PART 1

REACTIVE INTERMEDIATES

CHAPTER 1

Tetrahedral Intermediates Derived from Carbonyl Compounds, Pentacoordinate Intermediates Derived from Phosphoryl and Sulfonyl Compounds, and Concerted Paths Which Avoid Them

J. PETER GUTHRIE

Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7

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1.1. TETRAHEDRAL INTERMEDIATES

This chapter will deal mainly with tetrahedral intermediates from carbonyl derivatives, with some discussion on the much less-studied analogs for phosphorus and sulfur. It will also address the issue of concerted mechanisms which can sometimes bypass these intermediates.

Carbonyl reactions are extremely important in chemistry and biochemistry, yet they are often given short shrift in textbooks on physical organic chemistry, partly because the subject was historically developed by the study of nucleophilic substitution at saturated carbon, and partly because carbonyl reactions are often more difficult to study. They are generally reversible under usual conditions and involve complicated multistep mechanisms and general acid/base catalysis. In thinking about carbonyl reactions, I find it helpful to consider the carbonyl group as a (very) stabilized carbenium ion, with an O^- substituent. Then one can immediately draw on everything one has learned about carbenium ion reactivity and see that the reactivity order for carbonyl compounds:

$$CH_2{=}O > CH_3CH{=}O > PhCH{=}O > (CH_3)_2C{=}O > CH_3COPh$$

corresponds almost perfectly to the order for carbenium ions (see Table 1.1).

$$CH_3CH_2^+ > (CH_3)_2CH^+ > Ph(CH_3)CH^+ \sim (CH_3)_3C^+ > (CH_3)_2(Ph)C^+$$

The difference between carbonyl chemistry and (simple) carbocation chemistry is a result of much greater stability of the carbonyl group relative to a simple carbenium

TABLE 1.1. Reactivity of carbonyl compounds and carbenium ions.[a]

	$CH_3CH_2^+$	$(CH_3)_2CH^+$	$Ph(CH_3)CH^+$	$(CH_3)_3C^+$	$(CH_3)_2(Ph)C^+$
pK_R^+	−29.6[b]	−22.7[b]	−16.2[c]	−16.4[d]	−13.1[e]
	$CH_2{=}O$	$CH_3CH{=}O$	$PhCH{=}O$	$(CH_3)_2C{=}O$	CH_3COPh
$\log K_{H_2O}$[f]	1.61	−1.72	−3.82	−4.60	−6.92

[a]All in aqueous solution at 25°C; standard states are 1M ideal aqueous solution with an infinitely dilute reference state, and for water the pure liquid.
[b]Reference 1.
[c]Reference 2.
[d]Reference 3.
[e]Reference 4.
[f]Reference 5.

ion. This means that for many carbonyl group/nucleophile combinations the carbonyl compound is more stable than the adduct, which is not the case for what are traditionally considered carbenium ions until one gets to stabilized triaryl cations (e.g., crystal violet) or to very non-nucleophilic solvents such as magic acid.[6]

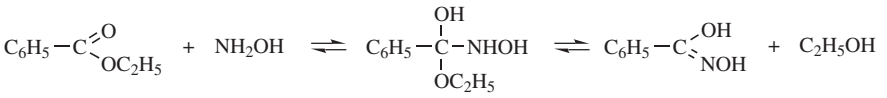
Thus carbonyl chemistry can be considered as analogous to S_N1 chemistry and is in fact inherently faster than S_N2 chemistry (not that S_N2 reactions cannot be fast, but this requires a strong thermodynamic driving force: for a comparable driving force the carbonyl reaction is faster).

The big difference is that for simple carbenium ions the cation is a transient intermediate and the covalent adduct is the normally encountered form, while for carbonyl compounds the "carbenium ion" is the stable form (with a few exceptions) and the covalent adduct is the transient intermediate. In fact, in many cases, the tetrahedral intermediate is too unstable to be detected (at least with current techniques) and yet the rate of overall reaction is strongly influenced by the height of this thermodynamic barrier. By Hammond's Postulate, a reaction leading to a high energy intermediate will have a transition state resembling this intermediate in structure and energy. If we can estimate the energy of the intermediate, then we have taken the first step toward estimating the rate of reaction.

For many carbonyl reactions, attempts have been made to prepare catalytic antibodies which accelerate the reaction. Such antibodies are normally obtained by challenging the immune system of a suitable animal with a compound resembling the tetrahedral intermediate in the reaction of interest. The idea is that if the antibody binds to and thus stabilizes the tetrahedral intermediate it will facilitate the reaction.[7,8] If the intermediate is a tetrahedral intermediate based on carbon then the analog is often a phosphate or phosphonate derivative, which is a stable tetrahedral species with a geometry and surface charge distribution resembling those of the intermediate in the reaction to be catalyzed.[9] A complimentary idea is that anything which resembles the transition state for an enzyme-catalyzed reaction, but is unreactive, will be a very strong inhibitor of that reaction.[10,11] Thus mimics of the tetrahedral intermediate can be strong inhibitors of enzymes catalyzing reactions which proceed by way of reactive tetrahedral intermediates.

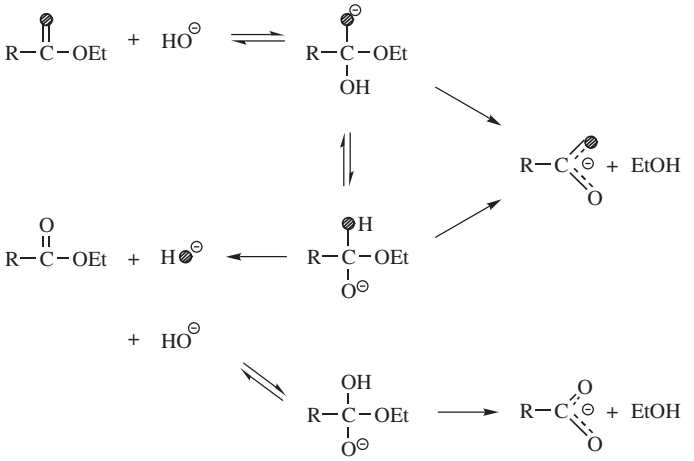
1.1.1. Evidence for Tetrahedral Species as Reactive Intermediates

As early as 1899, Stieglitz[12] proposed a tetrahedral intermediate for the hydrolysis of an imino ether to an amide. Thus it was clear quite early that a complicated overall transformation, imino ether to amide, would make more sense as the result of a series of simple steps. The detailed mechanism proposed, although reasonable in terms of what was known and believed at the time, would no longer be accepted, but the idea of tetrahedral intermediates was clearly in the air. Stieglitz stated of the aminolysis of an ester that "it is now commonly supposed that the reaction takes place with the formation of an intermediate product as follows:" referring to work of Lossen.[13] (Note that the favored tautomer of a hydroxamic acid was as yet unknown.)



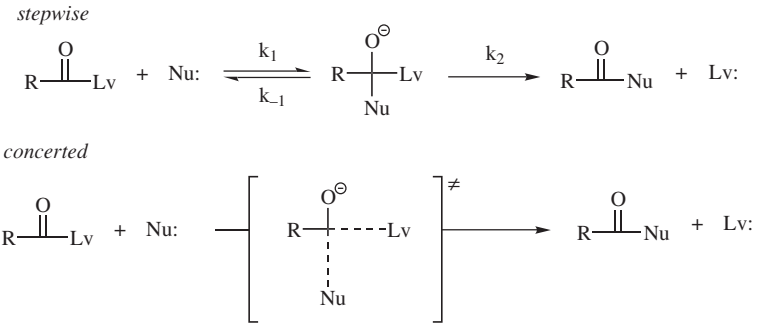
For many reactions of aldehydes or ketones with nucleophiles, the tetrahedral adduct is more or less readily detectable. Formaldehyde is overwhelmingly converted to methylenediol in water,[14] acetaldehyde is about 50% hydrated in water,[15] and acetone is only slightly converted to the hydrate, although the hydrate is readily detected by modern NMR instruments (the signal for the hydrate CH_3 is somewhat smaller than that for the ^{13}C satellite for the CH_3 of the keto form).[16] Thus, it is reasonable to assume that all carbonyl compounds can undergo nucleophilic addition, even when it is not directly detectable. For functional groups such as esters, the adduct with water or alcohol or even alkoxide is, for normal esters, at such low concentrations as to be undetectable. However, electron-withdrawing groups favor the addition of nucleophiles, so that CF_3COOMe will add MeO^-[17,18] and the equilibrium constant in methanol can be determined by ^{19}F NMR titration; at high concentrations of methoxide the conversion is essentially complete.[19]

A more difficult challenge is to establish that a tetrahedral intermediate is on the reaction path for the transformation of a carbonyl containing functional group. Isotopic exchange occurring with rates and a rate law very similar to hydrolysis provides strong evidence that the tetrahedral intermediate is on the reaction path and is partitioning between proceeding on to product or reverting to starting material with the loss of isotope.[20] This simple interpretation assumes that proton transfers involving the tetrahedral intermediate are fast relative to breakdown, which need not always be true.[21]



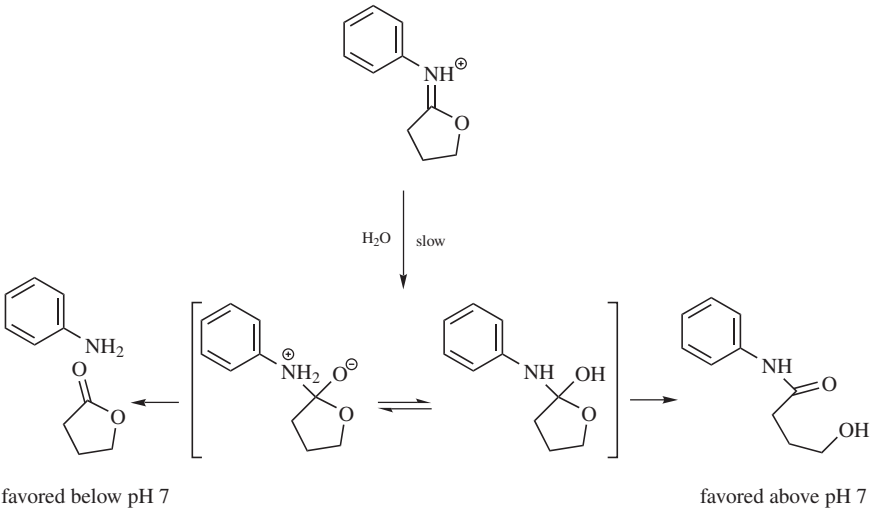
In other ester reactions, there may be concern that the reaction might be concerted, bypassing the tetrahedral intermediate. We will return to this question later. If the properties of Nu: or Lv: can be varied so that the relative leaving group

abilities within the tetrahedral intermediate change from "Lv:" being poorer than "Nu:" to "Lv:" being better than "Nu:" (allowing where necessary for any other factors which influence relative leaving group ability), then there will be a change in rate determining step if the mechanism is stepwise by way of a tetrahedral intermediate. This will show up as a break in a linear free energy relation (whether Hammett, or Taft, or Brønsted plot) for the stepwise mechanism, but as a simple linear relationship for the concerted mechanism[22] (see below). This test requires that the two competing steps of the stepwise reaction (breakdown of the intermediate to starting material or to product) have sufficiently different slopes for the linear free energy relation to give a clear break. This need not be the case if both are fast; that is, if the intermediate is of relatively high energy, so that by Hammond's Postulate the two transition states are close to the structure of the intermediate (and necessarily also to each other) and thus respond similarly to changes in reactant structure.



If the formation and breakdown steps of a mechanism involving a tetrahedral intermediate respond differently to changes in pH or catalyst concentration, then one can find evidence from plots of rate versus pH or rate versus catalyst concentration for a change in rate determining step and thus for a multistep mechanism. An example would be the maximum seen in the pH rate profile for the formation of an imine from a weakly basic amine (such as hydroxylamine).[23] On the alkaline side of the maximum, the rate determining step is the acid-catalyzed dehydration of the preformed carbinolamine; on the acid side of the maximum, the rate determining step is the uncatalyzed addition of the amine to form the carbinolamine. The rate decreases on the acid side of the maximum because more and more of the amine is protonated and unable to react.

