not change appreciably as a function of (X). Owing to similar pK_a values of imidazole and N-methylimidazole one can assume that the difference between their K values reflects the part due to H bonding between imidazole H(1) and the surfactant carboxylate group.

The effect of increasing the number of carbon atoms (X) in the alkylammonium ion on the observed K values is a modest one when compared with the corresponding case for aqueous micelles[25,26] where hydrophobic interactions are operative. The variation of K as a function of increasing (X) is not easy to rationalize because of the complexity of the variables involved (vide supra), but one can attempt to explain the trend of variation. Two factors can be considered, viz., the tightness of the micelle and the steric effects of the surfactant alkyl groups. The possibility of steric interactions between the solubilizates and the hydrophobic tails increases as (X) increases. This makes the penetration of the substrate into the micelle more difficult and its K falls off as (X) increases.[27] On the other hand, the equilibrium constant and the pK_a of the amines (both indicate micelle tightness)[9] change in a different way,[28,29] so that their contribution to K does not parallel that due to the steric effects. The delicate balance of these forces seems to favor association with OAP for most of the solubilizates (see Table II). Complete understanding of the factors affecting solubilization by these surfactants and by reversed micelles in general has to wait for the separation and quantitative estimation of the above-mentioned variables and for more data on the effects of solubilization on the micellar structure.[3]

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Registry No.—BAP, 17081-35-5; HAP, 39107-99-8; OAP, 39108-00-4; DAP, 17448-65-6.

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Base-Catalyzed β-Elimination Reactions. VI. Elimination from *tert*-Butyl 3-(Para-substituted phenoxy)- and 3-(Para-substituted benzoyloxy)thiolpropionates in 45% (Weight/Weight) Dioxane–Water[1]

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Triethylamine catalyzed and hydroxide ion catalyzed β-elimination reactions of the title compounds are second order overall. The Elcb mechanism with thiol ester carbanion formation rate determining is postulated on the basis of the insensitivity of the second-order rate constants to leaving group tendencies (small ρ's) and the linear relationship between log k_{OH} for thiol esters of this study and log k_{OH} for analogously substituted β-oxy-2-butanones for which the Elcb mechanism likely operates.

The probability that enzyme-catalyzed dehydration of β-hydroxythiol esters proceeds via a carbanion mechanism[2,3] prompted us to examine nonenzymic, base-catalyzed elimination reactions of *tert*-butyl β-oxythiol esters

Table I. *tert*-Butyl 3-(Para-substituted phenoxy)thiolpropionates

Registry no.	Compd		Bp,[b] °C	% yield[c]	Column[d] eluent
58228-77-6	1	4-CH_3	100 (3)	76.3	PE
58228-78-7	2	4-H	95–97 (70)	75.5	PE
58228-79-8	3	4-Cl	122–124 (3)	42.2	B
58228-80-1	4	4-CN	65–67 (mp)	91.0	B, H[e]
58228-81-2	5	4-NO_2	155–156 (10) (43–45, mp)	58.3	B, B–PE[e]
58228-82-3		4-OCH_3	123–124 (1)	54.0	H

[a] Satisfactory combustion analytical data for C, H (±0.4%) were provided for these compounds. Ed. [b] Pressure in microns. [c] Based on amount of analytically pure sample. [d] B = benzene; PE = petroleum ether (bp 30–60 °C); H = hexane; B–PE = benzene–petroleum ether mixture. [e] Recrystallization solvent.

as models for the enzyme-catalyzed reaction. It was soon apparent to us that elimination of methanol from *tert*-butyl β-methoxythiolpropionate is not competitive with thiol ester aminolysis and hydrolysis and we took the approach of studying elimination reactions of β-oxythiol esters with good leaving groups so as to make elimination competitive with ester cleavage. We justified this approach to the problem on the grounds that the proton transfer aspect of elimination (dehydration) of this biologically important class of compounds could be conveniently studied. As well we proposed that if a carbanion mechanism operates for crotonase and β-hydroxydecanoyl thiol ester dehydratase, the enzyme may mediate proton transfer (the α-H of the thiol ester?) to the departing OH group so as to facilitate β-C–O bond breaking; thus the models could be more representative of the enzymic reactions than might at first appear.

