Monoacyl Sulfates as Intermediates for α-Halogenation of Aliphatic Acids[1]

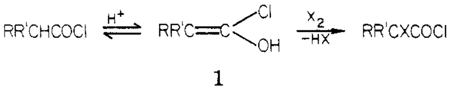
Yoshiro Ogata* and Koichi Adachi

Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya 464, Japan

Received September 2, 1981

The mechanism of the α-halogenation of aliphatic carboxylic acids, promoted by $ClSO_3H$ or oleum, has been reexamined. Ketenes, which have been postulated as the intermediates in this halogenation, have been found to react with I_2 much faster than a mixture of the corresponding acid and $ClSO_3H$. Evidence is presented to support the hypothesis that the halogenation proceeds through the cyclic enol form of the monoacyl sulfate $RR'CHCO_2SO_3H$ (3) rather than through the ketene.

Several procedures are known for the substitution of halogen at the α-position of carboxylic acids. Most of them use molecular halogen with a promoter such as phosphorus trihalide (Hell–Volhard–Zelinsky reaction),[2] thionyl chloride,[3] or chlorosulfonic acid, or oleum.[4-6] Methods using *N*-chlorosuccinimide, *N*-bromosuccinimide, or $CuCl_2$[7] are also known. Two types of intermediates in these halogenation reactions have been postulated: enols of acid halides (1)[8-10] and ketenes (2) formed by dehydration of the acids[4-11] (eq 1).


(1a)

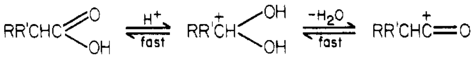
1

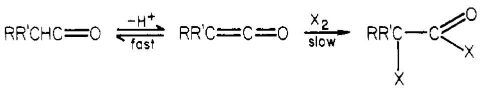
$$RR'CHCO_2H \underset{-H_2O}{\overset{H^+}{\rightleftharpoons}} RR'CHCO^+ \overset{-H^+}{\rightleftharpoons} \underset{2}{RR'C{=}C{=}O} \xrightarrow{X_2} RR'CXCOX \qquad (1b)$$

In view of the instability of alcohols such as 1 in strong acid, we have favored the ketene intermediate 2 for the $ClSO_3H$-promoted halogenation of acids. However, our investigation of the kinetics of the halogenation of some ketenes suggests that ketenes are not intermediates in acid halogenation. We here report our study of the strong-acid-promoted halogenation of aliphatic acids and propose a mechanism that involves monoacyl sulfates as the intermediates.

Results and Discussion

The mechanism that has been proposed for the $ClSO_3H$-promoted halogenation of aliphatic acids is shown in eq 2a,b. This mechanism is supported by the observed rate expression (eq 3), by the trapping of ketenes with aniline,[12] and by NMR and Raman peaks attributed to ketenes in oleum solutions of the corresponding acids.[12]


(2a)


(2b)

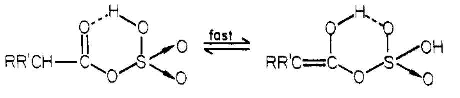
$$v = k[ClSO_3H]_0[RR'CHCO_2H][X_2] \qquad (3)$$

However, we have now found that the reaction of dimethylketene with iodine in $ClCH_2CH_2Cl$ is very fast, with a second-order rate constant estimated spectrophotometrically to be 46 $M^{-1}\ s^{-1}$ at 20 °C. In contrast, the second-order rate constant $k[ClSO_3H]_0$ in eq 3, for the $ClSO_3H$-promoted iodination of isobutyric acid at 80 °C is $1.6 \times 10^{-3}\ M^{-1}\ s^{-1}$.[6b] This difference in rates cannot be due to a very slow conversion of acid to ketene, because the rate of acid halogenation would then be independent of $[X_2]$, which is contrary to our observation.[4] The rate of iodination of isobutyric acid in oleum at 80 °C indicates that the equilibrium concentration of dimethylketene in this system should be 5×10^{-5} M. Such a low concentration would be difficult to detect by NMR, thus our previous interpretation of the NMR spectrum of isobutyric acid in oleum as being attributable to dimethylketene[12] appears to be in error.

