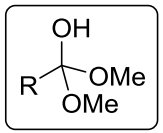
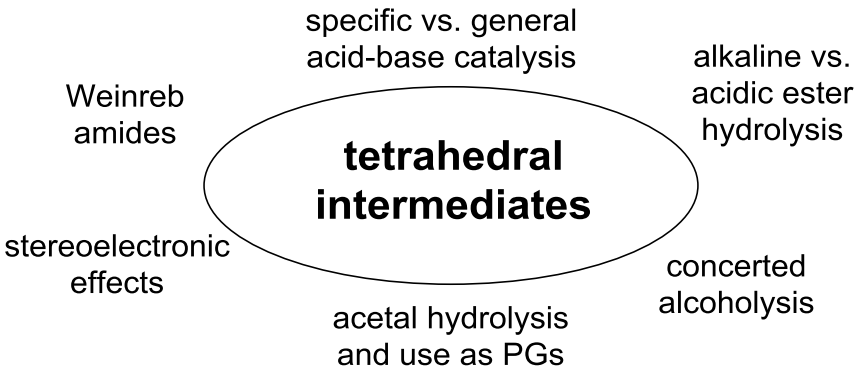
Tetrahedral Intermediates

Eugene E. Kwan

October 29, 2014.



Scope of Lecture



Helpful References

1. "Concerted Mechanisms of Acyl Group Transfer Reactions..." Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387-392.

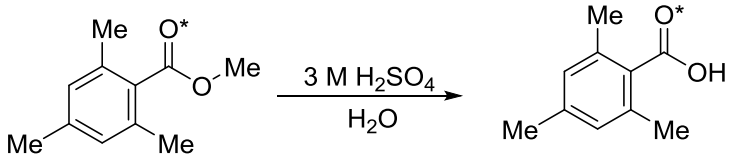
2. "Mechanism and Catalysis for Hydrolysis of Acetals..." Cordes, E.H.; Bull, H.G. Chem. Rev. **1974**, *74*, 581-603.

3. "Direct Observation of Simple Tetrahedral Intermediates." Capon. B.; Ghosh, A.K.; Grieve, D.M.A. *Acc. Chem. Res.* **1981**, *14*, 306-310.

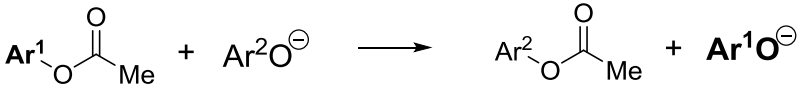
4. "Tetrahedral Intermediates in the Reactions of Carboxylic Acid Derivatives with Nucleophiles." Adler, M; Adler, S.; Boche, G. *J. Phys. Org. Chem.* **2005,** *18,* 193-209.

Key Questions

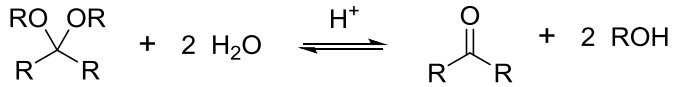
What does isotopic exchange tell us about the mechanism of this reaction?



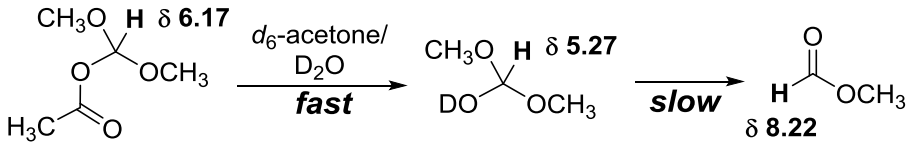
Could this occur by a concerted mechanism?



What's the rate-determining step here?

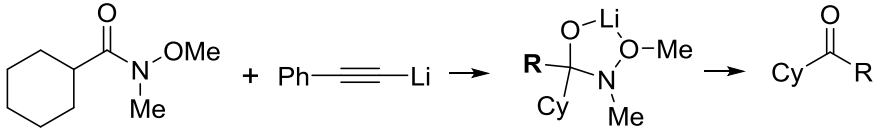


Can tetrahedral intermediates be observed directly?



high energy precursor

Why does this reaction stall at 50% conversion?



not appreciably complexed by Li

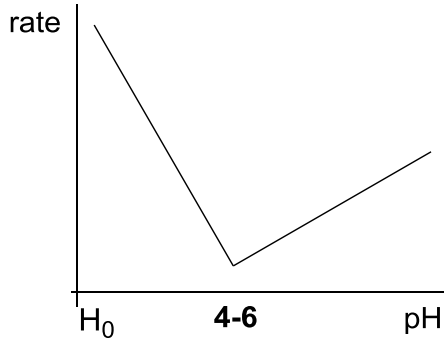
1.0 equiv

lecture notes edited by Richard Liu

Mechanisms of Ester Hydrolysis

"Mechanisms of Catalysis of Nucleophilic Reactions of Carboxylic Acid Derivatives." Bender, M.L. *Chem. Rev.* **1960** *60* 53.

The pH-rate profiles for the hydrolysis of simple alkyl ester generally have two regions, with a clear minimum at pH 4-6:



In general, concave up curvatures of this kind are attributed to *changes in mechanism*. In this case, there is a change from an acid-catalyzed pathway to a base-catalyzed pathway. More precisely, one may express the pseudo-first-order rate constant as a linear combination of contributions from different mechanisms, whose dominance changes with varying pH (see Kwan *J Chem Ed* **2005** *82* 1026). In this case:

$$k = k_0 + k_{H+}[H+] + k_{OH-}[OH^-]$$

Note that in very acidic solutions, two very strong acids will give rise to solutions of the same pH ("levelling by solvent"). Yet, an acid which is 50% dissociated is considered to be stronger than one which is only 10% dissociated:

$$BH^+ \rightleftharpoons B + H^+$$

In the Hammett H_0 scale, the dissociation of protonated nitroanilines is considered for solutions in concentrated sulfuric acid. This is used as a proxy for pH (unfortunately, there is no single *acidity function*).

Specific vs. General Acid Catalysis

In studies of this type, one distinguishes between *specific* and *general* acid-base catalysis:

specific acid catalysis:

$$S + H^+ \overset{slow}{\rightleftharpoons} SH^+$$

$$SH^+ \xrightarrow{fast} \text{product}$$

Specific acid catalysis refers to catalysis by proton itself, which means that the rate is proportional to $[H^+]$:

$$d[P]/dt = k_{H+}[S][H^+]$$

Similarly, specific base catalysis refers to catalysis by hydroxide.

general acid catalysis:

$$S + H\text{-}A \overset{slow}{\rightleftharpoons} SH^+ + A^-$$

$$SH^+ \xrightarrow{fast} \text{product}$$

General acid catalysis refers to catalysis by weaker acids, which means that rate is proportional to the amount of unionized general acid:

$$d[P]/dt = k_{HA}[S][HA]$$

Similarly, general base catalysis refers to catalysis by HO-R.

Linear Free Energy Relationships

(1) How does one measure how effective a general acid is at catalyzing a reaction?

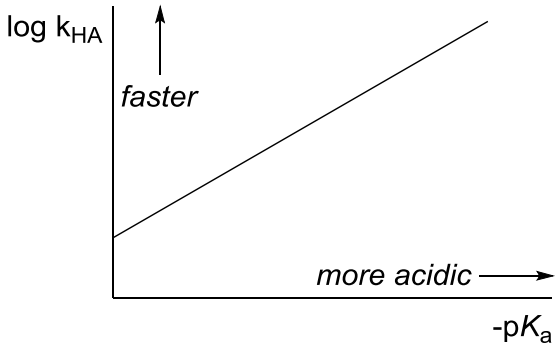
(2) How sensitive is a reaction to electronic effects compared to another reaction?

To answer these questions, we need to consider the Brönsted and Hammett relationships, respectively.

Linear Free Energy Relationships

The **Brönsted catalysis law** says that rate is proportional to the acidity of the acid:

$$\log k_{HA} = \alpha \log K_a + c$$



(1) α is the slope of this line and c is a constant. For bases, there is an analogous Brönsted β slope.

