

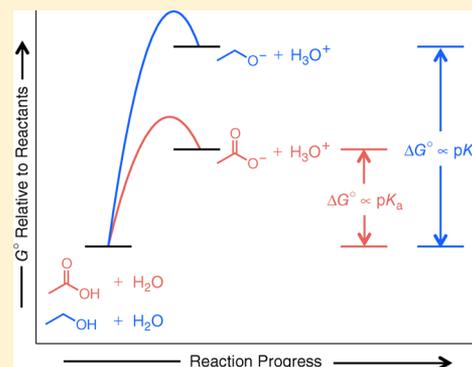
# What Does the Acid Ionization Constant Tell You? An Organic Chemistry Student Guide

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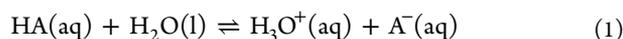
**S** Supporting Information

**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 outcomes 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.



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \quad (2)$$

$$pK_a = -\log K_a \quad (3)$$

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.<sup>1</sup>

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.<sup>2</sup> Ault illustrated the use of  $pK_a$  in the estimation of a solution pH.<sup>3</sup> Newton, Grant et al. demonstrated the use of  $pK_a$  to predict conductivity of an organic solute in aqueous solution.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup>

In a recent survey of organic chemistry instructors to discern which concepts are considered to be “important”, “core”, or “fundamental”

in organic chemistry, Duis found that acid–base theory consistently placed at or near the top.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9,10</sup> 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.<sup>11</sup>

## ■ 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

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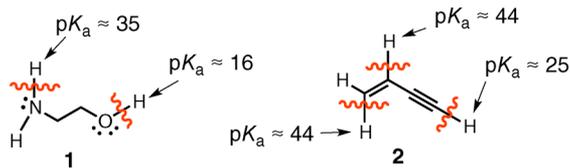
here is an itemized list of the organic chemical predictions (the “what”) that can be gleaned from knowledge of a substance’s  $pK_a$  and how this information is derived (the “how”), with examples. Each numbered item that follows constitutes one row of the summary table given to the student. The examples show how each item can be elaborated and highlighted in a classroom discussion.

### Item 1: Comparing Acid Strengths

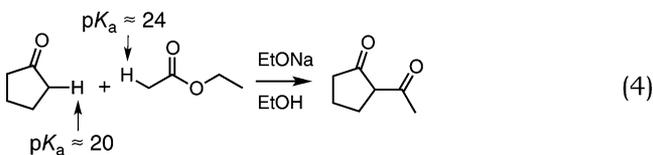
**What:** In comparing two acids, the  $pK_a$  predicts which is the thermodynamically stronger acid.<sup>12</sup>

**How:** The lower the  $pK_a$ , the stronger the acid.

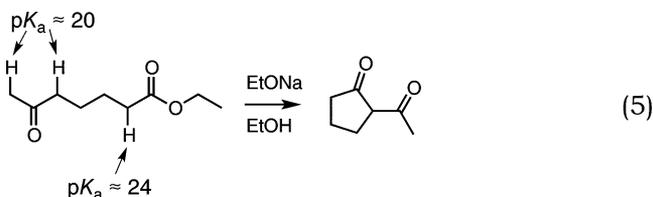
Undoubtedly, the most common use of the value of  $pK_a$  is comparison of two or more substances for relative acid strength. This is what is typically taught in general chemistry for comparing two, or more, distinctly different acid species. However, that comparison also applies to polyprotic organic 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.<sup>5</sup>



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  $\alpha$ -hydrogen, the enolate anion produced will be primarily from the more acidic, lower  $pK_a$  site.



