Addition of Halogenated Acetic Acids to Vinyl Ketones. A Nuclear Magnetic Resonance Study of the Kinetics[1]

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The kinetics of addition of CF_3COOH (1) to $CH_2{=}CHCOCH_3$ (2) to form $CF_3COOCH_2CH_2COCH_3$ (3) were investigated by an nmr technique. The reaction was followed by observing a decrease in the nmr signal from the methyl peak of 2 at τ 7.55 and a concurrent increase in the corresponding signal from 3 at 7.63 as a function of time. An analysis of the kinetic data indicates that the reaction does not proceed to completion. Instead, equilibrium is reached after 24 hr with around 90% reaction at a 2:1 ratio of 1 to 2, and with 76% reaction at a 1:1 ratio. Relative reactivities of 1 and a series of halogenated acetic acids with 2 directly relate to pK_a values of the acids. Mechanistic aspects and the potential synthetic utility of the addition reaction of halogenated acetic acids to conjugated systems are discussed.

In a study designed to relate reactivities of the terminal double bonds of activated olefins in nucleophilic additions with their nmr parameters, it was noted that the spectrum of methyl vinyl ketone (2) in trifluoroacetic acid (1) changed with time. Examination of the nmr spectra of the reaction mixture indicated that 1 was adding to 2 in a reaction yielding a trifluoroacetate ester of 4-hydroxy-2-butanone (3) as shown in eq 1.

$$\underset{1}{CF_3CO_2H} + \underset{2}{CH_2{=}CHCOCH_3} \longrightarrow \underset{3}{CF_3CO_2CH_2CH_2COCH_3} \quad (1)$$

Since carboxylic acids do not usually add to activated olefins, a kinetic study of the addition of 1 and related acids to vinyl compounds was made to investigate the scope and mechanistic aspects of the reactions.

Experimental Section

All reactions were carried out with commercially available materials and 2 contained 1% hydroquinone as a stabilizer.

Nmr Spectra.—All spectra were determined on a Varian A-60[3] spectrometer. Chemical shifts, referenced to internal tetramethylsilane, and splitting patterns of the regions concerned are given in Table I.

TABLE I

NMR ASSIGNMENTS TO ESTERS OF 4-HYDROXY-2-BUTANONE

$$\underset{(A)}{Y\overset{O}{\overset{\|}{C}}OCH_2CH_2\underset{(B)}{\overset{O}{\overset{\|}{C}}}CH_3}$$

Y	Registry no.	τ CH_3 (A)	τ CH_2 (B)	τ CH_3
CH_3	10150-87-5	5.70	7.18	7.83
CH_2Cl	17244-71-2	5.40	7.08	7.78
$CHCl_2$	17244-72-3	5.45	7.00	7.73
CCl_3	17244-73-4	5.33	6.92	7.70
CF_3	17244-74-5	5.33	6.91	7.63
CBr_3	17244-75-6	5.35	6.93	7.68

Kinetic Measurements.—The rate constants were determined by an nmr technique. Methyl peaks of the starting material and of the product were chosen to follow the reaction because of their sharpness and separation from other peaks in the spectrum. The spectrometer was optimized and adjusted to give the best possible spectrum of the starting material before addition of acid. The offset was adjusted to position the methyl peak at the left side of the chart paper to allow the largest number of scans on a single sheet. The offset was changed by 15 cps between scans to move the peaks to the right as the reaction progressed. The peaks were scanned at regular intervals.

Solutions to be studied were prepared by introducing a known amount of starting material into a standard 5-mm (o.d.) nmr sample tube, and a known amount of acid was added as rapidly as possible with a syringe. The resultant solution was then thoroughly mixed and placed in the spectrometer where it was allowed to come to equilibrium at the probe temperature.

Kinetic measurements were made by following the disappearance of the methyl peak due to the starting material and the appearance of the methyl peak produced by the product. This procedure allowed our determination of the rate constant by two methods simultaneously, according to standard second-order plots as in Figure 1. Peak heights of the methyl groups were assumed to be directly proportional to concentration. The temperature of each reaction was obtained from a methanol calibration chart supplied by Varian Associates.