(2) One can show that general acid catalysis is most likely to be observed near pH = p*K*a. Below this pH, there is a lot of H^+ present, so specific acid catalysis is likely to dominate. Above this pH, other mechanisms such as catalysis by water or base are likely to dominate

(3) Although α is usually between 0 and 1, and is often taken as a measure of how protonated the transition state is, there are some problems with this approach.

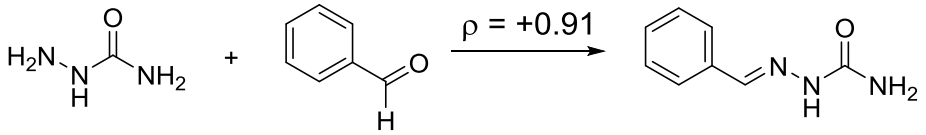
(4) Despite this limitation, α values of 0.5 are most likely to display general acid catalysis since barely or fully protonated TSs are unlikely to display much sensitivity to acid structure.

(5) Another perspective is that α reflects how sensitive the reaction is to changes in the structure of the general acid.

The Hammett Equation

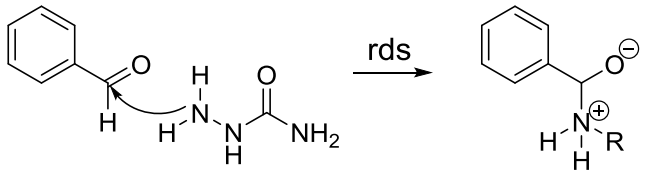
$$\log \frac{k_{R=X}}{k_{R=H}} = \sigma\rho$$

In lecture 1, we briefly examined the Hammett equation, shown above. Let's examine a reaction with more complicated behavior.

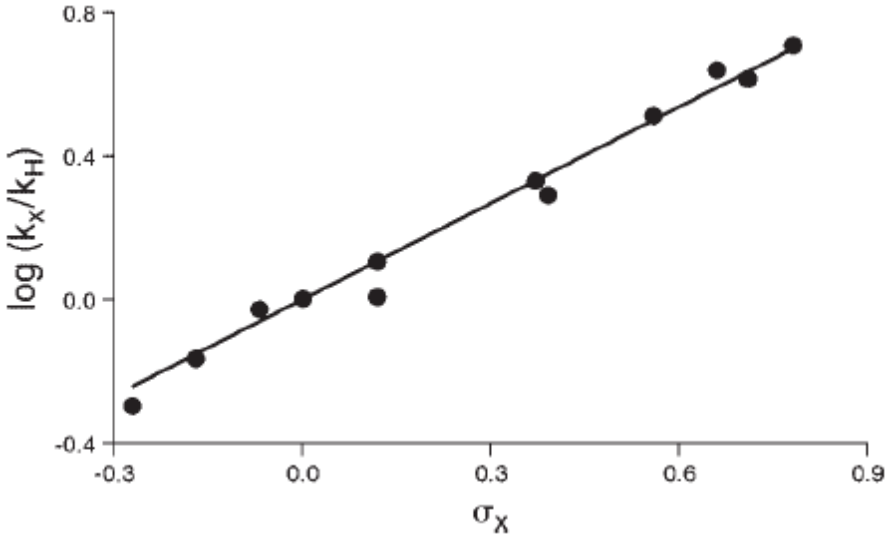


In semicarbazone formation (Jencks *JACS* **1960** *82* 1773), ρ = +0.91, which means that the reaction is sped up by electron withdrawing groups (ρ is positive) but is a little less sensitive to electronic effects than benzoic acid dissociations is (the magnitude of ρ is less than 1).

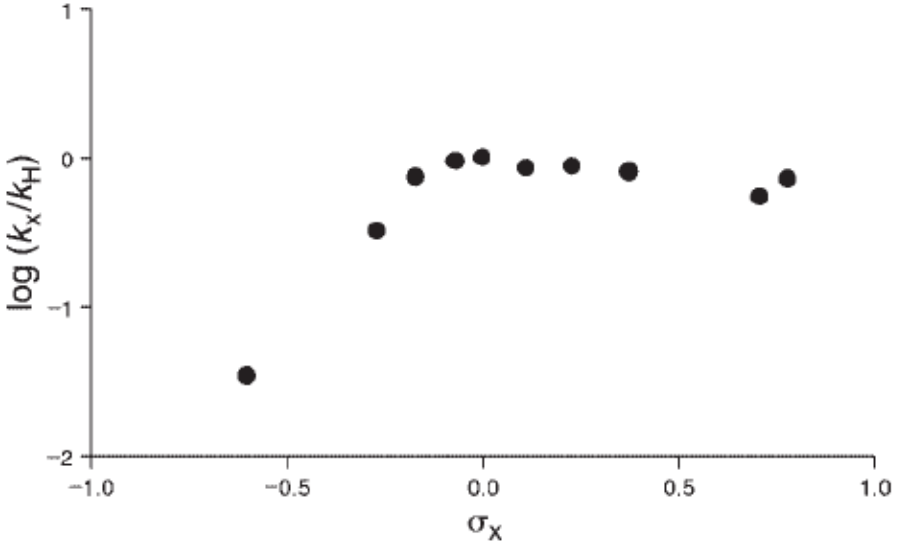
This ρ value was obtained at pH=1.75 (acidic solution), which is interpreted as rate-limiting nucleophilic addition:



(At this pH, a substantial portion of the semicarbazide (pK_a ~ 4) is protonated, but only the non-protonated, lone-pair bearing form is active.) The rate of reaction is increased for a more electron poor aromatic ring. In energetic terms, this is ground state destabilization; a more electron poor aromatic ring destabilizes the partial positive charge at the benzylic carbon. (Dicks *J Chem Ed* **2006** *83* 1341).

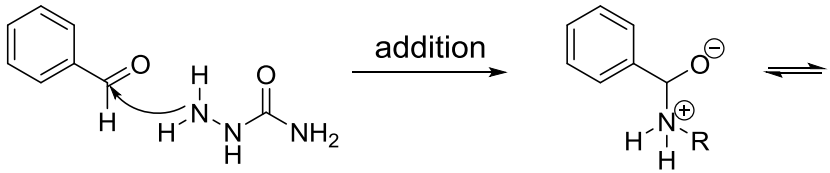


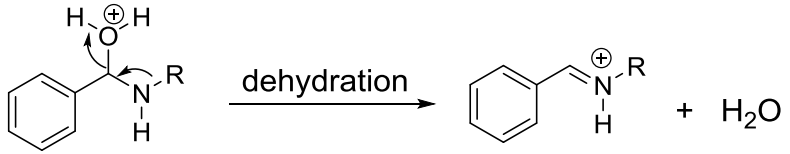
However, at pH = 6.5, the Hammett plot is concave



What does this mean?

In general, concave down curvatures are indicative of a change in rate determining step (cf. concave up curvatures, which mean a change in mechanism):



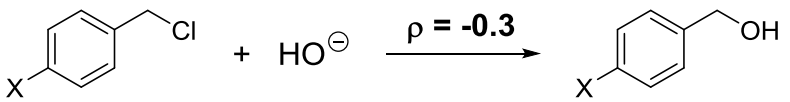


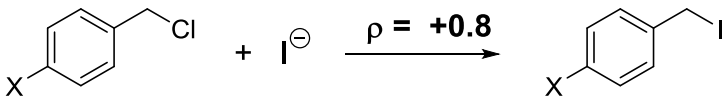
With electron donating substituents, the initial addition is slowed, which means that the first step remains rate determining. With electron withdrawing substituents, the initial addition is fast, so the dehydration is slow (this is a neutral pH, so having a protonated leaving group is harder).

The rate of dehydration is increased by electron donating groups which stabilize the forming iminium ion. However, the carbocation is already quite stabilized by the nitrogen, so substituents on the aromatic ring have a small effect. Thus, the ρ is small and negative.