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



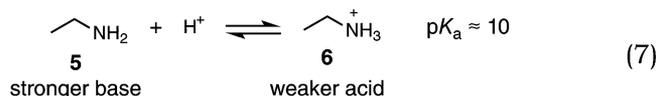
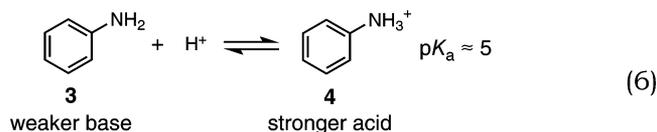
### Item 2: Comparing Base Strengths

**What:** In comparing two bases, the  $pK_a$  predicts which is stronger.<sup>13</sup>

**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

Brønsted–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.



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.<sup>14</sup>

**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.<sup>15,16</sup> 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

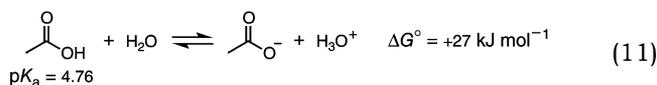
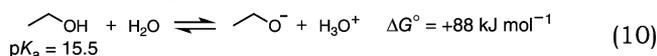
$$\Delta G^\circ = -2.3RT \log K_{eq} \quad (8)$$

where  $R = 8.314 \text{ J}/(\text{mol K})$  and  $T$  is the absolute temperature, for an acid ionization  $K_{eq} = K_a$  and because  $pK_a = -\log K_a$ , this equation can be restated as

$$\Delta G^\circ = 2.3RT(pK_a) \quad (9)$$

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 ( $pK_a = 15.5$ )<sup>17</sup> and acetic acid ( $pK_a = 4.76$ )<sup>18</sup> ionizations in water is used. Applying eq 9,  $\Delta G^\circ$  values for these ionizations at 25 °C are  $+88 \text{ kJ mol}^{-1}$  ( $21 \text{ kcal mol}^{-1}$ ) and  $+27 \text{ kJ mol}^{-1}$  ( $6.5 \text{ kcal mol}^{-1}$ ), respectively.



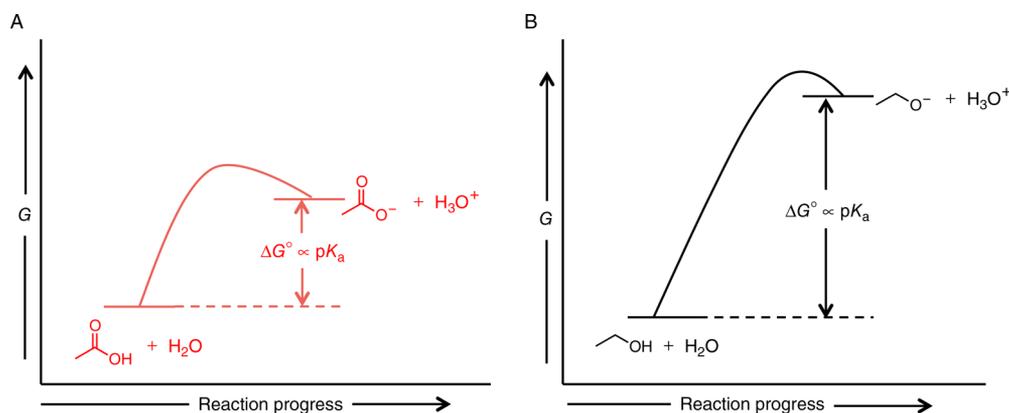


Figure 1. Gibbs energy diagrams for the ionization of (A) acetic acid and (B) ethanol in water.

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  $pK_a$ . The stronger acid (acetic acid), with a smaller, less positive  $pK_a$ , 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,<sup>19</sup> that is, acids with a  $pK_a$  greater than the hydronium ion ( $-1.74$ ) that ionize to less than 100%.

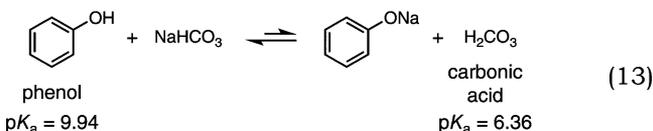
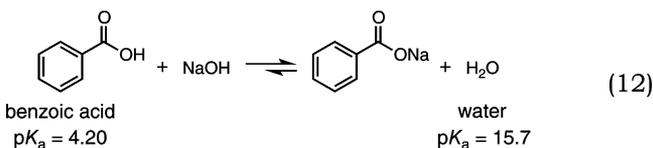
#### Item 4: Direction of an Equilibrium

What: In an acid–base equilibrium, the  $pK_a$  predicts the favored direction for that equilibrium.<sup>20</sup>

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

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 (Brønsted–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.



