. B. Saunders: Philadelphia, PA, 1969.

M. The plot of log k_{obsd} vs. the log of the right-hand side of eq 2 had a slope of 1.07 and correlation coefficient of 0.998.

After combination of eq 1 and 2 and inclusion of the first-order dependence on [I], the overall rate law for I with I_3^- is

$$d[I_3^-]/dt = -\frac{[I]K_a}{[H^+] + K_a}\frac{[I_3^-]}{[I^-]}\left(\frac{19.4}{0.5 + [I^-]} + (3.87 \times 10^8)[OH^-]\right) \text{ M s}^{-1} \qquad (3)$$

Miscellaneous Controls on I: Effect of Added Et_3N. In a solution containing 0.1 M borate buffer at pH 9.0, 0.25 M KI, and 0.75 M KCl, the rate of oxidation of 1.8×10^{-3} M I was 0.0253 ± 0.0003 s^{-1}. Under the same conditions, when the solutions contained 0.9×10^{-3} M I and 0.86×10^{-3} M Et_3N, the observed rate constant was 0.0107 s^{-1}.

Effect of Borate Buffer Concentration. At pH 9.1, 0.25 M KI, and 0.75 M KCl, there was no observable increase in the rate of reaction of 0.96×10^{-3} M I with I_2 over the range of buffer concentrations 0.029–0.10 M. The rate constant was 0.020 ± 0.002 s^{-1}.

***S*-*n*-Butyl Thioacetate (III).** In pH 9.0, 0.10 M borate buffer containing 0.125 M KI and 0.875 M KCl, the disappearance of triiodide in the presence of excess III was zero order in $[I_3^-]$. When $[III] = 0.836 \times 10^{-3}$ M, $k_{obsd} = (1.78 \pm <0.03) \times 10^{-9}$ M s^{-1}, and when $[III] = 1.67 \times 10^{-3}$ M, $k_{obsd} = (3.08 \pm 0.06) \times 10^{-9}$ M s^{-1}. Since the rates are proportional to [III], first-order rate constants are equal to $k_{obsd}/[III]$. The average of the values of the first-order rate constant for the triiodide consumption is $(2.0 \pm 0.2) \times 10^{-6}$ s^{-1}. Under the same conditions in the absence of I_2, III hydrolyzes at a rate of $(6.4 \pm 0.5) \times 10^{-6}$ s^{-1}. Using these values, the triiodide is consumed at about a third the rate at which III is hydrolyzed. Since the rate law for the I_3^- consumption in the presence of III is zero order in $[I_3^-]$ and first order in [III], the iodine does not interact with III until after the rate-determining step of the hydrolysis reaction.

***S*-2-(2-Pyridyl)ethyl Thioacetate (II).** When II was treated with I_3^- under pseudo-first-order conditions, the rate of disappearance of I_3^- was not first order and was considerably slower than the rates of I. The slopes of data plotted as t vs. $-\ln [I_3^-]$ appeared to increase with increasing t. In order to obtain meaningful numbers, it was necessary to subtract out from the overall triiodide consumption the portion of triiodide that was consumed in a rapid reaction by the thiol formed in the uncatalyzed hydrolysis at each time. The necessary information was obtained from the observation that 2 mol of I_2 reacts with 1 mol of 2-(2-pyridyl)ethanethiol and from the rate of hydrolysis of II in the absence of iodine. The rate of hydrolysis of II is directly proportional to $[OH^-]$ as seen in Table V. Thus, at an invariant iodide concentration, if $x = \Delta[II] = {}^1/_2\Delta[I_3^-]$ consumed, $b = [I_3^-]_0$, and $a = [II]_0$, the rate of triiodide consumption is

$$dx/dt = (a - x)(b - 2x)k_2 + (a - x)[OH^-]k_h$$

Under experimental conditions $(a - x) \simeq a_0$, giving

$$\begin{aligned} dx/dt &= a_0((b - 2x)k_2 + [OH^-]k_h) \\ &= a_0k_2((b - 2x) + [OH^-](k_h/k_2)) \end{aligned}$$

$$dx/(b + [OH^-](k_h/k_2) - 2x) = a_0k_2\, dt$$

Integrating

$$\tfrac{1}{2}\{\ln([OH^-](k_h/k_2) + b) - \ln([OH^-](k_h/k_2) + b - 2x)\} = a_0k_2t$$

