mum observed here is sharp and that this sharpness may be traced back to the great speed of the proton-transfer step. This suggests that isotope effect maxima for proton transfer between normal acids and bases may always be fairly narrow, and that a close match of donor and acceptor pK_a's will be required to produce an isotope effect with a significant primary component. Isotope effects large enough to be identified unmistakably as primary may therefore be scarce in such reactions simply because the necessary close match of pK_a's has seldom been achieved.[2d] A similar reason may apply to the general absence of large isotope effects from systems in which proton transfer between normal acid-base centers is accompanied by heavy-atom reorganization.[11]

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General Acid Catalysis of the Aminolysis of Phenyl Acetate by a Preassociation Mechanism[1]

Sir:

We wish to report evidence that the methoxyaminolysis of phenyl acetate is subject to general acid catalysis through a preassociation mechanism in which strong acids provide enforced general acid catalysis of amine attack by hydrogen bonding, weaker acids give partiallly rate-determining proton transfer to the addition intermediate, $T^{\pm}$, and weak acids lead to rate-determining separation of the encounter pair $T^{+}\cdot A^{-}$. The proton-transfer step gives rise to a solvent deuterium isotope effect with a sharp maximum at $pK_{HA} \sim 7$.

There is evidence that general acid catalysis of the aminolysis of phenyl acetate by basic amines involves rate-determining trapping of the dipolar addition intermediate, $T^{\pm}$, upon encounter with buffer acids.[2] This catalysis is enforced by the short lifetime of the intermediate, which was estimated to revert to reactants with a rate constant on the order of 10^9 s^{-1}. The experiments reported here were carried out to test the prediction that a less basic amine would give a still less stable intermediate, so that the lowest energy path for catalysis would become an enforced preassociation mechanism in which the attack of the amine on the ester must take place in the presence of the acid catalyst.[3,4]

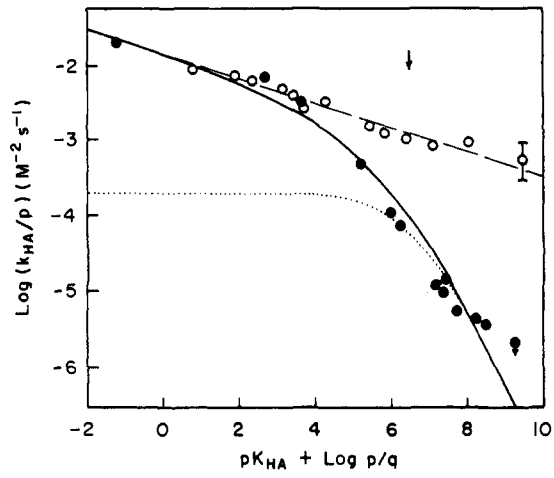

Figure 1. Brønsted plot for general acid catalysis of the methoxyaminolysis of phenyl acetate at 25 °C, ionic strength 1.0 (KCl). The rate constants were determined as described previously.[2,7,17] The closed circles represent monofunctional catalysts and open circles represent bifunctional catalysts. The dotted and solid curves are calculated[7,9] lines for trapping and preassociation mechanisms, respectively. The arrow at $pK = 6.5$ shows the calculated pK of T^{+}. The smallest rate constant represents an upper limit.

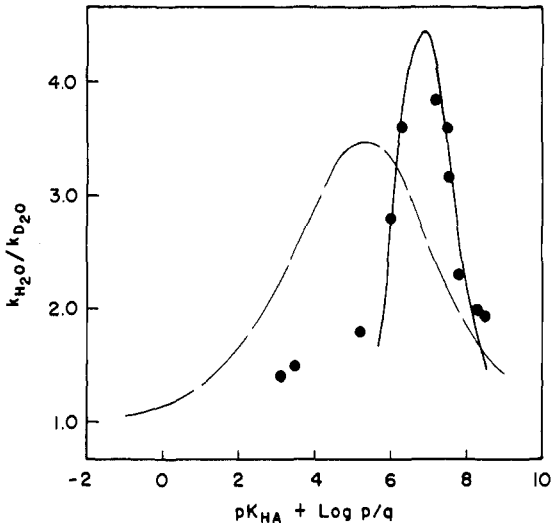

Figure 2. Solvent deuterium isotope effects for monofunctional general acid catalysis of the methoxyaminolysis of phenyl acetate. The dashed and solid lines were calculated assuming constant and changing isotope effects on the k_p step, respectively.[9,13]

The Brønsted plot for general acid catalysis of the methoxyaminolysis of phenyl acetate is shown in Figure 1. The rate constants for monofunctional catalysts (protonated amines and the proton) are shown as solid symbols and follow a curved line that approaches a slope of $\alpha = 1.0$ for weak acids and a slope of $\alpha = 0.16$ for the stronger acids. The rate constants for bifunctional catalysts (carboxylic acids and inorganic oxyacids) are shown as open symbols and are similar to those for monofunctional acids of $pK < 4$. However, for weak acids the

