What Does the Acid Ionization Constant Tell You? An Organic Chemistry Student Guide

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Supporting Information

ABSTRACT: Many students find the transition from first-year general chemistry to second-year organic chemistry a daunting task. There are many reasons for this, not the least of which is their lack of a solid understanding and appreciation of the importance of some basic concepts and principles from general chemistry that play an extremely critical role in organic chemistry. One such concept is the log of the acid dissociation constant, \( pK_a \). This article reviews eleven key organic chemical concepts that can be predicted from knowledge of \( pK_a \), highlighting its exceptional value as a physical quantity.

KEYWORDS: First-Year Undergraduate/General, Second-Year Undergraduate, Organic Chemistry, Acids/Bases, Lewis Acids/Bases, Reactions, Physical Properties

Arguably one of the most important physical constants for a Brønsted acid is its \( pK_a \). A thermodynamic property defined as \( -\log K_a \), where \( K_a \) is the acid ionization constant (acidity constant) for any acid species in water as represented by the equilibrium shown, it is a value that reveals a wealth of chemical information about a substance.

\[
\text{HA(aq)} + \text{H}_2\text{O}(l) \rightleftharpoons \text{H}_3\text{O}^+(aq) + \text{A}^-(aq) \tag{1}
\]

\[
K_a = \frac{\text{[H}_3\text{O}^+][\text{A}^-]}{\text{[HA]}} \tag{2}
\]

\[
pK_a = -\log K_a \tag{3}
\]

Many different organic compounds, containing functional groups other than just the carboxylic acid group, can be classified as acids and therefore have an associated \( pK_a \) value.3

Over the years, articles have appeared in this Journal and others revealing the use of acidity constants and \( pK_a \) as a tool to predict the properties of molecules and the outcome of chemical events. Hassanali used \( pK_a \) as a tool for students to predict the direction of an acid–base equilibrium.2 Ault illustrated the use of \( pK_a \) in the estimation of a solution pH.4 Newton, Grant et al. demonstrated the use of \( pK_a \) to predict conductivity of an organic solute in aqueous solution.5 Dicks discussed the use of hydrocarbon acidities as a teaching tool for such structure and bonding principles as hybridization, resonance, induction, and aromaticity in organic compounds.5 Further testimony to the significance of \( pK_a \) can be found in the numerous publications emphasizing methods that can be used to predict its value.

In a recent survey of organic chemistry instructors to discern which methods that can be used to predict its value.6

in organic chemistry, Duis found that acid–base theory consistently placed at or near the top.7 Nothing is more fundamental to an understanding of acid–base theory than the concept of \( pK_a \). The purpose of this article is to review and highlight those aspects of \( pK_a \) that can be applied to a better understanding and prediction of organic reactions. Most of these concepts can be found in introductory organic chemistry texts but are sometimes lost and diluted in the discussion of the specific organic chemistry. The summary described here is a useful tabulation of eleven predictions of organic chemical events made possible by knowledge of \( pK_a \).

It is recognized that \( pK_a \) values are highly dependent on the solvent (or lack of one) used during measurement, the most common being in the gas phase, dimethyl sulfoxide (DMSO), or water.8 For purposes of this article, the \( pK_a \) values discussed and applied to the prediction of a chemical outcome are limited to just those generally obtained in aqueous media, much like values typically found in introductory textbooks.9,10 Chemistry in aqueous media is a major thrust for health science-related interdisciplinary programs (biology, premedical, pharmacy, etc.), therefore, limiting \( pK_a \) discussions to water is appropriate for this level student.11

WHAT DOES \( pK_a \) TELL YOU?

At the beginning of the first semester of organic chemistry, students are presented with a summary table entitled “What Does \( pK_a \) Tell You?” (see the table in the Supporting Information). The table consists of two columns labeled “What” and “How”. Described
here is an itemized list of the organic chemical predictions (the “what”) that can be gleaned from knowledge of a substances’ pK\(_a\), and how this information is derived (the “how”), with examples. Each numbered item that follows constitutes one row of the summary table given to the student. The examples show how each item can be elaborated and highlighted in a classroom discussion.

**Item 1: Comparing Acid Strengths**

What: In comparing two acids, the pK\(_a\) predicts which is the thermodynamically stronger acid.

How: The lower the pK\(_a\), the stronger the acid.