A further corollary of this concept is that  $pK_a$  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  $pK_a$  is higher than that of the original acid.

#### Item 5: Calculate an Equilibrium Constant

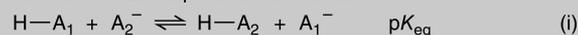
What: In an acid–base reaction, the  $pK_a$  of the acid species on both sides of the equation can be used to calculate the  $K_{eq}$  (equilibrium constant) for that reaction.<sup>21a,b</sup>

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

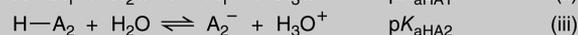
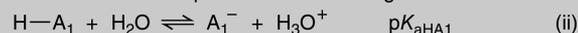
$$K_{eq} = 10^{[pK_a(\text{product acid}) - pK_a(\text{reactant acid})]} \quad (14)$$

This lesser known, yet broadly applicable relationship for the prediction of  $K_{eq}$  for a given acid–base reaction is the consequence of  $pK_a$  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

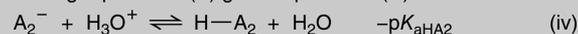
General acid–base equilibrium of interest:



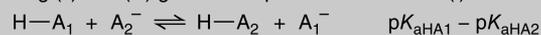
For each acid in this equilibrium the following is true:



Reversing equilibrium (iii) gives equilibrium (iv):



Adding (ii) and (iv) gives the equilibrium of interest (i):



Hence for this reaction:

$$pK_{eq} = (pK_{a\text{HA}1} - pK_{a\text{HA}2})$$

or:

$$K_{eq} = 10^{-(pK_{a\text{HA}1} - pK_{a\text{HA}2})} = 10^{(pK_{a\text{HA}2} - pK_{a\text{HA}1})}$$

or:

$$K_{eq} = 10^{[pK_a(\text{product acid}) - pK_a(\text{reactant acid})]}$$

Figure 2. Derivation of the formula for calculation of an equilibrium constant for any acid–base equilibrium.

general acid–base equilibrium shown. As can be seen, acid–base reactions that result in large increases in the  $pK_a$  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.

$$K_{\text{eq}} = 10^{[\text{p}K_{\text{a}}(\text{product acid}) - \text{p}K_{\text{a}}(\text{reactant acid})]}$$

$$K_{\text{eq}} = 10^{[\text{p}K_{\text{a}}(\text{water}) - \text{p}K_{\text{a}}(\text{benzoic acid})]}$$

$$K_{\text{eq}} = 10^{[15.7 - 4.20]} = 10^{11.5} \text{ or } 3.16 \times 10^{11.5}$$

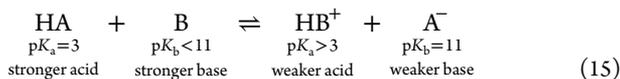
**Figure 3.** Calculation of the equilibrium constant for the reaction of benzoic acid with sodium hydroxide.

### Item 6: Stronger Acid and Stronger Base

**What:** In an acid–base reaction, the  $\text{p}K_{\text{a}}$  predicts the side with the stronger acid and base, and the side with the weaker acid and base.<sup>22</sup>

