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Solvent Effects on the Kinetics and Equilibria Associated with the Interconversion of 3-Methylacetylacetone in H₂O–D₂O Mixtures¹

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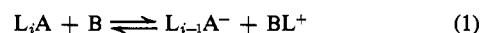
Abstract: The keto–enol and acid dissociation equilibrium constants for 3-methylacetylacetone have been measured in pure H₂O and D₂O at 25.0°. The rates of ionization of the keto form were determined by bromination in H₂O–D₂O mixtures for water and acetate catalysts. Fractionation factors ϕ and degenerate activity coefficients γ at 25.0° were determined for the keto ($\phi = 1.0$, $\gamma = 1.04$), enol ($\gamma = 1.4$), and enolate ($\gamma = 2.0$) forms of the β -diketone. These data are analyzed in terms of Gross–Butler equations containing medium effects terms, thus allowing the determination of the degenerate activity coefficient and the fractionation factor ($\gamma^* = 1.5$ and $\phi^* = 0.35$) for transition states involved in the ionization of the ketone. Fractionation factors are important for a transferred proton in the transition state, *i.e.*, for primary isotope effects, but do not influence equilibrium constants in H₂O and D₂O. Equilibrium constants are influenced predominately by degenerate activity coefficients, particularly for anions where γ 's deviate greatly from unity. Finally there seems to be no simple relationship between the degenerate activity coefficients of the reactants, products, and transition state of a simple proton transfer reaction.

The theory of kinetics of proton transfer in mixed H₂O–D₂O solvents was derived as early as 1936 by Gross and Butler and their coworkers.^{3–6} Further interest in application to mechanism determination was renewed through the review by Purlee in 1959,⁷ and a more recent review is available.⁸

Kingerly and La Mer⁹ were first to recognize that the Gross–Butler equation should be separated into “exchange” and “medium” effects. The importance of medium or transfer effects was also emphasized by Swain and Bader.¹⁰ Halevi, Long, and Paul¹¹ tested the view that variations in equilibrium constants were due entirely to medium effects. For most situations predictions were quite similar to those of the Gross–

Butler equation. Goodall and Long¹² found for the protonation of nitroalkane anions that the neglect of medium effects prevented a reasonable Gross–Butler fit of experimental results, while interpretation by use of medium effect terms was successful. Also, from kinetics in H₂O–D₂O mixtures, they were able to conclude that a water bridge in the transition state of the protonation of nitromethane anions by acetic acid was very unlikely.

This work utilizes the same formulation of the Gross–Butler equation as presented by Goodall and Long. The ratio of the equilibrium constants for



in an H₂O–D₂O mixture, represented by L₂O of atom fraction deuterium n , to the equilibrium constant in pure H₂O is given by the equation

$$\frac{K^{(L_2O)}}{K^{(H_2O)}} = \frac{(1 - n + n\phi_{L_{i-1}A^-})^{i-1}(1 - n + n\phi_{BL^+})}{(1 - n + n\phi_{L_iA})} \times \left(\frac{\gamma_{L_iA}\gamma_B}{\gamma_{L_{i-1}A^-}\gamma_{BL^+}} \right)^n \quad (2)$$

where ϕ , the fractionation factor, is the medium inde-

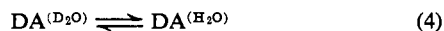
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- (1) Work supported by the Atomic Energy Commission.
- (2) To whom requests for reprints should be sent.
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pendent equilibrium constant for the exchange process in the standard state H_2O



and where γ , the degenerate activity coefficient, is the equilibrium constant for the transfer process

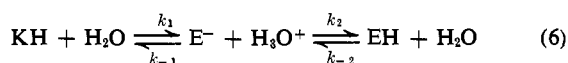


and is related to the free energy of transfer from H_2O to D_2O by

$$\Delta\bar{G}_t^\circ = RT \ln \gamma \quad (5)$$

Kinetics are treated in the same manner by assuming that the reactants are in equilibrium with the transition state. Such a treatment allows the separation of isotope effects into exchange and medium effects.

The system studied is the base-catalyzed halogenation of β -diketones and the accompanying keto-enol equilibrium



where KH is the ketone, E^- the enolate, and EH the enol form. The mechanism of this reaction has been well studied.¹³ The isotope effects for 3-methylacetylacetone¹⁴ and 2-acetylcyclohexanone¹⁵ have been studied by Long and coworkers.

Experimental Section

A. Materials. Light water was redistilled; 99.8% AR heavy water was purchased from International Chemical and Research Corp. and used without further purification. Applied Research Labs of Florida, Inc., synthesized 3-methylacetylacetone from acetylacetone and methyl iodide. 3,3-Dimethylacetylacetone was synthesized in this laboratory. Eastman Organic Chemical supplied the 2-acetylcyclohexanone, and acetylacetone was purchased from Fisher. All of these diketones are subject to decomposition and thus were purified just before use. Solutions of sodium deuteriooxide were prepared by placing sodium in D_2O and concentrations were determined by titrating against weighted potassium hydrogen phthalate. Monodeuterated acetic acid was prepared by hydrolyzing acetic anhydride in D_2O . Carefully distilled 3-methylacetylacetone still contains a small impurity of 3,3-dimethylacetylacetone, which did not interfere with first-order kinetic studies, but which had to be removed for other measurement. Results of zero-order kinetics agreed with first-order kinetics after the ketone had been purified by fractional freezing. This method was also used for equilibrium measurements, but ketones for nmr studies were purified by forming a copper chelate which was purified by fractional crystallization and from which the ketone could be regenerated. All other chemicals were of analytic grade and were used without further purifications.

