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Kinetics of Reversible Intramolecular Elimination Reactions. 2. A β-Alkoxy Ketone

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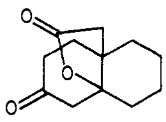
Abstract: The reaction of β-alkoxy ketone **7** to form enone alcohol **14** is readily reversible, and the equilibrium amount of **14** in aqueous solution is 6%. Like the previously studied irreversible dehydration of β-ketol **17**, the conversion **7** → **14** occurs by an $\mathrm{E1cB_I}$ mechanism at low general base catalyst concentration ([B]) and by an $\mathrm{E1cB_R}$ mechanism at high [B]. This conclusion, based initially on curvature in the plots of k_{obsd} vs. [B], was confirmed by direct measurement of the rate of deuterium incorporation into **7** when the reaction was run in D_2O. On the basis of the kinetic data it is estimated that the alkoxyl leaving group in **7** is expelled from intermediate enolate anion **19** at least 25 times faster than the hydroxyl group in **17** is expelled from enolate anion **18**. This is consistent with the proposal that there is strain in the bridged ring system of **7** (and **19**).

In the preceding paper[1] an E2 mechanism was proposed for the general base catalyzed elimination reaction of β-acyloxy ketone **1**[2] to form enone acid anion **2**. This proposal was based on the observations that **1** was far more reactive than and had different Brønsted behavior from the previously studied β-acetoxy ketones **3**[3] and **4**,[4] which had been shown to undergo elimination to form **5** by an $\mathrm{E1cB_I}$ mechanism. It was suggested[1] that the E2 mechanism becomes operative in the case of **1** → **2** because there is strain in the lactone ring of **1** which lowers the activation energy of transition state **6** in which the bond between the β carbon and ether oxygen is partially broken. In order to determine whether the reactivity of a leaving group incorporated into this type of bridged five-membered ring structure is indeed enhanced, we have studied the kinetic behavior of β-alkoxy ketone **7**. The results of this investigation, described herein, support the contention that the leaving groups of **1** and **7** are unusually reactive.



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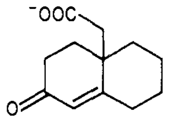

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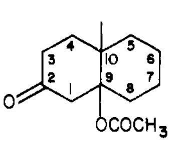

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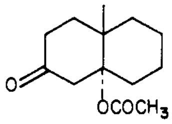

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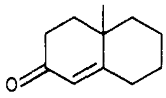

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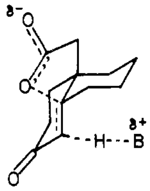

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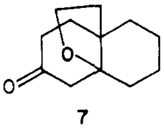

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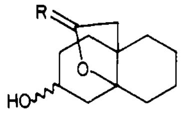
Results and Discussion

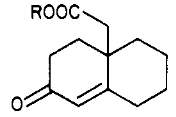
Synthesis. It was hoped that **7** could be prepared from **1** by reduction of the lactone function using $NaBH_4$ and BF_3, a mixture which has been reported[5] to effect conversion of lactones to ethers. In order to avoid elimination to **2** during this reduction, **1** was first reduced with $Zn(BH_4)_2$[6,7] to form a mixture of epimeric hydroxy lactones **8**. However, several attempts to reduce **8** with $NaBH_4$ and BF_3 failed to produce any detectable amount of hydroxy ethers **9**.

An alternate approach based on the use of the known enone ester **10**[2,8] proved more successful. We had previously shown[2] that although enone acid **11** cannot be isolated owing to its reconversion to **1**, its methyl ester **10** can be prepared by rapid acidification of a methanolic solution of **2** followed by treatment of the resulting **11** with diazomethane. Ketalization of **10** in the usual manner afforded 60% of **12**, in which the double bond had migrated to the $\Delta^{8,9}$ position, as expected.[9] Reduction of **12** with $LiAlH_4$ followed by a basic workup yielded 97% of **13**. Acidic hydrolysis of **13** afforded **7** in 74% yield, presumably via cyclization of enone alcohol **14**. On one occasion an acidic workup of the product from the reduction of **12** was used and **7** was obtained directly, but in substantially lower overall yield.

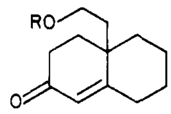
Since, as discussed below, the elimination reaction of **7** to form **14** is incomplete at any pH, and since **14**, like **11**, cannot be isolated and purified without ring closure occurring, it was necessary to have a model compound to use to estimate what the ultraviolet absorption of pure **14** would be. Treatment of **13** with NaH and CH_3I afforded ketal ether **15**, and acidic hydrolysis of



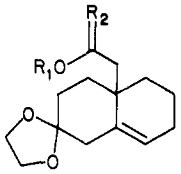
8, R = O
9, R = H_2



10, R = CH_3
11, R = H



14, R = H
16, R = CH_3



12, $R_1 = CH_3$, $R_2 = O$
13, $R_1 = H$, $R_2 = H_2$
15, $R_1 = CH_3$, $R_2 = H_2$

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(1) Mayer, B. J.; Spencer, T. A.; Onan, K. D. *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) Gula, M. J.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 805-809.
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(8) Enone ester **10** has also been previously reported as an unstable and incompletely characterized oil [Sims, J. J.; Honwad, V. K. *J. Org. Chem.* **1969**, *34*, 496-499].
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Table I. Rate Constants for the Reaction of **7** To Give an Equilibrium Mixture of **7** and **14** in Water at 25 °C and μ = 0.4 (KCl)

