pH Optimization of Nucleophilic Reactions in Water†

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Abstract: We present a way of prescribing the pH for a reaction so as to obtain either (a) maximum yield in competition with hydrolysis or (b) selective reaction at either of two sites in such nucleophile–electrophile reactions as C-alkylation of acidic ketones and the acylation and sulfonylation of amines. First, we derive the following general equation for pH_{max}, the pH giving the highest yield of the product (P) of the reaction of a nucleophile (Nu) with a hydrolyzable electrophile (E) in water:

$$pH_{max} = \tfrac{1}{2}[\log (k_w/k_{OH}) + pK_w + pK_a]$$

(k_w and k_{OH} refer to the water- and hydroxide-promoted hydrolyses of E, K_w is the autoprotolysis constant of water, and K_a is the acid dissociation constant of NuH^+, the conjugate acid of Nu). pH_{max} thus depends on a property of E (namely, k_w/k_{OH}) and a property of Nu (the pK_a of NuH^+), but *not* on the rate constant for the reaction of E with Nu or the concentration of Nu. We then deduce analogous approximate equations for maximum selectivity for reaction at either of two nucleophilic sites, specifically, equations giving pH_{xmax} and pH_{ymax}, the pH values for the maximum yields of the respective products (P_x and P_y) of the reactions of E with the two nucleophiles. We find that (a) pH–yield profiles calculated from the equations concur with observed yields for reactions under pseudo-first-order conditions and (b) preparative experiments at the estimated pH values give good to excellent yields of clean products and high selectivity in both the C-alkylation and Schotten–Baumann reactions.

In the light of the variety and efficiency of reactions in aqueous media in nature, it is remarkable that water is so little used as the reaction solvent in organic synthesis. This arises in part because of the relatively low solubility of many organic compounds in water, but also because the desired process often competes with hydrolysis. In this paper we show (a) how to estimate the pH for obtaining the maximum yield in competition with hydrolysis and, in addition, (b) how to use pH control of an aqueous solution to obtain selective reaction at either of two nucleophilic sites. We illustrate these methods with some examples involving the acylation and sulfonylation of amines and the C-alkylation of acidic ketones.

Results and Discussion

Optimization of Yields. Equation 1 gives[1] the pseudo-first-order rate constant ($k_{\psi o}$) for the hydrolysis of an electrophile (E) taking place by both uncatalyzed and hydroxide-promoted pathways, while eqs 2 and 3 give, respectively, $k_{\psi N}$, the pseudo-first-order rate constant for reaction of a nucleophile (Nu) with E to yield the product (P), and $k_{\psi T}$, that for the total consumption of E.

$$k_{\psi o} = k_w + k_{OH}[OH^-] = k_w + k_{OH}K_w/[H^+] \quad (1)$$

$$k_{\psi N} = k_N[Nu] = k_N Nu_T K_a/([H^+] + K_a) \quad (2)$$

$$k_{\psi T} = k_{\psi o} + k_{\psi N} \quad (3)$$

We may conveniently show the variation in the pseudo-first-order rate constants with change in $[H^+]$ by plots of log k_ψ vs pH as in Figure 1, from which one may see that P is the major product for the pH range in which $k_{\psi N} > k_{\psi o}$. In other words, the roughly parallelogram-shaped region enclosed by the log $k_{\psi o}$ and log $k_{\psi N}$ curves may be regarded as the "window" for the formation of P. Defining f_p, the theoretical yield of P under pseudo-first-order conditions (expressed as a fraction), we write eq 4.

$$f_p = k_{\psi N}/k_{\psi T} = \frac{k_N Nu_T K_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+] + k_N Nu_T K_a/([H^+] + K_a)} \quad (4)$$

The variation of f_p with pH for the reaction of benzenesulfonyl chloride (**1**) with aniline (**2**) has been calculated from eq 4 and rate constants reported by Rogne[2] and is shown by the solid line in Figure 2, while the experimental yields of benzenesulfonanilide (**3**) under pseudo-first-order conditions are given by the filled circles; theory and experiment clearly agree.

Figure 2 also shows the corresponding pH–yield profile for the reaction of **1** with benzylamine (**4**) to give *N*-benzylbenzenesulfonamide (**5**). It is evident from the two curves in Figure 2 that both pH_{max} (the value of the pH at which the highest yield is found) and the widths of the regions of relatively high yields vary with the reaction. To obtain pH_{max} as a function of pH, one may set the first derivative of the right side of eq 4 with respect to $[H^+]$ equal to zero and transform the resultant expression into its equivalent form with respect to pH, as in eq 5. The same relation may be derived more simply by inspection of Figure 1, from which it is apparent that pH_{max} is simply halfway between pH_i and pH_{iN}, i.e., $pH_{max} = {}^1/_2(pH_i + pH_{iN})$; since one may easily show[3] that $pH_{iN} = pK_a$ and $pH_i = \log (k_w/k_{OH}) + pK_w$, eq 5 immediately follows.[4]

$$pH_{max} = \tfrac{1}{2}[\log (k_w/k_{OH}) + pK_w + pK_a] \quad (5)$$

As a simple, concentration-independent measure of the width of the window, we suggest that width = $|pH_i - pH_{iN}|$ and that both components defining the region of best yield for a reaction be given by the descriptor $pH_{max} \pm ({}^1/_2$ width), as in eq 6.