Gas Chromatography.—Glpc was carried out on an F & M Model 810, equipped with a 6 ft × 0.25 in. column of methyl silicone gum (SE-30, 15% on Chromosorb W, 80–100 mesh). The analysis was run at 60°. The compounds had the following retention times: 1, 6 min; 2, 2 min; 3, 10 min.

Results

Progress of each reaction was monitored by an nmr technique wherein the peak height of methyl signals were followed with time for both 2 and the addition product. This procedure is illustrated in Figure 2, which shows the decrease in concentration of 2 and consequent increase in product. Nmr data for all products are summarized in Table I; relative reactivities of a series of acetic acids with 2 appear in Table II as a function of the K_a values of the acids.

TABLE II

RELATIVE REACTIVITIES OF HALOGENATED ACETIC ACIDS WITH METHYL VINYL KETONE (2) IN A 1:1 MOLAR RATIO AT 37°

Acid	K_a[a]	Time, hr: 0.5	1	2	5	24
		% reaction				
CH_3CO_2H	1.7×10^{-5}	NR[b]	NR	NR	NR	NR
CH_2ClCO_2H	1.5×10^{-3}	NR	NR	4	13	25
$CHCl_2CO_2H$	4.3×10^{-2}	9	14	20	31	51
CCl_3CO_2H	0.22	33	43	50	61	67
CF_3CO_2H	0.56	42	52	58	70	76
CBr_3CO_2H	...	45	57	65	73	78

[a] Data from G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co. Ltd., London, 1961. [b] No observable reaction.

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(3) The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

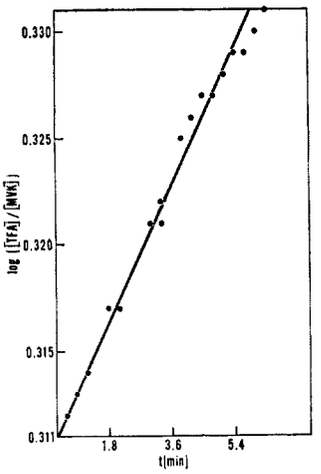


Figure 1.—Plot of log $[CF_3CO_2H/(CH_2{=}CHCOCH_3)]$ *vs.* time at 37°.

Investigating the effect of varying the nature of the reactants revealed that trifluoro-, tribromo-, trichloro-, dichloro-, and chloroacetic acids add to both **2** and ethyl vinyl ketone, but not to *trans*-4-phenyl-3-buten-2-one, methyl acrylate, acrylonitrile, methyl cyclopropyl ketone, and methyl vinyl sulfone.

Discussion

Nmr Assignments.—The nmr spectrum of the product of the reaction of **1** and **2** is consistent with the structure $CF_3CO_2CH_2CH_2COCH_3$. The product methyl group signal appears at 0.8 ppm upfield from the corresponding signal of **2**. The electron-withdrawing influence of the trifluoroacetate group is responsible for a large chemical-shift difference of 1.58 ppm between the adjacent methylene groups which appear as triplets with a characteristic split of 6 cps. The low field triplet at τ 5.33 is attributed to the methylene adjacent to the trifluoroacetate group, whereas the triplet at τ 6.91 is assigned to the methylene adjacent to the carbonyl group. Addition of water to the reaction mixture results in the appearance of a new triplet at τ 6.01 and a concomitant disappearance of the low field methylene peaks. Similarly, a new triplet arises at slightly higher field than that previously observed. These observations are consistent with the formation of 4-hydroxy-2-butanone (**4**) (eq 2).

$$\underset{\mathbf{3}}{CF_3CO_2CH_2CH_2COCH_3} + H_2O \longrightarrow \underset{\mathbf{4}}{HOCH_2CH_2COCH_3} \quad (2)$$

The nmr spectrum of **3** isolated by preparative glpc was identical with the corresponding spectrum obtained from the reaction mixture.