**How:** The side with the stronger acid (lower  $\text{p}K_{\text{a}}$ ) will be the same side containing the stronger base. The side with the weaker acid (higher  $\text{p}K_{\text{a}}$ ) 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–base pair, and the fact that the sum of the  $\text{p}K_{\text{a}}$  plus  $\text{p}K_{\text{b}}$  of any conjugate pair must be equal to a constant (typically stated to be 14 at 25 °C).<sup>23</sup> Consider the hypothetical example of acid HA reacting with base B to produce the conjugate pairs  $\text{A}^-$  plus  $\text{HB}^+$ . Assume HA is a stronger acid than  $\text{HB}^+$ , with a  $\text{p}K_{\text{a}}$  of 3. The conjugate base of the HA,  $\text{A}^-$ , must therefore have a  $\text{p}K_{\text{b}}$  of 11 in order for the sum of the  $\text{p}K_{\text{a}}$  and  $\text{p}K_{\text{b}}$  to equal 14. The weaker acid produced,  $\text{HB}^+$ , from the reaction, must have some  $\text{p}K_{\text{a}} > 3$ , and hence must have a conjugate base species, B, with a  $\text{p}K_{\text{b}} < 11$  (again sum to equal 14), making it a stronger base than the conjugate base,  $\text{A}^-$ , from the original stronger acid.

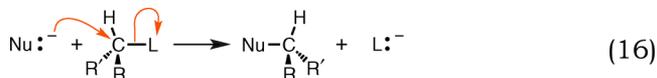


### Item 7: Magnitude of Gibbs Energy Change

**What:** Predict the magnitude and extent of  $\Delta G^\circ$  in a simple bimolecular nucleophilic substitution ( $\text{S}_{\text{N}}2$ ) reaction.<sup>24</sup>

**How:** When the  $\text{p}K_{\text{a}}$  of the conjugate acid of the nucleophile is much greater than the  $\text{p}K_{\text{a}}$  of the conjugate acid of the leaving group, the reaction will be highly exergonic with a large negative  $\Delta G^\circ$ . When the  $\text{p}K_{\text{a}}$  of the conjugate acid of the nucleophile is only slightly greater than the  $\text{p}K_{\text{a}}$  of the conjugate acid of the leaving group, the reaction will be only slightly exergonic with a small negative  $\Delta G^\circ$ .

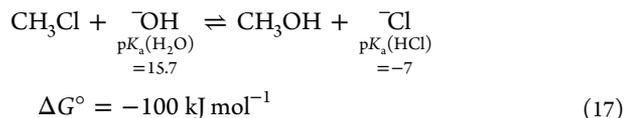
This prediction can be further explained using the following illustrations. Consider the generalized  $\text{S}_{\text{N}}2$  reaction shown:



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  $\text{p}K_{\text{a}}$ 's of the conjugate acids of the nucleophile ( $\text{Nu}^-$ ) and the leaving group ( $\text{L}^-$ ). If the  $\text{p}K_{\text{a}}$  of the conjugate acid of the nucleophile is much greater than the  $\text{p}K_{\text{a}}$  of the leaving group, thereby making the  $\text{p}K_{\text{b}}$  of the nucleophile much less than the  $\text{p}K_{\text{b}}$  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  $\Delta G^\circ = -RT \ln K_{\text{eq}}$ , which would be a large negative value, reactions proceed from strong base to weak base).

An example would be the reaction of chloromethane with hydroxide ion at 60 °C, reportedly having a  $\Delta G^\circ$  of  $-100 \text{ kJ mol}^{-1}$  ( $24 \text{ kcal mol}^{-1}$ ).<sup>25</sup> This large exergonic value is reflected in, and can be predicted from, the large differences in the  $\text{p}K_{\text{a}}$  for water (15.7) and HCl (−7).



On the other hand, if the  $\text{p}K_{\text{a}}$  of the nucleophile conjugate acid is only slightly greater than that of the leaving group, the reaction will have a small exergonic  $\Delta G^\circ$  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  $\text{p}K_{\text{a}}$ 's of HBr (−9) and HI (−10).<sup>26</sup>

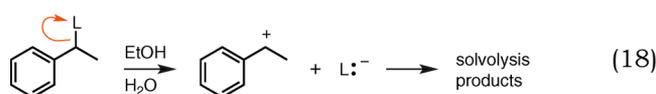
### Item 8: Leaving Group Ability

**What:** In the choice of a leaving group in a nucleophilic substitution ( $\text{S}_{\text{N}}$ ) reaction, it predicts which would be the better leaving group.<sup>27</sup>

**How:** The leaving group whose conjugate acid has the lower  $\text{p}K_{\text{a}}$  (stronger conjugate acid) will be the better leaving group (weaker conjugate base).

