converted to 24(*S*),25-epoxycholesterol (**3**),[4] which we now know to be a natural product of mammalian steroid biosynthesis,[26] but that **3**, at least in RLH, is not reduced to **5**.[4] The enzymic conversion of epoxide to alcohol which we sought to detect occurs instead with 24,25-epoxy steroids having the unnatural 24*R* configuration. Further investigation of this novel facet of enzyme chemistry will include the use of isotopically labeled NADPH to determine whether that reagent is indeed the source of the hydrogen introduced at C-25. It will also be of interest to see whether an inhibitor of the reduction of the $\Delta^{24,25}$ double bond, such as triparanol,[27] will inhibit reduction of the 24(*R*),25-epoxide.

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The pK_a of Acetone: A Kinetic Method for Determining the pK_as of Ketones in Aqueous Solution

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The enolization of simple ketones has long been recognized as mechanistically important and has been extensively studied.[2] Recently we reported some investigations concerning the equilibrium constants for such enolization.[3-5] In the course of these studies we realized[4] that implicit in some pioneering studies by Bartlett[6,7] was a potential method for determining the pK_a of simple ketones in water. Such determinations have not been possible by any direct method because simple ketones are far less acidic than water itself, and the available indirect methods,[8] although they have led to values which are widely accepted,[9] are necessarily lacking in rigor. Bordwell et al.[10] have determined pK_a values for simple ketones by direct methods in dipolar aprotic solvents, but there is a large and unknown solvent shift in pK_a on going from dipolar aprotic solvent to water[11] so that these values do not constitute a solution to the problem for aqueous solution. Wirz has reported[11a] a flash spectrophotometric method which gives enol pK_as and might give pK_as of ketones with a suitable chromophore; thus far it has only been applied to acetophenone.

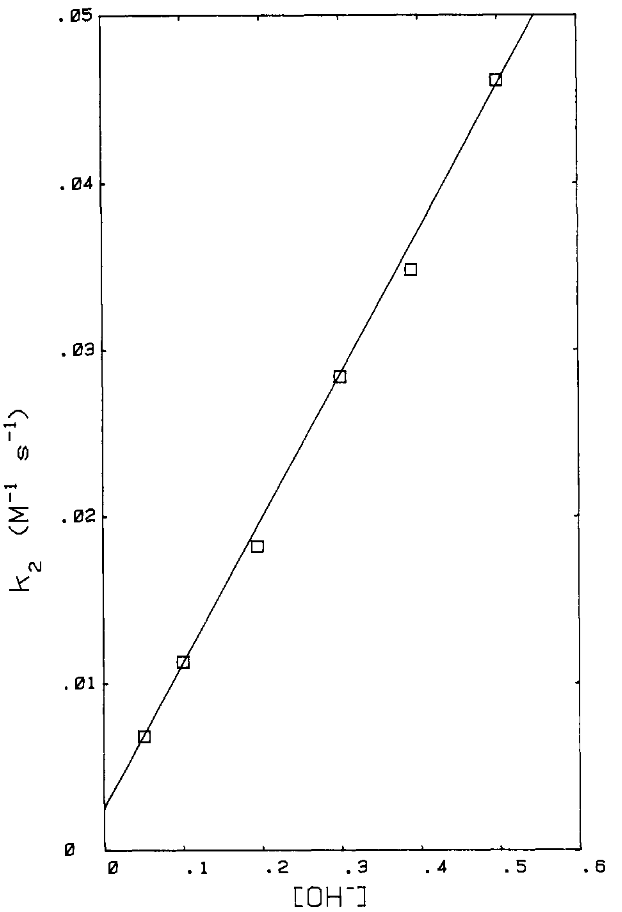

Figure 1. Second-order rate constants for the reaction of acetone with hypochlorite as a function of hydroxide concentration. Reactions were carried out with $[\text{acetone}]_0 \simeq 3 \times 10^{-4}$ M and $[\text{OCl}^-]_0 \simeq 5 \times 10^{-3}$ M. The line was fitted by least squares: $k_2 = 0.0025 \pm 0.0007 + (0.0869 \pm 0.0033)[\text{OH}^-]$.

