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Hydration of Thioesters. Evaluation of the Free-Energy Changes for the Addition of Water to Some Thioesters, Rate-Equilibrium Correlations over Very Wide Ranges in Equilibrium Constants, and a New Mechanistic Criterion

J. Peter Guthrie¹

Contribution from the Department of Chemistry, University of Western Ontario, London, Ontario, Canada. Received October 18, 1976

Abstract: Free energies of hydration of *S*-ethyl thioformate and trifluorothioacetate have been determined. The starting point for *S*-ethyl thioformate is the calorimetric heat of hydrolysis of triethyl monothioorthoformate, which leads to $\Delta H_f^\circ(1) = -116.6 \pm 0.4 \text{ kcal mol}^{-1}$. From this may be calculated the free-energy change for addition of water to *S*-ethyl thioformate, as $4.7 \pm 2.7 \text{ kcal mol}^{-1}$. For *S*-ethyl trifluorothioacetate, the starting points are the upper limit for the free energy of addition of hydroxide derived from Schmir's kinetic analysis and the lower limit imposed by the lack of any detectable accumulation of an intermediate. The limits permit calculation of the free-energy change for addition of water as $+3.8 \pm 1.6 \text{ kcal/mol}$. The free energies for addition of water to these thiol esters, combined with estimated $\text{p}K_a$ values for the tetrahedral intermediates, permit construction of more complete reaction coordinate diagrams than has previously been possible and the calculation of all of the rate constants required to describe the kinetics. With rate and equilibrium constants for addition reactions of amides, esters, thioesters, ketones, and aldehydes now available it is possible to construct rate-equilibrium comparisons over wide ranges of reactivity (as much as 20 orders of magnitude in equilibrium constant). It has been found that the data for these reactions may be described in terms of simple nonlinear curves, described by a one-parameter equation based on Marcus theory, provided that the rate and equilibrium constants are calculated for the microscopic process which is rate determining. It seems highly probable that this will be a powerful new technique for mechanistic analysis, whenever data over a wide enough range of reactivity are available. In the case of uncatalyzed hydration this approach leads to a clear conclusion that the rate-determining step is formation of a zwitterionic adduct, which rapidly undergoes proton transfer to give the neutral adduct. Although very few data are available for thiol additions to carbonyl compounds, a similar analysis leads to the conclusion that the rate-determining step for uncatalyzed thiol addition involves hydronium ion acting as general acid catalyst for the addition of thiolate ion leading to the neutral adduct. This mechanistic analysis immediately leads to a simple explanation for the previously puzzling phenomenon that acyl activated thiol esters show acid inhibition, whereas thiol esters without electron-withdrawing acyl substituents show acid catalysis.

Introduction

Although tetrahedral intermediates are generally considered to be involved in the majority of acyl transfer reactions,² the number of instances where there is direct and compelling experimental evidence for their involvement is still relatively limited.³ One of the first clear examples was the demonstration of a tetrahedral intermediate in the hydrolysis of ethyl trifluorothioacetate.³ Since then, studies of other thiol ester hydrolyses have shown complicated pH rate profiles, indicative of changes in rate-determining step and, hence, of an intermediate⁴ (presumably tetrahedral). A method has been developed for calculating the free energies of formation of tetrahedral intermediates by a simple extrathermodynamic ap-

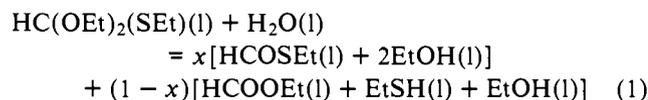
proach which has been applied to addition reactions of esters^{5,6} and amides.⁷ This paper reports an extension of this procedure to thiol esters. In addition, it was found that for the case of trifluorothioacetates (where the thermochemical approach would be very difficult) a combination of kinetic, thermodynamic, and spectroscopic information permits the specification of the free-energy level of the intermediate within rather narrow limits.

Thiol esters with electron-withdrawing acyl groups are unusual in that acid inhibition,^{3a,4b} rather than acid catalysis, is observed. This behavior has been rationalized in terms of rate-determining attack of water to give the neutral tetrahedral intermediate, followed by rapid proton loss and expulsion of thiolate, provided the pH is not too low. As the pH is lowered

the proton transfer becomes less favorable, until there is a change to rate-determining expulsion of thiol from the neutral intermediate, which is slower than expulsion of water and reversion to starting material. However, the reasons why this behavior is important if and only if powerful electron-withdrawing groups are present have remained obscure. In this paper, it will be shown that this question can be answered by more detailed consideration of the mechanisms for the uncatalyzed addition (and expulsion) of water and thiol, making use of rate-equilibrium correlation over very wide ranges of reactivity. These correlations, which are possible because of the availability of equilibrium constants for addition of water to esters,^{5,6} amides,⁷ and now thiol esters, as well as aldehydes and ketones, show that there is a striking uniformity of mechanism for all carbonyl reactions of a given type.

Results

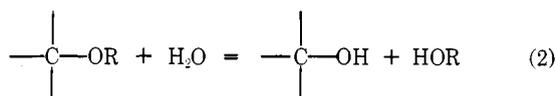
Heat and Free Energy of Formation of Triethyl Monothioorthoformate. The heat of hydrolysis of triethyl monothioorthoformate was measured using a simple calorimeter. It was necessary to use 3:1 v/v methanol-water as the solvent to ensure rapid dissolution of reactant and products. Heats of solution were measured and permit calculation of a heat of hydrolysis for the hypothetical reaction



The stoichiometry of the reaction was determined by ¹H NMR analysis of the product mixture obtained when triethyl monothioorthoformate was added to 0.1 N HCl in 3:1 methanol-water. Hydrolysis of the initial products occurred at a noticeable rate, so the product ratio was extrapolated to zero time. The heat of hydrolysis of *S*-ethyl thioformate was determined in 0.1 N NaOH in 3:1 methanol-water. Heats of formation of the other products were available from the literature. The heat of solution and reaction data are found in Table I.

The heat of formation of liquid triethyl monothioorthoformate calculated from these data is -116.55 ± 0.41 kcal mol⁻¹. There are insufficient data for a straightforward calculation of the heat of vaporization. An indirect procedure was employed to obtain the necessary data from one boiling point measurement at reduced pressure; see Appendix 1. The value so obtained was 12.2 kcal/mol. The standard entropy in the gas phase was estimated by the atomic contributions methods of Benson and Buss.⁸ Thus it was possible to calculate the free energy of formation in the gas phase. From values for the vapor pressure at 25 °C (estimated; see Appendix 1) and solubility (this work, see the Experimental Section) one can calculate the free energy of transfer, ΔG_t , as -1.72 kcal mol⁻¹. This leads to the desired quantity, the free energy of formation in aqueous solution of triethyl monothioorthoformate, as -51.21 ± 1.84 kcal mol⁻¹.

Free Energies of Formation of Tetrahedral Intermediates in *S*-Ethyl Thioformate Alcoholysis and Hydrolysis. It has been shown that for reactions such as (2) the free energy



change is small and can be calculated by taking account of symmetry, steric, and electronic effects.⁹ Following this procedure free-energy changes for the appropriate (hypothetical) reactions were calculated and, from these, the free energies of formation of the species HC(OH)(OEt)(SEt) and HC(OH)₂(SEt). The values so obtained are found in Table II.

Tetrahedral Species from *S*-Ethyl Trifluorothioacetate. The

Table I. Heats of Solution and Reaction in 75% Methanol^a

compd	ΔH_{obsd} , kcal mol ⁻¹	x^b	$\Delta H_f^\circ(\text{l})$, kcal mol ⁻¹
(a) heat of solution ^c			
H ₂ O	-0.32 ± 0.02		
EtOH	-0.08 ± 0.02		
EtSH	$+1.56 \pm 0.27$		
HCOOEt	$+0.95 \pm 0.27$		
HCOSEt	$+1.63 \pm 0.18$		
(b) heat of solution and ionization ^d			
EtSH	-1.67 ± 0.02		
HCOOH	-8.44 ± 0.67		
CF ₃ COOH	-13.63 ± 0.46		
(c) heat of hydrolysis			
HC(OEt) ₂ SEt	1.21 ± 0.13^c	0.23 ± 0.02	-114.97 ± 0.37
HCOSEt	-9.3 ± 0.40^d		-51.62 ± 0.61
CF ₃ COSEt	-13.65 ± 0.27^d		-64.01 ± 0.21
HCOOEt	-6.53 ± 0.18^d		-101.74 ± 0.69
	$-13.56 \pm 0.55^{d,e}$		-103.11 ± 0.55
	$-13.04 \pm 0.22^{e,f}$		-102.59 ± 0.23

^a At 25 °C; each value is an average \pm standard deviation for three determinations. ^b Fraction of hydrolysis leading to thiol ester; see text. ^c In 0.1 N HCl. ^d In 0.1 N NaOH. ^e In water. ^f In 0.02 M aqueous NaOH; ref 47.

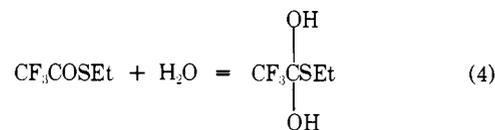
simple thermochemical approach employed for the thioformate ester is not applicable to trifluorothioacetate derivatives, because of the slow acid-catalyzed hydrolysis of orthoesters of trifluoroacetic acid.⁶ This is unfortunate because it is this case which is of greatest interest since the clearest demonstration^{3a,4b} of a kinetically significant tetrahedral species in thiol ester hydrolysis involved *S*-ethyl trifluorothioacetate.

In order to place a lower limit on the concentration of the intermediate at steady state, an experiment was conducted to determine the UV absorbance, extrapolated to zero time, for solutions with 0.001, 0.01, 0.1, and 1.0 M HCl, all at ionic strength 1.0 M with KCl. The rationale for this experiment was that over this range of pH there is a change in the rate-determining step from the addition of water (rate determining at low acidity) to expulsion of thiolate (rate determining at high acidity), and, therefore, any accumulation of intermediate, when breakdown is rate determining, would manifest itself as a lower initial absorbance than in a parallel experiment where formation is rate determining. In fact, the initial absorbance was the same for all concentrations of HCl, within an experimental error of about 3%.

In terms of Schmir's kinetics analysis,^{4b} the concentration of the intermediate at steady state may be expressed as

$$[\text{I}^0] = k_1'[\text{S}]/[k_2'(1 + k_3'/k_2')(1 + K''/[\text{H}])] \quad (3)$$

(this expression has been simplified by omitting terms negligible below pH 3). Since Schmir has evaluated k_3'/k_2' and K'' ,^{4b} the limit placed above on $[\text{I}^0]/[\text{S}]$ may be converted into a limit on k_1'/k_2' ; for the result at 1 M HCl this turns out to be that $k_1'/k_2' < 0.05$ and, consequently, that for the reaction



$\Delta G^\circ > 1.8$. (Here and throughout this paper, the standard state for water is the pure liquid, with activity = 1.)