Up to this point, the predictions discussed based on  $\text{p}K_{\text{a}}$  have all been thermodynamic properties; therefore, it is no great surprise that  $\text{p}K_{\text{a}}$ , 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  $\text{p}K_{\text{a}}$  will never be absolute and exceptions will abound.

Whether nucleophilic substitution reactions proceed through a unimolecular ( $\text{S}_{\text{N}}1$ ) or bimolecular ( $\text{S}_{\text{N}}2$ ) 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  $\text{p}K_{\text{a}}$  of the conjugate acid of that leaving group.<sup>28</sup> Table 1 shows the relative rates for the solvolysis ( $\text{S}_{\text{N}}1$ ) of several 1-phenylethyl esters and halides and relates those to the corresponding  $\text{p}K_{\text{a}}$  of the conjugate acid of leaving group.<sup>29</sup> Note that within each category of leaving group (sulfonate or carboxylate ester and halide), there is a good linear correlation of reaction rate to  $\text{p}K_{\text{a}}$  (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  $\text{p}K_{\text{a}}$ . This makes an overall order prediction based solely on  $\text{p}K_{\text{a}}$  difficult.

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

Leaving Group ( $L^-$ )	$k_{rel}^a$	$pK_a$
Sulfonate Ester		
$CF_3SO_3^-$	$1.4 \times 10^8$	$-5.9^b$
$p\text{-NO}_2\text{-C}_6\text{H}_4\text{-SO}_3^-$	$4.4 \times 10^5$	$-4.0^b$
$p\text{-CH}_3\text{-C}_6\text{H}_4\text{-SO}_3^-$	$3.7 \times 10^4$	$-2.8^c$
$CH_3SO_3^-$	$3.0 \times 10^4$	$-1.92^b$
Carboxylate Ester		
$CF_3CO_2^-$	2.1	$0.23^{d,e}$
$p\text{-NO}_2\text{-C}_6\text{H}_4\text{CO}_2^-$	$5.5 \times 10^{-6}$	$3.41^f$
$CH_3CO_2^-$	$1.4 \times 10^{-6}$	$4.76^e$
Halides		
$I^-$	91	$-10^{d,e}$
$Br^-$	14	$-9^{d,e}$
$Cl^-$	1.0	$-7^e$
$F^-$	$9 \times 10^{-6}$	$3.2^e$

<sup>a</sup> $S_N1$  solvolysis of 1-phenylethyl substrate in 80% aqueous ethanol.<sup>29</sup>

<sup>b</sup>Ref 30. <sup>c</sup>From ref 30 reported for  $PhSO_3H$ . <sup>d</sup>Ref 10a. <sup>e</sup>Ref 31. <sup>f</sup>Ref 10b.

In the case of an  $S_N2$  pathway, this same trend is observed, although the nature of the nucleophile and the solvent significantly affect that dependence making an absolute order impossible.<sup>32</sup> Table 2 relates the average relative rate for the  $S_N2$  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.<sup>33</sup> 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.

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

What: Predict the relative strength of a nucleophile in a nucleophilic substitution reaction.<sup>34</sup>

