4-Methylphenyl *sec*-butyl ketone (1d): 50% yield; bp 87–88 °C (0.5 mm) (lit.[22] 80 °C (0.5 mm)); IR (neat) 1678 cm^{-1} (C–O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.15 (d, 3), 1.3–2.1 (m, 2), 3.3 (sextet, 1), 7.3 (d, 2), 8.0 (d, 2).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.82; H, 9.20. Found: C, 81.29; H, 9.14.

Ketones **1e–h** were prepared by the reaction of the corresponding substituted arylcadmium reagent with 2-methylbutanoyl chloride.[23] The arylmagnesium bromide was prepared by the reaction of the substituted aryl bromide (0.14 mol) with magnesium turnings (0.145 mol) in dry diethyl ether. The Grignard solution was cooled in an ice bath and anhydrous cadmium chloride (0.08 mol) was added over a 5-min period. The resulting grey reaction mixture was heated at reflux with stirring for 2 h. Most of the ether was then removed by distillation and replaced with dry benzene. A solution of 2-methylbutanoyl chloride (0.11 mol) in 20 mL of benzene was added to the cadmium reagent at room temperature. The reaction mixture was heated at reflux for ca. 4 h and allowed to stir at room temperature overnight. Dilute sulfuric acid was added to the cooled reaction mixture to decompose the salts and give a slurry that was extracted with ether. The ether extracts were washed with 10% aqueous sodium bicarbonate and water. Drying over anhydrous magnesium sulfate and removal of solvent yielded crude product. The product was fractionally distilled, chromatographed on silica gel (methylene chloride–hexane), and redistilled to give pure ketone in 30–50% yield. The pure ketone was identified by boiling point, NMR and IR spectra, and elemental analysis.

4-Chlorophenyl *sec*-butyl ketone (1e): 34% yield; IR (neat) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 3.4 (sextet, 1), 7.4 (d, 2), 7.7 (d, 2).

Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.19; H, 6.62; Cl, 18.05. Found: C, 67.31; H, 6.54; Cl, 17.92.

3-Fluorophenyl *sec*-butyl ketone (1f): 40% yield; IR (neat) 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 3.4 (sextet, 1), 7.5 (d, 2), 7.9 (d, 2).

Anal. Calcd for $C_{11}H_{13}FO$: C, 73.33; H, 7.22; F, 10.56. Found: C, 73.27; H, 7.28; F, 10.67.

(23) Carson, J.; Prout, F. S. *Org. Synth.* **1948**, *28*, 75. Shirley, D. A. *Org. React. (N. Y.)* **1954**, *8*, 28.

3-(Trifluoromethyl)phenyl *sec*-butyl ketone (1g): 44% yield, bp 29–30 °C (0.36 mm); IR (neat) 1683 cm^{-1} (C=O); ^1H NMR δ 0.9 (t, 3), 1.2 (d, 3), 1.3–2.1 (m, 2), 7.5 (m, 2), 8.1 (m, 2).

Anal. Calcd for $C_{12}H_{13}F_3O$: C, 62.61; H, 5.65, F, 24.78. Found: C, 62.42; H, 5.76; F, 24.61.

3,5-Bis(trifluoromethyl)phenyl *sec*-butyl ketone (1h): 22% yield; bp 96–97 °C (0.18 mm); IR (neat) 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3), 1.3 (d, 3), 1.3–2.0 (m, 2), 3.4 (sextet, 1), 8.0 (s, 1), 8.3 (s, 2).

Anal. Calcd for $C_{13}H_{12}F_6O$: C, 52.35; H, 4.03; F, 38.26. Found: C, 52.22; H, 3.93; F, 38.25.

Product Analyses. Effluents from the stopped-flow instrument were collected from the reaction of excess *sec*-BuLi with **1a–d**. Each mixture was neutralized with dilute sulfuric acid and extracted with ether. The ether extracts were washed with aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and concentrated. The crude product mixture were analyzed by NMR and IR spectroscopy and gas chromatography. In all cases, the tertiary alcohol (addition product) was the predominant constituent (>70%) of the product mixture. The reduction and enolization side products (i.e., secondary alcohol and recovered ketone) accounted for the remaining portion of the product mixture. For example, the stopped-flow effluent from the reaction of **1a** with *sec*-BuLi contained 86% addition product, 12% reduction product, and 1% recovered ketone by GC.