Undoubtedly, the most common use of the value of pK\(_a\) is comparison of two or more substances for relative acid strength. This is what is typically taught in general chemistry for comparing two or more distinctly different acid species. However, that comparison also applies to polyprotic organic molecules allowing students to predict which proton will be lost in reaction with a base. The polyprotic aminoalcohol 1 possesses two main sites for possible reaction with a base: the alcohol hydrogen or the amino hydrogen. The pK\(_a\) of the hydrogen that is lower will be the preferred reaction site, specifically the hydrogen on oxygen. Likewise, with alkenyne 2, of the three potential C–H sites for base attack, the preferred reaction site is that of the terminal alkyne, possessing hydrogen attached to carbon that is sp hybridized thereby having a lower pK\(_a\) by some 19 orders of magnitude compared to a vinyl hydrogen.

Another important example is the use of pK\(_a\) to predict the direction in which a crossed-Claisen condensation will occur between an aldehyde or ketone and an ester. When both types of carbonyl compounds contain an α-hydrogen, the enolate anion produced will be primarily from the more acidic, lower pK\(_a\) site.

\[
\text{pK}_a = 24 \\
\text{pK}_a = 20
\]

As illustrated, this also holds for a crossed-Dieckmann condensation.

\[
\text{pK}_a = 24 \\
\text{pK}_a = 20
\]

**Item 2: Comparing Base Strengths**

What: In comparing two bases, the pK\(_a\) predicts which is stronger.

How: The base whose conjugate acid is the weaker acid (has the higher pK\(_a\)) is the stronger base.

This concept is derived from the reciprocal strength relationship that exists for a conjugate acid–base pair according to Bronsted–Lowry theory; that is, the stronger the conjugate acid, the weaker the conjugate base and vice versa. When presented in organic chemistry, it is best illustrated with amines, the most common organic bases, by making the conjugate acid and comparing their relative strengths.

\[
\begin{align*}
\text{NH}_2\text{H}^+ & \rightleftharpoons \text{NH}_3^+ \quad \text{pK}_a = 5 \\
\text{NH}_2\text{H}^+ & \rightleftharpoons \text{NH}_3^+ \quad \text{pK}_a = 10
\end{align*}
\]

In a comparison of base strength for amines 3 versus 5, the conjugate acids are considered and their pK\(_a\)'s are compared. Because the anilinium ion 4 is a stronger acid than the aminium ion 6, the conjugate base 3 must be the weaker of the two bases. This process can be broadly applied to the comparison of any two base species.

**Item 3: Gibbs Energy Change of Ionization**

What: The sign and magnitude of the pK\(_a\) for an acid ionization in water is directly related to the sign and magnitude of the Gibbs energy change (\(\Delta G^\circ\)) for that ionization.

How: Large positive values of pK\(_a\) indicate a large positive \(\Delta G^\circ\). Small positive values of pK\(_a\) indicate a small positive \(\Delta G^\circ\). Large negative values of pK\(_a\) indicate a large negative \(\Delta G^\circ\). Small negative values of pK\(_a\) indicate a small negative \(\Delta G^\circ\).

With this particular point, it is important to follow up with a class discussion as to why this is the case, which includes the use of reaction Gibbs energy diagram representations. Using Gibbs energy diagrams to illustrate and interpret an organic reaction process is fundamental and helps in a student’s transition from general to organic chemistry. Efforts should be made to use these throughout general chemistry whenever the situation arises.

Starting with the relationship

\[
\Delta G^\circ = -2.3RT \log K_{eq}
\]

where R = 8.314 J/(mol K) and T is the absolute temperature, for an acid ionization \(K_{eq} = K_{a}\) and because pK\(_a\) = −log \(K_{eq}\), this equation can be restated as

\[
\Delta G^\circ = 2.3RT(pK_a)
\]

As a result, the sign and magnitude of the pK\(_a\) for an acid ionization in water is directly related to the sign and magnitude of \(\Delta G^\circ\) for that ionization. Hence, a large positive pK\(_a\) results in a large positive \(\Delta G^\circ\) and a small positive pK\(_a\) results in a small positive \(\Delta G^\circ\) for their respective ionizations.

As a specific example, the common textbook comparison of ethanol (pK\(_a\) = 15.5) and acetic acid (pK\(_a\) = 4.76) ionizations in water is used. Applying eq 9, \(\Delta G^\circ\) values for these ionizations at 25°C are +88 kJ mol\(^{-1}\) (21 kcal mol\(^{-1}\)) and +27 kJ mol\(^{-1}\) (6.5 kcal mol\(^{-1}\)), respectively.

\[
\begin{align*}
\text{OH}^- + \text{H}_2\text{O} & \rightleftharpoons \text{OH}^- + \text{H}_2\text{O}^+ \quad \Delta G^\circ = +88 \text{ kJ mol}^{-1} \\
\text{OH}^- + \text{H}_2\text{O} & \rightleftharpoons \text{OH}^- + \text{H}_2\text{O}^+ \quad \Delta G^\circ = +27 \text{ kJ mol}^{-1}
\end{align*}
\]
These equilibria can be represented using the Gibbs energy diagrams (Figure 1), highlighting the Gibbs energy change in each case being directly proportional to the p\(K_a\). The stronger acid (acetic acid), with a smaller, less positive p\(K_a\), will also have the smaller, less positive \(\Delta G^\circ\). It is important to note the y axes (Gibbs energy) for alcohols and carboxylic acids are not to be considered the same.