$$pH_{max} \pm (\tfrac{1}{2}\text{ width}) = \tfrac{1}{2}(pH_i + pH_{iN}) \pm \tfrac{1}{2}(pH_i - pH_{iN}) = \tfrac{1}{2}[\log (k_w/k_{OH}) + pK_w + pK_a] \pm \tfrac{1}{2}[\log(k_w/k_{OH}) + pK_w - pK_a] \quad (6)$$

Note two important conclusions from eq 6: (a) *pH_{max} is inde-*

† Dedicated to Professor Zdenek Valenta on the occasion of his 65th birthday.

(1) Symbols. (i) Rate constants: k_w, hydrolysis of E by water; k_{OH}, hydrolysis of E by hydroxide ion; k_N, reaction of E with Nu. (ii) K_a, acid dissociation constant of NuH^+ (the conjugate acid of Nu); $K_w = [H^+][OH^-]$; $Nu_T = [Nu] + [NuH^+]$; pH_i, the point of intersection of the tangents to the sloped and flat limbs of the $k_{\psi o}$ curve; pH_{iN}, the analogous point of intersection with respect to the $k_{\psi N}$ curve; at pH_i, $k_w = k_{OH}[OH^-]_i$; at pH_{iN}, $k_N Nu_T = k_N Nu_T K_a/[H^+]_i$, i.e., $K_a = [H^+]_i$ or $pH_i = pK_a$. (iii) In eqs 8–11: k_x, the rate constant for the reaction of E to form P_x; K_x, K_a for Nu_xH^+; $Nu_{xT} = [Nu_x] + [Nu_xH^+]$; pH_{xmax}, the pH value for maximum yield of P_x; pH_{ix}, the point of intersection of the tangents to the sloped and flat limbs of the log $k_{\psi x}$ curve; pH_a and pH_b, the points of intersection of the log $k_{\psi o}$ curve with the sloped limb of the log $k_{\psi y}$ and the flat limb of the log $k_{\psi x}$ curves, respectively; the y-subscripted terms are defined analogously.

(2) Rogne, O. *J. Chem. Soc. B* **1968**, 1294–1296; **1970**, 1056–1058.

(3) (a) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin: New York, 1966; Vol. 1, pp 12–13. (b) Mabey, W.; Mill, T. *J. Phys. Chem. Ref. Data* **1978**, *7*, 383–415.

(4) Professor O. S. Tee (Concordia University) has pointed out to us that the Kurz equation for the pK_a of a protonated transition state[5] in the present context and notation is $pK_a(\ddagger) = \log (k_w/k_{OH}) + pK_w$, and hence that $pH_i \equiv pK_a(\ddagger)$. It is interesting, and at least mnemonically useful, that eq 5 then becomes $pH_{max} = {}^1/_2[pK_a(\ddagger) + pK_a]$, i.e., pH_{max} may be regarded as the average of the pK_a's of, respectively, the protonated nucleophile and the protonated transition state for hydrolysis. We are grateful to Professor Tee for drawing this point to our notice.

(5) Kurz, J. L. *Acc. Chem. Res.* **1972**, *5*, 1–9.

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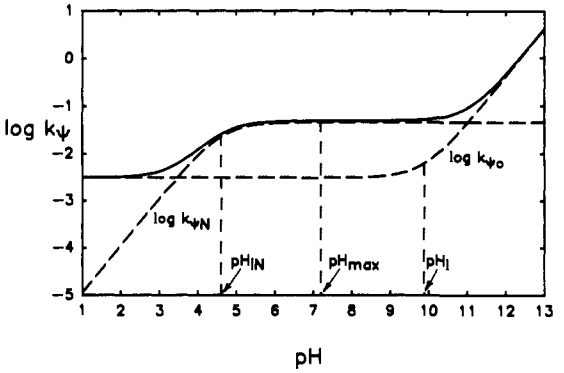


Figure 1. pH–rate profiles for the reaction of a nucleophile with an electrophile in water competing with hydrolysis. The broken lines are calculated for the reactions of benzenesulfonyl chloride (**1**) with water (log $k_{\psi o}$) and with aniline (**2**) (log $k_{\psi N}$) in 0.05 M NaCl at 25 °C, using eqs 1 and 2 and Rogne's parameters:[2] k_w 3.06 × 10^{-3} s^{-1}, k_{OH} 40.4 M^{-1} s^{-1}, k_N 4.6 M^{-1} s^{-1}. Solid line: log ($k_{\psi o}$ + $k_{\psi N}$).