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Registry No. **1a**, 938-87-4; **1a**·*sec*-Bu_4Li_4, 90269-53-7; **1b**, 90269-45-7; **1b**·*sec*-Bu_4Li_4, 90269-52-6; **1c**, 90269-46-8; **1d**, 90269-47-9; **1e**, 90269-48-0; **1e**·*sec*-Bu_4Li_4, 90269-54-8; **1f**, 49660-96-0; **1g**, 90269-49-1; **1g**·*sec*-Bu_4Li_4, 90269-55-9; **1h**, 90269-50-4; *sec*-BuLi, 598-30-1; *sec*-Bu_4Li_4, 90269-51-5; *n*-BuLi, 109-72-8; *n*-Bu_6Li_6, 90269-56-0; 2-methylbutanoyl chloride, 5856-79-1; benzene, 71-43-2; diphenyl ether, 101-84-8; anisole, 100-66-3; toluene, 108-88-3; 1-bromo-4-chlorobenzene, 106-39-8; 1-bromo-3-fluorobenzene, 1073-06-9; 1-bromo-3-(trifluoromethyl)benzene, 401-78-5; 1-bromo-3,5-bis(trifluoromethyl)benzene, 328-70-1.

Notes

Evidence Defining Rate-Determining Diffusional Separation for the Hydrolysis of Acetals of Benzaldehyes

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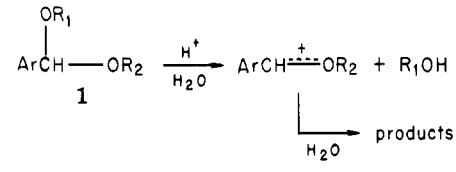
There has been a rekindling of interest in hydrolytic reaction mechanisms in recent years; of particular interest have been those hydrolytic reactions where catalysis (e.g., proton transfer) is concerted with other bond-making/breaking processes. In these cases the usual mechanistic tools can prove deceptive, unless one is careful to conduct experiments designed to examine both the catalytic and the bond-making/breaking process. The acetals of benzaldehydes **1** are an interesting case in point (Scheme I).

Scheme I



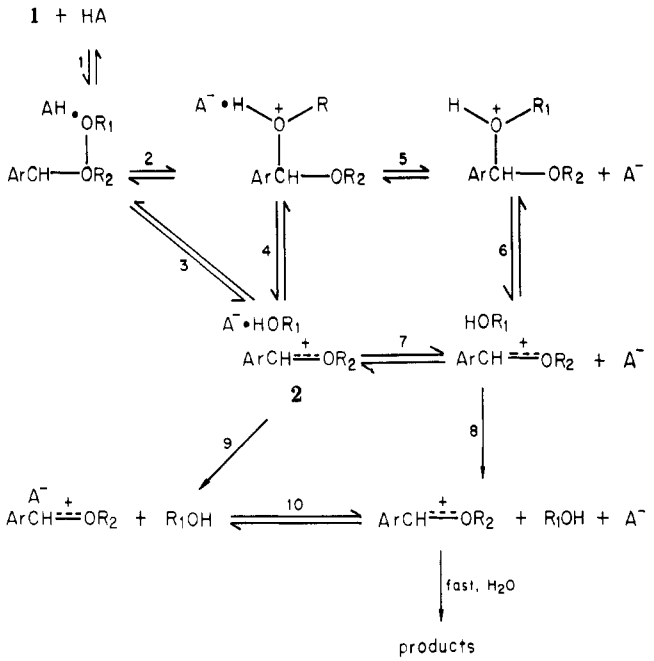
It has been shown that when R_1OH is an excellent leaving group (e.g., R_1 = aryl[1] or trifluoroethyl[2]), hydrolysis occurs with a rate-limiting step of proton transfer concerted with C–O bond breaking. This reaction is characterized by a large, negative Hammett ρ value of about −2 and a Brønsted α value of about 0.6. The coupling of the proton-transfer process and the C–O bond-breaking process has been measured quantitatively by Capon:[1] the Hammett ρ is more negative for weaker acid catalysts, and the Brønsted α is smaller when Ar contains electron-do-

(1) (a) Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1113–1118. (b) Capon, B.; Page, M. I. *Ibid.* **1972**, 522–529.

(2) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4772–4677.