Table V. Rate Constants for the Hydrolysis of II at Different pH Values[a]

pH	rate constant for the first-order hydrolysis of II (10^6k), s^{-1}	pH	rate constant for the first-order hydrolysis of II (10^6k), s^{-1}
8.50	1.09	9.38	8.94
8.85	2.38	9.65	15.9
9.05	3.50		

[a] Slope of pH vs. log k = 1.03, correlation = 0.998; 1×10^{-4} M II, 0.028 borate buffer, KCl added; $[Cl^-] + [B(OH)_4^-] = 0.01$ M, 26.1 °C.

Table VI. Rate Constants of the Reaction of *S*-2-(2-Pyridyl)ethyl Thioacetate, II, with I_3^- in pH 9.0, 0.10 M Borate Buffer[a]

10^3[II], M	[KI], M	[KCl], M	10^5k_2, M^{-1} s^{-1}	10^6k_1,[b] s^{-1}
0.97	0.125	0.875	50.5 ± 0.5	0.48
0.97	0.030	0.970	208 ± 5	2.02
0.97	0.015	0.985	366 ± 6	3.55
1.94	0.015	0.985	381 ± 3	

[a] Slope of log [KI] vs. log $k_2 = -0.94$; correlation = 0.999.

[b] The pseudo-first-order rate constant $k_1 = [II]k_2$, since $[I_3^-]_0 \simeq 1.2 \times 10^{-4}$ M.

The value of $[OH^-]k_h$ is 1.53×10^{-6} s^{-1} at pH 9.0 in 0.10 M borate containing 1.0 M KCl. By use of iteration, plots of the left side of the equation vs. the right side of the equation were made until matching values of k_2 were obtained. Table VI contains these values as well as values of pseudo-first-order rate constants, a_0k_2, for comparison with other data. The last values in Table VI show that doubling [II] does not affect the second-order rate constant. When the values of log k_2 vs. log $[I^-]$ are treated by linear regression, the slope is −0.94 and the correlation coefficient is 0.999. Thus the rate law for II with I_3^- is

$$-[II]/dt = [II][OH^-]k_h + [II][I_3^-][I^-]^{-1}k_2$$

(The term k_2 may be pH dependent, but the complexity of the data treatment did not encourage further investigation.)

Discussion

Rate Laws and Products. Each thioester included in this study has a unique response to the presence of iodine in the basic hydrolysis solution. The simple thioester III consumes I_2 at a rate that is zero order in iodine and slightly slower than half its hydrolysis rate. The only organic product of that reaction, besides acetate, is *n*-butyl disulfide. The overall reaction of III is

$$2III + I_2 + 4OH^- = (n\text{-}C_4H_9S\text{-})_2 + 2CH_3CO_2^- + 2I^- + 2H_2O$$

The lack of acceleration and the zero-order dependence on iodine indicates either that any interaction between the simple thioester, III, and the iodine occurs following the rate-determining step or that any intermediate in which an interaction between III and I_2 occurs does not compete with the hydrolysis of III alone. The disulfide product is consistent with the observation made by Danehy[9] and others that aqueous I_2 oxidizes most thiols to disulfides.