The overall endergonic energy diagram profiles shown in Figure 1 are, in general, representative of weak acid ionizations in water,\(^{19}\) that is, acids with a p\(K_a\) greater than the hydronium ion (\(-1.74\)) that ionize to less than 100%.

**Item 4: Direction of an Equilibrium**

What: In an acid–base equilibrium, the p\(K_a\) predicts the favored direction for that equilibrium.\(^{20}\)

How: A reaction will always proceed in the direction going from the side of the stronger acid (lower p\(K_a\)) to the side with the weaker acid (higher p\(K_a\)).

This prediction is a direct consequence of the Gibbs energy changes that occur during an acid–base reaction. Recognizing an acid and base species can be identified on both sides of the equilibrium arrows for any acid–base reaction (Brensted–Lowry acid–base theory), going from stronger acid (higher in energy) to weaker acid (lower in energy) will be the favorable direction.

This concept is illustrated using the examples of benzoic acid and phenol. Reaction of benzoic acid with sodium hydroxide proceeds spontaneously to the right, whereas reaction of phenol with sodium bicarbonate favors the reactants over products at equilibrium.

\[
\text{benzoic acid} \quad \text{p}K_a = 4.20
\]

\[
\text{phenol} \quad \text{p}K_a = 9.94
\]

A further corollary of this concept is that p\(K_a\) can be used to predict the strength of the base required to effectively favor conjugate base formation for a given acid. A favorable equilibrium will only arise when the base employed possesses a conjugate acid whose p\(K_a\) is higher than that of the original acid.

**Item 5: Calculate an Equilibrium Constant**

What: In an acid–base reaction, the p\(K_a\) of the acid species on both sides of the equation can be used to calculate the \(K_{eq}\) (equilibrium constant) for that reaction.\(^{21a,b}\)

How: The \(K_{eq}\) for an acid–base reaction can be calculated from the following relationship:

\[
K_{eq} = 10^{\frac{p(K_a \text{product acid}) - p(K_a \text{reactant acid})}{10}}
\] (14)

This lesser known, yet broadly applicable relationship for the prediction of \(K_{eq}\) for a given acid–base reaction is the consequence of p\(K_a\) always being derived from the ionization of an acid in water under standard conditions (dilute aqueous solution at 25 °C). Figure 2 illustrates its derivation for the general acid–base equilibrium shown. As can be seen, acid–base reactions that result in large increases in the p\(K_a\) of the acid species will have a very large equilibrium constant, proceeding readily in the forward direction. This calculation for the specific reaction of benzoic acid with sodium hydroxide is illustrated in Figure 3.

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**Figure 1.** Gibbs energy diagrams for the ionization of (A) acetic acid and (B) ethanol in water.

**Figure 2.** Derivation of the formula for calculation of an equilibrium constant for any acid–base equilibrium.
Item 6: Stronger Acid and Stronger Base

What: In an acid–base reaction, the pKₐ predicts the side with the stronger acid and base, and the side with the weaker acid and base.  

How: The side with the stronger acid (lower pKₐ) will be the same side containing the stronger base. The side with the weaker acid (higher pKₐ) will be the side with the weaker base.

Once again, this concept is a consequence of the reciprocal strength relationship that exists between a conjugate acid pair, and the fact that the sum of the pKₐ values for each conjugate pair must be equal to a constant (typically stated to be 14). Assume HA is a stronger acid than HB⁺, with a pKₐ of 3. The conjugate base of the HA, A⁻, must therefore have a pKₐ of 11 in order for the sum of the pKₐ and pKₐ to equal 14. The weaker acid produced, HB⁺, from the reaction, must have some pKₐ > 3, and hence must have a conjugate base species, B⁻, with a pKₐ < 11 (again sum to equal 14), making it a stronger base than the conjugate base, A⁻, from the original stronger acid.

\[
\begin{align*}
\text{HA} + \text{B} & \rightleftharpoons \text{HB}^+ + \text{A}^- \\
pK_a = 3 & \quad pK_a < 11 & \quad pK_a > 3 & \quad pK_a = 11
\end{align*}
\]

stronger acid \quad \text{stronger base} & \quad \text{weaker acid} \quad \text{weaker base}

(15)

Item 7: Magnitude of Gibbs Energy Change

What: Predict the magnitude and extent of ΔG° in a simple bimolecular nucleophilic substitution (S_N2) reaction.