catalyst	pK_a^{a}	k_H^f, k_{OH}^f, or k_B^{fi},^{b} M^{-1} s^{-1}	k_B^{ff},^{b} M^{-1} s^{-1}	k_H^r, k_{OH}^r, or k_B^{ri},^{b} M^{-1} s^{-1}	k_B^{rf},^{b} M^{-1} s^{-1}
hydroxide ion	15.7	0.83		13.8	
quinuclidine	11.2	0.59	4.2×10^{-2}	9.9	0.80
3-hydroxyquinuclidine	9.9	5.4×10^{-2}	2.7×10^{-3}	0.9	4.5×10^{-2}
3-chloroquinuclidine	8.7	1.3×10^{-2}	8.7×10^{-4}	0.22	1.4×10^{-2}
Dabco	8.7	2.4×10^{-2}	1.1×10^{-3}	0.4	1.8×10^{-2}
3-quinuclidinone	7.2	3.0×10^{-3}	5.6×10^{-5}	5.0×10^{-2}	9.3×10^{-4}
Dabco·H^+	3.3	7.7×10^{-5}	*c*	1.3×10^{-3}	*c*
hydronium ion	−1.7	8.0×10^{-5}	*c*	1.33×10^{-3}	*c*

[a] Determined at 25 °C and μ = 0.4 (KCl) as described in ref 1. [b] The uncertainty in the rate constants is ca. ±5%. [c] This term could not be detected with this catalyst.

15 produced **16** in 82% overall yield. This enone ether (**16**) was considered to be a good model for **14**, and its value of ϵ 15 000 at 247 nm was used as the value of ϵ for **14** throughout this investigation.

Kinetics. In aqueous solution, an equilibrium mixture of **7** and **14** is formed which contains 6% **14** at all pH's between 1.4 and 12.2. This corresponds to a value for K_{eq} = 0.064 for **7** ⇌ **14**, which is not markedly different from the value of K_{eq} = 0.19 for **1** ⇌ **11** at pH <3.5.[1]

The rate of formation of **14**, determined by following the increase in absorbance at 247 nm, is catalyzed by hydronium ion. As in the formation of **11** from **1**, the rate constant for the approach to equilibrium, k_{obsd}, is the sum of the rate constants k^f for **7** → **14** and k^r for **14** → **7**, where $k^f/k^r = K_{eq}$. The rate expression given in eq 1 is followed, with $k_{obsd}^f = k_H^f[H_3O^+]$ and

$$d[\mathbf{14}]/dt = k_{obsd}[\mathbf{7}] = (k_H^f + k_H^r)[H_3O^+][\mathbf{7}] \qquad (1)$$

$k_{obsd}^r = k_H^r[H_3O^+]$, and the values of k_H^f and k_H^r are 8.0×10^{-5} and 1.25×10^{-3} M^{-1} s^{-1}, respectively. The similarity of this value of k_H^f for **7** to the previously determined values of k_H and k_H^f for the hydronium ion catalyzed elimination reactions of **1**,[1] **3**,[3] and **4**[4] suggests that all of these reactions occur by the same mechanism, which, we have previously concluded,[1] involves rate-limiting enol formation followed by rapid leaving-group expulsion.

The reaction of **7** to form an equilibrium mixture of **7** and **14** is also catalyzed by hydroxide ion. The rate law given in eq 2 is followed, where k_{OH}^f = 0.88 M^{-1} s^{-1} and k_{OH}^r = 13.8 M^{-1} s^{-1}.

$$d[\mathbf{14}]/dt = k_{obsd}[\mathbf{7}] = (k_{OH}^f + k_{OH}^r)[OH^-][\mathbf{7}] \qquad (2)$$

In the presence of tertiary amine buffers, general base catalysis of the approach to equilibrium is observed. The same set of structurally similar, unhindered tertiary amines employed in the preceding study[1] was used to study this general base catalysis. For the reaction with the weakly basic monoprotonated diazabicyclooctane (Dabco·H^+, pK_a = 3.3), a plot of k_{obsd}^f vs. free amine concentration is linear with slope = k_B^f. However, for the other amines, which all have pK_a > 7, plots of k_{obsd}^f vs. [B] are nonlinear, with a large initial slope at low buffer concentrations and a smaller final slope at higher buffer concentrations. This is illustrated in Figure 1 for the reaction of **7** with 3-quinuclidinone.

The initial slopes are designated k_B^{fi} and the final slopes are designated k_B^{ff}. Similarly, k_{obsd}^r can be plotted against [B] to determine k_B^{ri} and k_B^{rf}. The values of all four rate constants are given in Table I. A Brønsted plot for k_B^{fi}, depicted in Figure 2, shows β = 0.47, and a Brønsted plot for k_B^{ff}, depicted in Figure 3 shows β = 0.68.

Since a comparison of the rates of general base catalyzed elimination reactions of **1** with those of **3** had provided mechanistic insight into the reaction of **1**,[1] it was decided to study the kinetic behavior of a comparable analogue of **7**, β-hydroxy ketone **17**,[10] in the presence of the same set of catalysts. As found previously for other catalysts,[10] plots of k_{obsd} vs. [B] for the irreversible reaction of **17** to form **5** yielded initial slopes (k_B^i) and final slopes (k_B^f). The values of the derived rate constants are given in Table II.

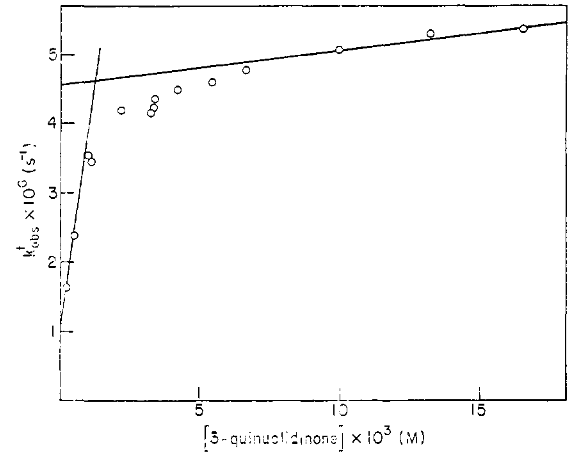

Figure 1. Plot of k_{obsd}^f vs. [B] for the reaction of **7** with 3-quinuclidinone (pK_a = 7.2). The solid lines were drawn through the points to indicate the initial slope (k_B^{fi}) and the final slope (k_B^{ff}).