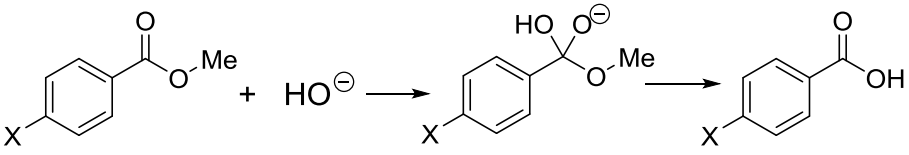
Alkaline Ester Hydrolysis

S_N2 reactions have relatively small ρ values, which can be either positive or negative, reflecting the a competition between bond formation (negative charge buildup) and bond cleavage (negative charge departing, which is like positive charge buildup):



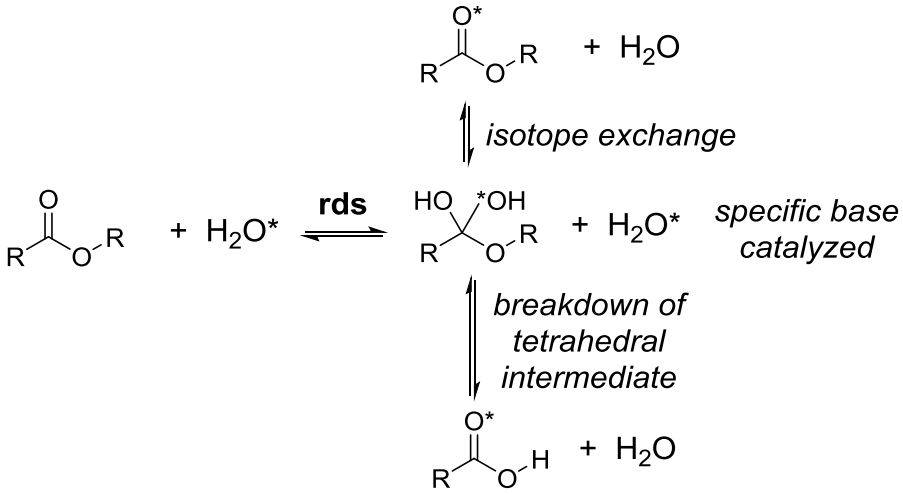


On the other hand, the hydrolysis of methyl benzoate has a ρ of +2.2, which is indicative of a $B_{AC}2$ mechanism:



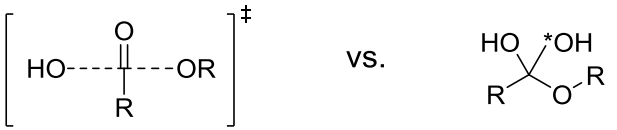
ρ = +2.2 **tetrahedral intermediate**

In this terminology, "B" means base-promoted, AC means that the attack is occuring on the acyl group, and 2 means bimolecular, (just as in SN2 reactions). However, the most compelling evidence comes from a classic solvent isotope partitioning experiment (Bender *JACS* **1951** *73* 1626):



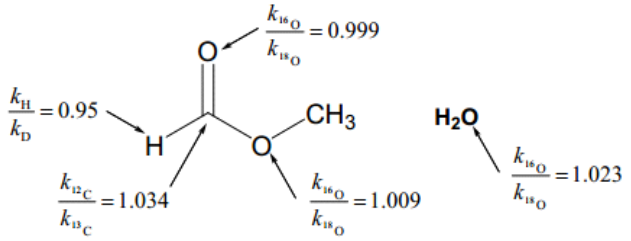
This means that if starting material is re-isolated after partial conversion, some of it becomes isotopically labelled. The fact that this is actually observed suggests a true intermediate, rather than a transition state. Why?

One considers a tetrahedral intermediate as an energy *minimum* and a transition state as an energy *maximum*:



If the reaction proceeded directly from starting to product via a transition state, then it would be impossible to observe any ^{18}O incorporation in the re-isolated starting material. For exchange to occur, there must be an intermediate with an appreciable lifetime.

What do kinetic isotope effects say? Marlier has reported data for the hydrolysis of methyl formate (*JACS* **1993** *115* 5953):



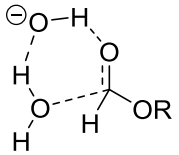
Similar numbers are obtained for methyl benzoate. Both reactions are believed to proceed via early transition states. For this substrate, hydrolysis is 18.3x faster than exchange.

(1) Note that heavy-atom kinetic isotope effects are much smaller than H/D isotope effects, but are still meaningful if they are measured accurately.

(2) The H/D KIE is a secondary isotope effect indicative of a change in hybridization from sp^2 to sp^3 at the carbonyl, although this interpretation may be too simplistic.

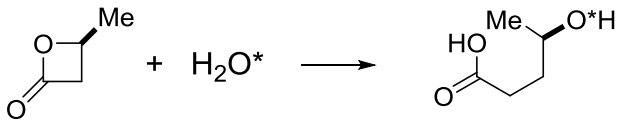
(3) The carbonyl carbon isotope effect is large and primary.

(4) Interestingly, the solvent isotope effect and other data suggest that water, rather than hydroxide, is the nucleophile here, and the reaction is general base catalyzed:



potential TS?

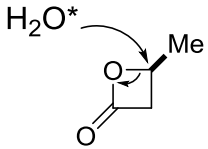
Not all ester cleavages occur by the $B_{AC}2$ mechanism, however. How do you think this reaction works (*JACS* **1938** *60* 2687)?



(1) This means inversion of configuration.

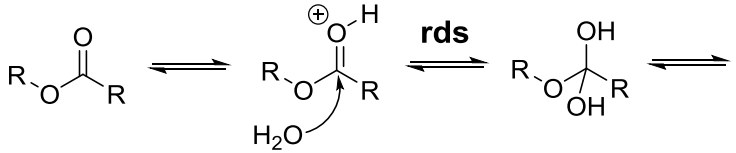
(2) The label ends up on the secondary carbon.

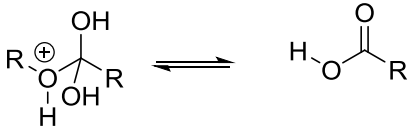
This is indicative of a $B_{AL}2$ mechanism (alkyl group attack):



Acidic Ester Hydrolysis

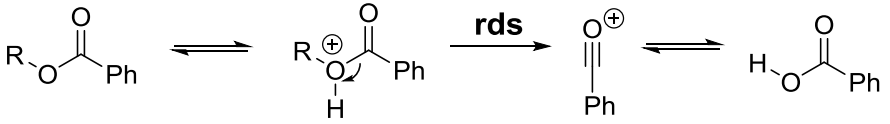
Under mildly acidic conditions, most esters are cleaved by the $A_{AC}2$ mechanism:



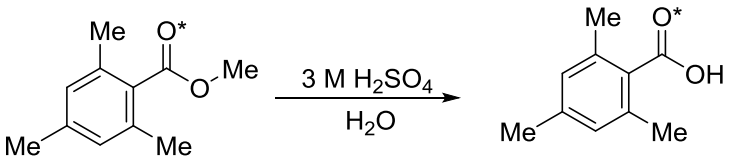


(A means acidic cleavage.)

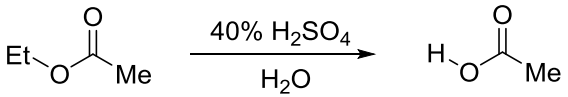
However, other mechanisms are possible. For example, $A_{AC}1$ cleavage is also possible:



This is most common when the ester will form a relatively stable acylium ion and when steric hindrance either prevents addition of water to the carbonyl group or inhibits resonance between the carbonyl group and the ester oxygen. For example, there is no isotopic exchange in the cleavage of this mesityl derivative:

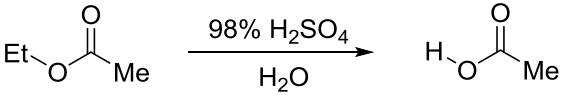


Yates has shown (*Acc Chem Res* **1971** *4* 136) that in very concentrated acid, there is a changeover from $A_{AC}2$ to $A_{AC}1$ mechanisms even for normal esters:



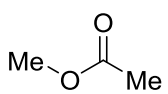
$\Delta H^{\ddagger}$ = 16.9 kcal/mol
$\Delta S^{\ddagger}$ = -15.3 e.u.

