imidazole to nickel at the 3 position eliminates this term. The uncatalyzed term in eq 1 was ascribed to attack of the anion by I^+, which would demand a strict $(I^-)^{-2}$ dependence of the rate on iodide ion concentration.[10] This explanation is untenable in the iodination of the nickel(II) complex of imidazole because a more complicated dependence of the rate on iodide ion concentration is found. Since the activation parameters for the ligand and complex are so similar, it seems unlikely that coordination of imidazole leads to a change in the iodinating species, so that the iodine molecule probably is the attacking species in the iodination of both imidazole and its nickel(II) complex. The catalytic term in eq 1 is then due to the base catalysis of the reaction by the imidazole molecule,[4] which cannot occur when the basic site is coordinated to nickel(II).

Relative Rates of Base-Catalyzed Enolization of 2-Butanone[1,2]

J. Warkentin and O. S. Tee

Contribution from the Department of Chemistry, McMaster University, Hamilton, Ontario, Canada.

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Abstract: Base-catalyzed enolization at the α carbons of 2-butanone in D_2O and in D_2O–dioxane mixtures was followed by nmr. In D_2O the reactivity of the methylene protons exceeds slightly that of the α-methyl protons for the catalyst OD^-. With $p\text{-}O_2NC_6H_4O^-$ and AcO^- the effect increases in that order. The accelerating effect of the β-CH_3 substituent can be accounted for in terms of a transition state that resembles enol and not enolate.

A large amount of work has been reported concerning substituent effects on rates of enolization of ketones. If the substituent at α-carbon is alkyl, it appears that the rate of base-catalyzed enolization is reduced while that of acid-catalyzed enolization is accelerated, relative to the corresponding rate for unsubstituted ketone. This generalization is based on over-all rates of enolization of aryl alkyl ketones,[3] of dialkyl ketones,[4–6] and of ring-substituted acetophenones,[7–10] as well as on a limited number of experiments in which relative rates at two sites in the same molecule were observed.[11–13] While it is clear that the alkyl-group effect changes sign between strongly basic and strongly acidic media, the borderline region does not appear to be well defined. In order to determine the dependence of substituent effects in enolization on base strength and on medium, we began a study of relative rates of H–D exchange into two α sites of simple dialkyl ketones.

Experimental Section

Materials. Methyl ethyl ketone (Fisher, reagent grade) was distilled through a helices-packed column. The fraction distilling at 78–79° showed no extraneous signals in the nmr and gave only one peak in the gas chromatograph. Deuterium oxide was used as supplied by Merck Sharp and Dohme. Dioxane (Fisher, purified grade) was also used as supplied.

Anhydrous NaOAc (BDH, reagent grade) was finely ground and then heated at 160° for 2 days. The material was cooled in a desiccator. Sodium p-nitrophenoxide was prepared from p-nitrophenol (mp 113–114°, benzene) by shaking 13.9 g of the phenol, in 50 ml of ether, with 50 ml of approximately 2 N NaOH. The orange-yellow curd formed in the aqueous layer was filtered, washed three times with ether and once with water, and recrystallized three times from 95% ethanol, in which the salt but not the phenol is sparingly soluble. The yellow crystals of the tetrahydrate were heated at 160° for 2–3 hr to form anhydrous, red sodium p-nitrophenoxide.[14]

Solutions of sodium deuteroxide were prepared by dissolving sodium hydroxide (BDH, reagent grade) in D_2O. Aliquots were titrated with standard acid to the bromocresol green end point. Solutions of p-nitrophenoxide were titrated using the bright yellow p-nitrophenoxide itself as indicator. Solutions of sodium acetate were prepared in volumetric flasks from the anhydrous salt. All solutions were stored in bottles sealed with rubber serum stoppers.

Procedures. Exchange was followed to one half-life or more by integrating the nmr signals due to the 1 and 3 positions,[15] relative to that of the β-methyl group as internal standard, with a Varian A-60 instrument. Exchanges were carried out in the probe and also in constant temperature baths. The 0° runs were sampled at intervals, and the samples were rapidly quenched by addition to, and shaking with, a phosphate buffer. There was no detectable exchange in such buffered solutions over a period of 16 hr which was much longer than the analysis time. Reactions carried out at 59.2° were quenched by chilling to 0°. Integrations were then performed between 0 and 35°, with negligible exchange during the analysis time.