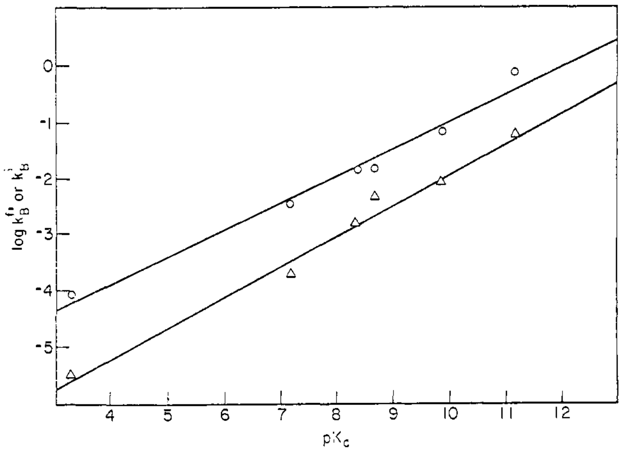

Figure 2. Brønsted plots of k_B^{fi} values for the reaction of **7** (open circles) and k_B^i values for the reaction of **17** (open triangles) with the tertiary amine catalysts listed in Tables I and II. The least-squares slope of a line through the six points for **7** is 0.47; for **17** it is 0.54. The points for Dabco are corrected as described by Jencks.[29]

Brønsted plots for k_B^i and k_B^f are shown in Figures 2 and 3, with β = 0.54 for k_B^i and β = 0.50 for k_B^f. No curvature was observed in plots of k_{obsd} vs. [B] for the reaction of **17** with Dabco·H^+, and since the Brønsted line for the k_B^i values extends through the point determined from k_{obsd} for this base, it is evident that this rate constant is k_B^i. Plots of k_{obsd} vs. [B] for the reactions of **4** with 3-chloroquinuclidine and 3-quinuclidinone showed curvature, but final slopes could not be determined for these reactions because the free amines were insufficiently soluble in water to give concentrations large enough to permit observation of the final slopes.

In our earlier study of the conversion of **17** to **5** it was concluded that the change in the slope of the plot of k_{obsd} vs. [B] was indicative of a change in rate-determining step and, therefore, of

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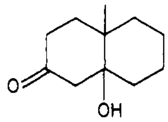
(10) Hupe, D. J.; Kendall, M. C. R.; Sinner, G. T.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 2260–2270.



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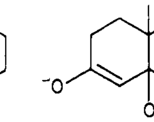

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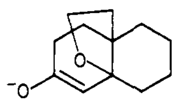

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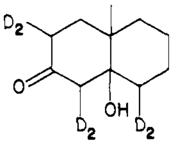

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the existence of an intermediate.[10] It was demonstrated that the initial steep slope, $k_B{}^i$, corresponded to the second-order rate constant for rate-limiting general base catalyzed proton removal from **17** to form enolate anion **18** ($E1cB_I$ mechanism), and that the final lesser slope, $k_B{}^f$, corresponded to specific base catalyzed, reversible formation of a small equilibrium concentration of **18**, followed by rate-limiting general acid catalyzed breakdown of **18** to **5** plus H_2O ($E1cB_R$ mechanism), as shown in Scheme I.

Scheme I

$$\mathbf{17} + B \rightleftharpoons \mathbf{18} + BH^+ \rightarrow \mathbf{5} + H_2O + B$$

The kinetic data for the reaction of **7** similarly suggest a change from an $E1cB_I$ mechanism at low [B] to an $E1cB_R$ mechanism at high [B], with the added complication that the elimination step **19** ⇌ **14** is reversible. The interconversion of **7** and **14** via intermediate enolate anion **19** is summarized in Scheme II, where k_1, k_{-1}, k_2, and k_{-2} are the first-order rate constants for each step of the reaction.

Scheme II

$$\mathbf{7} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{19} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{14}$$

The rate of appearance of **14** then follows the rate law given in eq 3.

$$d[\mathbf{14}]/dt = k_2[\mathbf{19}] - k_{-2}[\mathbf{14}] \qquad (3)$$

If the steady-state assumption is made for the concentration of **19** in eq 3, the expression given in eq 4 can be derived, where $k_1k_2/(k_{-1} + k_2) = k_{obsd}{}^f$ and $k_{-1}k_{-2}/(k_{-1} + k_2) = k_{obsd}{}^r$.

$$\frac{d[\mathbf{14}]}{dt} = \frac{k_1k_2}{k_{-1} + k_2}[\mathbf{7}] - \frac{k_{-1}k_{-2}}{k_{-1} + k_2}[\mathbf{14}] \qquad (4)$$

When $k_2 \gg k_{-1}$, the first step in Scheme I is rate limiting, with $k_{obsd}{}^f = k_1$ and $k_{obsd}{}^r = k_{-1}k_{-2}/k_2$. This is consistent with the kinetic data at low catalyst concentrations, where $k_{obsd}{}^f$ is described by eq 5.

$$k_{obsd}{}^f = k_{OH}{}^f[OH^-] + k_B{}^{fi}[B] \qquad (5)$$

Alternatively, when $k_{-1} \gg k_2$, $k_{obsd}{}^r = k_{-2}$ and $k_{obsd}{}^f = k_1k_2/k_{-1}$. This is consistent with the kinetic data at high catalyst concentrations, where $k_{obsd}{}^f$ is described by eq 6.

$$k_{obsd}{}^f = k_{OH}{}^f[OH^-] + k_B{}^{ff}[B] + k_c{}^f \qquad (6)$$

The constant term $k_c{}^f$ is simply the k_{obsd} intercept of the line with slope $k_B{}^{ff}$. Uncertainty in the experimental data makes it difficult to obtain an accurate value of $k_c{}^f$, but it is approximately 7×10^{-6} s^{-1}. A value of $k_c{}^f = 8.1 \times 10^{-7}$ s^{-1} was determined for the reaction of **17**,[10] and it was concluded that $k_c{}^f$ was the rate constant for spontaneous or water-catalyzed reaction of **18** to form **5**. The value of $k_c{}^f$ for **7** is larger than that for **17**, in accord with the conclusion, presented below, that leaving-group expulsion from **19** is faster than from **18**.