Kinetic Course of the Reaction.—A second-order rate constant ($k_2 = 15 \times 10^{-6}$ l./mol/sec) for the addition reaction (eq 1) was obtained from the plot shown in Figure 1. An analysis of the kinetic data by nmr indicates that the reaction does not proceed to completion, but that equilibrium is reached after 24 hr with around 90% reaction at a 2:1 mole ratio of **1** to **2**, and with 76% reaction at a 1:1 ratio, ($K_{eq} = 1.1$).

Mechanism of the Reaction.—Relative reactivities of acetic acid and a series of halogenated acetic acids with **2** as a function of the K_a values of the acids (Table II) demonstrate a direct relationship between observed reactivities and K_a values. These results are consistent with a mechanism in which protonation of the carbonyl group of the ketone (eq 1) facilitates the addition of the carboxylic acid anion in the rate-determining step (eq 3).

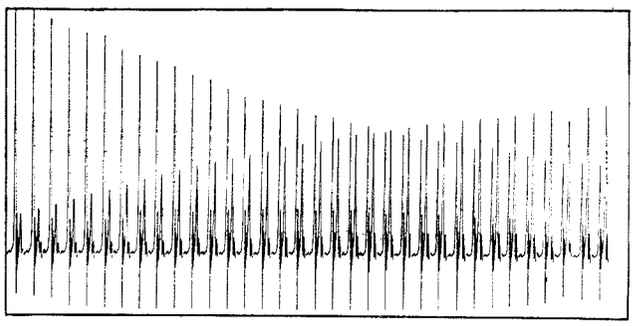
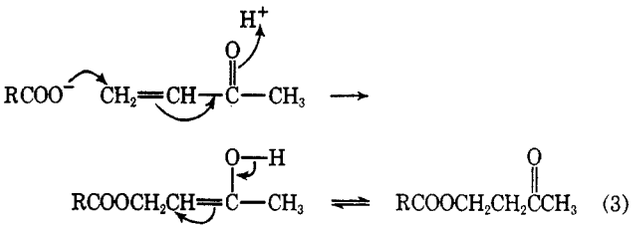


Figure 2.—Decrease in nmr signal of the CH_3 group of $CH_2{=}CHCOCH_3$ at τ 7.55 and concurrent increase of the corresponding signal for the CH_3 group in $CF_3COOCH_2CH_2COCH_3$ at τ 7.63 as a function of time at 37°. Peaks were measured at 0.3-min intervals.



(3)

The postulated mechanism is analogous to that previously proposed for the nucleophilic addition of amino and thiol groups in amino acids and peptides to α,β-unsaturated compounds.[4,5]

The question naturally arises why does **1** add readily to methyl and ethyl vinyl ketones and not at all to a number of other vinyl derivatives? A possible explanation comes from a relevant study on the relative reactivities of a series of vinyl compounds in nucleophilic addition reactions with amino acids and peptides where it was demonstrated that **2** was the most reactive vinyl compound.[6,7] Evidently, the equilibrium constant for the addition of **1** to alkyl vinyl ketones under our conditions favors the formation of products, whereas the corresponding equilibrium constants for the other vinyl compounds do not.

Synthetic Applications.—On the basis of the described kinetic and nmr studies it is concluded that the postulated addition reaction should find synthetic utility for preparation of two classes of compounds: (1) compounds with structure YCH_2CH_2COR, where Y is a halogenated acetate side chain and R is an alkyl group and (2) compounds with structure $HOCH_2CH_2COR$ formed upon hydrolysis of the keto esters under mild conditions. The net result of this reaction is a hydration of the double bond.

(4) M. Friedman and J. S. Wall, *J. Amer. Chem. Soc.*, **86**, 3735 (1964).
(5) M. Friedman, J. F. Cavins, and J. S. Wall, *ibid.*, **87**, 3672 (1965).
(6) M. Friedman and J. S. Wall, *J. Org. Chem.*, **31**, 2888 (1966).
(7) M. Friedman and J. A. Romersberger, *ibid.*, **33**, 154 (1968).