Elimination of acetate ion from β-acetoxythiol esters was previously shown to be catalyzed by tertiary amines and hydroxide ion.[4] This result was interpreted to mean that β-acetoxythiol esters undergo β-elimination by a concerted mechanism or by an Elcb mechanism with proton transfer from thiol esters to general bases rate determining. Here we report the results of base-catalyzed β-elimination reactions of *tert*-butyl β-phenoxythiolpropionates (**1–5**) and *tert*-butyl β-benzoyloxythiolpropionates (**6–10**) (eq 1).

$$ROCH_2CH_2COSC(CH_3)_3 \rightarrow CH_2{=}CHCOSC(CH_3)_3 + ROH \quad (1)$$

R = p-XC_6H_4 [X = CH_3 (**1**); H (**2**); Cl (**3**); CN (**4**); NO_2 (**5**)]; R = p-XC_6H_4CO [X = CH_3 (**6**); H (**7**); Cl (**8**); CN (**9**); NO_2 (**10**)]

These compounds were chosen for study with the expectation of distinguishing between the concerted mechanism and the Elcb mechanism with proton transfer rate determining: for the latter mechanism ρ should be small, consistent with nonparticipation of β-C–O bond cleavage in the rate-determining step and in analogy to the small ρ value obtained for analogous reactions of similarly constituted methyl ketones.[5,6] As well the rate law for reactions of **1–5** could prove diagnostic of the Elcb mechanism as is the case for the above-mentioned ketones.[6]

Experimental Section

Apparatus. The apparatus was previously described.

Reagents. Fisher certified ACS grade inorganic reagents were used. Tap distilled water was redistilled through a Corning AGla still before use. Organic reagents were purchased from Aldrich Chemical Co. and Fisher Chemical Co. Para-substituted phenoxypropionic acids were prepared by the reaction of the appropriately substituted phenol in aqueous sodium hydroxide with β-propiolactone by the procedure of Gresham et al.[7] β-(*p*-Cyanophenoxy)propionic acid was fractionally crystallized from acetonitrile, mp 144–147 °C.

***tert*-Butyl 3-(Para-substituted phenoxy)thiolpropionates.** Under anhydrous conditions 10 ml of thionyl chloride was added in one portion to a stirred solution of the appropriately para-substituted β-phenoxypropionic acid (0.02 mol) in 25–30 ml of sodium-dried benzene. The mixture was refluxed for 24 h and the system continuously purged with dried nitrogen (flow, ca. 10 ml/min) to remove the HCl and SO_2 gas formed in the reaction. The residue which remained after codistilling the excess thionyl chloride with dry benzene (3 × 20 ml) in vacuo on the rotary evaporator was dissolved in 30 ml each of dry 2-methyl-2-propanethiol distilled from calcium hydride and dry benzene. The latter mixture was then refluxed for 72 h with continuous purging with dry nitrogen. After removal of excess mercaptan and solvent, first by distillation at atmospheric pressure and then by momentary warming at reduced pressure, the light yellow oily residue was rapidly filtered through 30 g of silica gel (70–328 mesh) in a 20–22 mm i.d. glass column with a distilled, nonpolar eluent. The one spot (TLC) column fractions were collected and the oil which remained after removal of the solvent was either distilled or crystallized (Table I). The ir and NMR spectra supported the structure assignments.

3-Trifluoroacetoxypropionic Acid. Freshly distilled β-propiolactone was added via a constant rate addition funnel over a 4.5-h period at room temperature to a rapidly stirred solution of trifluoroacetic acid in 100 ml of dry dichloromethane maintained at 5–7 °C. The reaction was allowed to continue for an additional 3 h at the same temperature. The solvent and unreacted trifluoroacetic acid were removed in vacuo while maintaining the temperature below 50 °C. The product was distilled, bp 104–106 °C (7.5 mmHg), 48.0 g, 51.8% yield.