Results

Pseudo-first-order rate constants and their standard deviations were obtained by fitting experimental values of N_H^t and t to the equation $N_H^t = N_H^0 e^{-kt}$ by means of a nonlinear, least-squares program for the IBM 7040 computer. In the equation N_H^t and N_H^0 represent, respectively, the number of α-hydrogens at a given site at time t and at time zero, relative to the internal standard $N_{\beta\text{-}CH_3} = 3$. Good fits were obtained, even for exchanges followed to two half-lives, suggesting that the secondary isotope effect is small. Representative data

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[1] Financial support of this work by the National Research Council of Canada is gratefully acknowledged.

[2] A preliminary communication of some of this work appeared in *Chem. Commun.*, 7, 190 (1966).

[3] D. P. Evans and J. J. Gordon, *J. Chem. Soc.*, 1434 (1938).

[4] H. M. E. Cardwell, *ibid.*, 2442 (1951).

[5] H. M. Dawson and R. Wheatley, *ibid.*, 2048 (1910).

[6] C. F. Cullis and M. S. Hasmi, *ibid.*, 2512 (1956).

[7] W. S. Nathan and H. B. Watson, *ibid.*, 217 (1933); 890 (1933).

[8] D. P. Evans, V. G. Morgan, and H. B. Watson, *ibid.*, 1167 (1935).

[9] V. G. Morgan and H. B. Watson, *ibid.*, 1173 (1935).

[10] D. N. Kursanov, V. I. Zdanovich, and Z. N. Parnes, *Proc. Acad. Sci. USSR, Chem. Sect.* (*English Transl.*), **128**, 899 (1959).

[11] P. D. Bartlett and J. R. Vincent, *J. Am. Chem. Soc.*, **55**, 4992 (1933).

[12] P. D. Bartlett and C. H. Stauffer, *ibid.*, **57**, 2580 (1935).

[13] H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

[14] "Handbook of Chemistry and Physics," 45th ed, The Chemical Rubber Co., Cleveland, Ohio, 1964, p 870.

[15] O. S. Tee and J. Warkentin, *Can. J. Chem.*, **43**, 2424 (1965).

Table I. Rate Data for H–D Exchange of 2-Butanone in D_2O–OD^- [a]

Temp, °C	Ketone, mole/l.	OD^-, mole/l.	$k^{obsd} \times 10^4$ sec^{-1} $k_{CH_2}{}^{obsd}$	$k_{CH_3}{}^{obsd}$	$k_{CH_2}{}^{obsd}/k_{CH_3}{}^{obsd}$
~35[b]	1.67	0.0406	24.0 ± 1.0	22.7 ± 0.6	1.06 ± 0.07
~35[b]	1.65	0.0094	5.35 ± 0.10	5.23 ± 0.04	1.03 ± 0.03
~35[b]	1.40	0.0205	13.6 ± 0.3	13.6 ± 0.1	1.00 ± 0.02
0.00 ± 0.05[c]	2.2	0.0393	1.74 ± 0.07	1.82 ± 0.04	0.95 ± 0.06
0.00 ± 0.05[c]	2.2	0.0393	1.78 ± 0.12	1.71 ± 0.04	1.04 ± 0.09
0.00 ± 0.05[c]	2.2	0.0393	1.93 ± 0.18	1.88 ± 0.08	1.03 ± 0.12
0.00 ± 0.05[c]	1.1	0.0393	2.50 ± 0.15	2.09 ± 0.05	1.20 ± 0.10

[a] Solutions were homogeneous under the reaction conditions. [b] Reaction was carried out in an nmr tube in the A-60 probe. As a result of the uncertainty in temperature, only the ratio of rate constants is reliable. [c] Samples were withdrawn at intervals and reaction was quenched by addition of a buffer as described in the Experimental Section.