Here, the large negative entropy of activation represents the translational penalty of bringing two molecules together. In more concentrated acid, where there is very little water:

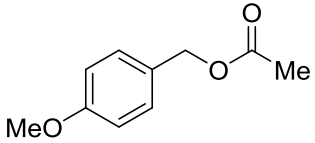


$\Delta H^{\ddagger}$ = 23.7 kcal/mol
$\Delta S^{\ddagger}$ = +2.3 e.u.

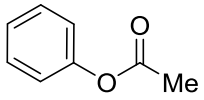
Now, the ester is being cleaved through an $A_{AC}2$ process, which does not involve a significant change in translational entropy. The changeover in mechanism from $A_{AC}2$ to $A_{AC}1$ occurs at different concentrations (volume% in H_2O) of H_2SO_4:



75-90%

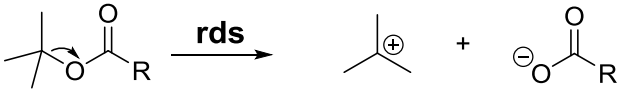


>60%

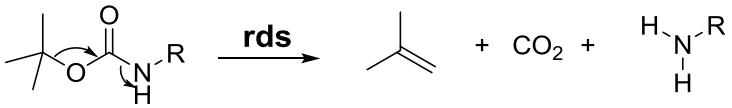


dilute

These all form the same acylium ion, so the difference reflects leaving group ability. However, *tert*-butyl esters are thought to cleave by the $A_{AL}1$ mechanism:



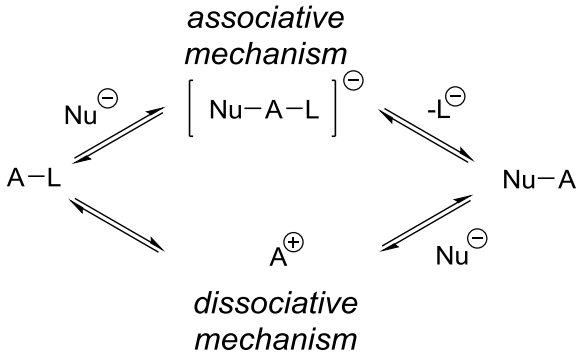
This is what happens when BOC groups are cleaved with TFA:



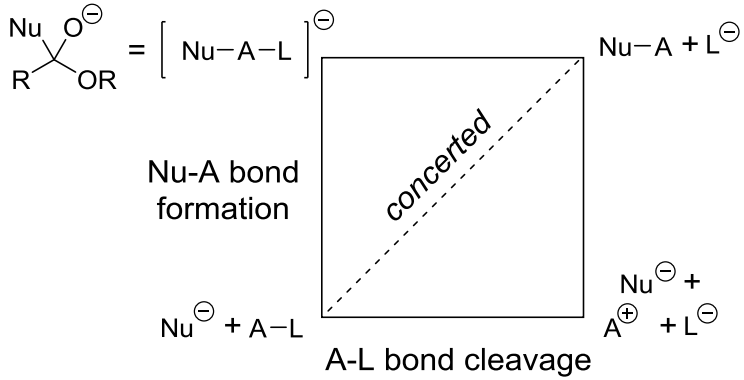
Concerted Alcoholysis?

"Concerted Mechanisms of Acyl Group Transfer Reactions..." Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387-392.

"When Is an Intermediate Not an Intermediate? Enforced Mechanisms..." Jencks, W.P. *Acc. Chem. Res.* **1980** *13* 161. All of the reactions described above can be described as being either associative or dissociative. In general form:

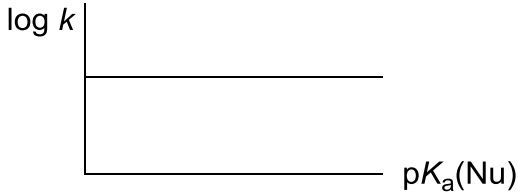


These two mechanisms are the limiting corners of a Jencks-More O'Ferrall diagram:

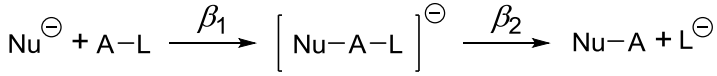


How does one determine if the reaction passes through a stepwise associative, stepwise dissociative, or concerted mechanism?

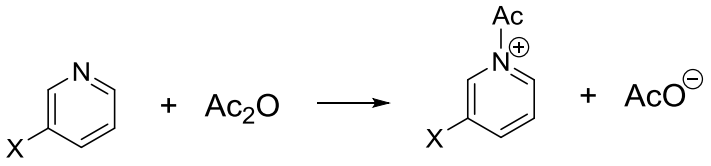
(1) For a **dissociative process** in which dissociation is rate-limiting, putting polar groups on Nu will not affect the rate at all. That is, $\beta_{Nu}=0$:

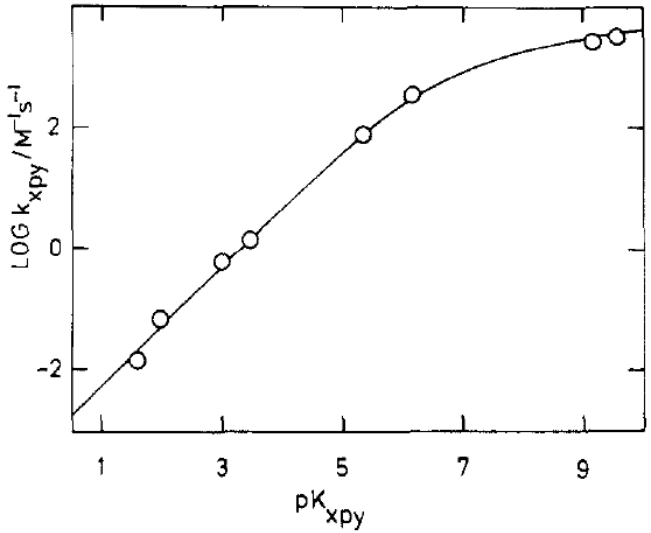


(2) In an **associative process**, the slope of the Brönsted plot will depend on which step is rate-determining:

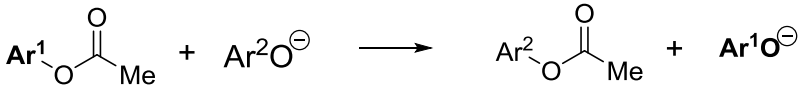


Both Brönsted slopes β_1 and β_2 are positive, since more basic nucleophiles are also more nucleophilic (at least within a closely related series) and more likely to "push" the leaving group out. This means that over a large enough range of nucleophiles, the Brönsted plot will be concave down, displaying a "break":

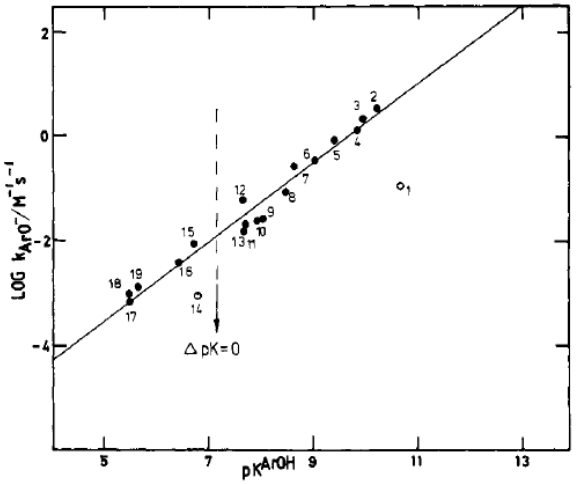




(3) For systems where the nucleophile and leaving group are similar in structure, it is possible to predict where this break will occur. For example, aryl ester alcoholysis:

