Factors Affecting the Relative Efficiency of General Acid Catalysis

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Abstract

Specific acid catalysis (SAC) and general acid catalysis (GAC) play an important role in many organic reactions. Elucidation of SAC or GAC mechanisms requires an understanding of the factors that affect their relative efficiency. A simple model reaction in which SAC and GAC occur concurrently is analyzed to provide guidelines for such analyses. Simple rules which predict the effect of pH on the relative efficiency of GAC are discussed. An explicit expression for determining the optimal pH at which the effects of GAC are maximized is provided as well as an analogous expression for the general base case. The effects of the pK_a of the general acid and the total catalyst concentration on GAC efficiency are described. The guidelines are graphically illustrated using a mixture of theoretical data and literature data on the hydrolysis of di-*tert*-butyloxymethylbenzene. The relationship between the model and the Brønsted equation is developed to explain the common observation that GAC is most easily observable when the Brønsted coefficient α is near 0.5. The ideas presented enable systematic evaluations of experimental kinetic data to provide quantitative support for SAC or GAC mechanisms. This material is suitable for the curriculum of a senior-level undergraduate course in physical-organic chemistry.

Keywords: Organic chemistry; physical chemistry; curriculum; acid-base chemistry; catalysis; kinetics.

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Background

Proton transfer catalysis by Brønsted acids and bases is a recurring theme in organic reaction mechanisms. This form of catalysis has received considerable attention in physical-organic chemistry for its mechanistic role not only in standard transformations but also in enzymatic reactions. For example, reversible protonation was recently found to play a key role in the action of the enzyme enolase (*1*). The simplest Brønsted species, H_3O^+ and OH^-, are termed *specific* catalysts and the rest, generically denoted HA and A^-, are termed *general* (*2*).

The relationship between the effectiveness of an acid catalyst and its catalyzed rate constant is described by the Brønsted equation, the original free energy relationship (*3*). The acid form of the Brønsted equation is usually given in its logarithmic form,

$$\log k = \alpha \log K_1 + C, \quad (1)$$

where k is the catalyzed rate constant, α is the Brønsted coefficient, K_1 is the acid dissociation constant, and C is constant (*4*). Its equivalent exponential form is

$$k = GK_1^{\alpha}, \quad (2)$$

where $G = 10^C$. α is usually found between zero and one and indicates the degree of protonation in the transition state (*5*).

Undergraduate students are usually introduced to these concepts in senior-level physical-organic chemistry courses, but tend to have difficulty applying them when writing reasonable "curved arrow" reaction mechanisms. Often, the complicated procedures necessary to determine the rate constants for a reaction impede student understanding of the relationships between the rate constants and the reaction mechanism. This article describes a simple framework for evaluating experimental kinetic data to provide support for specific acid catalyzed (SAC) or general acid catalyzed (GAC) mechanisms.

Multiple Mechanisms

Organic reactions often proceed simultaneously through multiple mechanisms towards the same products. Acetal hydrolysis (*6*, *7*), for example, may occur through a SAC or GAC mechanism (see Figure 1). Although in certain cases thermodynamic or stereoelectronic considerations allow *a priori* prediction of one dominant mechanism, distinguishing SAC from GAC is challenging in general. For example, while GAC is observed in the hydrolysis of substituted 2-aryloxytetrahydropyrans (*8*), it is not observed in the hydrolysis of substituted benzaldehyde diethyl acetals (*9*). When chemical intuition cannot be relied upon, experimental rate constants must be used to support a proposed mechanism. However, once rate constants are obtained, some simple rules allow prediction of the dominant mechanism for a given set of conditions.