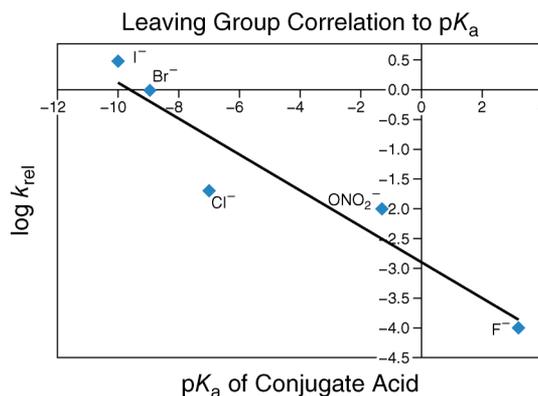
How: In polar protic solvents, generally the stronger the base (conjugate acid with the higher  $pK_a$ ), the stronger the nucleophile, with the exception of going down a periodic group, where the base gets weaker but the nucleophile gets stronger. In polar aprotic solvents, the stronger the base, the 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,

**Table 2. Relative Rate Dependence for the  $S_N2$  Reaction on a Methyl Substrate Containing Various Leaving Groups and Their Conjugate Acid  $pK_a$** 

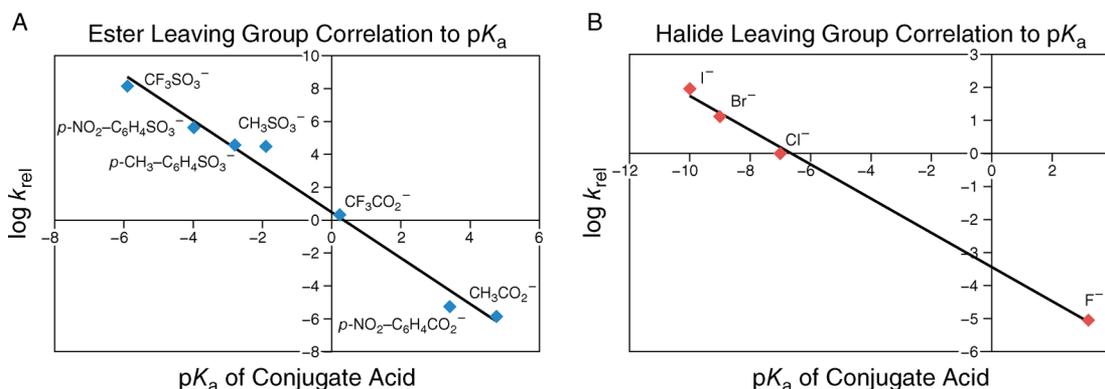
Leaving Group ( $L^-$ )	$k_{rel}^a$	$pK_a$
$PhSO_3^-$	6	$-2.8^b$
$I^-$	3	$-10^{c,d}$
$Br^-$	1	$-9^{c,d}$
$H_2O$	1	$-1.7^c$
$Cl^-$	$2 \times 10^{-2}$	$-7^d$
$ONO_2^-$	$1 \times 10^{-2}$	$-1.3^c$
$F^-$	$1 \times 10^{-4}$	$3.2^d$

<sup>a</sup>Ref 33. <sup>b</sup>Ref 30. <sup>c</sup>Ref 10a. <sup>d</sup>Ref 31.



**Figure 5.** Leaving group ability linear correlation to  $pK_a$  for an  $S_N2$  reaction.

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.<sup>35</sup> 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 these larger atoms.<sup>36</sup> 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.<sup>37</sup> Higher values of  $n$ , derived from the Swain–Scott



**Figure 4.** Ester (A) and halide (B) leaving group ability linear correlation to  $pK_a$  for an  $S_N1$  reaction.

**Table 3. Nucleophilicity of Common Nucleophiles as a Function of  $pK_a$  of Their Conjugate Acid**

Nucleophile	Nucleophilic Constant <sup>a</sup>	$pK_a$
SH <sup>-</sup>	5.1	7.00 <sup>b</sup>
CN <sup>-</sup>	5.1	9.4 <sup>b</sup>
I <sup>-</sup>	5.04	-10 <sup>b,c</sup>
HO <sup>-</sup>	4.20	15.7 <sup>b</sup>
Br <sup>-</sup>	3.89	-9 <sup>b,c</sup>
Cl <sup>-</sup>	3.04	-7 <sup>c</sup>
CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	2.72	4.76 <sup>b</sup>
F <sup>-</sup>	2.0	3.2 <sup>d</sup>
Picrate anion	1.9	0.38 <sup>e</sup>
<i>p</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -SO <sub>3</sub> <sup>-</sup>	<1	-2.8 <sup>f</sup>
H <sub>2</sub> O	0.00 <sup>g</sup>	-1.7 <sup>b</sup>