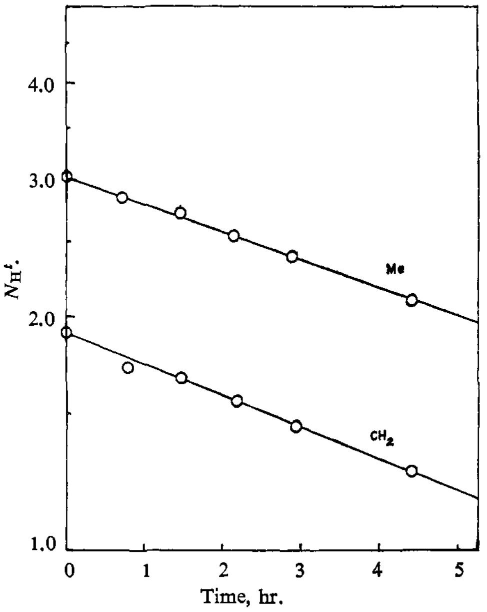

Figure 1. Exchange of methyl ethyl ketone in 0.103 *M* p-NO_2PhONa–D_2O at 59.2°.

are plotted in Figure 1, in which each point represents the average of four or five integrations. Table I lists pseudo-first-order constants obtained for deuterioxide catalysis.

Catalysis by acetate and *p*-nitrophenoxide is complicated because of hydrolysis of these weak bases to their conjugate acids and deuterioxide ion. The observed pseudo-first-order rate constant is then given by eq 1.[16] If the degree of hydrolysis, α, is small so that $1 - \alpha \approx 1$, then eq 2 and 3 hold, where K_d is the hydrolysis constant of the weak base B^- in heavy water and where C is its stoichiometric concentration. The catalytic constant of a weak base can then be obtained as the intercept of a plot of k^{obsd}/C against $C^{-1/2}$. Such a plot, pertaining to acetate ion catalysis, is reproduced in Figure 2. The linearity of the plots suggests that a term in $[B^-][BD]$ is unimportant. Data for both acetate and *p*-nitrophenoxide catalysis are listed in Tables II and III, respectively.

$$k^{obsd} = k^{B^-}[B^-] + k^{BD}[BD] + k^{OD^-}[OD^-] \qquad (1)$$

$$\alpha = (K_d/C)^{1/2} \qquad (2)$$

$$k^{obsd}/C = k^{B^-} + (k^{BD} + k^{OD^-})(K_d)^{1/2}/C^{1/2} \qquad (3)$$

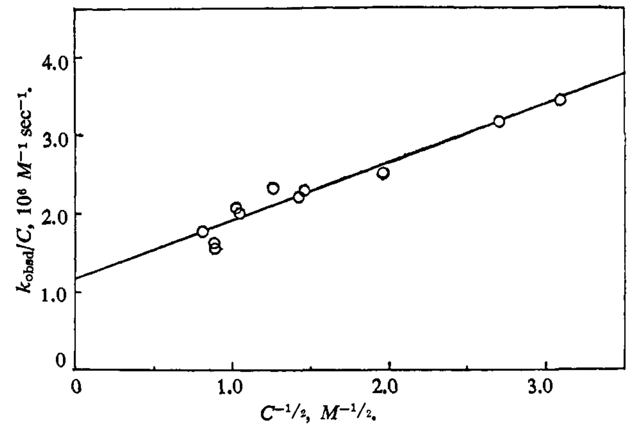

Figure 2. Plot of $(k_{CH_2}{}^{obsd}/C)$ *vs.* $(C^{-1/2})$ for AcO^- catalysis at 59.2°.

Table II. Rate Data for H–D Exchange of 2-Butanone, Catalyzed by OAc^- in D_2O at 59.2°; Ketone Concn 1.1 *M*

Stoichiometric base concn, *M*	$k^{obsd} \times 10^7$ sec^{-1} CH_2	CH_3
0.104	3.60	3.19
0.136	4.34	3.88
0.260	6.56	5.75
0.468	10.8	8.68
0.490	11.0	5.94
0.630	14.6	12.0
0.930	19.1	13.4
0.946	19.7	13.9
1.310	21.3	14.3
1.310	20.6	14.8
1.500	26.7	21.5

Table III. Rate Data for H–D Exchange of 2-Butanone, Catalyzed by p-$O_2NC_6H_4O^-$ in D_2O at 59.2°; Ketone Concn 1.1 *M*

Stoichiometric base concn, *M*	$k^{obsd} \times 10^5$ sec^{-1} CH_2	CH_3
0.041	1.30	1.15
0.062	1.53	1.26
0.082	2.14	1.80
0.103	2.50	2.25
0.144	3.09	2.59
0.185	4.18	3.21

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[16] Water, acting either as acid or base, has been omitted from the three right-hand terms by convention. An additional term k_0, for catalysis by water alone, can be shown to be negligible. From data of others,[17,18] the contribution from such catalysis was estimated to be only about 1% of the total rate at 60°.