It was initially surprising that no curvature was observed in the plot of k_{obsd} vs. $[OH^-]$ for hydroxide ion catalysis of the reaction of **7**. In the case of **17**, such curvature was observed and values of $k_{OH}{}^i$ and $k_{OH}{}^f$ were determined.[10] The lack of curvature in the case of **7** is probably due to the fact that the values of $k_{OH}{}^{fi}$ and $k_{OH}{}^{ff}$ happen to be very similar. If the Brønsted plots for $k_B{}^{fi}$ and $k_B{}^{ff}$ in Figures 2 and 3 are extrapolated to $pK_a = 15.7$, both predict approximately the same value of $k_{OH}{}^f$.[11]

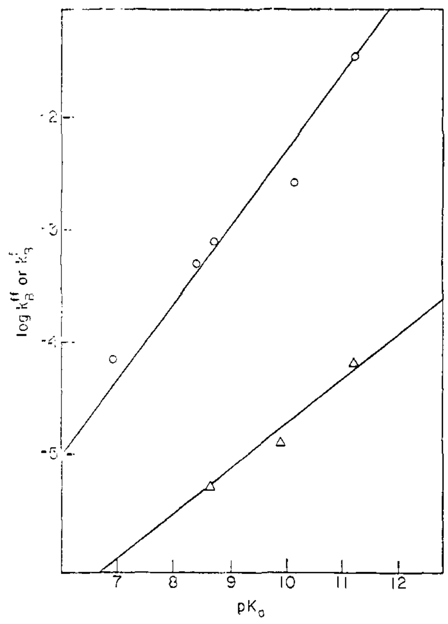
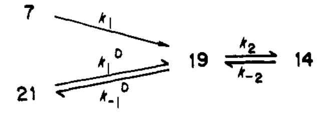


Figure 3. Brønsted plots of $k_B{}^{ff}$ values for the reaction of **7** (open circles) and $k_B{}^f$ values for the reaction of **17** (open triangles) with the tertiary amine catalysts listed in Tables I and II. The least-squares slope of a line through the five points for **7** is 0.68, and the least-squares slope of a line through the three points for **17** is 0.50. The points for Dabco are corrected as described by Jencks.[29]

Scheme III



In the case of β-hydroxy ketone **17** it was possible to confirm the proposed mechanism by studying hexadeuterated derivative **20**.[10] A large, invariant primary kinetic isotope effect was observed when the reactivities of **17** and **20** were compared at low catalyst concentration, indicating that proton removal was rate determining ($E1cB_I$).[10] At high catalyst concentrations, however, the isotope effect disappeared as the reaction progressed owing to isotopic exchange with the solvent, consistent with rate-limiting expulsion of leaving group ($E1cB_R$).

The study of isotope effects in the case of **7** is complicated by the reversibility of the elimination reaction, since isotopic exchange will occur regardless of which step is rate determining. Verification that proton abstraction from **7** is rate limiting at low catalyst concentrations required a means for direct measurement of that deprotonation. It proved possible to do this by observing the rate of incorporation of deuterium into **7** when the reaction was run in D_2O containing Dabco buffer as catalyst, using ^{13}C NMR to follow the rate of loss of the original signal for C-1. As shown in Scheme III, in D_2O enolate anion **19** cannot be reprotonated to give **7** and will instead either be converted directly to its α-deuterated analogue, **21** (if $k_{-1}{}^D > k_2$) or undergo reversible elimination to **14** (if $k_2 > k_{-1}{}^D$) before being converted, via **19**, to **21**.

Samples were removed at regular intervals from the solution of **7** and Dabco in D_2O, worked up with D_3O^+ and anhydrous

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[11] The value of $k_{OH}{}^f$ predicted by such extrapolations is 40 M^{-1} s^{-1}. This is much larger than the experimental value of $k_{OH}{}^f = 0.83$ M^{-u} s^{-1}, but such a negative deviation from a Brønsted slope defined by tertiary amines is to be expected; see: ref 10; Spencer, T. A.; Kendall, M. C. R.; Reingold, I. D. *J. Am. Chem. Soc.* **1972**, *94*, 1250–1254; Bender, M. L.; Williams, A. *Ibid.* **1966**, *88*, 2502–2508; Hine, J.; Hampton, K. G.; Menon, B. C. *Ibid.* **1967**, *89*, 2664–2668.

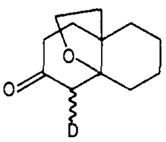
Table II. Rate Constants for the Reaction of **17** To Form **5** in Water at 25 °C and μ = 0.4 (KCl)

catalyst	pK_a[a]	k_{OH}^{i}, k_H^{i}, or k_B^{i},[b] M^{-1} s^{-1}	k_{OH}^{f}, k_H^{f}, or k_B^{f},[b] M^{-1} s^{-1}
hydroxide ion	15.7	0.12[c]	0.016[c]
quinuclidine	11.2	4.8×10^{-2}[c]	7.2×10^{-5}[c]
3-hydroxyquinuclidine	9.9	7.1×10^{-3}	1.5×10^{-5}
3-chloroquinuclidine	8.7	3.8×10^{-3}	$<1.4 \times 10^{-5}$[d]
Dabco	8.7	2.4×10^{-3}[c]	5.4×10^{-6}[c]
3-quinuclidinone	7.2	1.5×10^{-5}	$<5.1 \times 10^{-5}$[d]
Dabco·H^+	3.3	1.0×10^{-6}	*e*
hydronium ion	−1.7	3.0×10^{-5}[c]	2.0×10[c]