0022-3263/84/1949-2613$01.50/0

Scheme II



nating groups or when R_1 contains electron-withdrawing groups. Qualitatively, a concerted catalysis mechanism is most favored by structural features that (1) make R_1OH a better leaving group and (2) stabilize the oxocarbocation intermediate;[1-4] however, the former feature is of predominant importance.[6]

When the R_1 moiety of 1 is not aryl or trifluoroethyl, the mechanism of hydrolysis is not so clear,[2,7-9] e.g., the hydrolysis of the diethyl acetals of substituted benzaldehydes[2] is characterized by large Brønsted α values (0.85 or larger) and by a Hammett $\rho = -3$. Jencks[7] and Kreevoy[8b] have recently reported evidence that has helped to clarify and define how this catalysis to C–O bond-breaking coupling differs from the "simple" concerted catalysis mechanism occurring when R_1 = aryl or trifluoroethyl. Scheme II[8b] nicely relates the mechanisms proposed: The heavy dots indicate specific hydrogen bonds; thus in aggregate 2 there is no heavy dot between $A^-\cdot HOR_1$ and the oxocarbocation in spite of the fact that their respective locations on the page are meant to imply electrostatic attractive forces. At spectral concentrations, diffusional separation of R_1OH is irreversible. Whether or not the aggregates formed by steps 3, 4, 6, 7, or 9 are directly attacked by water is not answerable at this time and will not be mentioned further, since the basic thrust of this work is whether the rate-limiting step occurs prior or subsequent to 2; it is, however, an important point that we ultimately hope to address.

The traditional A-1 mechanism consists of steps 1, 2, 5, 6, and 8, with step 6 being rate limiting; there is evidence that this mechanism is operable for the hydrolysis of hemicyclic acetals.[6] The $A_{SE}2$ mechanism proposed for acetals whose hydrolysis exhibit Brønsted α values of ~0.6 consists of steps 1, 3, 7 (or 9), and 8 (or 10), with step 3 rate limiting. Two other mechanisms are possible: Step 4 may be rate limiting (spectator catalysis)[10] or step 7 (or 9) may be rate limiting (rate limiting diffusional separation).[2] Both of these have been proposed for hydrolysis characterized by large Brønsted α values (0.85 or greater)[2,8b] and large negative Hammett ρ values (<–3). These two mechanisms are similar to the reverse of the preassociation mechanism proposed for carbonyl addition reactions.[11]

Thus the acid-catalyzed hydrolysis of 1, which a decade ago appeared to be well understood,[3-5] has recently[2,6-9] been shown to be an excellent series for investigating the parameters which favor one mechanism over another. With this in mind, we set out to measure kinetic solvent isotope effects (ksie), which can be used as a measure of the primary deuterium isotope effect on these reactions.[3] The hope was that isotope effects, taken with the previously measured Brønsted α values,[2] would lend additional definition to the reaction scenario shown in Scheme II. The expectation was achieved, in part, because the Brønsted α measures the catalytic effect of the entire general acid while the ksie reported herein measure the catalytic role of a particular acid catalyst, the solvated hydrogen ion.

Table I. Kinetic Solvent Isotope Effects on the Acid Catalyzed Hydrolysis of Benzaldehyde Acetals in Dilute Hydrochloric Acid Solution at 25 °C, μ = 0.5 (KCl)

acetal	k_{H^+}, M^{-1} s^{-1}	k_{D^+}/k_{H^+}	α^a
$PhCH(OCH_2CH_3)_2$	180	3.17[b]	0.87
PhCH(OCH2CH2OCH3)(OCH2CH3)	65	2.77[c]	0.86
PhCH(OCH2CF3)(OCH2CH3)	11	2.18[b]	0.70
$CH_3OC_6H_4CH(OCH_2CH_3)_2$	2100	2.90[b]	0.85
m-$ClC_6H_4CH(OCH_2CH_3)_2$	14	3.31[c]	≥0.9
m-$O_2NC_6H_4CH(OCH_2CH_3)_2$	1.1	3.29[c]	≥0.9

[a] Reference 2. [b] Calculated[12] by fitting k_{obsd} and antilog (–pL) data to $k_{obsd} = k_{L^+}[L^+]$; correlation coefficients ≥0.999; intercept/smallest k_{obsd} = 0 to –0.5; pL range = 1–2.4. [c] Calculated[12] in 0.1 N LCl solution by using $k_{L^+} = k_{obsd}$/antilog (–pL); using this same method of calculation for the other acetals listed gives exactly the same ksie (well within 1% of that listed and calculated according to footnote b).