[17] H. M. Dawson and A. Key, *J. Chem. Soc.*, 543 (1928).

[18] C. G. Swain, *J. Am. Chem. Soc.*, 72, 4578 (1950).

Plotting the data of Tables II and III as described gave, for acetate catalysis, $k_{CH_2} = 11.8 \pm 0.5 \times 10^{-7}$ M^{-1} sec^{-1}, $k_{CH_3} = 5.47 \pm 0.70 \times 10^{-7}$ M^{-1} sec^{-1}, $k_{CH_2}/k_{CH_3} = 2.16 \pm 0.36$, and, for *p*-nitrophenoxide catalysis, $k_{CH_2} = 13.4 \pm 0.7 \times 10^{-5}$ M^{-1} sec^{-1}, $k_{CH_3} = 8.93 \pm 0.78 \times 10^{-5}$ M^{-1} sec^{-1}, $k_{CH_2}/k_{CH_3} = 1.50 \pm 0.21$.

Two medium effects on exchange rate were investigated. Table IV lists rate data for *p*-nitrophenoxide catalysis, as a function of added NaCl, up to 0.2 *M* NaCl. The high concentration of ketone required for reliable nmr integrals prevented investigation of the effect of still higher ionic strength. Table V shows the effect of added dioxane on absolute and relative exchange rates of deuterioxide-catalyzed exchange.

Table IV. Effect of Ionic Strength on H–D Exchange Rates of 2-Butanone in D_2O–*p*-$O_2NC_6H_4O^-$ at 50°; Ketone Concn 1.1 *M*; *p*-$O_2NC_6H_4O^-$, 0.103 *M*

NaCl, *M*	Total salt, *M*	$k^{obsd} \times 10^6$ sec^{-1} CH$_2$	CH$_3$	Ratio $k_{CH_2}{}^{obsd}/k_{CH_3}{}^{obsd}$
0.000	0.103	6.80 ± 1.26	7.74 ± 0.35	0.88
0.052	0.155	7.63 ± 1.32	7.20 ± 0.12	1.06
0.104	0.207	7.98 ± 1.06	7.50 ± 1.70	1.05
0.208	0.311	6.89 ± 1.35	7.27 ± 0.57	0.95

Table V. Effect of Solvent Composition on Rates of H–D Exchange of 2-Butanone Catalyzed by OD$^-$ at 0°; Ketone Concn 1.1 *M;* NaOD, 0.03925 *N*

Medium compn, vol %					
D$_2$O	Dioxane	2-Butanone	$k^{obsd} \times 10^4$ sec^{-1} CH$_2$	CH$_3$	Ratio $k_{CH_2}{}^{obsd}/k_{CH_3}{}^{obsd}$
90	0	10	2.50 ± 0.15	2.09 ± 0.05	1.20 ± 0.10
70	20	10	1.96 ± 0.12	2.14 ± 0.04	0.915 ± 0.073
50	40	10	1.71 ± 0.12	2.10 ± 0.07	0.814 ± 0.083
30	60	10	1.09 ± 0.11	1.79 ± 0.06	0.612 ± 0.083

Discussion

It has been well established for many years that halogenation, racemization, and H–D exchange of ketones have a common rate-determining step. It is also generally accepted that this step is the formation of enol in acid medium and of enolate in strongly basic medium.[19] In principle, then, reaction at α-hydrogen of a ketone can be assigned to one of two broad mechanistic categories; either there is a proton at carbonyl oxygen in the rate-determining step or there is not. Each category encompasses a spectrum of transition states, ranging from conjugate acid of ketone to enol for the former and from ketone to enolate anion for the latter. An operational distinction between these categories is the sign of the charge in the ketonic moiety at the transition state, for this is a factor about which substituent effects give information. Thus all mechanisms leading to enol in the rate-determining step should involve positive or zero charge in the O–C–C system, while those leading to enolate would involve some buildup of negative charge in that system.[20] If one assumes that the inductive effect of an α-alkyl group on enolization rate will reflect the charge situation at the transition state,[21] then such rate effects can be used to obtain information about charge distribution. It is clear that observed rates may need correction for purely statistical factors and for steric factors before they can be used in this way.[22] We next consider such corrections for our system.