<sup>a</sup>Ref 37. <sup>b</sup>Ref 10a. <sup>c</sup>Ref 31. <sup>d</sup>Ref 30. <sup>e</sup>Ref 10b. <sup>f</sup>From ref 30 reported for PhSO<sub>3</sub>H. <sup>g</sup>In this nucleophilicity scale, water is the standard nucleophile and assigned 0.00.

equation,<sup>38</sup> indicate a better nucleophile.<sup>39</sup> The prediction trends described above in polar protic solvents are clearly apparent in this rate data.

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

**Table 4. Common Nucleophiles with Their Conjugate Acid  $pK_a$ 's Measured in DMSO and Water**

Nucleophile	$pK_a$ (DMSO)	$pK_a$ (Water)
HO <sup>-</sup>	31.4 <sup>a</sup>	15.7 <sup>b</sup>
CH <sub>3</sub> O <sup>-</sup>	29.0 <sup>a</sup>	15.5 <sup>b</sup>
CN <sup>-</sup>	12.9 <sup>c,d</sup>	9.4 <sup>b</sup>
F <sup>-</sup>	15.0 <sup>c,d</sup>	3.2 <sup>e</sup>
CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	12.6 <sup>f</sup>	4.76 <sup>a</sup>
Cl <sup>-</sup>	1.8 <sup>c,d</sup>	-7 <sup>e</sup>
Br <sup>-</sup>	0.9 <sup>c,d</sup>	-9 <sup>a,e</sup>

<sup>a</sup>Ref 40. <sup>b</sup>Ref 10a. <sup>c</sup>Ref 8a. <sup>d</sup>Ref 8b. <sup>e</sup>Ref 31. <sup>f</sup>Ref 41.

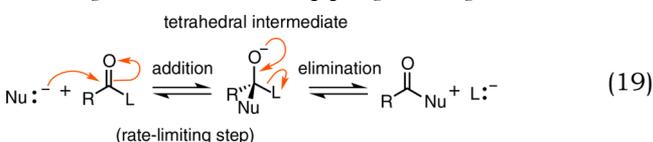
in DMSO (a representative polar aprotic solvent) in order of decreasing nucleophilicity and their corresponding  $pK_a$ 's measured in DMSO and in water.

### 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).<sup>42</sup>

How: The lower the  $pK_a$  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.



Unlike S<sub>N</sub>1 or S<sub>N</sub>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  $pK_a$  of the conjugate acid of the leaving group when subjected to attack by the same nucleophile (Table 5).<sup>43</sup>

**Table 5. Decreasing Order of Reactivity of Carboxylic Acid Derivatives toward Nucleophilic Acyl Substitution versus the  $pK_a$  of the Conjugate Acid of the Leaving Group**

Carboxylic Acid Derivative	Leaving Group (L <sup>-</sup> )	Approximate $pK_a$ (LH)
RCOCl	Cl <sup>-</sup>	-7
RCOOCOR	RCOO <sup>-</sup>	5
RCOSAr	ArS <sup>-</sup>	6.5 <sup>a</sup>
RCOOAr	ArO <sup>-</sup>	10
RCOSR'	R'S <sup>-</sup>	10.5 <sup>a</sup>
RCOOR'	R'O <sup>-</sup>	16
RCONH <sub>2</sub>	NH <sub>2</sub> <sup>-</sup>	35 <sup>b</sup>
RCONR' <sub>2</sub>	R' <sub>2</sub> N <sup>-</sup>	36 <sup>b,c</sup>

<sup>a</sup>Ref 8c. <sup>b</sup>Ref 32. <sup>c</sup>Ref 11.