If some change in reaction conditions leads to a change in the products of a reaction, without changing the observed rate, then there must be an intermediate which partitions in ways which respond to these changed reaction conditions, and formation of the intermediate must be rate determining. For instance, the products from the hydrolysis of the iminolactone shown below change with changing pH over a range where there is no change in the observed rate law.[24]



1.1.2. Stable Analogs

It is worth noting that the reactivity and short lifetime of most tetrahedral intermediates are a consequence of the presence of several electronegative atoms on a single center, with at least one of these atoms bearing a hydrogen. This means that an elimination pathway is accessible, which leads to a neutral product that is likely to be more stable than the tetrahedral intermediate. Without at least one electronegative atom bearing a hydrogen, any elimination must lead to a cationic species, which in most cases provides an additional barrier to reaction. Such analogs of tetrahedral intermediates are in fact well-known materials, acetals, aminals, orthoesters, and so forth and are relatively stable (compared with tetrahedral intermediates) because they do not have a facile elimination pathway. They are nonetheless reactive, especially to acid or, in some cases, simply exposure to polar solvents.[25] Mixed orthoacid derivatives [acetals of amides, R-C(OR′)$_2$(NR″$_2$), monothioorthoesters, R-C(OR′)$_2$(SR″), and even mixed orthoesters, R-C(OR′)$_2$(OR″)] are also prone to disproportionation, especially in the presence of even traces of acid.[26] Thus HC(OEt)$_2$(OR), R=cyclohexyl, becomes a mixture of HC(OEt)$_3$, HC(OEt)$_2$(OR), HC(OEt)(OR)$_2$, and HC(OR)$_3$.[26] Monothioorthoesters have a distinct tendency to go to mixtures of orthoesters and trithioorthoesters: HC(OEt)$_2$(SEt) goes to HC(OEt)$_3$ and HC(SEt)$_3$.[26]

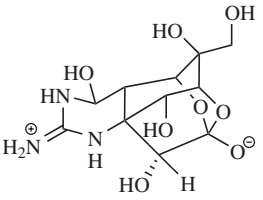
1.1.3. Special Cases

There are some special cases where tetrahedral intermediates are unusually stable; there are three phenomena which lead to this stability enhancement. The first is an unusually reactive carbonyl (or imine) compound which is very prone to addition. An example of such a compound is trichoroacetaldehyde or chloral, for which the covalent hydrate can be isolated. A simple way to recognize such compounds is to think of the carbonyl group as a (very) stabilized carbocation, bearing an O^- substituent.

Groups which would destabilize a carbocation (H, or an electron-withdrawing group) will make the carbonyl more reactive to addition, both kinetically and thermodynamically. Formaldehyde is a peculiar case, because it is overwhelmingly converted to methylenediol in water, but upon evaporation it breaks down to gaseous formaldehyde rather than remaining as the liquid diol. It can (with acid catalysis) be trapped either as paraformaldehyde or trioxane. Similarly, hexafluoroacetone hydrate is a liquid, with useful solvent properties and little tendency to lose water.[27] CF_3 groups are even more destabilizing to an adjacent C^+ than H. The same reasoning explains why one can titrate methyl trifluoroacetate with methoxide in dry methanol, observing formation of the anionic tetrahedral species by ^{19}F NMR.[19]

The second special case is addition of a very good nucleophile; hydrogen cyanide and bisulfite are the most common examples, and cyanohydrins, α-cyanoamines and bisulfite adducts (α-hydroxy sulfonates) are commonly stable enough to isolate, at least for reactive carbonyl compounds. All these compounds are prone to fall apart under suitable conditions, regenerating the carbonyl compound.

The third phenomenon which favors tetrahedral intermediates is intramolecularity, and if a nucleophile is contained in the same molecule as a carbonyl group, it will show an enhanced tendency to add; the less entropy is lost in this addition (the fewer free rotations must be frozen out) the more the addition is favored. A famous example of this phenomenon is tetrodotoxin (**1**), the toxin of the puffer fish.[28] This molecule is a hemiorthoester in which there is an O^- on a carbon atom which also has two alkoxy groups, yet it does not break down to give a lactone. The explanation is that a secondary alcohol is held very close to the lactone carbonyl and thus there is an entropic advantage to the addition relative to a corresponding intermolecular reaction. In addition, there are numerous electron-withdrawing groups which enhance the reactivity of the lactone carbonyl toward addition.



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A more recent example is the twisted amide (**2**) devised by Kirby,[29] which despite the lack of electron-withdrawing groups (other than nitrogen) is completely hydrated upon protonation on nitrogen; here the "amide" is unable to delocalize the nitrogen electrons onto the carbonyl, which means there is none of the usual amide stabilization.

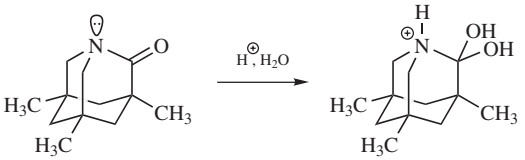

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TABLE 1.2. Equilibrium constants for addition of nucleophiles to carbonyl compounds.[a]

Nucleophile/ Carbonyl compound	H_2O	HOMe	RSH[b]	RNH_2[c]	R_2NH[d]	NH_2OH	HCN	HSO_3^-
CH_2O	41[e]	1310[e]	1.4×10^6[f,g]	3.4×10^6[h]	2.6×10^6[i]	–	9.18×10^8[e]	6.6×10^9[j]
CH_3CHO	0.019[e]	0.741[e]	36.[k,l]	–	61.[s]	–	3.7×10^4[e]	6.8×10^5[o]
$(CH_3)_2CHCHO$	0.011[e]	0.360[e]	16[p]	8.5[m]	1.7[n]	–	–	4.8×10^4[j]
$(CH_3)_3CCHO$	4.2×10^{-3}[e]	0.128[e]	4.8[p,q]					
PhCHO	1.5×10^{-4}[r]	3.6×10^{-3}[s] 0.09[t]			1.5[s]	11.3[u]	236[v]	6.4×10^3[e]
4-pyridine-CHO	0.023[w]	0.50[w]	193[h,g]	87[w]		1500[h]		
4Cl-Ph-CHO	4.0×10^{-4}[r]	0.24[t]	2.3[h,g]			24[h]	3.0×10^2[h]	1.1×10^4[h]
4-NO_2-Ph-CHO	3.1×10^{-3}[r]	3.0[t]				153[x]	1820[v]	
CH_3COCH_3	2.5×10^{-5}[e]	2.2×10^{-4}[e]				1.0[u]	14[e]	230[e]
Ph-CO-CH_3	1.2×10^{-7}[y]						0.77[z,aa]	5.5[bb]
Ph-CO-CF_3	1.40[cc]			100[dd, ee]		1.5 × 10^3[dd]	760[dd]	2.3 × 10^3[dd]
$HCOOCH_3$	3×10^{-7}[ff] 8×10^{-8}[s]				4×10^{-5}[s]			
CH_3COOCH_3	6×10^{-9}[ff] 9×10^{-11}[s]				1×10^{-8}[s]			
CF_3COOCH_3	0.1[ff]							
$HCOSCH_2CH_3$	3×10^{-4}[ff]							
$CH_3COSCH_2CH_3$	6×10^{-9}[ff] 8×10^{-7}[s]				1×10^{-4}[s]			
$CF_3COSCH_2CH_3$	2×10^{-3}[ff]							
$HCON(CH_3)_2$	2×10^{-14}[ff] 1×10^{-12}[s]	8×10^{-13}[s]						
$CH_3CON(CH_3)_2$	6×10^{-15}[ff] 3×10^{-14}[s]	2×10^{-14}[s]	1.1×10^{-12}[s]					
$CF_3CON(CH_3)_2$	5×10^{-9}[s]							
$PhCON(CH_3)_2$	5×10^{-14}[s]	2×10^{-14}[s]						

[a]All in aqueous solution at 25°C unless otherwise noted; equilibrium constants have dimensions of M^{-1}. [b]Various alkane thiols, of similar equilibrium reactivity. [c]Methylamine or a primary alkyl amine of similar reactivity. [d]Dimethylamine or a secondary alkyl amine of similar reactivity [e]Reference 30. [f]Reference 14. [g]RSH is mercaptoethanol. [h]Reference 31. [i]Reference 32. [j]Reference 33. [k]Reference 21. [l]RSH is ethanethiol [m]Reference 34. [n]Reference 35. [o]Reference 36. [p]Reference 37. [q]RSH is 2-methoxyethanethiol. [r]Reference 38. [s]Reference 39. [t]Reference 40. [u]Reference 23. [v]Reference 41. [w]Reference 31. [x]Reference 42. [y]Reference 5. [z]Reference 43. [aa]In ethanol. [bb]Reference 44. [cc]Reference 45. [dd]Reference 46. [ee]RNH_2 is *n*-butylamine. [ff]Reference 47.

1.1.4. Equilibrium Constants

Table 1.2 gives a representative sampling of equilibrium constants for additions to various types of carbonyl compounds. Notice that there are numerous gaps in the table. This means that much remains to be done in the study of carbonyl addition reactions. In trying to devise schemes for predicting the equilibrium constants for such reactions, the scarcity of experimental data is a serious handicap. There are many fewer equilibrium constants for additions to imines, and even fewer cases where

TABLE 1.3 Equilibrium constants for addition to imines.[a]

Imine/ nucleophile	Ph-CH=N-CH_2Ph	Ph-CH=N-Ph	4-NO_2-Ph-CH=N-Ph	4-NO_2-Ph-CH=N-Ph-4-OCH_3
HCN	8.1×10^{3} [b,c]			
n-BuSH		5.21[d]	27.5[d]	
MeOH		1.5×10^{-3} [e]	7.1×10^{-3} [e]	0.6×10^{-3}[e]
		2.0×10^{-3} [f]	8.1×10^{-3}[f]	

[a]In methanol at 25°C unless otherwise noted; equilibrium constants have dimensions M^{-1}.
[b]Reference 48.
[c]In aqueous solution.
[d]Reference 49.
[e]Reference 50.
[f]Reference 51.

there is any kind of systematic set. Table 1.3 gives some representative values. There are also a few equilibrium constants for the addition of water to imines, but these do not overlap with the other additions.

1.1.5. Indirect Equilibrium Constants

For many addition reactions of carbonyl compounds, it is not possible to measure equilibrium constants directly because they are too unfavorable, and there is no selectively sensitive assay for the adduct. Two indirect methods allowing calculation of these equilibrium constants have been reported. The first takes advantage of the existence, for many unstable tetrahedral adducts, of orthoester analogs, which are stable because there are no OH (or NH or SH) groups in the analog, where they are present in the adduct of interest. If one can prepare and purify the analog, then its heat of hydrolysis can be measured, its solubility can be measured or estimated, and its entropy can be estimated by standard methods. This means that the free energy of formation of the analog can in principle be determined. Then one needs only to calculate the equilibrium constant for the hypothetical hydrolysis which converts the orthoester analog into the tetrahedral adduct,[30] to be able to calculate the free energy of formation of the adduct. From this, plus the free energies of formation of the carbonyl compound and the nucleophile, one can calculate the equilibrium constant for the addition reaction. The nice thing about the hypothetical hydrolysis is that one can say with confidence that its free energy change will be small. This must be so because in this hydrolysis the number of OH and CO bonds is conserved (so that by the bond energy additivity approximation ΔH will be zero), and the number of molecules is the same before and after the reaction (so that to a first approximation ΔS will be zero). The free energy change does depend on symmetry (the number of OR groups on the LHS), on steric interactions (OH is smaller than OR and thus will have smaller steric interactions), and on electronic effects (there is a small dependence on σ^* for the R^1,R^2, R^3 groups). This method has been applied to esters,[52] amides,[53] and

thioesters.[47] Various values determined by this approach are included in the tables in this chapter.

A quite different and complimentary approach is to assume that addition of a nucleophile to an acyl derivative (RCOX) would follow the linear free energy relationship for addition of the nucleophile to the corresponding ketone (RCOR′, or aldehyde if R=H) if conjugation between X and the carbonyl could be turned off, while leaving its polar effects unchanged.[39] This can be done if one knows or can estimate the barrier to rotation about the CO–X bond, because the transition state for this rotation is expected to be in a conformation with X rotated by 90° relative to RCO. In this conformation X is no longer conjugated, so one can treat it as a pure polar substituent. Various values determined by this approach are included in the tables in this chapter.

1.1.6. Equations for the Effect of R, R′

For a given type of reaction (addition of a particular nucleophile to a particular functional group), one can get useful predictive equations on the basis of the Hammett ρσ or the Taft ρ*σ* formalism. Unfortunately, there is some ambiguity in the literature about the definition and, consequently, the numerical values of Taft σ* parameters. The values which some authors give to σ* for a substitutent X correspond to what other authors would say is the σ* value for the related substitutent CH_2-X. The problem arises because Taft used several different definitions of σ* [54] which led to different and inconsistent values. These have then been quoted, not always consistently, by various textbook authors. For example, for OCH_3, Wiberg[55] gives 0.52, the value for CH_2OCH_3,[54] while Hine[56] gives no value for OCH_3 and 0.64[57] for CH_2OCH_3. Carroll[58] gives −0.22 which is the value for ortho substituted benzenes;[54] Perrin[59] gives 1.81.