[a] Determined at 25 °C and μ = 0.4 (KCl) as described in ref 1. [b] The uncertainty in the rate constants is ca. ±5%. [c] Determined previously in ref 10. [d] Owing to the limited solubility of these amines, final linear slopes could not be determined. [e] No curvatuve was detected in the slope for this catalyst.

ether, and analyzed by ^{13}C NMR. A singlet at δ 47.66 showed a regular diminution with concomitant appearance of a triplet at δ 48.05.[12] During the time required for complete loss of the signal at δ 47.66 no other change in the spectrum was observed, indicating that only one deuterium was being incorporated at a single site in **7**.

Quantitative analysis of ^{13}C NMR spectra by direct peak integration is often impossible,[13] but decreasing peak intensity has been successfully used to determine the extent of deuterium incorporation.[12] To test the accuracy of this approach in the present context, mixtures of **17**, **20**, and the specifically monodeuterated **22**, prepared as described in the Experimental Section, were analyzed by ^{13}C NMR, and it was found that the amount of **17** present could be determined within ±5%. This gave us confidence that by comparing the intensity of the signal at δ 47.66 with that of the signal at δ 62.91, asigned to the methylene carbon α to the ether oxygen,[14] we were obtaining a reliable measure of deuteration of **7**.



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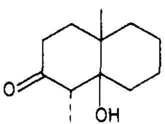
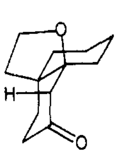


22



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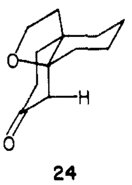

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Moreover, since the ^{13}C NMR analyses showed that a single deuterium was selectively incorporated into **7**, mass spectroscopy could also be used to follow the rate of loss of the α proton. Reassuringly, the mass spectroscopic analyses gave a rate of deuterium incorporation consistent with that obtained by ^{13}C NMR. The rate of deprotonation of **7** was measured twice by the two techniques, and an average value of $k_1 = 3.2 \times 10^{-3}\ s^{-1}$ was obtained.

In order to establish whether this value of k_1 is consistent with the mechanistic scheme proposed above, it was necessary to estimate the value of k_1 which would be predicted by the kinetic data obtained by UV spectroscopy. The values of k_{OH}^{f} and k_B^{fi} for Dabco are available, but since the reaction was run in D_2O, the appropriate rate constants for catalysis of deprotonation of **7** would be k_{OD}^{f} and $k_B^{fi}(D_2O)$, because in D_2O, $k_1 = k_{OD}^{f}[OD^-] + k_B^{fi}(D_2O)[B]$.

The values of k_{OD}^{f} and $k_B^{fi}(D_2O)$ unfortunately cannot be measured directly because of the isotopic exchange which occurs when the elimination reaction of **7** is run in D_2O. Instead, ratios of k_{OD}/k_{OH} and $k_B(H_2O)/k_B(D_2O)$ were determined by using the familiar irreversible reaction of **3** to form **5** as a model system. Values of k_{OD} and $k_B(D_2O)$(Dabco) and of k_{OH} and $k_B(H_2O)$(Dabco) were determined for **3** → **5** in the usual manner,[3] and the ratios found were $k_{OD}/k_{OH} = 2.5$ and $k_B(H_2O)/k_B(D_2O) = 1.3$. These results are reasonably consistent with literature values for such ratios in closely related reactions.[15,16]

When these factors were used to adjust the measured values of k_{OH}^{f} and k_B^{fi} and the resulting values of k_{OD}^{f} and $k_B^{fi}(D_2O)$ were used to calculate k_1 for the reaction conditions used in the isotope exchange experiment, a value of $k_1 = 2.0 \times 10^{-3}\ s^{-1}$ was obtained. This is quite close to the experimental value of $3.2 \times 10^{-3}\ s^{-1}$, even though the deprotonation–deuteration experiment was run with a high catalyst concentration which would make the overall mechanism of **7** → **14** E1cB$_R$. The value of k_f predicted by eq 6 for these reaction conditions, assuming the same solvent effect on k_B^{ff} as on k_B^{fi}, is ca. $1.3 \times 10^{-4}\ s^{-1}$, substantially smaller than either the measured or calculated value of k_1. These results are consistent with the conclusion that **7** undergoes an E1cB$_I$ reaction at low general base concentrations and an E1cB$_R$ reaction at high catalyst concentrations.

The observation that a single specific α proton is removed from **7** during the exchange experiment deserves discussion. The elimination reaction requires that a C-1 proton be removed, so it is obvious that the peak at δ 47.66 which disappears during the reaction of **7** is that of C-1. This chemical shift of δ 47.66 is reasonably close to that of δ 51.19 for C-1 of **17**, which was identified by comparison of the spectrum of **17** with that of α-monodeuterated **22**.

The fact that a C-1 proton is removed in preference to an α proton at C-3 can be explained on the basis of the inductive effect of the leaving group on the acidity of the C-1 α carbon. A study by Ahlberg[17] of α proton removal from methyl-substituted 1-methylindenes showed a rate enhancement of 30 for a methoxy substituent compared to hydrogen, and studies by More O'Ferrall and Warren of proton removal from 9-fluorenylmethyl derivatives in methanol showed a rate enhancement of 85 for a β-methoxy substituent[18] and 27 for a β-hydroxy substituent.[19]

The fact that only one of the C-1 protons is exchanged may reflect preferential proton removal from one conformer of *cis*-decalin **7**. It is probable that it is an axial α proton which is being abstracted,[20] but it is not clear from examination of molecular models that there is any distinct difference in steric hindrance between approach to the C-1 beta[21] proton in conformation **23**

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[12] The downfield shift of C-1 on substitution by deuterium is the opposite of the upfield shift which is usually observed (Stothers, J. B. In "Topics in Carbon-13 NMR Spectroscopy"; Levy, G. C., Ed.; Wiley-Interscience: New York, 1974; Vol. 1, Chapter 6, pp 234–237).