From his kinetic analysis of the hydrolysis of *S*-ethyl trifluoroacetate,^{4b} Schmir deduced (subject to the assumption that proton-transfer steps were at equilibrium) that the partitioning factor for the anionic form of the tetrahedral intermediate, expressed as ratio of rate constants for expulsion of

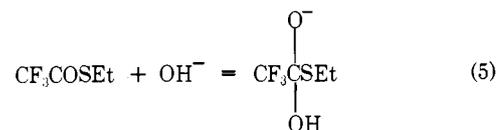
Table II. Thermochemical Data for Compounds Used in This Paper^a

compd	$\Delta H_f^\circ(\text{g})^b$	$S^\circ(\text{g})^c$	$\Delta G_f^\circ(\text{g})^b$	$\Delta H_v^{b,d}$	$\Delta H_f^\circ(\text{l})^b$	$\Delta G_t^{b,e}$	$\Delta G_f^\circ(\text{aq})^b$
H ₂ O	-57.80 ^f	45.11 ^f	-54.68 ^f		-68.32 ^f		-56.69 ^{f,g}
HCOOH	-90.49 ^h	59.45 ^h	-83.89 ^h		-101.60 ⁱ	-4.94 ^j	-88.83 ^j
CH ₃ OH	-48.08 ^f	56.8 ^f	-39.09 ^f		-57.02 ^f	-3.19 ^j	-41.88 ^j
CH ₃ COOH	-103.26 ⁱ	67.52 ^h	-89.36 ^k		-115.75 ⁱ	-4.85 ^j	-94.21 ^j
CF ₃ COOH	-243.2 ± 1.1 ⁱ	79.6 ± 1.5 ⁱ	-225.2 ± 1.1 ⁱ	9.8 ± 0.7 ⁱ	-253.0 ± 0.8 ⁱ	-4.75 ^j	-230.0 ± 1.2 ⁱ
CH ₃ CH ₂ OH	-56.24 ± 0.07 ^f	67.4 ^f	-40.30 ^f		-66.42 ⁱ	-3.01 ^j	-43.31 ^k
CH ₃ CH ₂ SH	-11.00 ± 0.14 ⁱ	70.77 ^h	-1.10 ± 0.21 ^k	6.53 ± 0.01 ⁱ	-17.53 ± 0.14 ⁱ	1.08 ^m	-0.02 ± 0.21 ^k
HCOOC ₂ H ₅	-94.90 ± 1.03 ^k	82.00 ± 1.5 ^m	-75.61 ± 1.12 ^k	7.69 ± 1.0 ^o	-102.59 ± 0.23 ^o	-0.76 ^m	-76.36 ± 1.12 ^k
HCOSC ₂ H ₅	-42.48 ± 1.22 ^k	83.41 ± 5 ^m	-28.64 ± 1.92 ^k	9.14 ± 1.0 ^m	-51.62 ± 0.61 ⁿ	-0.69 ^m	-29.28 ± 1.93 ^k
CH ₃ COSC ₂ H ₅	-54.45 ± 0.22 ^k	90.63 ± 5 ^m	-33.05 ± 1.51 ^k	9.56 ± 0.05 ^p	-64.01 ± 0.21 ^{i,q}	-0.41 ^m	-33.46 ± 1.51 ^k
CF ₃ COSC ₂ H ₅	-194.90 ± 1.40 ^k	104.13 ± 5 ^m	-169.74 ± 2.04 ^k	8.7 ± 1.0 ^m	-203.61 ± 0.97 ⁿ	+2.03 ^m	-167.72 ± 2.05 ^k
HC(OC ₂ H ₅) ₂ - SC ₂ H ₅	-104.40 ± 1.08 ^k	131.6 ± 5 ^m	-49.48 ± 1.84 ^k	12.15 ± 1.0 ^m	-116.55 ± 0.41 ⁿ	-1.72 ^m	-51.21 ± 1.84 ^k
HC(OC ₂ H ₅)- (OH)SC ₂ H ₅							-65.22 ± 1.85 ^m
HC(OH) ₂ SC ₂ H ₅							-79.71 ± 1.86 ^m
CH ₃ C(OH ₂ H ₅) ₂ - SC ₂ H ₅	-108.47 ± 3.97 ^k	138.9 ± 5 ^m	-46.00 ± 3.68 ^k			-1.56 ^m	-47.56 ± 3.36 ^m
CH ₃ C(OC ₂ H ₅)- (OH)SC ₂ H ₅							-63.64 ± 3.36 ^m
CH ₃ C(OH) ₂ - SC ₂ H ₅							-78.68 ± 3.36 ^m
CF ₃ C(OC ₂ H ₅) ₂ - SC ₂ H ₅	-254.67 ± 2.53 ^k	152.4 ± 5 ^m	-188.45 ± 2.04 ^k			2.02 ^m	-188.62 ± 1.98 ^m
CF ₃ C(OC ₂ H ₅)- (OH)SC ₂ H ₅							-206.23 ± 1.96 ^m
CF ₃ C(OH) ₂ - SC ₂ H ₅							-222.80 ± 1.94 ^m

^a At 25 °C; standard states are ideal gas at 1 atm, pure liquid, and 1 M aqueous solution with an infinitely dilute reference state, unless otherwise noted. ^b kcal mol⁻¹. ^c cal deg⁻¹ mol⁻¹. ^d Heat of vaporization. ^e Free energy of transfer from gas to aqueous solution. ^f Reference 48. ^g Standard state is the pure liquid. ^h Reference 49. ⁱ Reference 50. ^j Reference 5. ^k Calculated from values in this table. ^l Reference 6. ^m Calculated as described in the text. ⁿ This work. ^o Reference 47. ^p Reference 24. ^q Reference 51.

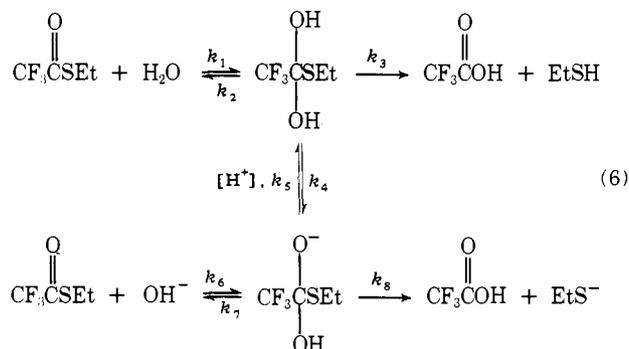
hydroxide and thiolate, was 4.6×10^{-8} with a corresponding $\Delta\Delta G^\ddagger = 10.01$ kcal mol⁻¹. The rate constant for attack of hydroxide ion to give this anionic intermediate was 6.7×10^3 M⁻¹ s⁻¹, so that $\Delta G^\ddagger = 12.24$ kcal mol⁻¹. Thus the transition state for breakdown of the anionic intermediate (with expulsion of ethanethiolate ion) lies 2.23 kcal mol⁻¹ higher than the starting materials (CF₃COSEt and OH⁻). In dilute acid solution there is a change in the rate-determining step, from breakdown of the anionic form of the tetrahedral intermediate at lower [H⁺] to formation of this intermediate (by at least two steps, addition of water, and loss of a proton) at higher [H⁺]. The partitioning is measured by the parameter which Schmir^{4b} labels K'' ; subject to the assumption of rapid proton transfer this is equal to the K_a for the tetrahedral intermediate times the ratio of the rate constants for expulsion of thioethoxide from the anionic intermediate and for expulsion of water from the neutral intermediate. The maximum possible value for the rate of breakdown of the anionic intermediate to give water and thioester is the rate of protonation of the intermediate, which is expected to be diffusion controlled. Schmir assumed that the breakdown of the neutral intermediate was slower, so that proton-transfer steps were at equilibrium. Since the rate constant for reaction of H⁺ with an anion is typically $1-5 \times 10^{10}$ M⁻¹ s⁻¹¹⁸ and K'' is 0.25, this sets an absolute upper limit of about 10^{10} s⁻¹ on the rate of expulsion of thioethoxide from the anionic intermediate. This means that the intermediate must lie ca. 4 kcal mol⁻¹ lower in free energy than the transition state for its decomposition, or lower than -1.5 kcal mol⁻¹ relative to starting materials. (In terms of eq 7 below this argument leads to $k_8 \leq d \times k_5$.)

On the basis of the experiment discussed above, it was concluded that for hydration of CF₃COSEt, $\Delta G^\circ > 1.8$. From the pK_a for CF₃C(OH)₂SEt (see Table III), and the ion product of water, it is possible to calculate that for



$\Delta G^\circ > -5.4$. Combining the two limits, we can say that $\Delta G^\circ = -3.5 \pm 1.9$ for addition of hydroxide and, consequently, that for addition of water to give the neutral species $\Delta G^\circ = +3.8 \pm 1.9$. Thermodynamic data for CF₃C(OH)₂SEt, CF₃C(OH)(OEt)SEt, and CF₃C(OEt)₂SEt deduced from this value of ΔG° are found in Table II.

Examination of reaction coordinate diagrams for the hydrolysis of *S*-ethyl trifluorothioacetate showed that, as has been suggested,¹⁰⁻¹² the proton-transfer steps may *not* be assumed to be fast relative to heavy atom bond-breaking steps. When the steady-state equations are solved for the complete system, eq 6, a rate law is obtained which is of the correct empirical



form, but which contains eight unknown rate constants:

$$k_{\text{obsd}} = (a[\text{H}^+] + b + c/[\text{H}^+]) / (d + [\text{H}^+]) \quad (7)$$

Table III. pK_a Values for Species Discussed in This Paper^a

species	pK_a	species	pK_a
(a) thiols		HC(OH)(SEt)OH ₂ ⁺	-3.75 ^l
CH ₃ OCOCH ₂ SH	7.83 ^b		7.62 ^m
CH ₃ OCH ₂ CH ₂ SH	9.50 ^b	CF ₃ C(OH)(SEt)-	-5.65 ^l
CH ₃ CH ₂ SH	10.25 ^b	OH ₂ ⁺	4.87 ^m
(b) carboxylic acids		CH ₃ C(OH)(CH ₃ -	-1.91 ^l
CH ₃ COOH	4.76 ^c	OH ₂ ⁺	10.34 ^m
HCOOH	3.77 ^c	CH ₃ C(OH)(H)OH ₂ ⁺	-2.35 ^l
CF ₃ COOH	-0.78 ^d		9.68 ^m
(c) protonated carbonyl compd		HC(OH)(H)OH ₂ ⁺	-2.79 ^l
CH ₃ C(OH)NMe ₂ ⁺	-0.36 ^e		9.68 ^m
HC(OH)NMe ₂ ⁺	-1.5 ^e	CH ₃ C(H)(OH)-	-10.63 ^q
CH ₃ C(OH)OMe ⁺	-3.45 ^{f,g}	(SHR ₁) ⁺ ^o	6.21 ^m
HC(OH)OMe ⁺	-5.21 ^{f,h}	CH ₃ C(H)(OH)-	-8.80 ^q
CF ₃ C(OH)OMe ⁺	-8.74 ^{f,h}	(SHR ₂) ⁺ ^p	6.44 ^m
CH ₃ C(OH)SEt ⁺	-5.6 ^h	CH ₃ C(H)(OH)-	-7.91 ^q
HC(OH)SEt ⁺	-7.4 ^h	(SEt) ⁺	6.55 ^m
CF ₃ C(OH)SEt ⁺	-10.9 ^h	CH ₃ C(OH) ₂ -	-9.07 ^q
CH ₃ C(OH)CH ₃ ⁺	-6.2 ⁱ	(SEt) ⁺	7.19 ^m
HC(OH)CH ₃ ⁺	-7.2 ⁱ	HC(OH) ₂ -	-9.73 ^q
HC(OH)H ⁺	-8.2 ^j	(SEt) ⁺	6.55 ^m
CH ₃ C(OH) ₂ ⁺	-7.4 ^k	CF ₃ C(OH) ₂ -	-12.61 ^q
HC(OH) ₂ ⁺	-8.8 ^h	(SEt) ⁺	3.75 ^m
CF ₃ C(OH) ₂ ⁺	-15.2 ^h	CH ₃ C(NMe ₂)(OH) ₂	13.37 ⁿ
(d) tetrahedral intermediates		HC(NMe ₂)(OH) ₂	12.73 ⁿ
CH ₃ C(OH)(NMe ₂)-	-2.47 ^l	CH ₃ C(OMe)(OH) ₂	11.80 ⁿ
OH ₂ ⁺	9.51 ^m	HC(OMe)(OH) ₂	11.15 ⁿ
HC(OH)(NMe ₂)-	-2.91 ^l	CF ₃ C(OMe)(OH) ₂	8.36 ⁿ
OH ₂ ⁺	8.87 ^m	CH ₃ C(SEt)(OH) ₂	12.13 ⁿ
CH ₃ C(OH)(OMe)-	-3.54 ^l	HC(SEt)(OH) ₂	11.48 ⁿ
OH ₂ ⁺	7.94 ^m	CF ₃ C(SEt)(OH) ₂	8.69 ⁿ
HC(OH)(OMe)-	-3.97 ^l	CH ₃ C(CH ₃)(OH) ₂	14.19 ⁿ
OH ₂ ⁺	7.29 ^m	CH ₃ C(H)(OH) ₂	13.54 ⁿ
CF ₃ C(OH)(OMe)-	-5.88 ^l	HC(H)(OH) ₂	12.90 ⁿ
OH ₂ ⁺	4.49 ^m	CH ₃ C(H)(SR ₁)OH ^o	13.98 ⁿ
CH ₃ C(OH)(SEt)-	-3.31 ^l	CH ₃ C(H)(SR ₂)OH ^p	14.21 ⁿ
OH ₂ ⁺	8.27 ^m	CH ₃ C(H)(SEt)(OH)	14.34 ⁿ