What we wish to compare is the inherent reactivity of a properly oriented[23] hydrogen at C$_3$ with that of such hydrogen at C$_1$. Let these reactivities per hydrogen be denoted by $k^H{}_{CH_2}$ and $k^H{}_{CH_3}$, and let P_{CH_2} and P_{CH_3} represent the probabilities, respectively, of finding a given hydrogen of a group in a reactive conformation.[23] Further, let R_{CH_2} and R_{CH_3} define the respective rates of loss of H atoms from the ketone and let [CH$_2$] and [CH$_3$] represent the concentrations of reacting hydrogens, which are directly measured by nmr. We can then write eq 4 and 5 as well as their analogs in which every 2 is replaced by 3. Division gives the relationship between inherent reactivities and observed, pseudo-first-order constants: eq 6, which also holds for bimolecular constants.

$$R_{CH_2} = k^H{}_{CH_2}P_{CH_2}[CH_2][\text{base}] \qquad (4)$$

$$k_{CH_2}{}^{obsd} = k^H{}_{CH_2}P_{CH_2}[\text{base}] \qquad (5)$$

$$k^H{}_{CH_2}/k^H{}_{CH_3} = (P_{CH_3}/P_{CH_2})(k_{CH_2}{}^{obsd}/k_{CH_3}{}^{obsd}) \qquad (6)$$

Inspection of a model of 2-butanone shows that out of six degenerate, staggered, conformations of the α-CH$_3$ group there are two in which a given hydrogen can react, so that $P_{CH_3} = {}^1/_3$. For the methylene group, the six staggered conformations consist of three sets of degenerate pairs. Of these only one set involves skew interactions between the C$_1$ and C$_4$ groups. Two extreme views about these interactions are examined. First one can assume that the conformational energy differences are negligible in both the ground state and the transition state, in which case $P_{CH_2} = {}^1/_3$ also. Second, one might assume that repulsions are large enough in the system to prevent entirely the formation of a *cis* enol,[24] in which case P_{CH_2} would be ${}^1/_4$. These boundaries are those between which the conformational steric effect of the β-methyl group is confined. We are therefore left with the polar effect of the β-methyl group when the correction $k_{CH_2}{}^{obsd}/k_{CH_3}{}^{obsd} < k^H{}_{CH_2}/k^H{}_{CH_3} < 4k_{CH_2}{}^{obsd}/3k_{CH_3}{}^{obsd}$, is applied.

All our data for base-catalyzed H–D exchange in D$_2$O (Tables I, II, and III), even without correction for the steric factor, indicate that the polar effect of β-CH$_3$ is to accelerate rate.[25] The most likely reason for this result is that the α-carbon does not bear negative charge at the transition state. This situation could

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(19) See, for example, H. Schechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Am. Chem. Soc.*, **84**, 2905 (1962).

(20) It may be noted that a negatively charged transition state does not imply that there is much negative charge in the O–C–C system. For example, the transition state for enolization of a ketone by a very strong base in aprotic medium could be very ketone-like and, in a concerted process involving a neutral acid and a negative base, charge accumulation at carbon and oxygen of the developing enol might be avoided altogether.

(21) This appears to be a good assumption, in view of the signs of Hammett σ values and of Brown's σ^+ constants for alkyl groups.

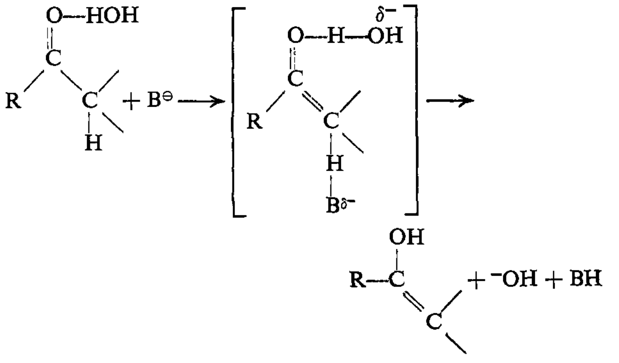
(22) D. M. Bishop and K. J. Laidler, *J. Chem. Phys.*, 42, 1688 (1965).

(23) It is assumed that a C–H bond must be directed perpendicular to the nodal plane of the π system for facile enolization.