In this chapter, the definitions used by Perrin in his book on pK_a prediction[59] (which also includes a very convenient compilation of σ* values) will be used. One must be alert to the importance of the number of hydrogens directly attached to the carbonyl carbon; several groups have pointed out that aldehydes and ketones give separate but parallel lines, with formaldehyde displaced by the same amount again.[60] What this means is that given one equilibrium constant for an aldehyde (or ketone) one may estimate the equilibrium constant for other aldehydes (or ketones) from this value and ρ* for the addition using a value from experiment, if available, or estimated if necessary. This assumes that there is no large difference in steric effects between the reference compound and the unknown of interest.

1.1.7. Equations for Effect of Nu

Sander and Jencks introduced a linear free energy relationship for nucleophilic addition to carbonyls. The equilibrium nucleophilicity of a species HNu is given by

a parameter γ, defined as the logarithm of the equilibrium constant for addition of HNu to pyridine-4-carboxaldehyde relative to methylamine.

$$\gamma = \log\left(\frac{K_{Hnu}}{K_{CH_3NH_2}}\right)$$

What this implies is that given one equilibrium constant for addition of a nucleophile of known γ to a carbonyl compound, one could estimate the equilibrium constant for addition of another nucleophile to the same carbonyl compound. This requires knowing the slope of the plot of log K versus γ; this slope is not very sensitive to the nature of the carbonyl compound, but it is at least known that K_{H2O}/K_{MeOH} depends on the electron-withdrawing power of the groups bonded to the carbonyl,[30] and thus more information is needed to estimate an equilibrium constant for strongly electron-withdrawing substituents. From Ritchie's studies of nucleophile addition to trifluoroacetophenone,[46] we can derive a slope for log K versus γ of 0.42, distinctly less than the value of 1 for formaldehyde or simple benzaldehydes.

1.1.8. Anomeric Effect

Another effect which can influence the equilibrium constants for addition to carbonyl groups is the presence of lone pairs in the adducts. Given the fragment RO-C-X, one can have contributing structures $RO^+{=}C\ X^-$ (in valence bond language) or overlapping of the lone pair orbital on oxygen with the antibonding orbital of the C–X bond (in molecular orbital language), which acts to make conformations with such an interaction more stable than those without such interaction. The number of these interactions is likely to have an important effect on the equilibrium constant.

1.1.9. Estimation of Equilibrium Constants for Tetrahedral Intermediate Formation

Addition of water is the best studied reaction, and so there are numerous equations permitting one to estimate log K from σ or σ^*, provided a suitable reference compound has been studied. For most cases, except where strong short range inductive effects are important, the ρ value can be estimated. For nucleophiles other than water, one can either use the same sort of linear free energy relation, provided one has a suitable reference reaction where K is known, or use an orthogonal approach, going from the K for water addition to the K for the desired nucleophile using the γ method. Because the slope of a plot of log K versus γ depends on the nature of the substrate carbonyl compound, this requires some knowledge of the appropriate slope parameter for at least a closely related system. Fortunately, the slope is not a strong function of the electronic nature of the carbonyl compound; even for $PhCOCF_3$ the slope only falls from 1.0 to 0.42. One must also note that anomeric effects will have

TABLE 1.4. Linear free energy relationships for addition to carbonyl groups: variation in carbonyl group.[a]

Compound	Nucleophile	σ values used	ρ	Experimental data
RCOR′	H_2O	σ*	1.70[b]	
ArCHO	H_2O	σ	1.71[c]	
ArCHO	HO^-	σ^+	2.37	[H, 4-Cl, 3-Cl, 4-CF_3, 3-NO_2, 3NO_2-4-Cl, 4-NO_2, 3,5-$(NO_2)_2$][c]
ArCHO	MeOH	σ^+	1.58	[4-OMe, 4-Me, H, 3-OMe, 4-Cl, 4-Br, 3-Cl, 3-Br, 3-NO_2, 4-NO_2][d]
ArCHO	MeO^-	σ^+	2.48	[4-OMe, 4-Me, H, 3-OMe, 4-Cl, 4-Br, 3-Cl, 3-Br, 3-NO_2, 4-NO_2][d]
RCOR′	MeOH	σ*	1.82	[R,R′ = Me_2, Me, $ClCH_2$, $(ClCH_2)_2$][e]
ArCHO	HCN	σ^+	1.01[f]	
ArCHO	CN^-	σ^+	1.49[f]	
ArCHO	HSO_3^-	σ^+	1.25[g]	
$ArCOCH_3$	HSO_3^-	σ^+	1.05	[4-OMe, 4-Me, H, 4-Cl, 4-Br, 3-Br, 4-NO_2][h]
ArCHO	NH_2OH	σ^+	1.18	[3-NO_2, 4-NO_2, 4-Cl, H, 4-NMe_3^+],[i] [4-OMe, 4-NMe_2][j,k]
$ArCOCH_3$	NH_2OH	σ^+	1.66	[3-NO_2, 4-Br, 4-F, 4-Me, 4-OMe][l]
RCOR′	HSO_3^-	σ*	0.37	[CH_3,CH_3],[m] [CH_3OCH_2, CH_3OCH_2][n]
$RCOOCH_3$	H_2O	σ*	3.08	[Me, Et, iPr, CF_3, $ClCH_2$, $NCCH_2$, $MeOCH_2$][o]
$RCOSCH_2CH_3$	H_2O	σ*	2.06	[CH_3, CF_3][p]
$RCON(CH_3)_2$	H_2O	σ*	1.99	[CH_3, CF_3][q]
PhCOR	H_2O	σ*	2.06	[CH_3,[r] CF_3][s]
PhCOR	HSO_3^-	σ*	1.00	[CH_3,[h] CF_3][s]
PhCOR	NH_2OH	σ*	1.80	[CH_3,[t] CF_3][s]

[a]All in aqueous solution at 25°C unless otherwise noted.
[b]Reference 60.
[c]Reference 38.
[d]Reference 40.
[e]Reference 30.
[f]Reference 41.
[g]Reference 61.
[h]Reference 44 (reported ρ = 1.2, ρ = 0.95 based on an extrapolation of the correlation line for $PhCOCH_3$ + HNu).
[i]Reference 42.
[j]Reference 62.
[k]At 30°C.
[l]Reference 63.
[m]Reference 5 and references cited therein.
[n]Reference 64.
[o]Reference 65.
[p]Reference 47.
[q]Reference 39.
[r]Based on an extraplolation of the correlation line for $PhCOCH_3$ + HNu.
[s]Reference 46.
[t]Based on an extrapolation of the correlation line for $ArCOCH_3$ + NH_2OH.

an important influence on the observed log K, so this approach can be used only for aldehydes and ketones. For acyl derivatives, the anomeric effects must be different and the magnitude of this effect is not yet known.

There are anomalies for compounds with CF_3 directly attached to a carbonyl group. Equilibrium constants for addition to such a carbonyl group are higher than expected, relative to the CH_3 compound. However, the rate constants for hydroxide addition to esters do not show this phenomenon. This might indicate that when CF_3 is directly attached to carbonyl (which is formally treated as C^+-O^-), there is, in addition to the field effect measured by σ^*, an important inductive contribution which augments the field effect. Alternatively, it may just reflect the large uncertainties in free energy changes based on extended thermochemical calculations.

Despite many papers over many years, there is still a serious shortage of information that allows linear free energy relation treatment of these reactions. The available linear free energy relations, some of them calculated for this chapter, are collected in Tables 1.4 and 1.5. There are definite indications that ρ is

TABLE 1.5 Linear free energy relationships for addition to carbonyl groups; variation in nucleophile.[a]

Substrate	Slope	Experimental data
CH_2O	1.0[b]	
Py-4-CHO	1.0[b]	
4-ClPhCHO	1.0[b]	
CH_3COCH_3	0.92[c]	
CH_3CHO	1.06[c]	
i-PrCHO	0.909	[H_2O, MeOH],[d] [$MeOCH_2CH_2SH$],[e] [HSO_3^-][f]
PhCHO	1.02[c]	
$MeOCH_2COCH_2OMe$	0.67	[H_2O, HSO_3^-][g]
$PhCOCF_3$	0.42	[H_2O, H_2O_2, HCN, HSO_3^-][h]
$PhCOCH_3$	1.04	[NH_2OH,[i] HCN,[j,k] HSO_3^-][l]
p-NO_2PhCHO	0.96	[H_2O,[m] HCN,[n] NH_2OH,[o] HSO_3^- [p]]

[a]All in aqueous solution at 25°C unless otherwise noted.
[b]Reference 31.
[c]Reference 5.
[d]Reference 30.
[e]Reference 37.
[f]Reference 33.
[g]Reference 64.
[h]Reference 46.
[i]Extrapolated from a correlation based on data of Lamaty.[63]
[j]Reference 43.
[k]In ethanol.
[l]Reference 44.
[m]Reference 38.
[n]Reference 41.
[o]Reference 42.
[p]Extrapolated from a correlation based on data in reference 66.

TABLE 1.6 Cross terms.

System	First correlation	Second correlation	Cross term
RCOR′	σ^*	γ	−0.19
PhCOR′	σ^*	γ	−0.13
ArCHO	σ	γ	−0.12
ArCOMe	σ	γ	−0.22
RCOR′	γ	σ^*	−0.19
ArCHO	γ	σ	−0.06

different for different nucleophiles and that Δ is different for different carbonyl compounds, though in neither case is the sensitivity very large. There are insufficient data to tell how elaborate a model must be. The simplest model for the observations is:

$$\log K = \rho_0^* \Sigma\sigma^* + \Delta_0\gamma + a_{\gamma\sigma} \Sigma\sigma^* \gamma + \text{const}$$

However, the data do not permit a proper test, although they indicate (see Table 1.6) that $a_{\gamma\sigma}$ is between −0.12 and −0.22 (with the exception of aromatic aldehydes where one sequence gives −0.12 and the other gives −0.06).

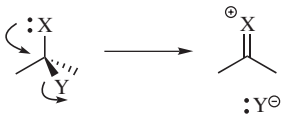
One reason why the necessary measurements have not been done is that it is not easy to get a set of compounds that would give clean reactions and have a strong electron withdrawing group. Cyanide can act as a nucleophile in the S_N2 sense as well as at a carbonyl group, so that alternative modes of reactions are possible for $ClCH_2COCH_3$ (including a Darzens-like reaction of the cyanohydrin anion). FCH_2COCH_3 might serve, but it is unpleasantly toxic. $CF_3CH_2COCH_3$ would be good but it is not commercially available and it might slowly eliminate HF by an Elcb mechanism. Many polar substituents will also form enolates by ionization and thus lead to complications. However, despite all of these difficulties, it would be very desirable to have more data to unscramble the linear free energy relations controlling these important reactions.

Another sign of complexity which has largely been ignored is that CH_2O, but not simple aldehydes or ketones, shows a dispersion of log $K-\gamma$ plots with nitrogen nucleophiles falling on a line parallel to but higher than the line for other nucleophiles. The same phenomenon is seen for $PhCOCF_3$! The common feature is that both have carbonyl groups with destabilizing substituents (two Hs or one CF_3). It is not obvious why this should be, but the phenomenon seems real.

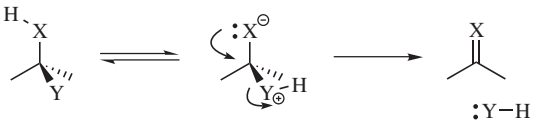
In principle, it should be possible to use computational thermochemistry to calculate free energies of formation for unknown tetrahedral intermediates. In practice this remains difficult because of the problem of estimating solvation energies. There is no doubt that computational methods will become increasingly important in this as in other areas.

1.1.10. Mechanisms of Tetrahedral Intermediate Formation and Breakdown

Uncatalyzed mechanisms for the breakdown of a tetrahedral intermediate are relatively rare because they require generation of a cation and an anion:

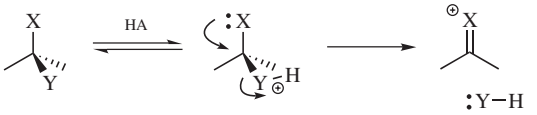


It is for this reason that orthoesters and acetals are (comparatively) stable in the absence of an acid. Alternatively, one can have an uncatalyzed mechanism involving preliminary tautomerization to a zwitterion, but the thermodynamic cost of this imposes a considerable barrier to reaction.

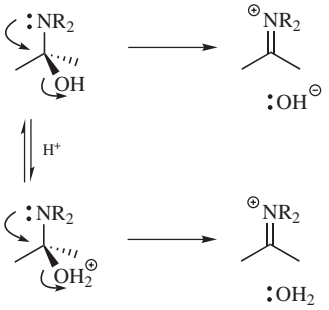


By contrast base-catalyzed mechanisms are generally fast, provided, of course, that one of the heteroatoms defining the tetrahedral intermediate has an ionizable proton.

