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ISOTOPIC PROBES OF THE TRANSITION STATE STRUCTURE FOR 1-ACETYL-3-METHYLIMIDAZOLIUM ION HYDROLYSIS

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The characterization of transition state structures for biological reactions is of extreme importance and a variety of experimental and theoretical approaches are currently being exploited as a means to this end.[1] Some of the most promising techniques involve the utilization of isotopic probes. The potential of such isotopic studies as descriptors of transition state structure is unmatched by other experimental approaches and the recent interest in theoretical calculations of isotope effects for model transition state structures will complement these studies significantly.

We report here the results of two different investigations of the pH-independent hydrolysis of 1-acetyl-3-methylimidazolium ion (**1**). Both the proton inventory technique and a secondary deuterium isotope effect technique have been used to characterize the transition state for this reaction. We have recently reported on the transition state for the hydrolysis of acetylimidazolium ion (**2**).[2]

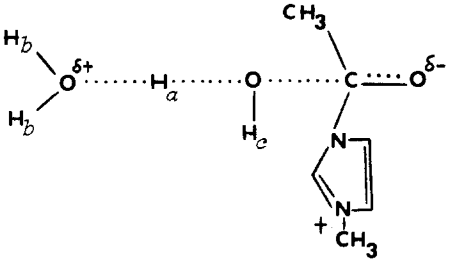
Wolfenden and Jencks have suggested that the pH-independent reactions for hydrolysis of **1** and **2** are similar.[3] In view of our recent study in which we suggested a catalytic proton bridge in the transition state for the pH-independent hydrolysis of **2** it was of interest to extend the study to **1**. If the two reactions are indeed identical then the transition state model proposed for **2** should also be a satisfactory model for the hydrolysis of **1**. The proton inventory technique, discussed more fully in the previous paper, allows us to characterize the transition state structure in considerable detail. Also the synthesis of **1** labeled with three deuteria in the acetyl group is straightforward and this allows the measurement of the secondary beta deuterium isotope effect as yet another probe of transition state structure.

The dependence of a reaction rate constant on the atom fraction of deuterium in the solvent can yield much more information than the observation of a simple solvent isotope effect. Such a study has been termed a proton inventory because it allows the sorting out of all the contributors to the observed solvent isotope effect.[4] The observed reaction rate constant, k_n, in an H_2O-D_2O mixture is related to the rate constant in pure H_2O, k_o, by equation 1.[5] The rate constant in solvent mixture of atom fraction of deuterium n is

$$k_n = k_o \prod_{i}^{TS} (1-n+n\phi_i^*) \Big/ \prod_{j}^{RS} (1-n+n\phi_j) \qquad (1)$$

dependent on the ratio of i transition state (TS) terms to j reactant state (RS) terms where i and j refer to isotopically exchangeable sites. Each such site will be characterized by an isotopic fractionation factor ϕ which relates the deuterium preference for the site in question relative to the deuterium preference for an average solvent site.

Table I and Figure 1 show the dependence of the observed first order rate constants on the isotopic composition of the solvent. Table I includes calculated values of the rate constants based on the chemical model for the transition state shown in equation 2. The solid line drawn through the data points in Figure 1 is based on this chemical model. This is the same model in every detail that was used for the transition state structure for the



(2)

hydrolysis of **2**. This removes any doubt that the exchangeable proton on the nitrogen could in any way contribute to the former result and is an additional test of the transition state model.

The secondary beta deuterium isotope effect for the hydrolysis of **1** was measured to be k_{3H}/k_{3D} = 0.944 ± 0.019 based on an average of six runs for each compound. These effects are generally accepted to arise from a loss of hyperconjugative stabilization, by the beta C-H(D) bonds, of the partial positive charge on the carbonyl carbon in going to a tetrahedral transition state.[6] Such an inverse isotope effect would be expected in the hydrolysis of **1** and it was our desire to see if these effects could be correlated with the transition state structure suggested by the proton inventory to give even more detail in terms of actual bonding changes occurring at the carbonyl carbon. Using the equilibrium isotope effect for the hydration of 1,3-dichloroacetone-d$_4$ of K_{4H}/K_{4D} = 0.82 and assuming the effects to be cumulative one can calculate an isotope effect "per deuterium" of K_H/K_D = 0.952.[7] This can be assumed to be the maximum effect per beta deuterium for complete conversion of an sp^2-hybridized carbonyl carbon to an sp^3-hybridized carbon. Thus, $(0.952)^3$ should give us a reasonable estimate for the maximum secondary beta deuterium isotope effect for complete conversion of the carbonyl carbon in **1** to a tetrahedral carbon in a fully developed tetrahedral intermediate. This gives a value of $k_{3H}^{MAX}/k_{3D}^{MAX}$ = 0.863. A recent theoretical calculation of such an effect for a theoretical model involving hydroxide addition to acetaldehyde suggested that the isotope effect for such reactions varies linearly with the bond order of the nucleophile-carbonyl carbon bond.[7] Using this theoretical plot one can estimate the value of the bond order corresponding to a measured experimental isotope effect. The measured value of 0.944 for the hydrolysis of **1** would correspond to a bond order of roughly 0.45. This gives an idea of the degree of bond formation between the attacking water molecule and the carbonyl carbon in the hydrolysis of **1**. This value suggests that proton transfer and nucleophile-carbon bond formation have occurred to the same extent in the transition state. Kurz and Ehrhardt have considered this question in more detail