***tert*-Butyl 3-Trifluoroacetoxythiolpropionate.** Under anhydrous conditions, a solution of 3-trifluoroacetoxypropionic acid (37.2 g, 0.2 mol) and thionyl chloride (47.5 g, 35.0 ml, 0.4 mol) in sodium-dried benzene (65 ml) was refluxed for 24 h while continuously purging the system with dry nitrogen. Codistilling the unreacted thionyl chloride with dry benzene (3 × 50 ml) in vacuo left a residue which was immediately refluxed, in the same flask without further purification, for 72 h with 2-methyl-2-propanethiol (36.1 g, 0.4 mol) (distilled from calcium hydride) in 65 ml of dry benzene. The system was continuously purged with dry N_2 for the duration of the reflux period. The solvent and excess mercaptan were distilled from the reaction mixture at atmospheric pressure leaving a residue, which was distilled at 86–89 °C (4.5–5.0 mmHg), yielding 37.2–40.1 g of product (72–77.5%).

***tert*-Butyl 3-Hydroxythiolpropionate.** Water was added in 75-ml portions every 0.5 h (over a 2-h period) to a stirred solution of *tert*-butyl 3-trifluoroacetoxythiolpropionate (53.7 g, 0.21 mol) in 100 ml of methanol at room temperature. The aqueous solution was stirred for an additional 2 h and then extracted with ether (3 × 100 ml). The ethereal extracts were combined, dried, and filtered and the ether was removed in vacuo. The residual oil was distilled, bp 96–98 °C (4.8–5.0 mmHg), to give 28.7 g (85%).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.88; H, 8.69; S, 19.77. Found: C, 52.08; H, 8.87; S, 20.02.

***tert*-Butyl 3-(Para-substituted benzoyloxy)thiolpropionates.** To a stirred solution of the appropriate acyl chloride (0.025 mol) in 25 ml of dry dichloromethane maintained at 5–10 °C was added dropwise a solution of dry distilled pyridine (1.66 g, 0.021 mol) in 15 ml of dry dichloromethane. After the mixture was stirred for 15–20 min a solution of distilled *tert*-butyl 3-hydroxythiolpropionate (3.25 g, 0.020 mol) in 15 ml of dry dichloromethane was added dropwise to the stirred mixture which was maintained at 0–4 °C. Stirring was continued at 4 °C for 30 min and then at room temperature for a total of 8–12 h (Table II). The reaction mixture was diluted with 100 ml of ether and washed with 25 ml of 5% aqueous HCl solution, two 25-ml portions of saturated aqueous sodium bicarbonate, 50 ml of water, and finally 50 ml of saturated sodium chloride solution. The ethereal extract was dried and the ether was removed in vacuo. The residue was either distilled or crystallized from the indicated solvent system. (Table II) All final products gave the expected ir and NMR spectra.

Kinetics. Reactions were carried out in 45% w/w dioxane–water solutions, μ = 0.1 M (KCl), t = 30 °C, using pseudo-first-order conditions as previously described.[4] Reactions were monitored at the following λ (nm) (compound): 275 (**1–4, 6–9**); 410 (**5**); 310 (**10**). Absorbance vs. time data were treated as previously described[4] except for **5** where 4-nitrophenolate absorbance was monitored and pseudo-first-order rate constants were obtained from slopes of

Table II. *tert*-Butyl 3-(Para-substituted benzoyloxy)thiolpropionates

Registry no.	Compd[a]		Mp or bp,[b] °C	% yield[c]	Total reaction time, h
58228-83-4	6	4-CH_3	120–122[b]	48.6	2
58228-84-5	7	4-H	115–116[b]	96.5	8
58228-85-6	8	4-Cl	32–33	36.7, H[d]	8
58228-86-7	9	4-CN	56–58	37.8, C–H[d]	10
58228-87-8	10	4-NO_2	78–80	86.7, C[d]	8
58228-88-9		4-OCH_3[e]	142–144[b]	52.3	12