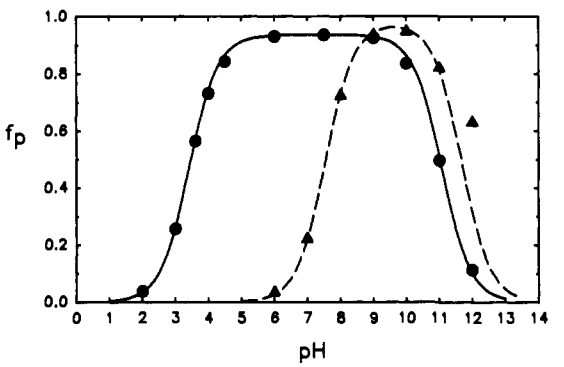


Figure 2. pH–yield profiles for the reactions, under pseudo-first-order conditions, of benzenesulfonyl chloride (**1**) (C_o 7.8 × 10^{-4}) with (a) aniline (**2**) (C_o 0.01 M) to form $PhSO_2NHPh$ (**3**) (solid line and circles) and (b) benzylamine (**4**) (0.01 M) to form $PhSO_2NHCH_2Ph$ (**5**) (broken line and triangles). The solid line is calculated from eq 4 and the parameters in the caption to Figure 1, plus pK_a 4.60 for **2**; the dotted line is also from eq 4, but uses k_N 19 M^{-1} s^{-1} (best fit to curve) and pK_a 9.34 for benzylamine.[6]

pendent of k_N and Nu_T and can be obtained simply from k_w/k_{OH} (or pH_i) for E and the pK_a of NuH^+; (b) *the window is narrowest (width equals zero) when pK_a = pH_i, becoming wider with increasing separation of pK_a and pH_i*. For the reaction of **1** (pH_i = 9.88) with **2** (pK_a 4.60[6]), pH_{max} ± ($^1/_2$ width) is 7.2 ± 2.6, a relatively wide window, whereas that (9.6 ± 0.3) for the corresponding reaction of benzylamine (**4**) (pK_a 9.34) to give $PhSO_2NHCH_2Ph$ (**5**) is narrow (cf. Figure 2).

We have applied eq 6 to the acylation and sulfonylation of amines (pH-controlled Schotten–Baumann conditions). Benzenesulfonyl chloride (**1**) and benzylamine (**4**) (C_o 0.105 and 0.10 M, respectively) at pH 9.6 for 1 h gave, after simple workup, clean **5** in >99% yield. In a set of experiments starting with 0.10 M benzenesulfonyl chloride (**1**) and 0.105 M benzylamine (**4**), the following yields were found: pH 7.5, 69%; pH 9.6, 96%; pH 12.0, 87%. To optimize Schotten–Baumann reactions of benzoyl chloride (**6**), we required k_w/k_{OH} for **6**. A k_w value has recently been reported,[7] but a search of the literature turned up no reliable reports of k_{OH} for the reaction in water at 25 °C. Accordingly, we determined pH_{max} for the reactions of benzylamine (**4**) and piperidine with benzoyl chloride (**6**) from the results shown in Figure 3 and obtained k_w/k_{OH} = 3.5 × 10^{-5} M (and hence k_{OH} = 4.0 × 10^2 M^{-1} s^{-1}) by using eq 7, a simple transformation of eq 5.

$$\log (k_w/k_{OH}) = 2pH_{max} - pK_a - pK_w \quad (7)$$

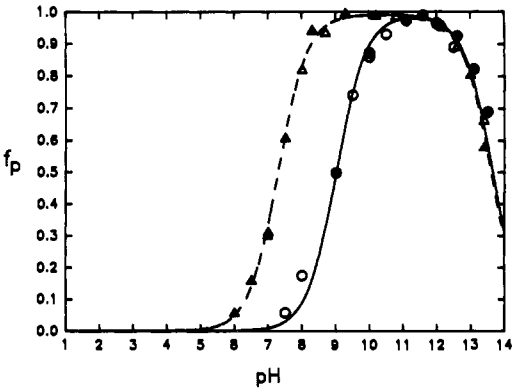
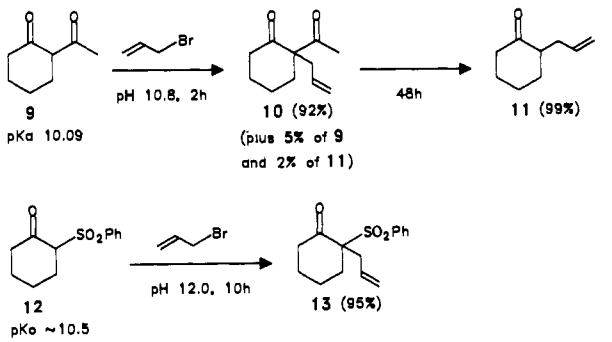