^a In water at 25 °C. ^b Reference 52. ^c Reference 53. ^d Reference 4b. ^e Reference 31. ^f Assumed to be the same as for the ethyl ester. ^g Reference 40. ^h Estimated as described in the text. ⁱ Reference 44. ^j Estimated after ref 44, assuming that the effect of the second replacement of CH₃ by H has the same effect as the first. ^k Reference 34. ^l Dissociation of -OH₂⁺ to give a neutral species. ^m Dissociation of -OH to give a zwitterion. ⁿ Dissociation to give an anion. ^o R₁ = CH₃OCOCH₂. ^p R₂ = CH₃OCH₂CH₂. ^q Dissociation of -SHR⁺ to give a neutral species.

with

$$a = k_1 k_3 / (k_2 + k_3)$$

$$b = k_1 [k_8 k_4 / k_5 (k_2 + k_3) + k_3 (k_7 + k_8) / k_5 (k_2 + k_3) + k_3 k_4 k_7 / k_2 k_5 (k_2 + k_3)]$$

$$c = k_1 k_7 k_8 k_4 [1 + k_4 / (k_2 + k_3)] / k_5^2 k_2$$

$$d = (k_7 + k_8) [1 + k_4 / (k_2 + k_3)] / k_5$$

In order to solve this system, four additional pieces of information are needed. Suitable data are the equilibrium constant for addition of water, K^0 , the equilibrium constant for addition of hydroxide, K^- (both evaluated as described above), the acid ionization constant for the neutral intermediate, K_a (estimated from the equations for 1,1-diols; see Appendix 2), and the rate constant for reaction of hydronium ion with an alkoxide, k_5 (assumed to be a diffusion-controlled process). With these four additional relations, the system is solvable, although still intractable by direct methods.

Simple algebraic manipulation can lead to an analytical

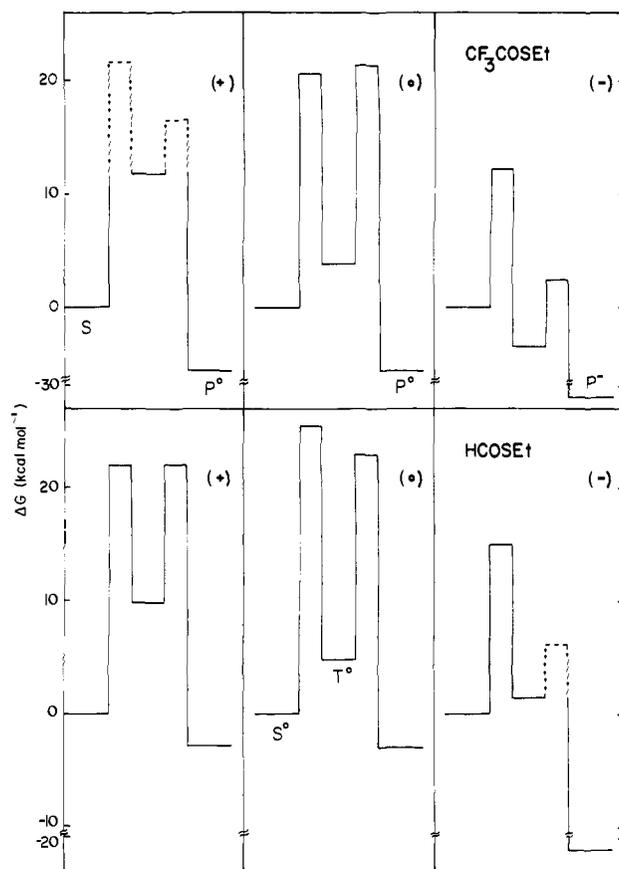


Figure 1. Reaction coordinate diagrams for the acid-catalyzed, uncatalyzed, and hydroxide-catalyzed hydrolyses of *S*-ethyl thioformate and trifluoroacetate. The free-energy levels of the intermediates (cationic, neutral, or anionic) are calculated as described in the text. Free-energy levels of transition states are calculated from observed rate constants or partitioning ratios (solid lines). The dotted lines represent processes which have not been measured or have not been observed.

solution for rate constants in terms of known quantities, but the solutions are cubic equations and far too complex to be useful. Furthermore, the known quantities are subject to error, and propagation of errors would lead to severe problems during the arithmetic of the solution. An alternative method of solution seemed more desirable. Values of the eight rate constants were chosen to satisfy the least-squares criterion, minimizing the sum of weighted deviations from the known quantities.¹³ The least-squares program was, in effect, being used to achieve a numerical solution of the set of equations. The best fit gives excellent agreement, as is shown in Table IV. Since some of the equilibrium constants used in the solution have large uncertainties associated with them, it necessarily follows that some of the rate constants are rather imprecise.

In Figure 1 are presented reaction coordinate diagrams summarizing the information available to this point concerning the acid-, un-, and base-catalyzed hydrolysis of thiol esters. Although these diagrams are more detailed than any previously available, in that values of the free-energy levels for the intermediates in the formate and trifluoroacetate cases are available, there are still considerable areas of uncertainty concerning the detailed mechanism for the formation and breakdown of the intermediates.

Rate-Equilibrium Correlations for Addition to Carbonyl Groups. In Table V are gathered a set of data for rate and equilibrium constants for the hydration of carbonyl compounds by uncatalyzed, hydroxide-catalyzed, and acid-catalyzed paths. These constants were calculated for the microscopic processes

Table IV. Rate Constants for the Hydrolysis of *S*-Ethyl Trifluorothioacetate^a

rate constant ^b	quantity used in soln	expt value	calcd value
log $k_1 = -2.13 \pm 0.08$	a) parameters	1.73×10^{-3}	1.73×10^{-3}
log $k_2 = +0.65 \pm 0.71$	b) from the	1.51×10^{-3}	1.50×10^{-3}
log $k_3 = +0.13 \pm 0.57$	c) pH rate	2.37×10^{-11}	2.35×10^{-11}
log $k_4 = +1.31 \pm 0.67$	d) profile ^c	2.45×10^{-1}	2.43×10^{-1}
log $k_5 = +10.00 \pm 0.33$	e = K_a^d	2.06×10^{-9}	2.06×10^{-9}
log $k_6 = +3.99 \pm 0.90$	f = K^{oe}	1.66×10^{-2}	1.66×10^{-2}
log $k_7 = +1.45 \pm 0.25$	g = K^{-f}	3.47×10^{-3}	3.47×10^{-3}
log $k_8 = +8.73 \pm 0.88$	h = k_5^g	1.00×10^{10}	1.00×10^{10}

^a In water at 30 °C. ^b Values calculated to satisfy the conditions listed below, as described in the text. ^c Experimental values calculated from the derived quantities reported by Schmir.^{4b} ^d Acid dissociation constant for the neutral tetrahedral species, estimated as described in the text. ^e Equilibrium constant for hydration of the thioester, calculated as described in the text. ^f Equilibrium constant for addition of hydroxide to the thioester, calculated as described in the text. ^g Rate constant for reaction of H⁺ with the anionic intermediate; assumed to be diffusion controlled.

Table V. Rate and Equilibrium Data for Carbonyl Hydration Reactions^a

carbonyl compd	log $K^0_{H_2O}$ ^b	log $K^z_{H_2O}$ ^c	log $k^0_{H_2O}$ ^d	log K_{OH} ^e	log k_{OH} ^f	log $K^+_{H_2O}$ ^g	log $k^+_{H_2O}$ ^h
CH ₃ CONMe ₂	-14.2 ⁱ	-26.1 ^j		-13.5 ^j	-4.75 ^k	-16.3 ^j	-5.6 ^k
HCONMe ₂	-13.8 ⁱ	-25.5 ^j		-12.5 ^j	-3.75 ^k	-15.2 ^j	-5.0 ^k
CH ₃ COOMe	-8.2 ^l	-19.7 ^j	-9.5 ^m	-6.0 ^j	-0.82 ^m	-8.3 ^j	-0.5 ^m
HCOOMe	-6.6 ^l	-17.9 ^j	-6.2 ⁿ	-3.8 ^j	+1.58 ^m	-5.4 ^j	+2.7 ^m
CF ₃ COOMe	-0.9 ^l	-11.3 ^j	-2.06 ^p	+4.7 ^j	5.53 ^q	+2.0 ^j	
CH ₃ COSEt	(-8.2) ^o	-19.8 ^j	(-7.3) ^o	-6.3 ^o	-0.92 ^r	(-5.9) ^j	+1.3 ^s
HCOSEt	-3.5 ^l	-14.8 ^j	-5.57 ^u	-0.9 ^j	+2.1 ^v	+0.2 ^j	+4.3 ^v
CF ₃ COSEt	-2.8 ^l	-13.3 ^j	-2.34 ^w	+2.5 ^j	+3.77 ^x	+2.1 ^j	
CH ₃ COS- <i>n</i> -Bu	-2.85 ^y	-15.1 ^j	<-4.7 ^z	-3.0 ^j	+2.04 ^z	+1.4 ^j	+7.72 ^x
HCOCH ₃	0.03 ^y	-12.0 ^j	-2.32 ^z	+0.5 ^j	+4.68 ^z	+4.9 ^j	+9.9 ^z
HCOH	3.36 ^y	-8.5 ^j	+1.0 ^z	+4.46 ^j	+6.51 ^z	6.3 ^j	+11.9 ^z

