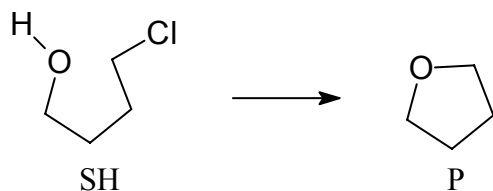**Bronsted Catalysis Law and acid base catalysis**.

Most chemical reactions involve some proton transfer steps accompanying the process. Now we will look at how we get information about the timing of these proton transfer processes to decide on the detailed mechanism. For example consider the overall reaction shown:
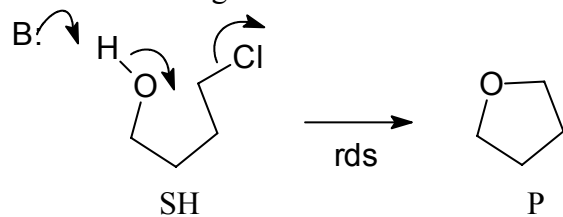

SH   P

We can write three mechanisms differing in the timing of the proton transfer. It could be after the r.d.s. :
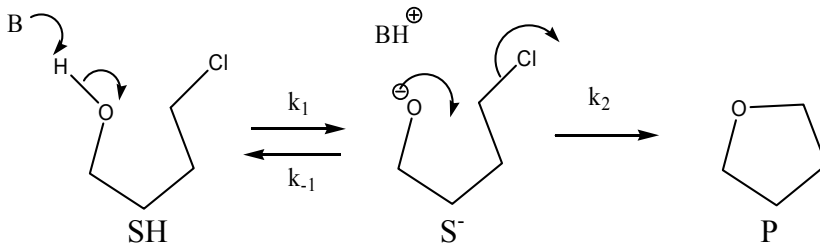

SH   PH$^+$ P
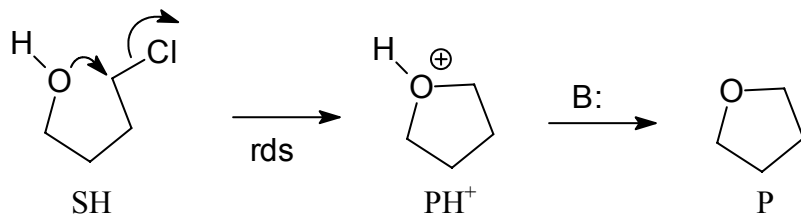
$d[P]/dt = - d[SH]/dt = k_1[SH]$

It could be during the r.d.s. :

SH   P

$d[P]/dt = - d[SH]/dt = k_1[B][SH]$

It could be before the r.d.s. :

SH   S$^-$ P

$d[P]/dt = - d[SH]/dt = k_1k_2[B][SH]/(k_{-1}[BH^+] + k_2) = k_2[S^-]$

We would like to demonstrate that the two forms of the rate law are equivalent and that either is actually going to look like catalysis by HO$^-$.

$$\frac{d[P]}{dt} = k_2[S^-] = \frac{k_1 k_2[B][SH]}{k_{-1}[BH^+] + k_2} \approx \frac{k_1 k_2[B][SH]}{k_{-1}[BH^+]}$$

$$K_1 = \frac{k_1}{k_{-1}} = \frac{[BH^+][S^-]}{[B][SH]}$$

$$\frac{d[P]}{dt} = \frac{[BH^+][S^-]}{[B][SH]} \frac{k_2[B][SH]}{[BH^+]} = k_2[S^-]$$

$$K_a^{SH} = \frac{[S^-][H^+]}{[SH]}$$

$$[S^-] = \frac{K_a^{SH}[SH]}{[H^+]} = \frac{K_a^{SH}[SH][OH^-]}{K_w}$$

$$\frac{d[P]}{dt} = \frac{k_2 K_a^{SH}}{K_w}[SH][OH^-]$$

We will now look at the Linear Free Energy approach which allows us to distinguish these three. As a preliminary consideration, what is the nature of the rate law for each mechanism?

In a solution there may be more than one acid (or base) present. We will illustrate for water as solvent, but this is more general.

Bases: H_2O, HO^-, A_1^-, A_2^-, ...
Acids: H_3O^+, H_2O, HA_1, HA_2, ...

For base catalysis there are two possible situations

1. Specific base catalysis
     Rate = k[HO⁻][X][Y]
i.e. rate depends on the concentration of HO⁻, and not on $[A_1^-]$, $[A_2^-]$, ...

2. General base catalysis
     The rate depends on the concentration of every acid in solution; there will be a term in the rate law for each possible acid, though some contributions may be too small to matter.
     Rate = $k_{OH}[HO^-][X][Y] + k_w[H_2O][X][Y] + k_1[A_1^-][X][Y] + k_2[A_2^-][X][Y] +$
         $= \Sigma(k_{cat})_i[A_i^-][X][Y]$
This is the empirical definition: if only HO⁻ catalyzes a reaction and not other bases in solution then the reaction is specific base catalyzed. If all bases in solution catalyze the reaction then it is general base catalyzed.

For acid catalysis there are two possible situations

1. Specific acid catalysis

   $$Rate = k[H_3O^+][X][Y]$$

i.e. rate depends on the concentration of H_3O^+, and not on $[HA_1]$, $[HA_2]$, ...

