

A Search for General Acid Catalysis of Acetal and Ketal Hydrolysis Reactions Based on Stability of the Intermediate Carbonium Ion

THOMAS H. FIFE* AND EDWIN ANDERSON¹

Department of Biochemistry, University of Southern California, Los Angeles, California 90033

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A search has been made for general acid catalysis by weak buffer acids in the hydrolysis reactions of (1) benzophenone diethyl ketal, (2) 2,2-(*p*-methoxyphenyl)-1,3-dioxolane, (3) 2,3-diphenylcyclopropenone diethyl ketal, (4) ferrocene carboxaldehyde dimethyl acetal, and (5) tropone ethylene ketal. General acid catalysis could not be detected in any of the reactions except with tropone ethylene ketal in which case the weak acids $\text{Tris}(\text{H})^+$ and H_2PO_4^- are good catalysts. Thus, for general acid catalysis to be observed, the intermediate carbonium ion must be exceedingly stable when the leaving group is poor. For a series of acetals and ketals of aliphatic alcohols, the boundary between the normal A1 mechanism for acetal hydrolysis and the mechanism involving catalysis by general acids lies somewhere between the intermediate carbonium ion stability exemplified by the alkoxy tropylium ion and that of the alkoxy 2,3-diphenylcyclopropenyl ion.

The generally accepted mechanism for the acid-catalyzed hydrolysis of simple acetals and ketals involves preequilibrium protonation by hydronium ion followed by rate-determining unimolecular decomposition to an alcohol and a resonance-stabilized carbonium ion.² In order to observe protonation by hydronium ion as part of the rate-limiting step, along with general acid catalysis by buffer acids, either protonation must be made more difficult by reducing basicity or the bond-breaking process must be made relatively easy. In the case of 2-(*p*-nitrophenoxy)tetrahydropyran, with which a pronounced general acid catalysis is observed,^{3,4} the strong electron withdrawal in the leaving group will both lower basicity and facilitate C-O bond breaking. General acid catalysis has also been detected in the hydrolysis of benzaldehyde methyl phenyl acetals⁵ where the structural features promoting general acid catalysis are undoubtedly the same as with the phenoxytetrahydropyrans.

Buffer acid catalysis is seen with tropone diethyl ketal,⁶ a ketal having a poor leaving group but one in which C-O bond breaking is relatively easy, because of the exceedingly great stability of the intermediate carbonium ion. An important question then concerns the degree of carbonium ion stability necessary for general acid catalysis to be detectable with acetals having poor leaving groups. We have therefore studied the hydrolysis of a series of acetals and ketals of aliphatic alcohols with which progressively more stable carbonium ions are formed (compounds I-V).

Experimental Section

Materials. 2,2-(*p*-Methoxyphenyl)-1,3-dioxolane was prepared by treating *p,p'*-dimethoxybenzophenone, from K and K Laboratories, with ethylene glycol in refluxing benzene. A trace of *p*-toluenesulfonic acid was added as a catalyst. Water was continuously removed from the reaction by azeotropic distillation with the benzene. Refluxing was continued until a theoretical amount of H_2O had been removed. The mixture was cooled and allowed to stand over NaOH pellets. Removal of the benzene left a solid residue which, after recrystallization from an ether-petroleum ether mixture, melted at 48–50°.

Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4$: C, 71.31; H, 6.34. Found: C, 71.03; H, 6.11.

(1) Postdoctoral Fellow, Department of Biochemistry, University of Southern California.

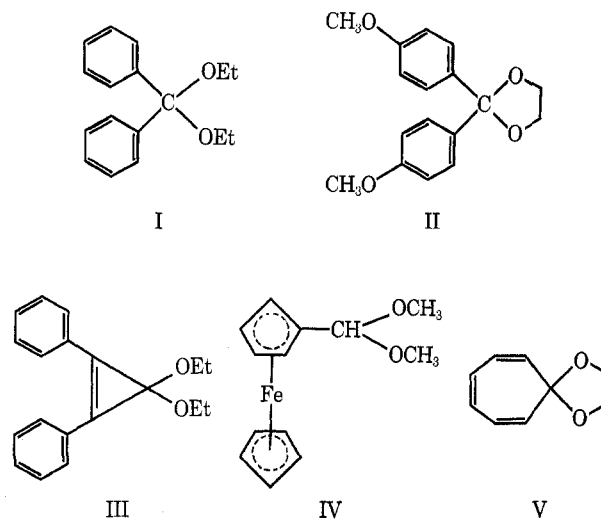
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Benzophenone diethyl ketal was prepared by adding dichlorodiphenylmethane (17.8 g, 0.075 mol) to a solution of sodium (3.45 g, 0.15 mol) in absolute ethanol. The mixture was stirred overnight and filtered. The ethanol was removed on a rotary evaporator, and the liquid residue was distilled. The product boiled at 128° (2.7 mm), n_D^{20} 1.5944, and solidified, mp 50–51° (lit.⁷ mp 51–52°).