It is possible that a highly reactive ketene, if present in such a solution, would be converted rapidly into another species that reacts slowly with halogen and exists in mobile equilibrium with the acid. Literature reports on the reaction of aliphatic acids with SO_3 suggest that this intermediate species may be a monoacyl sulfate 3[13] (eq 4).

$$RR'CHCO_2H \xrightarrow[ClSO_3H]{SO_3\ \text{or}} \underset{3}{RR'CHCO_2SO_3H} \qquad (4)$$

Evidence for the formation of 3 is the quantitative evolution of HCl in the reaction of $ClSO_3H$ with propionic acid at 100 °C. In addition, the Raman spectrum of a mixture of acetic acid and $ClSO_3H$ was found to be identical with that of an authentic sample of $CH_3CO_2SO_3H$. The sulfate 3 can be considered as an adduct of H_2SO_4 to a ketene, and it can be in equilibrium with a hydrogen-bonded cyclic enol 4[14] (eq 5), which has been postulated as an intermediate


(5)

3 4

---

(1) Contribution No. 295.

(2) Harwood, H. J. *Chem. Rev.* **1962**, *62*, 99.

(3) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *40*, 3420.

(4) (a) Ogata, Y.; Harada, T.; Matsuyama, K.; Ikejiri, T. *J. Org. Chem.* **1975**, *40*, 2960. (b) Ogata, Y.; Sugimoto, T. *Chem. Ind.* (*London*) **1977**, *538*. (c) Ogata, Y.; Ikejiri, T. *Nippon Kagaku Kaishi* **1975**, 1517. (d) Ogata, Y.; Sugimoto, T.; Inaishi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 255. (e) Ogata, Y.; Sugimoto, T.; Inaishi, M. *Org. Synth.* **1979**, *59*, 20.

(5) Ogata, Y.; Sugimoto, T. *J. Org. Chem.* **1978**, *43*, 3684.

(6) (a) Ogata, Y.; Watanabe, S. *J. Org. Chem.* **1979**, *44*, 2768. (b) Ogata, Y.; Watanabe, S. *Ibid.* **1980**, *45*, 2831. (c) Ogata, Y.; Watanabe, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2417.

(7) Louw, R. *Chem. Commun.* **1966**, 544.

(8) (a) Watson, H. B. *Chem. Rev.* **1930**, *7*, 173. (b) Watson, H. B. *J. Chem. Soc.* **1925**, 2067. (c) Watson, H. B.; Roberts, E. H. *Ibid.* **1928**, 2779. Watson presented little evidence for the enol intermediate except the halogen acid catalysis for the halogenation of carboxylic acids.

(9) West, R. W. *J. Chem. Soc.* **1924**, 1277.

(10) Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 237.

(11) Little, J. C.; Sexton, A. R.; Tong, Y. C.; Zurawic, T. E. *J. Am. Chem. Soc.* **1969**, *91*, 7098.

(12) Ogata, Y.; Harada, T.; Sugimoto, T. *Can. J. Chem.* **1977**, *55*, 1268.

(13) Gilbert, E. E. *Chem. Rev.* **1962**, *62*, 549.