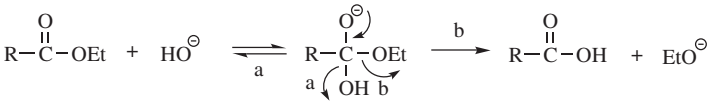
Finally, acid-catalyzed mechanisms are generally fast but must overcome the relatively low basicity of the tetrahedral intermediate (with electron-withdrawing substituents necessarily present, the basicity is low).

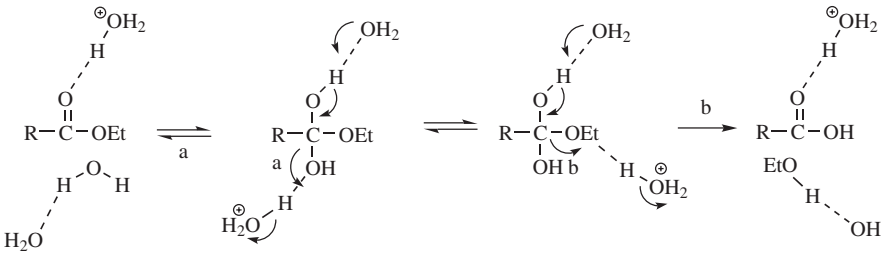


It is helpful to think of these as displacement reactions: if the leaving group Y is poor, then a good "nucleophile" X is needed; whereas if Y is a good leaving group, then a poor "nucleophile" will suffice. Thus rapid reaction will often require enhancing either X (by base catalysis) or Y (by acid catalysis). For example, the dehydration of carbinolamines derived from strongly basic amines can proceed by an uncatalyzed path,[34,67] but carbinolamines derived from weakly basic amines require acid catalysis.[23] The breakdown of cyanohydrins requires base catalysis,[68] and does not occur in acid; the cyano group is not very basic, and with strong acid one gets hydrolysis to the amide or acid instead.

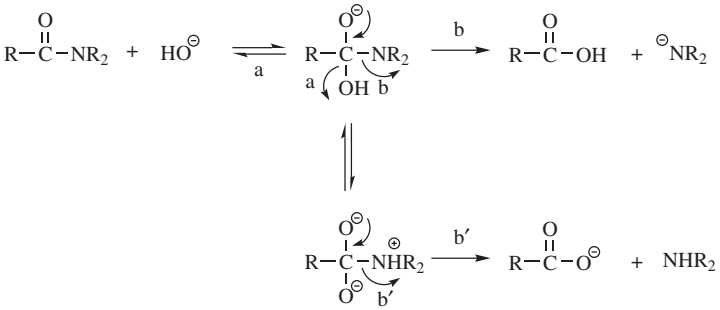


Much of the complication in the chemistry of acyl transfer reactions can be understood in terms of the relative leaving group abilities of the possible leaving groups. Thus, it is reasonable that oxygen exchange should accompany the hydrolysis of esters either in acid or in base,[20] because in each case the competing leaving groups are very similar.

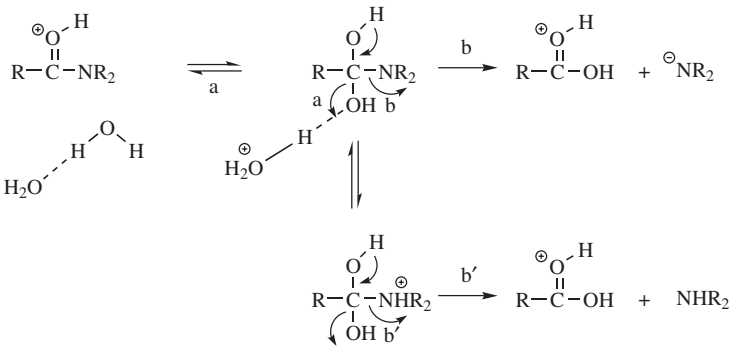




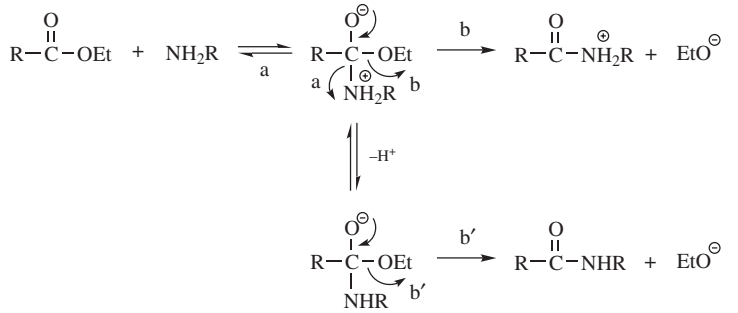
For amide hydrolysis in base, the initial adduct would revert to starting materials (without remarkable stabilization, an amide ion is a hopeless leaving group, so that path b does not compete with path a), but a not very difficult proton transfer gives an intermediate in which the amine is the better leaving group and path b′ can compete with path a.[69]



For amide hydrolysis in acid, proton transfer to give a cationic intermediate is easy, and breakdown to products is favored over reversion to starting material;[70] process b is hopelessly bad, but process b′ is better than a.



Aminolysis of simple esters is surprisingly difficult, despite the greater thermodynamic stability of amides than esters; the problem is that the initial tetrahedral intermediate preferentially reverts to starting material (not only is the amine the better leaving group, but loss of alkoxide would lead to an *N*-protonated amide), and only trapping of this intermediate by proton transfer allows the reaction to proceed.[53,71]

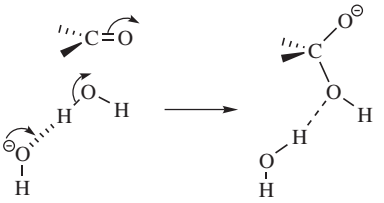


1.1.11. Rates of Breakdown of Tetrahedral Intermediates

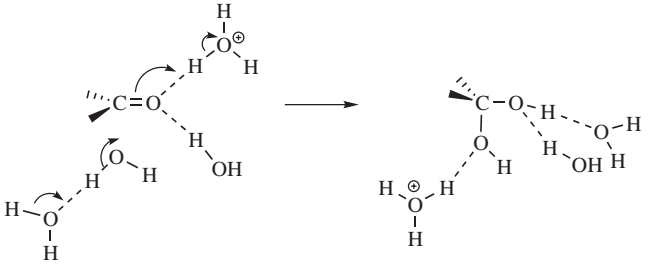
Rates of addition to carbonyls (or expulsion to regenerate a carbonyl) can be estimated by appropriate forms of Marcus Theory.[72–75] These reactions are often subject to general acid/base catalysis, so that it is commonly necessary to use Multidimensional Marcus Theory (MMT)[76,77] to allow for the variable importance of different proton transfer modes. This approach treats a concerted reaction as the result of several orthogonal processes, each of which has its own reaction coordinate and its own intrinsic barrier independent of the other coordinates. If an intrinsic barrier for the simple addition process is available then this is a satisfactory procedure. Intrinsic barriers are generally insensitive to the reactivity of the species, although for very reactive carbonyl compounds one finds that the intrinsic barrier becomes variable.[77]

Alternatively one can make use of No Barrier Theory[78–81] (NBT), which allows calculation of the free energy of activation for such reactions with no need for an empirical intrinsic barrier. This approach treats a real chemical reaction as a result of several simple processes for each of which the energy would be a quadratic function of a suitable reaction coordinate. This allows interpolation of the reaction hypersurface; a search for the lowest saddle point gives the free energy of activation. This method has been applied to enolate formation,[82] ketene hydration,[83] carbonyl hydration,[80] decarboxylation,[84] and the addition of water to carbocations.[79]

Both these methods require equilibrium constants for the microscopic rate determining step, and a detailed mechanism for the reaction. The approaches can be illustrated by base and acid-catalyzed carbonyl hydration. For the base-catalyzed process, the most general mechanism is written as general base catalysis by hydroxide; in the case of a relatively unreactive carbonyl compound, the proton transfer is probably complete at the transition state so that the reaction is in effect a simple addition of hydroxide. By MMT this is treated as a two-dimensional reaction: proton transfer and C–O bond formation, and requires two intrinsic barriers, for proton transfer and for C–O bond formation. By NBT this is a three-dimensional reaction: proton transfer, C–O bond formation, and geometry change at carbon, and all three are taken as having no barrier.



For acid catalyzed hydration, the general mechanism is:

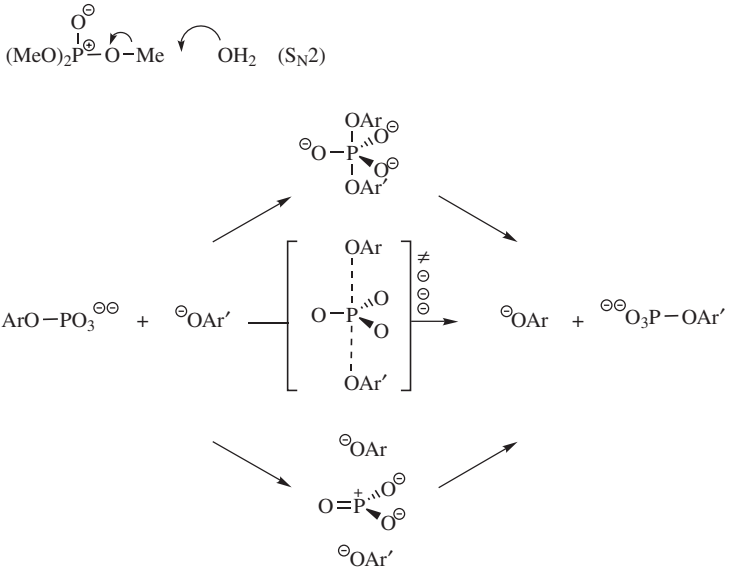


and is written as a general acid-catalyzed process; with the more basic carbonyl compounds the proton transfer from hydronium ion may be complete at the transition state. A second water molecule acts as a general base to deprotonate the nucleophilic water because the product of simple attack, a cationic tetrahedral intermediate, would be significantly more acidic than water and thus would lose a proton to the solvating water. By MMT this is treated as a three-dimensional reaction: proton transfer from

hydronium ion, proton transfer from water to water, and C–O bond formation, and requires intrinsic barriers for proton transfer and C–O bond formation. By NBT this is treated as a four-dimensional reaction: proton transfer from hydronium ion, proton transfer from water to water, C–O bond formation, and geometry change at carbon. Treating proton transfer as a no barrier process is clearly only an approximation because there is a small intrinsic barrier to proton transfer between electronegative atoms[76b] but this seems to be a workable approximation as long as there are also heavy atom bond changes in the overall reaction.

1.2. PENTACOORDINATE INTERMEDIATES INVOLVING P

Phosphate esters have a variety of mechanistic paths for hydrolysis.[85] Both C–O and P–O cleavage are possible depending on the situation. A phosphate monoanion is a reasonable leaving group for nucleophilic substitution at carbon and so S_N2 or S_N1 reactions of neutral phosphate esters are well known. PO cleavage can occur by associative (by way of a pentacoordinate intermediate), dissociative (by way of a metaphosphate species), or concerted (avoiding both of these intermediates) mechanisms.

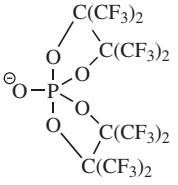


The pentacoordinate intermediate is the analog of the tetrahedral intermediate, and stable phosphoranes are the analogs of ortho esters and related species in carbon chemistry. $Ph_3P(OPh)_2$[86] and $P(OPh)_5$[87] were reported in 1959, and in 1958 a general synthesis of pentaalkoxy phosphoranes containing an unsaturated five-membered ring was reported.[88,89] In 1964 a synthesis of pentaethoxyphosphorane was devised[90] which led to the preparation of a number of saturated and unsaturated pentaalkoxy

phosphoranes. A less hazardous route using an alkyl benzene sulfenate as an oxidizing agent makes these compounds more accessible.[91] Thus, analogs of the putative intermediate in the associative mechanisms are known, but these compounds are very sensitive to water; much more so than simple orthoesters.

For a number of reactions of cyclic di- and triesters of phosphoric acid, there are exchange data which can be rationalized on the assumption of trigonal bipyramidal intermediates which readily interconvert by pseudorotation.[92] This constitutes a strong argument that at least these cyclic esters react by an associative mechanism and is suggestive evidence that simple trialkyl phosphates also react by this mechanism. The pH dependence of exocyclic versus endocyclic cleavage of methyl ethylene phosphate is readily interpreted in terms of the effect of ionization of the intermediate on the pseudorotation of these pentacoordinate intermediates.[93]

Analogous to tetrodotoxin are phosphoranoxides **3**,[94] **4**,[95,96] and **5**,[97] where chelation, steric bulk, and proper arrangement of electron-withdrawing and electron-donating substituents make them stable enough to isolate.