2,3-Diphenylcyclopropenone was prepared by elimination of HBr from α,α' -dibromodiphenyl ketone by the method of Breslow, *et al.*⁸ Chromatography on silica gel (Baker) gave the ketone, mp 120–121° (lit.⁹ mp 121–121.5°).

1-Ethoxy-2,3-diphenylcyclopropenyl fluoroborate was prepared by adding a solution of diphenylcyclopropenone (0.06 mol) in methylene dichloride (10 ml) dropwise to a stirring solution of triethyloxonium fluoroborate (0.06 mol) in methylene dichloride (25 ml). The product separated as white needles in 95% yield, mp 153–154° (lit.¹⁰ mp 152° dec).

2,3-Diphenylcyclopropenone diethyl ketal was prepared by adding 1-ethoxy-2,3-diphenylcyclopropenyl fluoroborate (0.05 mol) to a solution of sodium ethoxide (0.07 mol) in 25 ml of absolute ethanol. After the vigorous reaction subsided, the resultant solution was poured into 100 ml of 2% aqueous Na_2CO_3 solution, and the suspension was extracted with ether. Evaporation of the ether left a pale yellow liquid still containing ethanol. After being allowed to stand for 2 hr the solution deposited white crystals. After recrystallization from ethanol the material melted at 67–68°.

Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2$: C, 81.43; H, 7.14. Found: C, 81.67; H, 7.14.

Ferrocene carboxaldehyde dimethyl acetal was prepared by treatment of ferrocene carboxaldehyde (Aldrich) with trimethyl-

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TABLE I
 RATE CONSTANTS FOR HYDROLYSIS OF BENZOPHENONE KETALS IN 20% OR 50% DIOXANE-WATER (v/v) AT 30°

Compd	Buffer	HA, <i>M</i>	A ⁻ , <i>M</i>	pH	<i>k</i> _{obsd} × 10 ⁴ sec ⁻¹
Benzophenone diethyl ketal	Chloroacetate ^a	0.6	0.2	3.50	1.88
		0.3	0.1	3.50	1.88
		0.06	0.02	3.50	1.87
2,2-(<i>p</i> -Methoxyphenyl)- 1,3-dioxolane	Chloroacetate ^b	0.24	0.24	3.17	93.7
		0.03	0.03	3.16	96.2
		0.60	0.20	2.54	5.46
	Dichloroacetate ^c	0.33	0.11	2.56	5.21
		0.06	0.02	2.58	3.92
		0.24	0.24	3.17	6.24
0.17		0.17	3.17	6.47	
0.132		0.132	3.16	6.30	
0.024		0.024	3.15	6.28	
Formate ^c	1.0	0.2	3.78	1.23	
	0.5	0.1	3.79	1.21	
	0.25	0.05	3.79	1.21	
	0.04	0.008	3.80	1.22	

^a 50% dioxane-H₂O, $\mu = 0.20$ maintained with KCl. ^b 20% dioxane-H₂O, $\mu = 0.24$ maintained with KCl. ^c 50% dioxane-H₂O, $\mu = 0.50$ maintained with KCl, at 50°.

orthoformate in acidic methanol. The product was obtained as a red liquid boiling at 106° (0.6 mm).

Anal. Calcd for C₁₃H₁₆FeO₂: C, 60.04; H, 6.16; Fe, 21.49. Found: C, 60.24; H, 6.20; Fe, 21.22.

Tropone ethylene ketal was prepared by the method of Simmons and Fukunaga.¹¹ Acetonitrile was Eastman Kodak Spectrograde which was further purified by twice distilling from P₂O₅ and once from K₂CO₃. Dioxane was purified by the method of Fieser¹² and stored frozen in brown bottles.