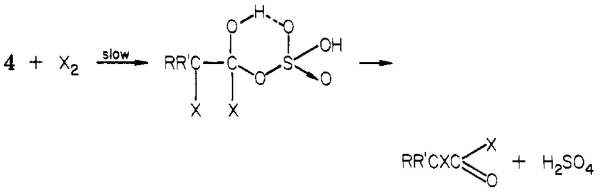
0022-3263/82/1947-1182$01.25/0

Table I. Rates of Halogenation of Acids and Derivatives in 1,2-Dichloroethane

substrate	second-order rate constant, M^{-1} s^{-1} iodination (80 °C)	second-order rate constant, M^{-1} s^{-1} bromination (60 °C)
$CH_3CO_2SO_3H$[a]	1.1×10^{-4}	1.2×10^{-3}
CH_3CO_2H[f]	4.0×10^{-4}[c]	1.9×10^{-4}[d]
$C_2H_5CO_2SO_3H$[b]	1.4×10^{-4}	1.5×10^{-3}
$C_2H_5CO_2H$[f]	1.2×10^{-3}[c]	1.3×10^{-3}[d]
$(C_6H_5)_2C{=}C{=}O$		7[e]
$(C_6H_5)_2CHCO_2H$[f]		1.2×10^{-3}
$(C_6H_5)_2CHCO_2SO_2CH_3$		4.3×10^{-3}

[a] In acetic acid. [b] In propionic acid. [c] Reference 6b. [d] Reference 5. [e] At 30 °C. [f] $ClSO_3H$ added as a promoter.

in the α-sulfonation of ω-phenylalkanoic acids.[15] Enol **4** would be expected to add halogen at the C═C double bond to form an α-haloacyl halide (eq 6). Diacetyl sulfate, formed from acetic anhydride and SO_3, has been reported to exist in an analogous cyclic keto–enol equilibrium.[14c] Diacetyl sulfate is also a minor product in the reaction of acetic acid and SO_3. However, if a diacyl sulfate were the intermediate in the α-halogenation of the acid, the reaction rate should be proportional to $[RCO_2H]^2[X_2]$, which is contrary to our results. Accordingly, we exclude a diacyl sulfate intermediate in the strong-acid-promoted halogenation.



(6)

Monopropionyl sulfate **3** (R = H, R′ = CH_3) was prepared from propionic anhydride and H_2SO_4[16] and iodinated at 80 °C. The second-order rate constant for this iodination was 1.4×10^{-4}, comparable to the rate of the $ClSO_3H$-promoted iodination of propionic acid (Table I). This result suggests that the rate-determining step in the latter reaction is that of halogen addition to the enol **4**.

Carboxylic anhydrides alone or in the presence of CH_3SO_3H were not halogenated; accordingly the enol form of the carboxylic anhydride is not an intermediate in the halogenation of the carboxylic acid.

We now suppose that the NMR peaks in the spectrum of a solution of isobutyric acid in oleum that had been attributed to dimethylketene[12] are instead attributable to $(CH_3)_2CHCO_2SO_3H$. It is known that ketenes react rapidly with strong acids such as CH_3SO_3H.[17] The formation of ketene on heating the solution of acetic acid in oleum, established by aniline trapping,[12] is believed to result from thermal decomposition of the monoacyl sulfate.[14c]

$$RR'CHCO_2SO_3H \rightleftharpoons RR'C{=}C{=}O + H_2SO_4$$

As shown in Table I, the bromination of diphenylketene is very rapid, whereas the rate of the $ClSO_3H$-promoted bromination of diphenylacetic acid is comparable to that of the similar reaction of propionic acid. A 1:2 mixture of diphenylketene and $ClSO_3H$, which should form $(C_6H_5)_2CHCO_2SO_2Cl$, brominated very slowly in 1,2-dichloroethane, only 60% of the bromine being consumed after 3 h at 60 °C.

The rate of bromination of $(C_6H_5)_2CHCO_2SO_2CH_3$ was comparable to that of the $ClSO_3H$-promoted bromination of $(C_6H_5)_2CHCO_2H$ (Table I). Since this sulfonate is known to decompose thermally to a ketene,[17] its halogenation might have proceeded through the ketene intermediate (eq 7). However, the rate constant for step 7b is 7 M^{-1} s^{-1} at 30 °C, so that the concentration of diphenylketene and the equilibrium constant for step 7a should be 10^{-5} M and 10^{-9}, respectively. Consequently, the rate constant for the reverse of step 7a must be 10^{10} M^{-1} s^{-1}, which is abnormally high for a second-order rate constant in a 10^{-1} M solution and improbable.