^a In water at 25 °C. ^b $K^0_{H_2O}$ is the equilibrium constant (dimensionless) for addition of water to the neutral carbonyl compound with neutral tetrahedral adduct as product. ^c $K^z_{H_2O}$ is the equilibrium constant (dimensionless) for addition of water to the neutral carbonyl compound with zwitterionic tetrahedral adduct as product. ^d $k^0_{H_2O}$ is the rate constant (s⁻¹) for uncatalyzed addition of water to the carbonyl compound. ^e K_{OH} is the equilibrium constant (M⁻¹) for addition of hydroxide ion to the neutral carbonyl compound with anionic tetrahedral adduct as product. ^f k_{OH} is the rate constant (M⁻¹ s⁻¹) for addition of hydroxide ion to the carbonyl compound. ^g $K^+_{H_2O}$ is the equilibrium constant (dimensionless) for addition of water to the protonated carbonyl compound with cationic tetrahedral adduct as product (expressed in terms of the product of direct addition, with -OH₂⁺, even where a different cation is more stable). ^h $k^+_{H_2O}$ is the rate constant (s⁻¹) for reaction of water with the protonated carbonyl compound. ⁱ Calculated from free energies of formation of the tetrahedral species (ref 9) and the amide (ref 7). ^j Calculated from log K_{H_2O} and pK_a values in Table III. ^k Reference 7. ^l Calculated from the free energies of formation of the tetrahedral species (ref 6). ^m Reference 5. ⁿ Estimated from the value for HCOOCH₂Cl, assuming that the ratio of rate constants for HCOOCH₂CH₃ and HCOOCH₂Cl is the same as for ClCH₂COOCH₂CH₃ and ClCH₂COOCH₂Cl, using rate constants quoted in ref 23. ^o Estimated as described in the text. ^p Reference 54. ^q Estimated from a value for the ethyl ester at 15 °C (ref 55) assuming that ΔS^\ddagger will be the same as for the alkaline hydrolysis of CHCl₂COOEt, CHBr₂COOEt, and CCl₃COOEt, i.e., -26 eu (ref 55), and that k_{Me}/k_{Et} will be the average of the values observed for CH₂ClCOOR, CH₂BrCOOR, and CHCl₂COOR, i.e., 1.94 (ref 55). ^r Calculated from the rate constant for CH₃COS-*n*-Bu (ref 56) measured in water at 25 °C and the rate ratio k_{Et}/k_{n-Bu} based on rate constants in 40% dioxane at 35 °C (ref 57). ^s Calculated from rate constants measured in 24.6 and 44.0% acetone (ref 46), by making a linear extrapolation to pure water. Rate constants at 25 °C were calculated for each solvent from measured values at 30 °C and measured activation energies (ref 46). ^t This work. ^u Calculated from the value of k_1 for HCOSMe at 30 °C (ref 4b) assuming that ΔS^\ddagger is the same as for the reaction of water with HCOOCH₂Cl, i.e., -39 eu (ref 23), and that k_{Me}/k_{Et} is the same as for HCOOR (ref 5). ^v Calculated from the value for k_1 for HCOSMe at 30 °C (ref 4b), assuming that ΔS^\ddagger is the same as for the reaction of hydroxide ion with HCOOEt, i.e., -9.8 eu (ref 23), and that k_{Me}/k_{Et} is the same as for HCOOR (ref 5). ^w Calculated from the value for k_1 for CF₃COSEt at 30 °C (ref 4a) and the ratio of the apparent rate constants for the water reaction at 25 and 30 °C (ref 3a). ^x Calculated from the value for k_1 for CF₃COSEt at 30 °C (ref 4b), assuming that ΔS^\ddagger is the same as for the reaction of water with CF₃COOEt, i.e., -26 eu (ref 54). ^y Reference 9. ^z References 58-60.

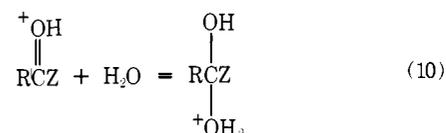
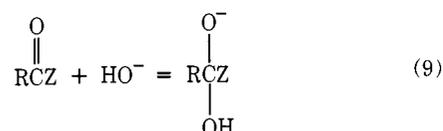
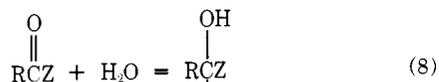


Figure 2 shows graphs of log k as a function of log K . The calculated lines are drawn using eq 11, which is based on the theoretical considerations of Marcus.¹⁶ This equation is derived by starting with the simplest equation given by Marcus (eq 1, ref 16a) and expressing it in terms of rate and equilibrium constants instead of free energies. In eq 11 b is the log k equivalent¹⁷ of the Marcus intrinsic barrier Δ^\ddagger .^{16b} The collision rate for species in aqueous solution is taken as $10^{10} \text{ M}^{-1} \text{ s}^{-1}$.¹⁸ Equation 11 holds for $|\log K| \leq 4b$; outside these limits, the log k values will fall on the limiting lines of slope 0 or 1. For the Marcus approach to be applied, the rate and equilibrium constants must refer to a single elementary step.

$$\log k = 10 - b(1 - \log K/4b)^2 \quad (11)$$

Marcus originally derived his theoretical expressions for

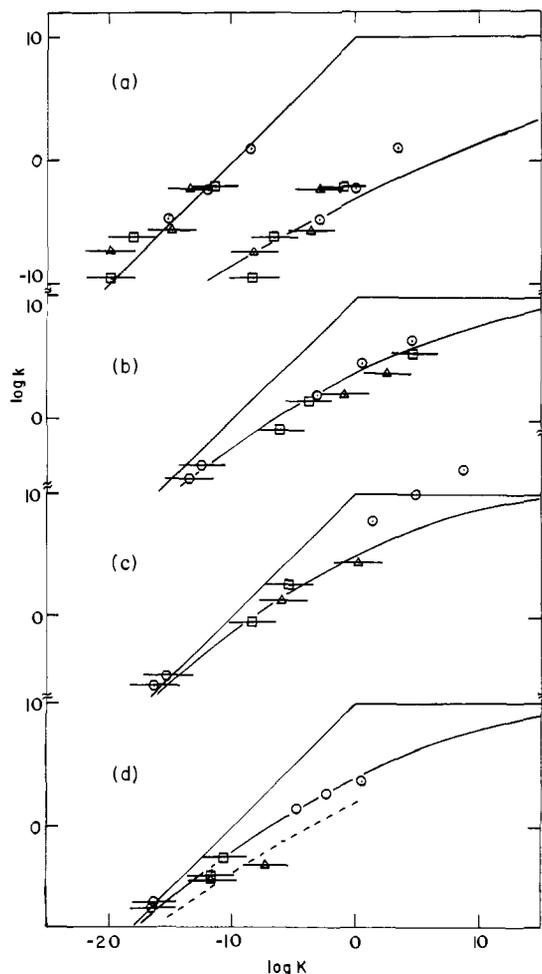


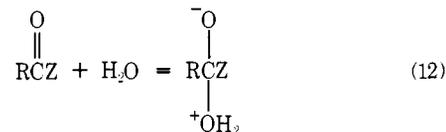
Figure 2. Correlation between $\log k$ and $\log K$ for addition of water to carbonyl compounds. (a) Uncatalyzed addition of water calculated for process 8, right-hand points, or process 12, left-hand points; the curve through the right-hand set of points is calculated with $b = 13$. (b) Addition of hydroxide ion to carbonyl compounds, process 9; the curve is calculated with $b = 6$. (c) Addition of water to the conjugate acid of carbonyl compounds, process 10; the curve is calculated with $b = 5$. (d) Addition of water to carbonyl compounds, catalyzed by hydronium ion, process 14; the solid curve is calculated with $b = 6$, the dotted curve is calculated with $b = 7$. (○) acetone, acetaldehyde, and formaldehyde; (□) oxygen esters, methyl acetate, methyl formate, and methyl trifluoroacetate; (Δ) thioesters, ethyl thioacetate, ethyl thioformate, and ethyl trifluorothioacetate; (○) amides, dimethylacetamide, and dimethylformamide.

electron-transfer reactions^{16c} and later extended them to proton-transfer reactions,^{16a,b} where they have been employed extensively.^{16d} Hine has shown that the Marcus treatment can be applied to a wide variety of reactions involving addition to electrophilic carbon.¹⁷ Murdoch has shown that an equation of the form of eq 11 is a logical consequence of the extended Hammond postulate.^{16e} In this paper the validity of eq 11 as an approximate description of the relationship between rate and equilibrium constants is assumed, and the consequences of this assumption are examined. It should be borne in mind that this assumption underlies the mechanistic analysis which follows and that only if the assumption is valid do the conclusions follow.

In applying eq 11 to a particular process, values of b were chosen to give the best fit to the data. For the base-catalyzed hydrations, the data can be fitted by eq 11 with $b = 6$. It is remarkable that with only one adjustable parameter, data spanning 20 orders of magnitude in equilibrium constant, and 10 orders of magnitude in rate constant, can be correlated so well. It is clear, however, that as so often happens, each class

of compounds defines a slightly different line, with its own value of b (least-squares fitting gives $b = 5.74 \pm 0.14$ for all compounds, 5.35 ± 0.09 for the amides, 6.68 ± 0.30 for the esters, 7.41 ± 0.02 for the thioesters, and 5.70 ± 0.26 for the carbonyl compounds).

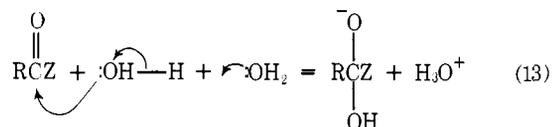
For the uncatalyzed hydrations, the best line, with $b = 13$, is not satisfactory, so that this reaction appears not to be described by eq 11. This dilemma can be resolved if the assumption is made that the process involved is actually



The zwitterion content of the neutral intermediate can be estimated from literature $\text{p}K_a$ data, thus permitting calculation of the equilibrium constants for process 12, which are included in Table V. Figure 2 shows that when the data are plotted in this way, they are described quite satisfactorily by eq 11, with $b \leq 3$. It should be noted that the zwitterion content is relatively independent of the nature of the intermediate, so that the data plotted for process 8 are fitted reasonably well by a line of unit slope.

This mechanism for hydration (process 12) requires that the breakdown of the zwitterion to water and carbonyl compound be very rapid ($k = 10^{10} \text{ s}^{-1}$) and independent of the nature of the compound (for the range of compounds included in Table V) and also that the water mediated proton switch⁷⁴ to give the neutral species be very fast ($k = 10^{10} \text{ s}^{-1}$). This latter requirement is initially rather disturbing, since in the somewhat analogous case of ester aminolysis, the rate-determining step can be trapping of the zwitterion by a water-mediated proton switch, in the absence of other trapping reagents;¹⁹ i.e., in this case breakdown of the intermediate is *faster* than the water-mediated proton switch. The crucial difference in the present case is the driving force for the proton transfer to give the neutral intermediate, which is only a $\text{p}K_a$ difference of 4 in the aminolysis case, but is a $\text{p}K_a$ difference of 12 for hydration.

The conditions for process 12 to be the initial and rate-determining step for uncatalyzed hydration of carbonyl groups are not unreasonable. That neither general acid nor general base (water as catalyst in both cases) catalyzed processes are significant can be rationalized in terms of Jencks' "libido rule",²⁰ as follows. For the process wherein water acts as a general base, the water which attacks the carbonyl would have a $\text{p}K_a$ of ca. -3 after bond formation was completed; since the catalyst water is the conjugate base of an acid of $\text{p}K_a -1.74$, there is little or no driving force for concerted proton removal. For the process wherein water acts as a general acid, the carbonyl oxygen ends up as an oxy anion of $\text{p}K_a$ ca. 12, which would have to abstract a proton from a water molecule of $\text{p}K_a$ 15.74, which is unfavorable. This case illustrates an interesting pitfall in the use of eq 11 for mechanistic analysis: if the equilibrium constants for water addition were calculated for process 13, the fit would be essentially as good as for process



12, since the $\text{p}K_a$ values of the tetrahedral intermediate, going to anions, are about 12, and the zwitterion content is about 10^{-12} for these compounds.