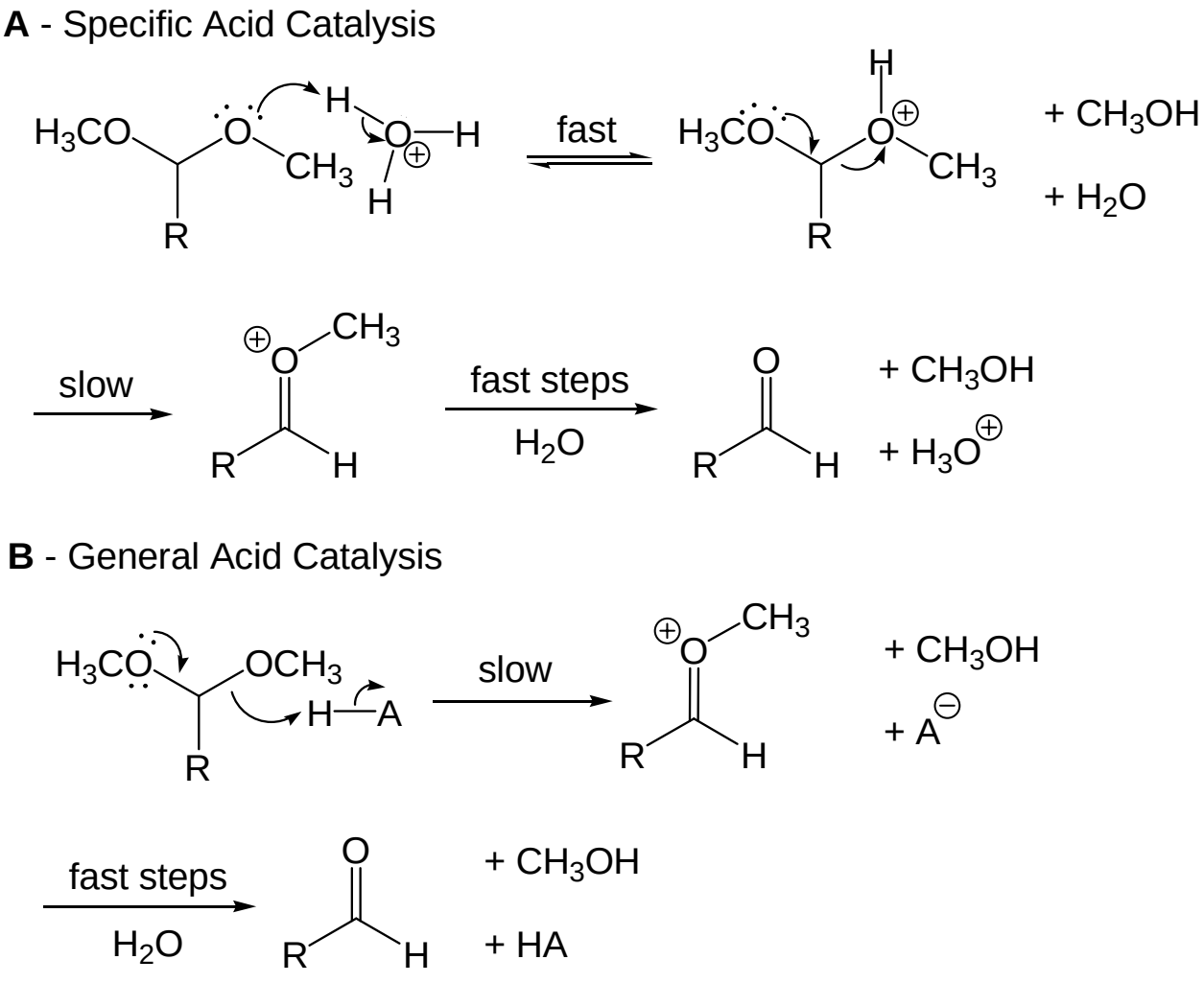

Figure 1. Acetal hydrolysis via SAC (**A**) and GAC (**B**).

Consider a hypothetical reaction which is simultaneously undergoing SAC and GAC. One way to write the rate expression is

$$k_{\text{obs}} = k_{\text{H}_3\text{O}^+}[\text{H}_3\text{O}^+] + k_{\text{HA}}[\text{HA}] + k_0, \quad (3)$$

where k_{obs} is the pseudo first-order rate constant, $k_{\text{H}_3\text{O}^+}$ is the SAC rate constant, k_{HA} is the GAC rate constant, $[\text{H}_3\text{O}^+]$ is the hydronium ion concentration, and [HA] is the concentration of HA, a monoprotic general acid catalyst whose catalytically inactive conjugate base is A^-. Most reactions display a constant background rate k_0 which is unaccounted for by the presence of hydronium ions or general acids. Since this is usually due to substrate reacting with water, the rate expression may be rewritten as

$$k_{\text{obs}} = k_{\text{H}_3\text{O}^+}[\text{H}_3\text{O}^+] + k_{\text{HA}}[\text{HA}] + k_{\text{H}_2\text{O}}[\text{H}_2\text{O}], \quad (4)$$

where $k_{\text{H}_2\text{O}}$ is the water-related rate constant and $[\text{H}_2\text{O}]$ is the concentration of water, a constant in dilute solution. The above rate expression is a realistic scenario; for example, the SAC and GAC hydrolysis of 1,1-dimethoxyethane and trimethoxyethene has been studied using a similar rate expression (*10*).

Effect of pH

The relative efficiency of GAC at a total catalyst concentration $T = [\text{HA}] + [\text{A}^-]$ may be expressed by defining a *fractional function*,

$$f \equiv \frac{k_{\text{HA}}[\text{HA}]}{k_{\text{obs}}} = \frac{k_{\text{HA}}[\text{HA}]}{k_{\text{H}_3\text{O}^+}[\text{H}_3\text{O}^+] + k_{\text{HA}}[\text{HA}] + k_{\text{H}_2\text{O}}[\text{H}_2\text{O}]}, \quad (5)$$

where f is the fraction of the total rate that GAC is responsible for. A more instructive form is