[a] Footnote *a*, Table I. [b] Boiling point at 1 μm pressure. [c] Based on amount of analytically pure sample. [d] Recrystallization solvent: C = cyclohexane; H = hexane; C–H = cyclohexane–hexane mixture. [e] This compound was not used in this study; it gave unreliable kinetics data.

plots of log $OD_\infty/(OD_\infty - OD_t)$ vs. time. pK_a values were determined by the method of fractional neutralization using the pH meter. Hydroxide ion activity was determined from K_w/a_H where $-\log K_w = 15.59$.[8]

Products. Scans of the absorption spectra during reactions showed that the products are *tert*-butyl thiolacrylate and 4-substituted benzoates and 4-substituted phenoxides. The thiolacrylate product is unstable, as shown by a decrease in absorbance following the initial increase in absorbance. Formation of this product was confirmed by the near identity of the pseudo-first-order rate constants for absorbance loss following initial product formation for some of the compounds of this study. Thus $k_{obsd} = 0.203 \pm 0.016$ min^{-1} for absorbance loss at 275 nm, 0.1 M KOH, for **1, 2, 3, 7, 8, 9, 10**; under identical conditions, *tert*-butyl thiolacrylate lost absorbance with $k_{obsd} = 0.198 \pm 0.003$ min^{-1}. *tert*-Butyl 3-methoxythiolpropionate, synthesized for use in this study, was found not to undergo β-elimination reactions in dilute alkali; instead this compound undergoes hydrolysis as measured by absorbance loss at 235 nm. In 0.1 M KOH solution, pH 13.87, $k_{OH} = 8$ M^{-1} min^{-1}. Infinity absorbance values slowly decrease with time, presumably owing to oxidation of *tert*-butyl thiolate ion to the disulfide. Comparison of k_{OH} with k_{elim} for **1–10** (Table III) shows that elimination is much faster than hydrolysis.

Results

The reactions of **1–10** to give *tert*-butyl thiolacrylate and para-substituted phenols and para-substituted benzoic acids (eq 1) in 45% (w/w) dioxane–water solutions of catalytic tertiary amine buffers obey the kinetics law of eq 2.

$$v/[\mathbf{1\text{–}10}] = k_{obsd} = [k_2K_a/(K_a + H^+)][\text{amine}]_t + k_{OH}K_w/a_{OH} \quad (2)$$

At constant pH, plots of k_{obsd} vs. $[\text{amine}]_t$ are linear with slope $k_2K_a/(K_a + H^+)$ and intercept $k_{OH}K_w/a_{OH}$. Division of the slope by $K_a/(K_a + H^+)$, the mole fraction of the base form of the buffer, gave k_2 (Table IV). The values of k_{OH} were determined by dividing k_{obsd} values by K_w/a_{OH} for reactions of **1–10** run in 0.01–0.04 M KOH solution (Table III).

Table III. Rate Constants for the Hydroxide Ion Catalyzed β-Elimination Reactions of 1–10[a]

Compd	k_{OH},[b] M^{-1} min^{-1}	No. of runs
p-CH_3O[c]	121 ± 3	9
1	120 ± 5	9
2	154 ± 21	9
3	204 ± 9	9
4	469 ± 29	9
5	598 ± 76	9
6	339 ± 9	4
7	375 ± 5	4
8	444 ± 15	4
9	791 ± 29	8
10	823 ± 34	6

[a] Solvent, 45% (w/w) dioxane–water, t = 30 °C, μ = 0.1 M (KCl). [b] pH range 12.19–13.37 (**1–5**) and 12.65–13.02 (**6–10**). [c] *tert*-Butyl 3-(*p*-methoxyphenoxy)thiolpropionate.