$$(C_6H_5)_2CHCO_2SO_2CH_3 \xrightleftharpoons{\text{fast}} (C_6H_5)_2C{=}C{=}O + HOSO_2CH_3 \quad (7a)$$

$$(C_6H_5)_2C{=}C{=}O + Br_2 \xrightarrow{\text{slow}} (C_6H_5)_2CBrCOBr \quad (7b)$$

We investigated the halogenation of some acyl sulfonates RCO_2SO_2R' in 1,2-dichloroethane: R = CH_3, R′ = CH_3; R = C_2H_5, R′ = CH_3; R = C_2H_5, R′ = p-$CH_3C_6H_4$; R = i-C_3H_7, R′ = CH_3. These sulfonates underwent bromination at 60 °C in 3 h, giving the α-bromo acids after hydrolysis. Iodination of these sulfonates did not occur at 80 °C after 5 h, probably because of the lower reactivity of iodine compared with bromine and the very low concentration of the enol form of these sulfonates owing to the lack of internal hydrogen bonding to favor the enolization (see eq 5).

We conclude that the α-halogenation of aliphatic acids promoted by $ClSO_3H$ or oleum proceeds by way of monoacyl sulfate intermediates **3** and **4**, rather than by way of an enol or ketene intermediate.

Experimental Section

UV and IR spectra were measured with a Hitachi 124 UV spectrophotometer and a Perkin-Elmer 337 IR spectrophotometer, respectively. NMR spectra were recorded on a Hitachi R-24B spectrometer using tetramethylsilane as an internal standard. GLC analysis was carried out on a Yanagimoto G-180 gas chromatograph using a column packed with PEG 20 M. Raman spectra were recorded on a JASCO R-300 laser Raman spectrophotometer using a 514.5-nm Ar ion laser.

Materials. Methanesulfonic, toluenesulfonic, diphenylacetic, isobutyric, propionic, and acetic acids and propionic and acetic anhydrides were of commercial grade. The volatile materials gave a single peak in GLC. Other organic solvents were purified by fractionation before use. Diphenylketene [bp 117–121 °C (6 mm)] and dimethylketene were prepared according to the literature.[18,19] Diphenylketene: NMR (CCl_4) δ 7.37 (s); IR (CCl_4) 3020, 2090, 1600, 1490, 1460, 1290, 1120, 1080, 1040 cm^{-1}. Dimethylketene: NMR (CCl_4) δ 1.65 (s).

---

(14) (a) Montoneri, E.; Fornaroli, M.; Giuffrè, L.; Tempesti, E.; Sioli, G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1784. (b) Montoneri, E., Giuffrè, L.; Cassago, M.; Tempesti, E.; Fonaroli, M. *Can. J. Chem.* **1977**, *55*, 355. (c) Montoneri, E.; Tempesti, E.; Giuffrè, L.; Castoldi, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 662. They obtained diacetyl sulfate $(AcO)_2SO_2$ from both equimolar $AcOH–SO_3$ and $Ac_2O–SO_3$ systems in liquid SO_2 at ≤–20 °C. At room temperature a cleavage occurred through intermediacy of ketene, which reacts further to give oligomers and sulfo derivatives.

(15) Truce, W. E.; Olson, C. E. *J. Am. Chem. Soc.* **1953**, *75*, 1651.

(16) (a) Russell, J.; Cameron, A. E. *J. Am. Chem. Soc.* **1938**, *60*, 1345. (b) Murray, T. F., Jr.; Kenyon, W. O. *Ibid.* **1940**, *62*, 1230. They prepared $RCOO–SO_2OH$ from $(RCO)_2O$ and H_2SO_4. (c) Casadevall, A.; Commeyras, A.; Paillous, P.; Collet, H. *Bull. Soc. Chim. Fr.* **1970**, 719. (d) Casadevall, A.; Commeyras, A. *Ibid.* **1970**, 1850.

(17) Tempesti, E.; Giuffrè, L.; Sioli, G.; Fornaroli, M.; Airoldi, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 771.

(18) Smith, L. I.; Hoehn, H. H. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 356.

(19) Smith, C. W.; Norton, D. G. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 345.