Figure 3. pH–yield profiles for the pseudo-first-order reactions at 25 °C of benzoyl chloride (**6**) (C_o 0.001 M) with (a) benzylamine (**4**) (C_o 0.01 M) to form *N*-benzylbenzamide (triangles) and (b) piperidine (C_o 0.01 M) to form *N*-benzoylpiperidine (circles). The lines were calculated from eq 4 using k_w 1.4 s^{-1} k_{OH} 400 M^{-1} s^{-1} (Table I) and k_N 1.6 × 10^4 M^{-1} s^{-1} (best fit to curve) and K_a 4.57 × 10^{-10} M for the dashed line (a) (benzylamine), and k_N 1.8 × 10^4 M^{-1} s^{-1} (best fit) and K_a 6.03 × 10^{-12} M for the solid line (b) (piperidine). The closed points refer to experiments in which **6** was added as the neat liquid, the open points to those in which **6** was added as a solution in DME (2.5 mL into 500 mL of water).

Scheme I. C-Allylation of Acidic Ketones in Water[a]



[a] Initial concentrations: allyl bromide, 0.10 M; **9** or **12**, 0.05 M.

At pH 10.4, **6** and **4** (C_o 0.011 and 0.010 M, 30-min reaction time) gave *N*-benzylbenzamide showing no sign of impurity, in 97% isolated yield; with benzoyl chloride (**6**) and piperidine, the same conditions, except for pH 11.4, gave *N*-benzoylpiperidine in 98% yield. A series of experiments with variation of the pH with the initial concentration of benzylamine (**4**) set at 0.010 M and initial concentrations of benzoyl chloride (**6**) of 0.010 and 0.012 M gave the following yields of *N*-benzylbenzamide: pH 7.5, 53% and 55%; pH 10.45, 86% and 99%; pH 13.0, 39% and 48%.

To illustrate carbon–carbon bond formation in pH-controlled aqueous medium, we chose the allylation of acidic ketones. The k_w/k_{OH} ratio for allyl bromide was also apparently unavailable from literature sources, and values of k_w/k_{OH} = 4.2 × 10^{-2} M and pH_i = 12.6 were obtained from eq 7 and the pH_{max} (12.2) observed for the reaction of allyl bromide with *N*-methylmethanesulfonamide (pK_a 11.79) to form *N*-allyl-*N*-methylmethanesulfonamide. Scheme I summarizes the observed reactions of allyl bromide with **9** and **12**; the products of the reactions in Scheme I (and Scheme III) were obtained by simple workup and were, judging from their ^1H and ^{13}C NMR spectra, remarkably clean and free from impurities. The reaction of **9** is of further interest because it gives a serviceable route to either **10** or **11**, depending simply on the reaction time.

In these examples, the yields around the calculated pH_{max} are clearly satisfactory for many needs. The procedure is very simple

(6) Amine pK_a's are taken from the following: Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965. Acid pK_a's (except for sulfones): Serjeant, E. P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*; Pergamon Press: Oxford, 1979.

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Table I. Representative Hydrolysis Rate Constants and pH_i Values[a]

electrophile	k_w (s^{-1})	k_{OH} (M^{-1} s^{-1}	pH_i
CH_3Cl	2.39×10^{-8} [b]	6.67×10^{-6} [c]	11.55
CH_3Br	4.07×10^{-7} [b]	1.44×10^{-4} [c]	11.45
CH_3I	7.41×10^{-8} [b]	6.36×10^{-5} [c]	11.07
$CH_2{=}CHCH_2Cl$	1.18×10^{-7} [b]	6.24×10^{-5} [d]	11.28
$CH_2{=}CHCH_2Br$	1.70×10^{-5} [b]	4.2×10^{-4} [e]	12.6
$PhCH_2Cl$	1.32×10^{-5} [b]		>13[f]
$CH_3OSO_2CH_3$	5.39×10^{-6} [b]	3.92×10^{-4} [b]	12.14
$CH_3CH_2OSO_2CH_3$	3.94×10^{-6} [b]	6.4×10^{-5} [g]	12.8
$CH_3(CH_2)_3OSO_2CH_3$	3.50×10^{-6} [b]	3.6×10^{-5} [g]	13.0
$CH_3OSO_2OCH_3$	1.79×10^{-4} [b]	9.16×10^{-3} [b]	12.29
CH_2CH_2O	6.75×10^{-7} [h]	1.02×10^{-5} [i]	12.82
$(CH_3O)_3PO$	1.8×10^{-8} [j]	1.7×10^{-4} [j]	10.0
$(CH_3CO)_2O$	2.8×10^{-3} [k]	9.70×10^{2} [k]	8.5
CH_3COCl[l]	1.1×10^{3} [m]	6.25×10^{3} [m]	13.3
CH_3COF[n]	2.95×10^{-3} [o]	5.7×10^{4} [o]	7.64
$CH_3COOC_6H_3$-2,4-$(NO_2)_2$	1.1×10^{-5} [p]	53.7[p]	7.3
CH_3CH_2OCOCl	4.85×10^{-4} [g]	40.6[q]	9.08
$PhCOCl$	1.4[r]	4.0×10^{2} [e]	11.5
$PhSO_2Cl$	3.06×10^{-3} [s]	40.4[s]	9.88
p-$CH_3C_6H_4SO_2Cl$	3.00×10^{-3} [s]	16.1[s]	10.27
p-$NO_2C_6H_4SO_2Cl$	2.82×10^{-3} [s]	6.31×10^{2} [s]	8.65
$CH_2{=}CHSO_2Cl$	1.32×10^{-3} [t]	1.24×10^{2} [t]	9.03
CH_3SO_2Cl	2.10×10^{-4} [u]	4.03×10^{3} [u]	6.71
$CH_2{=}SO_2$			11.8[u,v]
$PhCH_2SO_2Cl$	2.4×10^{-4} [u]	8.4×10^{4} [u]	5.45