Results and Discussion

Table I presents the kinetic solvent isotope effects (ksie) and k_{H^+} values measured by using recently published recommended procedures[12] (as summarized in the table), alongside previously measured Brønsted α values.[2] The acetals studied were chosen so as to cover the proposed changeover in mechanism: clearly benzaldehyde ethyl trifluoroethyl acetal hydrolyzes by an $A_{SE}2$ mechanism, the "simple" concerted catalysis nature of the mechanism (step 3, Scheme II) is required by the Brønsted α of 0.7. While ksie = 2.18 is large and inverse, it is within the range for an $A_{SE}2$ reaction catalyzed by hydronium ion (<2.3[13] to <2.75[14]).

(3) (a) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603. (b) Cordes, E. H.; Bull, H. G. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Ed.; Plenum Press: New York, 1978; Chapter 11, pp 429–465.
(4) (a) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264–272. (b) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1–122.
(5) Dunn, B. M.; Bruice, T. C. *Adv. Enzymol.* **1973**, *37*, 1–60.
(6) Jensen, J. L.; Wuhrman, W. B. *J. Org. Chem.* **1983**, *48*, 4686–4691.
(7) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8248.
(8) (a) Eliason, R.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 7037–7041. (b) Wann, S. R.; Kreevoy, M. M. *J. Org. Chem.* **1981**, *46*, 419–423.
(9) Young, P. R.; Bogseth, R. C.; Rietz, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 6268–6271.
(10) Kershner, L. D.; Schowen, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 2014–2024.
(11) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.
(12) Jensen, J. L.; Carr, M. D.; Yamaguchi, K. S. *Int. J. Chem. Kinet.* **1983**, *15*, 235–248.
(13) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275–332.
(14) (a) Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188. (b) Fife, T. H.; Bruice, T. C. *Ibid.* **1961**, *65*, 1079. (c) Salomaa, P.; Schaleger, L.; Long, F. A. *J. Am. Chem. Soc.* **1964**, *86*, 1. (d) Covington, A. K.; Paabo, M.; Robinson, R. A.; Bates, R. G. *Anal. Chem.* **1968**, *40*, 700.

The most striking feature of the data in Table I is the invariance of both the Brønsted α and ksie for acetals of widely different reactivity; only changes in the R_1 moiety of 1 cause a substantial lowering from the "average" ksie = 3.2, α = 0.9. The slightly lower values observed for Ar = p-OCH_3 and for $R_1 = CH_2CH_2OCH_3$ may be statistically significant for the ksie = 2.90 and 2.77, respectively, but are not for the α = 0.85 and 0.86, respectively. Thus, these two acetals are examples of substances designed to model behavior at the point of mechanism changeover. Table I, therefore, contains data for one acetal hydrolyzing by a concerted catalysis ($A_{SE}2$) mechanism, three acetals hydrolyzing by a mechanism consistent with ksie = 3.2 and α = 0.9, and two acetals at the changeover point.

The mechanism for the hydrolysis of 1 where R_1 does not contain strongly electron withdrawing groups cannot be $A_{SE}2$: ksie = 3.2 requires a preequilibrium proton transfer.[13,14] However, the transition state must contain the elements of general acid, since general acid catalysis is measurable for at least one of these acetals. Therefore, the observation of large, inverse ksie (>3), the observation of general acid catalysis (α = 0.9), and the large, negative Hammett ρ (–3), taken together, require a transition state closely resembling the aggregate 2. The constancy of the ksie requires that the nature of the isotopic bond in the transition state not change substantially as Ar is changed, despite a change in reactivity of 2×10^3 (ksie = 3.2 ± 0.2 for 1 when $R_1 = R_2 = CH_2CH_3$, Ar = Ar); this is inconsistent with a rate-limiting step 4, which changes an onium O–H bond to an alcohol O–H bond.

Thus, Table I provides good evidence for rate-limiting diffusional separation, and the changeover in mechanism is simply a change in rate-limiting step, brought about by a decreased lifetime of 2; that is, when 2 is longer lived because the oxocarbocation is exceptionally stabilized or becaused R_1OH is weakly nucleophilic, 2 is formed irreversibly by step 3. When 2 is shorter lived, because the oxocarbocation is less stable or because R_1OH is more nucleophilic, the fate of 2 is normally reversed to starting material. In this latter case, whether 2 is produced by step 3 or step 4 is impossible to say; however, we have shown that the rate-limiting step is subsequent to formation of 2. Also, in cases where the oxocarbocation does not have an aryl group to provide some stabilization, step 5 may occur faster than step 4, and 2 may no longer be a viable intermediate. This is an example of catalysis being enforced by an intermediate serving as a reaction intermediate and denied by its inviability as a reaction intermediate.[11]