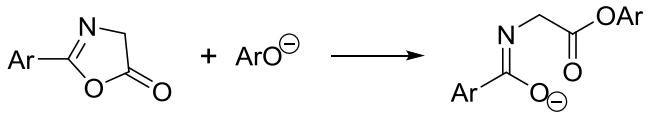


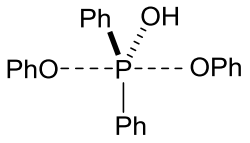
There is no break in the Brönsted plot for phenolate adding to 4-nitrophenyl acetate (Williams *JACS* **1987***109* 6362):

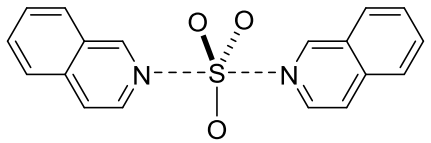


Guthrie has used Marcus theory to estimate (*JACS* **1991** *113* 3941) that for strongly acidic phenols (p*K*a < 1), the reaction will proceed via a dissociative mechanism (acylium ion), while for strongly basic phenols (p*K*a > 11), the reaction will proceed via an associative mechanism (tetrahedral intermediate). Phenols of intermediate acidity react via a concerted transition state.

Other acyl transfers with concerted mechanisms:





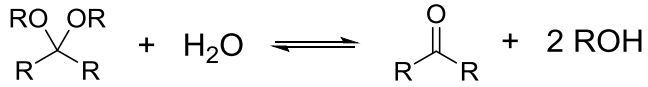


Acetal Hydrolysis

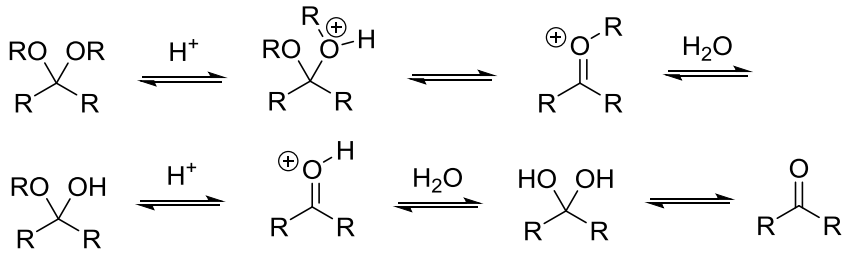
"General Acid Catalysis of Acetal...Hydrolysis." Fife, T.H. *Acc. Chem. Res.* **1972** *5* 264-272.

"Mechanism and Catalysis for Hydrolysis of Acetals..." Cordes, E.H.; Bull, H.G. *Chem. Rev.* **1974** *74* 581-603.

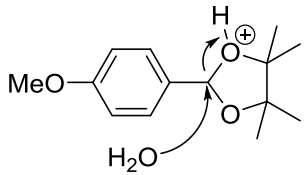
How does this reaction work?



Most acetals hydrolyze by a dissociative "A1" pathway:



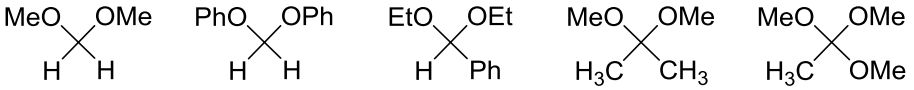
In some cases, an A2 mechanism is dominant:



$\Delta S^{\ddagger}$ = -15 eu

In general, the A2 mechanism is restricted to cases where the A1 process is somehow disfavored (Kreevoy *JOC* **1981** *46* 419).

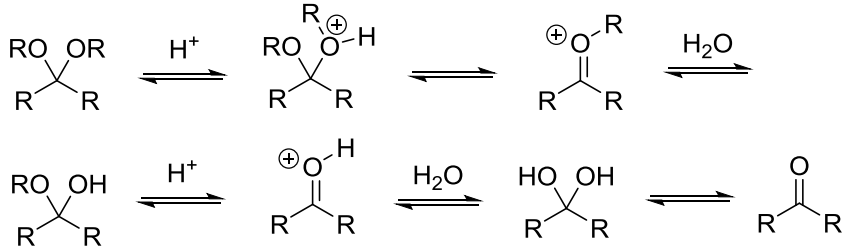
The initial step is a protonation, so it is instructive to look at the p*K*a's of some protonated acetals (conjugate base shown):



-4.6 **-6.5** **-5.7** **-5.2** **-5.7**

Thus, the marked stability of orthoformates is not due to basicity.

What is the rate-determining step in this mechanism?



Here is some evidence:

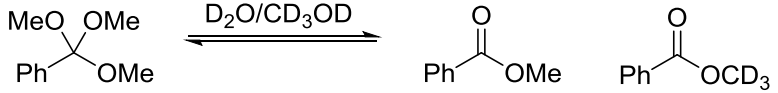
(1) **Hammett ρ Values (Approximate)**

the carbonyl part: -3
the non-departing alkoxy group: -3
the departing alkoxy group: 0

This is indicative of oxocarbenium ion formation in the TS.

(2) **Solvent Isotope Exchange**

The hydrolysis of methyl orthobenzoate in deuterated solvent gives mostly methyl benzoate:



not observed

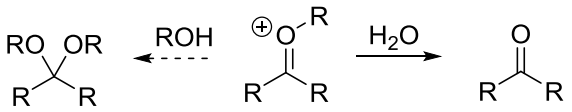
(3) **Relative Nucleophilicities**

Methanol is more nucleophilic than water:

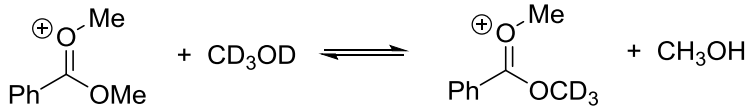
Water: N=5.2 (s=0.89)
Methanol: N=7.54 (s=0.92)
Ethanol: N=7.44 (s=0.90)
Trifluoroethanol: N=1.23 (s=0.92)

However, oxocarbenium ions are very electrophilic (E = 2).

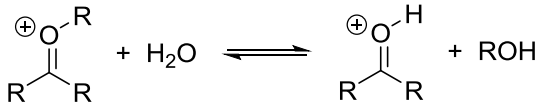
Thus, the predicted rate constant for attack of solvent (water or methanol) on oxocarbenium ion is near the diffusion limit. Another perspective is that water and methanol are about equally nucleophilic, and since there is much more water than methanol, the rate of oxocarbenium going forward to product should be much higher than the rate going backwards:



Thus, **oxocarbenium ion formation is not reversible.** If it were, then solvent exchange would be possible:

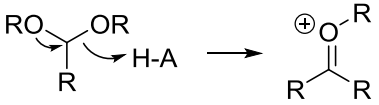


Over time, since there is much more deuterium in the solvent than there is protium in the substrate, one would expect the product to incorporate quite a lot of deuterium (but it doesn't). Rather, it seems, **oxocarbenium ion formation is the rate-limiting step.**



Which oxocarbenium ion is it? Based on the same kind of argument, there is a lot more water than alcohol, so the right side of this equilibrium is favored. Thus, the alkylated oxocarbenium ion is higher in energy, and its formation is rate-limiting.

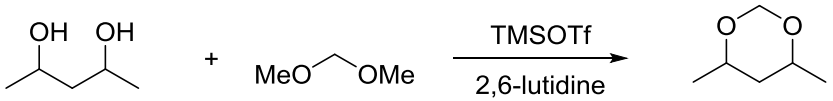
In some cases, general acid catalysis is believed to be at work, since *increasing buffer concentration* at constant pH increases rate. This implicates mechanisms like:



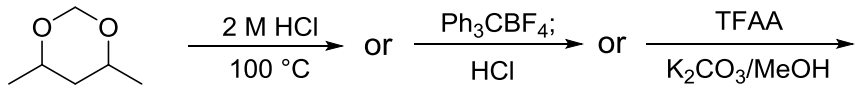
Acetal Protecting Groups

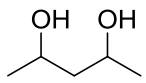
Acetals are important protecting groups for alcohols (e.g., MOM ether) as well as 1,2- and 1,3-diols (e.g., acetonide). In this section, we restrict our attention to the latter. For a very detailed treatment of virtually every protecting group known to man, see *Greene and Wuts*.