2. General acid catalysis

   The rate depends on the concentration of every acid in solution; there will be a term in the rate law for each possible acid, though some contributions may be too small to matter.

   $$Rate = k_H[H_3O^+][X][Y] + k_w[H_2O][X][Y] + k_1[HA_1][X][Y] + k_2 [HA_2][X][Y] +$$
   $$= \Sigma(k_{cat})_i[HA_i][X][Y]$$

This is the empirical definition: if only H+ catalyzes a reaction and not other acids in solution then the reaction is specific acid catalyzed. If all acids in solution catalyze the reaction then it is general acid catalyzed.

If H_2O is to be treated as a catalyst then to compare on the same scale we must put in the concentration of water in water (55.5 M), and also use the pKa for water and H_3O^+ as acids on the same scale as all other acids: pKa for H_2O is 15.74; pKa for H_3O^+ is -1.74.

Sensible people try to control the complexity by designing experiments to limit the number of terms in the rate law for any set of experiments. What the general rate law does warn us is that there are going to be at least there terms in any buffered system.

$$Rate = k_H[H_3O^+][X][Y] + k_w[H_2O][X][Y] + k_1[HA_1][X][Y]$$

You must always be careful to check how the water rate constant is defined; k_w may mean either the second order rate constant as above or the pseudo first order rate constant, $k_w[H_2O]$. For use on a Bronsted plot one wants the second order rate constant.

General acid catalysis is characterized experimentally in a Bronsted plot where logarithms of rate constants for the various acids are plotted as a function of the acidity, log Ka (or -pKa)

k_{cat} = catalytic constant
= k_H, k_w, k_1, k_2 above
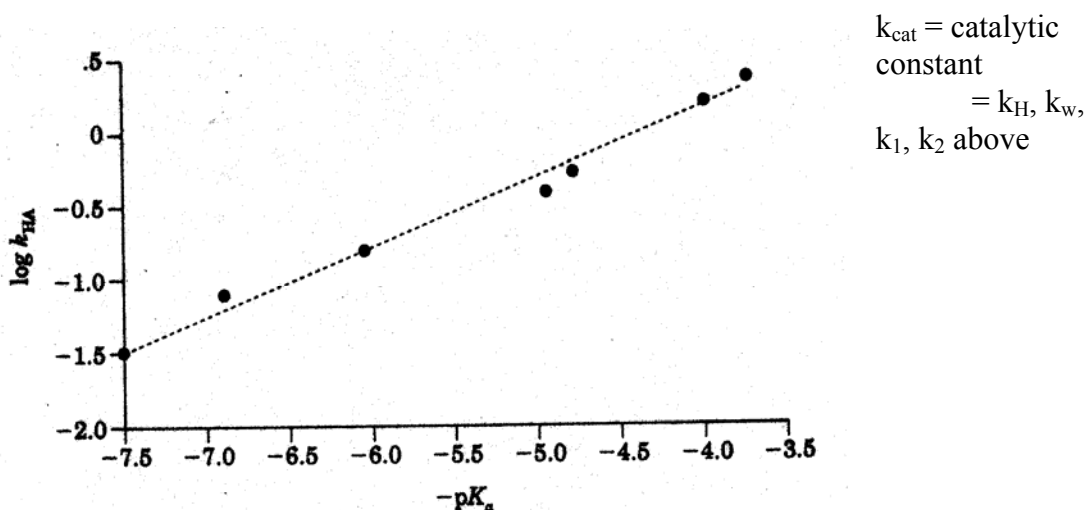
The equation for the linear relation is:

$$\log k_{cat} = \alpha \log K_a + C :$$ the Bronsted Catalysis Law

The normal range of α is: $0 < \alpha < 1$
The analogous plot for general base catalysis is described by the relation

$$\log k_{cat} = \beta \log K_a + C$$
and the normal range of β is $-1 < \beta < 0$

This is a linear free energy relation where we compare formation of the transition state to complete proton transfer to or from solvent. If all that changes is the strength of the acid or base catalyst, how does the rate constant respond? If proton transfer is complete in the transition state then the change in the free energy of the transition state should be the same as the change in free energy for the reference reaction; slope = 1.

Although it is common to use only a narrow range of general acids as in the example above, the plot really should extend from H_2O to H_3O^+, but this is not always practical. If H_2O and H_3O^+, fall on the same line as the other general acids, then they follow the same mechanism. If they do not then we need an explanation for why the mechanism is different for the one(s) that deviate.

At $\alpha = 0$, there is no acid catalysis: only solvent matters.
At $\alpha = 1$, there is specific acid catalysis; only H_3O^+ matters.

At $\beta = 0$, there is no acid catalysis: only solvent matters.
At $\beta = -1$, there is specific acid catalysis; only HO^- matters.

Interpretation of α or β. The Bronsted slope is a rough measure of the extent of proton transfer at the transition state: how much does the transition state respond to a change in catalyst relative to the change in the reference reaction.

$\underline{\alpha} = 1.0$ proton is fully transferred
$\alpha = 0.0$ proton is not transferred at all
α in between   proton is in "flight" at the transition state.

How are k_{cat}'s determined?
     Take the simplest case

X + Y ⟶ Product
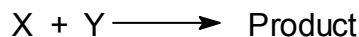
with catalysis by H_3O^+ and HA_1
then under pseudofirst order conditions ($[H_3O^+]$, $[HA_1]$ constant)
     Rate = $k_{obs}[X][Y]$

where $k_{obs} = k_H[H_3O^+] + k_1[HA_1] + k_w[H_2O]$

Measure rates at one pH and different buffer concentrations. pH is set by the buffer ratio, $[HA]/A^-]$

Recall $\quad\quad K_a = [H_3O^+][A^-]/[HA]\quad \log K_a = \log [H_3O^+] + \log ([A^-]/[HA])$

and so $\quad\quad pK_a = pH + \log ([HA]/[A^-])$

or $\quad\quad pH = pK_a - \log ([HA]/[A^-])$

Experiments are done at constant buffer ratio ($[HA]/[A^-]$), but different actual values of $[HA]$, i.e. $[HA]_T$ varies

$$[HA]_T = [HA] + [A^-]$$

For a plot of k_{obs} vs $[HA]_T$

slope $= k_1$

if slope $= 0$, then there is no general acid catalysis!