[13] Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972, Chapter 2, pp 29–33.

[14] The signal at δ 62.1 in the spectrum of **7** was assigned to the methylene carbon α to the ether oxygen because it has a large downfield shift, as expected for a carbon α to an oxygen (see Levy and Nelson, ref 13, pp 45–49), and because it is distinguished from C-9, also adjacent to oxygen, by a large nuclear Overhauser enhancement.

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[21] To avoid confusion, the words "alpha" and "beta" are used to denote substituents which are respectively underneath and above the plane of the decalin ring system as drawn herein, as opposed to the more common use in this paper of the symbols α and β to designate the positions of carbon atoms relative to a carbonyl or derived functional group.

and the C-1 alpha proton in conformation **24**. The X-ray structures of lactone **1** and *cis*-ketol **17** show that these compounds have conformations analogous to **24** in the crystalline state,[1] and it may be that it is the C-1 alpha proton which is selectively removed from **7**, just as it is the C-1 alpha proton which is postulated to be involved in the elimination reaction of lactone **1**.[1] However, this is not required in the case of **7**, because its elimination to **14** is not concerted.

Upon comparison of the rate constants, k_B^{fi} and k_B^{i}, for proton abstraction from **7** and **17**, respectively, it is evident that deprotonation of **7** is about an order of magnitude faster than that of **17**. Although the Taft σ^* (or δ_I) values for the effect of an alkoxy substituent and a hydroxy substituent on the acidity of an α carbon are about the same,[22] it has been observed[18] that 9-(methoxymethyl)fluorene ionizes three times as fast as 9-(hydroxymethyl)fluorene. A similar effect may account, at least in part, for the greater reactivity of **7**. In addition, some geometric peculiarity of the bridged structure of **7** may contribute to the faster rate of deprotonation of **7**.

Comparison of the rates of the second step of the elimination reactions of **7** and **17**, expulsion of the leaving group from enolate anions **19** and **18**, respectively, is, of course, considerably more complicated, since the experimentally determined rate constants k_B^{ff} and k_B^{f} are complex functions involving reversible enolate anion formation as well as leaving-group expulsion. Stirling[23,24] has approached this task of determining relative nucleofugalities (values of k_2) for $E1cB_R$ reactions by assuming that k_{-1} is about the same for the two reactions to be compared and then calculating ratios of k_{obsd}/k_1. In the present context, this approach involves a comparison of k_B^{ff}/k_B^{fi} for **7** with k_B^{f}/k_B^{i} for **17**. When these ratios were calculated from the data in Tables I and II, the alkoxyl group of **7** is found to be, on the average, ca. 25 times better than the hydroxyl of **17** as a leaving group.

The two leaving groups in question are, of course, quite different in structure, and it is difficult to estimate their inherent relative nucleofugalities in the absence of strain, because there is a dearth of information about ^-OR as a leaving group when R is larger than methyl. Ethoxide ion, which is slightly more basic than hydroxide ion,[25] has been found to be just threefold better than hydroxide ion as a leaving group in a system in which it was suggested that departure of ^-OH was retarded by intramolecular hydrogen bonding.[26] It seems likely that the alkoxide ion leaving group in **19** is more basic than ethoxide, and that general acid catalysis of its expulsion is less effective for steric reasons than general acid catalysis of the breakdown of **18**, so that the ratios of ca. 25 calculated above probably underestimate the greater nucleofugality of the bridged leaving group in **19**.

The Brønsted β values observed for the reactions of **7** and **17** are also consistent with there being a better leaving group in **17**. The β values of 0.54 for **17** and 0.47 for **7** for rate-limiting general base catalyzed proton removal are quite similar. The β values of 0.50 for **17** and 0.67 for **7** for rate-limiting general acid catalyzed expulsion of the leaving groups from **18** and **19** should be interpreted as $\alpha = 1 - \beta$, since they reflect transfer of a proton from BH^+ to the leaving group. The resulting α of 0.50 for **17** and 0.32 for **7** suggest that the latter has an earlier transition state for the second step, as would be expected with a better leaving group.

In conclusion, although it is not possible to determine accurately the rates of expulsion of the two leaving groups, the one in **19** does seem to possess enhanced reactivity. As in the case of lactone **1**,[1] this is most reasonably ascribed to strain in the propellane-like structure of **7**. An analogous observation of enhanced reactivity in the intramolecular β-elimination reaction of ethyl tetrahydrofurfuryl sulfone has previously been explained similarly by Palmer and Stirling[27] on the basis of strain in a five-membered ring.

Experimental Section

All reactions except hydrolyses were run under nitrogen. Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer as KBr pellets for solids and as thin films for liquids. ^1H NMR spectra were recorded on a Perkin-Elmer R-24 instrument with $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded on a JEOL FX-600 instrument in 1.7% solutions with $CDCl_3$ as solvent and internal standard. Shifts are reported in ppm downfield from Me_4Si. Mass spectra were determined on a Finnegan Model 4000 mass spectrometer by Christopher Hill or Richard Abbott. UV spectra were recorded on a Cary 219 spectrophotometer. Determinations of pH were made on a Corning Model 130 pH meter equipped with a Fisher Microprobe Combination Electrode or a Markson Phleximark Pencil Combination Electrode. Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm plates coated with 1-mm-thick layers of silica gel PF (254 + 366) (EM). UV light was used to visualize preparative TLC plates. Qualitative TLC was performed on 5 × 20 cm plates coated with a 0.25-mm silica gel HF (254 + 366) (EM) or precoated silica gel GHLF plates (Analtech). Qualitative TLC plates were visualized by UV light and by spraying with a 5% solution of phosphomolybdic acid (Fisher) in 2-propanol followed by heating at 140 °C. THF was dried by distillation from $LiAlH_4$. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