[a] At 25 °C, except where otherwise specified, varying ionic strengths; $pH_i = \log (k_w/k_{OH}) + 14$ (at 25 °C, see text). [b] Reference 9. [c] Reference 10. [d] Quoted in ref 3b. [e] This work; see text. [f] Rate reported[11] to be independent of pH below 13. [g] Reference 12. [h] Reference 13. [i] Reference 14. [j] Reference 15. [k] Reference 16. [l] At 22 ± 2 °C. [m] Reference 17. [n] At 0.4 °C. [o] Reference 18. [p] Reference 19. [q] Reference 20. [r] Reference 7. [s] Reference 2. [t] Reference 21. [u] Reference 22. [v] From the sulfene trapping ratio, $k_{TOH}/k_{TW} = 146$ M^{-1}.

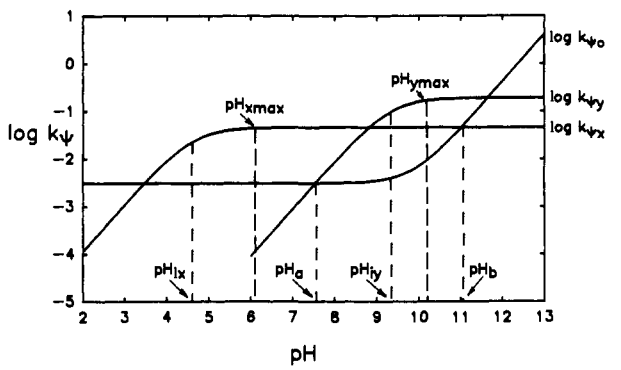


Figure 4. pH–rate profiles for the reactions of two nucleophiles with an electrophile in the face of competing hydrolysis. The lines are calculated from eqs 1 and 2 and the parameters given in the captions to Figures 1 and 2.

and the cost of materials and apparatus minimal; all that one has to know in order to find pH_{max} is the pK_a of the conjugate acid of the nucleophile and the k_w/k_{OH} ratio for hydrolysis of the electrophile. Tables of pK_a's are available,[6] and where these are lacking, sufficiently accurate pK_a values can be estimated by analogy or with the aid of linear free energy relationships, as described by Perrin et al.[8] Table I provides a representative

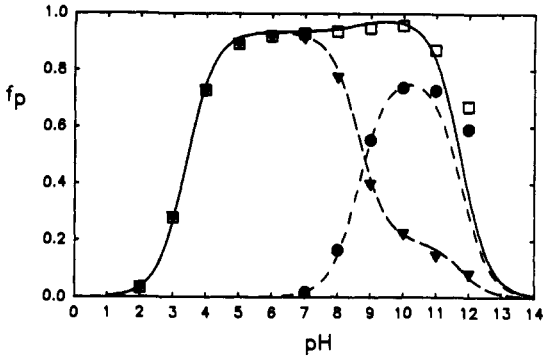
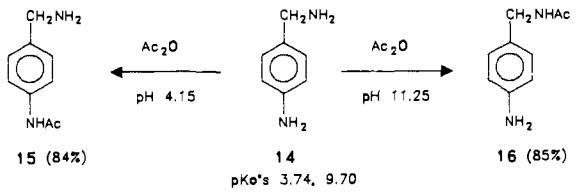


Figure 5. pH–yield profiles for the reactions of **1** (C_o 0.001 M) with a mixture of **2** and **4** (C_o 0.01 M, each) to form $PhSO_2NHPh$ (**3**) and $PhSO_2NHCH_2Ph$ (**5**). The lines are calculated from (expanded versions of) eqs 8 and 9 and the parameters for Figures 1 and 2: triangles, yield of **3**; circles, yield of **5**; squares, sum of **3** and **5**.