Analogously if the reaction were catalyzed by B_1, H_2O, and HO^-, then under pseudofirst order conditions ($[HO^-]$, $[B_1]$ constant), then

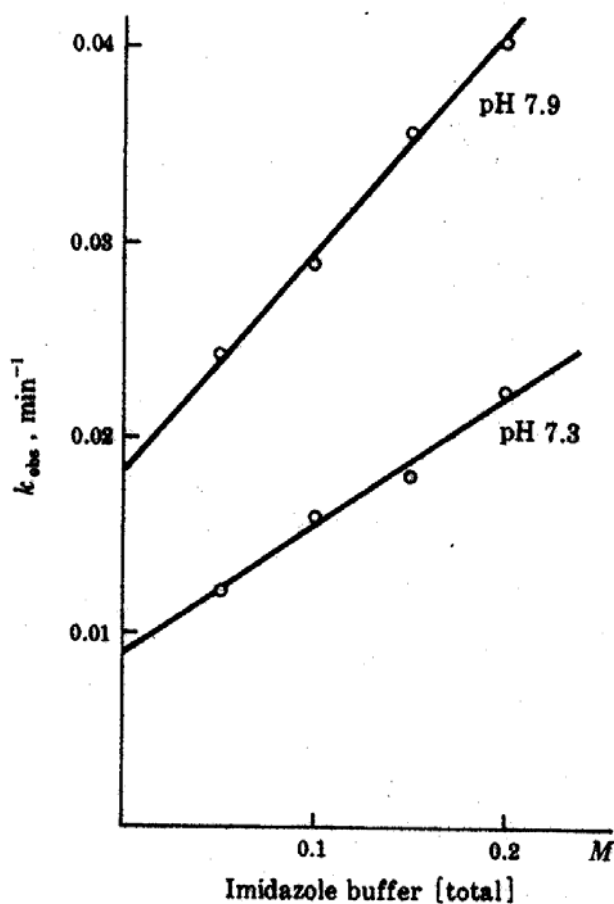$$k_{obs} = k_{OH}[HO^-] + k_w[H_2O] + k_1[B_1]$$

Experiments are done at constant buffer ratio ($[HB^+]/[B]$), but different actual values of $[B]$, i.e. $[B]_T$ varies

$$[B]_T = [HB^+] + [B]$$

For a plot of $_{kobs}$ vs $[B]_T$

slope $= k_1$

if slope $= 0$, then there is no general base catalysis

An example: the general base catalyzed hydrolysis of acetylimidazole, with imidazole as catalyst. The advantage of this example is that there is no possibility of the catalyst being other than a base because if it acted as a nucleophile there would be no net reaction. k_{obs} clearly depends on the concentration of buffer, and the slope of the line at pH 7.9 is greater than that of the line at pH 7.3. This tells us that the base form of the buffer is the more important. The intercept is greater at pH 7.9 than at pH 7.3. This tells us that there is also a contribution to the observed rate from hydroxide catalysis.
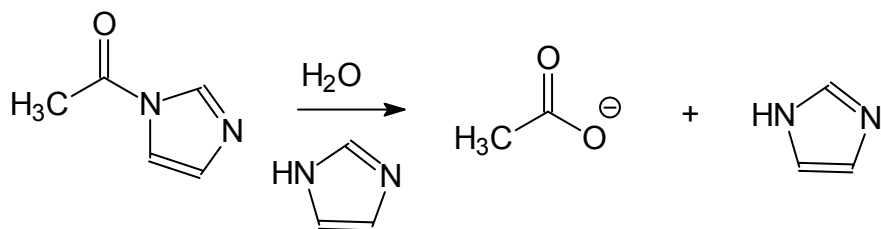
In practice it is hard to determine very small or very large values of α, except in rare cases where H_2O or H_3O^+ fall off the line because of a change in mechanism.

Specific and General Acid Catalysis can be more complex than one might imagine at first glance. Some examples follow:
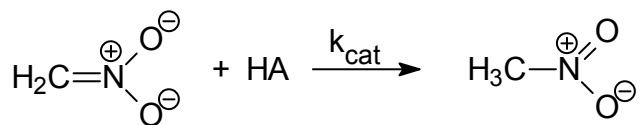
1. Simple general acid catalysis

$$S + HA \xrightarrow{k_{cat}} P$$
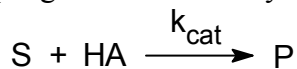
Rate = $k_{cat}[HA][S]$

under pseudofirst order conditions, [HA] constant

$k_{obs} = k_{cat}[HA]$

An example

$$H_2C=\overset{\oplus}{N}\overset{O^{\ominus}}{\underset{O^{\ominus}}{}} \quad + \ HA \quad \xrightarrow{\ k_{cat}\ } \quad H_3C-\overset{\oplus}{N}\overset{O}{\underset{O^{\ominus}}{}}$$

    nitronate   nitromethane

Nitromethane has a pKa of ca. 10. The presumed transition state has the structure:

$$\overset{\delta\ominus}{A}\cdots H \atop H_2\overset{}{C}=\overset{\oplus}{N}\overset{O^{\delta\ominus}}{\underset{O^{\ominus}}{}}$$
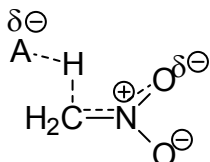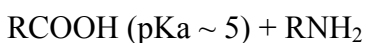
Three features to note:
       1) the reaction goes at a readily measurable rate (i.e. measurably slow even though it is a proton transfer, acid - base reaction
       2) Note the extensive geometrical rearrangement involved in moving from starting material to TS to products: bond lengths change, geometry changes from sp^2 to sp^3.
       3) The microscopic reverse of general acid catalysis is general base catalysis.