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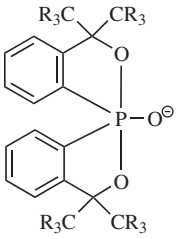

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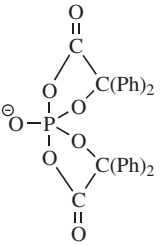
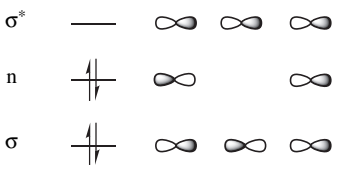


5

1.2.1. Bonding in Pentacoordinate Phosphorus and Sulfur Compounds

These compounds are often referred to as hypervalent. The apical bonds in a trigonal bipyramid are described by molecular orbitals constructed from a p-orbital on the central atom and σ-bonding orbitals (p- or sp^n hybrid) on the apical ligands. The molecular orbitals can be drawn as:



For a discussion of hypervalent bonding see reference 98. This picture indicates that there is an accumulation of partial negative charge on the apical ligands and thus a partial positive charge on the central atom.[99] Thus the apical ligands should be electronegative.

TABLE 1.7. Equilibrium constants for addition or elimination from phosphoric acid esters.[a]

Starting compound	log K for elimination	log K for addition of water[b]	log K for addition of hydroxide[c]
H_3PO_4	−23[d]	−12	—
$H_2PO_4^-$	−20[e]	−19	—
$HPO_4^=$	−26[f]	−25	—
$(EtO)_3PO$	−46[g]	−10	−3
$(EtO)_2PO_2H$	−21[h]	−12	—
$(EtO)_2PO_2^-$	−35[i]	−18	−16
$EtOPO_3H_2$	−21[j]	−12	—
$EtOPO_3H^-$	−18[k]	−18	—
$EtOPO_3^=$	−27[l]	−24	−27

[a]All in aqueous solution at 25°C; standard states are 1 M ideal solution with an infinitely dilute reference state, and the pure liquid for water; equilibrium constants from reference 100, except as noted.
[b]K = [adduct]/[orthophosphate]
[c]K = [adduct]/[orthophosphate][HO^-]
[d]$K = [HPO_3]/[H_3PO_4]$
[e]$K = [PO_3^-]/[H_2PO_4^-]$
[f]$K = [PO_3^-][HO^-]/[HPO_4^=]$
[g]$K = [(EtO)_2PO^+][EtO^-]/[(EtO)_3PO]$; estimated as described in Section 1.4.3.
[h]$K = [EtOPO_2][EtOH]/[(EtO)_2PO_2H]$
[i]$K = [EtOPO_2][EtO^-]/[(EtO)_2PO_2^-]$
[j]$K = [HPO_3][EtOH]/[EtOPO_3H_2]$
[k]$K = [PO_3^-][EtOH]/[EtOPO_3H^-]$
[l]$K = [PO_3^-][EtO^-]/[EtOPO_3^=]$

1.2.2. Indirect Equilibrium Constants

By methods analogous to those used for the tetrahedral intermediates related to carboxylic acid derivatives, Guthrie proceeded from the heat of formation of pentaethoxyphosphorane to free energies of the $P(OEt)_n(OH)_{5-n}$ species.[100] This allowed the calculation of the equilibrium constants for addition of water or hydroxide to simple alkyl esters of phosphoric acid; see Table 1.7.

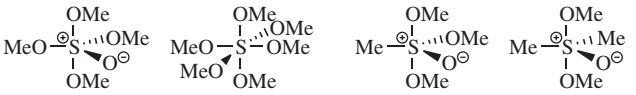
1.3. PENTACOORDINATE INTERMEDIATES INVOLVING S

Sulfate monoesters can react by dissociative paths, and this is the favored path.[101] Whether such reactions are concerted or involve a very short-lived sulfur trioxide intermediate has been the subject of debate.[102,103] Benkovic and Benkovic reported evidence suggesting that the nucleophile is present (though there is little bond formation) in the transition state for the reaction of amines with *p*-nitrophenyl sulfate.[104]

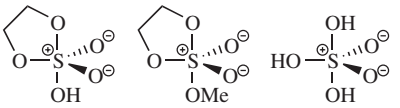
Alkyl esters of sulfuric or sulfonic acids normally react with C–O cleavage; only when this is disfavored, as in aryl esters, does one see S–O cleavage. Sulfate diester

and sulfonate ester reactions (with S-O cleavage) have been discussed in terms of concerted or stepwise (addition elimination) mechanisms,[105,106] but recent authors[22] have favored concerted mechanisms. In suitable sulfonates, with an ionizable hydrogen next to the sulfur, there are also stepwise elimination addition pathways by way of sulfenes[107] or analogs.

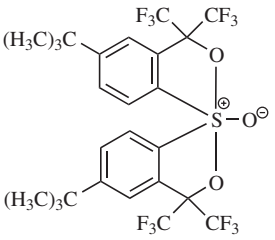
The simplest sulfur analogs of tetrahedral intermediates are the sulfuranes



none of which are known experimentally, although computational results suggest



that they are at least energy minima.[108,109–111] Other than various halogen derivatives, the sulfuranes closest to those of interest here which have actually been prepared are the chelated derivatives **6**[112] and **7**[105] prepared by Martin et al. The former is an analog of the adduct of a sulfone, whereas the latter is an analog of a sulfonate ester adduct.



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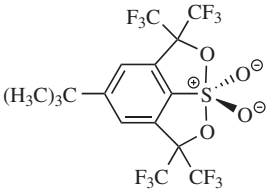

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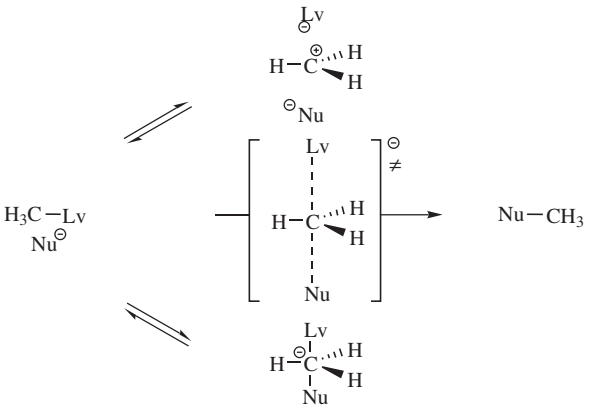
1.4. CONCERTED REACTIONS

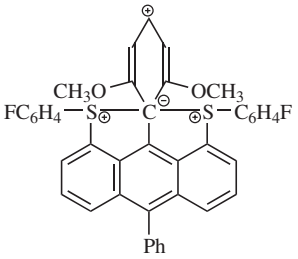
1.4.1. General Principles

A useful general rule when considering concerted reactions is that a concerted reaction path is followed in order to avoid unstable intermediates.[113] A concerted path has more things happening (more partial bonds, more atoms undergoing geometry change) so it is to be expected that such a path will be slower (will have a higher intrinsic barrier) than an alternative stepwise path,[76,114–116] unless the stepwise path is disfavored by leading to a high-energy species. The classic examples of this principle are the S_N2 and E2 reactions. The S_N2 is observed when the S_N1 alternative is disfavored because of the instability of the carbocation which would have to form. The other

stepwise alternative is the pentacoordinate species with five full bonds to carbon, and this is almost invariably too high energy to be a viable reaction intermediate.



However an example of a [10-C-5] species has been reported.[117,118]

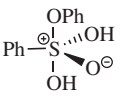


Similarly, the E2 is observed when both the E1 and E1cb alternatives are disfavored. Thus we expect that a concerted acyl transfer will be most likely when the intermediates in both the stepwise alternatives (tetrahedral intermediate and acylium ion) are of high energy.[119,120] Similarly, a phosphoryl transfer is expected to be concerted when both the pentacoordinate intermediate and the metaphosphate species are of high energy, and to shift to a stepwise path when one or the other is accessible. Sulfonyl transfer will be concerted when the corresponding stepwise alternatives (pentacoordinate sulfurane or sulfur trioxide for a sulfate monoester; sulfurane and *O*-alkylated sulfur trioxide for a sulfate diester; and sulfurane and a sulfonylium ion, RSO_2^+, for a sulfonate ester) are high energy species. Because so few sulfuranes have been prepared, the sulfurane species seem to be more inaccessible than is the case for phosphate esters, and this, in isolation, would suggest that there is a greater likelihood of concerted pathways for sulfate or sulfonate derivatives. However, the dissociative intermediates are all unlikely and very high energy species, which would suggest that stepwise reaction by an addition–elimination mechanism is more likely. Kice reviewed the evidence[106] and concluded that sulfonylium ions are much more difficult to form than the corresponding acylium ions.

1.4.2. Evidence for Concerted Reactions

For acyl transfer, oxygen exchange has been observed in various reactions,[20,69,70] providing evidence supporting a stepwise addition–elimination mechanism. It is of course now generally accepted that most acyl transfer reactions occur by stepwise mechanisms, although in some cases concerted mechanisms are believed to be preferred. For various simple phosphate esters, oxygen exchange into the unreacted ester has been observed accompanying hydrolysis.[121] This suggests that at least some phosphate ester reactions occur by stepwise mechanisms, although there are also situations where concerted mechanisms have been proposed.

Oae found that for both base- and acid-catalyzed hydrolysis of phenyl benzenesulfonate, there was no incorporation of ^{18}O from solvent into the sulfonate ester after partial hydrolysis.[122,123] This was interpreted as ruling out a stepwise mechanism, but in fact it could be stepwise with slow pseudorotation. In fact this nonexchange can be explained by Westheimer's rules[92] for pseudorotation, assuming the same rules apply to pentacoordinate sulfur. For the acid-catalyzed reaction, the likely intermediate would be **8** for which pseudorotation would be disfavored because it would put a carbon at an apical position. Further protonation to the cationic intermediate is unlikely even in 10 M HCl (the medium for Oae's experiments) because of the high acidity of this species: a Branch and Calvin calculation[124] (See Appendix), supplemented by allowance for the effect of the phenyl groups (taken as the difference in pK_a between sulfuric acid and benzenesulfonic acid[125]), leads to a pK_a of -7 for the first pK_a of this cation; about -2 for the second pK_a, and about 3 for the third pK_a. Thus, protonation by aqueous HCl to give the neutral intermediate is likely but further protonation to give cation **9** would be very unlikely.



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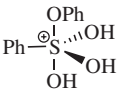
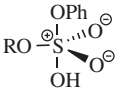


9

For the intermediates in base-catalyzed hydrolysis of a sulfate ester (**10**), pseudorotation about any of the equatorial bonds will necessarily put at least one O^- in an apical position, which is strongly disfavored.[126]



10

Okuyama et al. have presented evidence that at least some sulfenates and sulfinate derivatives react by way of hypervalent intermediates.[127–129]

For acyl transfer, phosphoryl transfer, and sulfonyl transfer, the primary kind of evidence in favor of concerted mechanisms for some reactions is a linear Bronsted plot of log k versus pK_a^{nuc} for a range of nucleophiles, spanning $pK_a^{nuc} - pK_a^{lg} = 0$, coupled

with an assumption that the β values for addition and elimination would be quite different. Much of this argument is based on the large β_{eq} values which are interpreted as meaning that the oxygen in an aryl ester bears a substantial δ^+ charge which will be markedly diminished only by cleavage of the bond from oxygen to the carbonyl carbon (or phosphoryl phosphorus or sulfonyl sulfur). If the carbonyl carbon is regarded as $C^+–O^-$ (for which there is considerable support[130–132]), then the β_{eq} values reflect the interaction of the alcoholic or phenolic group with this (+) charge, and formation of a tetrahedral intermediate, with cancellation, will drastically change the interaction without significant C–O bond cleavage.

The problem is that "proving" concerted reaction requires negative evidence: a Bronsted plot with a clear break is strong evidence for a stepwise reaction; absence of a break could mean a concerted reaction or similar β values for both modes of breakdown of the intermediate, which is likely if the intermediate is high in energy relative to starting materials and products. The situations where concerted reactions are proposed are in fact ones where the tetrahedral intermediate is indeed likely to be of high energy, because while a good leaving group (electron deficient phenol) will favor addition to form a tetrahedral intermediate, the same phenol is a poor nucleophile which makes addition unfavorable.