Comparing the  $pK_a$  of the conjugate acid of the nucleophile to that of the conjugate acid of the leaving group can also give insight as to which direction the equilibrium for the acyl substitution reaction will lie. If the  $pK_a$  of the conjugate acid of the leaving group (LH) is lower than that of the nucleophile (NuH), product formation will be favored.

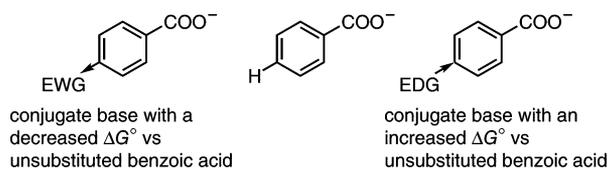
### Item 11: Activating or Deactivating Group Nature

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.<sup>44</sup>

How: By comparing the  $pK_a$  of a benzoic acid para-substituted with that group versus unsubstituted benzoic acid ( $pK_a = 4.17$ ). If the  $pK_a$  of the para-substituted benzoic acid is smaller, that group is an electron withdrawing group and most likely a deactivating group. If the  $pK_a$  of the para-substituted benzoic acid is larger, that group is an electron donating group and likely an activating group.

Derivatives of benzoic acid have historically been analyzed in the context of structure–activity relationships.<sup>45,46</sup> The basis for

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



**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.

Electron donating groups act to do just the opposite, enriching the electronic nature of the aromatic ring, producing a more localized charge on the carboxylate, and thereby increasing the standard Gibbs energy change for deprotonation resulting in a stronger conjugate base and weaker acid. Table 6 lists some

**Table 6.**  $pK_a$  Values of Unsubstituted and Para-Substituted Benzoic Acids and Selective Relative Rates for Nitration of the Corresponding R-Substituted Benzenes

R	$pK_a^a$	$k_{rel}^b$
Deactivating Groups		
$(CH_3)_3N^+$	3.43	$1.2 \times 10^{-8}$
$O_2N-$	3.44	$6 \times 10^{-8}$
$HOOC-$	3.51	$3.7 \times 10^{-3d}$
$CH_3SO_2-$	3.52	$3.5 \times 10^{-3c}$
$NC-$	3.55	—
$Cl-$	3.99	$3.3 \times 10^{-2}$
$Br-$	4.00	$3.0 \times 10^{-2}$
$F-$	4.14	0.15
<b>H-</b>	<b>4.20</b>	<b>1</b>
Activating Groups		
$CH_3-$	4.34	25
$(CH_3)_3C-$	4.40	—
$CH_3O-$	4.47	—
$PhO-$	4.52	—
$HO-$	4.58	1000
$H_2N-$	4.92	—
$(CH_3)_2N-$	5.03	—

<sup>a</sup>Ref 10a. <sup>b</sup>Relative rates of nitration of substituted benzene from ref 47. <sup>c</sup>From ref 47 reported for  $PhSO_2-$ . <sup>d</sup>From ref 47 reported for  $EtOOC-$ .

representative examples of this effect along with selected values of relative rates of nitration of the corresponding R substituted benzene for comparison. Para-substituted phenols and para-substituted anilinium ions ( $p-R-C_6H_4NH_3^+$ )<sup>48</sup> can be used in much the same way (see the Supporting Information).

## CONCLUSIONS

Presented here is a compilation of organic chemical events that can be predicted by use and knowledge of  $pK_a$ . Organized in this fashion, the student readily recognizes how  $pK_a$  reinforces an understanding of organic chemistry. When used in conjunction with the requirement that the student memorize the approximate

$pK_a$  values of the fundamental organic functional groups along with other “benchmark” molecules (e.g., hydrogen, ammonia, and water), transitioning to organic chemistry becomes easier.

## ASSOCIATED CONTENT

### Supporting Information

Student handouts consisting of summary tables entitled “What Does  $pK_a$  Tell You” and “Relative  $pK_a$ ’s of Organic Functional Groups”; additional data in support of item 11. This material is available via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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