Contrast this behavior with that of oxygen and nitrogen acids (and even sulfur, etc.). For ROH, ROH_2^+, RNH_2, RNH_3^+, H^+ transfers in oxygen and nitrogen acids have low activation barriers. For these reactions there is essentially no geometry change accompanying proton transfer. In fact in the favorable direction, (i.e. the thermodynamically exergonic direction) they are diffusion controlled. This means that the rate determining step is diffusion together of acid and base; once they are in the same solvent cage reaction is faster than diffusion apart.
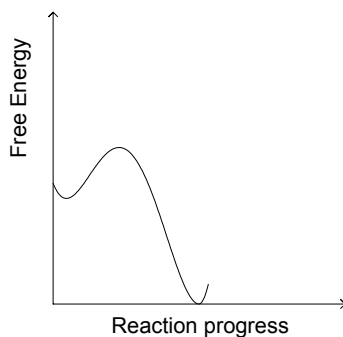
NH and OH acids
RCOOH (pKa ~ 5) + RNH_2
$\Delta G^\ddagger$ very small
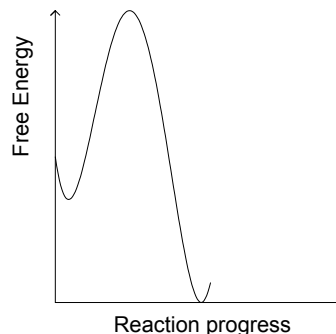
But for carbon acids
$CH_2=N^+(O^-)_2$ + RCOOH (pKa ~ 5)
$\Delta G^\ddagger$ large enough to yield

relatively slow k's

k ~ 10^{10} M^{-1}s^{-1} "diffusion controlled"   k ~ 400 M^{-1}s^{-1}

specific acid, $\alpha = 0$ or 1   general acid, $\alpha \sim 0.5$

reaction leads to: reaction leads to:

RCOO$^-$ + RNH$_3^+$ (pKa ~ 10 or 11)   CH$_3$-NO$_2$ (pKa ~ 10) + OAc$^-$

Other classes of acids (SH, PH are intermediate)

2. Preequilibrium protonation followed by rate determining step.
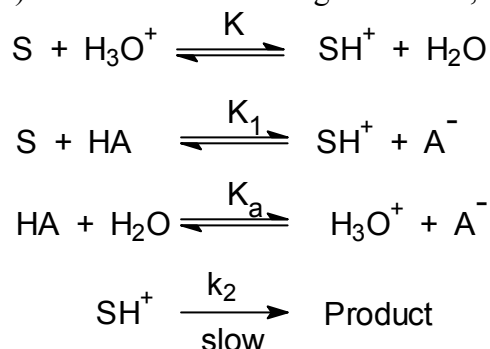a) H$_3$O$^+$ as the acid.

$$S + H_3O^+ \xrightleftharpoons{K} SH^+ + H_2O \qquad K = \frac{[SH^+]}{[S][H_3O^+]}$$
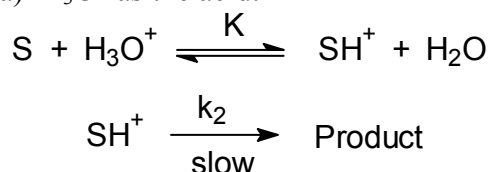
$$SH^+ \xrightarrow[\text{slow}]{k_2} \text{Product} \qquad thus\,[SH^+] = K[S][H_3O^+]$$

Rate = d[P]/dt = k$_2$[SH$^+$]
  = k$_2$K[S][H$_3$O$^+$]

b) same reaction with a general acid, HA, as the catalyst.

$$S + H_3O^+ \xrightleftharpoons{K} SH^+ + H_2O$$

$$K = \frac{[SH^+]}{[S][H_3O^+]} \quad [SH^+] = K[S][H_3O^+]$$

$$S + HA \xrightleftharpoons{K_1} SH^+ + A^-$$

$$K_1 = \frac{[SH^+][A^-]}{[S][HA]} \quad [SH^+] = \frac{K_1[S][HA]}{[A^-]}$$

$$HA + H_2O \xrightleftharpoons{K_a} H_3O^+ + A^-$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \quad \frac{[HA]}{[A^-]} = \frac{[H_3O^+]}{K_a}$$

$$SH^+ \xrightarrow[\text{slow}]{k_2} \text{Product}$$

Rate

$$\frac{d[P]}{dt} = k_2[SH^+] = k_2 K_1 \frac{[S][HA]}{[A^-]} = k_2 K_1 \frac{[S][H_3O^+]}{K_a} = \left\{ k_2 \frac{K_1}{K_a}[H_3O^+] \right\}[S]$$

This is the same as (2a) if $K_1/K_a = K$

Check: $\dfrac{K_1}{K_a} = \dfrac{[SH^+][A^-][HA]}{[S][HA][H_3O^+][A^-]} = \dfrac{[SH^+]}{[S][H_3O^+]} = K$

∴ Rate = d[P]/dt = k$_2$K[H$_3$O$^+$][S]   the same as in 2a.