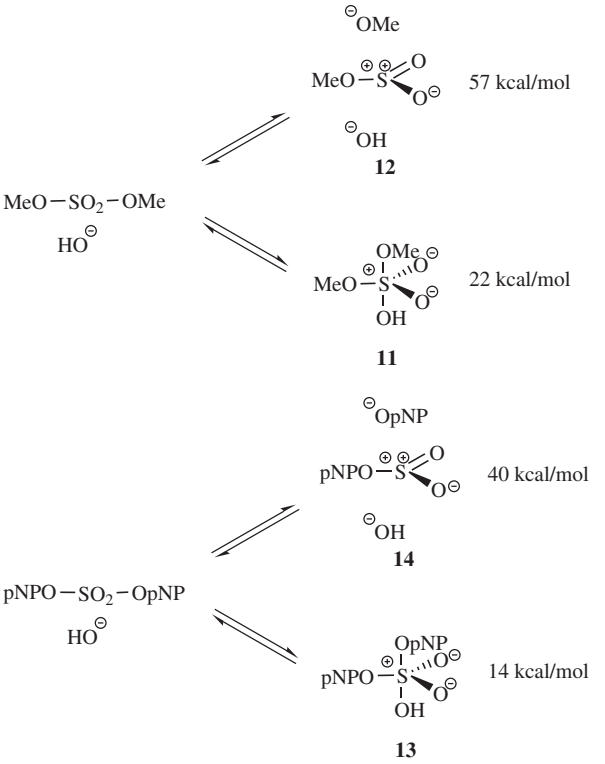
From the *a priori* point of view, when would one expect concerted reactions? On the basis of the model presented earlier, concerted reactions occur when both the stepwise alternatives require high energy intermediates. Then a concerted path, avoiding both bad intermediates, can have a transition state lower in free energy than either. If one stepwise intermediate is much higher in energy than the other, then any change in structure from the lower energy intermediate toward the higher energy one is likely to raise, not lower the free energy, and thus a concerted path becomes unlikely. For the reaction of aryloxides with aryl acetates, an analysis of the energetics[120] suggested that the energies of the acylium ion with two phenoxides and of the tetrahedral intermediates were comparable, which predisposes this system to becoming concerted. Unfortunately, the only equilibrium data for acylium ions are for acetylium ion,[133] a few alkanecarboxylium ions, and benzoylium[134] ion and nothing is known about substituent effects. For phosphate esters, nucleophilic substitution of monoester dianions is likely to be concerted because both stepwise intermediates are bad, with dissociative reaction by a nearly free monomeric metaphosphate intermediate being an alternative absent a good nucleophile, while for diesters or triesters, the dissociative intermediate is high in energy relative to the associative intermediate making concerted reaction unlikely. For sulfate diesters and sulfonate esters, the high energy of the dissociative intermediates make concerted reactions with S–O cleavage unlikely, while for sulfate monoesters the dissociative stepwise reaction or concerted reaction (with a very open transition state) look feasible.

By linear free energy relation arguments, Williams et al. concluded that in the case of a five-membered ring sultone the reaction with a phenoxide was either stepwise or, if concerted, had a transition state close to the pentacoordinated intermediate.[135]

Thus, there is suggestive evidence that both stepwise intermediates for sulfonyl transfer reactions may be relatively high-energy species. Now we will try to estimate the energetics for such species; first for the simplest parent cases, even though they

react by other mechanisms, and then for the aryl esters which do react with S–O cleavage. The goal is not to get estimates good enough to estimate the rate but to see if what is now known is enough to rule out some mechanistic paths. We will see that this is, in fact, the case.

First we will look at hydroxide attack on sulfate diesters, and estimate the free energy changes for the two stepwise limiting cases corresponding to concerted displacement.



For species **11** we will use the intrinsic barrier for hydroxide addition to trimethyl phosphate, $\widetilde{G} = 19$ (calculated using rate and equilibrium data from reference 100) and assume the same value for the attack of hydroxide at sulfur on dimethyl sulfate. This (nonobservable) rate will be estimated using a Brønsted type plot from the rate constants for diaryl sulfates (diphenyl sulfate,[136] and bis *p*-nitrophenyl sulfate), estimated from the rate for phenyl dinitrophenyl sulfate,[137] assuming equal contributions for the two nitro groups. This gives $\beta_{lg} = -0.95$, and thus for dimethyl sulfate $\log k = -11.3$ and $\Delta G^{\neq} = 33$, which affords $\Delta G^{\circ} = 22$ kcal/mol for the formation of **11**.

For the same reaction, Thatcher and Cameron calculated (MP2/6-31+G*//HF/3-21+G* with continuum solvation[111]) $\Delta G^\circ = 21$ kcal/mol.

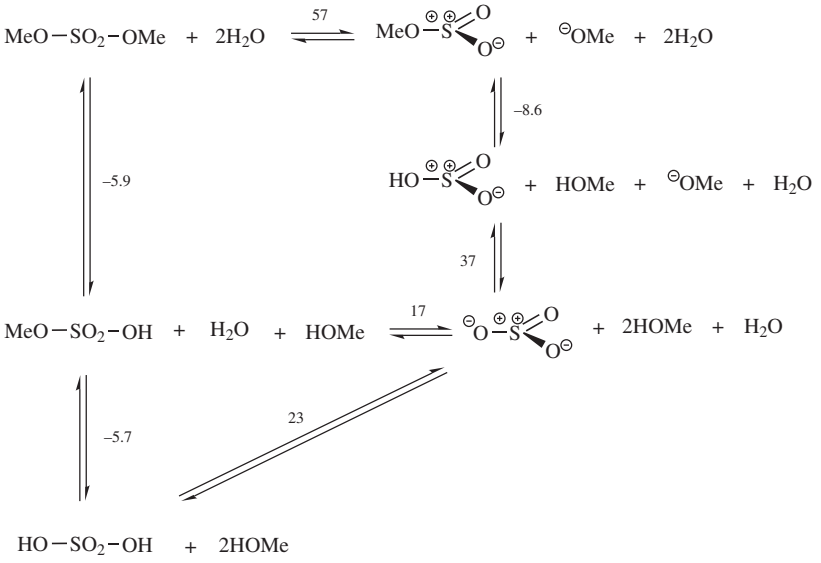
For species **12**, we first estimate the pK_a of HO-SO_2^+ using the method of Branch and Calvin[124] (see Appendix), knowing full well that this will not be accurate because the central atom is highly charged, the estimate for sulfuric acid with S^{++} is too acidic, and resonance will also make a contribution, so that the crude estimate will not be acidic enough. However, the errors may partly cancel.

$$\log K_a = -16 + 13.2*2 - 13.2/2.8 + 2*4/2.8 + 3.4 + \log(1/3) = 11.5$$

From this and the relation between the equilibrium for ester formation and the pK_a of the acid,[100] we estimate the free energy change for the reaction

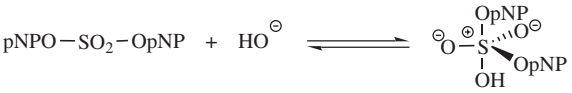
$$CH_3OH + HO\text{-}SO_2^+ \rightleftharpoons CH_3O\text{-}SO_2^+ + H_2O$$

as $\Delta G^\circ = 8.6$ kcal/mol. Then from the thermodynamic cycle:



we estimate $\Delta G^\circ = 57$ kcal/mol for formation of **12** and methoxide from $(MeO)_2SO_2$. In this and all following thermodynamic cycles, the numbers are free energies, in kcal/mol, in the direction indicated by the arrow next to the number. (Numbers used in the cycle: ΔG° for hydrolysis of dimethyl sulfate;[125] ΔG° for hydrolysis of monomethyl sulfate—calculated from the pK_a;[125] ΔG° for dissociation of sulfuric acid to SO_3.[138]) Despite all the uncertainties in this calculation, it looks like sulfate diester hydrolysis should be stepwise or very close to it, because the dissociative intermediate **12** is 35 kcal/mol higher in energy than the associative intermediate **11**.

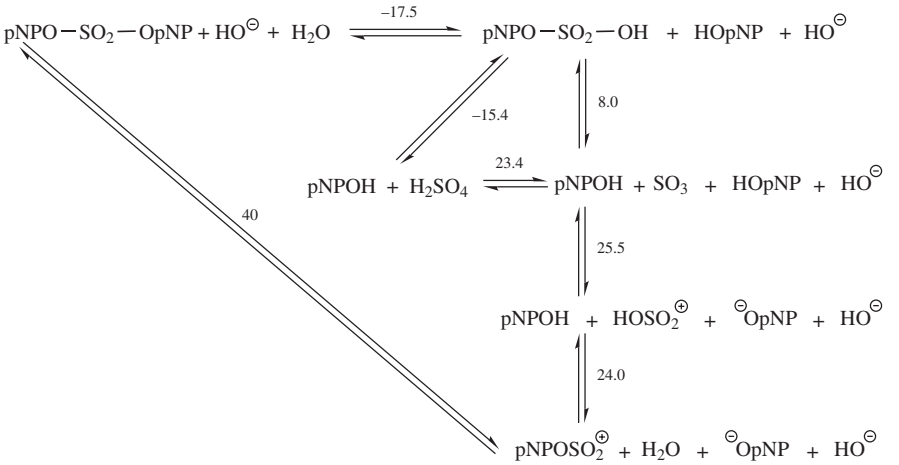
To estimate the effects of changing from methyl to *p*-nitrophenyl ester on the addition reaction, we use the change in equilibrium constant for addition of hydroxide to acetate esters, which was estimated[120] as $\Delta\Delta G^\circ = 4.3$ kcal/mol. We assume the same change applies to sulfates and phosphates. Then, from the free energy change for addition of hydroxide to dimethyl sulfate, we get $\Delta G^\circ = 14$ kcal/mol for the reaction given below.



The starting points are the free energies of hydrolysis for $pNPOSO_3H$[138] and $pNPOPO_3H_2$.[100] From these we may deduce an equation relating ΔG_{hydrol} to pK_a of HOX for

$$pNPOX + H_2O \rightleftharpoons pNPOH + HOX$$

as $\Delta G_{hydrol} = -12.69 + 0.98pK_a$. From this we may calculate ΔG_{hydrol} for $(pNPO)_2SO_2$ as −17.5, and for $pNPOSO_2^+$ as −24.0 kcal/mol, respectively. Then the energy of the dissociative corner can be calculated following the thermodynamic cycle:

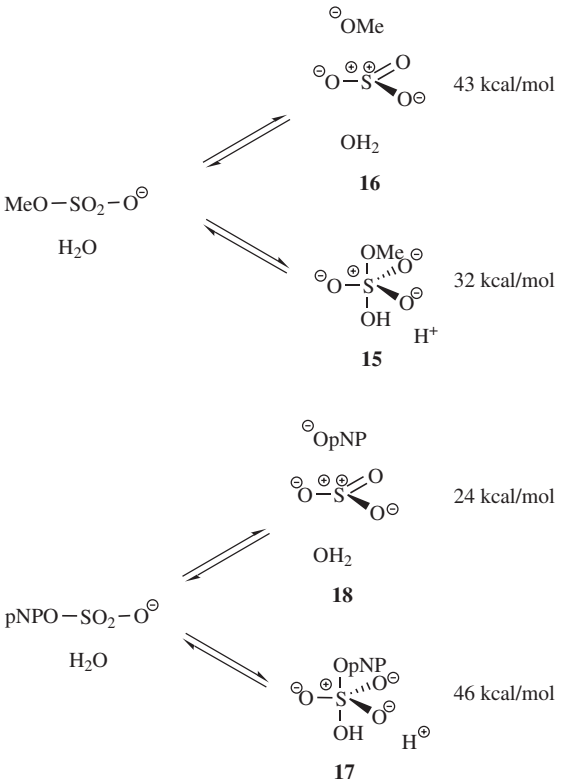


(Numbers used in this cycle: ΔG° for dissociation of sulfuric acid to sulfur trioxide;[138] ΔG° for hydrolysis of bis-*p*-nitrophenyl sulfate, estimated as described above; ΔG° for hydrolysis of mono-*p*-nitrophenyl sulfate;[138] ΔG° for esterification to give $pNPOSO_2^+$, estimated as described above; ΔG° for ionization of protonated SO_3, estimated as described above; ΔG° for ionization of p-nitrophenol[139].)

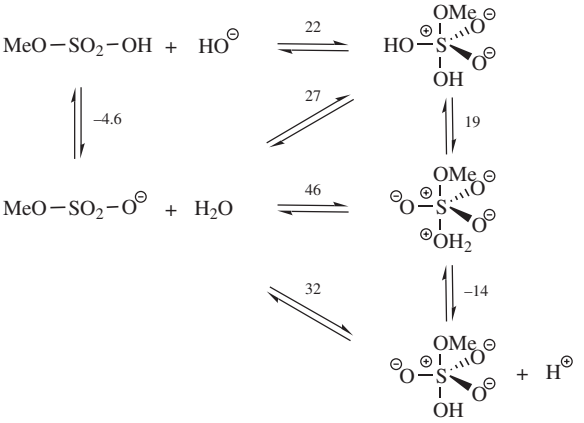
The reaction of hydroxide with dimethyl sulfate clearly should not be concerted: the dissociative corner, **12**, is far too high in energy, yet the reaction would not show

^{18}O exchange because pseudorotation is strongly inhibited. Similarly, the reaction of hydroxide with bis-*p*-nitrophenyl sulfate should not be concerted because **14** is far too high in energy. The free energy of activation for reaction (estimated from data of Hengge[137]) is 22 kcal/mol, enough higher than the equilibrium free energy change for intermediate formation to be reasonable.