Finally, although Scheme II nicely accommodates the data, there is an alternative interpretation that appears not to have been discussed previously. Namely, the hydronium ion catalyst is >6 pK units stronger an acid than the general acid catalysts employed in the buffer studies: The hydronium ion catalysis might be occurring via a classical A-1 mechanism (steps 1, 2, 5, 6, 8 in Scheme II) while the weaker carboxylic acids might catalyze hydrolysis via step 3 or 4 (step 3 being more likely in these cases, on the basis of an analysis of steps 2, 3, and 4 using contour energy diagrams).[2] That is, the assumption that all acid catalysts effect hydrolysis by the same mechanism is no more (or less) a truism than the assumption that structural changes in the substrate do not affect the nature of the reaction mechanism. (This latter assumption is one frequently employed in Hammett LFER studies.) Evidence for or against the validity of this assumption is of the most difficult type to generate definitively—a "break" in the LFER relationship. In the case of the Brønsted relationship this is particularly difficult, since the catalyst of greatest interest in this regard is usually 4–6 pK units away from a "cluster" of general acid catalysts whose pK_a span is often only 3 pK_a units or so. For the Brønsted α experiments cited in Table I, the hydronium ion lies "on" the Brønsted α line generated by the pK_{HA} vs. log k_{HA} data for the buffer acids, within a reasonable experimental error; in other words, the Brønsted α is the same, ±0.05, whether or not the k_{H^+} point is included in the computation. In addition, the "break" in the Brønsted relationship, were k_{H^+} to be for an A-1 mechanism (α = 1.0) and k_{HA} to be for any of the catalytic processes in Scheme II (α < 0.9), would place the k_{H^+} point *above* the line generated by the pK_{HA} vs. log k_{HA} data. In no case was this evident; k_{H^+} tends to fall below the Brønsted line generated in this manner, and thus the Brønsted α typically is 0.05 unit smaller when k_{H^+} is incorporated into the calculation.[2] These results argue against a change in mechanism with changing catalysts in this series of studies.

Experimental Section

Materials. The acetals were synthesized as reported earlier.[2] Deuterium chloride solutions were prepared by dilution of 20% DCl/D_2O with D_2O, both purchased from Aldrich Chemical Co. Concentrations of acid and chloride were checked by titration.[12]

Kinetic Method. The rate of production of aldehyde was monitored at λ_{max} for at least 3 half-lives of reaction time, using either a modified Beckman DU or a Durrum stopped-flow spectrophotometer. The traditional procedures used to obtain rate constants have been described previously.[2] Specific problems arising from the calculation of second-order rate constants from experimental measurements of acidity and k_{obsd} data have been defined recently,[12] and our exact method is defined in footnote b of Table I. The pH and pD measurements were obtained by using a Beckman Model 4500 pH meter and a Beckman 39030 combination glass electrode. pD values for the deuterated solutions were obtained by adding 0.41 to the observed meter reading.[14] In all solutions the "slope control" was used, using 0.100 N HCl, standard pH 4 buffer, and standard pH 7 buffer. All rate and pH (pD) measurements were made in solutions 0.1–0.005 N HCl (DCl), μ = 0.5 (KCl).

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Registry No. $PhCH(OC_2H_3)_2$, 774-48-1; $PhCH(OCH_2CH_3)(OCH_2CH_2OCH_3)$, 71412-86-7; $PhCH(OCH_2CH_3)(OCH_2CF_3)$, 71412-85-6; p-$CH_3OC_6H_4CH(OCH_2CH_3)_2$, 2403-58-9; m-$ClC_6H_4CH(OCH_2CH_3)_2$, 68578-52-9; m-$O_2NC_6H_4CH(OCH_2CH_3)_2$, 2403-49-8; deuterium, 7782-39-0.

The Bicyclo[3.3.1]nonane Solution to the Problem of Vicinal Stereochemical Control at a Substituted Cyclohexane Ring. A Total Synthesis of *dl*-*erythro*-Juvabione

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We have recently reported an efficient construction of bicyclo[3.3.1]non-3-en-2-ones by intramolecular enolate alkylation; the flexibility of the method was demonstrated by a formal total synthesis of *dl*-clovene.[1] In this paper,

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0022-3263/84/1949-2615$01.50/0