How: When the pKₐ of the conjugate acid of the nucleophile is much greater than the pKₐ of the conjugate acid of the leaving group, the reaction will be highly exergonic with a large negative ΔG°. When the pKₐ of the conjugate acid of the nucleophile is only slightly greater than the pKₐ of the conjugate acid of the leaving group, the reaction will be only slightly exergonic with a small negative ΔG°.

This prediction can be further explained using the following illustrations. Consider the generalized S_N2 reaction shown:

\[
\begin{align*}
\text{Nu}^- + \text{R}^+ + \text{L}^- & \rightarrow \text{Nu}^- \text{C}^- + \text{L}^-
\end{align*}
\]

Assuming no other stabilizing or destabilizing effects occur as the result of the displacement (extended conjugation in the product, etc.), the Gibbs energy change outcome can be predicted by comparing the pKₐ’s of the conjugate acids of the nucleophile (Nu⁻) and the leaving group (L⁻). If the pKₐ of the conjugate acid of the nucleophile is much greater than the pKₐ of the leaving group, thereby making the pKₐ of the nucleophile much less than the pKₐ of the leaving group, that is, the nucleophile is a much stronger base than the leaving group, then the reaction will be predicted to proceed nearly to completion (based on ΔG° = −RT ln K_eq, which would be a large negative value, reactions proceed from strong base to weak base).

An example would be the reaction of chloroethane with hydroxide ion at 60 °C, reportedly having a ΔG° of −100 kJ mol⁻¹ (24 kcal mol⁻¹). This large exergonic value is reflected in, and can be predicted from, the large differences in the pKₐ for water (15.7) and HCl (−7).

\[
\begin{align*}
\text{CH}_3\text{Cl} + \text{OH}^- & \rightleftharpoons \text{CH}_3\text{OH} + \text{Cl}^-
\end{align*}
\]

\[
\Delta G° = -100 \text{ kJ mol}^{-1}
\]

(17)

On the other hand, if the pKₐ of the nucleophile conjugate acid is only slightly greater than that of the leaving group, the reaction will have a small exergonic ΔG° and, in fact, be predicted to be reversible. An example of this would be the reaction of bromoethane with iodide ion where there is a small difference in the pKₐ’s of HBr (−9) and HI (−10).

Item 8: Leaving Group Ability

What: In the choice of a leaving group in a nucleophilic substitution (S_N) reaction, it predicts which would be the better leaving group.

How: The leaving group whose conjugate acid has the lower pKₐ (stronger conjugate acid) will be the better leaving group (weaker conjugate base).

Up to this point, the predictions discussed based on pKₐ have all been thermodynamic properties; therefore, it is no great surprise that pKₐ itself a thermodynamic quantity, can be used to some extent to predict the outcome. When we talk about leaving group ability, we are actually referring to how fast a reaction proceeds under a controlled set of conditions, with the more reactive substrate possessing the better leaving group. Therefore, what is different about item 8 is that it is a kinetic outcome (rate of reaction) based on a thermodynamic value. The kinetics of any reaction is governed by the Gibbs energy of activation (activation energy), which is unrelated to the overall Gibbs energy change a reaction undergoes, for example, endergonic or exergonic. Hence, it needs to be pointed out that any predictions of a kinetic property, such as leaving group ability, based on pKₐ will never be absolute and exceptions will abound.

Whether nucleophilic substitution reactions proceed through a unimolecular (S_N1) or bimolecular (S_N2) pathway, it is generally accepted that the relative ease by which a leaving group departs is based on its stability, which in turn can be predicted from the pKₐ of the conjugate acid of that leaving group. Table 1 shows the relative rates for the solvolysis (S_N1) of several 1-phenylethyl esters and halides and relates those to the corresponding pKₐ of the conjugate acid of leaving group. Note that within each category of leaving group (sulfonate or carbonate ester and halide), there is a good linear correlation of reaction rate to pKₐ (see Figure 4).

The correlation is less clear when considering substrates from different categories of leaving group (ester vs halide), obviously due to factors, for example, bond strength or polarizability of the C–L bond, not considered in the value of pKₐ. This makes an overall order prediction based solely on pKₐ difficult.

In the case of an $S_N$2 pathway, this same trend is observed, although the nature of the nucleophile and the solvent significantly affect that dependence making an absolute order impossible. Table 2 relates the average relative rate for the $S_N$2 reaction on a methyl substrate (see eq 16 where R and R’ are hydrogen) containing the leaving group shown and the pK_a of their conjugate acid. As can be seen in Figure 5 with the exclusion of the points for the sulfonate ester and water leaving groups, a reasonable linear correlation indeed exists.