B. Kinetics. All kinetics were followed by using bromine (in the presence of 0.1 M KBr) as a scavenger except for the reactions involving phosphate buffers which used iodine in order to avoid other halogen-water equilibria found at this pH. Stopped-flow measurements reconfirmed that the bromination of the enol was very fast (complete in 0.3 sec). The ionization of the ketone was followed by observing the disappearance of bromine on a Cary 14 spectrophotometer at 350 μ . One-centimeter cells were used, thermostated at $25.00 \pm 0.05^\circ$ by pumping water through brass cell holders.

Reactions involving light substrate KH in H_2O - D_2O mixtures (represented by L_2O) were followed by injecting approximately 1 μ l of light substrate into a L_2O solution containing approximately 2×10^{-3} M Br_2 , 0.1 M KBr, and 0.1 M NaCl. Buffered solutions were made in the same manner, using NaCl to maintain 0.2 ionic

strength. The first-order reactions were plotted using the Swinbourne¹⁶ technique in order to avoid the use of untrustworthy infinity values. For these reactions the light substrates had been distilled until clear (3-methylacetylacetone, 58° at 10 mm).

For the "equilibrated" reaction where the substrate had been allowed to exchange with the L_2O solution before the addition of bromine, it was necessary to employ zero-order kinetics (with known concentrations of ketone) in order to prevent the disturbance of the deuterium content of the ketone. Carefully purified 3-methylacetylacetone was weighed into a 0.1 M KBr, 0.1 M NaCl, L_2O solution and allowed to equilibrate for approximately 24 hr. Corrections were made for per cent enol. The ketone concentrations were in the vicinity of 4×10^{-2} M. To this was added a small amount of saturated bromine in L_2O to initiate the reaction. Dilution due to the addition of the bromine solution was less than 1%. Rates were in good agreement with those obtained by the first-order technique in pure light water and heavy water.

Rate constants were also obtained for the base ionization of 3-methylacetylacetone in light water for four catalytic species. These values yield a Brønsted $\beta = 0.49$ with water slightly below the line, which is typical of the values obtained for the ionization of related β -diketones.^{13b} The determination of the Brønsted β involved the use of the statistical factors "p" and "q" which correct for identical labile protons of the conjugate acid as well as identical sites for receiving protons of the conjugate base.

C. Equilibria. The per cent enol of an aqueous solution of a β -diketone can be measured by adding excess bromine and rapidly titrating the bromine which remains after reaction of the enol. In the present case a Durrum stopped flow apparatus was employed to measure the loss in bromine concentration due to the fast attack on the enol, before further ketone could isomerize. Carefully weighed substrate was equilibrated in 0.1 M KBr, 0.1 M NaCl, and light or heavy water for 24 hr. Bromine in 0.1 M KBr and H_2O was standardized by injecting it alongside a 0.1 M KBr solution and reading the per cent transmittance. Then a standardized bromine solution was injected into the stopped flow apparatus alongside the equilibrated ketone solution. Bromination of the enol was complete after 300 msec. Formation of further enol from the ketone was not observed until 2 sec after mixing. Thus 600 msec after mixing was chosen as an appropriate time for measuring the bromine which remained after reaction of the enol. The per cent enol is given by

$$\% \text{ enol} = \frac{(A_s - A_E)(100)}{\epsilon_{Br_2}[\text{substrate}]} \quad (7)$$

where A_s is the bromine absorbance in the standardization, A_E the bromine absorbance after injection alongside the equilibrated ketone solution, and ϵ_{Br_2} the extinction coefficient of Br_2 in 0.1 M KBr at 350 μ . A factor of 2 due to the mutual dilution of the solutions through mixing is canceled by the fact that the stop chamber was equipped with a 2-cm light path. The equilibrium constant is then obtained as follows

$$K_{EL/KL}^{(L_2O)} = \frac{\% \text{ enol}}{\% \text{ ketone}} \quad (8)$$

The enol-enolate acid-base equilibrium was determined by a similar procedure, taking advantage of the fact that the bromine rapidly attacks both the enol and the enolate. The weighed substrate was equilibrated in 0.01 M NH_3 , 0.01 M NH_4OH , 0.1 M KBr, and 0.09 M NaCl in light or heavy water for 5 hr. The solution was then mixed with an acidic bromine solution on the stopped-flow apparatus. The K_a value for the enol is given by¹⁷

$$K_a(\text{enol}) = \left[\frac{K_{EL'/KH}}{K_{EL/KL}} - 1 \right] [K_{\text{buffer}}] \quad (9)$$

where EL' , which represents the enol plus enolate concentration, was determined as described in the basic buffer solutions. The above measurements were performed at an ionic strength of 0.2 M for comparison with kinetics. The pK_a of ammonia was taken as 9.245¹⁸ in H_2O . The $\Delta pK_a = pK_a^{D_2O} - pK_a^{H_2O} = 0.60$ was measured with a glass electrode which gave $pK_a.ND_4^{D_2O} + 9.85$, in

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agreement with previous measurements.¹⁹ It was assumed that activity coefficients cancel for the buffer components.