3-Hydroxy-11-oxatricyclo[4.4.3.0^{1,6}]tridecan-12-ones (8). To a solution of 0.589 g (2.83 mmol) of **1**[1,2] in 10 mL of THF at 0 °C was added 10 mL of 3.75 M ethereal $Zn(BH_4)_2$,[5] prepared by the method of Yoon and co-workers.[6] The mixture was stirred at 0 °C for 1 h, and then saturated $NaHCO_3$ solution was added dropwise until gas evolution ceased. The resulting suspension was filtered, and the precipitate was washed with ether. The ethereal layer of the filtrate was separated, dried over Na_2SO_4, and evaporated to give 0.601 g of yellow oil. Preparative TLC (1:1 ether/chloroform) yielded two fractions. The less polar gave 0.213 g of crystals: mp 130–132 °C; ^1H NMR δ 4.0 (br s, 1 H), 1.5–2.2 (m), 2.7 (s), 3.0 (s); IR 3509, 1754 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.62; H, 8.62. The more polar fraction was 0.153 g of clear oil which crystallized upon trituration with ether to afford 0.153 g (26%) of crystals: mp 87–89 °C; ^1H NMR δ 3.6 (br s, 1) 2.54 (s), 2.7 (s), 1.5–2.2 (m); IR 3333, 1754 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.49.

Attempted Reduction of 8. In a typical procedure, 0.089 g (0.424 mmol) of mixture **8** was dissolved in 10 mL of anhydrous dimethoxyethane. To this was added 1.5 mL (12.2 mmol) of BF_3–Et_2O (Eastman, freshly distilled) and then a solution of 0.016 g (0.428 mmol) of $NaBH_4$ in dimethoxyethane dropwise at 0 °C. The resulting mixture was gradually warmed to 70 °C and stirred for 72 h. During this time the course of the reaction was monitored by TLC (3:1 ether/chloroform), which showed that small amounts of several less polar products were being formed. After 72 h several drops of 10% HCl were added, and the reaction mixture was saturated with NaCl and extracted with ether (3 × 15 mL). The combined ether fractions were washed with 5% $NaHCO_3$ solution (2 × 3 mL), dried over $MgSO_4$, and concentrated to afford 0.173 g of brown oil. Preparative TLC (hexane) yielded several products, but none of these showed the strong IR absorption at 1030 cm^{-1} which was subsequently observed in the IR spectrum of **7**.

One reaction was run with a 10-fold excess of $BH_3{\cdot}THF$ (Aldrich) in place of $NaBH_4$ and BF_3, but with equal lack of success.

1-((Carbomethoxy)methyl)-3,3-(ethylenedioxy)bicyclo[4.4.0]dec-6-ene (12). A solution of 0.286 g (1.27 mmol) of **10**,[2] 0.170 g (2.93 mmol) of ethylene glycol, and 0.012 g (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 20 mL of benzene was refluxed through a column containing a thimble filled with 4-Å molecular sieves which had been activated by being heated at 325 °C for 18 h. After 4.5 h, TLC (2:1 hexane/ether) showed only a trace of **10** remaining. The mixture was cooled, washed with 5% aqueous $NaHCO_3$ solution (2 × 10 mL), and dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford 0.316 g of crude oily **12**. Preparative TLC (2:1 hexane/ether) gave 0.204 g of **12** as an oil which solidified on cooling to give **12**: mp 33.5–37.5 °C; ^1H NMR δ 1.3–2.8 (m, 14), 3.6 (s, 3), 3.9 (s, 4), 5.45 (q, 1); IR 1740, 1200, 1090 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.57; H, 8.32.

3,3-(Ethylenedioxy)-10-(2-hydroxyethyl)-$\Delta^{8,9}$-octalin (13). A solution of 0.329 g (1.24 mmol) of **12** in 5 mL of anhydrous ether was added to a stirred suspension of 0.113 g (2.97 mmol) of $LiAlH_4$ in 10 mL of

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anhydrous ether. After the mixture was stirred for 30 min, several drops of concentrated KOH solution were added, followed by 5 mL of water. The mixture was filtered through a sintered-glass funnel, and the precipitate was washed with ether. The organic layer of the filtrate was separated, the combined organic fractions were dried over $MgSO_4$, and the solvent was evaporated to afford 0.289 g of clear oily **13**, which was triturated with hexane and cooled at -10 °C to afford 0.285 g (97%) of **13**, mp 61–64 °C. Recrystallization from 2-methylbutane gave 0.246 g (83%) of **13**: mp 68–69 °C; ^1H NMR δ 1.2–2.4 (m, 14), 3.6 (t, 2), 3.85 (s, 4), 5.4 (q, 1); IR 3270, 1100 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.55; H, 9.43.

11-Oxatricyclo[4.4.3.0^{1,6}]tridecan-3-one (7). A solution of 0.0954 g (0.401 mmol) of crystalline **13** in 4 mL of methanol and 1 mL of 10% aqueous HCl was refluxed for 30 min. The mixture was cooled and extracted with ether (3 × 5 mL), and the combined ether extracts were dried over $MgSO_4$ and concentrated to give 0.0924 g of yellow oil. Preparative TLC (1:1 hexane/ether) afforded 0.0576 g (74%) of clear oil which solidified upon standing at -10 °C to afford **7**, mp 39–43 °C. Recrystallization from 2-methylbutane gave 0.0553 g (71%) of **7**: mp 45–45.5 °C; ^1H NMR 1.1–2.4 (m), 1.95 (t, J = 11 Hz), and 3.96 (t, J = 11 Hz); IR 1720, 1030 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.16, H, 9.33.