Kinetic Measurements.—The rates of hydrolysis were measured on a Cary 15 spectrophotometer by following the appearance of the aldehyde or ketone product. Temperature was maintained constant ($\pm 0.05^\circ$) by circulating water from a Precision Scientific Temptrol 154 water bath through a Thelma thermostated cell. Temperature was measured inside the cuvette. Buffers were maintained at constant ionic strength with KCl. The reactions were followed to completion and pseudo-first-order rate constants (*k*_{obsd}) were calculated by a rigorous least-squares procedure with an IBM 360-40 computer. The spectra of solutions upon completion of the reaction were identical in each case with that of the parent ketone or aldehyde. pH values were determined at the temperature of the experiments with a Radiometer pHM-22 meter. The glass electrode gives the correct pH reading in dioxane-H₂O mixtures.¹³

Results

In Table I rate constants are given for hydrolysis of benzophenone diethyl ketal and 2,2-(*p*-methoxyphenyl)-1,3-dioxolane in dioxane-water mixtures (20 and 50%) in the presence of various buffers. It is apparent that buffer catalysis is not observed for these ketals in chloroacetate or formate buffers. A small rate enhancement is seen in dichloroacetate buffer with 2,2-(*p*-methoxyphenyl)-1,3-dioxolane as the buffer concentration is increased. Since general acid catalysis will be easier to detect with weaker acids in cases where spontaneous hydrolysis is hydronium ion catalyzed (see Discussion), which is the case with this dioxolane, the enhancement in rate in the dichloroacetate buffer must not be caused by genuine, general acid catalysis. It is possible that a medium effect is important at high dichloroacetic acid concentrations. That this is at least a partial explanation is indicated by the fact that *k*_{obsd} in the presence of

0.1 *M* HCl in 50% dioxane-H₂O is increased from 1.11 × 10⁻² sec⁻¹ to 1.17 × 10⁻² sec⁻¹ by the addition of 0.3 *M* dichloroacetic acid. At such high hydronium ion concentration, general acid catalysis would not be seen. Thus, the 6% increase in the rate constant is most likely a medium effect.

Rate constants for hydrolysis of 2,3-diphenylcyclopropenone diethyl ketal in 20% dioxane-water in phosphate buffers (H₂PO₄⁻/HPO₄²⁻ = 1.0) are presented in Table II. Buffer catalysis cannot be detected. The

 TABLE II
 RATE CONSTANTS FOR HYDROLYSIS OF 2,3-DIPHENYLCYCLOPROPENONE DIETHYL KETAL IN 20% DIOXANE-WATER (v/v) AT 30° AND $\mu = 0.48$ (MAINTAINED WITH KCl)^a

Buffer	HA, <i>M</i>	A ⁻ , <i>M</i>	pH	<i>k</i> _{obsd} × 10 ³ sec ⁻¹
Phosphate	0.125	0.125	6.75	3.27
	0.0625	0.0625	6.75	3.06
	0.025	0.025	6.75	2.95
	0.0125	0.0125	6.75	3.13

^a Reactions were followed at 288 m μ .

reactions in phosphate buffers followed excellent pseudo-first-order kinetics, but, with imidazole and ethanolamine buffers, deviations from pseudo-first-order kinetics were observed. This was also the case with ferrocene carboxaldehyde dimethyl acetal and tropone ethylene ketal.

Buffer catalysis is not observed in the hydrolysis of ferrocene carboxaldehyde dimethyl acetal in acetate or phosphate buffers in water at 15°. These rate constants are presented in Table III. It will be noted that a small decrease in *k*_{obsd} is seen as the buffer is diluted at a ratio, CH₃COO⁻/CH₃COOH, of 3. This decrease is accounted for primarily by a small increase in the pH of the solutions. Second-order rate constants (*k*_{obsd}/*a*_H) are reasonably constant in these acetate buffers (5000 ± 200 *M*⁻¹ sec⁻¹). The pseudo-first-order rate constants in phosphate buffers are much less than those in acetate buffer indicating that the reaction is predominantly hydronium ion catalyzed in that pH range, but the calculated second-order rate constants were slightly greater (7500 ± 300 *M*⁻¹ sec⁻¹) than calculated from the acetate buffer data.