Now we turn to the reaction of water with the sulfate monoester monoanion, which, in the case of aryl esters, is believed to react either by a dissociative path, or a concerted path with a transition state resembling the dissociative limit. There is a problem for this reaction in the case of an alkyl ester. Simple attack of water leads to a very acidic species with H_2O^+ bonded to S^+; loss of a proton to solvent water would be extremely fast, occurring before the O–S bond was fully formed. For an alkyl ester, microscopic reversibility would require that the very similar leaving groups, MeO^- and HO^-, depart by the same mechanism. For the intermediate acting as limiting case in a concerted reaction, this would require a complex with two H^+ ions, in fact an acid catalyzed path. There is no problem with a fully stepwise reaction, since H^+ could diffuse from one position to another to allow MeO^- to depart as MeOH. For an aryl ester, with a much better leaving group, the mechanism of loss of ArO^- is not required to be the same as that for loss of HO^-.

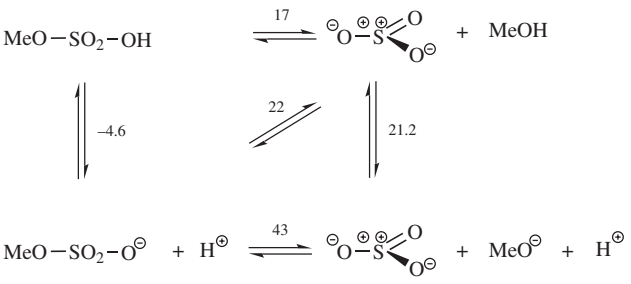


For species **15**, we estimate as follows:



(Numbers used in this cycle: ΔG° for hydroxide plus monomethyl sulfate, assumed to be the same as for dimethyl sulfate estimated above; ΔG° for ionization of monomethyl sulfate;[138] ΔG° for tautomerization of the anionic adduct, based on pK_a values estimated by the method of Branch and Calvin; ΔG° for ionization of the apically protonated adduct, based on a pK_a estimated by the method of Branch and Calvin.)

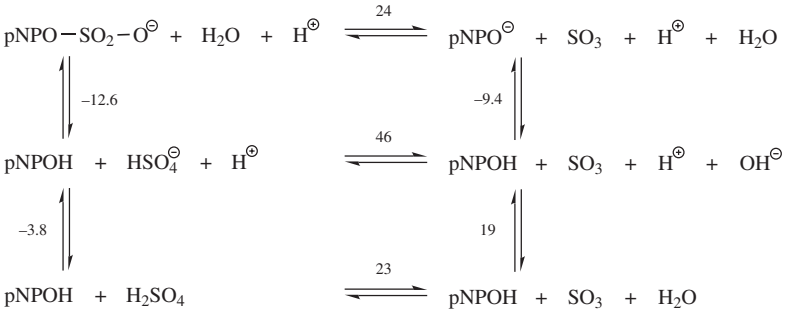
For species **16**, we estimate the dissociative process as follows.



(Numbers used in this cycle: ΔG° for dissociation of monomethyl sulfate to give sulfur trioxide, estimated above; ΔG° for ionization of monomethyl sulfate;[138] ΔG° for ionization of methanol, calculated from the pK_a of methanol, 15.54.[139])

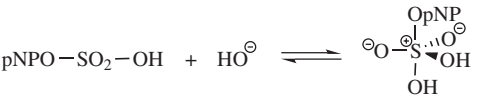
The energies for the stepwise intermediates for the two paths are within 11 kcal, suggesting a concerted mechanism is possible for S–O cleavage, but that the reaction would be very slow. In fact, of course, C–O cleavage predominates for alkyl esters.

Next, we do the estimations for *p*-nitrophenyl sulfate.

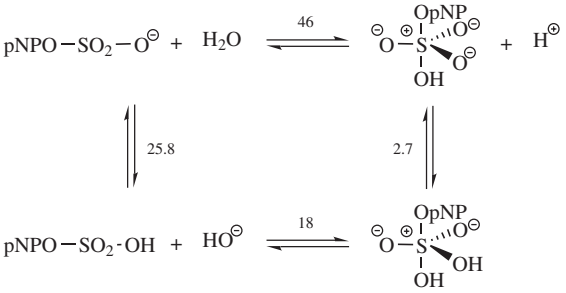


(Numbers used in this cycle: ΔG° for dissociation of H_2SO_4 to give SO_3;[138] ΔG° for acid dissociation of H_2SO_4;[125] ΔG° for hydrolysis of *p*-nitrophenyl sulfate monoanion;[138] ΔG° for ionization of *p*-nitrophenol.[139])

Then from the free energy change for addition of hydroxide to monomethyl sulfate and the correction from methyl to *p*-nitrophenyl used above we get $\Delta G^\circ = 18$ kcal/mol for



Allowing for proton transfer equilibria leads to:

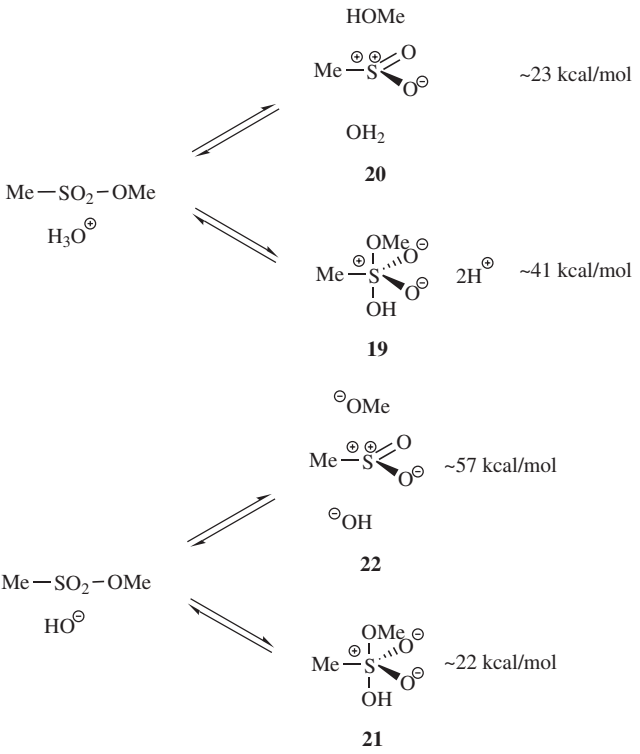


(Numbers used in the cycle: ΔG° for addition of hydroxide to *p*-nitrophenyl sulfate, see above; ΔG° for proton transfer from *p*-nitrophenyl sulfate to hydroxide, based on pK_a values;[125] ΔG° for ionization of the monoanionic adduct of *p*-nitrophenyl sulfate, estimated by the method of Branch and Calvin, supplemented by the difference in pK_a between sulfuric acid and *p*-nitrophenyl sulfate.)

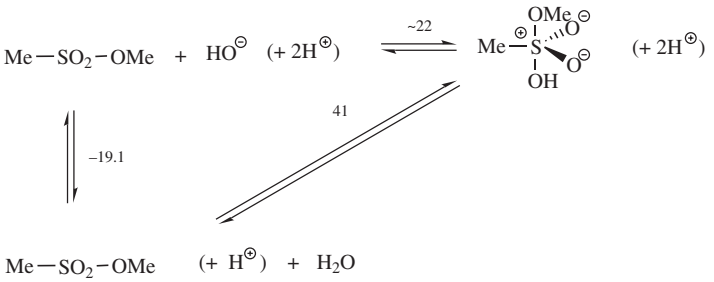
It is clear that the water reaction of *p*-nitrophenyl sulfate monoanion should occur by a dissociative mechanism, because **17** is too high in energy. (This was

in fact assumed in the derivation of the numbers for SO_3 formation from aryl sulfates,[138] but the independently calculated value for the associative intermediate shows that the reaction is clearly expected to be dissociative via **18** or very close to it.)

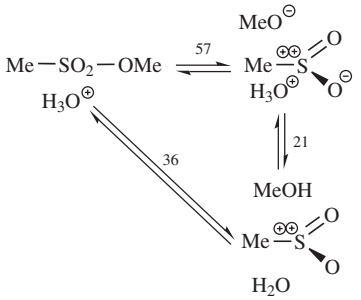
Now we turn to the reactions of esters of sulfonic acids. Here we have less basis for estimation because the structural changes are more serious. It seems likely that **20** (or **22**) is, if anything, less stable than **12**, because **12** has at least the possibility of p-electron release from the RO group, which **20** does not, and the ferociously electron deficient S^{++} will need all the stabilization it can get. On the contrary, carbon is less electronegative than oxygen. For lack of anything better, we will assume similar energetics for dissociation. Moreover, a trigonal bipyramidal intermediate with a C in place of a neutral O should be favored, so that **19** or **21** should be easier to form than **1** or **3**. Benzenesulfonylium ion is not likely to be stabilized significantly by π-overlap because the charges on the sulfur cannot be delocalized onto the benzene ring, in contrast to the benzoylium ion. Benzenesulfonylium ion may then be less stable than methanesulfonylium ion because of the greater electronegativity of sp^2 than sp^3 carbons.



For acid-catalyzed hydrolysis of a sulfonate we use the following cycles.

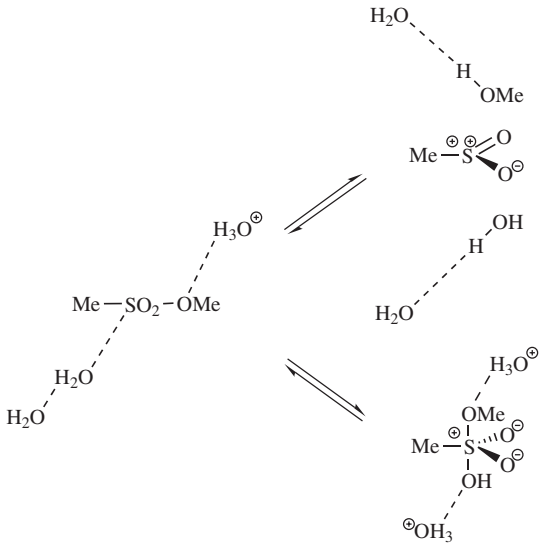


(Numbers used in the cycle: $\Delta G°$ for addition of hydroxide, assumed to be the same as for dimethyl sulfate; $\Delta G°$ for ionization of the neutral adduct, based on a pK_a estimated by the method of Branch and Calvin; $\Delta G°$ for ionization of the cationic adduct, based on a pK_a estimated by the method of Branch and Calvin.)



(Numbers used in this cycle: $\Delta G°$ for dissociation of methyl methanesulfonate to methanesulfonylium ion and methoxide, assumed to be the same as for dimethyl sulfate, estimated above; $\Delta G°$ for ionization of methanol.[130])

In this case, the dissociative path via **20** looks slightly favored though a concerted path looks possible. For this reaction the likely mechanism would be as follows:



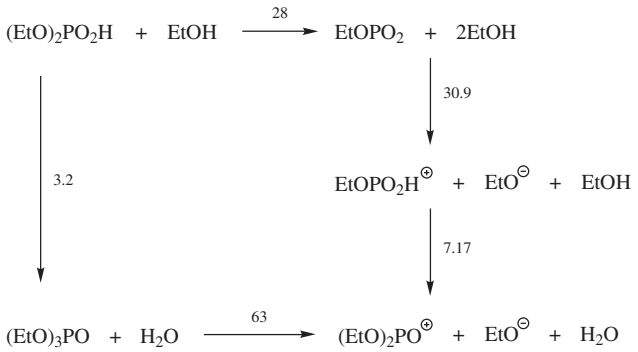
For the alkaline hydrolysis of a simple sulfonate ester, the associative mechanism via **21** looks better. The assumption that ΔG° for the additions of hydroxide to a sulfate or an analogous sulfonate ester are similar is supported by similar rate constants for analogous phosphate, phosphonate, and phosphinate esters. The rate constants for alkaline hydrolyses of $(MeO)_3PO$ ($k = 1.6 \times 10^{-4}$),[100] $MePO_3Me_2$ ($k = 2.5 \times 10^{-3}$),[140] and Et_2PO_2Et ($k = 1.2 \times 10^{-4}$)[141] are all similar, suggesting that the free energies of addition are also similar. This certainly suggests that the free energies of addition to dimethyl sulfate and methyl methanesulfonate will also be similar.