Acyl sulfonates $(CH_3)_2CHCOOSO_2CH_3$, $CH_3CH_2COOSO_2CH_3$, $CH_3CH_2COOSO_2C_6H_4CH_3$-*p*, and $CH_3COOSO_2CH_3$ were prepared according to the literature.[20] Diphenylacetyl methanesulfonate was prepared by the reaction of diphenylketene (1.05 g, 5.4 mmol) with methanesulfonic acid (0.35 mL, 5.4 mmol) in CCl_4 (3 mL) at room temperature: NMR (CCl_4) δ 3.0 (s, 3 H, SO_2CH_3), 5.0 (s, 1 H, =CHCO), 7.2 (s, 10 H, aromatic).

Raman Spectrum. The Raman spectrum of a mixture of acetic acid (3 mL, 52 mmol) and $ClSO_3H$ (1.3 mL, 25 mmol) after heating at 80 °C for 30 min showed two new peaks at 395 and 1050 cm^{-1} in addition to the peaks assigned to the components of the mixture. These two peaks were identical with those of *O*-monoacetyl sulfate.[16c]

Kinetics of Iodination of Dimethylketene and Bromination of Diphenylketene. The reaction of dimethylketene with iodine followed by hydrolysis and esterification with diazomethane gave methyl α-iodoisobutyrate, which was identified by GLC. The kinetics of iodination of dimethylketene were determined in a quartz UV cell themostated at 20 °C. The reaction was started by addition of a 1,2-dichloroethane solution (1 mL) of 3.6×10^{-3} M dimethylketene into a dichloroethane solution (2 mL) of 2.4×10^{-3} M iodine. The rate of the reaction was followed by measuring the UV absorbance of iodine at 500 nm (ϵ 910). The initial concentration of dimethylketene was determined iodometrically after addition of excess bromine to consume the ketene.

Bromination of diphenylketene in dichloroethane to give α-bromodiphenylacetyl bromide was done similarly in a quartz UV cell at 30 °C. The rate was followed by measuring the UV absorbances of diphenylketene and bromine. Since their absorbances overlapped at their absorption maxima at 405 nm, three wavelengths, 390, 405, and 420 nm, were used for the measurements of concentrations.

Kinetics of Reactions of Iodine and Bromine with Carboxylic Anhydride–Sulfuric Acid (Monoacyl Sulfates). Into a solution of iodine (1 g, 4 mmol) in propionic acid (30 mL) maintained at 80 °C was added 97% H_2SO_4 (1 mL, 18.8 mmol), and the reaction was started by addition of propionic anhydride (2 mL, 15.4 mmol). Aliquots were taken at appropriate time intervals, and the concentration of iodine was determined iodometrically.

Similarly, the bromination of monopropionyl sulfate was conducted with bromine (1.2 g, 7.8 mmol) at 60 °C. The rate measurements for the iodination and bromination of monoacetyl sulfate were conducted in acetic acid in the same way as above, where acetic anhydride (4 mL, 42.3 mmol) and H_2SO_4 (1 mL, 18.8 mmol, for iodination; 0.23 mL, 4.7 mmol, for bromination) were dissolved in acetic acid (25 mL).

Kinetics of Bromination of Diphenylacetyl Methanesulfonate. Diphenylacetyl methanesulfonate was prepared by the reaction of diphenylketene (3.3 g, 17 mmol) with methanesulfonic acid (1.1 mL, 17 mmol) in 1,2-dichloroethane (5 mL) at room temperature, and the solution was diluted to 10 mL with dichloroethane to prepare 1.7 M diphenylacetyl methanesulfonate. The solution (3 mL) was added to dichloroethane (30 mL) containing bromine (1.2 g, 7.5 mmol) at 60 °C. Aliquots were taken at appropriate time intervals to follow iodometrically the decrease in the concentration of bromine.

Iodination and Bromination of Acyl Sulfonates. Iodinations of isobutyryl, propionyl, and acetyl methanesulfonates and propionyl *p*-toluenesulfonate were attempted in 1,2-dichloroethane (50 mL) containing iodine (2 g, 7.9 mmol) and the acyl sulfonate (20 mmol) at 80 °C for 5 h, but no reaction was observed.