Scheme II. Selective Monoacetylation of 4-Aminobenzylamine



collection of k_w, k_{OH}, and pH_i values. When pH_i's are not available, the simple procedure of finding pH_{max} for a convenient reaction and applying eq 7 works well for synthetic purposes and indeed, as with benzoyl chloride, when k_w is known, for providing hard-to-get k_{OH}'s for mechanistic studies as well.

Selectivity Optimization. By extension, we depict the reaction of E with *two* different nucleophiles, Nu_x and Nu_y, as in Figure 4. The respective windows for the formation of the products, P_x and P_y, appear as the lower left and upper right "rounded parallelogram" zones, with the fractions of the products given by eqs 8 and 9.

$$f_x = k_x[Nu_x]/(k_w + k_{OH}[OH^-] + k_x[Nu_x] + k_y[Nu_y]) \quad (8)$$

$$f_y = k_y[Nu_y]/(k_w + k_{OH}[OH^-] + k_x[Nu_x] + k_y[Nu_y]) \quad (9)$$

Figure 5 shows plots of the yields of **3** and **5** from reaction of **1** with an equimolar mixture of **2** and **4** under pseudo-first-order conditions.

Reasoning similar to that in the previous section leads to approximate eqs 10 and 11.[23] From these we estimate for the

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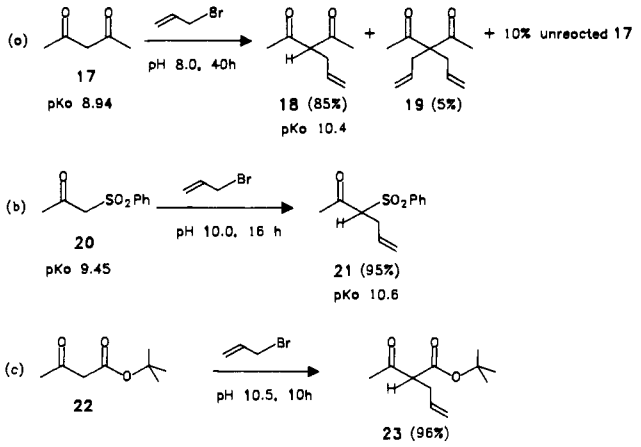
(23) The derivation and limits of applicability of eqs 10 and 11 are as follows. It is evident from Figure 4 that

$$pH_{xmax} = \tfrac{1}{2}(pH_a + pH_{ix}) \quad (i)$$

$$pH_{ymax} = \tfrac{1}{2}(pH_{iy} + pH_b). \quad (ii)$$

The general solution to the evaluation of pH_a and pH_b is complex, but a useful approximation may be obtained by restricting application to those cases in which (as in Figure 4) there is a clear separation (of, say, >1 pH unit) between the key points, specifically (a) between pH_a and both pH_i and pH_{ymax}, such that at pH_a, $k_{\psi o} \approx k_w$ and $k_{\psi y} \approx k_y Nu_{yT} K_y/[H^+]_a$, and (b) between pH_b and both pH_i and pH_{xmax}, such that at pH_b, $k_{\psi o} \approx k_{OH} K_w/[H^+]_b$ and $k_{\psi x} \approx k_x Nu_{xT}$. From this we readily obtain $pH_a \approx \log (k_w/k_y Nu_{yT}) + pK_y$ and $pH_b \approx k_x Nu_{xT}/k_{OH} + pK_w$ which, when taken with $pH_{ix} = pK_x$ and $pH_{iy} = pK_y$ and substituted in eqs i and ii, lead to approximate eqs 10 and 11.

Scheme III. Selective Monoallylation of Acidic Ketones in Water



reaction of **1** with the mixture of **2** and **4**, respectively, pH_{xmax} 6.1 ± 1.5 and pH_{ymax} 10.2 ± 0.9, in good agreement with the experimental points in Figure 4.

$$pH_{xmax} \pm (\tfrac{1}{2}\text{ width}) \approx \tfrac{1}{2}[\log (k_w/k_yNu_{yT}) + pK_y + pK_x] \pm \tfrac{1}{2}[\log (k_w/k_yNu_{yT}) + pK_y - pK_x] \quad (10)$$

$$pH_{ymax} \pm (\tfrac{1}{2}\text{ width}) \approx \tfrac{1}{2}[\log (k_xNu_{xT}/k_{OH}) + pK_w + pK_y] \pm \tfrac{1}{2}(\log (k_xNu_{xT}/k_{OH}) + pK_w - pK_y] \quad (11)$$

Closely related to the system described by Figure 4 and eqs 8–11 is the general problem of obtaining selective reaction at either of two nucleophilic sites in the same molecule;[24] we chose monoacetylation of 4-aminobenzylamine (**14**) as a specific example. Using the k_w and k_{OH} values from Table I plus rough k_x's and k_y's estimated from related rate constants in the literature (e.g., refs 16 and 19), we obtained plots of f_x and f_y vs pH. From these, with minimal further exploration for reaction conditions, we obtained the selective acetylation of either amino group, summarized in Scheme II; the yields refer to the isolated, crystalline hydrochloride salts.