**Table 1. Relative Rate Dependence of Solvolysis of 1-Phenylethyl Substrate on Leaving Group Conjugate Acid pK_a**

<table>
<thead>
<tr>
<th>Leaving Group (L^-)</th>
<th>$k_{rel}$</th>
<th>pK_a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonate Ester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF_3SO_3^-</td>
<td>1.4 x 10^8</td>
<td>-5.9^b</td>
</tr>
<tr>
<td>p-NO_2-C_6H_4SO_3^-</td>
<td>4.4 x 10^5</td>
<td>-4.0^b</td>
</tr>
<tr>
<td>p-CH_3-C_6H_4SO_3^-</td>
<td>3.7 x 10^4</td>
<td>-2.8^a</td>
</tr>
<tr>
<td>CH_3SO_3^-</td>
<td>3.0 x 10^5</td>
<td>-1.9^a</td>
</tr>
<tr>
<td>Carboxylate Ester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF_3CO_2^-</td>
<td>2.1</td>
<td>0.23</td>
</tr>
<tr>
<td>p-NO_2-C_6H_4CO_2^-</td>
<td>5.5 x 10^-6</td>
<td>3.4</td>
</tr>
<tr>
<td>CH_3CO_2^-</td>
<td>1.4 x 10^-6</td>
<td>4.76</td>
</tr>
<tr>
<td>Halides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I^-</td>
<td>91</td>
<td>-10^de</td>
</tr>
<tr>
<td>Br^-</td>
<td>14</td>
<td>-9^de</td>
</tr>
<tr>
<td>Cl^-</td>
<td>1.0</td>
<td>-7^e</td>
</tr>
<tr>
<td>F^-</td>
<td>9 x 10^-6</td>
<td>3.2^e</td>
</tr>
</tbody>
</table>

\(^{a}S_N1\) solvolysis of 1-phenylethyl substrate in 80% aqueous ethanol.\(^{29}\)
\(^{b}Ref\) 30. \(^{c}From\) ref 30 reported for PhSO_3H. \(^{d}Ref\) 10a. \(^{e}Ref\) 31.
\(^{f}Ref\) 10b.

**Table 2. Relative Rate Dependence for the $S_N$2 Reaction on a Methyl Substrate Containing Various Leaving Groups and Their Conjugate Acid pK_a**

<table>
<thead>
<tr>
<th>Leaving Group (L^-)</th>
<th>$k_{rel}$</th>
<th>pK_a</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhSO_3^-</td>
<td>6</td>
<td>-2.8</td>
</tr>
<tr>
<td>I^-</td>
<td>3</td>
<td>-10^d</td>
</tr>
<tr>
<td>Br^-</td>
<td>1</td>
<td>-9^d</td>
</tr>
<tr>
<td>H_2O</td>
<td>1</td>
<td>-1.7</td>
</tr>
<tr>
<td>Cl^-</td>
<td>2 x 10^-2</td>
<td>-7^d</td>
</tr>
<tr>
<td>ONO_3^-</td>
<td>1 x 10^-2</td>
<td>-1.3</td>
</tr>
<tr>
<td>F^-</td>
<td>1 x 10^-4</td>
<td>3.2^d</td>
</tr>
</tbody>
</table>

\(^{a}Ref\) 33. \(^{b}Ref\) 30. \(^{c}Ref\) 10a. \(^{d}Ref\) 31.

**Figure 5.** Leaving group ability linear correlation to pK_a for an $S_N$2 reaction.

**Item 9: Relative Strength of a Nucleophile**

**What:** Predict the relative strength of a nucleophile in a nucleophilic substitution reaction.\(^{34}\)

**How:** In polar protic solvents, generally the stronger the base (conjugate acid with the higher pK_a), the stronger the nucleophile, with the exception of going down a periodic group, where the base gets weaker but the nucleophile gets stronger. In polar aprotic solvents, the stronger the base, the stronger the nucleophile, at least for the case of small, anionically charged base species (period 2 atoms). However, it should be pointed out that this does not apply to neutral or large anionic bases, where size again appears to be the dominant factor.