A concerted process involving simultaneous proton transfer (through one or more solvating water molecules) and nucleophilic attack, process 8, would necessarily involve a substantial entropic barrier and, consequently, a large value of b . It seems reasonable that eventually, as hydration becomes increasingly

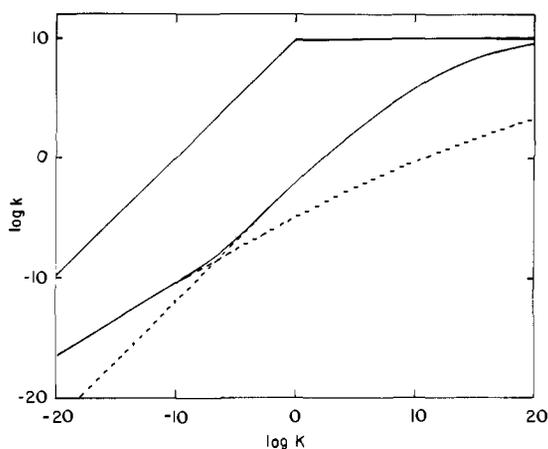
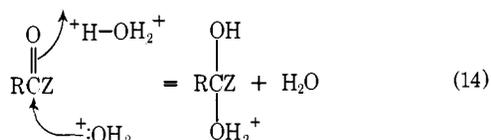


Figure 3. Curve expected for a plot of $\log k$ vs. $\log K$ when there are two competing mechanisms for uncatalyzed addition to carbonyl compounds. The curve is drawn for the hypothetical case where $b = 3$ for the zwitterion mechanism (the average zwitterion content is one part in 10^{12}) and $b = 15$ for the concerted path. The solid curve shows the (potentially) observable portions of these curves, and the dotted curves show the unobservable portions.

difficult, the concerted path would become the preferred one. This is illustrated in Figure 3, which shows the behavior expected if there are two competing paths, one by way of a zwitterion ($pK_z = 12$, $b = 3$) and one by a concerted path ($b = 15$). The solid line shows the observable portion of the two intersecting curves. For the hydration of carbonyl compounds, the concerted path has not yet manifested itself at $\log K^0 = -8$, and therefore $b \geq 15$. These considerations make it more difficult to estimate the rate of the (unobserved) water rate for hydrolysis of, e.g., *N,N*-dimethylacetamide, since the rate constant would be expected to be ca. 10^{-16} if process 12 applies but would be 10^{-13} if process 8 had become important, with $b = 15$, and any value in between if b were greater.

When the data for acid-catalyzed hydration are plotted for process 10, the points for the acyl derivatives fit a line for $b = 5$, but the points for acetone, acetaldehyde, and formaldehyde fall progressively farther off the line and, in the case of formaldehyde, the rate constant calculated for process 10 is unrealistically large.⁶⁷ When the data for the acid-catalyzed reaction are plotted for process 14, the points, with the ex-



ception of that for *S*-ethyl thioformate, fit a line for $b = 6$. Unfortunately, although a process in which hydronium ion serves as a general acid to facilitate the addition of water (process 14) is satisfactory for addition to aldehydes and ketones, it is not satisfactory for acid-catalyzed hydration of amides, where process 10 seems far more reasonable.²¹ A unified picture of acid-catalyzed hydrations is possible if the combination of carbonyl group with hydronium ion is regarded as a stepwise process,²² with the equilibrium constant for the initial step, formation of a hydrogen-bonded complex, insensitive to the nature of the carbonyl compound. Palm et al.²² have proposed that the equilibrium constant for this hydrogen-bond dissociation is in the range of 1–10 M. In aqueous solution the addition would occur by attack of water on the carbonyl carbon of the complex of carbonyl compound and hydronium ion, with proton transfer occurring as bond formation proceeded, except for relatively basic carbonyl compounds such as amides, where the proton transfer would have occurred first. The distinction between process 10 and 14 is

then seen to be one of the position of a hydrogen-bonded proton along the line joining two oxygens. The failure of the point for *S*-ethyl thioformate to fall on the same line as the other compounds may reflect the tendency, seen for hydroxide additions, for thioesters to have a somewhat larger b value than oxygen esters.

These results suggest the generalization that for carbonyl addition reactions, data for a given process for all carbonyl compounds from amides to formaldehyde will fall on a single curve if the data are plotted for a single microscopic step corresponding to the actual mechanism. Furthermore, this should prove to be a useful mechanistic probe, whenever data over a wide enough range of rate and equilibrium constants are available.

It should be possible to evaluate the equilibrium constant for hydration of any carbonyl compound from the rate constants for hydrolysis reactions and the curves shown in Figure 2. For this purpose the hydroxide ion reaction is likely to be the most useful, since this reaction is the simplest overall process. The major limitation is that the rate constant must refer to the addition step. The observed rate constant is less than that for addition to the extent that breakdown of the intermediate to starting materials competes with breakdown to products. Review of the available data^{5,7} suggests that there will rarely be a large error if the observed rate constant is used. By calculating the pK_a values for the intermediate, it will then be possible to obtain equilibrium constants for formation of the neutral and cationic intermediates. This procedure will lead to equilibrium constants subject to uncertainties of a few orders of magnitude, which will be precise enough to be useful in mechanistic analysis. This proposed method will be tested in this laboratory and reported upon later.

From the rate constant for the hydroxide-catalyzed hydrolysis of *S*-ethyl thioacetate, an equilibrium constant for the addition of hydroxide was determined, using the b value for thioesters; this value of $\log K$ was -6.3 . From this value and the pK_a value (Table III) an equilibrium constant for the addition of water ($\log K = 8.2$) was calculated. This permitted calculation of the various equilibrium constants for *S*-ethyl thioacetate in Table V. Figure 2 includes points for *S*-ethyl thioacetate (other than the hydroxide reaction) which are consistent with the rest of the points.

Thiol Addition Reactions. To complete the analysis of thiol ester hydrolysis, information concerning the mechanism and structure dependence of the thiol expulsion reaction is required. In order to maintain a parallel with the analysis of hydration presented above, the analysis will be presented in terms of the microscopic reverse of thiol expulsion, namely, thiol addition. The data are remarkably limited, but in Table VI are gathered rate and equilibrium constants for uncatalyzed, base-catalyzed, and acid-catalyzed additions of alkyl thiols to carbonyl compounds. These values are calculated for the microscopic processes

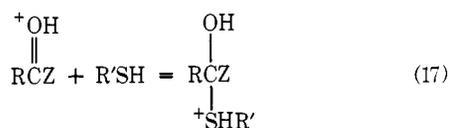
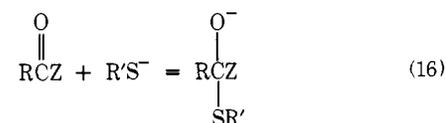
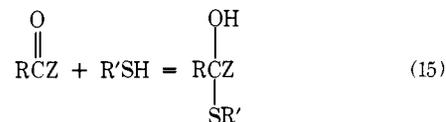


Table VI. Rate and Equilibrium Data for Thiol Addition Reactions^a

carbonyl compd	log K^0	log K^z ^c	log k^0 ^d	log K^- ^e	log k^- ^f	log K^+ ^g	log k^+ ^h
CH ₃ CHO + CH ₃ OCOCH ₂ SH	1.78 ⁱ	-15.1 ^j	<-2.2 ^{i,k}	-4.37 ^j	5.37 ⁱ	-1.65 ^j	+7 ⁱ
CH ₃ CHO + CH ₃ OCH ₂ CH ₂ SH	1.51 ⁱ	-13.7 ^j	<-2.3 ^{i,k}	-3.20 ^j	5.67 ⁱ	-0.09 ^j	+8.1 ⁱ
CH ₃ CHO + CH ₃ CH ₂ SH	1.56 ⁱ	-12.9 ^j	<-2.5 ^{i,k}	-2.51 ^j	5.67 ⁱ	+0.85 ^j	+8.7 ⁱ
CH ₃ COOH + CH ₃ CH ₂ SH	-11.4 ^l	-27.5 ^j	(-9.4) ⁿ	-13.1 ^j	(-3.1) ⁿ	-12.9 ^j	(-2.9) ⁿ
HCOOH + CH ₃ CH ₂ SH	-6.7 ^l	-21.8 ^j	-5.9 ^m	-6.8 ^j	(2.8) ⁿ	-6.5 ^j	+2.3 ^m
CF ₃ COOH + CH ₃ CH ₂ SH	-6.9 ^l	-23.3 ^j	-6.7 ^m	-5.3 ^j	3.3 ^m	-4.3 ^j	(+5.5) ⁿ

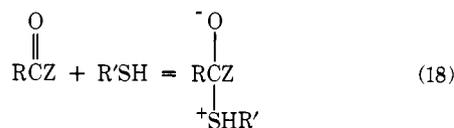
^a In water at 25 °C. ^b K^0 is the equilibrium constant (M⁻¹) for addition of the thiol to the neutral carbonyl compound to give the neutral tetrahedral adduct. ^c K^z is the equilibrium constant (M⁻¹) for addition of the thiol to the neutral carbonyl compound to give the zwitterionic (S positive) tetrahedral adduct. ^d k^0 is the rate constant (M⁻¹ s⁻¹) for the uncatalyzed addition of the thiol to the neutral carbonyl compound. ^e K^- is the equilibrium constant (M⁻¹) for the addition of the thiolate anion to the neutral carbonyl compound to give the anionic tetrahedral adduct. ^f k^- is the rate constant (M⁻¹ s⁻¹) for the addition of the thiolate anion to the neutral carbonyl compound. ^g K^+ is the equilibrium constant (M⁻¹) for the addition of the thiol to the protonated carbonyl compound to give the S-protonated tetrahedral adduct. ^h k^+ is the rate constant (M⁻¹ s⁻¹) for the addition of the thiol to the protonated carbonyl compound. The observed rate constant for hydronium ion catalyzed reaction was divided by the fraction of carbonyl compound which was protonated. ⁱ Reference 52. ^j Calculated from log K_{H_2O} and p K_a values in Table III. ^k Upper limit: no uncatalyzed reaction was observed. ^l Calculated from free energies in Table II. ^m Calculated from k_1 (Table V), k_2/k_3 (ref 4b), and the overall equilibrium constants (Table VII). ⁿ Estimated from Figure 4.

Table VII. Hydrolysis Equilibria for Thiol Esters^a

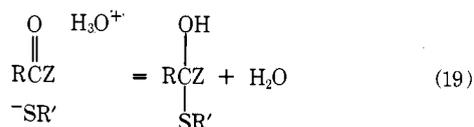
reaction	ΔG° ^b	log K^c
CH ₃ COSEt + H ₂ O = CH ₃ COOH + EtSH	-4.1 ± 1.5	+3.0 ± 1.1 ^d
HCOSEt + H ₂ O = HCOOH + EtSH	-2.9 ± 2.0	+2.1 ± 1.5 ^d
CF ₃ COSEt + H ₂ O = CF ₃ COOH + EtSH	-5.6 ± 2.4	+4.1 ± 1.7 ^d
CH ₃ COSCH ₂ CH ₂ NHAc + H ₂ O = CH ₃ COOH + HSCH ₂ CH ₂ NHAc	-4.46	+3.26 ^e

^a In water at 25 °C. ^b kcal mol⁻¹; standard states are 1 M (with an infinitely dilute reference state) for solutes, pure liquid for water. ^c Dimensions of K are molar. ^d This work; calculated from values of ΔG_f° (aq) in Table II. ^e Reference 61.