For reactions of **1–5** and **6–10** catalyzed by triethylamine, ρ (k_2) = 0.25 ± 0.11 and ρ (k_2) = 0.05 ± 0.07, respectively. For reactions of **1–5** and **6–10** catalyzed by hydroxide ions, ρ (k_{OH}) = 0.72 ± 0.03 and ρ (k_{OH}) = 0.43 ± 0.04, respectively. For comparison purposes, we determined ρ's for elimination reactions of 4-(para-substituted phenoxy)-2-butanones and 4-(para-substituted benzoyloxy)-2-butanones catalyzed by hydroxide ions in 45% (w/w) dioxane–water: they are ρ (k_{OH}) = 0.57 ± 0.03 and ρ (k_{OH}) = 0.37 ± 0.05, respectively. A plot of log k_{OH} for **1–8, 10** vs. log k_{OH} for identically substituted β-oxy-2-butanones (water solvent) gave slope 2.7 ± 0.16 (r = 0.988) for nine pairs of compounds for which data were available.[5,6] A similar plot of log k_{OH} for **1–5** vs. log k_{OH} for identically substituted β-phenoxy-2-butanones (45% w/w dioxane–water solvent) gave slope 1.2 ± 0.13 (r = 0.982).

Discussion

Results of elimination reactions of β-substituted phenoxy ketones[6] and β-substituted benzoyloxy ketones[7] suggest that these compounds undergo β-elimination via an Elcb mechanism. The major lines of support for this conclusion are (1) the Hammett ρ values are quite small and positive, (2) for certain phenoxy ketones there is kinetics evidence for formation of an intermediate enolate ion whose partitioning is dependent on the concentration of

Table IV. Rate Constants for the Amine Catalyzed β-Elimination Reactions of 1–10[a]

Compd	Base[b]	k_2, M^{-1} min^{-1}	Fr base	No. of runs	Concn range, M
2	TEDA	0.06 ± 0.004	0.8, 0.96	12	0.06–0.40
5	TEDA	0.14 ± 0.02	0.8, 0.96	18	0.06–0.50
1	TEA	0.22 ± 0.07	0.67, 0.8, 0.9	18	0.06–0.3
2	TEA	0.27 ± 0.05	0.67, 0.8, 0.9	18	0.06–0.3
3	TEA	0.43 ± 0.03	0.67, 0.8, 0.9	18	0.06–0.3
4	TEA	0.35 ± 0.08	0.67, 0.8, 0.9	18	0.06–0.3
5	TEA	0.45 ± 0.06	0.67, 0.8, 0.9	18	0.06–0.3
6	TEA	0.67 ± 0.06	0.67, 0.8, 0.9	18	0.06–0.3
7	TEA	0.66 ± 0.05	0.67, 0.8, 0.9	18	0.06–0.3
8	TEA	0.79 ± 0.05	0.67, 0.8, 0.9	18	0.06–0.3
9	TEA	0.87 ± 0.13	0.67, 0.8, 0.9	18	0.06–0.3
10	TEA	0.65 ± 0.11	0.67, 0.8, 0.9	18	0.06–0.3
5	DMAE	0.109 ± 0.007	0.5, 0.75, 0.8	18	0.05–0.5

[a] Solvent, 45% (w/w) dioxane–water, t = 30 °C, μ = 0.1 M (KCl). [b] TEDA = triethylenediamine; TEA = triethylamine; DMAE = *N,N*-dimethylaminoethanol.

general acid, and (3) the equation log $k_{OH} = -1.16\ pK_a + 6.25$, where k_{OH} is the second-order rate constant for hydroxide ion catalyzed elimination reactions of β-oxy ketones and hydroxide ion catalyzed hydrogen–deuterium exchange in 4-methoxy-2-butanone, and pK_a is that for the appropriately substituted phenoxyacetic acid, benzoyloxyacetic acid, and methoxyacetic acid, reasonably establishes a mechanisms relationship among the members of this family of ketones. In a comprehensive related study, Hupe et al.[10] presented detailed kinetics evidence for operation of the Elcb mechanism in the amine-catalyzed dehydration of 9-hydroxy-10-methyl-*cis*-decalone-2. We believe that the results and conclusions from these studies are pertinent to those from β-elimination reactions of **1–10** because of the demonstrated similarity of ketones and thiol esters with respect to reactions occurring at carbon α to the carbonyl functional group.[11–13]