$$f = \frac{k_{\text{HA}} \dfrac{[\text{H}_3\text{O}^+]}{[\text{H}_3\text{O}^+] + K_1} T}{k_{\text{H}_3\text{O}^+}[\text{H}_3\text{O}^+] + k_{\text{HA}} \dfrac{[\text{H}_3\text{O}^+]}{[\text{H}_3\text{O}^+] + K_1} T + k_{\text{H}_2\text{O}}[\text{H}_2\text{O}]}, \quad (6)$$

where [HA] has been rewritten in terms of K_1 (the acid dissociation of HA), $[\text{H}_3\text{O}^+]$, and T. The first derivative with respect to $[\text{H}_3\text{O}^+]$ is

$$\frac{\partial f}{\partial\left([\mathrm{H_3O^+}]\right)} = \frac{k_{\mathrm{HA}}T\left(k_{\mathrm{H_2O}}K_1[\mathrm{H_2O}] - k_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]^2\right)}{\left[k_{\mathrm{H_2O}}[\mathrm{H_2O}]\left(K_1 + [\mathrm{H_3O^+}]\right) + [\mathrm{H_3O^+}]\left(k_{\mathrm{HA}}T + k_{\mathrm{H_3O^+}}\left(K_1 + [\mathrm{H_3O^+}]\right)\right)\right]^2}. \quad (7)$$

Equating this expression to zero gives one admissible critical point,

$$[\mathrm{H_3O^+}] = \sqrt{\frac{k_{\mathrm{H_2O}}[\mathrm{H_2O}]K_1}{k_{\mathrm{H_3O^+}}}}. \quad (8)$$

Calculation of the second derivative shows the critical point to be a maximum. Therefore, the contribution by GAC to the overall rate is maximized at this pH. A proposed GAC reaction mechanism can then be justified using eq. (8), given the appropriate rate constants.

The observation of significant GAC is not limited to the pH given by eq. (8); in fact, most reactions display GAC over a range of pH values. The lower bound reflects the competition between GAC and SAC at low pH and is controlled by the relative size of their corresponding rate constants (see Figure 2). If the lower bound is defined as the point where the GAC rate is equal to the SAC rate, then the lower bound is found at

$$k_{\mathrm{HA}}[\mathrm{HA}] = k_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]. \quad (9)$$

Simplification gives the pH of the lower bound,

$$\mathrm{pH} = -\log\left[\frac{k_{\mathrm{HA}}T}{k_{\mathrm{H_3O^+}}} - K_1\right]. \quad (10)$$

The upper bound of the range is approximately the pK_a of the general acid (see Figure 3), since the dominant acid-base species is the catalytically inactive conjugate base A^-.

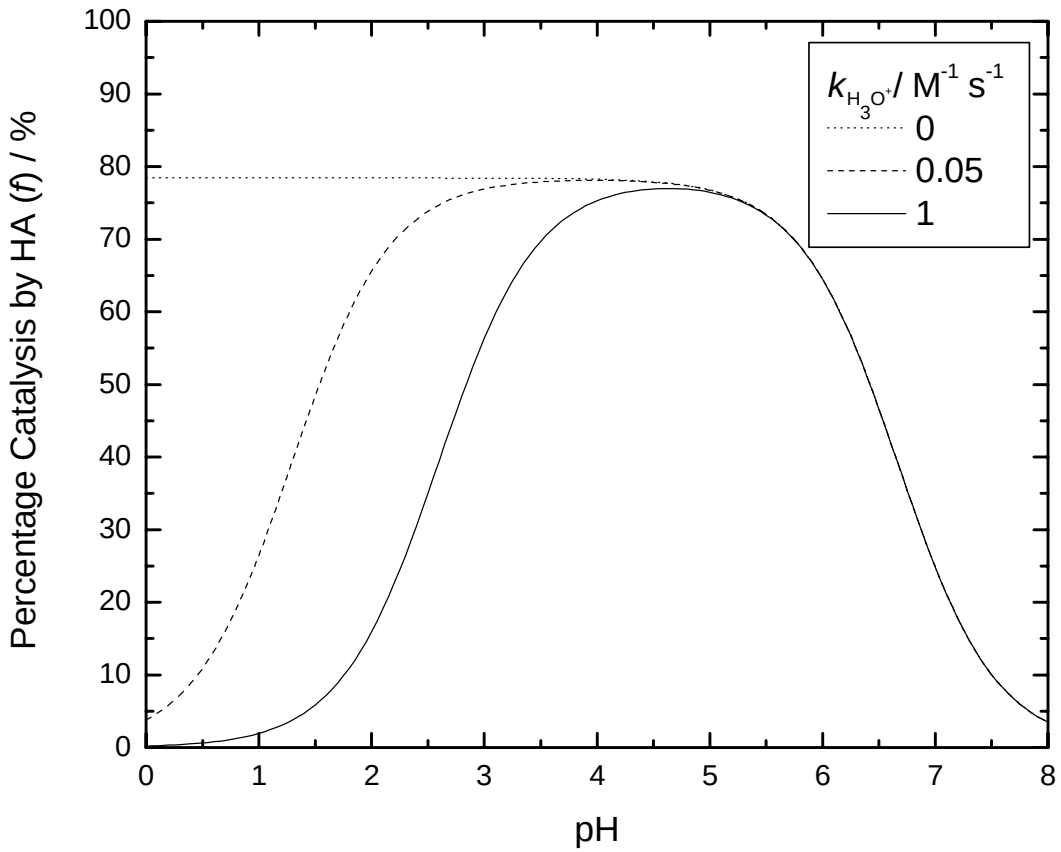

Figure 2. Dependence of GAC efficiency on the SAC rate constant, $k_{H_3O^+}$.