The parent methylene acetal is extremely stable to hydrolysis and therefore, it does not see much use:



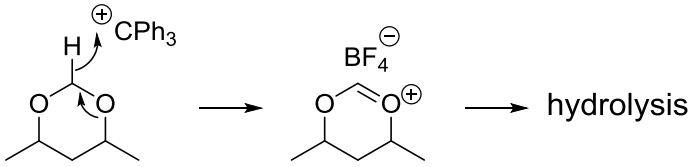
Cleavage requires strongly Brönsted or Lewis acidic conditions:



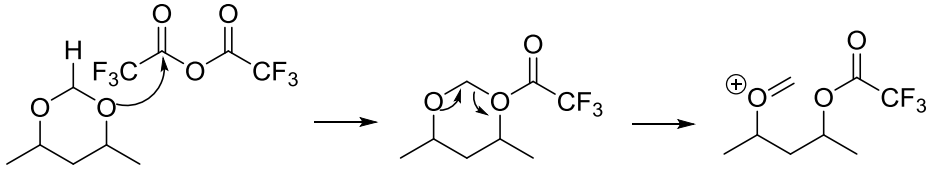


Certainly, the first set of conditions probably proceeds via an A1 mechanism. But how do the other conditions work?

Trityl is a strong Lewis acid which abstracts a hydride:

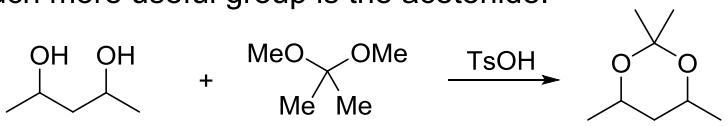


Trifluoroacetic anhydride *O*-acylates to form oxocarbenium ion:

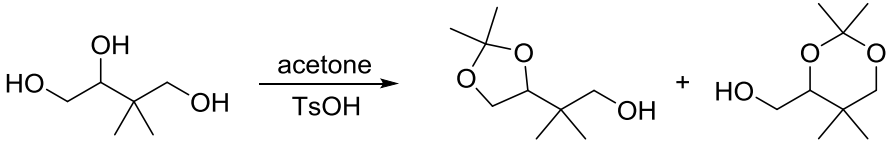


The oxocarbenium and the trifluoroacetate are then cleaved.

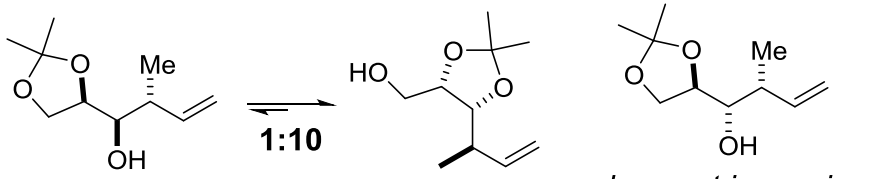
A much more useful group is the acetonide:



This is a transacetalization (acetone can also be used with azeotropic water removal). The increased substitution on the acetal stabilizes any oxocarbenium ions it might form, easing its removal. If there is a choice between forming a 1,2- or 1,3-acetonide, the 1,2-acetonide is favored:

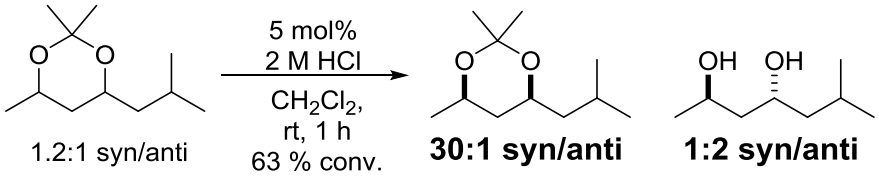


However, selectivity is highly substrate-dependent. Secondary alcohol acetonides are preferred over primary alcohol ones and 1,2-*cis* acetonides are favored over 1,2-*trans* acetonides:



does not isomerize

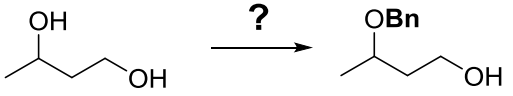
The corollary is that 1,3-acetonides (1,3-dioxanes) cleave faster than 1,2-acetonides (1,3-dioxolanes). This happens in the presence of acid and water or alcohol under mild conditions:



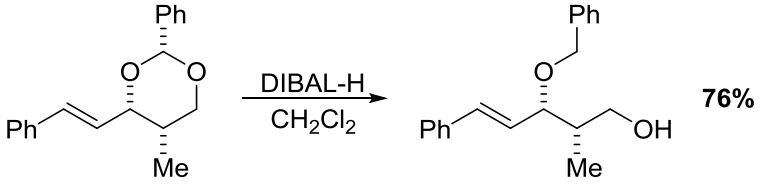
1.2:1 syn/anti **30:1 syn/anti** **1:2 syn/anti**

This shows that the *anti* acetonide was cleaved faster.

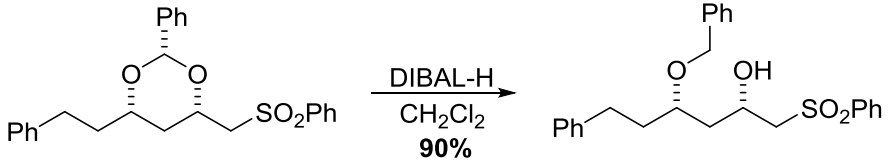
How would you prepare a *secondary* benzyl ether selectively over a primary benzyl ether?



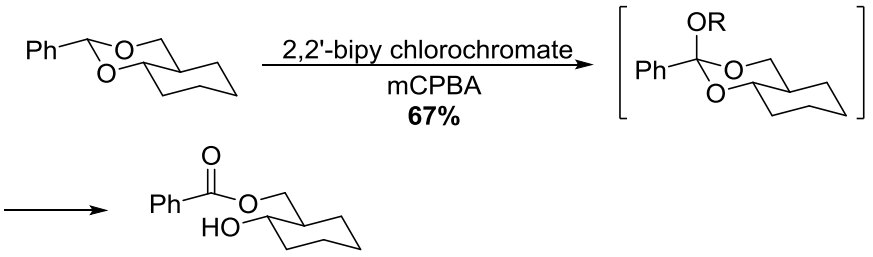
The partial reductive cleavage of a benzylidene acetal:



In general, the more substituted benzyl ether is formed, although selectivity is substrate-dependent. If an adjacent coordinating coordinating group is present, then reduction can be directed:

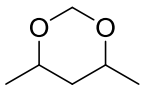
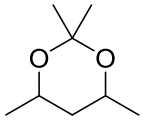
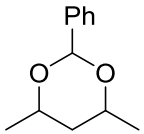
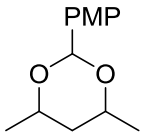


Alternatively, benzoates (rather than benzyl ethers) can be produced by oxidative cleavage:



This time, the primary benzoate is formed. In general, the selectivity varies depending on the substrate. We will examine the stereoelectronic issues surrounding the breakdown of tetrahedral intermediates shortly.

To calibrate you on the stability of these various protecting groups, here are some data:

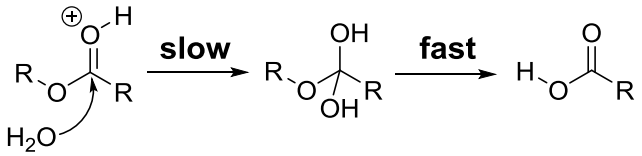
	pH=1	pH=2-4	pH=4-6	NaOMe	H_2/Pd
	low	high	high	high	high
	low	marginal	high	high	high
	low	low	high	high	low
	low	low	marginal	high	low

(1) Benzylidene and PMB acetals can be cleaved under hydrogenolysis conditions.