Figure 4 shows graphs of log k as a function of log K . The uncatalyzed process may be satisfactorily described in terms of process 15, in which addition and proton transfer are concerned. Although the data fit eq 11 with $b = 13$, such a mechanism implies a transfer of a proton along a chain of hydrogen bonds from S to O and thus implies that the SH is hydrogen bonded in the initial state. This is not necessarily the case since SH is very weakly hydrogen bonding.²³ An alternative mechanism, involving initial formation of the zwitterionic adduct, process 18, is clearly unsatisfactory, since points



calculated for this mechanism fall in impossible regions of the graph. A final possibility which must be considered is hydronium ion catalyzed attack of thiolate upon the carbonyl compound, process 19, which is presumably attack of thiolate upon



the hydrogen-bonded complex of hydronium ion and the carbonyl compound, analogous to the case of acid-catalyzed hydration discussed above. When the data are plotted in terms of this process,⁷¹ a good fit is obtained with $b = 8$. There are now two possible mechanisms for this reaction, processes 15 and 19. Process 19 appears preferable, although there is no compelling evidence; process 15 requires preequilibrium for-

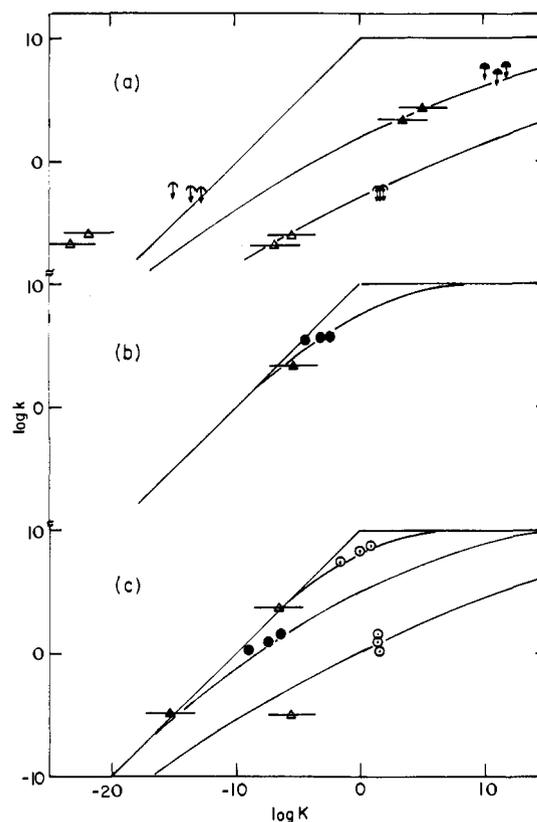


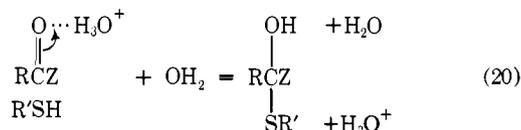
Figure 4. Correlations between log k and log K for addition of thiols to carbonyl compounds. (a) Uncatalyzed additions of thiols: left-hand open points, process 18; right-hand open points, process 15, with the curve drawn for $b = 13$; solid points, process 19, with the curve drawn for $b = 8$. (b) Addition of thiolate anions to carbonyl compounds, calculated for process 16; the curve is drawn for $b = 2.5$. (c) Acid-catalyzed addition of thiols to carbonyl compounds: upper open points, process 17, with the curve drawn for $b = 2$; lower open points, process 20, with the curve drawn for $b = 10$; solid points, process 21, with the curve drawn for $b = 5$. (O) acetaldehyde plus methyl mercaptoacetate, methoxyethanethiol, and ethanethiol; (Δ) formic acid and trifluoroacetic acid plus ethanethiol.

mation of a chain of hydrogen bonds from SH through one or more bridging water molecules to the carbonyl oxygen, in order that proton transfer can take place simultaneously with C-S bond formation, and this seems improbable.

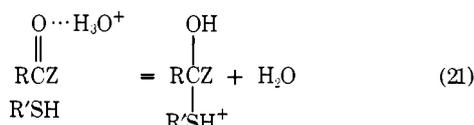
The addition of thiolate ions to carbonyl compounds is satisfactorily described by eq 11 with $b = 2.5$.

The acid-catalyzed addition of thiols is also subject to mechanistic ambiguity, since two processes lead to satisfactory

fits to eq 11. Process 17 is a satisfactory description in that a good fit is obtained with $b = 2$. However, this process requires that the attack of the thiol is on the protonated carbonyl compounds ($pK_a = -7$ to -8) and that it leads to the cationic intermediate ($pK_a = -8$ to -10), and both of these requirements seem at first to be surprising. In the analysis of acid-catalyzed hydrations given above, it was found that the best description was in terms of the carbonyl compound hydrogen bonded to hydronium ion; the libido rule²⁰ would lead to an expectation that general-base catalysis by water of the addition of thiol is possible, so that the process would be



When the data are plotted in terms of this process, the fit is poor. However, if, despite the libido rule, one assumed that attack of thiol upon the carbonyl compound hydrogen bonded to hydronium ion leads to the cationic intermediate, process 21, one obtains a satisfactory fit to eq 11, with $b = 5$.⁷² The



reason for the apparent preference for the nonconcerted paths 17 or 21, rather than the concerted path 20, is probably that the thiol SH is hydrogen bonded to water weakly if at all,²³ so that concerted proton transfer becomes more difficult than if there were a hydrogen bond. Furthermore, there are grounds for believing that the S-protonated tetrahedral intermediate is not significantly hydrogen bonded either,^{23b} so that the equilibrium constants calculated from equilibrium pK_a values are appropriate for process 21.

There is no obvious reason why full protonation of the carbonyl compounds should be required for thiol addition and not for water addition; since it was concluded above that acid-catalyzed hydration involves process 14, it seems reasonable to prefer process 21 for acid-catalyzed thiol addition.

The curves for thiol addition reactions may now be used to estimate values for the additions of ethanethiol to acetic, formic, and trifluoroacetic acids, where these are unknown, and so to estimate values for the thiol expulsion reactions; these rate constants are found in Table VIII.

Acid Inhibition in Acyl Activated Thiol Esters. Thiol esters with electron-withdrawing groups such as CF_3COSR or CHF_2COSR do not show the typical ester pH-rate profile, with hydroxide, water, and hydronium ion rates,²⁴ but rather show an acid inhibition at low pH with acid catalysis at still lower pH for acyl groups which are not too strongly electron withdrawing.^{3,4b,10-12} This acid inhibition requires a change in rate-determining step and was explained in terms of a shift from rate-determining attack of water on the thiol ester to rate-determining expulsion of thiolate ion from the anionic form of the tetrahedral intermediate^{3a} to rate-determining expulsion of thiol from the neutral form of the intermediate^{4b} as the pH is lowered. It has since been proposed that the proton transfer converting the neutral to the anionic intermediate,¹⁰⁻¹² rather than thiolate expulsion, may be rate limiting for some acyl-activated thiol esters, but otherwise this explanation is still accepted. There has, however, been no satisfactory explanation for why acyl-activated thiol esters, and not others, should show acid inhibition. The analysis of water and thiol addition reactions presented above permits a rationale to be developed for this behavior.

The essential feature which must be present if acid inhibition is to be readily observable is a partitioning ratio, k_3'/k_2' ,⁷³

Table VIII. Rate Constants for Thiol Ester Hydrolysis^a

thiol ester	process	rate constant ^b		
		log k_1	log k_2	log k_3
CH ₃ COSEt	acid	-4.3 ^c	+7.2 ^d	+4.3 ^e
	neutral	-7.3 ^c	+0.9 ^d	+2.0 ^e
	base	-0.9 ^c	+5.4 ^d	+10.0 ^e
HCOSEt	acid	-3.0 ^c	4.2 ^d	4.2 ^f
	neutral	-5.6 ^c	-2.1 ^d	-0.5 ^f
	base	+2.1 ^c	+3.1 ^d	+9.6 ^e
CF ₃ COSEt	acid	-2.8 ^g	5.7 ^d	9.5 ^e
	neutral	-2.1 ^h	+0.7 ^h	+0.1 ^h
	base	+4.0 ^h	+1.5 ^h	+8.7 ^h

^a In water at 25 °C. ^b Dimensions: for k_1 , M⁻¹ s⁻¹ for acid- and base-catalyzed reactions, s⁻¹ for neutral reactions; for k_2 and k_3 , s⁻¹ for all cases. k_2 and k_3 are calculated for total intermediate of the designated charge type. ^c Table V. ^d Calculated from log k_1 and log K (Table V). ^e Calculated from log K (Table VI) and Figure 4. ^f Calculated from k_2 and (k_3/k_2) . ^g Estimated from log K (Table V) and Figure 2. ^h Table IV.

which is <1 .^{4b} If this obtains, then the rate constant for the reaction, when only the neutral form of the tetrahedral intermediate is kinetically significant, is $k_1'/(k_2'/k_3' + 1)$, and anything which leads to more rapid product formation will cause an increase in observed rate of reaction. It is intuitively reasonable and is borne out by Figure 4 (a and b) that expulsion of thiol from a neutral intermediate is more difficult (has a higher intrinsic barrier) than expulsion of thiolate from an anionic intermediate. When it is thermodynamically possible to have both neutral and anionic intermediates present in kinetically significant concentrations, then breakdown by way of the anionic intermediate will be preferred and will lead to an increase in rate relative to the rate if only the neutral path were available, up to the limit of having k_1' as the rate-determining step. On the other hand, if $k_3'/k_2' \gg 1$, then k_1' is already rate determining, and no further increase is possible, even if the product-forming step changes from one involving neutral to anionic intermediate.

The problem can now be reduced to the question of why the partitioning changes from being in favor of product with nonelectron-withdrawing acyl groups to being in favor of starting materials with electron-withdrawing acyl groups. Qualitatively, the reasons can be seen from the discussion above; expulsion of thiol from the neutral tetrahedral intermediate occurs either by a concerted C-S bond breaking-proton switch mechanism, with $b = 13$ or by a general base-catalyzed expulsion of thiolate, with $b = 8$; for either case in the region of thiol esters the logarithm of the rate constant for breakdown depends on the logarithm of the equilibrium constant for the addition with a slope of ca. -0.5 . Since addition of thiols is favored by electron withdrawal, this means that expulsion of thiol becomes slower as the acyl group becomes more electron withdrawing. On the other hand, expulsion of water from the neutral tetrahedral intermediate occurs only from the zwitterion, with a rate constant of ca. 10^{10} s⁻¹, and the zwitterion content relative to the neutral adduct is increased by electron-withdrawing acyl groups. (This seemed surprising at first but results from the greater effect of electron withdrawal upon the stability of oxy anions than upon oxy cations; see eq 42 in Appendix 2.) Thus electron-withdrawing substituents in the acyl group favor loss of water, and slow loss of thiol, leading to the observed phenomenon.

Over short ranges in log K , the curves in Figure 4 may be approximated by straight lines; for the expulsion of thiol from the neutral intermediate, assuming process 19 is appropriate, this line is described by

$$\log k_3 = 2.77 - 0.55 \log K_{19}$$

The thiol esters of interest for the present discussion all involve

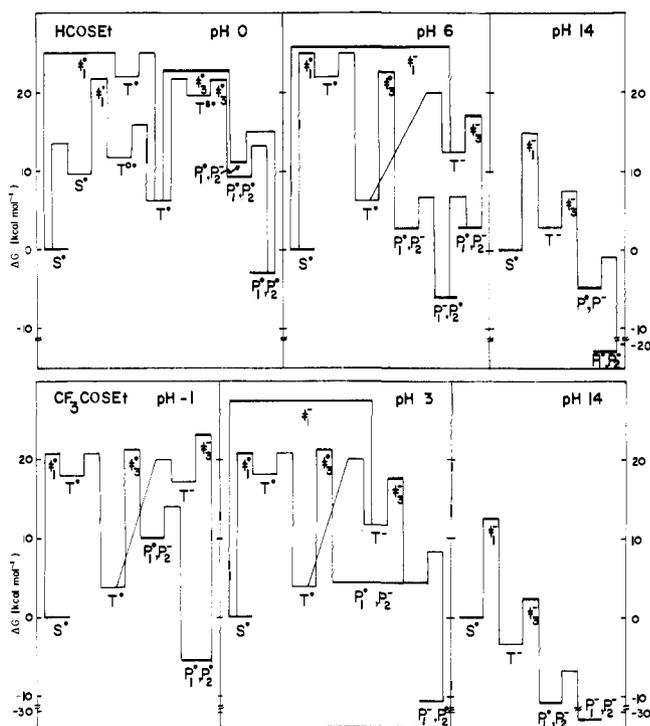


Figure 5. Detailed reaction coordinate diagrams for the hydrolysis of *S*-ethyl thioformate and *S*-ethyl trifluorothioacetate, at several pH values. S^0 is the neutral substrate; S^+ is the protonated substrate; T^\pm , T^0 , T^{0+} , T^{S+} , and T^- are the zwitterionic, neutral, O-protonated, S-protonated and anionic forms of the tetrahedral intermediates; P_1^+ , P_1^0 , and P_1^- are the protonated, neutral, and anionic forms of the acid product of hydrolysis; P_2^0 and P_2^- are the neutral and anionic forms of the thiol; \ddagger_1^+ , \ddagger_1^0 , and \ddagger_1^- are the overall transition states for acid-, un-, and base-catalyzed addition or expulsion of water; and \ddagger_3^+ , \ddagger_3^0 , and \ddagger_3^- are the corresponding overall transition states for expulsion of thiol. Free-energy levels of intermediates were calculated as described in the text. Free-energy levels of transition states were calculated from observed rate constants for addition or expulsion, where these are available, or estimated from Figures 2 and 4. Free energies of activation for proton-transfer steps were calculated assuming that these reactions occurred at diffusion-controlled rates in the thermodynamically favored direction.