[When $k_{H_3O^+}$ increases, SAC becomes competitive at higher pH values and the effective GAC pH range narrows.

$k_{HA} = 0.02\ M^{-1} \cdot s^{-1}$, $k_{H_2O} = 10^{-5}\ M^{-1} \cdot s^{-1}$, p$K_1$ = 6, and T = 0.1 M.]

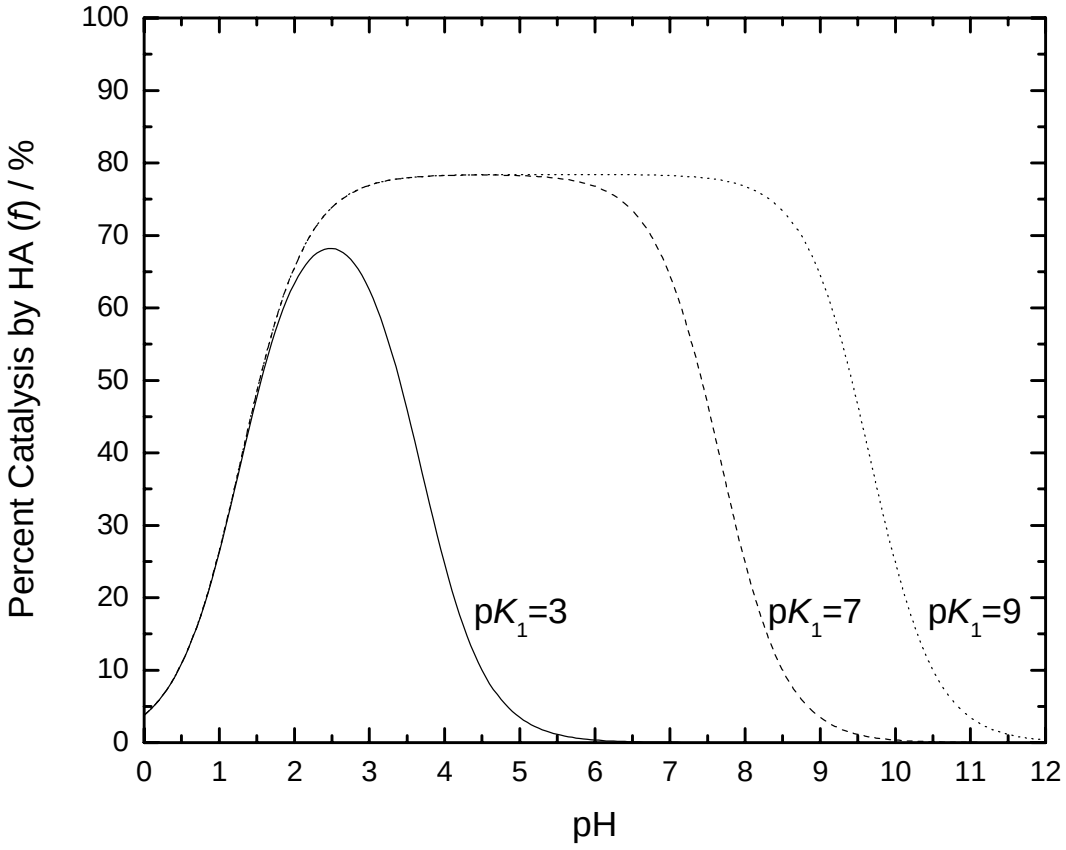

Figure 3. Dependence of GAC efficiency on the pK_a of the general acid for a hypothetical reaction.

[GAC cannot occur efficiently above the pK_a of HA. Strong acids are poor at GAC. $k_{H_3O^+} = 0.05\ M^{-1} \cdot s^{-1}$, $k_{HA} = 0.02\ M^{-1} \cdot s^{-1}$, $k_{H_2O} = 10^{-5}\ M^{-1} \cdot s^{-1}$, T = 0.1 M.]

Effect of pK_a and Catalyst Concentration

Strong acids, such as HCl or HNO_3, have low pK_a values and do not exist in their undissociated forms in solution in catalytically significant amounts; therefore, SAC is favored over GAC when strong acids are used. Moderately acidic organic acids, such as acetic acid or benzoic acid, are relatively effective at GAC. Weak acids, with high pK_a values above that of water, would be unlikely to participate in GAC. For example, it is highly implausible that *n*-hexane would act as an effective proton transfer agent. These trends are shown in Figure 3.