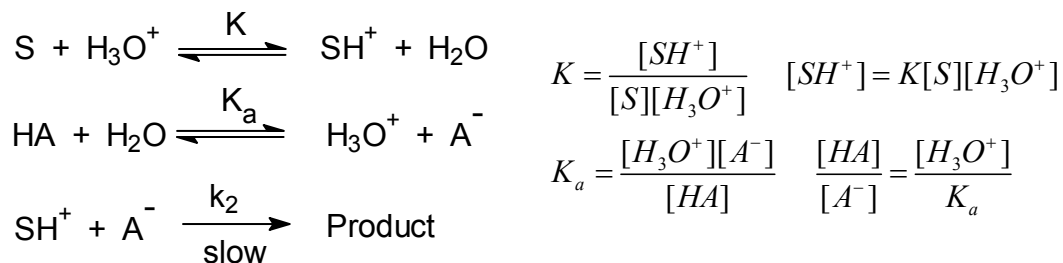The rate law predicts that the rate will depend on [H$_3$O$^+$] but not on [HA].
Experimentally this is specific acid catalysis. This is true for any reaction in which HA is

involved only in equilibria before the RDS. I.e. HA is not in the TS, $\therefore$ not in the rate law. The transition state contains only the elements of SH^+ (and perhaps some solvent).

Remember that kinetics can only tell you the composition of the transition state.

Remember that specific acid catalysis implies $\alpha \sim 1$, and a proton $\sim$ fully transferred at the TS; this is the case with pre-equilibrium protonation.

3. Reversible proton transfer followed by rate determining reaction with the conjugate base.

$$S + H_3O^+ \underset{}{\overset{K}{\rightleftharpoons}} SH^+ + H_2O$$

$$K = \frac{[SH^+]}{[S][H_3O^+]} \quad [SH^+] = K[S][H_3O^+]$$

$$HA + H_2O \underset{}{\overset{K_a}{\rightleftharpoons}} H_3O^+ + A^-$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \quad \frac{[HA]}{[A^-]} = \frac{[H_3O^+]}{K_a}$$

$$SH^+ + A^- \xrightarrow[\text{slow}]{k_2} \text{Product}$$

Rate:

$$\frac{d[P]}{dt} = k_2[SH^+][A^-] = k_2K[H_3O^+][S][A^-] = k_2K\frac{[H_3O^+][S]K_a[HA]}{[H_3O^+]} = k_2KK_a[HA][S]$$

This is the equation for **general acid catalysis**.

Exercise for independent study: Show that one obtains the same result by writing the first step using a general acid, HA, in place of H_3O^+.

Conclusions:

Specific acid catalysis, SAC, followed by general base catalysis, GBC, has the same kinetic form as general acid catalysis. I.e. GAC and SAC-GBC are kinetically indistinguishable, and are two alternative mechanisms which must be considered whenever one observes GAC kinetics. Analogously SBC followed by GAC will look like GBC and these are kinetically indistinguishable.
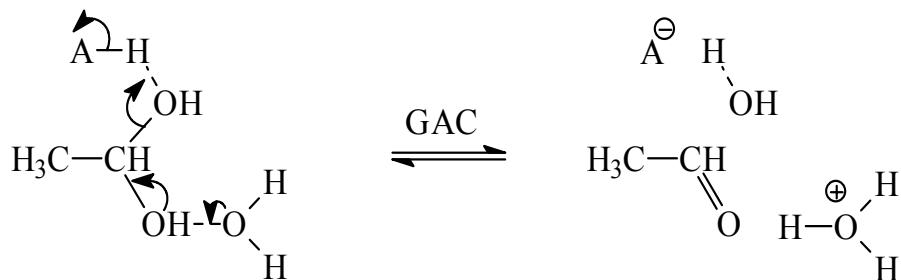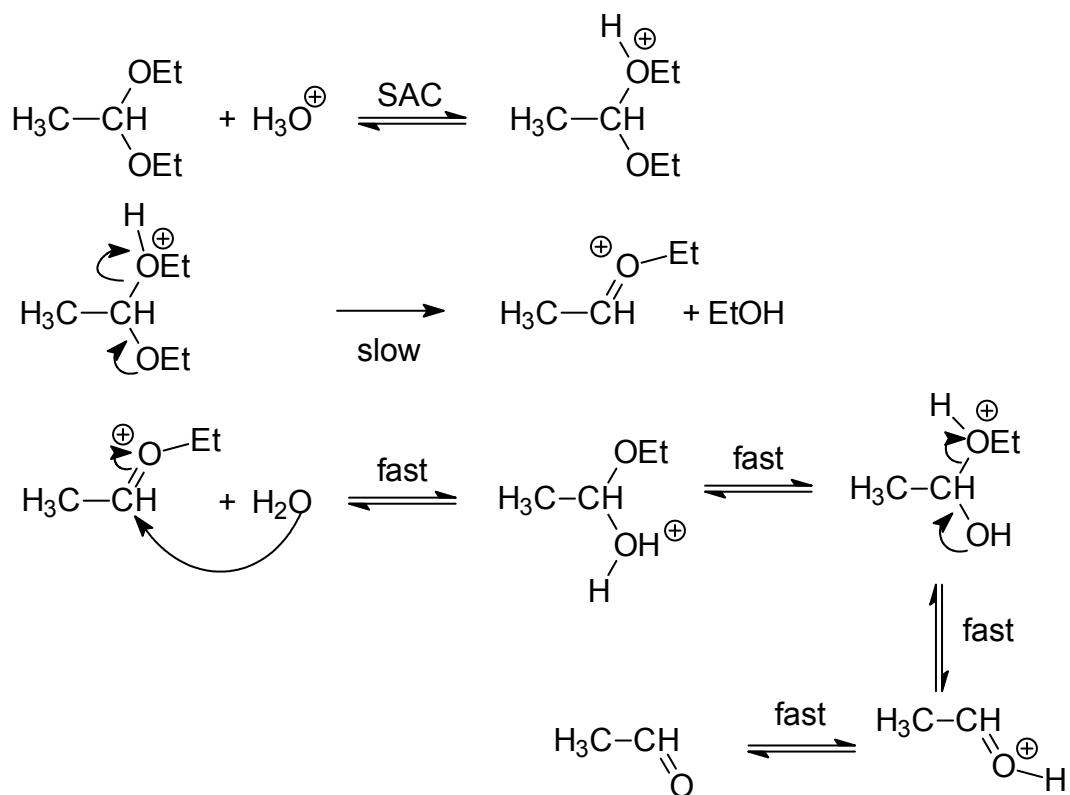
Examples
a)
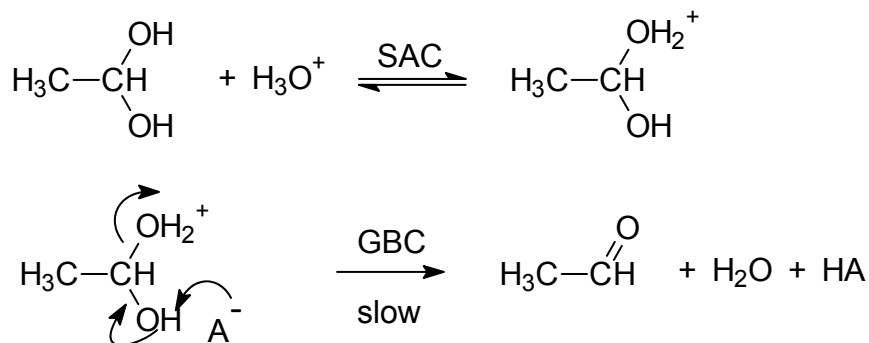
SAC-GBC