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TABLE III
RATE CONSTANTS FOR HYDROLYSIS OF FERROCENE
CARBOXYALDEHYDE DIMETHYL ACETAL IN H₂O AT
15° AND $\mu = 1.0 M$ (MAINTAINED WITH KCl)^a

Buffer	HA, M	A ⁻ , M	pH	$k_{\text{obsd}} \times 10^2$ sec ⁻¹
Acetate	0.33	1.0	5.11	3.80
	0.165	0.495	5.14	3.48
	0.11	0.33	5.16	3.25
	0.033	0.10	5.17	3.11
Acetate	0.167	1.0	5.42	1.95
	0.1167	0.70	5.38	2.11
	0.087	0.536	5.41	2.08
	0.0557	0.334	5.39	2.06
	0.0167	0.10	5.41	2.06
Phosphate	0.25	0.25	6.51	0.251
	0.125	0.125	6.46	0.249
	0.095	0.095	6.46	0.257
	0.0625	0.0625	6.46	0.265

^a Appearance of aldehyde was measured at 470 m μ .

As was the case with tropone diethyl ketal,⁶ significant buffer catalysis can be observed in the hydrolysis of tropone ethylene ketal in phosphate and Tris buffers [tris(hydroxymethyl)aminomethane]. Rate constants for these reactions are given in Table IV. The values

TABLE IV
RATE CONSTANTS FOR HYDROLYSIS OF TROPONE
ETHYLENE KETAL IN H₂O AT 25°

Buffer	HA, M	A ⁻ , M	pH	$k_{\text{obsd}} \times 10^3$ sec ⁻¹
Phosphate ^a	0.15	0.15	6.75	2.79
	0.075	0.075	6.75	2.45
	0.015	0.015	6.75	2.16
Tris ^b	0.30	0.30	8.25	0.415
	0.15	0.15	8.25	0.345
	0.03	0.03	8.25	0.290

^a $\mu = 0.6$ maintained with KCl. Appearance of ketone was measured at 311 m μ . ^b $\mu = 0.3$ maintained with KCl.

of k_{HA} are $4.48 \times 10^{-3} M^{-1} \text{sec}^{-1}$ for H₂PO₄⁻ and $4.64 \times 10^{-4} M^{-1} \text{sec}^{-1}$ in the case of Tris (H)⁺. A rate constant for hydronium ion catalysis, k_{H^+} , was calculated from the values of k_{obsd} at zero phosphate buffer concentration and has the value $1.19 \times 10^4 M^{-1} \text{sec}^{-1}$. Thus the rate constants for both general acid and hydronium ion catalysis are considerably smaller with tropone ethylene ketal at 25° than in the case of tropone diethyl ketal at 15°.⁶

Discussion

A fundamental question that must be asked in any search for general acid catalysis concerns the buffer concentration that will be necessary in order to observe catalysis if indeed it is present. The weaker the catalyst general acid, the easier it will be to detect general acid catalysis if spontaneous hydrolysis is a hydronium ion catalyzed reaction. This is because the observed pseudo-first-order rate constant for hydronium ion catalysis will decrease by a factor of 10 per pH unit with increasing pH, whereas the second-order rate constant for general acid catalysis will decrease by a factor of less than 10 per pK_a unit of the catalyst, the magnitude of the Brønsted coefficient α being less than one. An exception to this general rule obtains if the spon-

taneous reaction is pH independent, since as the pK_a of the general acid is increased a progressively larger portion of the reaction will then be due to spontaneous hydrolysis. Thus, in the hydrolysis of tropone ketals, general acid catalysis is observed over a rather narrow range of pK_a values, only data from H₂PO₄⁻ and Tris (H⁺) buffers being reported, since at pH values below approximately 6 the hydronium ion catalysis is too great to allow easy detection of general acid catalysis, while at high pH the relatively rapid pH-independent spontaneous reaction makes detection of general acid catalysis difficult; indeed, catalysis by HCO₃⁻ was not observed.⁶

In Table V the fractional increase in the rate constant produced by general acids of various pK_a values at a concentration of 1.0 M (half-neutralized buffer, total concentration 2.0 M) in comparison to the intercept rate constants [$(k_{\text{obsd}} - k_0)/k_0$] is given for a series of pK_a and α values,¹⁴ assuming that the point for hydronium ion lies on the Brønsted line. This may not always be the case, but in ortho ester hydrolysis reactions this point does not deviate greatly,¹⁵⁻¹⁷ and in general acid catalyzed acetal hydrolysis reactions investigated to date the fit of the point for hydronium ion on Brønsted plots is actually quite good.^{4,5,18} If the above assumption is not valid for a given reaction, the numbers in Table V will still indicate relative changes in the fractional increase. For a given value of α , the fractional increase becomes greater as the acid becomes weaker with the exception noted previously for low values of α and at high pK_a. With reactions in which α is greater than approximately 0.70, the necessity of employing either very high concentrations of general acids or relatively weak acids is clear. For example, assuming an α of 0.75, a 1.0 M concentration of an acid of pK_a 2.0 (HA = A⁻) would increase the rate of hydrolysis by only a factor of 16%.

