General Acid Catalysis of Acetal Hydrolysis. The Hydrolysis of Substituted Benzaldehyde Di-*tert*-butyl Acetals

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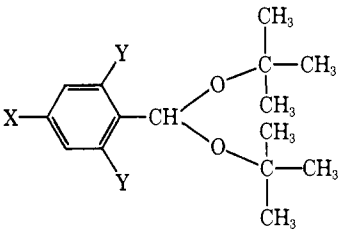
Received May 15, 1970

Abstract: The rates of hydrolysis of a series of substituted benzaldehyde di-*tert*-butyl acetals have been measured in water at 25°. A pronounced general acid catalysis is observed in the hydrolysis of these compounds. Steric strain in the ground state which is relieved in the transition state is undoubtedly important in leading to general acid catalysis. The value of ρ for acetic acid catalyzed hydrolysis is −2.0 while that for hydronium ion catalysis is −4.0. A Brønsted plot of log k_{HA} *vs.* the pK_a of the catalyzing acid in the hydrolysis of benzaldehyde di-*tert*-butyl acetal has a slope, α, of −0.6. The point for hydronium ion fits on this line with the buffer acids.

It has been generally accepted that the acid-catalyzed hydrolysis of simple acetals involves preequilibrium protonation of the acetal followed by a unimolecular, rate-determining decomposition of the protonated intermediate to an alcohol and a resonance stabilized carbonium ion.[2] General acid catalysis by buffer acids has been found in the hydrolysis of 2-(substituted phenoxy)tetrahydropyrans when the substituent group is electron withdrawing,[3] and in the hydrolysis of tropone diethyl ketal.[4] In both cases the mechanism most likely involves rate-determining protonation of the substrate by the general acid in concert with C–O bond breaking. Strong electron withdrawal in the leaving group will lower basicity of an acetal and increase the ease of C–O bond breaking, thereby leading to a reaction in which the bond-breaking process alone is not the slow step in the reaction as with simple acetals. In the case of tropone diethyl ketal, the leaving group is poor, but bond breaking is facilitated by the great stability of the intermediate carbonium ion. With both the 2-phenoxytetrahydropyrans[5] and tropone diethyl ketal[4] the ease of bond breaking is the most critical feature in giving rise to the observed effects.

Glycosidic enzymes such as lysozyme are undoubtedly employing functional groups at their active sites as general catalysts despite the fact that the natural substrates have poor leaving groups. It is likely, therefore, that the enzyme is, in some manner, greatly facilitating C–O bond breaking. Several mechanisms have been postulated for the action of lysozyme[6] involving aspartic acid 52 and glutamic acid 35. It has been suggested, but not proved, that a feature of the lysozyme reaction is the distortion of the hexose unit undergoing cleavage from the stable chair conformation to a half-chair conformation resembling that of a carbonium ion intermediate.[6] Such steric strain in the ground state would enhance the ease of formation of the transition state and could explain general acid catalysis in the enzymatic reaction.

To determine whether steric strain in the ground state, which would be relieved in the hydrolytic reaction, would enhance bond breaking to an extent sufficient to enable general acid catalysis to occur, we have studied the hydrolysis of para-substituted benzaldehyde di-*tert*-butyl acetals I–IV and also the corresponding 2,6-dichlorobenzaldehyde derivative V. General



I, X = OCH_3; Y = H
II, X = CH_3; Y = H
III, X = H; Y = H
IV, X = Cl; Y = H
V, X = H; Y = Cl

acid catalysis has been searched for in the hydrolysis of substituted benzaldehyde diethyl acetals and is absent,[7,8] but in the case of I–IV general acid catalyzed hydrolysis has now been observed.

Experimental Section

Materials. Benzaldehyde di-*tert*-butyl acetals were prepared from substituted α,α-dichlorotoluenes and potassium *tert*-butoxide by the procedure of Cawley and Westheimer.[9]

***p*-Methoxybenzaldehyde di-*tert*-butyl acetal I**[9] had bp 97–98° (0.3 mm); mp 29–31°.

***p*-Methylbenzaldehyde di-*tert*-butyl acetal II** had bp 74–78° (0.15 mm); mp 39–40°. *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.80; H, 10.40. Found: C, 76.55; H, 10.19.

Benzaldehyde di-*tert*-butyl acetal III[9] had bp 58–60° (0.10 mm); $n^{25}D$ 1.4752.

***p*-Chlorobenzaldehyde di-*tert*-butyl acetal IV** had bp 98–99° (0.10 mm); mp 61–62°. *Anal.* Calcd for $C_{15}H_{23}ClO_2$: C, 66.54; H, 8.50. Found: C, 66.23; H, 8.53.