D. Fractionation Factors. The fractionation factor ϕ_{KH} of the ketone form of the substrate, defined as the equilibrium constant for eq 3, was obtained by nmr measurements, utilizing samples of 3-methylacetylacetone from which the 3,3-dimethylacetylacetone impurity had been removed. The samples were equilibrated in a series of H₂O–D₂O mixtures at 25°, followed by rapid extraction with carbon tetrachloride. The carbon tetrachloride was removed with an aspirator, and the diketone was immediately analyzed in a Varian A60 nmr spectrometer. This involved 15 integrations of nmr peaks associated with the α -proton (228 cps from TMS) and those associated with the α -methyl protons (75 cps)²⁰ which are not exchangeable. The fractionation factor was obtained as follows

$$\phi_{KL} = \frac{[KD][H_2O]^{1/2}}{[KH][D_2O]^{1/2}} = \left[\frac{(I_{\alpha-CH_3})}{3(I_{\alpha-H})} - 1 \right] \frac{(1-n)}{(n)} \quad (10)$$

where $I_{\alpha-H}$ is the area under the peaks corresponding to the α -proton and $I_{\alpha-CH_3}$ that for the α -methyl protons. The result gave $\phi_{KL} = 1.0 \pm 0.1$. The fractionation factor for the hydrogen-bonded enol proton could not be obtained due to the small amount of enol at equilibrium in H₂O.

A similar study was performed on acetylacetone. The compound was pure enough after distillation to use directly. The integration of appropriate nmr peaks yielded the following fractionation factors. For the acidic protons of the ketone $\phi_{KH} = 1.12 \pm 10\%$, roughly in agreement with that obtained for 3-methylacetylacetone. For the proton on the number three carbon of the enol form $\phi_{EH} = 1.03 \pm 6\%$, and, finally, for the hydroxyl proton $\phi_{EH} = 1.12 \pm 16\%$. The precision was much less for the hydroxyl proton due to peak broadening from hydrogen bonding between the oxygens.

E. Degenerate Activity Coefficient. The degenerate activity coefficient is defined as the equilibrium constant for a partition experiment wherein 10 ml of a starting solution in H₂O or D₂O containing the substrate was partitioned against 10 ml of cyclohexane while thermostated in a bath at 25.0° and stirred with a magnetic stirrer for 3 to 4 days. One milliliter of this starting solution was added to 1 ml of a standard solution containing 3 drops of pure cyclopentanone in 50 ml of water and run three times on a HiFi 600 glc using a 5% D.C. 710 on Chromosorb G column at 100°. The results were integrated using the cut and weigh method and normalized with respect to the cyclopentanone peak. The procedure was repeated with two samples of the partitioned H₂O or D₂O solutions to determine the relative concentrations of ketone in the four phases after correcting for per cent enol in each phase. The degenerate activity coefficient is shown in eq 11. This technique was first used

$$\gamma_{KH} = (\phi_{KH}) \times \frac{\frac{[\text{substrate in partitioned H}_2\text{O}][\% \text{ ketone in H}_2\text{O}]}{[\text{initial substrate in starting sample}] - [\text{substrate in partitioned H}_2\text{O}]} - \frac{[\text{substrate in partitioned D}_2\text{O}][\% \text{ ketone in D}_2\text{O}]}{[\text{initial substrate in starting sample}] - [\text{substrate in partitioned D}_2\text{O}]}}{[\text{substrate in partitioned H}_2\text{O}][\% \text{ ketone in H}_2\text{O}]} \quad (11)$$

with purified 3,3-dimethylacetylacetone, since it has no enol form and no exchangeable proton. It yielded a γ of 1.07 ± 0.09 . With 3-methylacetylacetone purified by fractional freezing, a value of $\gamma/\phi = 1.04 \pm 0.04$ was obtained.

Results and Discussion

Equilibrium. Table I summarizes the equilibrium constants $K_{EH/KH}$ for the keto–enol equilibrium of 3-methylacetylacetone in pure H₂O and pure D₂O at 25° and ionic strength of 0.2 M. Also included are the acid dissociation constants of the enol form determined in the same conditions.

Using the Gross–Butler formalism the ratio of the keto–enol equilibrium constants shown in Table I

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Table I. Keto–Enol Equilibrium Constant and Acid Dissociation Constant of the Enol at Ionic Strength 0.2 M and 25.0°

Solvent	Enol, %	$K_{a(\text{enol})}^{(H_2O)} \times 10^{10}$
H ₂ O	2.84; 2.75; 2.78	6.71; 7.11; 7.09; 6.70; 7.15; 6.95
Mean =	$2.79 \pm 0.03^{a,b}$	6.95 ± 0.16
$K_{EH/KH}^{H_2O} =$	2.87×10^{-2}	$pK_{a(\text{enol})}^{(H_2O)} =$ 9.16×0.01
D ₂ O	2.11; 2.14; 2.14	1.46; 1.57
Mean =	2.12 ± 0.01^b	1.52 ± 0.06
$K_{ED/KD}^{D_2O} =$	2.17×10^{-2}	$pK_{a(\text{enol})}^{(D_2O)} =$ 9.82 ± 0.02

^a G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944), give a value of 2.8% at 20°. ^b Long and Watson¹⁴ give values in H₂O as 3.3% and in D₂O as 2.4% too high because of slow titrations.

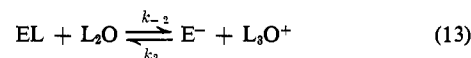
is given by

$$\frac{K_{ED/KD}^{(D_2O)}}{K_{EH/KH}^{(H_2O)}} = \frac{\phi_{EH} \gamma_{KH}}{\phi_{KH} \gamma_{EH}} = \frac{0.0217}{0.0287} = 0.76 \quad (12)$$

where the superscript indicates the solvent and the subscript describes the equilibrium constant.

It has been determined that $\phi_{KH} = 1.0 \pm 0.1$ and $\gamma_{KH} = 1.04 \pm 0.08$. These numbers when applied to eq 12 yield $\phi_{EH}/\gamma_{EH} = 0.73 \pm 0.13$. As indicated by the nmr study of acetylacetone, ϕ_{EH} is near unity which would make $\gamma_{EH} = 1.4$, giving it the main responsibility for the isotope effect on the keto–enol equilibrium. This unusually large value is discussed later.