Compounds such as benzophenone ketals would be expected to have α values close to unity if general acid catalysis could in fact be detected. Very high concentrations of buffer acids were employed in the present study of these compounds, and it is concluded that the reaction is not general acid catalyzed. The enhancements in the rate of hydrolysis of 2,2-(*p*-methoxyphenyl)-1,3-dioxolane produced by increasing dichloroacetic acid buffer concentration must be due to causes such as medium effects or specific salt effects since weaker acids are not catalysts. De Wolfe, *et al.*,¹⁹ have recently claimed that hydrolysis of that ketal is general acid catalyzed because of studies in dichloroacetic acid, although they did not observe catalysis in formic acid buffers. Buffer acid catalysis of the hydrolysis of benzophenone diethyl ketal was also claimed in dichloroacetate and chloroacetate buffers.¹⁹ We can find no evidence for catalysis of the hydrolysis of either ketal in chloroacetate buffer. Capon and Smith²⁰ could not detect catalysis of benzophenone diethyl ketal hydroly-

(14) These values were calculated on an IBM-360-40 computer from a program written by E. Anderson.

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TABLE V
FRACTIONAL INCREASE IN THE OBSERVED RATE CONSTANT $[(k_{\text{obsd}}^{\text{HA}} - k_0)/k_0]$ PRODUCED BY A 1.0 M CONCENTRATION OF A GENERAL ACID CATALYST^a AT DIFFERENT α VALUES AND AT DIFFERENT VALUES OF $\text{p}K_{\text{a}}$ OF THE CATALYST

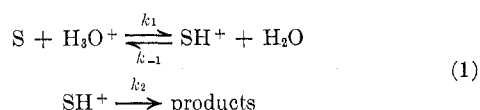
α	$\text{p}K_{\text{a}} = 1$	$\text{p}K_{\text{a}} = 2$	$\text{p}K_{\text{a}} = 3$	$\text{p}K_{\text{a}} = 4$	$\text{p}K_{\text{a}} = 5$	$\text{p}K_{\text{a}} = 6$	$\text{p}K_{\text{a}} = 7$	$\text{p}K_{\text{a}} = 8$
0.20	2.27	5.15	4.39	2.87	1.82	1.15	0.72	0.46
0.25	1.99	8.54	14.22	9.95	5.73	3.23	1.82	1.02
0.30	1.50	7.17	24.85	30.45	17.84	9.10	4.57	2.29
0.35	1.10	4.87	20.37	55.61	50.82	25.35	11.46	5.12
0.40	0.80	3.19	12.56	45.53	95.53	66.39	28.56	11.46
0.45	0.58	2.07	7.35	25.70	79.79	125.88	68.15	25.52
0.50	0.43	1.35	4.26	13.45	41.66	109.22	127.47	55.14
0.55	0.31	0.88	2.47	6.96	19.56	53.48	116.22	99.55
0.60	0.23	0.57	1.43	3.60	9.03	22.58	54.29	95.64
0.65	0.17	0.37	0.83	1.86	4.16	9.30	20.68	43.50
0.70	0.12	0.24	0.48	0.96	1.91	3.82	7.61	15.04
0.75	0.09	0.16	0.28	0.50	0.88	1.57	2.78	4.94
0.80	0.06	0.10	0.16	0.26	0.41	0.64	1.02	1.61
0.85	0.05	0.07	0.09	0.13	0.19	0.26	0.37	0.53
0.90	0.03	0.04	0.05	0.07	0.09	0.11	0.14	0.17

^a Half-neutralized buffers.

sis in acetate buffers. The highest concentration of chloroacetic acid employed by De Wolfe, *et al.*,¹⁹ in any buffer was only 0.131 M. On the other hand, the maximum concentration of formic acid employed in 20% dioxane (0.207 M) might have been sufficient to detect catalysis but none was seen.