Compound II, possessing a pyridine nitrogen in the position γ to the sulfur, reacts with aqueous I_2 at a rate competitive with its rate of hydrolysis (rate constant k_h). The rate law is

$$-d[I_3^-]/dt = ([I_3^-]/[I^-])[II]k_2' + [II][OH^-]k_h$$

The relative contributions of the two terms will change with the ratio $[I_3^-]/[I^-]$ in the reaction solution at a given pH. At pH 9.0, $[OH^-]k_h = 1.53 \times 10^{-6}$ s^{-1} when borate buffer is 0.10 M and [KCl] is 1.0 M. The pH dependence of the first term was not determined. From the values in Table V, the value of $[I_3^-]k_2'/[I^-]$ is 4.8×10^{-7} s^{-1} when $[I_3^-] = 1.2 \times 10^{-4}$ M and $[I^-] = 0.125$ M, and it is 4.04×10^{-6} s^{-1} when $[I_3^-] = 1.2 \times 10^{-4}$ M and $[I^-] = 0.015$ M. In one case the thioester hydrolyzes independently of the I_3^- concentration at a rate that is 3 times faster than the triiodide-dependent rate. The ratio increases as the I_3^- is consumed. In 0.015 M I^-, the thioester undergoes an iodine-assisted

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(9) Danehy, J. P.; Oester, M. Y. *J. Org. Chem.* **1967**, *32*, 1491.

Table VII. Bond Distances (Å) and Angles (deg) for $(CH_3)_2{}^+NHCH_2CH_2CH_2SO_3{}^-$

S-O(1)	1.454 (2)	O(1)-S-O(2)	113.0 (1)
S-O(2)	1.449 (2)	O(1)-S-O(3)	112.2 (1)
S-O(3)	1.461 (2)	O(2)-S-O(3)	112.4 (1)
S-C(1)	1.780 (2)	O(1)-S-C(1)	105.1 (1)
N-C(3)	1.505 (3)	O(2)-S-C(1)	106.9 (1)
N-C(4)	1.491 (3)	O(3)-S-C(1)	106.6 (1)
N-C(5)	1.494 (3)	C(3)-N-C(4)	113.0 (2)
C(1)-C(2)	1.517 (3)	C(3)-N-C(5)	112.8 (2)
C(2)-C(3)	1.516 (3)	C(4)-N-C(5)	111.0 (2)
N-H	0.92 (3)	C(3)-N-H	104 (2)
C-H (av)	0.96 (2)	C(4)-N-H	106 (2)
H···O(3)′	1.85 (2)	C(5)-N-H	109 (2)
		S-C(1)-C(2)	113.8 (1)
		C(1)-C(2)-C(3)	108.1 (2)
		N-C(3)-C(2)	114.5 (2)
		N-H···O(3)′	160 (2)

hydrolytic cleavage 2.6 times faster than unassisted hydrolysis. It should be noted that as the reaction progresses, the rate of hydrolysis remains the same, but the rate of the iodine-assisted hydrolysis becomes slower due to $I_3{}^-$ consumption. Although the dilute solution stoichiometry indicates that 2 mol of I_2 reacts per mole of II, only the 2-(2-pyridyl)ethanesulfonic acid was isolated. Since no 2-(2-pyridyl)ethyl disulfide was observed, the initial product from the I_2 reaction was probably 2-(2-pyridyl)ethylsulfinic acid, which was air-oxidized during the reaction workup.

The rate of triiodide consumption when I is oxidized is accelerated relative to its rate of hydrolysis such that only the iodine-dependent path was measurable. The rate follows eq 3. The product of this reaction is the 3-(dimethylamino)propanesulfonic acid zwitterion, IV, which was characterized by X-ray diffraction.

Comparison of the $I_3{}^-$-dependent rates of I and II at pH 9.0 and 0.125 M KI reveals that the half-lives are 14.5 and 1.44×10^6 s, respectively. Thus under these conditions the reaction of I with I_2 is 10^5 times faster than the corresponding reaction of II.