The total catalyst concentration T also affects the width of the pH range. Increasing T makes more HA available at all pH values and therefore increases the width of the pH range. The hydrolysis of substituted

benzaldehyde di-*tert*-butyl acetals (see Figure 4), for example, is known to involve GAC (*11*). Figure 5 illustrates the broadening of the pH range with increasing *T*. *f* vs. pH is plotted for the hydrolysis of the unsubstituted acetal, di-*tert*-butylmethoxybenzene, in acetic acid/acetate buffer for various *T*.

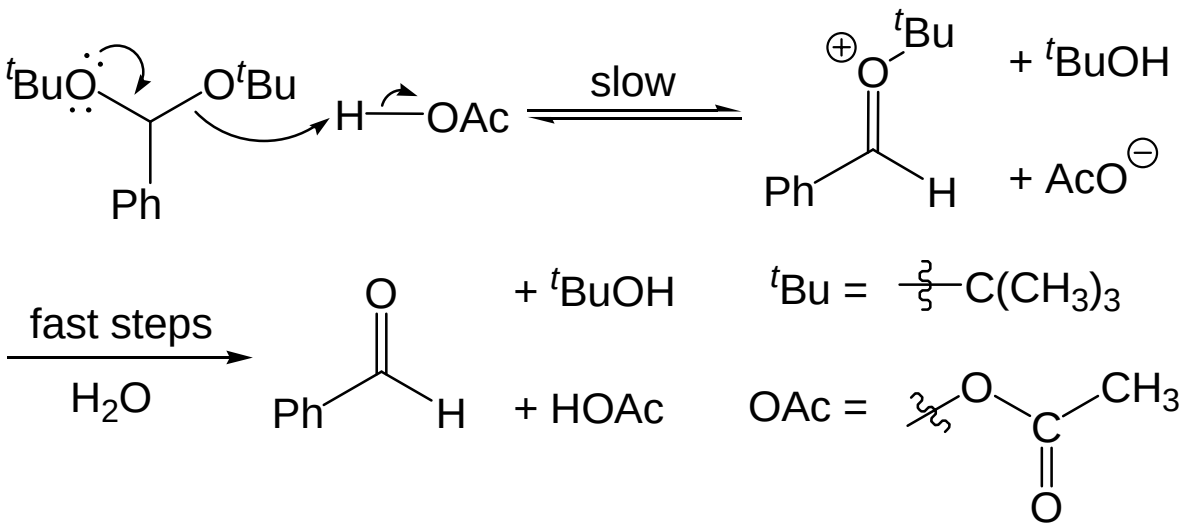

Figure 4. GAC hydrolysis of di-*tert*-butyloxymethylbenzene by acetic acid.