2,6-Dichlorobenzaldehyde di-*tert*-butyl acetal had bp 104–105° (0.4 mm); mp 54–55°. *Anal.* Calcd for $C_{15}H_{22}Cl_2O_2$: C, 59.01; H, 7.21. Found: C, 58.70; H, 7.14.

Attempts at preparing the *p*-nitro and *m*-nitro derivatives by the method of Cawley and Westheimer[9] were unsuccessful.

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(2) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).
(3) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).
(4) E. Anderson and T. H. Fife, *ibid.*, **91**, 7163 (1969).
(5) T. H. Fife and L. H. Brod, *ibid.*, **92**, 1681 (1970).
(6) G. Lowe, G. Sheppard, M. L. Sinnott, and A. Williams, *Biochem. J.*, **104**, 893 (1967); M. A. Raftery and T. Rand-Meir, *Biochemistry*, **7**, 3281 (1968).
(7) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(8) T. H. Fife, *J. Amer. Chem. Soc.*, **89**, 3228 (1967).
(9) J. J. Cawley and F. H. Westheimer, *Chem. Ind. (London)*, 656 (1960).

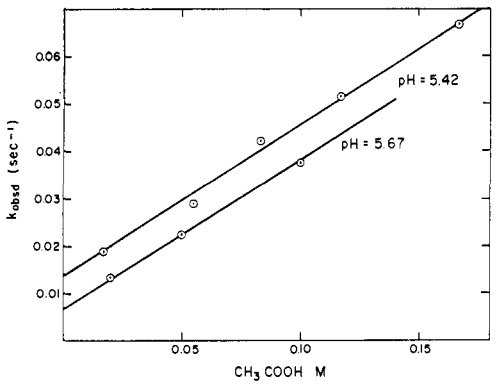


Figure 1. Plot of k_{obsd} *vs.* acetic acid concentration for hydrolysis of benzaldehyde di-*tert*-butyl acetal in H_2O.

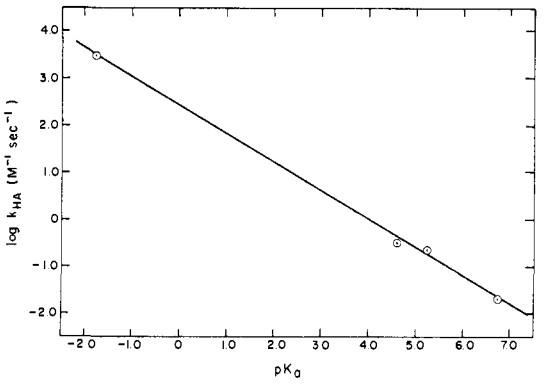


Figure 2. Plot of log k_{HA} for general acid catalysis of the hydrolysis of benzaldehyde di-*tert*-butyl acetal at 25° *vs.* the pK_a of the catalyzing acid.

Dioxane was purified by the method of Fieser[10] and was stored frozen in brown bottles. Acetonitrile was Eastman Kodak Spectrograde which was further purified by twice distilling from P_2O_5 and once from K_2CO_3.

Kinetic Measurements. The rates of hydrolysis were measured with a Gilford 2000 recording spectrophotometer by following the appearance of the aldehyde product at suitable wavelengths. Temperature was maintained constant at 25 ± 0.1° by circulating water from a Precision Scientific Temptrol 154 water bath around the cell compartment. To initiate the reactions, an acetonitrile solution of acetal was added to 3.0 ml of buffer in the cuvette by means of a Hamilton syringe so that the final concentration of acetal in the cuvette was 8×10^{-5} *M* and the solution was 1% acetonitrile. The spectra of the solutions upon completion of the reaction were identical with that of the appropriate aldehyde. Pseudo-first-order rate constants were calculated by a rigorous least-squares procedure on an IBM 360-40 computer.