For the equilibrium



the ratio of the acid dissociation constant in Table I can be represented by

$$\frac{K_{a(\text{enol})}^{(D_2O)}}{K_{a(\text{enol})}^{(H_2O)}} = \frac{(\phi_{H_3O^+})^3 \gamma_{EH}}{(\phi_{EH}) \gamma_{E^-}} = \frac{1.52 \times 10^{-10}}{6.95 \times 10^{-10}} = 0.219 \quad (14)$$

Salomaa and Aalto²¹ have determined that $\phi_{H_3O^+} = 1 = 0.69$ by assuming that $\gamma_{H_3O^+} = \gamma_{C^+} = 1.00$, where γ_{C^+} is the degenerate activity coefficient of any small cation. This was justified by the observation that the free energy of transfer from H₂O to D₂O of several chloride salts was independent of the cation when extrapolated to infinite dilution. This assumption may be in doubt and neglect of $\gamma_{H_3O^+}$ should, therefore, be considered a convention until more independent experimental information can be provided. This means that all degenerate activity coefficients for single ions are given relative to $\gamma_{H_3O^+} = 1.00$. Using $\phi_{H_3O^+} = 0.69$ and the above value for ϕ_{EH}/γ_{EH} , eq 12 and 14 yield $\gamma_{E^-} = 2.0$, again a very large number which will be discussed shortly.

It is at least theoretically possible to determine the ϕ 's and γ 's for all the species involved, and thus test the Gross–Butler equation. Unfortunately direct measurements on species such as the enol and enolate are impossible to perform at this time due to the low concentration of these species relative to the keto form.

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Fortunately for the present system it has been possible to determine a sufficient number of the ϕ and γ constants to calculate the others using the Gross-Butler relationship.

The first set of constants of interest is the fractionation factors. For acetylacetone ϕ for the α -protons of the ketone form is $1.1 \pm 10\%$; for the hydroxyl proton of the enol $\phi = 1.1 \pm 16\%$. In the case of 3-methylacetylacetone ϕ for the α -proton of the ketone is $1.0 \pm 10\%$. The fractionation factors are a measure of the preference of a molecule for protium or deuterium relative to some standard, chosen here as water in a pure H_2O medium (see eq 3). Albery and Davies²² have shown in studies of the decomposition of ethyl diazoacetate that fractionation factors as determined by nmr do not vary with the deuterium content of the aqueous medium. Thus values determined in an H_2O - D_2O mixture may be used in place of the theoretical limiting case of pure H_2O .

It has previously been noted that fractionation factors for stable compounds with water are usually near unity as is the case here.¹² It is possible to calculate a fractionation factor in the gas phase using the gas-phase stretching frequencies of the exchangeable protons.²³ The situation in solution is much more complex. Rough calculations employing the gas-phase approach but using the ir data of acetylacetone in carbon tetrachloride²⁴ and the stretching frequencies of H_2O and D_2O in their respective liquid states²⁵ yield fractionation factors near 2, *i.e.*, much larger than observed. We conclude that simple calculations of this sort are not useful in explaining fractionation factors in aqueous solutions.

A more useful calculation can be done for the isotope exchange of hydrogen between the enol and the keto forms of the diketone. The stretching frequencies of the keto and enol forms of acetylacetone in carbon tetrachloride²⁴ should constitute a good approximation to the gas-phase values. Calculations with these lead to a "gas-phase" value of $K_{ED/KD}/K_{EH/KH} = 0.85$, not very different from the value of 0.76 in aqueous solution, which of course includes medium effects. This calculated value is also in reasonable agreement with the ratio of the keto-enol equilibrium constants obtained by Thompson and Allred in neat acetylacetone.²⁶ Their work, however, showed a large change in the equilibrium constant ratio with temperature (0.51 at -19° to 1.18 at 37°) which cannot be explained by a simple gas-phase vibrational analysis but which is perhaps not surprising for such concentrated solutions.

Medium isotope effects as expressed by the degenerate activity coefficients seem to be the dominant feature in the aqueous solution equilibrium. The degenerate activity coefficient for the ketone form of 3-methylacetylacetone is $\gamma_{KH} = 1.04$, while for the enol form $\gamma_{EH} = 1.4$. For the enolate ion $\gamma_{E^-} = 2.0$ as-