At the outset of this study we anticipated finding kinetics evidence for a thiol ester anion; finding such evidence would establish the Elcb mechanism for β-oxythiol esters. Experience with β-oxy ketones suggested to us that detection of thiol ester anions among **1–10** in a given catalytic amine buffer system would be most probable for reactions of **1** and **2**: this is based on the result that partitioning of the anion depends on the leaving tendency of the β-oxy group as well as on the rate of protonation of the anion to give **1–10**, and in a given buffer the latter rate should be largely independent of the leaving group, except as it influences carbon acid acidity. Respecting this latter point there is a rough correlation between acidity of tertiary amine general acids and the tendency of enolates to undergo protonation to give β-phenoxy ketones such that low pK_a amines favor the proton transfer. Accordingly we examined reactions of **2** with triethylenediamine (mole fraction of acid form 0.2) and found that k_{obsd} is linearly dependent on the concentration of total amine: no evidence was found for curvature in the plot. In an effort to make partitioning of putative carbanion to **2** more favorable, we attempted a similar experiment (mole fraction of acid form 0.5): reactions were very slow and the first-order rate data were unreliable. We conclude that if thiol ester carbanions are formed on the reaction pathway to elimination products, they are not sufficiently stable to assure detection in a convincing way using catalytic tertiary amine buffers and our reaction conditions.

We next sought indirect evidence for the operation of the Elcb mechanism for **1–10**. For the aforementioned benzoyloxy ketones, their elimination reactions are characterized by small, positive ρ values which show that β-C–O bond breaking is likely not a feature of the transition state, i.e., proton transfer from the ketones is rate determining, giving rise to enolates which quickly undergo β-C–O bond breaking to give the products. Similarly, for phenoxy ketones ρ is small and positive for the initial proton transfer reaction which generates enolates. Similar insensitivity of **1–10** to electronic effects of para substituents in the departing group would provide indirect evidence for rate-determining formation of carbanions and the Elcb mechanism. At least, small ρ values could be interpreted in terms of a concerted reaction with an Elcb-like transition state. Perhaps the distinction is somewhat artificial since the difference involves the stability of the thiol ester carbanion, which in terms of its partitioning is already presumed to be unstable (vide supra); thus the Elcb mechanism merges to the E2 mechanism as one limit.[14,15] The reactions of **1–10** catalyzed by triethylamine provide dramatic evidence for the insensitivity of the elimination reactions to the leaving tendencies of para-substituted phenoxides and para-substituted benzoates. For **1–5**, $\rho = 0.25 \pm 0.11$; for **6–10**, $\rho = 0.05 \pm 0.07$. Although these ρ values could be identical, the apparent greater sensitivity of **1–5** to electronic effects could reflect the shorter distance between para substituents and the incipient carbanion for **1–5** vs. **6–10**. These data may be compared with those for elimination reactions of 4-(para-substituted phenoxy)-2-butanones catalyzed by *N,N*-dimethylaminoethanol in water solution ($\rho = 0.17$) and for similar reactions of 4-(para-substituted benzoyloxy)-2-butanones ($\rho = 0.14$). It seems clear that for triethylamine-catalyzed reactions of **1–10** there is an insensitivity to electronic effects of leaving groups which is similar to that shown by analogous ketones for which the Elcb mechanism appears to operate.