As both nucleophilicity and basicity involve the donation of electrons, these concepts are inherently related. As with item 8, this too is the prediction of a kinetic outcome, that is, strength of a nucleophile (nucleophilicity) based on rate data, from a thermodynamic quantity. Adding to the complexity of this prediction, solvent is found to play a key role. In fact there are at least 17 different factors that reportedly contribute to nucleophilicity.\(^{35}\) Nonetheless, in polar protic solvents, nucleophilicity is found to parallel basicity going across a row in the periodic table or when the nucleophilic atom is the same. The exception noted going down a periodic group is likely due to increased size of the nucleophilic species, becoming poorly solvated and therefore more reactive, and the increased polarizability of the these larger atoms.\(^{36}\) This effect is especially prevalent with nucleophiles such as iodide, sulfur, and phosphorus. Table 3 shows a list of common nucleophiles in decreasing order of nucleophilicity, measured by its nucleophilic constant (n), as a function of pK_a of the conjugate acid.\(^{37}\) Higher values of n, derived from the Swain–Scott
measured in DMSO and in water. Decreasing nucleophilicity and their corresponding pK\textsubscript{a} in DMSO (a representative polar aprotic solvent) in order of parallel their basicity. Table 4 gives a list of common nucleophiles and as such made very reactive, which again is found to closely described above in polar protic solvents are clearly apparent in for PhSO\textsubscript{3}H. In this nucleophilicity scale, water is the standard nucleophile and assigned 0.00.

In polar aprotic solvents, small anions are “naked” (unsolvated) and as such made very reactive, which again is found to closely parallel their basicity. Table 4 gives a list of common nucleophiles in DMSO (a representative polar aprotic solvent) in order of decreasing nucleophilicity and their corresponding pK\textsubscript{a}‘s measured in DMSO and in water.

**Item 10: Reactivity of a Carboxylic Acid Derivative**

What: Predict the relative reactivity of a carboxylic acid derivative in nucleophilic acyl substitution reactions (addition–elimination reactions). How: The lower the pK\textsubscript{a} of the conjugate acid of the leaving group on the carboxylic acid derivative, the more reactive that carboxylic acid derivative will be in nucleophilic acyl substitution reactions (addition–elimination reactions).

Despite this being yet another case of predicting a kinetic outcome based on thermodynamic quantities, the predictions here are good. In the absence of any steric effects, the generally accepted mechanism for a nucleophilic acyl substitution proceeds in two steps. The nucleophile adds to the acyl derivative in a rate-limiting first step producing a tetrahedral intermediate, which, upon loss of the leaving group, forms product.

\[
\text{Nu}^- + RCO-L \rightarrow \text{Nu}^\cdot + RCO-L^+ \quad (\text{rate-limiting step})
\]

Unlike S\textsubscript{N}1 or S\textsubscript{N}2 pathways, which involve bond breaking to the leaving group in the rate-limiting step, here the leaving group is still bonded. That being the case, one would think that the nature of the leaving group would have no impact on the rate of this reaction. However, the nature of the leaving group plays a role in the reactivity of these acyl derivatives in two important aspects: by altering the electron density around the acyl carbon (impacting the first step) and affecting the position of the overall equilibrium of the reaction (impacting both first and second steps).

Changing the electron density around the acyl carbon will alter the partial positive charge on that carbon, thereby influencing attack by the nucleophile. Leaving groups that withdraw electrons to a greater extent will produce a greater partial positive charge on the acyl carbon, increasing its electrophilicity toward reaction with a nucleophile and hence the rate of reaction. Once the tetrahedral intermediate forms, the group that is lost can either be the nucleophile that added in the first step or the leaving group. The group that is better able to sustain a negative charge will be lost preferentially (weaker base), driving the equilibrium toward product.

The reactivity of the most common carboxylic acid derivatives (acid chloride, anhydride, ester, amide) are found to nicely follow pK\textsubscript{a} of the conjugate acid of the leaving group when subjected to attack by the same nucleophile (Table 5).

**Item 11: Activating or Deactivating Group Nature**

What: Predict the relative nature of a group attached to a benzene ring as being activating (electron donating group, EDG), or deactivating (electron withdrawing group, EWG) toward electrophilic aromatic substitution reactions. How: By comparing the pK\textsubscript{a} of a benzoic acid para-substituted with that group versus unsubstituted benzoic acid (pK\textsubscript{a} = 4.17). If the pK\textsubscript{a} of the para-substituted benzoic acid is smaller, that group is an electron donating group and most likely a deactivating group. If the pK\textsubscript{a} of the para-substituted benzoic acid is larger, that group is an electron donating group and likely an activating group.

Table 3. Nucleophilicity of Common Nucleophiles as a Function of pK\textsubscript{a} of Their Conjugate Acid