suming that $\gamma_{H_3O^+} = 1.00$. It is difficult to interpret these results due to the fact that the degenerate activity coefficients are related to the free energies of transfer, which in turn are the sum of two competing effects, the enthalpy $\Delta\bar{H}_t^\circ$ and entropy $\Delta\bar{S}_t^\circ$ of transfer. The situation is further complicated by the fact that the enthalpy of transfer grows linearly with the entropy of transfer with a slope near 300 for both ions and non-electrolytes, a phenomenon called "compensation." This means that the two effects just about cancel at 25° , yielding relatively small values for $\Delta\bar{G}_t^\circ$. It has, however, been found in this laboratory that certain small changes in solute structure can make significant changes in the $\Delta\bar{G}_t^\circ$.²⁷ For example, benzene and benzyl alcohol have a zero $\Delta\bar{G}_t^\circ$, while toluene shows a barely significant increase in $\Delta\bar{G}_t^\circ$ of 25 cal/mol. Xylenes and naphthalene have substantial $\Delta\bar{G}_t^\circ$'s. There is even a significant difference between the values for *m*-xylene and *o*-xylene, 45 and 84 cal/mol, respectively. It is apparent that the addition of side groups to benzene often significantly upsets the balance between the $\Delta\bar{H}_t^\circ$ and $\Delta\bar{S}_t^\circ$, causing a positive $\Delta\bar{G}_t^\circ$. The ketone form of 3-methylacetylacetone, as most ketones, has a near zero $\Delta\bar{G}_t^\circ$ while the apparent $\Delta\bar{G}_t^\circ$ for the enol is about 200 cal/mol or $\gamma_{EH} = 1.4$. The highly cyclic structure of the enol form as determined by Bauer and coworkers^{28,29} contains the general shape, size, and π cloud characteristic of 1,2,3-trimethylbenzene, which would be expected to have a very large $\Delta\bar{G}_t^\circ$ as determined by the other alkylbenzenes discussed previously. A similar result is obtained for 2-acetylcyclohexanone, where the ratio of the degenerate activity coefficients of the enol to the keto form is 1.2. Here the difference between the enol and keto forms is much smaller, which may be due to the ring structure already contained in the keto form. Analysis of such data is difficult due to the lack of systematic studies in the area of solution structure. It has, however, been shown that cyclic solutes have unusually small values of $\Delta\bar{H}_t^\circ$. This is probably due to the inability of water to approach many areas near the molecule, which greatly decreases the structural influence of the atoms in the solute molecule. The inability of $\Delta\bar{S}_t^\circ$ to completely cancel the $\Delta\bar{H}_t^\circ$ in certain situations is not understood.

Another situation where large positive values of $\Delta\bar{G}_t^\circ$ occur is in the case of anions of salts. Salomaa and coworkers²¹ have shown that $\Delta\bar{G}_t^\circ$ for several chlorides is independent of the cation. From this they concluded that the cations have a zero free energy of transfer, while anions show a positive free energy of transfer due to the isotope effect of hydrogen bonding from the solvent to the anion. Such hydrogen bonding does not occur for cations which are attracted by the oxygens of the solvent water. In the study of ionization of 3-methylacetylacetone, it is observed that the enolate has, as expected, an unusually high value of $\Delta\bar{G}_t^\circ = 420$ cal/mol ($\gamma_{EH} = 2.0$).

It is interesting to note that significant deviations from zero values of $\Delta\bar{G}_t^\circ$ are almost always positive. This means that for such structure makers as xylene,

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Table II. Data for Determination of Brønsted β^a

Catalyst	p	q	K_A	k_1
H ₂ O	1	1	55.5	1.68×10^{-6}
(H ₂ O)	(3)	(2)	55.5	1.68×10^{-6}
ClCH ₂ COO ⁻	1	2	1.38×10^{-3}	1.41×10^{-3}
CH ₃ COO ⁻	1	2	1.76×10^{-5}	1.34×10^{-2}
HPO ₄ ²⁻	2	3	6.23×10^{-8}	2.60×10^{-1}

^a The values for H₂O were not used in the determination of the Brønsted β .

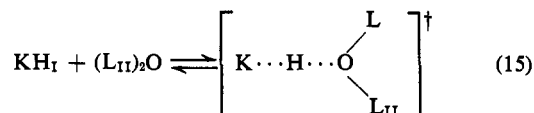
Table III. Second-Order Rate Constants for the Base-Catalyzed Ionization of the Keto Form of 3-Methylacetylacetone in H₂O–D₂O Mixtures at Ionic Strength 0.2 M and 25.0°

n	$[k_{\text{KH}}^{(\text{L}_2\text{O})}]_{\text{L}_2\text{O}} \times 10^7, \text{sec}^{-1} M^{-1}$			$[k_{\text{KL}}^{(\text{L}_2\text{O})}]_{\text{L}_2\text{O}} \times 10^7, \text{sec}^{-1} M^{-1}$			$\frac{[k_{\text{KH}}^{(\text{L}_2\text{O})}]_{\text{OAc}^-}}{\times 10^3 \text{sec}^{-1} M^{-1}}$ Exptl
	Obsd	Calcd ^a	Calcd ^b	Obsd	Calcd ^c	Calcd ^d	
0	16.8 ^a	(16.8)	(16.8)	16.8	(16.8)	(16.8)	1.34 ^e
0.25	14.2	14.4	14.1	12.1	11.9	11.8	
0.50	11.8	12.1	11.9	7.87	8.06	7.90	
0.75	9.82	1.00	9.92	4.67	5.05	4.98	
1.00	8.13 ^a	(8.13)	(8.13)	2.85 ^a	(2.85)	(2.85)	1.33 ^e

^a Calculated assuming no medium effects, *i.e.*, $\gamma_{\text{KH}}/\gamma_{\text{H}^+} = 1.00$. ^b Calculated assuming $\phi_{\text{II}} = l^\beta$ and by choosing $\gamma_{\text{KH}}/\gamma_{\text{H}^+} = 0.70$ by fitting rate in pure H₂O and D₂O. ^c Calculating assuming $\phi_{\text{KL}} = 1.00$. ^d Calculated assuming $\phi_{\text{KL}} = 1.10$. ^e Long and Watson¹⁴ give a value of 17.3×10^{-7} for KH + H₂O; 12.6×10^{-7} for KH + D₂O; 3.8×10^{-7} for KD + D₂O; 0.725×10^{-2} for KH + OAc⁻(H₂O); and finally 0.580×10^{-2} for KH + OAc⁻(D₂O). We do not know the reason for the discrepancy.

the negative entropy of transfer dominates over the negative enthalpy of transfer, while for structure breakers such as the chloride ion, the positive enthalpy of transfer dominates over the positive entropy of transfer. More data are needed for simple solutes to interpret such an observation, but there seems to be enough to substantiate the belief that keto-enol-enolate equilibria in H₂O and D₂O are predominantly determined by medium and not exchange effects.