or:

GAC

What is the composition of the transition state for the rds?
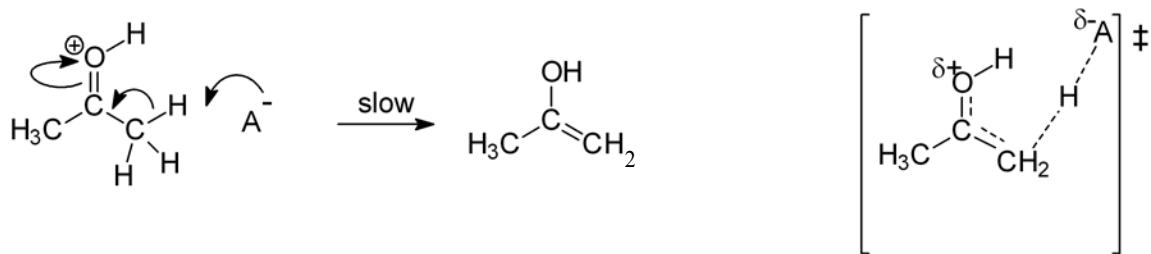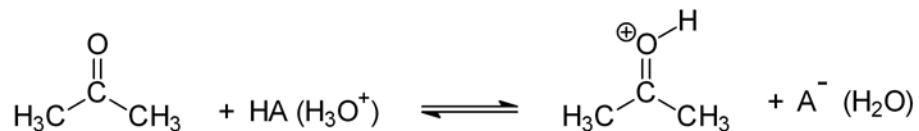What is the rate law for the reverse reaction?
We see this kind of catalysis because in the second step there is a proton which can be removed, and removal of which avoids a bad intermediate. Removal of the proton is unfavorable before the C-O cleavage but is favorable afterwards.
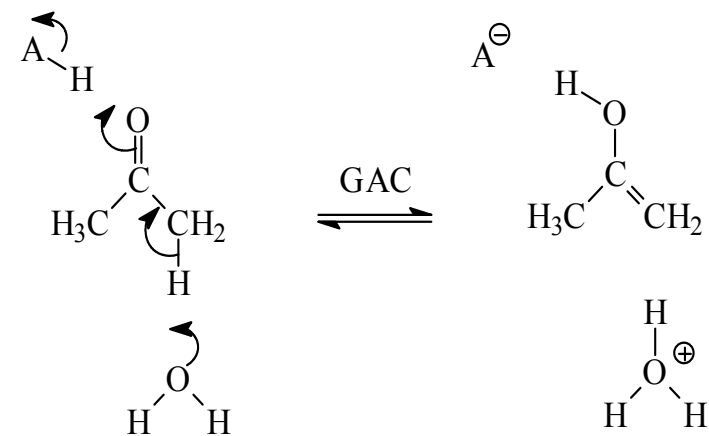
b)

all steps after the rds are fast. Here there is no removable proton in the second step
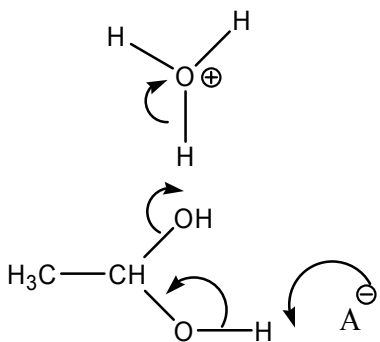
c)

SAC-GBC

or

GAC

How does one distinguish GAC from SAC-GBC?