1.4.3. Possible Concerted Reactions of Phosphate Esters

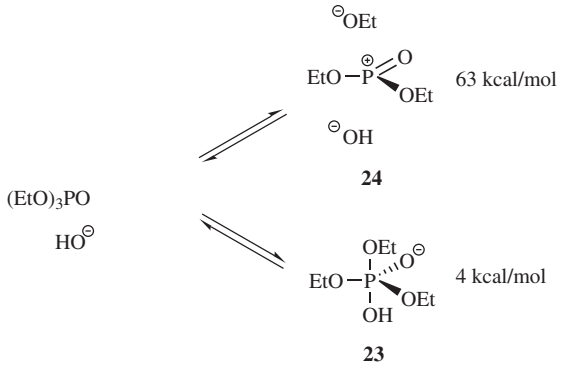
The free energy of dissociation for triethyl phosphate to give the diethoxymetaphosphylium ion can be calculated as follows. The pK_a of HPO_3 is taken as -1.4, the value for HNO_3. The pK_a for $(HO)_2PO^+$ is then estimated as -6.4, using the increment of 5 pK_a units per step from Pauling's rules.[142] Then the pK_a for $(EtO)PO_2H^+$ is assumed to be -7.1 (increment of 0.66 per ethoxy[100]). This allows a calculation of the ΔG for replacement of OH in $(EtO)PO_2H^+$ by OEt, using eq. (4) in reference 100, as:

$$(HO)(EtO)PO^+ + EtOH \rightleftharpoons (EtO)_2PO^+ + H_2O \qquad \Delta G = 7.17$$

The free energy of esterification for diethyl phosphate will be taken as +3.2 kcal/mol (average value per step of hydrolysis[100]); the free energy of dissociation of diethyl phosphate to ethyl metaphosphate and ethanol is +28 kcal/mol (Table 1.7); the free energy change for proton transfer from ethanol to ethyl metaphosphate is +30.9 kcal/mol (based on the pK_a value above and 15.5 for ethanol). This leads to the cycle and $\log K = -46$ for the dissociation of $(EtO)_3PO$ to $(EtO)_2PO^+$; this is the origin of the value in Table 1.7.

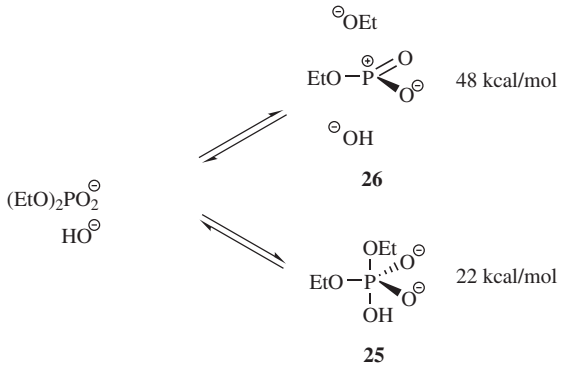


We can now calculate the energies of the two stepwise intermediates relative to the starting materials for mono-, di-, and triesters of phosphoric acid. Starting with the triester we get:



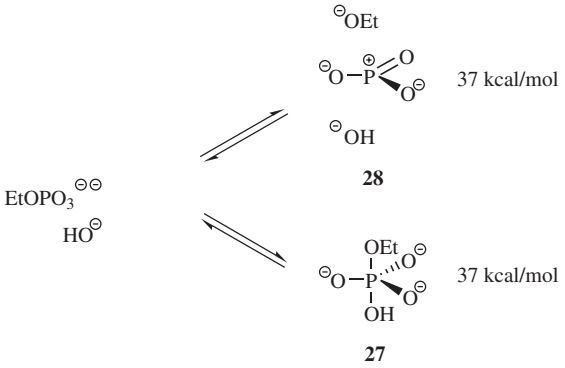
Here the thermodynamics strongly favor stepwise reaction by way of pentacoordinate intermediate **23**.

Turning now to the diester monoanion we get:



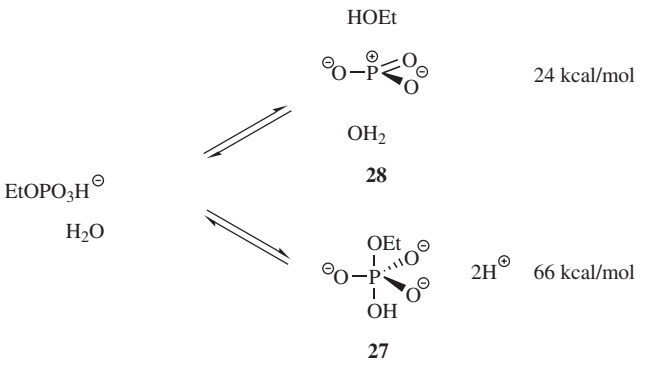
Here the thermodynamics still favor stepwise reaction by way of pentacoordinate intermediate, **25**, but the preference is weaker than in the triester case above. A concerted path might be barely possible here but would be expected to be close in structure and transition state energy to the pentacoordinate intermediate.

Finally we consider the monoester dianion:

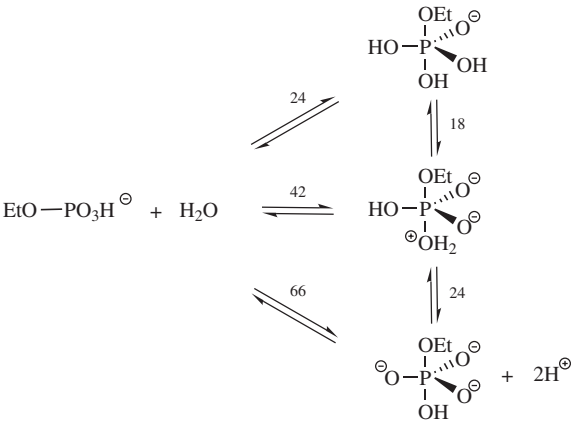


Here the thermodynamics seem set up for a concerted process, since both intermediates are bad. The reaction is, however, likely to be very slow for an alkyl ester.

For comparison one could look at the well known case of the monoester monoanion, which is known to have a transition state close to the metaphosphate anion.

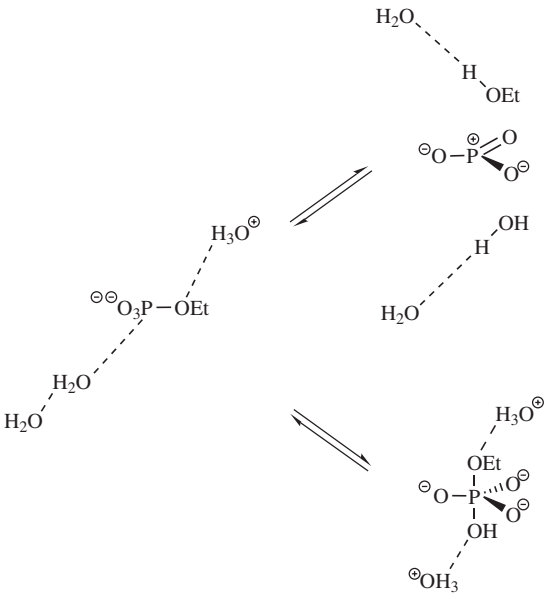


The associative energy is calculated from the cycle given below.



(Numbers used in this cycle: ΔG° for addition of water to give a monoanionic adduct, Table 1.7; ΔG° for proton transfer reactions, based on pK_a values estimated by the method of Branch and Calvin.) The dissociative energy is taken from Table 1.7.

There is an extra complication for the associative limit of this reaction. Addition of water to the monoanion would give a species with very acidic hydrogens, so that dissociation must be expected to be concerted. By microscopic reversibility, the very similar leaving group ethanol must depart by an analogous path. Thus the mechanism becomes:



The zwitterionic form of monoethyl phosphate is unlikely to have a significant lifetime because loss of a proton from cationic oxygen would be very fast.

Set against this argument based on energetics is the work of Williams, who has presented evidence for concerted reactions involving aryl diphenyl phosphates.[145] The key assumption here is that a linear Brønsted type plot requires a single transition state with no change in rate-determining step. This might be consistent with a stepwise reaction where breakdown in either direction is fast because the leaving groups are good. Hengge has reviewed the literature[143] and concluded that phosphate monoesters undergo hydrolysis by loose transition states close to the dissociative limit; that diesters and triesters with good leaving groups react by concerted mechanisms; and that triesters react by stepwise associative mechanisms. This analysis did not include consideration of the energetics of the dissociative species (alkyl metaphosphate ester or dialkyl metaphosphate cation). The analysis presented here suggests that concerted mechanisms will be strongly disfavored. More weight needs to be given to these simple energetic considerations.

1.5. CONCLUSION AND OUTLOOK

Tetrahedral intermediates vary enormously in stability relative to the corresponding carbonyl compounds, from extremes like hexafluoroacetone hydrate where it is difficult to remove the nucleophile from the adduct, to amide hydrates where the obligatory intermediate in acyl transfer is present at undetectably low concentrations. Linear free-energy relations provide a route to calculating the equilibrium constant

for tetrahedral intermediate formation from carbonyl compounds, although there is still a shortage of experimental information on which to base these methods. There are several indirect ways to calculate these equilibrium constants if experiment is not feasible. Direct computational methods are coming along, but there remains a problem in calculating solvation energies. In the not very distant future, computational methods will become an important source of equilibrium information.

Calculating rate constants for the formation and breakdown of tetrahedral intermediates is possible provided the corresponding equilibrium constant is known. The mechanism must be known or postulated; these mechanisms often involve proton transfer steps.

Much less is known about the thermodynamics of the pentacoordinate intermediates in phosphoryl and sulfonyl chemistry, although such species clearly exist and are intermediates in at least some of the reactions of these classes of compounds.

Concerted mechanisms are possible for acyl, phosphoryl, and sulfonyl transfer. By thinking about the stepwise limits for each possible concerted process, one can, even with quite crude calculations, make some judgment about the feasibility of the concerted process. This area of chemistry is as yet unsettled and will see some changes in what is now generally accepted.

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Appendix. The method of Branch and Calvin.[124]

This method estimates pK_a values for oxygen acids from that of the reference molecule water (corrected for the number of acidic hydrogens) using terms

for electrostatic effects (based on formal charges) and inductive effects. Their equation is:

$$\log K_a = -16 + \sum I_{atom}\alpha_i + \sum I_{charge}\alpha_i + \log\left(\frac{n}{m}\right)$$

where −16 is the acid dissociation constant for water per hydrogen, I_{atom} is an inductive effect parameter for a particular atom, α_i is the fall-off factor, I_{charge} is the electrostatic parameter for unit charge, n is the number of equivalent acidic hydrogens in the acid, and m is the number of equivalent basic sites in the conjugate base. The parameters given by Branch and Calvin are:

Inductive constants for elements and formal charge	
$\alpha_i = 1/2.8$	$I_S = +3.4$
$I_{charge} = \pm 12.3$	$I_{Se} = +2.7$
$I_{Cl} = +8.5$	$I_{Te} = +2.4$
$I_{Br} = +7.5$	$I_N = +1.3$
$I_I = +6$	$I_P = +1.1$
$I_O = +4$	$I_{As} = +1.0$
	$I_C = -0.4$

By analogy with the proposal of Branch and Calvin, we can calculate the pK_a of an oxonium ion X–OH_2^+ by the related equation

$$\log K_a = 1.3 + \sum I_{atom}\alpha_i + \sum I_{charge}\alpha_i + \log\left(\frac{n}{m}\right)$$

where 1.3 is the log K_a value for hydronium ion, per acidic hydrogen.

For an *O*-methylated oxonium ion, X–O(Me)H^+, we use a related equation based on the pK_{BH+} for dimethyl ether.[144] Per acidic hydrogen

$$\log K_a = 2.5 + \sum I_{atom}\alpha_i + \sum I_{charge}\alpha_i + \log\left(\frac{n}{m}\right)$$

Thus, for example, the K_a for $HOSO_2^+$ is calculated as

$$\log K_a = -16 + 13.2*2 - 13.2/2.8 + 2*4/2.8 + 3.4 + \log(1/3) = 11.5.$$

and K_a for $MeOSO_3(^{3-})OH_2^+$ is calculated as

$$\log K_a = +1.3 + 13.2 - 13.2*3/2.8 + 4*4/2.8 + 3.4 + \log(2/1) = 9.8.$$

Every time a hydroxyl substitutent is replaced by an alkoxyl, a correction of 0.66 is added;[100] this is based on the pK_a increments observed for H_3PO_4 and its mono and dialkyl esters.

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