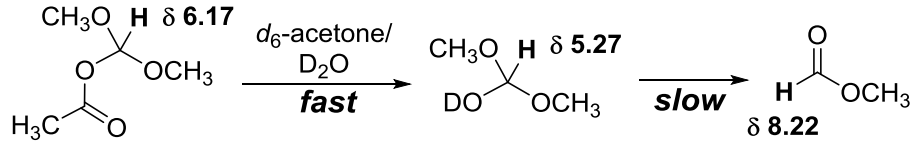
(2) The PMB acetal is particularly acid-labile.

Stability of Tetrahedral Intermediates

In most acyl transfer reactions, the tetrahedral intermediate is fleeting because its rate of formation is slow, but its rate of breakdown is fast:

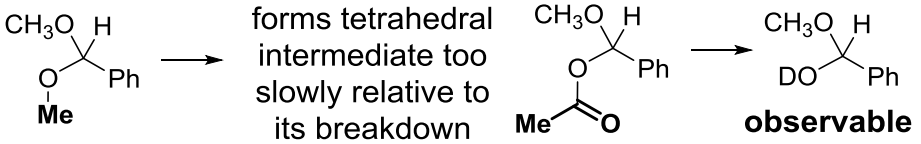


However, if the tetrahedral intermediate is generated along a direction orthogonal to the usual reaction coordinate, then it is possible to observe its buildup and decay of this hemiorthoester (Capon *ACR* **1981** *14* 306):

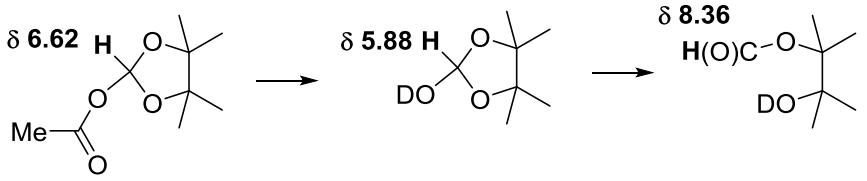


high energy precursor

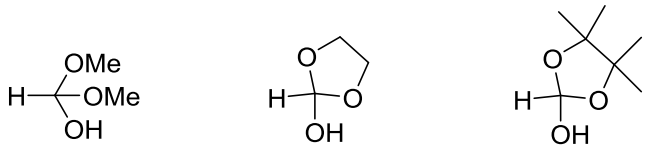
The decomposition of benzaldehyde dimethyl acetal is too slow to observe the hemiacetal, but the acetate works:



On the other hand, we can also slow the rate of breakdown of the tetrahedral intermediate by constraining it in a ring. The ring makes the backwards reaction entropically much more favorable. For example, 1,2-dioxolanes:

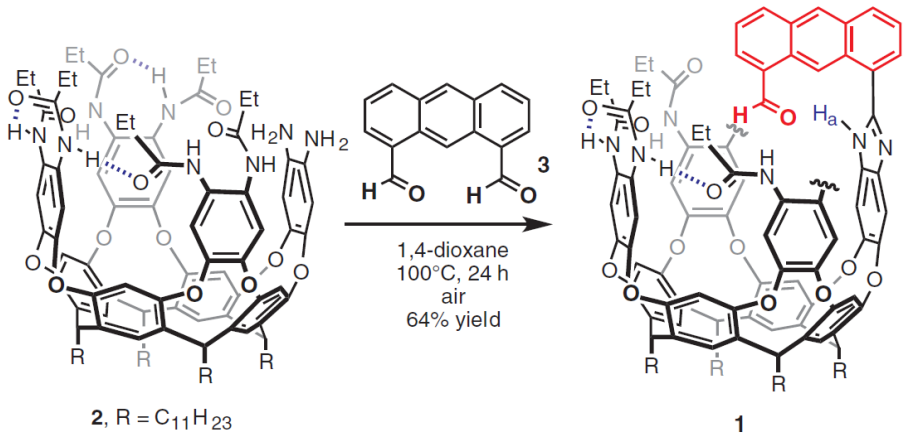


Here are some relative rates of breakdown:



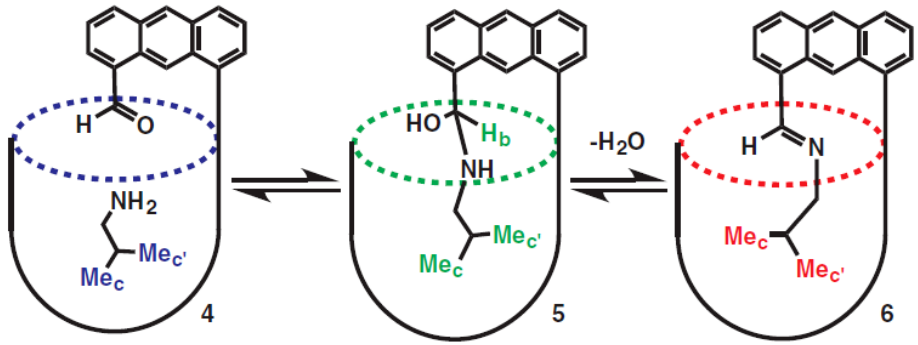
33 **9** **1**

In a similar vein, Rebek has shown that hemiaminals can be stabilized in "self-folding cavitands" (*Science* **2007** *317* 493). First, the condensation of a dialdehyde with a diamine assembles a benzimidazole (air is the oxidant):



2, R = $C_{11}H_{23}$ **1**

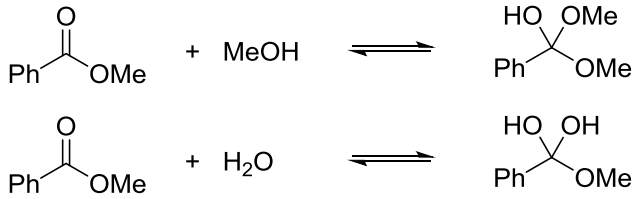
Then, a primary amine is added, which forms an usually stable hemiaminal:



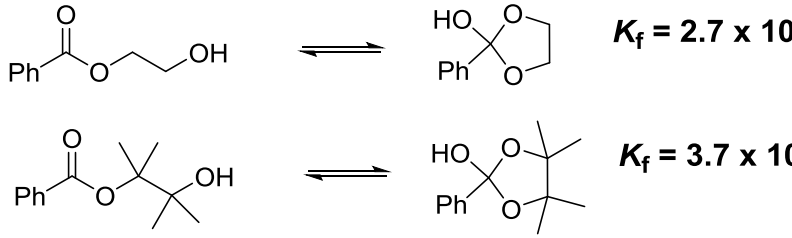
$t_{1/2}$ = minutes

The cavitand recognizes the amine, increasing the effective molarity of this reaction. The secondary amides inside the cavity stabilize the tetrahedral intermediate by H-bonding; also, it prevents general bases from the bulk solution from decomposing the intermediate. It may also be unfavorable to eject water into the cavity.

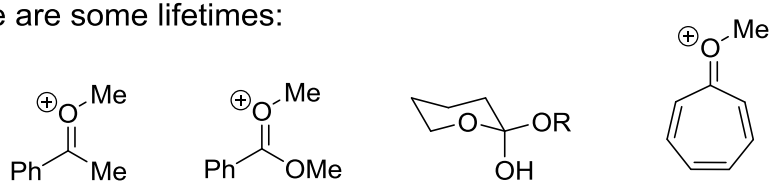
In general, the equilibrium constants for the formation of hemiacetals reflect the considerations described above (McClelland *ACR* **1983** *16* 394):



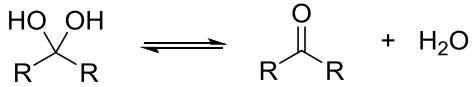
So methanol and water are pretty similar. However, intramolecular alcohols are very effective:



Here are some lifetimes:



The equilibrium constants of cabonyl hydrate dissociation have also been measured (Bell *Adv Phys Org Chem* **1966** *4* 1):

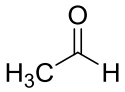


The hydrate is favored when R is electron donating (this means a weaker C=O bond, and therefore less of a penalty for breaking it, but other factors are at work, too.