Study a model compound with H replaced by CH_3 or C_2H_5; see if rate depends on [HA] or [A⁻].

Dehydration of acetaldehyde hydrate: The reaction is observed to be general acid catalyzed. There are two mechanisms to consider:

SAC-GBC

GAC (GBC by water)

the proton transfer from H_3O^+ to $MeCH(OH)_2$ is
unfavorable but not by much; a little progress along
the reaction coordinate will make it favorable so that
at the transition state the proton will be fully transferred.
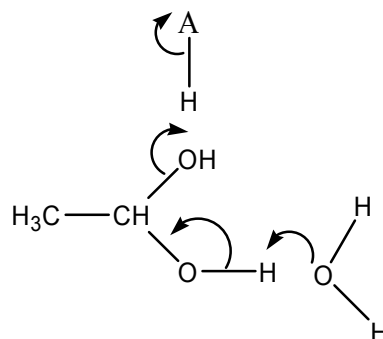
If the reaction of the hydrate is SAC-GBC,   If the reaction of the hydrate is
we predict that the reaction of the acetal   GAC-(GBC by water)
will be SAC   we predict that the reaction of
                                             the acetal will be GAC

The second example, hydrolysis of acetaldehyde diethyl acetal, serves as the test
reaction by the alkyl trick.

SAC

the proton transfer from H_3O^+ to $MeCH(OR)_2$ is
unfavorable but not by much; a little progress along
the reaction coordinate will make it favorable so that
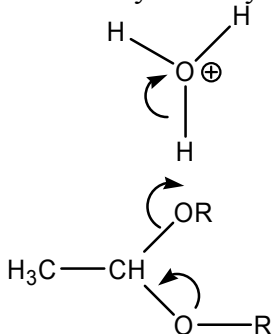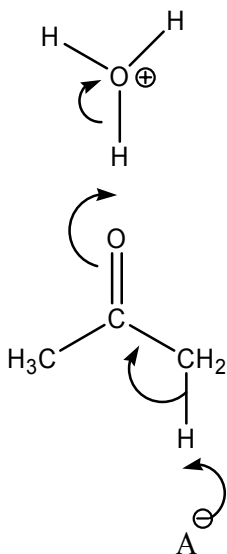at the transition state the proton will be fully transferred.

The acetal hydrolysis reaction is observed to be Specific Acid Catalyzed and NOT
General Acid Catalyzed. Therefore we conclude that the reaction of acetaldehyde
hydrate is Specific Acid General Base catalyzed.

The enolization of acetone is observed to be (among other catalytic paths) subject to
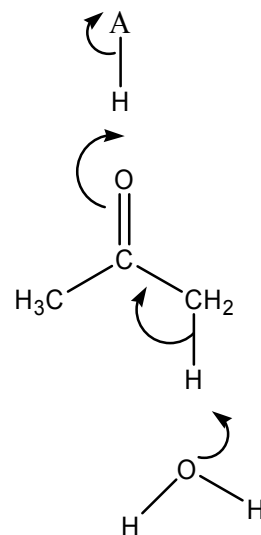General Acid Catalysis. This could be SAC-GBC or GAC-(GBC by water).

SAC-GBC GAC (GBC by water)

the proton transfer from H_3O^+ to acetone is
unfavorable but not by much; a little progress along
the reaction coordinate will make it favorable so that
at the transition state the proton will be fully transferred.

In order to apply the alkyl trick we will have to consider the
reverse reaction. The problem is that if we were to generate a
solution of the oxocarbenium ion:
it would preferentially do something else (add water and
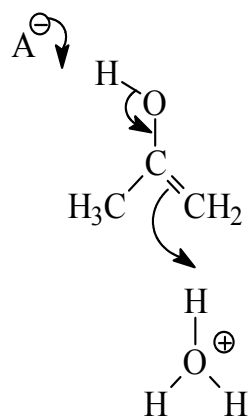hydrolyze) rather than lose a proton to form the enol ether
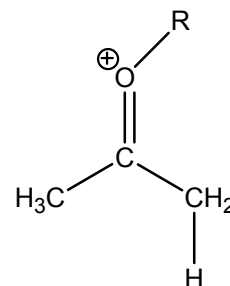
The microscopic reverse is ketonization and if enolization is mechanistically SAC-GBC,
then ketonization must be kinetically GAC. We can use the alkyl trick for the
ketonization reaction by studying the hydrolyis of an enol ether; the rate determiningstep
is the first step, protonation at carbon.
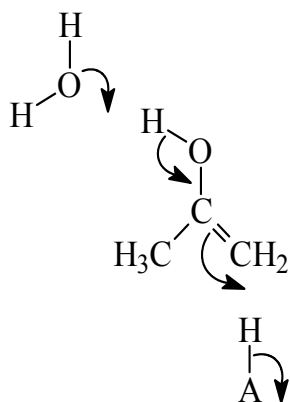
GAC-GBC (by water)   SAC-GBC

If the enolization reaction is SAC-GBC, If the enolization reaction is
then the ketonization reaction is   GAC-(GBC by water)
GAC-(GBC by water) and we predict that then the ketonization is SAC-GBC and
the reaction of the enol ether will be GAC we predict that the reaction of
                                        the enol ether will be SAC

What is observed is that the hydrolysis of enol ethers is kinetically GAC.