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Nucleophilic Constant\textsuperscript{a}</th>
<th>pK\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH\textsuperscript{1-}</td>
<td>5.1</td>
<td>7.00\textsuperscript{b}</td>
</tr>
<tr>
<td>CN\textsuperscript{1-}</td>
<td>5.1</td>
<td>9.4\textsuperscript{b}</td>
</tr>
<tr>
<td>F\textsuperscript{1-}</td>
<td>5.04</td>
<td>-10\textsuperscript{b,c}</td>
</tr>
<tr>
<td>HO\textsuperscript{1-}</td>
<td>4.20</td>
<td>15.7\textsuperscript{b}</td>
</tr>
<tr>
<td>Br\textsuperscript{-}</td>
<td>3.89</td>
<td>-9\textsuperscript{b,c}</td>
</tr>
<tr>
<td>Cl\textsuperscript{-}</td>
<td>3.04</td>
<td>-7\textsuperscript{b}</td>
</tr>
<tr>
<td>CH\textsubscript{3}CO\textsuperscript{2-}</td>
<td>2.72</td>
<td>4.76\textsuperscript{b}</td>
</tr>
<tr>
<td>F\textsuperscript{-}</td>
<td>2.0</td>
<td>3.2\textsuperscript{d}</td>
</tr>
<tr>
<td>Pictate anion</td>
<td>1.9</td>
<td>0.38\textsuperscript{e}</td>
</tr>
<tr>
<td>p-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}SO\textsubscript{3}H</td>
<td>&lt;1</td>
<td>-2.8\textsuperscript{f}</td>
</tr>
<tr>
<td>H\textsubscript{2}O</td>
<td>0.00\textsuperscript{g}</td>
<td>-1.7\textsuperscript{f}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Ref 37. \textsuperscript{b}Ref 10a. \textsuperscript{c}Ref 31. \textsuperscript{d}Ref 30. \textsuperscript{e}From ref 30 reported for PhSO\textsubscript{3}H. \textsuperscript{f}In this nucleophilicity scale, water is the standard nucleophile and assigned 0.00.

Table 4. Common Nucleophiles with Their Conjugate Acid pK\textsubscript{a}‘s Measured in DMSO and Water

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>pK\textsubscript{a} (DMSO)</th>
<th>pK\textsubscript{a} (Water)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO\textsuperscript{1-}</td>
<td>31.4\textsuperscript{b}</td>
<td>15.7\textsuperscript{b}</td>
</tr>
<tr>
<td>CH\textsubscript{3}O\textsuperscript{2-}</td>
<td>29.0\textsuperscript{a}</td>
<td>15.5\textsuperscript{b}</td>
</tr>
<tr>
<td>CN\textsuperscript{1-}</td>
<td>12.9\textsuperscript{e,d}</td>
<td>9.4\textsuperscript{e}</td>
</tr>
<tr>
<td>F\textsuperscript{-}</td>
<td>15.0\textsuperscript{e,d}</td>
<td>3.2\textsuperscript{e}</td>
</tr>
<tr>
<td>CH\textsubscript{3}CO\textsuperscript{2-}</td>
<td>12.6\textsuperscript{e}</td>
<td>4.76\textsuperscript{e}</td>
</tr>
<tr>
<td>Cl\textsuperscript{-}</td>
<td>1.8\textsuperscript{e,d}</td>
<td>-7\textsuperscript{e}</td>
</tr>
<tr>
<td>Br\textsuperscript{-}</td>
<td>0.9\textsuperscript{e,d}</td>
<td>-9\textsuperscript{e,e}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Ref 30. \textsuperscript{b}Ref 10a. \textsuperscript{c}Ref 8a. \textsuperscript{d}Ref 8b. \textsuperscript{e}Ref 31. \textsuperscript{f}Ref 41.

Table 5. Decreasing Order of Reactivity of Carboxylic Acid Derivatives toward Nucleophilic Acyl Substitution versus the pK\textsubscript{a} of the Conjugate Acid of the Leaving Group

<table>
<thead>
<tr>
<th>Carboxylic Acid Derivative</th>
<th>Leaving Group (L\textsuperscript{-})</th>
<th>Approximate pK\textsubscript{a} (LH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCOCl</td>
<td>Cl\textsuperscript{-}</td>
<td>-7</td>
</tr>
<tr>
<td>RCOOCOR</td>
<td>RCOO\textsuperscript{-}</td>
<td>5</td>
</tr>
<tr>
<td>RCOSAr</td>
<td>Ar\textsuperscript{2-}</td>
<td>6.5\textsuperscript{a}</td>
</tr>
<tr>
<td>RCOOAr</td>
<td>ArO\textsuperscript{-}</td>
<td>10</td>
</tr>
<tr>
<td>RCOS\textsuperscript{R}</td>
<td>R\textsuperscript{2-}</td>
<td>10.5\textsuperscript{a}</td>
</tr>
<tr>
<td>RCO\textsuperscript{OR}</td>
<td>R\textsuperscript{-}</td>
<td>16</td>
</tr>
<tr>
<td>RCONH\textsubscript{2}</td>
<td>NH\textsubscript{2}</td>
<td>35\textsuperscript{b}</td>
</tr>
<tr>
<td>RCON\textsubscript{Ar}\textsubscript{2}</td>
<td>R\textsuperscript{2-}</td>
<td>36\textsuperscript{b,c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Ref 32. \textsuperscript{b}Ref 11.
this particular prediction can be best understood by looking at the stability of the conjugate base for each of these aromatic acids (Figure 6). Electron withdrawing groups will electronically (by