(24) The interaction in the ground state should be less than the skew interaction energy in 2-butane (800 cal/mole) because of the 120° angle at sp^2 carbon. Transition states for formation of *cis* and *trans* enol could differ in energy by as much as 1 kcal, which is the difference in heats of hydrogenation of the isomeric 2-butenes.

(25) A second correction for the medium effect is needed. At the concentrations of ketone required for reliable integration in the nmr, there is a medium effect which reduces $k_{CH_2}{}^{obsd}/k_{CH_3}{}^{obsd}$ just like added dioxane reduces that ratio (Table V). We estimate that the ratios in Table I would be at least 1.1 at infinite dilution of ketone.

obtain if the transition state were very ketone-like or if it were enol-like. The former transition state is thermochemically unlikely[26] unless the catalyzing base is stronger than the potential enolate anion. On the other hand the transition state for acid-catalyzed enolization is probably close to enol in geometry.[27] We therefore suggest that even with bases as strong as OD^- in D_2O, enolization of a ketone by a charged base in water should be represented as in eq 7, in which the bracketed species is meant to represent the transition state. All



(7)

our results are in keeping with such a picture. Stabilization of enolic systems by α-alkyl groups has been demonstrated by House and Trost[28] who found that the more highly substituted of a pair of lithium (or potassium) enolates predominates at equilibrium in 1,2-dimethoxyethane. Lithium enolates in such a medium cannot be highly ionic and should, therefore, be fair models for enols. The weaker the base B^-, the more the transition state should resemble enol[29] and the greater should be the alkyl group effect. This expectation is borne out in the higher ratios of catalytic constants (k_{CH_2}/k_{CH_3}) for *p*-nitrophenoxide and for acetate catalysis (*vide supra*). On the other hand, increasing the base strength should have the opposite effect on reactivity ratio. This was demonstrated by working with OD^- at increased activity,[30] brought about by decreasing the water content (Table V). As expected the rate ratio drops with increased dioxane content[31] (Table V).

A further expectation of concerted, base-catalyzed enolization in water is that there should not be much salt effect on rates. Where $B^- = OH^-$, the effect should be particularly small because the charged species produced is the same as the one destroyed. Our data for *p*-nitrophenoxide catalysis in the presence of added salt are not compelling but they are in keeping with expectation.[32]

It should be emphasized that the concerted mechanism for enolization by weak bases like acetate is not new.[33] Further, there is no doubt that there is a definite kinetic preference for attack at the less alkyl-substituted site of an unsymmetrical dialkyl ketone by strong bases in media less acidic than water.[28,34] What is a little unexpected is that the polar effect of an α-methyl group is to enhance enolization rate in water, not only at pH values below and slightly above seven, but also in quite alkaline solutions (pH >12).[35] Our results are of significance to processes such as the haloform reaction, normally carried out in light water, for the D_2O solvent effect[36] on ratios of rates should be very small.

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(26) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(27) Reference 19 and literature cited therein.

(28) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(29) R. F. W. Bader, *Can. J. Chem.*, **42**, 1822 (1964).

(30) There are numerous examples in the literature of this effect. Halide ions, for example, are much more powerful bases in DMSO than in water.

(31) The decrease in over-all rate brought about by adding dioxane can be accounted for, at least qualitatively, in terms of a decrease in concentration of free base. Professor E. Buncel, Queen's University, reported to us in a private communication than the conductivity of NaOH in aqueous medium drops very considerably as the dioxane content is raised from zero to 80%.

(32) The reader is remainded that about half of the catalysis is really due to OD^-, even when p-$O_2NC_6H_4O^-$ is the formal catalyst, because of hydrolysis of the weak base.

(33) C. G. Swain, *J. Am. Chem. Soc.*, **72**, 4578 (1950); W. D. Emmons and M. F. Hawthorne, *ibid.*, **78**, 5593 (1956); C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *ibid.*, **80**, 5885 (1958).

(34) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); D. Caine, *ibid.*, **29**, 1868 (1964).

(35) It is interesting to note that rate enhancement by alkyl substituents has recently been reported by E. T. Harper and M. L. Bender, *J. Am. Chem. Soc.*, **87**, 5625 (1965). They accounted for the result in terms of steric acceleration superimposed upon inductive retardation. Examination of models indicates that there is no relief of steric strain accompanying enolization of 2-butanone at CH_2, so that steric acceleration cannot be invoked in that case.

(36) K. B. Wiberg, *Chem. Rev.*, **55**, 722 (1955).