4) The presentation so far has been mainly in terms of GAC, whether mechanistically
GAC or SAC-GBC. Of course many reactions are GBC, and similar considerations
apply and there are SBC-GAC reactions as well. Even worse, reactions can be
simultaneously GAC and GBC; enolization of carbonyl compounds is a simple example.
Thus if one observes that the rate of a reaction in buffered solution depends on the
concentration of the buffer at fixed pH (fixed buffer ratio), then one must ask whether the
catalysis is kinetically GAC or GBC or both.

Imagine the following general case
$$k_{obs} = k_o + k_H[H_3O^+] + k_{OH}[OH^-] + k_{HA}[HA] + k_A[A^-]$$
Procedure
The last two terms involve the buffer. We group the buffer terms and write
$$k_{buff}[buffer] = + k_{HA}[HA] + k_A[A^-]$$
where [buffer] = [HA] + [A^-]
$$k_{buff} = k_{HA}\frac{[HA]}{[buffer]} + k_A\frac{[A^-]}{[buffer]}$$
now we define

$$f_{HA} = \frac{[HA]}{[buffer]}$$

$$f_A = \frac{[A^-]}{[buffer]}$$

Necessarily, $f_{HA} + f_A = 1$, and thus $f_A = 1 - f_{HA}$

$$k_{buff} = k_{HA}f_{HA} + k_A(1 - f_{HA})$$

Thus
$$= k_{HA}f_{HA} + k_A - k_A f_{HA}$$
$$= (k_{HA} - k_A)f_{HA} + k_A$$

A plot of k_{buff} vs f_{HA} yields a straight line
  The intercept at $f_{HA} = 0$ is k_A
  The intercept at $f_{HA} = 1$ is k_{HA}

Alternatively, $f_{HA} = 1 - f_A$
$$k_{buff} = k_{HA}(1 - f_A) + k_A f_A$$
$$= k_{HA} - k_{HA}f_A + k_A f_A$$
$$= k_{HA} + (k_A - k_{HA})f_A$$
and a plot of k_{buff} vs f_A yields a straight line
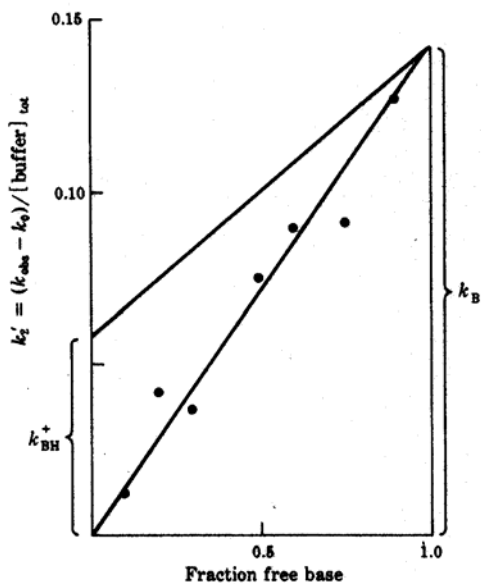 The intercept at $f_A = 0$ is k_{HA}
  The intercept at $f_A = 1$ is k_A

Procedure:
1) plot k_{obs} vs [buffer] for a series of pH's; for each pH calculate k_{buff}.

Recall $k_{buff}[buffer] = + k_{HA}[HA] + k_A[A^-]$

2) plot k_{buff} values vs f_{HA} or f_A:

Fraction free base

It is best to determine the line by least squares; a good least squares program gives uncertainties in the intercepts. If an intercept differs from zero by less than its uncertainty, then we can conclude that it is zero, and the reaction is simple GAC or GBC. If both intercepts differ from zero by more than their uncertainty then the reaction is both GAC and GBC. This plot is an example of an inherently honest plot, because the total possible range of f_A is used to define the plot and one can see qualitatively how well the two intercepts are defined.

Some generalization s about specific/general acid/base catalysis

SPECIFIC ACID	GENERAL ACID
Only H_3O^+ is effective; pH alone matters	Any acid may be an effective catalyst; pH is also important
Proton transfer is completed by the TS for the RDS	Proton transfer is occurring in the TS
Usually the RDS involves reaction of the protonated substrate	The catalyst is too weakly acidic to protonate the substrate
	The proton is added to a site that becomes more basic in the TS
	Unless H is transferred to C, some other bond making or bond breaking process is involved in RDS
Usually only simple uni or bi-molecular steps.	Can be "termolecular" reaction, with large -ve $\Delta S^{\ddagger}$
SPECIFIC BASE	GENERAL BASE
Only HO^- is effective: pH alone matters	Any base may be an effective catalyst; pH is also important
Proton transfer is completed by the TS for the RDS	Proton transfer is occurring in the TS for the RDS
Usually RDS involves reaction of the deprotonated substrate	The catalyst is too weakly basic to deprotonate the substrate
	The proton which is removed becomes more acidic in the TS
	Unless H is on C, someother bond making or bond breaking process is involved in RDS
Usually only simple uni or bi-molecular steps.	Can be "termolecular" reaction, with large -ve $\Delta S^{\ddagger}$

The "termolecular" reaction in a general acid/base catalyzed mechanism is actually only bimolecular because a hydrogen bonded complex can form between catalyst and one of the reactants, which then need only collide with the remaining reactant.