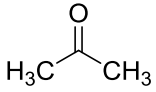
Tetrahedral Intermediates

What are your predictions for the K_d of these carbonyl hydrates?

4.5×10^{-4}

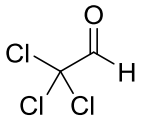


0.83

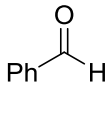


720

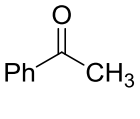
very small



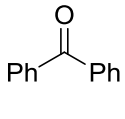
3.6×10^{-6}



120



1.5×10^{5}



8.5×10^{6}

(Bigger numbers mean that the hydrate is less favored; the carbonyl form is shown.)

(1) Cyclopropanone hydrate is favored because it relieves a lot of angle strain. Chloral hydrate (bottom left) relieves dipole and steric interactions (these are "knockout drops").

(2) Aldehyde hydrates are much more stable than ketone hydrates, presumably because they are both less hindered on the product side and more electron poor on the starting material side.

(3) Conjugation of a phenyl group to the carbonyl group stabilizes the product side of the reaction, which is why acetophenone hydrate is much less favored than acetone hydrate.

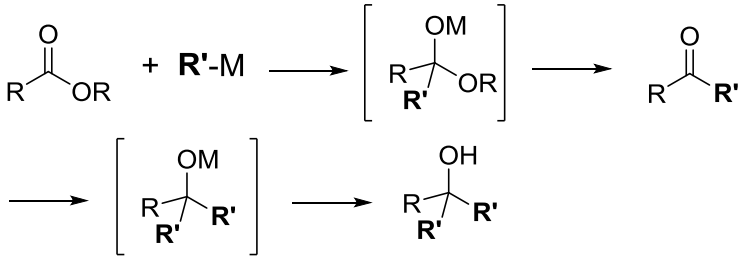
Weinreb Amides: Stable Tetrahedral Intermediates

"...Application of *N,O*-Dialkylhydroxylamines..." Khlestkin, V.K.; Mazhukin, D.G. *Curr. Org. Chem.* **2003** *7* 967-993.

"The Growing Synthetic Utility of the Weinreb Amide." Balasubramaniam, S.; Aidhen, I.S. *Synthesis* **2008** *23* 3707-38.

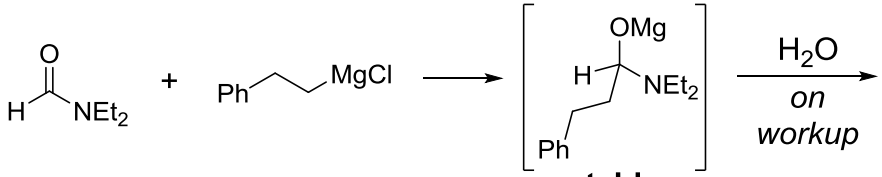
"Tetrahedral Intermediates in the Reactions of Carboxylic Acid Derivatives with Nucleophiles." Adler, M; Adler, S.; Boche, G. *J. Phys. Org. Chem.* **2005** *18* 193-209.

Q: Why can't you turn an ester into a ketone with an organometallic reagent directly?

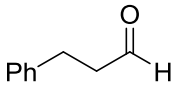


Evidently, O-M bonds are very good donors, which make the tetrahedral intermediate too unstable. This generates the ketone during the reaction, which reacts again. As before, we want to ask: *what can be done to stabilize the tetrahedral intermediate?*

Bouveault (1904) figured out that one way to do it is to use formamides, which have bad amide leaving groups:

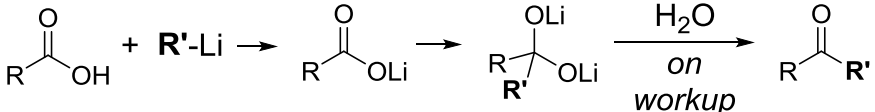


stable



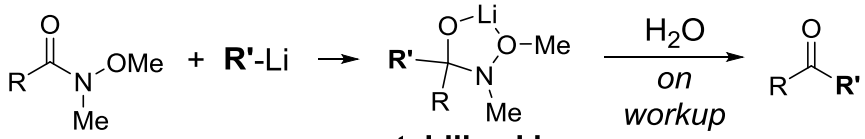
Formamides give aldehydes; amides give aldehydes. (But these aren't very electrophilic reagents.)

With organolithium reagents, carboxylic acids can be used directly (*di*lithium oxide is also a bad leaving gruop), but these often give mixed results:



stable

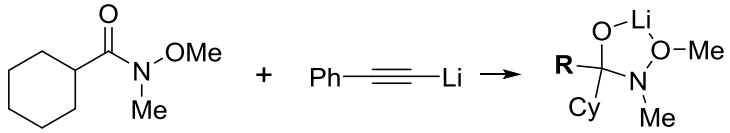
In 1981, Weinreb introduced *N*-methoxy-*N*-methyl amides as more reliable, more reactive reagents (*TL* **1981** *22* 3815):



stabilized by chelation

Not only are the tetrahedral intermediates stabilized by chelation, but also (calculations suggest) acceleration arises from preferential chelation of the transition state. This allows the use of normally unreactive amides.

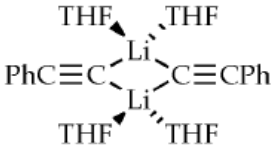
Of course, mixed aggregation effects can be important. For example, Collum notes (*JOC* **2006** *71* 7117) that this phenyl-acetylide addition stalls at 50% conversion with one equivalent of nucleophile in THF at -50 °C:



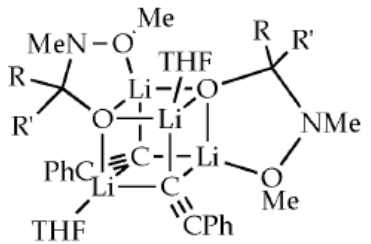
not appreciably complexed by Li

Warming to 20 °C then causes slow conversion to product over several hours. In contrast, use >2.0 equivalents gives product within 1 h in 90% yield. Neither the ketone nor tertiary alcohol are observed by IR spectroscopy. What is the source of this autoinhibition?

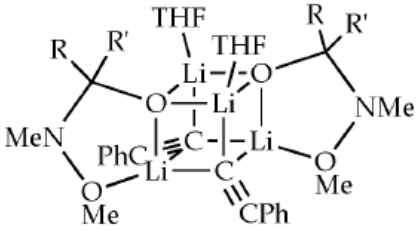
NMR spectroscopy shows that a complex mixture of aggregates is present: 1:1 acetylide·THF_2 dimer; a mixed 2:2 acetylide·THF/product tetramer; and a mixed 1:3 acetylide·THF/product tetramer upon warming (**6** is not observed):



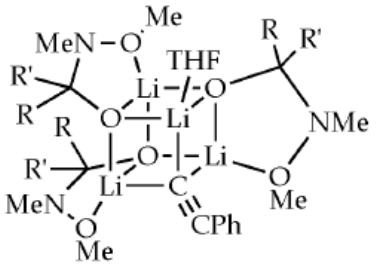
4



5 (C_1)



6 (C_{2v})



7 (C_1)

R = cyclohexyl, R' = -C≡CPh

Kinetics show that the reaction is half order in acetylide and inverse order in THF (meaning transition state dissociation to a monomer is necessary) and first order in Weinreb amide.

It is not known how the mixed aggregates react, but calculations at B3LYP/6-31G* on the monomeric TS are shown at right.

From anecdotal experience, autoinhibition due to highly stabilized mixed aggregates appears to be quite a general phenomenon in the reactivity of Weinreb amides, which is why many of these reactions require more than one equivalent of organolithium. However, the formation of these mixed aggregates might actually be further stabilizing these tetrahedral intermediates by shielding them from nucleophilic attack. So, nobody knows exactly what's going on here, but this is a pretty decent guess.