Bartlett and Vincent[7] discovered that in alkaline solution the rate of chlorination of ketones was first order in ketone and first order in hypochlorite (in alkaline solution Cl_2 is essentially completely converted to Cl^- plus OCl^- [12]) and of mixed zero and first order in hydroxide. The term in the rate law first order in hydroxide is simply interpreted as the reaction of enolate ion with OCl^-. The term in the rate law zero order in hydroxide is kinetically ambiguous; it could represent either reaction of the enol with OCl^- or reaction of the enolate with HOCl. Since the slope and intercepts of plots of apparent second-order rate constants against hydroxide concentration are of comparable magnitude, and the enol should be much less reactive than the enolate toward a relatively feeble halogenating agent such as OCl^-, the first possibility appears very improbable.[13] Since it is known that enols react with halogens at diffusion-controlled rates,[14] and that enolates are more reactive than enols, and since it appears probable that HOCl will not be drastically less reactive than Cl_2, it seemed plausible to propose that the reaction of enolate with HOCl will also be diffusion controlled. In support of this speculation, it should be recalled that Bell and Yates,[15a] found that for diethyl malonate,

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(13) If the intercept were due to reaction of enol with OCl-, the microscopic rate constant would have to be comparable to or even larger than the microscopic rate constant for reaction of the enolate with OCl^-: this seems unlikely.

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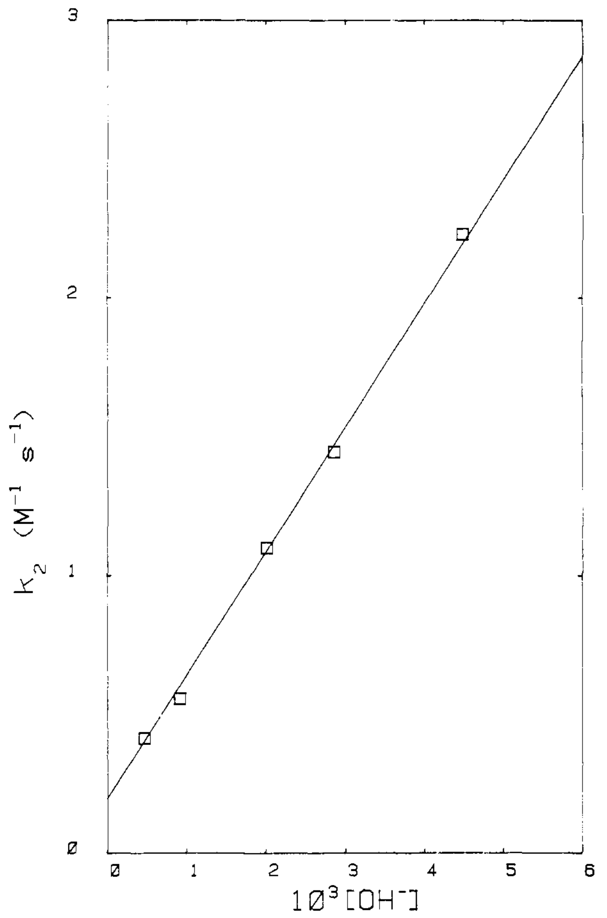

Figure 2. Second-order rate constants for the reaction of acetone with hypobromite as a function of hydroxide concentration. Reactions were carried out with $[\text{acetone}]_0 \simeq 10^{-3}$ M and $[OBr^-] \simeq 10^{-4}$ M. The line was fitted by least squares: $k_2 = 0.132 \pm 0.033 + (499 \pm 15)[OH^-]$.

which has a pK_a between 3 and 6 log units more acidic than that of acetone, the rate of reaction of Cl_2 with the enolate was close to diffusion control, and HOCl was of similar reactivity. If this be so, then the apparent rate constant for the term zero order in hydroxide is a function only of the rate constant for diffusion together of two species in water, the pK_a of HOCl and the pK_a of the ketone. Since only the last value is unknown, it can at once be calculated.