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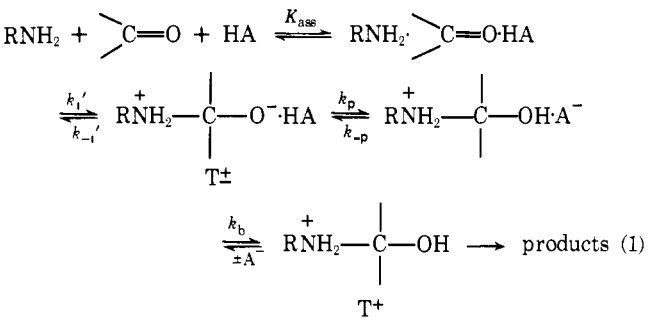
bifunctional catalysts are more active by factors of up to 200.

The nonlinear Brønsted plot for monofunctional catalysts is consistent with the preassociation mechanism of eq 1 in



which the different regions of the Brønsted plot represent three different rate-determining steps: k_1', k_p, and k_b for strong, weaker, and weak acids, respectively.

The following evidence supports the preassociation mechanism. (1) The curvature cannot be accounted for by a trapping mechanism involving only diffusion and proton-transfer steps. The "Eigen curve" for such a mechanism,[5] based on a calculated pK[6] of 6.5 for T^+, is shown as the dotted line in Figure 1; catalysis by a trapping mechanism has been shown to follow Eigen curves for more basic amine nucleophiles.[2] (2) The limiting slope of the Brønsted plot is $\alpha = 0.16$, consistent with catalysis of amine addition by hydrogen bonding,[7] and not with the value of $\alpha = 0$ that is required for diffusion-controlled proton transfer.[5] (3) The proton fits on the Brønsted line defined by the stronger acids; it does not show the positive deviation of 10–50-fold that is required for diffusion-controlled proton transfer.[5] (4) The rate constants for catalysis by chloroacetic acid (pK = 2.65) were found to exhibit no decrease with increasing viscosity in solutions containing up to 60% glycerol. (5) The calculated Brønsted curve for a preassociation mechanism,[7,9] shown as the solid line in Figure 1, provides a satisfactory fit to the experimental data.

Cordes and co-workers[10] observed intersecting Brønsted lines for catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate and suggested that the break is caused by bifunctional, acid–base catalysis by carboxylic acids. The data in Figure 1 show that bifunctional catalysis by the stronger acids does not cause a rate enhancement compared with monofunctional acids, but does provide an explanation for the greater catalytic effectiveness of weaker bifunctional catalysts. The fact that these rate constants are larger than those for simple monofunctional catalysts in the region in which monofunctional catalysis is limited largely by the k_p step requires either concerted proton transfers or additional stabilization by hydrogen bonding with the bifunctional catalysts.

The solvent isotope effects for monofunctional catalysts show a sharp maximum at pK = 6.8 (Figure 2), close to the calculated pK of 6.5 for T^+. Similar maxima have been observed for catalysis of nitramide decomposition[11] and for catalysis of methoxyamine addition to *p*-methoxybenzaldehyde by a trapping mechanism.[12] This isotope effect maximum confirms the existence of a kinetically significant proton transfer step in the preassociation mechanism when the ΔpK between the proton donor and acceptor is small.

The isotope effect maximum cannot be explained by the change in rate-determining step from k_1' to k_p to k_b (eq 1). The calculated isotope effects for this explanation[9] are shown as the dashed line in Figure 2 and are inconsistent with the observed isotope effects; in particular, the observed isotope effects fall off with increasing acid strength at much higher pK than the calculated line. Variation of the estimated maximum isotope effect and other parameters does not improve the agreement. The decrease in the isotope effect with acid catalysts of pK = 7–4, for which the proton-transfer step is largely rate determining, requires a decrease in the isotope effect of the k_p step itself with increasing acid strength. The shape of the observed curve is attributed to a maximum in the isotope effect for the k_p step and to a decrease in the observed isotope effect as the k_b step becomes rate determining with weak acid catalysts.[13] The maximum may reflect asymmetric transition states for proton transfer,[15] tunneling,[16] or both in the proton-transfer step, k_p.

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Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal[1]

Sir:

The use of nuclear magnetic resonance spectroscopy in the vision field has largely been limited to the isolated chromophore. Both the ^1H NMR[2] and ^{13}C NMR[3] spectra of retinal isomers and their Schiff bases[4] have been analyzed in great detail. Application of the technique to probing structural information of the pigments directly, because of background noise, is expected to be difficult. However, with the use of a ^{13}C-enriched retinal, the ^{13}C spectrum of rhodopsin has been successfully recorded.[5] Fluorine-19 magnetic resonance spectroscopy will not have any background noise to contend with. However, it remains to be established that fluorine labeled pigment analogues do exist. To test this possibility we have synthesized isomers of 10-fluoro- and 14-fluororetinal (I and II). In this paper we describe the preparation and

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