Analogously, brominations of acyl sulfonates (20 mmol) were conducted in dichloroethane (50 mL) containing bromine (1.2 g, 7.5 mmol) at 60 °C. The consumptions of bromine after 3 h were 40% for propionyl methanesulfonate, 15% for propionyl *p*-toluenesulfonate, 50% for isobutyryl methanesulfonate, and 40% for acetyl methanesulfonate. These brominations gave the corresponding methyl α-bromocarboxylates on hydrolysis and esterification, identified by GLC comparison with authentic specimen.

Acknowledgment. We thank Daicel Chemical Industries Ltd. and Mitsubishi Chemical Industries Ltd. for their gifts of materials and also Mr. M. Inaishi for typing the manuscript.

Registry No. $CH_3CO_2SO_3H$, 2308-54-5; CH_3CO_2H, 64-19-7; $C_2H_5CO_2SO_3H$, 40268-66-4; $C_2H_5CO_2H$, 79-09-4; $(C_6H_5)_2C{=}C{=}O$, 525-06-4; $(C_6H_5)_2CHCO_2H$, 117-34-0; $(C_6H_5)_2CHCO_2SO_2CH_3$, 80583-49-9; propionyl methanesulfonate, 26926-30-7; propionyl *p*-toluenesulfonate, 26926-29-4; isobutyryl methanesulfonate, 26926-34-1; acetyl methanesulfonate, 5539-53-7; dimethylketene, 598-26-5.

---

(20) Karger, M. H.; Mazur, Y. *J. Org. Chem.* 1971, *36*, 528.

Substituent Parameter Analysis of the Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of 4-Substituted *p*-Terphenyls[1]

Nancy K. Wilson* and Robert D. Zehr

U.S. Environmental Protection Agency, Research Triangle Park, North Carolina 27711

Received September 14, 1981

The effects, $\Delta\delta$ values, of substituents at the 4-position of 1:1′,4′:1″-terphenyl on the ^{13}C NMR chemical shifts were measured. For the set of substituents R = NO_2, $COOCH_3$, CN, H, CH_3, I, Br, Cl, NH_2, and $N(CH_3)_2$, correlations between $\Delta\delta$ values and various inductive and resonance σ parameters were sought by using three models: a single-parameter relationship, $\Delta\delta = \rho\sigma$; a dual substituent parameter (DSP) relationship, $\Delta\delta = \rho_I\sigma_I + \rho_R\sigma_R$; a nonlinear dual substituent parameter (DSP-NLR) relationship, $\Delta\delta = \rho_I\sigma_I + \rho_R\sigma_R/(1 - \epsilon\sigma_R)$. No acceptable correlations were obtained for the ^{13}C shifts of C-3,5 and C-4. A single parameter, σ_R^0, was adequate at only two positions, C-2′,6′ and C-2″,6″. At positions C-1, C-2,6, C-3′,5′, C-1″, C-3″,5″, and C-4″ the DSP model and σ_R^0 were best. At para-type positions in the central ring (C-1′ and C-4′) the DSP-NLR model was best. The magnitude of the ratio $\lambda = \rho_R/\rho_I$ of mesomeric to inductive transmission of electronic substituent effects ranged from 0.535 to 4.58, indicating the importance of inductive electronic effects at nearly all positions in *p*-terphenyl, even at C-4″, the carbon farthest from the substituent, where $\lambda = 1.70$.

The nature of substituent effects on ^{13}C NMR spectra and the best choices of models to correlate them with classical measures of substituent effects on chemical reactivity such as the Hammett σ parameters have been of research interest for some time[2-13] and are the subjects of

---

(1) Presented in part at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979, and at the Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, LA, Dec 1980.

(2) Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1–20.

(3) Hehre, W. J.; Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 159–187.

(4) Nelson, G. L.; Williams, E. A. *Prog. Phys. Org. Chem.* **1976**, *17*, 229–342.