Another well-known situation requiring selectivity arises when both the starting material and product are capable of reacting with the reagent and only the product of the first reaction is wanted. Scheme III shows the results for the reaction of allyl bromide with three simple acidic carbonyl substrates. Again, using eqs 8–11 with only a little trial and error experimentation, a synthetically useful level of monoallylation was attained.[25] By way of comparison, we note that the reaction of **20** with LDA in THF followed by allyl iodide in HMPA has been reported to give **21** in 71% yield.[26]

Limits of the Methods. Equations 4–11 are derived on the assumptions that (a) the rate law is given by eq 3, (b) the solutions are ideal, and (c) mixing of reactants is much faster than the reaction.[27] In addition, the application of these relations requires that the response time of the pH-controlling system, whether manual or automatic, be fast relative to the reaction; with either slow mixing or sluggish pH adjustment, the actual (local) concentrations of the reactants at the points of the reaction will not be those calculated and the results will not necessarily conform to the equations. In most of the examples that we have encountered to date, the measure of agreement that we have found gives us reason to believe that the above assumptions are reasonably good, but further work is needed to define the full range of validity of the equations. We have, for example, observed two cases, namely, the reactions of (a) aryloxides with benzenesulfonyl chloride (**1**) and (b) amines with acetic anhydride, where the pH–yield profiles point to the apparent consumption of a portion (usually ≤10%) of the electrophile by hydrolysis assisted by the nucleophile acting as a general base. We plan to describe these results more fully elsewhere, but for the present we note that the general base promoted hydrolysis (a) may be shown to have no effect on the calculation of pH_{max}, but (b) does make the quantitative conversion of equimolar amounts of reactants to products impossible. In the commonly occurring case in which one seeks a high-yield conversion of nucleophile to product and loss of some of the electrophile is unimportant, one merely has to add an appropriate excess of the electrophile. In this context, we point out that pH–yield profiles (e.g., Figures 2 and 3) are useful as sensitive indicators of deviations from expected rate laws.

Perfect mixing and ideal solutions are readily obtained whenever one may work with slow reactions and at low concentrations, but with many organic systems this may be difficult to arrange, owing to either the high reactivity of the reactants or the low solubility of starting materials or products. If, for example, an organic phase separates out and a significant portion of the reaction takes place in the organic phase, the results may be quite different from those calculated. In the experiments with benzenesulfonyl and benzoyl chlorides (**1** and **6**), the product usually precipitated as an oil or a solid. This did not appear to lead to deviations from the calculated yields, provided a sufficiently long time was allowed for reaction, perhaps to permit the acid chloride (which can become entrained in the product[28]) to return to the aqueous medium and complete the reaction. Provided the predictions hold, such separation of the product may be advantageous. For many preparations it enables isolation of the product by simple filtration or liquid–liquid separation and, in addition, may yield more subtle benefits. Though the high selectivity in the conversion of **20** to **21** without further allylation of **21** can be ascribed, at least in part, to the pK_a difference between **20** and **21** and a (presumed) steric effect of the allyl group leading to a lowering of the nucleophilicity of the anion of **21**, it was observed that some of the product in this reaction separated as an oil; the effect of this would be to lower the concentration of **21** in the water, thereby slowing its further reaction with allyl bromide and hence enhancing the selectivity.

Further study should show the limits of the size (or solubility) of the reactants that can be readily handled in water and the extent to which these can be extended by the addition of water-miscible cosolvents. In our experiments with benzoyl chloride, we found that the use of a little 1,2-dimethoxyethane (DME, up to 0.5%) had no evident effect on yields (see Figure 3). This was interpreted as indicating not only that small amounts of cosolvent may be used without altering the equations but also that mixing and response time effects were probably not perturbing the system, since any such effects would be expected to be different for the different modes of addition. This result indicates that the simplest procedures involving a standard pH meter and manual addition of base are adequate even for reagents as reactive as benzoyl chloride. The rapid mixing procedure required by Palling and Jencks[17] for the reactions of acetyl chloride in water, however, points up the need to keep these effects in mind and to take appropriate precautions if one expects to observe conformance to eqs 4–11.