ethanethiol, so that the equilibrium constant for process 19 differs from that for the overall reaction (equivalent to process 15) only by the pK_a for ethanethiol. Thus $\log k_3$ may be expressed in terms of the overall equilibrium constant as

$$\log k_3 = -2.92 - 0.55 \log K_{\text{overall}} \quad (22)$$

The equilibrium constants for thiol addition to carboxylic acids (K_{overall}) may be described by eq 23; substitution in eq 22 gives eq 24. For the expulsion of water from the neutral intermediate, process 8,

$$\log K_{\text{overall}} = -6.38 + 1.46\sigma_R^* \quad (23)$$

$$\log k_3 = 0.61 - 0.80\sigma_R^* \quad (24)$$

one may write eq 25, which, upon substitution of the equation for $\log K_z$ (where K_z is the equilibrium constant for zwitterion formation from the neutral adduct) (eq 44 in Appendix 2) becomes eq 26.

$$\log k_2 = 10 + \log K_z \quad (25)$$

$$\log k_2 = -1.57 + 0.43\sigma_R^* \quad (26)$$

Finally, combination of eq 24 and 26 gives an expression for $\log(k_3/k_2)$ as a function of σ^* (eq 27).

$$\log(k_3/k_2) = 2.18 - 1.23\sigma_R^* \quad (27)$$

This equation is acceptably similar to the equation which re-

sults when Schmir's data (k_3/k_2 values calculated from the P^0 values reported^{4b}) are plotted against σ (eq 28).

$$\log(k_3/k_2) = (2.14 \pm 0.15) - (1.02 \pm 0.07)\sigma_R^* \quad (28)$$

Detailed Reaction Coordinate Diagrams. In Figure 5 are presented detailed reaction coordinate diagrams for the hydrolyses of *S*-ethyl trifluorothioacetate and thioformate. These diagrams were constructed from rate constants determined experimentally, free energies of the tetrahedral species evaluated in this work, and rate constants for proton-transfer reactions evaluated on the assumption that bimolecular proton transfers have rate constants of $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ in the direction favored by equilibrium.

In the diagrams for the hydrolysis of *S*-ethyl thioformate, the diagram for pH 0 shows the protonated thioester on the reaction path, although this may not be the best description of the reaction. Comparing the diagrams for pH 0 and 6, one can see that at pH 0 addition of water and expulsion of thiol have very similar transition state free-energy levels for the acid-catalyzed path, but that as the pH is raised the preferred path for expulsion of thiol will change from the acid-catalyzed to the uncatalyzed path before the corresponding change for addition will occur, and the hydration step will become rate determining. By pH 6 the lowest activation energy path for breakdown involves the anionic intermediate, but since addition of water is rate determining, the changeover from breakdown of T^0 to breakdown of T^- does not lead to any significant rate increase. Although it might have been helpful to include the acid-catalyzed paths in the diagram for pH 6, and the base-catalyzed paths in the diagram for pH 0, this would have further cluttered already complicated pictures.

In the diagrams for the hydrolysis of *S*-ethyl trifluorothioacetate, the origins of the observed acid inhibition can be seen by comparing the diagrams for pH -1 and 3. At pH 3, the lowest energy path for thiol expulsion involves T^- ; as the acidity increases, the free energy level of T^- relative to T^0 rises and eventually there is a changeover in lowest energy path expulsion of thiol from T^0 . Accompanying this changeover is a change from rate-determining addition of water (pH 3) to a situation where addition of water and expulsion of thiol are both partially rate determining (pH -1).

Summary and Conclusions

The thermochemical method which has been devised for the evaluation of free energies of formation of tetrahedral intermediates gives internally consistent results when applied to thiol esters.

For carbonyl addition reactions, *rate and equilibrium constants, referring to the same microscopic step, are related by a common curve over very wide ranges*, as much as 20 powers of 10 in equilibrium and 10 powers of 10 in rate. The nature of the correlation can provide a powerful clue as to the exact mechanism of the step. Since all classes of carbonyl and acyl derivatives for which data are available appear to fit a single curve when $\log k_{\text{OH}}$ is plotted as a function of $\log K_{\text{OH}}$, this implies that *the equilibrium constant for addition of hydroxide ion to any carbonyl compound may be calculated from the rate constant for addition of hydroxide*. Estimation of the pK_a of the tetrahedral species then permits evaluation of the equilibrium constant for hydration of the carbonyl compound.

The simple, uncatalyzed addition of water to carbonyl compounds appears to involve formation of a zwitterionic adduct as the obligatory intermediate for all the compounds considered in this work. Although it is possible that the concerted mechanism will become important for less reactive compounds, the rate constants involved are so small ($k < 10^{-15} \text{ s}^{-1}$) that this mechanism may never be observed.

Table IX. Free Energies of Transfer at 25 °C from the Ideal Gas State to 1 M Aqueous Solution

compd	solubility, M	vapor pressure, Torr	ΔG° , kcal mol ⁻¹
CH ₃ CH ₂ SH	0.112 ^a	526 ^b	+1.08
HCOOC ₂ H ₅	1.2 ^c	255.4 ^c	-0.755
HCOSC ₂ H ₅	0.149 ± 0.004 ^d	38 ^e	-0.641
CH ₃ COSC ₂ H ₅	0.056 ± 0.004 ^d	21 ^e	-0.98
CF ₃ COSC ₂ H ₅	0.0026 ^f	60 ^e	+2.03
HC(OC ₂ H ₅) ₂ -SC ₂ H ₅	0.030 ^d	1.3 ^e	-1.60

^a Reference 62. ^b Reference 63. ^c Reference 64. ^d This work. ^e Estimated, as described in the text, from the boiling point. ^f Estimated from the solubility of the thioacetate, using the relation between log (solubility) and π (ref 65) and the π values for CH₃(-CO-) and CF₃(-CO-) (ref 66).

Experimental Section

Material. *S*-Ethyl thioformate [bp 100 °C (lit.⁴⁵ bp 100–101 °C)] was prepared by the method of Bax et al.,⁴⁵ *S*-ethyl thioacetate [bp 114–116 °C [lit.⁴⁶ bp 113.5 °C (735 mm)]] was prepared from acetic anhydride and ethanethiol, with a catalytic amount of pyridine, and triethyl monothioorthoformate [bp 71 °C (11 mm) [lit.²⁷ bp 77 °C (7 mm)]] was prepared by the method of Scheeren and Stevens.²⁷ *S*-Ethyl trifluorothioacetate was redistilled before use.

Methods. Heats of solution and reaction were measured using a simple calorimeter as previously described.⁷ Solubility of organic liquids was measured as previously described.⁵ Free energies of transfer (ideal gas at 1 atm to 1 M aqueous solution with an infinitely dilute reference state) were calculated from solubilities and vapor pressures; the values used are found in Table IX. The stoichiometry of the hydrolysis of triethyl monothioorthoformate was determined by adding 0.1 mL of the orthoester to 1.0 mL of 0.1 N HCl in 3:1 methanol-water and immediately recording the NMR spectrum. The ratio of HCOSR to HCOOR was determined by electronic integration. This ratio changed with time, as hydrolysis of products occurred, to give HCOOH (the signals for HCOOH and HCOOR almost coincide). The ratio was determined repeatedly at known times after mixing and extrapolated to zero time to give the stoichiometry of hydrolysis of the orthoester.

The hydrolysis of *S*-ethyl trifluorothioacetate was followed at 244 nm using a Gilford Model 240 spectrophotometer with a Heath SR 205 recorder. To HCl solution (3.0 mL) in 1-cm cuvettes thermostated at 25.0 ± 0.1 °C was added 60 μL of a stock solution of *S*-ethyl trifluorothioacetate in dry acetonitrile. The thiol ester solution was placed on the flattened end of a glass stirring rod which was rapidly plunged into the HCl solution (five times) to initiate reaction with the recorder running and the light level in the room reduced. Zero time was taken as the time the light path was first broken; mixing was complete within about 6 s. This technique permitted a very short extrapolation to initial absorbance. The initial concentration of thiol ester was 3.7 × 10⁻⁵ M; the initial absorbances were ([HCl], absorbance, number of runs) 0.001 M, 0.380 ± 0.013, 4; 0.01 M, 0.388 ± 0.016, 5; 0.1 M, 0.384 ± 0.015, 8; and 1 M, 0.383 ± 0.009, 8. The average of all the absorbance values is 0.384 ± 0.013. There is no apparent tendency for the initial absorbance to be lower at higher acid concentrations; it seems safe to conclude that the intermediate is present at levels less than 3% of the total substrate.

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Appendices

1. Calculation of Vapor Pressure and Heat of Vaporization from Meagre Vapor Pressure Data. Wadso has shown²⁵ that the heat of vaporization for nonhydroxylic compounds can be estimated from the normal boiling point by eq 29.

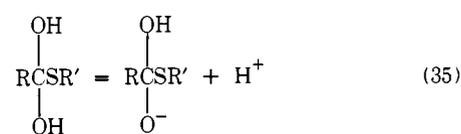
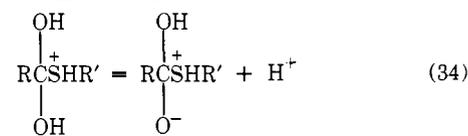
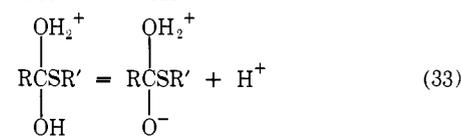
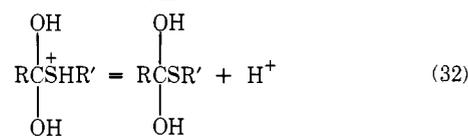
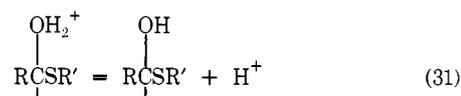
$$\Delta H_v = 5.0 + 0.042t_b \quad (29)$$

However, it is quite common for there to be only very limited boiling point data, at reduced pressure, for organic liquids, particularly if they are thermally sensitive. Vapor pressure is related to temperature by eq 30, where θ is the boiling point at pressure p_θ and T is the boiling point at pressure p .

$$\ln \left(\frac{p}{p_\theta} \right) = \frac{\Delta H_{v\theta}}{R} \left(\frac{1}{\theta} - \frac{1}{T} \right) - \frac{\Delta C_p}{R} \left(1 - \frac{\theta}{T} + \ln \frac{\theta}{T} \right) \quad (30)$$

When θ is the known boiling point and T is the unknown normal boiling point, one can take advantage of the linear relationship between ΔH_v and T and the essential constancy of ΔC_p for organic liquids ($\Delta C_p = -12 \pm 4$ cal deg⁻¹ mol⁻¹);²⁶ then eq 30 can be converted to a form in which T is the only unknown. [Since the Wadso equation (29) gives ΔH_v for 25 °C, it is necessary to correct ΔH_v to the value for θ , using $\Delta C_p = -12$.] In practice this is most readily done iteratively, using the ΔC_p term in eq 30 as a correction. For HC(OEt)₂SEt, bp 77 °C (17 mm),²⁷ this procedure leads to bp 174 °C (760 mm). Equation 30 may now be used, with $\theta = 298$ K, $T =$ normal boiling point to calculate p_θ , and the vapor pressure at 25 °C.