When the rates of hydrolysis are too slow to measure accurately with buffers of weak acids at relatively high pH, it may not be possible to determine clearly whether compounds with which α must be close to 1.0 are subject to general catalysis. In such cases it is generally preferable to consider that the compounds hydrolyze by the well established A1 mechanism rather than by a borderline ASE2 mechanism. The only convincing evidence for a mechanism change in these acid-catalyzed reactions at the present time is the observation of general acid catalysis.²¹

It would appear that the boundary between the A1 and ASE2 mechanism may in fact be rather sharp. In eq 1 is the scheme followed by a typical acid-cata-



lyzed reaction. If k_2 is small relative to k_{-1} (H_2O), then the reaction will be an example of an A1 mechanism. If, however, k_2 is much greater than k_{-1} (H_2O), then k_1 will be rate determining. Taking the borderline case to be $k_2 \cong k_{-1}$ (H_2O)

$$k_{\text{obsd}} = \frac{k_1 k_2}{k_{-1} (\text{H}_2\text{O}) + k_2} (\alpha_{\text{H}^+}) \quad (2)$$

A structural change for a true borderline case that changed the magnitude of k_2 relative to k_{-1} (H_2O) by a factor of only 10 could therefore produce a situation in which the mechanism of the reaction would be for all practical purposes an example of one of the extreme cases. If the conjugate acid is not a discrete intermediate in acetal and ketal hydrolysis, the mechanism

(21) As an example, we prefer to regard the mechanism of acid-catalyzed hydrolysis of 2-phenyl-1,3-oxathiolanes and benzaldehyde methyl *S*-(substituted phenyl) thioacetals as A1 even though the solvent isotope effect is lower than normal and ΔS^\ddagger is more negative, since these changes can be explained in ways other than by postulating a mechanism change and since general acid catalysis cannot be observed even in cases which should be very favorable: T. H. Fife and E. Anderson, *J. Amer. Chem. Soc.*, **92**, 5464 (1970).

must involve protonation and C-O bond breaking occurring in a concerted manner.²² Bond breaking would then necessarily be facile enough so that the transition state could be attained without complete proton transfer. Increasing the stability of the carbonium ion intermediate would then give rise to a transition state in which less bond breaking was occurring and in which proton transfer would be less complete, thereby lowering the Brønsted α . Once the mechanism had changed from A1 to concerted, it would be expected that only a small further increase in carbonium ion stability would allow general acid catalysis to be observable. Thus, when the borderline area between these classes of mechanism is approached, a fairly small change in structure will be sufficient to produce a clear mechanism change.

General acid catalysis was also not observable in the hydrolysis of 2,3-diphenylcyclopropenone diethyl ketal and ferrocene carboxaldehyde dimethyl acetal. These data are subject to the reservations expressed above; however, it would be expected that general acid catalysis would be detectable with the buffers employed if it were indeed present. It can be seen in Table II that in phosphate buffer, where catalysis of troponone ketals is easily detected, catalysis is absent in the case of 2,3-diphenylcyclopropenone diethyl ketal.

These compounds will give rise to carbonium ion intermediates that are quite stable. In Table VI values of $\text{p}K_{\text{R}^+}$ are given for some carbonium ions related to the compounds studied. The $\text{p}K_{\text{R}^+}$ is the pH value at which a solution of an alcohol will give rise to a 50% concentration of carbonium ion. Thus, these $\text{p}K_{\text{R}^+}$ values can be considered an indication of the relative stability of the alkoxy carbonium ion intermediate produced in the hydrolysis of the corresponding ketal. The values become more positive upon going from diphenylmethyl to 2,3-diphenylcyclopropenyl to tropylium. The $\text{p}K_{\text{R}^+}$ of the ferrocenyl carbonium ion is not known, but the second-order rate constant for hydronium ion catalyzed hydrolysis of ferrocene carboxaldehyde dimethyl acetal is comparable to that for

(22) The positive ρ values for general acid catalyzed hydrolysis of 2-(substituted phenoxy)tetrahydropyrans⁴ and benzaldehyde methyl (substituted phenyl)acetals⁵ provide evidence against protonation being strictly rate determining in cases where buffer catalysis has been observed in acetal hydrolysis.