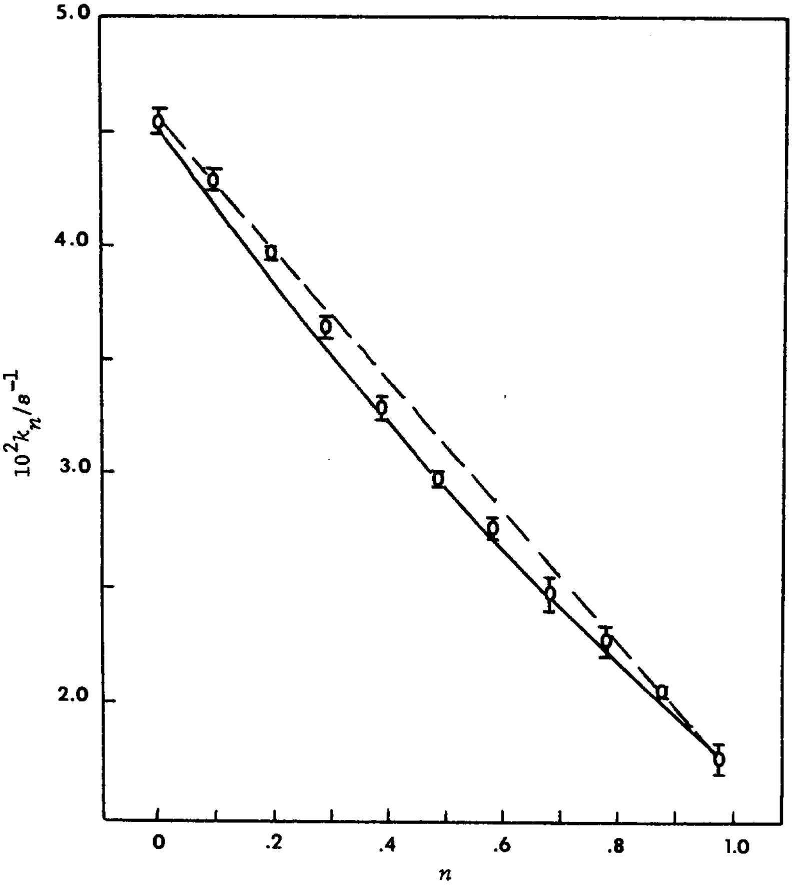


Figure 1. Dependence of the observed first order rate constants, k_n, for the hydrolysis of 1-acetyl-3-methylimidazolium ion on the atom fraction of deuterium, n, in the solvent. The data are from Table I. The solid line is calculated for the chemical model of equation 2 using $\phi_a^* = 0.56$ and $\phi_b^* = 0.83$. The broken line is included to emphasize the nonlinear nature of the data. Details of the experimental procedure used to obtain these data can be found in the previous paper.[2]

recently for ethyl trichloroacetate hydrolysis.[8]

The combination of these two effects coupled with theoretical calculations of isotope effects has allowed us to suggest a very detailed transition state structure for this reaction. As more and more theoretical models are calculated and this information is coupled with multiple experimental isotope effects within the same system the degree of transition state structure that can be specified will be remarkable.

Table I. First-Order Rate Constants for the Hydrolysis of 1-Acetyl-3-Methylimidazolium Ion in Mixtures of 0.02 N HCl/H_2O and 0.02 N DCl/D_2O at 25.00 ± 0.05° C.[a]

Atom Fraction of deuterium (n)	No. of Runs	$10^2k_n/s^{-1}$	Calculated[b] $10^2k_n/s^{-1}$
0.000	4	4.54±0.075	4.54
0.099	6	4.28±0.062	4.20
0.198	6	3.97±0.034	3.87
0.297	5	3.64±0.053	3.56
0.396	3	3.29±0.067	3.26
0.495	4	2.98±0.044	2.98
0.594	4	2.78±0.043	2.71
0.693	3	2.49±0.075	2.46
0.792	4	2.29±0.071	2.22
0.891	3	2.07±0.015	1.99
0.990	4	1.77±0.066	1.77

[a] These experiments were done exactly as previously reported.[2] [b] Calculated based on the model discussed in the text.

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