Kinetics. The same type of analysis can be applied to kinetics if it is assumed that the reactants and transition state are in equilibrium. The results for the reaction



are given in Table III for five values of n , the atom fraction deuterium in the solvent. Since the transferring proton is not allowed to exchange due to the initial presence of bromine, $\phi_{\text{KH}} = \phi_{\text{I}} = 0$ leaving the Gross-Butler equation as

$$\frac{k_{\text{KH}}^{(\text{L}_2\text{O})}}{k_{\text{KH}}^{(\text{H}_2\text{O})}} = (1 - n + n\phi_{\text{II}}^\ddagger)^2 \left(\frac{\gamma_{\text{KH}}}{\gamma_{[\text{KHO}(\text{L}_2)]}^\ddagger} \right)^n \quad (16)$$

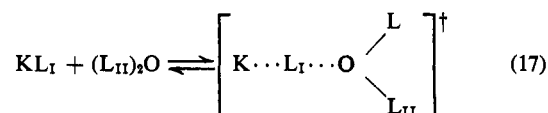
The fractionation factor for H₂O is defined as 1.00 and $\phi_{\text{II}}^\ddagger$ is the fractionation factor for the two lyons labeled L_{II} in the transition state of eq 15. If one neglects medium effects, *i.e.*, assumes $\gamma_{\text{KH}}/\gamma_{\text{H}^+} = 1.00$ and fits the end points ($n = 0$ and 1) by assigning $\phi_{\text{II}} = 0.696$, good agreement with experimental results for other values of n is obtained (see Table III). Such a value for ϕ_{II} seems unreasonable since it is the same value as ϕ for the hydronium ion. An alternate approach was suggested by Kresge³⁰ wherein $\phi_{\text{II}}^\ddagger$ is set equal to l^β where $\beta = 0.49$ (see Table II) is the slope of the general base Brønsted plot and is

(30) A. J. Kresge, *Pure Appl. Chem.*, **8**, 243 (1964).

believed to be a measure of the degree of proton transfer in the transition state. The justification for this approach is that, when $\beta = 0$, the proton has not yet been transferred to the base water in the transition state so that the fractionation factors for the two water protons should still be unity. When $\beta = 1$, then the proton has been completely transferred in the transition state and the water molecule has virtually become a hydronium ion with a fractionation factor

of 0.69. Since in this case the proton is only half transferred in the transition state, the fractionation factors for the protons labeled L_{II} should be between that for water and hydronium ion. Such an approach yields the more satisfactory $\phi_{\text{II}} = 0.83$, and, by fitting the end points, one obtains the better agreement with experiment listed in Table III and the result that $\gamma_{\text{KH}}/\gamma_{\text{H}^+} = 0.70$. Since $\gamma_{\text{KH}} = 1.04$, then $\gamma_{[\text{KOH}(\text{L}_2)]}^\ddagger = 1.5$. A similar analysis for acetate catalysis yields a value of $\gamma_{[\text{KHOAc}]^\ddagger} = 1.2$.

If the reacting ketone is allowed to equilibrate with the solvent L₂O, bromination yields the rate constants for the following reaction



where now the fractionation factors for the transferred lyon I_I of the ketone and the transition state must be included in the Gross-Butler equation

$$\frac{k_{\text{KL}}^{(\text{L}_2\text{O})}}{k_{\text{KL}}^{(\text{H}_2\text{O})}} = \frac{(1 - n + n\phi_{\text{I}}^\ddagger)(1 - n + n\phi_{\text{II}}^\ddagger)^2 (\gamma_{\text{KL}})^n}{(1 - n + n\phi_{\text{KL}})} \left(\frac{\gamma_{\text{KL}}}{\gamma_{\text{H}^+}} \right)^n \quad (18)$$

If this equation is then divided by the corresponding equation for the secondary and medium effects (eq 16), it leaves the primary isotope effect

$$\frac{k_{\text{KL}}^{(\text{L}_2\text{O})}}{k_{\text{KL}}^{(\text{H}_2\text{O})}} = \frac{(1 - n + n\phi_{\text{I}}^\ddagger)}{(1 - n + n\phi_{\text{KL}})} \stackrel{\text{for } n=1}{=} \frac{\phi_{\text{I}}^\ddagger}{\phi_{\text{KL}}} \quad (19)$$

This operation assumes that $\phi_{\text{II}}^\ddagger$ is not changed significantly by the isotopic nature of the approaching lyon. Given the experimental values for $k_{\text{KL}}^{(\text{L}_2\text{O})}/k_{\text{KL}}^{(\text{H}_2\text{O})}$ and the end points for the primary isotope effect, one obtains the ratio of fractionation factors $\phi_{\text{I}}^\ddagger/\phi_{\text{KL}} = 0.353$. If $\phi_{\text{KL}} = 1.00$ then $\phi_{\text{I}}^\ddagger = 0.353$, which yields a good fit with the total isotope effects listed in Table III. Since the uncertainty in ϕ_{KL} is

about 10%, about the same error should be assumed for $\phi_{I\ddagger}$, but predictions for the total isotope effect seem to be fairly insensitive to such changes in their values as shown in Table III.

The very small value for $\phi_{I\ddagger}$ is due to the fact that the transferred proton is being shared between the acid and the base in the transition state. The bending and vibrational frequencies of a half transferred proton are not dependent on the mass of the proton. The ratio of $\phi_{I\ddagger}/\phi_{KL}$ must be looked upon as just a different formalism for expressing a primary isotope effect.