A similar, if less dramatic, result was obtained for hydroxide ion catalyzed reactions of **1–10**: for **1–5**, $\rho\ (k_{OH}) = 0.72 \pm 0.03$; for **6–10**, $\rho\ (k_{OH}) = 0.43 \pm 0.04$. For comparison purposes, $\rho\ (k_{OH}) = 0.57 \pm 0.03$ for reactions of phenoxy ketones and $\rho\ (k_{OH}) = 0.37 \pm 0.05$ for reactions of benzoyloxy ketones in 45% (w/w) dioxane–water solution. Comparison of the ρ values shows that **1–10** are approximately 1.3 times more sensitive to electronic effects of para substituents than the comparable ketones which likely reflects, in part, the different capability of thiol esters and ketones to stabilize carbanions; for **1–10** more of the developing anionic charge is supported by para substituents.

A plot of log k_{OH} for **1–8, 10** vs. log k_{OH} for identically substituted β-oxy-2-butanones gave slope 2.7 ± 0.16; a similar linear plot using k_{OH} for **1–5** and k_{OH} determined for reactions of identically substituted β-phenoxy-2-butanones in 45% (w/w) dioxane–water gave slope 1.2 ± 0.13. Gregory and Bruice[16] showed that for nucleophilic reactions of 2,2,2-trifluoroethyl thiolacetate and *p*-nitrophenyl acetate the linear log k_s – log $k_{p\text{-NPA}}$ plot, a consequence of transition state theory, requires a linear relationship between the free energy changes of one reaction series (thiol ester and nucleophiles) and the free energy changes of another (*p*-NPA and the same nucleophiles). For these reactions the further implication is that their transition states (and mechanisms) are similar. This argument, applied to reactions of **1–8, 10** (**1–5**) and analogous β-oxy ketones with hydroxide ions, permits the conclusion that E2 reactions of thiol esters and ketones pass through similar transition states and that their mechanisms are similar.

The insensitivity of **1–10** and analogous ketones to leaving group tendency and the proportionality between log k_{OH}'s provide evidence for similar mechanisms of β-elimination. The liklihood that β-oxy ketones undergo β-elimination via the Elcb mechanism suggests that **1–10** similarly undergo β-elimination via that mechanism with carbanion formation rate determining under the conditions of this study. Although direct kinetics evidence for carbanion formation was not found during the course of this study, evidence was found for carbanions during the amine-catalyzed isomerization of *tert*-butyl thiolbut-3-enoate to *tert*-butyl thiolcrotonate. The evidence took the form of a deuterium solvent kinetic isotope effect $k^H/k^D > 6$ for the apparent general-base-catalyzed isomerization, a result interpreted as general acid catalysis of proton transfer to the thiolester carbanion (allylic carbanion) formed in a prior equilibrium. As well the previously cited stereochemical evidence for a multistep mechanism for crotonase-catalyzed dehydration of L-(+)-β-hydroxybutyryl coenzyme A supports the intermediacy of carbanions (carbonium ions?) in transformations of thiol esters which involve β-methylene protons. We suggest that these collective results support the formation of carbanion intermediates for reactions of **1–10** with bases.

Registry No.—β-(*p*-Cyanophenoxy)propionic acid, 58228-89-0; β-(*p*-methylphenoxy)propionic acid, 25173-37-9; β-phenoxypro-

pionic acid, 7170-38-9; β-(p-chlorophenoxy)propionic acid, 3284-79-5; β-(p-nitrophenoxy)propionic acid, 10572-16-4; β-(p-methoxyphenoxy)propionic acid, 20811-60-3; 2-methyl-2-propanethiol, 75-66-1; 3-trifluoroacetoxypropionic acid, 58228-90-3; β-propiolactone, 57-57-8; trifluoroacetic acid, 76-05-1; *tert*-butyl 3-trifluoroacetoxythiolpropionate, 58228-91-4; *tert*-butyl 3-hydroxythiolpropionate, 58228-92-5; p-methylbenzoyl chloride, 87-60-2; benzoyl chloride, 98-88-4; p-chlorobenzoyl chloride, 122-01-0; p-cyanobenzoyl chloride, 6068-72-0; p-nitrobenzoyl chloride, 122-04-3; p-methoxybenzoyl chloride, 100-07-2.