2. Ionization Constants of the Tetrahedral Species. In order to interpret the pH-rate profiles for the hydrolysis of thiol esters, it is necessary to have pK_a values for the reactions



For process 31, we start with the relation between pK_a and σ^* for RCH₂OH₂⁺, which may be expressed^{28,29} as

$$pK_a = -1.0 - 0.89\sigma^* \quad (36)$$

We then resume that the effect of further substituents on the α carbon will be additive and so calculate that for R₂R₂R₃C-OH₂⁺

$$pK_a = -0.13 - 0.89\Sigma\sigma^* \quad (37)$$

For process 32, we start with the pK_a for CH₃SH-CH₂CH₃⁺ of -6.85 measured by Scorrano et al.³⁰ and the ΔH_i values for CH₃SCH₂Cl and (CH₃CH₂)₂S measured by Arnett et al.³¹ Using Arnett's relation between ΔH_i and pK_a ,³¹ to calculate ΔpK_a , and a pK_a for (CH₃CH₂)₂SH⁺ [estimated from that for CH₃CH₂SHCH₃⁺ by adding the small increment observed³⁰ on going from (CH₃)₂SH⁺ to CH₃SHCH₂CH₃⁺ to the pK_a for CH₃SHCH₂CH₃⁺], we obtain a pK_a for

$\text{CH}_3\text{SHCH}_2\text{Cl}^+$. This permits evaluation of the relationship for $\text{RCH}_2\text{SCH}_2\text{CH}_3$.

$$\text{p}K_a = -6.75 - 1.36\sigma^* \quad (38)$$

As before this leads to the relationship for $\text{R}_2\text{R}_2\text{R}_3\text{CSHCH}_2\text{CH}_3^+$

$$\text{p}K_a = -5.42 - 1.36\Sigma\sigma^* \quad (39)$$

This equation is based on too few data to inspire great confidence, but it is based on the only data available to date. One can hope that basicities of other sulfides with electron-withdrawing substituents will be determined so that eq 39 can be more securely established.

For process 33, the equation reported by Cohen³² for the $\text{p}K_a$ of alcohols can be used, once the reference point is changed from RCH_2OH to $\text{R}_1\text{R}_2\text{R}_3\text{COH}$. This gives

$$\text{p}K_a = 17.03 - 1.32\Sigma\sigma^* \quad (40)$$

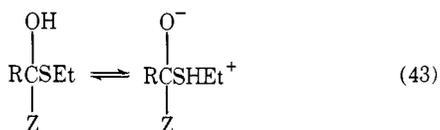
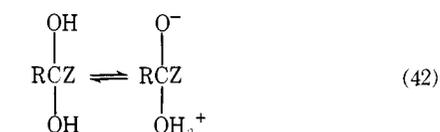
However, there is no value in the literature for σ^* of $-\text{OH}_2^+$. An approximate value was estimated on the basis of the assumption that σ^* for a protonated group will be equal to σ for the unprotonated group plus a contribution from the charge. Then from the known difference, $\sigma^*_{\text{NH}(\text{CH}_3)_2^+} - \sigma^*_{\text{N}(\text{CH}_3)_2} = 3.74$, one can estimate $\sigma^*_{\text{OH}_2^+} \approx 5.1$.

For processes 34 and 35, the equation proposed by Hine for carbonyl hydrates³³ may be used.

$$\text{p}K_a = 14.19 - 1.32\Sigma\sigma^* \quad (41)$$

The problem of σ^* for $-\text{SHEt}^+$ is treated as was done for $-\text{OH}_2^+$; the value so estimated is $\sigma^*_{\text{SHEt}^+} \approx 5.3$. The $\text{p}K_a$ values calculated using these equations are found in Table III.

It will also be valuable to have expressions for the zwitterion content of the neutral tetrahedral species, i.e., equilibrium constants for the processes



These can be calculated from the relations derived above. For reaction 42, starting from eq 37 and 40, one obtains

$$\text{p}K_Z = 11.65 - 0.43(\sigma_R^* + \sigma_Z^*) \quad (44)$$

For reaction 43, starting from eq 39 and 41, one obtains

$$\text{p}K_Z = 17.28 + 0.04(\sigma_R^* + \sigma_Z^*) \quad (45)$$

3. Ionization Constants for Protonated Substrates. For the dissociation of protonated carboxylic acids, the $\text{p}K_{\text{BH}^+}$ values from the literature³⁴⁻³⁸ were plotted vs. σ^* to give the following equation for the $\text{p}K_a$ of $\text{RC}(\text{OH})_2^+$.

$$\text{p}K_a = -(7.08 \pm 0.19) - (2.39 \pm 0.16)\sigma^* \quad (46)$$

Since plots of $\log I$ vs. H_0 are reported to be linear with unit slope,^{35,37} the Bunnett-Olsen criterion³⁹ predicts that $\text{p}K_{\text{BH}^+}$ values will be thermodynamic $\text{p}K_a$ values for aqueous solution. For the haloacetic acids, for which the $\text{p}K_{\text{BH}^+}$ values were determined in 100% sulfuric acid³⁸ this assignment becomes tenuous. Nevertheless, eq 46 summarizes what is known and permits estimation of $\text{p}K_a$ values for $\text{HC}(\text{OH})_2^+$ and $\text{CF}_3\text{C}(\text{OH})_2^+$ (-8.8 and -15.2 , respectively).

For the dissociation of protonated esters, the best available

values appear to be $\text{p}K_a$ values for protonated CH_3COOEt and $\text{CH}_3\text{CH}_2\text{COOEt}$ evaluated by Lee and Sadar⁴⁰ by applying the Bunnett-Olsen treatment to NMR data. A $\text{p}K_a$ for protonated $\text{ClCH}_2\text{CH}_2\text{COOEt}$ can be calculated from data reported by Lee and Sadar,⁴⁰ by applying the Bunnett-Olsen treatment. (These data extend into sulfuric acid concentrations beyond the usual limit of applicability of the Bunnett-Olsen method, but the plot obtained was linear; the $\text{p}K_a$ so calculated was -5.01 ± 0.19 .) In order to extend the set of $\text{p}K_a$ values, use was made of the empirical observation that the difference between $\text{p}K_{\text{BH}^+}$ (evaluated as H_0 at half protonation) and $\text{p}K_a$ (thermodynamic value evaluated by the Bunnett-Olsen method) was constant at 3.3 ± 0.2 . Making the assumption that this value will hold for protonated $\text{ClCH}_2\text{COOEt}$, a $\text{p}K_a$ value of -6.2 may be estimated. Finally, values of $\text{p}K_a$ for protonated HCOOEt and CF_3COOEt could be estimated by taking advantage of the relationship between solubility of HCl in a compound and the basicity of that compound.⁴¹ The relationship, eq 47, permits

$$\text{p}K_a = -(2.56 \pm 0.37) + (6.42 \pm 1.12) \log(\text{solubility}) \quad (47)$$

estimation of $\text{p}K_a$ values of -5.2 and -8.7 , respectively, assuming that CF_3COOEt and CCl_3COOEt have the same basicity.

For the dissociation of protonated thiol esters, we begin with a value, determined by the Bunnett-Olsen method, of -5.6 for protonated *S*-ethyl thiobenzoate⁴² and take advantage of the approximate linear relationship between the C-H stretching frequency of $\text{PhC}\equiv\text{CH}$ hydrogen bonded to a carbonyl oxygen and the basicity of the carbonyl compound.⁴¹ Since this frequency is identical for PhCOSEt and for CH_3COSMe ,⁴³ we assume that both esters have identical basicities and, further, that CH_3COSEt will also have the same basicity. For lack of any better guide it will be assumed that the effect of substituents on basicity is the same as for esters, leading to estimated $\text{p}K_a$ values for protonated HCOSEt and CF_3COSEt of -7.4 and -10.9 , respectively.

For the $\text{p}K_a$ of protonated acetone, the value reported by Hine⁴⁴ was used; for protonated acetaldehyde, the value estimated by Hine⁴⁴ was used; for protonated formaldehyde, it was assumed that the effect of replacing the second methyl of acetone by hydrogen was the same as that of replacing the first, leading to an estimated $\text{p}K_a$ of -8.2 .

4. Solution of the Kinetics Equations for *S*-Ethyl Trifluorothioacetate. Schmir^{4b} reported a steady-state rate equation of the correct empirical form to describe his data in terms of four parameters. His equation (4) can be rewritten in the form of eq 7 of this paper as

$$k_{\text{obsd}} = (a[\text{H}^+] + b + c/[\text{H}^+]) / (d + [\text{H}^+])$$

with

$$a = k_1'(1 - P^0)$$

$$b = k_1'[(1 - P^0)K''P^-/P^0 + (1 - P^-)K'']$$

$$c = k_1'(1 - P^-)(K'')^2P^-/P^0$$

$$d = K''$$

where P^0 , P^- , k_1' , and K'' are defined in ref 4b. In deriving these equations use has been made of the identity (expressed here in terms of the rate constants defined in eq 6) $k_6/k_1 = k_7k_4/(k_2k_5K_w)$.

Schmir's parameters were obtained by fitting his equation to his data and provide four of the essential facts required to solve the complete system. Since we have four additional independent facts, it is possible to obtain a solution if the algebraically intractable nature of the equations can be overcome. This problem is not uncommon; the more usual method of so-

lution has been to seek approximations which simplify the algebra. We suggest that use of a computer to solve the original equations iteratively is a superior and more general method. The least-squares program used in this work was simply one that was at hand and readily modified for the purpose. Its use should not imply that we have indulged in curve fitting with eight adjustable parameters.

References and Notes

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- (72) A final process which might be considered is general base (water as general base) catalyzed attack of thiol upon the fully protonated carbonyl compound. As discussed in the text the requirement for full protonation seems improbable but cannot be ruled out. When the data are plotted for this mechanism, the points are totally inconsistent with eq 11 since they fall on a line of nearly unit slope, displaced to the right of the theoretical limiting line of unit slope by about 9 log units. This is the pattern seen for uncatalyzed water addition; in the present case the process involving one-step conversion of the protonated carbonyl compound to neutral adduct plus hydronium ion is not an acceptable mechanism, whereas the two-step version, with rate-determining addition followed by fast proton transfer would be acceptable. The latter mechanism is that of process 17. The points for the general base-specific acid mechanism are not shown in Figure 4; they are easily calculated from Table VI, since $\log k = \log k^+$, and $\log K = \log K^+ - pK_{\text{atish}^+}$, where TISH^+ is the S-protonated form of the tetrahedral adduct, whose pK_a is given in Table III.
- (73) The rate constants used in this paragraph are numbered as in ref 4b, for

$$\text{thiol ester} \xrightleftharpoons[k_2]{k_1'} \text{TI} \xrightarrow{k_3'} \text{products}$$
- (74) An alternative to the proton switch would be a stepwise path involving proton transfer to water: for at least some of the compounds considered the pK_a values for the acidic hydrogen (derived from Table III) make this transfer slightly unfavorable and so unlikely to be fast enough.