Results

The hydrolysis of the substituted benzaldehyde di-*tert*-butyl acetals I–IV is subject to pronounced general acid catalysis. Second-order rate constants for general acid catalysis are presented in Table I. In Figure 1 a plot is shown of k_{obsd} *vs.* acetic acid concentration at constant pH and ionic strength (1.0 *M* maintained constant with KCl) for hydrolysis of benzaldehyde di-*tert*-butyl acetal in H_2O. It can be seen that an extremely large catalysis is observed. An identical second-order rate constant was obtained when the buffer ratio was varied, thereby showing catalysis to be by the acid component of the buffer. A large D_2O solvent isotope effect, $k_{HA}/k_{DA} = 2.52$, is obtained for the

(10) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

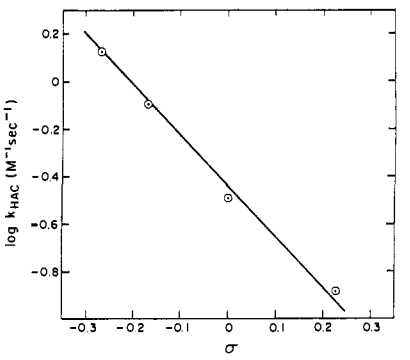


Figure 3. Plot of log k_{HA} for acetic acid catalyzed hydrolysis of para-substituted benzaldehyde di-*tert*-butyl acetals at 25° *vs.* σ.

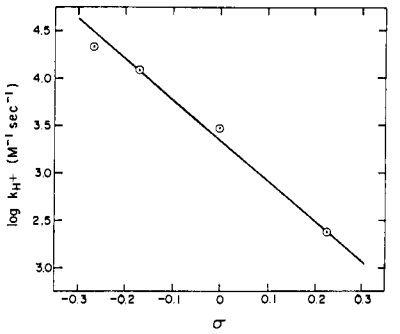


Figure 4. Plot of log k_{H^+} for hydronium ion catalyzed hydrolysis of para-substituted benzaldehyde di-*tert*-butyl acetals at 25° *vs.* σ.

acetic acid catalyzed hydrolysis of III. The intercept in Figure 1 represents hydronium ion catalysis since second-order rate constants (k_0/a_H) calculated from the intercepts of plots of k_{obsd} *vs.* buffer acid concentration remain constant as the pH is varied. The values of k_{H^+} for all of the di-*tert*-butyl acetals were obtained by extrapolation to zero buffer concentration and are reported in Table I. The ratio k_{D^+}/k_{H^+} for hydrolysis of III is 0.9. Similar solvent isotope effects are also observed with the *p*-methyl derivative II in both the acetic acid and hydronium ion catalyzed reactions.

Table I. Rate Constants for Hydrolysis of Substituted Benzaldehyde Di-*tert*-butyl Acetals in H_2O at 25° (μ = 1.0 *M* Maintained with KCl)

Substituent	Buffer	pK_a[a]	k_{HA}, M^{-1} sec^{-1}	k_{H^+}, M^{-1} sec^{-1}
p-OCH_3	Acetate	4.60	1.34	21,550
p-CH_3	Acetate	4.60	0.802	12,300
	Acetate (D_2O)	5.14	0.254	16,300
p-H	Phosphate	6.75	0.029	4,400
	Succinate	5.26	0.237	2,950
	Acetate	4.60	0.325	3,310
	Acetate (D_2O)	5.14	0.129	2,875
p-Cl	Acetate	4.60	0.136	238
2,6-Dichloro[b]	Formate	3.85	0.00016	8.42

[a] pK_a of the acid of the buffer, determined by half-neutralization. [b] 20% dioxane–H_2O, μ = 0.8.

From the data in Table I, the Brønsted plot of log k_{HA} *vs.* the pK_a of the catalyzing acid shown in Figure 2 was made for hydrolysis of benzaldehyde di-*tert*-butyl acetal. The slope is −0.6.

A plot of the logarithms of the second-order rate constants for acetic acid catalysis of the hydrolysis of

I–IV *vs.* σ, the Hammett substituent constant,[11] shown in Figure 3, is linear with these four compounds and has a ρ value of -2.0. A plot of log k_{H^+}, the second-order rate constant for hydronium ion catalysis, *vs.* σ is also reasonably linear (Figure 4) with a slope of -4.0.

The ortho-disubstituted compound 2,6-dichlorobenzaldehyde di-*tert*-butyl acetal was also studied in formic acid buffers. A catalytic effect of the buffer can barely be distinguished. Rate constants at various concentrations of formic acid are given in Table II. A second-order rate constant for formic acid catalysis is given in Table I, but the very small effect could also be due to a medium effect or specific salt effects.

Table II. Rates of Hydrolysis of 2,6-Dichlorobenzaldehyde Di-*tert*-butyl Acetal in Formic Acid Buffers at pH 3.85 and 25° [a]

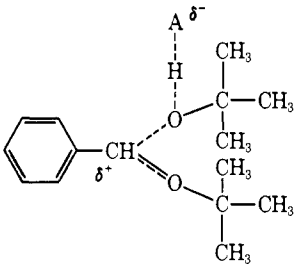
HCOOH, *M*	$k_{obsd} \times 10^3$, sec^{-1}
0.60	1.30
0.40	1.245
0.08	1.21

[a] 20% dioxane–H_2O, μ = 0.8 maintained with KCl.