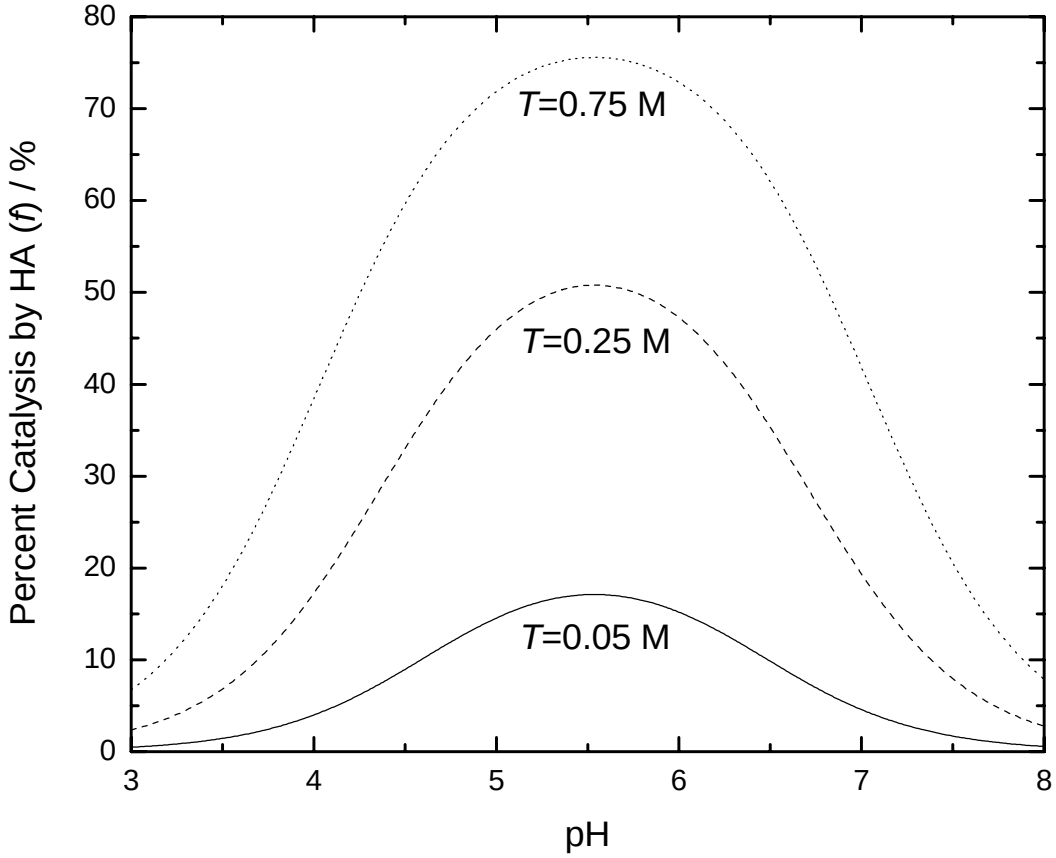

Figure 5. Catalyst concentration and GAC efficiency.

[Calculated GAC efficiencies in the hydrolysis of di-*tert*-butyloxymethylbenzene in acetic acid/acetate buffer are shown for various catalyst concentrations *T* (*11*). As *T* increases, the range of effective pH values for GAC increases. $k_{H_3O^+}$ = 3.31 × 10^3 M^{-1} s^{-1}, k_{HA} = 3.25 × 10^{-1} M^{-1} s^{-1}, and k_{H_2O} = 2.9 × 10^{-5} M^{-1} s^{-1}. SAC and GAC rates are taken from literature data; the offset rate is extrapolated. The acetal was hydrolyzed at 25 ºC in aqueous acetonitrile solutions (1% v/v) maintained at a constant ionic strength μ of 1.0 M with KCl.]

General Base Catalysis

The same analysis applies to the analogous general base case where the rate law is

$$k'_{obs} = k_{OH^-}[OH^-] + k_{A^-}[A^-] + k_{H_2O}[H_2O], \qquad (11)$$

where k_{OH^-} is the rate constant for specific base catalysis, k_{A^-} is the rate constant for general base catalysis (GBC), k_{H_2O} is the background water-related rate constant, and A^- is the catalyzing general base whose catalytically inactive conjugate acid is HA. Replacing $[A^-]$ with its fractional composition form,

$$[A^-] = \frac{K_1}{[H_3O^+] + K_1} T, \tag{12}$$

and $[OH^-]$ with $K_w/[H_3O^+]$, where K_w is the auto-ionization constant of water, gives the corresponding fractional function,

$$g \equiv \frac{k_{A^-}[A^-]}{k'_{obs}} = \frac{k_{A^-} \dfrac{K_1}{[H_3O^+] + K_1} T}{k_{OH^-} \dfrac{K_w}{[H_3O^+]} + k_{A^-} \dfrac{K_1}{[H_3O^+] + K_1} T + k_{H_2O}[H_2O]}. \tag{13}$$

Maximization of g in a similar manner gives the H_3O^+ concentration at which the contribution to the overall rate from GBC is maximized:

$$[H_3O^+] = \sqrt{\frac{k_{OH^-} K_w K_1}{k_{H_2O}[H_2O]}}. \tag{14}$$

Relation to the Brønsted Equation

It is often noted that GAC is most easily observed when the Brønsted coefficient α is near 0.5 (*12*). Relation of the rate constants using the Brønsted equation provides a justification for this common rule. The relevant Brønsted relations are

$$k_{HA} = G K_1^{\alpha}, \tag{15}$$

$$k_{H_3O^+} = G \cdot 55^{\alpha}, \text{ and} \tag{16}$$

$$k_{H_2O} = G \cdot 10^{-16\alpha}, \tag{17}$$

where 55 and 10^{-14} are the acid dissociation constants of hydronium ion and water (*13*), respectively, and α and G are assumed to be constants for simplicity. The observed rate constant k_{obs} of eq. (3) is therefore

$$k_{obs} = G\left(55^{\alpha}[H_3O^+] + K_1^{\alpha}[HA] + 55 \cdot 10^{-16\alpha}\right), \tag{18}$$

where $[H_2O] = 55\ M$ has been used. The quantities within the parantheses in eq. (18) are in concentration units (M) and will now be omitted.

Suppose $\alpha = 0$. Eq. (18) reduces to

$$k_{obs} = G\left([H_3O^+] + [HA] + 55\right). \tag{19}$$

Since $55 \gg [H_3O^+] + [HA]$, it is clear that the water rate dominates. Now suppose $\alpha = 1$. Eq. (18) reduces to

$$k_{obs} = G\left(55\,[H_3O^+] + K_1[HA] + 55 \cdot 10^{-16}\right). \tag{20}$$

Ordinarily, $[H_3O^+] \gg 10^{-16}$, so eq. (20) further reduces to

$$k_{obs} = G\left(55\,[H_3O^+] + K_1[HA]\right) = G\left(55\,[H_3O^+] + K_1\frac{[H_3O^+]}{[H_3O^+] + K_1}T\right). \tag{21}$$

Rewriting, the expression becomes

$$k_{obs} = G[H_3O^+]\left(55 + \frac{K_1T}{[H_3O^+] + K_1}\right). \tag{22}$$

Since K_1 and $[H_3O^+]$ are positive, the fraction must be less than or equal to 1. Therefore, when $\alpha = 1$, the SAC rate dominates. $\alpha = 0.5$ is the "balancing point" between these opposing factors, and that is where the GAC rate dominates.