The stoichiometry of the γ-amino thioesters with aqueous I_2 resembles that observed by Lavine[10] and Danehy[9] for γ-mercaptopropionic acids, as well as our own results for the 2-(2-pyridyl)ethanethiol. The overall reactions for I and II are

$$RSCOCH_3 + 2I_2 + 6OH^- = RSO_2{}^- + CH_3CO_2{}^- + 4I^- + 3H_2O$$

$$2RSO_2{}^- + O_2 = 2RSO_3{}^-$$

The rates of alkaline hydrolysis of the thioesters were determined in order to compare the rates of thioester consumption at a given pH with and without I_2. While the log of the rate constants for the hydrolysis of II are linear over the pH range studied, the rates of hydrolysis of I (Table IIIB) are not directly proportional to the hydroxide concentration. However, the effect of pH on the hydrolysis rates of I cannot be interpreted as evidence of amine participation in the hydrolysis since the mechanism of hydrolysis at the intermediate pH range has not been unequivocally defined even in simple cases.[11]

Description of the Structure of IV. A drawing of the structure of $(CH_3)_2{}^+NHCH_2CH_2CH_2SO_3{}^-$ is given in Figure 1. Bond distances and angles are listed in Table VII. The presence of a hydrogen atom bonded to nitrogen clearly shows the zwitterionic character of the molecule. Adjacent molecules are packed with opposite ends perpendicular such that a single, strong hydrogen bond is formed between the ammonium hydrogen atom and one of the sulfonate oxygen atoms. Bond lengths and bond angles are consistent with known values.

Mechanism of the I_2-Assisted Reaction of I. The mechanism will involve two paths, a and b, in order to account for the two terms in the rate law of eq 3.

The rate of oxidation of I is proportional to $[I_3{}^-][I^-]^{-1}$, a result that has generally been interpreted as due to the predissociation of the triiodide and to the invovement of molecular iodine in the reaction.[1] The additional term in iodide, $(0.5 + [I^-])^{-1}$, can be accounted for if a steady-state intermediate is formed along with iodide ion in one step of the mechanism. In both paths, the term $K_a/([H^+] + K_a)$ indicates that I reacts only as the free amine.

A mechanistic scheme which would account for the first term of the rate law is shown in Scheme I. If there is a steady-state concentration of $[RSCOCH_3{\cdot}I]^+$ in Step 4a, then eq 4–6 hold.

Scheme I

$$\text{Path a:}\ {}^+HRSCOCH_3 \xrightleftharpoons{k_a} RSCOCH_3 + H^+ \qquad \text{step 1}$$

$$I_3{}^- \xrightleftharpoons{K_{I_3^-}} I_2 + I^- \qquad \text{step 2}$$

$$RSCOCH_3 + I_2 \xrightleftharpoons{K_1} RSCOCH_3{\cdot}I_2 \qquad \text{step 3}$$

$$RSCOCH_3{\cdot}I_2 \xrightleftharpoons[k_{-3}]{k_3} [RSCOCH_3{\cdot}I]^+ + I^- \qquad \text{step 4a}$$

$$[RSCOCH_3{\cdot}I]^+ \xrightleftharpoons{k_4} \text{products} \qquad \text{step 5a}$$

$$\text{rate} = [RSCOCH_3{\cdot}I^+]k_4 \tag{4}$$

$$[RSCOCH_3{\cdot}I_2]k_3 = [RSCOCH_3{\cdot}I^+](k_{-3}[I^-] + k_4) \tag{5}$$

$$\text{rate} = [RSCOCH_3{\cdot}I_2]k_3k_4(k_{-3}[I^-] + k_4)^{-1} = \frac{[I_3{}^-]}{[I^-]}K_{I_3^-}\frac{[RSCOCH_3]K_aK_1}{[H^+] + K_a}\,\frac{k_3k_4}{k_{-3}[I^-] + k_4} \tag{6}$$

Equation 6 shows a dependence on $K_a/([H^+] + K_a)$ with pH and an iodide dependence proportional to $[I_3{}^-][I^-]^{-1}(k_{-3}[I^-] + k_4)^{-1}$, where $k_4/k_{-3} = 0.5$.

The second term of eq 3 is described by path b:

Path b: steps 1–3 are followed by

$$RSCOCH_3{\cdot}I_2 + OH^- \xrightarrow[\text{fast}]{k_5} \text{products} \qquad \text{step 4b}$$

by making the same assumptions as for path a:

$$\text{rate} = \frac{[I_3{}^-]}{[I^-]}K_{I_3^-}\frac{[RSCOCH_3]K_aK_1}{[H^+] + K_a}[OH^-]k_5$$

which shows a dependence on $[OH^-]K_a/([H^+] + K_a)$ with pH and an iodide dependence proportional to $[I_3{}^-][I^-]^{-1}$.