3,3-(Ethylenedioxy)-10-(2-methoxyethyl)-Δ^{8,9}-octalin (15). To a suspension of 0.484 g (10.0 mmol) of NaH (50% oil dispersion, Alfa) in dry THF was added a solution of 0.160 g (0.825 mmol) of **13** in 5 mL of THF. The mixture was stirred at room temperature for 15 min, and then a solution of 0.1 mL (1.60 mmol) of methyl iodide (Aldrich) in 5 mL of THF was added dropwise. The mixture was heated at reflux for 7 h and then diluted with 1 mL of methanol followed by 10 mL of water. Most of the organic solvent was removed by rotary evaporation, and the aqueous layer was saturated with NaCl and extracted with ether (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give 0.168 g (89%) of crude **15** as a clear oil. Preparative TLC (1:1 hexane/ether) afforded 0.135 g(65%) of **15**: ^1H NMR 1.2–2.5 (m), 3.4 (s, m, 5), 4.0 (s, 4), 5.4 (m, 1); IR 1100 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; M, 9.59. Found: C, 71.43; H, 9.53.

10-(2-Methoxyethyl)-Δ$^{1(9)}$-decal-2-one (16). A 0.152-g (0.603 mmol) sample of **16** was refluxed for 30 min in a mixture of 5 mL of methanol and 1 mL of 10% aqueous HCl. The methanol was removed by distillation, and 10 mL of water was added. Extraction with ether (3 × 10 mL), drying over $MgSO_4$, and concentration gave 0.136 g (100%) of **16** as a clear oil. Preparative TLC (2:1 ether/hexane) of 0.042 g of this **16** afforded 0.040 g (95%) of **16** as a clear oil: IR 1685, 1625, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.84; H, 9.59.

1α-Deuterio-9-hydroxy-10-methyl-*cis*-decalone (22). Reduction of 10-methyl-1,9β-epoxy-2-decalone, prepared as described previously,[3] with $LiAlD_4$ (Stohler) yielded a mixture of epimeric alpha C_1, C_2-d_2, 2,9-dihydroxy-10-methyldecalins (40%): IR 3400, 2170 cm^{-1}. Jones oxidation of this mixture, as previously described for the heptadeuterated substrate,[10] yielded 66% of **22**: mp 120–121 °C; IR 3380, 1710 cm^{-1}.

Kinetics. All of the kinetic experiments were performed as described previously[1] except for the measurement of the rate of proton removal from **7** in D_2O which was determined as follows. For each of the two experiments, a solution of 0.8 M Dabco was prepared in D_2O (Aldrich, 99.8% D), and DCl (20% in D_2O, Diaprep) was added until the pH of the solution was indicated by pH meter to be 9.0. For each experimental sample, 0.075 g of **7** was dissolved in 1–2 mL of MeOD (Stohler, 99% D) in a 25-mL volumetric flask. To this was added 10 mL of D_2O and 4 mL of 2.0 M KCl in D_2O. Immediately, to initiate the reaction, 5 mL of the 0.8 M Dabco buffer was added, and the solution was diluted to 25 mL with D_2O. Samples were run for 2, 5, 10, and 15 min in one experiment and for 1, 3, 4, 7, and 15 min in the other experiment. The apparent pH of each sample was measured at the end of the reaction period, at which time the solution was mixed with 2 mL of DCl (4% in D_2O) and rapidly extracted with anhydrous ether (3 × 25 mL). The combined extracts were dried over $MgSO_4$ for 1 h and evaporated to give 0.04–0.07 g of residue which was recrystallized from hexane prior to analysis.

The pD of the solutions was calculated by adding 0.4 to the apparent pH.[28] The pK_a of Dabco in D_2O was determined to be 9.7 by half-neutralization at 25 °C and μ = 0.4 (KCl).

In order to determine the accuracy of ^{13}C NMR for measuring the extent of deuterium substitution, solutions were made of weighed amounts of hydroxy ketones **17**, **20**, and **22**, totaling 0.05 g in 3 mL of $CDCl_3$, and ^{13}C NMR spectra were recorded. The amount of undeuterated **17** present in each sample was calculated by comparing the ratio of the integrated intensities of signals at 51.19 ppm (C-1) and 37.7 ppm for a solution of pure **17** to the ratio of the intensities of the same signals for each mixed sample. The percent of **17** determined in this manner for each sample agreed with the known composition of the samples to within ±5%.

The products of the deprotonation of **7** were analyzed by both ^{13}C NMR and by mass spectroscopy. The mass spectroscopy results were obtained by correcting the integrated intensities of the peaks at m/e 194 and 195 to allow for natural abundance ^{13}C contribution to the M + 1 peak and then calculating the percent remaining parent peak at 194. The mass spectroscopy results agreed within ±5% to the ^{13}C NMR results, except for the samples taken at 10 and 15 min, for which the NMR integrations showed no detectable signal at δ 48.05, while the mass spectra showed 5–8% of the parent peak at 194 remained. Plots of ln (% **7** at t/% **7** at $t = 0$) vs. time for each experiment were linear for the mass spectroscopy results and linear for the ^{13}C NMR results for the samples taken before 10 min and gave $k_{obsd} = 3.4 \times 10^{-3}$ and 3.0×10^{-3} s^{-1}.

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Registry No. 1, 72542-12-2; **7**, 91296-00-3; **8** (isomer 1), 91296-01-4; **8** (isomer 2), 91382-96-6; **10**, 18963-05-8; **12**, 91296-02-5; **13**, 91296-03-6; **14**, 91296-04-7; **15**, 91296-05-8; **16**, 91296-06-9; **17**, 4707-07-7; **22**, 91296-07-0; 10-methyl-1,9β-epoxy-2-decalone, 22241-36-7.

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