A good illustration of these concepts involves the aforementioned hydrolysis of di-*tert*-butyloxymethylbenzene in acetic acid/acetate buffer. Literature data show that the reaction has Brønsted parameters $\alpha = 0.60$ and $G = 290$ (*11*). Eq. (8) shows that the (G independent) optimal pH for observing GAC is 5.46, as corroborated by Figure 5. The use of Brønsted relations (15)-(17) allows the calculation of a series of new, theoretical rate constants for various α values. Calculation of the total rate from eq. (18) in turn allows calculation of the fraction of the total rate each catalytic mechanism is responsible for. The results, plotted in Figure 6 for $T = 1$ M, confirm that GAC is dominant near $\alpha = 0.5$. As predicted, SAC is dominant near $\alpha = 1$ and the water mechanism is dominant near $\alpha = 0$.

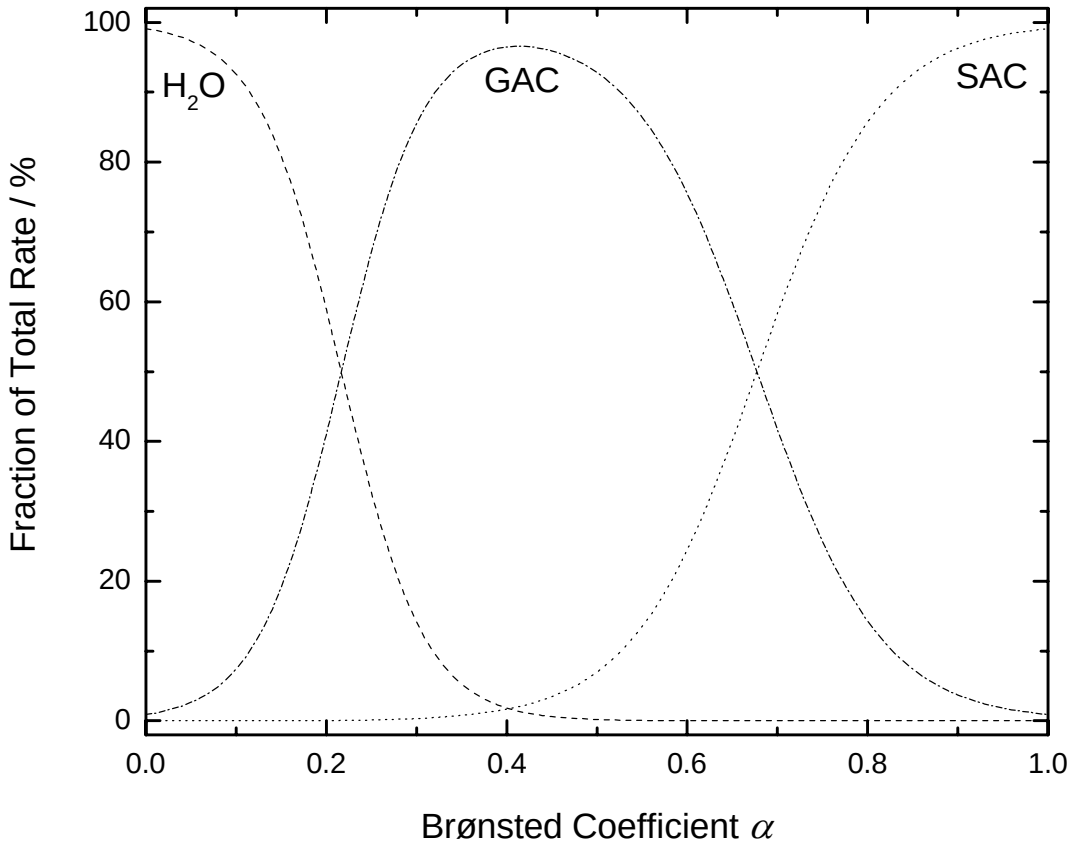

Figure 6. Dependence of dominant catalytic mechanism on the Brønsted coefficient.

[Note that GAC is effective for Brønsted α near 0.5. Low α values favor the water-catalyzed mechanism, while high α values favor SAC.]

Extensions and Limitations

The optimization technique described works for simple systems which can be described by expressions such as eq. (3) or eq. (11) but fails to give analytic solutions for more complex expressions because the obtained polynomials have intractable roots. In addition, multiple maxima or minima may complicate matters. However, given the appropriate rate constants, such problems can be solved using numerical techniques. Polyprotic general acids, with multiple catalytically active acid-base forms, would be expected to display similar pH, pK_a, and *T* effects.