TABLE VI
pK_{R+} VALUES FOR VARIOUS CARBONIUM IONS

Carbocation ion	pK _{R+}	General acid catalysis ^a
Diphenylmethyl ^b	-13.3	-
Di- <i>p,p'</i> -methoxyphenylmethyl ^b	-5.71	-
2,3-Diphenylcyclopropenyl ^c	-0.67	-
Tropylium ^d	+4.7	+

^a Catalysis of the hydrolysis of the respective ketal. ^b N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3051 (1955); N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955). ^c R. Breslow, H. Hover, and H. W. Chang, *ibid.*, **84**, 3168 (1962). ^d G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **43**, 1221, 1243 (1960); W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **76**, 3203 (1954).

2,3-diphenylcyclopropenone diethyl ketal, making a reasonable allowance for the difference in temperature

at which the rate measurements were made. Tropone ethylene ketal was the only compound in the series for which general acid catalysis was observed. Therefore, the boundary line between the A1 mechanism and one involving general acid catalysis, in terms of carbonium ion stability, lies somewhere between pK_{R+} values of -0.67 and +4.7, with probability that it lies closest to the more positive figure. Thus, for general acid catalysis of acetal hydrolysis to occur in cases where the leaving group is poor, the intermediate carbonium ion must be exceedingly stable, *i.e.*, the bond-breaking step must be quite easy.

Registry No.—I, 6397-77-9; II, 29182-66-9; III, 29182-67-0; IV, 12512-45-7; V, 17637-62-6.

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The Chemistry of Carbanions. XIX. The Alkylation of Enolates from Unsymmetrical Ketones^{1a}

HERBERT O. HOUSE,* MARTIN GALL,^{1b} AND HUGH D. OLMSTEAD^{1c}

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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The alkylation of specific structural isomers of lithium enolates derived from 1-decalone (1), 2-methylcyclohexanone (2), 2-benzylcyclohexanone (3), cyclohexanone, and 2-heptanone (23) has been studied. The more highly substituted enolate isomers are best obtained by reaction of the corresponding enol acetates or enol trimethylsilyl ethers with methyllithium. The advantage gained with the silyl enol ethers in avoiding dialkylation is offset by the frequent difficulty in obtaining a single structural isomer of the silyl ether. The less highly substituted lithium enolates of unsymmetrical ketones are best obtained by a kinetically controlled deprotonation of the ketone with the hindered base, lithium diisopropylamide. Although the less hindered lithium enolates from cyclic ketones can be alkylated with good structural specificity, this procedure was not satisfactory for alkylation at the methyl group of 2-heptanone because of a combination of an unfavorable position of enolate equilibria and, especially, an unfavorable ratio of alkylation rates for the structurally isomeric enolates.

Often in the course of a synthesis, the need arises to introduce an alkyl group selectively at one of the two α positions of an unsymmetrical ketone. Among the useful methods for accomplishing this synthetic objective,² the reaction of an alkylating agent with a particular structural isomer of an enolate anion is very common. The formation of the desired enolate isomer may be accomplished either by modifying the structure of the starting ketone with a blocking group or an activating group or by generating the enolate from a suitable precursor under conditions where equilibration among the possible enolate structural isomers does not occur.² The most useful methods in this latter category have been the reduction with metals of α,β -unsaturated ketones³ or α -halo ketones⁴ and

the reaction of enol esters⁵ or enol silyl ethers^{6,7} with organometallic reagents, especially alkyllithium reagents. Among these possibilities, the use of enol esters or ethers offers the most versatility since the starting material for the alkylation sequence is the saturated ketone. The methods now available for the formation of enol acetates or trimethylsilyl enol ethers sometimes allow a particular structural isomer to be isolated in high yield; furthermore, any of the undesired isomers of these enol derivatives may be easily reconverted to the starting ketone.

By use of equilibrating reaction conditions accompanied, if necessary, by selective hydrolysis, it is usually possible to convert an unsymmetrical ketone to the corresponding more highly substituted enol acetate isomer in 95% purity on a preparatively useful scale.^{2,5} The use of equilibrating reaction conditions permits preparation of mixtures of trimethylsilyl enol ethers in which the more highly substituted enol derivative predominates (typically 70–90% of the mixture).⁷ However, it is often very difficult to obtain a pure

* Address correspondence to this author at the Department of Chemistry, Georgia Institute of Technology, Atlanta, Ga. 30332.

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