The H₂O-D₂O mixed solvent kinetics have also provided an opportunity to examine the medium effect on the transition state of a simple proton transfer reaction. A first assumption might be that the free energy of the transition state would be intermediate to the free energies of transfer of the reactants and products and that the Brønsted β could be used to measure the degree of change from the reactants to the transition state. This could be expressed as

$$\beta(\sum_i \Delta \bar{G}_t^\circ(\text{products}) - \sum_i \Delta \bar{G}_t^\circ(\text{reactants})) = (\Delta \bar{G}_t^\circ(\text{transition state}) - \Sigma \Delta \bar{G}_t^\circ(\text{reactant})) \quad (20)$$

or in terms of degenerate activity coefficients

$$\left(\frac{\prod_i \gamma(\text{products})}{\prod_i \gamma(\text{reactants})} \right)^\beta = \left(\frac{\gamma(\text{transition state})}{\prod_i \gamma(\text{reactants})} \right) \quad (21)$$

The data for methylacetylacetone kinetics for water catalysis

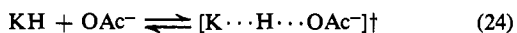
$$\left(\frac{\gamma_{E^-}}{\gamma_{KH}} \right)^\beta = (1.97)^{0.49} = 1.41 \quad (22)$$

and

$$\left(\frac{\gamma_{[KHOL_2]\ddagger}}{\gamma_{KH}} \right) = 1.43 \quad (23)$$

seem to demonstrate that the relationship of eq 21 holds. It should be noted once again that it has been assumed that $\gamma_{H_2O^+} = 1.00$ and $\phi_{KL} = \phi_{EL} = 1.00$.

It is also possible to test this relationship with acetate catalysis where the reaction



can be represented by

$$\frac{(k_{KH}^{(H_2O)})_{OAc^-}}{(k_{KH}^{(D_2O)})_{OAc^-}} = \frac{\gamma_{[KHOAc^-]\ddagger}}{\gamma_{KH}\gamma_{OAc^-}} = 1.00 \quad (25)$$

Goodall and Long¹² reported that $\gamma_{Cl^-}/\gamma_{OAc^-} = 1.19$ and Salomaa²¹ gives $\gamma_{Cl^-} = 1.37$ assuming that $\gamma_{H_2O^+} = 1.00$. Together they yield $\gamma_{OAc^-} = 1.15$ and $\gamma_{[KHOAc^-]\ddagger} = 1.20$. The equilibrium data for $KL + OAc^- \rightleftharpoons E^- + LOAc$ and the values $\gamma_{LOAc} = 1.03$ and $\phi_{LOAc} = 0.96$ derived by Gold and Lowe³¹ and Goodall and Long yield the results

$$\left(\frac{\phi_{KL}}{\phi_{LOAc}} \right) \left(\frac{\gamma_{E^-}\gamma_{LOAc}}{\gamma_{KL}\gamma_{OAc^-}} \right) = \frac{(1.00)(1.97)(1.03)}{(0.96)(1.15)} = 1.83 \quad (26)$$

which then brought to the β power predicts a medium isotope effect of 1.35 compared to the experimental value of 1.00. Even the addition of a reasonable

(31) V. Gold and B. M. Lowe, *J. Chem. Soc. A*, 936 (1968).

fractionation factor would not be enough to make the relationship hold.

Literature provides some other systems for comparison. Riley and Long¹⁵ studied the water- and acetate-catalyzed interconversion of 2-acetylcyclohexane in pure H₂O and D₂O. Analyses of the data in the same way as before yield for water catalyzers

$$\frac{\gamma_{E^-}}{\gamma_{KH}} = I^3 \left(\frac{K_{KH}^{(H_2O)}}{K_{KH}^{(D_2O)}} \right) \frac{1}{\phi_{KH}} = \frac{(0.69)^3(3.78)}{\phi_{KH}} = \frac{1.25}{\phi_{KH}} \quad (27)$$

and using their value for $\beta = 0.60$

$$\frac{\gamma_{[KHOL_2]\ddagger}}{\gamma_{KH}} = I^{2\beta} \left(\frac{k_{KH}^{(H_2O)}}{k_{KH}^{(D_2O)}} \right) = (0.69)^{1.20}(1.40) = 0.90 \quad (28)$$

If it is assumed that $\phi_{KH} \approx 1.00$, then

$$\left(\frac{\gamma_{E^-}}{\gamma_{KH}} \right) = (1.29)^{0.6} = 1.14 \quad (29)$$

and again the relationship does not hold for any reasonable value of ϕ_{KL} .

For acetate catalysis, the predicted isotope effect is 1.07 instead of the observed value of 1.2.

The relationship holds for the acetate catalysts of the ionization of nitromethane, using the kinetic data of Reitz³² and Goodall and Long¹² and the Brønsted $\beta = 0.67$ of Pedersen,³³ but fails again for the deuteriation studies of *tert*-butylmalononitrile in H₂O and D₂O, studied by Hibbert and Long.³⁴ Here the predicted medium isotope effect is 1.25, while the observed value is 1.65.

Table IV. Degenerate Activity Coefficients

Substrates	Degenerate act. coeff
3-Methylacetylacetone ($\beta = 0.49$)	$\gamma_{KH} = 1.04$ $\gamma_{[KHOAc^-]\ddagger} = 1.2$ $\gamma_{EH} = 1.4$ $\gamma_{[KHOL_2]\ddagger} = 1.5$ $\gamma_{E^-} = 2.0$
2-Acetylcyclohexanone ($\beta = 0.60$)	$\gamma_{[KHOL_2]\ddagger} = 0.9$ $\gamma_{KH} = 1.0^a$ $\gamma_{EH} = 1.2$ $\gamma_{E^-} = 1.3$ $\gamma_{[KHOAc^-]\ddagger} = 1.4$ $\gamma_{SH} = 1.06$
Nitromethane ($\beta = 0.67$)	$\gamma_{[SHOAc^-]\ddagger} = 1.4$ $\gamma_{S^-} = 1.5$ $\gamma_{RH} = 1.04$ $\gamma_{R^-} = 1.3$
<i>tert</i> -Butylmalononitrile ($\beta = 0.98$)	$\gamma_{[RLOL_2]\ddagger} = 1.7$

^a Assume γ_{KH} for 2-acetylcyclohexanone is 1.00 and set all others accordingly.