References and Notes

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Esterification by Alkylation of Carboxylate Salts. Influence of Steric Factors and Other Parameters on Reaction Rates[1]

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Alkylation of carboxylate salts with alkyl halides in dipolar aprotic solvents is an efficient method of esterification. The reaction kinetics were studied to determine the effects of variation of such parameters as gegenions (alkali metals), solvents, alkyl halide, and carboxylate structures. The reactions of numerous unhindered and hindered carboxylates with alkyl halides show small variation in rate relative to the large divergent rates observed in conventional acid-catalyzed esterification of the corresponding carboxylic acids. However, over a restricted range, the rate data for a group of carboxylate structures provided a correlation with increasing steric bulk leading to a converse application of Newman's rule of six. Rate constants for salts of aromatic acids were correlated well by Hammett parameters.

The classical acid-catalyzed methods of esterification of carboxylic acids with alcohols are recognized as having limited applications.[3,4] They are generally ineffective for the esterification of sterically hindered acids and of compounds containing acid-sensitive functional groups. Esterification of most carboxylic acids with diazoalkanes[4] or with the newer reagents, 1-alkyl-3-p-tolyltriazenes,[5] are effective but restricted in practicality to analytical preparations of methyl, ethyl, and propyl esters. Other recently developed procedures of reacting carboxylic acids with triethyloxonium fluoroborate[6] or of carboxylate ion with dimethyl sulfate,[7] while applicable to sterically hindered acids, are similarly limited to the preparations of ethyl and methyl esters, respectively. Less direct methods that require severe thermal conditions or conversion to more reactive intermediates such as the acid chlorides, the 2-butyl chlorosulfite,[8] or the tetramethylammonium salt[4] lack quantitation, convenience, and generality.

Reaction of metal salts of carboxylic acids with organic halides is a simple, though neglected, method of preparing esters. Although several reports[9-11] have disclaimed the value of metal salt alkylations, recent studies[12-15] have uncovered the method's general potentialities. Earlier uses of silver or alkali metal carboxylate salts in the presence or absence of amine[16,17] or in aprotic solvent[18,19] were confined to preparations of esters derived from the reactive benzyl or allylic halides. However, quaternary ammonium salts and highly polar aprotic solvents, either alone or in combination, have been shown to facilitate the direct alkylation of carboxylate salts for preparations of glycidyl esters,[20,21] lactones,[22] triglycerides,[23,24] and straight-chain aliphatic esters.[9,10,12,13,25-28a]

We have recently introduced and developed carboxylate salt alkylations in hexamethylphosphoramide[28b] (HMPA)–ethanol cosolvent as a rapid, quantitative method of preparing esters.[13] More importantly, we found the method to be uniquely superior for esterifications of highly hindered aliphatic and aromatic acids, the classes of acids that had been bypassed by former investigators of carboxylate salt alkylations. A subsequent report[14] confirmed these findings and provided indications of more rapid alkylations in neat HMPA. A comparable rapid, mild, and quantitative esterification of severely hindered carboxylic acids has been unattainable under acid-catalyzed conditions.[29-31]

To date, there has been no systematic and quantitative investigation of rates of carboxylate salt alkylations; all former reaction conditions were determined empirically. The present kinetic study was therefore initiated to acquire essential data for the factors affecting rates including the correlation of structural variations in the carboxylate salts.

Results and Discussion

The second-order alkylation rates of carboxylate salts are influenced by the nature of the cation, solvent, and organic halide. Clarification of the effects of these parameters with model carboxylates was essential for establishing efficient conditions for rate measurements of the series of carboxylate structures.

Carboxylate anions in association with large (soft) counterions are more reactive than with small (hard) counterions because of higher charge separation with the former.[32] The extent of the cation effect in salt alkylations was examined under a prescribed set of experimental conditions for which the results are recorded in Table I. Although the