The predicted optimal GAC/GBC pH values are only a guide. A more realistic model would account for activity coefficients and ionic strength effects. The optimal GAC pH might be inaccessible because the buffer ratio

[HA]/[A^-] required would be unobtainable. The optimal pH might occur when the total rate is very low, precluding accurate measurements. Reactions performed in non-aqueous media for solubility reasons may develop deviations due to severe non-ideality. One remedy may be to apply literature acidity functions (*14*).

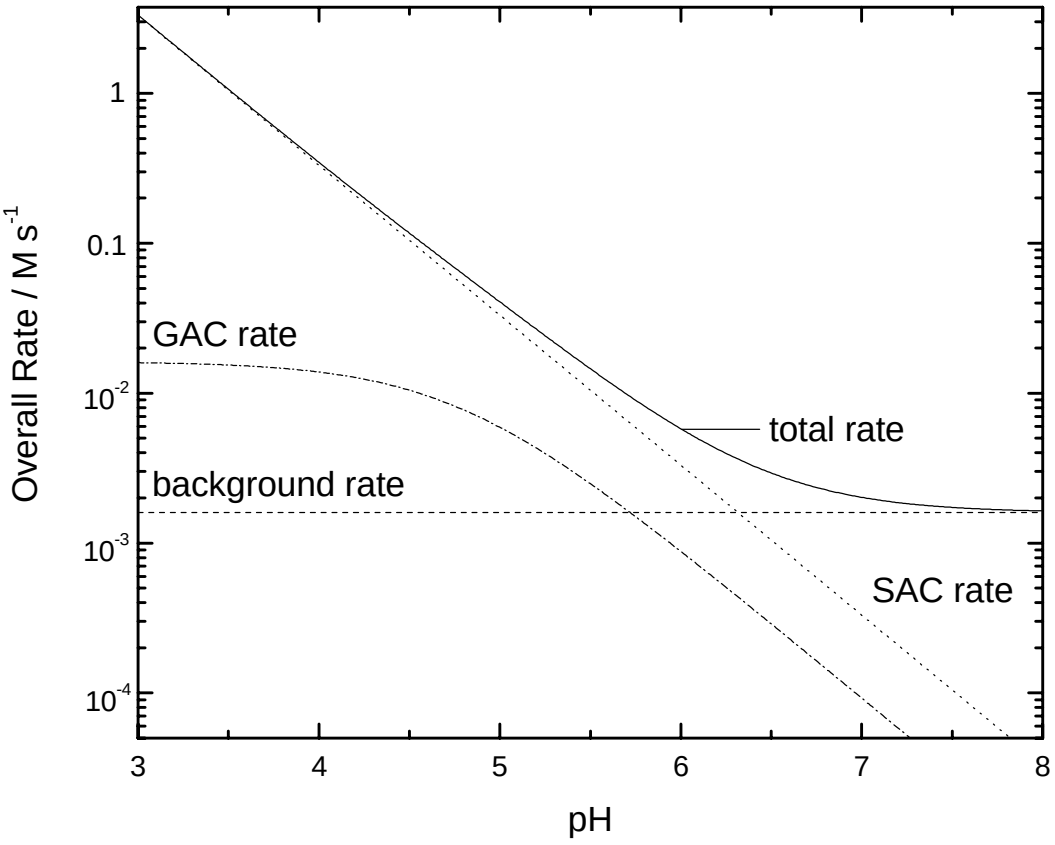

Figure 7. Graphical summary of the effect of pH on the calculated rates of SAC, GAC, and uncatalyzed hydrolysis of di-*tert*-butyloxymethylbenzene in acetic acid/acetate buffer for T = 0.05 M (*11*). In this case, GAC never becomes the dominant mechanism.

Conclusions

Some factors that affect the relative efficiency of SAC and GAC have been discussed. Due to competition with SAC at low pH, GAC is only effective at moderate pH levels. When the pH is above the pK_a of the general acid, the water-catalyzed rate dominates because insufficient general acid catalyst is available for GAC. Figure 7 summarizes these effects for the aforementioned hydrolysis of di-*tert*-butyloxymethylbenzene in acetic acid/acetate

buffer. Eq. (8) gives a simple expression for the hydronium ion concentration at which the relative efficiency of GAC is maximized. An analogous expression, eq. (14), gives the optimal concentration for the general base case. Increasing the SAC to GAC rate constant ratio reduces the effective pH range for GAC. Moderate strength general acids are most effective for GAC and higher total buffer concentrations considerably enhance the relative rate and acceptable pH range for GAC. By using the Brønsted equation to relate the SAC, GAC, and water-related rate constants, the common observation that GAC is most easily observable near $\alpha = 0.5$ can be explained. The ideas presented allow proposed SAC or GAC mechanisms to be verified using experimental rate constants and are suitable for the curriculum of a senior-level undergraduate course in physical-organic chemistry.

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