The simplest mechanism that accounts for the synergistic effect of an amine and iodine on the deacylation of thioesters will be described in detail. This mechanism is consistent with those previously published to account for anchimeric assistance by neighboring nucleophiles (e.g., amines,[1,12a,b] alcohols,[12c] thioethers,[12b] and carboxylate groups[12d]) on thioether oxidation by aqueous iodine. The iodine formed in step 2 coordinates to the thioester sulfur in step 3. In step 4a an iodide ion is reversibly lost from the complex to form $[RSCOCH_3{\cdot}I]^+$. When the pH is sufficiently high, step 4b occurs, and the thioester–iodine complex is attacked by hydroxide ion in the rate-determining step. The accelerated rate of I over II and III is attributable to the N–S interaction to form sulfurane V in steps 3 or 4a. In steps 5a and 4b deacylation occurs by attack of H_2O or OH^- on the carbonyl carbon.

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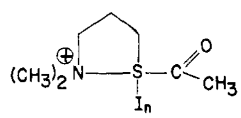
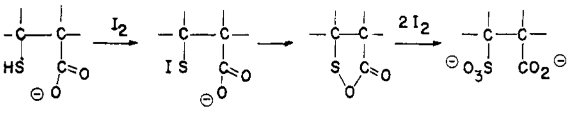


V, $n = 1$, step 4a
$n = 2$, step 4b

The structure of intermediate V has been proposed since similar sulfurane intermediates have been proposed in the aqueous I_2 oxidation of the thioethers 5-methyl-1-thia-5-azacyclooctane[12a] and methionine.[12b] In V an acyl group replaces the alkyl group of the thioethers and would be expected to stabilize the sulfurane.

The iodine-assisted reaction requires the presence of an intramolecular nucleophile in a position proximate to the thioester group. No intermolecular effect is observed when triethylamine is added to a solution of I_2 and I. The rate is 10^5 times more rapid at pH 9.0 and 0.125 M KI for a neighboring dimethylamino group ($pK_a = 9.5 \pm 0.2$) than for the 2-pyridyl group ($pK_a \simeq 6$). Because the reaction of II with I_2 is slow and there is competing hydrolysis, the rates of II (Table VI) were run at lower iodide concentrations than were the rates of I. For II, the rate constants show a simple inverse order in iodide, and when $[I^-] \leq 0.1$ M, the mechanisms outlined in both paths a and b would give this observed iodide dependence. If the mechanism proposed for the reaction of I is applied to the reaction of II, we must be able to account for the differences in rate. If steps 3 and 4 involve N–S bond formation, they are similar to the reactions of the corresponding thioethers[1] for which a factor of 25 can be calculated for $(CH_3)_2N$ vs. pyridyl participation at pH 9. Steps 4b and 4a are deacylation and would be accelerated by the $^+$N–S–I group adjacent to the carbonyl group. The intermediate formed from I has a localized charge on the nitrogen, whereas in the [pyridyl–S–I]$^+$ intermediate from II the charge can be delocalized. Attack of an OH^- or H_2O on the carbonyl group would be accelerated by a localized more than by a delocalized positive charge. The work of Schwyzer[13] has demonstrated that the rates of thioester ammonolysis decrease as SR′ becomes less positive. Alternatively, the lower reactivity of II may be due to a lower concentration of reactive intermediate in steps 3, 4a, and 4b.