![Diagram of conjugate bases]

**Figure 6.** Conjugate bases from the corresponding para-substituted and unsubstituted benzoic acids.

induction or resonance) stabilize the conjugate base by depleting the aromatic ring of electrons which will delocalize the anionic charge on the carboxylate, leading to a decrease in the standard Gibbs energy change for this deprotonation, resulting in a weaker base or correspondingly stronger acid relative to benzoic acid.


<table>
<thead>
<tr>
<th>R</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>k&lt;sub&gt;rel&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deactivating Groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;N&lt;sup&gt;+&lt;/sup&gt;–</td>
<td>3.43</td>
<td>1.2 × 10&lt;sup&gt;−5&lt;/sup&gt;</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt;N&lt;sup&gt;−&lt;/sup&gt;</td>
<td>3.44</td>
<td>6 × 10&lt;sup&gt;−5&lt;/sup&gt;</td>
</tr>
<tr>
<td>HOOCC&lt;sup&gt;−&lt;/sup&gt;</td>
<td>3.51</td>
<td>3.7 × 10&lt;sup&gt;−8&lt;/sup&gt;</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;C&lt;sup&gt;−&lt;/sup&gt;</td>
<td>3.52</td>
<td>3.5 × 10&lt;sup&gt;−9&lt;/sup&gt;</td>
</tr>
<tr>
<td>NC&lt;sup&gt;−&lt;/sup&gt;</td>
<td>3.55</td>
<td>—</td>
</tr>
<tr>
<td>Cl&lt;sup&gt;−&lt;/sup&gt;</td>
<td>3.99</td>
<td>3.3 × 10&lt;sup&gt;−2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Br&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.00</td>
<td>3.0 × 10&lt;sup&gt;−2&lt;/sup&gt;</td>
</tr>
<tr>
<td>F&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.14</td>
<td>0.15</td>
</tr>
<tr>
<td>H&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.20</td>
<td>1</td>
</tr>
<tr>
<td>Activating Groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;–</td>
<td>4.34</td>
<td>25</td>
</tr>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;C&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.40</td>
<td>—</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;O&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.47</td>
<td>—</td>
</tr>
<tr>
<td>PhO&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.52</td>
<td>—</td>
</tr>
<tr>
<td>HO&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.58</td>
<td>1000</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;N&lt;sup&gt;−&lt;/sup&gt;</td>
<td>4.92</td>
<td>—</td>
</tr>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;N&lt;sup&gt;−&lt;/sup&gt;</td>
<td>5.03</td>
<td>—</td>
</tr>
</tbody>
</table>

“Ref 10a. Relative rates of nitration of substituted benzene from ref 47. Ref 47 reported for PhSO<sub>2</sub>–. Ref 47 reported for EtOOC<sup>−</sup>.

Table 6. pK<sub>a</sub> Values of Unsubstituted and Para-Substituted Benzoic Acids and Selective Relative Rates for Nitration of the Corresponding R-Substituted Benzenes

represented a compilation of organic chemical events that can be predicted by use and knowledge of pK<sub>a</sub>. Organized in this fashion, the student readily recognizes how pK<sub>a</sub> reinforces an understanding of organic chemistry. When used in conjunction with the requirement that the student memorize the approximate pK<sub>a</sub> values of the fundamental organic functional groups along with other “benchmark” molecules (e.g., hydrogen, ammonia, and water), transitioning to organic chemistry becomes easier.

### CONCLUSIONS

Presented here is a compilation of organic chemical events that can be predicted by use and knowledge of pK<sub>a</sub>. Organized in this fashion, the student readily recognizes how pK<sub>a</sub> reinforces an understanding of organic chemistry. When used in conjunction with the requirement that the student memorize the approximate
(39) The nucleophilic constant (n) is a quantitative measure of nucleophilic reactivity (nucleophilicity) using the following relationship: \( n = \log(k/k^o) \), where k is the measured overall rate constant for the reaction studying the nucleophile in question, k° is the measured rate constant when water is used as the nucleophile, and s is a substrate constant defined as 1.00 for methyl bromide as the substrate. More details can be found in refs 38 and 39 and in the following reviews: (a) Wells, P. R. Chem. Rev. 1963, 63, 171–219. (b) Carrol, F. A. Perspectives on Structure and Mechanism in Organic Chemistry, 2nd ed.; John Wiley and Sons, Inc: New York, 2010; pp 507–508.