It is apparent from these systems summarized in Table IV that the degenerate activity coefficient for the transition state is not simply related to those of the reactants and products. It is doubtful that fractionation factors could be varied enough to make the relationship of eq 21 hold. For example, $\phi_{LOAc}/\phi_{KL} = 1.83$ is needed in order to make the relationship

(32) O. Reitz, *Z. Phys. Chem., Abt. A*, 176, 363 (1936).

(33) K. J. Pedersen, *Kgl. Dan. Vidensk. Selsk. Mat.-Fys. Medd.*, 12, 1 (1932).

(34) F. Hibbert and F. A. Long, *J. Amer. Chem. Soc.*, 93, 2829, 2836 (1971).

hold for acetate catalysis of methylacetylacetone. The possibility that there is a water bridge in the transition state is unlikely due to the inhibiting steric effects found for the base catalysis of α -substituted pyridines on simple ketones and nitroalkanes.³⁵ Kresge³⁶ has been reconsidering the idea that Brønsted exponents α or β are in fact a measure of the degree of proton transfer. In studies of vinyl ether hydrolysis he has noted that certain side groups on the substrate may interact with the acid H_3O^+ in the transition state causing deviations in the value of α . If the maximum value for a primary isotope occurs when $z = 0.5$, where z is the true degree of proton transfer, then α is too large by 0.1 to 0.15. Such a contribution to α need occur only from an interaction of 400–500 cal/mol. It has been shown that structure-making and structure-

(35) (a) Cf. V. Gold, *Chimia*, **19**, 508 (1965); (b) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

(36) A. J. Kresge, *et al.*, *J. Amer. Chem. Soc.*, **93**, 413 (1971).

breaking groups held closely together by chemical bonds or in concentrated solutions cause an overlap in the spheres of structural influence, greatly reducing the magnitude of the $\Delta\bar{H}_i^\ddagger$'s as compared with the isolated groups in water.²⁷ Such changes may or may not be accompanied by canceling changes in ΔS_i^\ddagger . It is, however, obvious that such interactions in dilute solutions would only occur in the transition state due to the fact that the various reactants (as well as the various products) are separated from each other and are close together only when exchanging the proton in the transition state. These solvent structure interactions could explain why the degenerate activity coefficient is not necessarily between those of the reactants and products.

Acknowledgment. We thank Professor C. Wilcox for the use of his gas-liquid chromatography unit and G. Hammes for the use of his stopped-flow apparatus.

Structural Chemistry of Cholinergic Neural Transmission Systems. II. A Quantum Theoretical Study of the Molecular Electronic Structure of Muscarine, Nicotine, Acetyl- α -methylcholine, Acetyl- β -methylcholine, Acetyl- α,β -dimethylcholine, and Further Studies on Acetylcholine

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Contribution from the Department of Chemistry, Hunter College, New York, New York, and the Departments of Neurosurgery and Neurology, the Mount Sinai School of Medicine, City University of New York, New York, New York. Received September 5, 1972

Abstract; The results of INDO molecular orbital calculations on the conformational energies and electronic structures of muscarine, nicotine, acetyl- α -methylcholine, acetyl- β -methylcholine, and acetyl- α,β -dimethylcholine are presented and discussed in terms of recently completed INDO studies on acetylcholine. The calculated potential energy surfaces and electronic charge distributions for each compound are systematically considered in terms of crystallographic, spectroscopic, and bioassay data.

This series of papers describes the calculated conformational energy and molecular electronic structure of a group of molecules relevant to cholinergic neural transmission using self-consistent field (SCF) molecular orbital (MO) theory. Our aim is to characterize the structural chemistry of these molecules as fully as possible from a quantum theoretical view point and consider the relationship between the calculated results, experimentally observed structural data from crystallographic and resonance spectral studies, and structures believed relevant to cholinergic processes at a molecular level. Paper I of this series² described a quantum theoretical study of acetylcholine (Ach) using valence electron SCF-MO methods at the level of intermediate neglect of differential overlap (INDO).

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(2) D. L. Beveridge and R. J. Radna, *J. Amer. Chem. Soc.*, **93**, 3759 (1971).

We report herein updated results on Ach and analogous studies of a series of compounds structurally related to Ach and important in the muscarinic and nicotinic subclassification of cholinergic receptors.

I. Background

Acetylcholine, as the endogenous synaptic chemical transmitting agent in cholinergic neural systems, is active at parasympathetic postganglionic sites, voluntary neuromuscular junctions, and autonomic ganglia.³ Cholinergic receptors are operationally divided into two practically nonoverlapping subclassifications based on the observed activities of muscarine, nicotine, and related compounds.⁴ Parasympathetic postganglionic sites are "muscarinic" since Ach action is

(3) B. Katz, "Nerve Muscle Synapse," McGraw-Hill, New York, N. Y., 1966.

(4) (a) R. B. Barlow, "Introduction to Chemical Pharmacology," Wiley, New York, N. Y., 1964; (b) D. Nachmansohn, "Chemical and Molecular Basis of Nerve Activity," Academic Press, New York, N. Y., 1959.