An intramolecular interaction between a neighboring nucleophile, iodine, and a thiol group has been proposed previously by others to account both for the conversion of thiols to sulfonic acids[9] and for a rapid deacylation reaction.[14] Danehy and Oester[9] proposed an interaction (eq 7) between a neighboring carboxylate group and a sulfenyl iodide to account for the reaction of γ-mercaptopropionic acid with 3 mol of iodine to give the sulfonic acid instead of the disulfide. The products of this reaction were not isolated. We observe a similar overoxidation to the sulfonic acid with thioesters I and II as well as with 2-(2-pyridyl)ethanethiol with aqueous I_2 and have kinetic evidence for the intermediate V from thioester I. In the oxidative acyl transfer from *S*-monoacyl-1,3-propanedithiols to methanol, a reaction related to the enzymatic mechanism of pyruvate dehydrogenase, Takagi[14] has proposed the scheme shown in eq 8 involving a nucleophilic attack of the thioester sulfur on a neighboring sulfenyl iodide. The formation of the thiasulfonium salt intermediate enhances deacylation and favors the formation of 1,2-dithiolane over the intramolecular reaction to form $(RCOS(CH_2)_3S-)_2$.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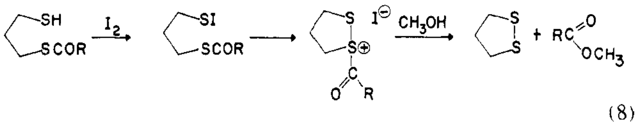
(8)

For *S*-*n*-butyl thioacetate, III, there is no internal nucleophile, and the equilibrium concentration of the iodine complex may be even lower. Furthermore, *n*-butylthiolate is a far poorer leaving group than the N–S–I interacted leaving group. Thus, no acceleration is seen, and the rate is zero order in I_3^-. The thiol is produced by hydrolysis and subsequently is oxidized to the disulfide by iodine. Unlike the reactions of soft metal ions with thioesters,[5] iodine, alone, does not promote thioester hydrolysis.

A few other mechanisms cannot be ruled out by the data, but they involve more steps or require intermediates that would be expected to lead to different products. For example, the mechanism proposed for the deacylation of thioesters I and II involves an iodine–thioester complex rather than an iodine–amine complex in step 3. The iodine–thioester complex is attacked by the neighboring amine to give intermediate V, in which sulfur has expanded its valence shell. Although an iodine–amine complex could be formed in solution, attack by the thioester sulfur would require that both iodine atoms be lost from the nitrogen in step 3 of the mechanism due to the inability of nitrogen to accommodate more than four substituents. However, since steps 5a and 4b are the rate-determining steps, reaction via the amine–I_2 complex would result in an overall inverse third-order iodide dependence and would not agree with the observed rate law.

An alternate structure for V is the tetrahedral intermediate formed by an initial intramolecular reaction between the tertiary amine and the acyl group. This intermediate has extensive charges, but subsequent acyl transfer would give a second intermediate, $IS-(CH_2)_3-N^+(CH_3)_2COCH_3$ (VI). If the product is formed directly from VI, it should be the disulfide $((CH_3)_2N(CH_2)_3S-)_2$ as was the case from III and not the sulfonic acid IV. In order to account for the formation of IV, additional steps are required: (a) hydrolysis of VI to $IS-(CH_2)_3N(CH_3)_2$; (b) intramolecular interaction between the $(CH_3)_2N$ and S–I moieties; (c) further oxidation of the N–S–I group to give IV. This alternative mechanism involves two intramolecular interactions and two tetrahedral intermediates. Although this mechanism is not ruled out by the kinetic data, the formation of sulfurane V is proposed as a more direct path to products.

The effect of I_2 on the rate of thioester cleavage is a 10^3–10^4-fold acceleration over its hydrolysis when the reactant is I. The acceleration is explained by the synergistic effect of iodine and a neighboring amine group, which leads to an intermediate best described as sulfurane with an adjacent carbonyl group. This sulfurane intermediate provides an excellent leaving group and leads to facile cleavage of the thioester C–S bond.

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Registry No. I, 66338-43-0; II, 59020-97-2; III, 928-47-2; IV, 29777-99-9.

Supplementary Material Available: Listing of thermal parameters for $C_5H_{13}NSO_3$ (1 page). Ordering information is given on any current masthead page.

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