Discussion

The large general acid catalysis observed with I–IV is undoubtedly due in part to facilitation of bond breaking by release of steric strain produced by the bulky *tert*-butyl groups in the ground state. Considerable restriction of rotation is evident from inspection of Stuart–Briegleb models. General acid catalysis might also arise if there was a marked reduction in basicity compared with structurally simpler acetals such as correspondingly substituted benzaldehyde diethyl acetals. However, lower basicity would slow the hydronium ion catalyzed reaction greatly whereas it is in fact enhanced, the second-order rate constant k_{H^+} for hydrolysis of III being 15 times greater at 25° than that for hydrolysis of benzaldehyde diethyl acetal in H_2O at 30°.[12] From the standpoint of inductive effects basicity might actually be expected to be increased by the *tert*-butyl groups,[13] although solvation effects are undoubtedly also of importance. The large *tert*-butyl groups could restrict solvation of the protonated species thereby lowering basicity, but in order to have an enhanced rate of hydrolysis the bond-breaking process would necessarily have to be facilitated to a greater extent. Bond breaking and basicity considerations are therefore possibly both important, but ease of C–O bond breaking caused by relief of steric strain in the ground state is most likely the predominant feature in giving rise to general acid catalysis.

The D_2O solvent isotope effects observed for the acetic acid catalyzed hydrolysis of II and III, which show the reactions to be much slower in D_2O than in H_2O, indicate that proton transfer is taking place in the rate-determining step. The most likely mechanism would involve concerted protonation and C–O bond breaking as in VI. The studies of Cawley and Westheimer[9] with



VI

I and III in ^{18}O enriched water showed conclusively that bond cleavage occurred to give the stable benzal carbonium ion, as in VI, in both the hydronium ion catalyzed reaction and also in aqueous acetic acid where the largest percentage of the reaction must have involved acetic acid catalysis.

The D_2O solvent isotope effects found for hydronium ion catalyzed hydrolysis are much less than normally encountered in acid-catalyzed acetal hydrolysis reactions where ratios of k_{D^+}/k_{H^+} greater than 2.7 are usually observed.[2,7] Thus, the hydronium ion catalyzed reaction also very likely involves proton transfer in the rate-determining step. It will be noted that in the Brønsted plot of Figure 2, the point for hydronium ion fits well on the line with the general acids. This has also been observed in other cases of general acid catalyzed acetal hydrolysis.[5,14] The magnitude of α, 0.6, is also comparable to the values 0.5[5] and 0.6[14] observed previously in hydrolysis reactions of acetals with phenolic leaving groups.

Increased electron withdrawal in the benzene ring of the substituted benzaldehyde di-*tert*-butyl acetals will decrease the rate of hydrolysis by decreasing basicity and by decreasing the ease of C–O bond breaking. The value of ρ for acetic acid catalyzed hydrolysis is -2.0 in comparison with -4.0 for hydronium ion catalysis.[15] Electronic effects are therefore of less importance with the carboxylic acid catalyst. Hydronium ion is, of course, positively charged whereas acetic acid is neutral so that the more negative ρ value found for hydronium ion could be explained by the fact that a more positively charged reaction center would be more electron demanding. Also, basicity is possibly of less importance in regard to the magnitude of ρ in the acetic acid catalyzed reaction, and bond breaking is being greatly aided by relief of steric strain. Thus, the adverse effects of electron withdrawal in the benzene ring are partially overcome in the general acid catalyzed reaction. Both basicity and bond breaking factors are probably important since C–O bond breaking would be expected to have progressed further in the transition state when concerted proton transfer is from a weak acid. Acceleration of the rate of hydrolysis by relief of steric strain will be more pronounced when bond breaking occurs to a greater extent in the transition state. This will be the case when electron-withdrawing substituents are present in the benzene ring, since the intermediate carbonium ion will then be less stable, and when catalysis is by weak acids. Substituted phenoxytetrahydropyrans[5] and benzaldehyde methyl phenyl acetals[14] give positive ρ values for general acid

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, Chapter VII.

(12) T. H. Fife and L. H. Brod, *J. Org. Chem.*, 33, 4136 (1968).

(13) The σ^* constant for *tert*-butyl is -0.30 in comparison with -0.10 for ethyl; R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.

(14) E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).