We have reported that the results of Bartlett and Vincent[7] lead to reasonable pK_a values for acetone and acetopheone.[4] We now wish to report that the speculation has been tested and appears to be correct. Since by hypothesis the reaction of the enolate is diffusion controlled for HOCl, it must also be diffusion controlled for HOBr. If then the kinetics of bromination lead to the same pK_a for a ketone as the kinetics of chlorination, the hypothesis is confirmed. This test is not experimentally feasible for iodination under the sorts of conditions which we have employed. Our kinetic data are shown in Figures 1 and 2;[15b] in both cases the intercepts are undeniably different from zero. When the pK_a values for acetone are calculated, using $pK_a = \log k_{\text{diffussion}} + pK_a^{\text{HOX}} - \log$ (intercept) and making due allowance for the difference in pK_a values of the two hypohalous acids, the results are 19.36 ± 0.51 (chlorination) and 18.79 ± 0.51 (bromination).[16] These values are identical within the precision with which the pK_a can be calculated and are close to the traditional value of 20 deduced by indirect arguments based on rate–equilibrium correlations by Bell.[8] On close examination the intercept for hypobromite appears larger than would have been expected relative to that for hypochlorite. The relevant comparison is for $pK_a^{\text{HOX}} - \log$ (intercept) which is equal to $pK_a^{\text{ketone}} + \log k_{\text{diffusion}}$ by our hypothesis. The actual values for $pK_a^{\text{HOX}} - \log$ (intercept) are 10.13 ± 0.12 for HOCl and 9.51 ± 0.11 for HOBr. The difference is small but greater than experimental error. However, rate constants for reactions which are considered to be diffusion controlled in water, i.e., proton transfers between electronegative atoms in the thermodynamically favored direction,[22] show considerable variation. For oxy anions reacting with H_3O^+, k varies from 3.1×10^{10} to $5.1 \times 10^{10}\ M^{-1}\ s^{-1}$;[22] for amines plus H_3O^+, k varies from 1.5×10^{10} to $4.3 \times 10^{10}\ M^{-1}\ s^{-1}$.[22] (These values are all larger than $10^{10}\ M^{-1}\ s^{-1}$ because of the high mobility of H_3O^+.[22]) Thus the variation in $pK_a^{\text{HOX}} - \log$ (intercept), although it is a source of concern, is no greater than the variation observed in sets of apparently closely related reactions.[23] We conclude that our method is approximately valid within the uncertainty of our knowledge of diffusion rates.

There is a dramatic increase in reactivity on going from OCl^- to OBr^-. The rate constants for reaction with the enolate of acetone are $2.0 \times 10^4\ M^{-1}\ s^{-1}$ for OCl^- and $2.8 \times 10^7\ M^{-1}\ s^{-1}$ for OBr^-. A similar effect has been observed for diisopropyl ketone.[24] The large value for the rate constant for the reaction of OBr^- was a source of experimental difficulties, since it was necessary to work at very low hypobromite concentrations in order to have halogenation the rate-limiting step and at very low hydroxide concentrations in order to make the term zero order in hydroxide a significant contributor to the rate law. Since IO^- is expected to be even more reactive, these problems would be even more severe, and in addition, the extinction coefficient for IO^- is much smaller than those for the other hypohalites.[25]

The method which we have described promises to provide a general solution to the problem of determining pK_a values for simple ketones; experiments to test whether this can in fact be done are under way.

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Registry No. Acetone, 67-64-1; HOCl, 7790-92-3; HOBr, 13517-11-8; OCl^-, 14380-61-1; OBr^-, 14380-62-2.

Supplementary Material Available: Tables of experimental conditions and pseudo-first-order rate constants (2 pages). Ordering information is given on any current masthead page.

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(16) (a) Uncertainties in pK_a are based on propagation of error calculations,[17] using the estimated standard deviation for the intercept from the least-squares treatment, and an uncertainty of ±0.5 in $\log k_{\text{diffusion}}$ which is taken as 9.23.[18,19] (b) A value of 18.8 has independently been determined by a kinetic method using halogenation in buffered solutions: Jencks, W. P.; Tapuhi, E., private communcation. We thank Drs. Jencks and Tapuhi for communicating this result to us prior to publication.

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(19) A value of 9.7 has been suggested as an average of experimental values[20] but is based on proton transfers and cation-anion recombinations, both of whhich may be faster than reaction of neutrals; a theoretical value for spherically symmetrical reactants is 9.97;[21] for nonspherical reagents the value must be lower, though it is difficult to say how much.

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(23) Although the observed differences in $pK_a^{\text{HOX}} - \log$ (intercept) may represent variation in the rates for diffusion-controlled reactions, we must consider other possibilities. One possible explanation is that the reaction of HOCl with the enolate is close to but not quite at the diffusion limit. This would mean that a pK_a value calculated from hypochlorite kinetics would be spuriously high; this appears unlikely because the value obtained is already more acidic than anticipated. Another possibility is that the intercept for hypobromite represents reaction both of HOBr with the enolate and of OBr^- with the enol. In the case of OBr^- this latter reaction path is more likely to be significant than in the case of OCl^- because of the much greater reactivity of OBr^-, which reacts with the enolate at a rate close to the diffusion limit. The question of the true origin of the observed variation in $pK_a^{\text{HOX}} - \log$ (intercept) is an ongoing cause for concern and requires further investigation.

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