(15) A ρ value of -3.35 was found previously for acid-catalyzed hydrolysis of a series of meta- and para-substituted benzaldehyde diethyl acetals in 50% dioxane–H_2O.[7]

catalysis in contrast to negative values for hydronium ion catalysis, most likely reflecting the greater importance of bond breaking with a weak acid catalyst. In both cases substituents were located in the leaving group in the reaction so that increased electron withdrawal would facilitate bond breaking.

If the steric situation is such that strain is not released in the transition state then steric strain in the ground state will not give rise to an enhancement of the rate. This must be the case with 2,6-dichlorobenzaldehyde di-*tert*-butyl acetal. The bulky ortho substituents should lead to increased restriction of groups in the ground state in comparison with the para-substituted derivatives. However, general acid catalysis is almost abolished, and the hydronium ion catalyzed reaction proceeds at a slow rate. In addition to the electronic effects exerted by the two chloro substituents it is likely that either groups are restricted in the transition state and/or coplanarity cannot be achieved for maximum stabilization of the carbonium ion intermediate.

The above considerations could be of considerable importance in regard to the mechanism of action of lysozyme. Since relief of ground state strain will lead to an enhancement of the rate and to general acid catalysis in a simple chemical system, it is apparent that distortion effects such as postulated for lysozyme,[6] in which a hexose ring is forced into a half-chair conformation, could indeed be quite important in producing general catalysis by groups in the active site even though the leaving group in the reaction is quite poor. Giudici and Bruice[16] have shown that ground state planarity will not by itself lead to general acid catalysis of acetal hydrolysis. As a consequence of the possible kinetic effects produced by binding of the substrate to lysozyme, it would appear that the introduction of strain into the substrate which will in turn facilitate bond breaking is probably of critical importance.

Acknowledgment. This work was supported by research grants from the National Institutes of Health and the National Science Foundation.

(16) T. Giudici and T. C. Bruice, *Chem. Commun.*, 690 (1970).

Mechanism for Inversion in Primary Organomagnesium Compounds

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Abstract: The kinetics of inversion of the Grignard reagents RMgX (R = 2-methylbutyl, X = Cl, Br, I, R_2Mg) have been investigated and molecular weight data obtained for ether solutions 0.1–0.15 *M*. It has been found that steric effects have relatively little influence on the rates of inversion. Reagents which are dimeric X = Cl give first-order kinetics while, for those which are monomeric, the inversion rates are second order in contained reagent. It is concluded that the inversion takes place in a dimeric species and that alkyl bridging is associated with the transition state for inversion. An intraaggregate electrophilic transfer of the bridged group between the two magnesiums in the dimeric transition state is proposed to account for the results.

The dynamic behavior of organometallic compounds in solution involves inversion at carbon bonded to metal, carbon–metal bond exchange, and solvent–metal coordination exchange.

Although rates of inversion in various organometallic compounds have been measured by means of the nmr line-shape method[1–5] very little is known about the mechanism of the inversion process. The kinetic order for inversion was found to be larger than one for 3,3-dimethylbutylmagnesium chloride,[2] 2.5 for 2-methylbutylmagnesium bromide, and 2.0 for bis(2-methylbutyl)magnesium.[3]

In principle any process which further polarized the carbon–metal bond in these reagents should facilitate inversion. One mechanism suggested to account for the high kinetic order originally observed involves attack of a magnesium in one aggregate on the methylene carbon in another.[3]

A second process responsible for carbon–magnesium bond exchange, much faster than inversion, was detected by several investigators.[6–8] For instance ether solutions of mixtures containing dialkylmagnesium and arylalkylmagnesium compounds gave single average resonance patterns indicative of fast carbon–magnesium bond exchange.[6–8] This process was found to be slowed down by tertiary amines.[8] The existing evidence on magnesium coordination exchange with ethers and

(1) G. M. Whitesides, M. Witanowski, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 2854 (1965).
(2) G. M. Whitesides and J. D. Roberts, *ibid.*, **87**, 4878 (1965).
(3) G. Fraenkel and D. T. Dix, *ibid.*, **88**, 979 (1966); G. Fraenkel, D. T. Dix, and D. G. Adams, *Tetrahedron Lett.*, 3155 (1964).
(4) M. Witanowski and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 737 (1966).
(5) G. Fraenkel, D. T. Dix, and M. J. Carlson, *Tetrahedron Lett.*, 579 (1968).
(6) G. Fraenkel, D. G. Adams, and R. R. Dean, *J. Phys. Chem.*, **72**, 944 (1968).
(7) G. Fraenkel, S. Koboyashi, and S. Dayagi, *ibid.*, **72**, 953 (1968).
(8) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).