Conclusions. This paper presents some easily derived equations which, when taken with readily available data, make it easy to carry out electrophile–nucleophile reactions in water with (a) high yield or (b) maximum selectivity. Alternatively, but still usefully, these relations may also reveal those reactions for which high yield or selectivity is not feasible in aqueous medium, thereby obviating

(24) Strictly speaking, a single molecule with two nucleophilic centers shows a log $k_{\psi x}$ curve like that in Figure 4 only if the nucleophilic reactivity of the less basic center (LBC) is quite unaffected by the presence or absence of a proton on the more basic center (MBC). For many bidentate nucleophiles, removal of the proton from MBC will increase the nucleophilicity of LBC, and in the region from just below pH_{iy} and above, log $k_{\psi x}$ may be expected to follow a curve parallel (and below) that of log $k_{\psi y}$.

(25) Preliminary experiments showed that alkylation of ethyl acetoacetate occurred in reasonable yield but was accompanied by partial hydrolysis of the ester function; use of the *tert*-butyl ester avoids this problem, and the reactions of the ethyl ester have not yet been further studied.

(26) Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817–4820.

(27) Rys has noted that "every chemical event that can occur in a time shorter than 0.01–1.0 s may be hindered by mixing processes": Rys, P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 807–817.

(28) See, for example: Vogel, A. I. *A Textbook of Practical Organic Chemistry*, 2nd ed.; Longmans, Green, and Co.: London, 1951; p 559.

fruitless experimentation. Because they are quantitative, the relations in this paper make it possible, given data of a readily accessible level of accuracy, to specify quite precisely the appropriate reaction pH, with the advantage over working by analogy or rules of thumb that a satisfactory procedure may be obtained with little or no preliminary experimentation.[29]

As was noted in the introduction, water is not a much-used solvent in current synthetic organic chemistry; this is especially so for carbon–carbon bond forming reactions. This paper specifically points out how knowledge of reaction mechanisms can readily provide practical procedures using water as the solvent, not only for organic synthesis but also for (a) reactions of materials of biological or biochemical interest often best handled in an aqueous medium and, in addition, (b) large-scale industrial preparations where the low toxicity of water, its ready availability in sufficiently pure form at low cost, and its ease of waste disposal all commend its use.

Finally, taking a wider view, we note that the basic method used in this paper, namely, the superposition of pH–rate profiles, is simple, useful, and general and that its application in systems quite different from that described in this paper has the potential for the development of both improvements in synthesis and new insights into reaction mechanisms.

Experimental Section

^{1}H and ^{13}C NMR spectra were run either on a Varian Gemini-200 spectrometer or, respectively, Varian XL200 or XL300 instruments and were taken on solutions in (a) $CDCl_3$ (where not specified otherwise), methanol-d_4 or dimethyl sulfoxide-d_6 calibrated with TMS (Me_4Si) or (b) D_2O calibrated with DSS ($Me_3Si(CH_2)_3SO_3^-Na^+$). Mass spectra were obtained with a Finnigan MAT 8230 instrument and infrared spectra with a Bruker IFS 32 FTIR spectrometer using NaCl plates for (neat) liquid samples and KBr pellets for solids. Melting points were determined on a Kofler Hot Stage and were not corrected. Solvents were evaporated using a Büchi Rotovap connected to a water aspirator; for those experiments (e.g., f_p vs pH) in which the yield of the product was important, the last traces of solvent were removed with a vacuum pump until constant weight or complete absence of solvent peaks in the NMR spectra was attained. In experiments with manual pH control, the pH was measured with a Sargent-Welch 6000 meter equipped with a Fisher all range (pH 1–14) combination electrode; the pH–stat apparatus was a Radiometer PHM 82 meter in conjunction with a TTT80 titrator and an ABU 80 autoburet. Except where otherwise noted, amines and halides were reagent grade commercial materials freshly distilled before use. 1,2-Dimethoxyethane (DME) was dried over CaH_2 and distilled.

pH–Yield Profiles. (a) Benzenesulfonyl Chloride (1). $PhSO_2Cl$ (**1**) (50 μL, 0.392 mmol) was quickly injected from a syringe into a vigorously stirred solution of the amine (**2** or **4**, 0.010 M) in water (500 mL, in a 1-L beaker) previously set at the desired pH with HCl or NaOH. The pH was maintained by manual addition of NaOH solution (~0.5 M for experiments above pH 10, ~0.1 M for lower pH's); reaction times varied from 10 min for high-pH runs to 1 h for low. The reaction mixture was then acidified with dilute H_2SO_4 and extracted with CH_2Cl_2, the extract was dried ($MgSO_4$), and the solvent was carefully removed as described above; the weight of the product so obtained was used to calculate f_p. The identity and purity of the product of each run were checked by comparison of the ^{1}H and ^{13}C NMR spectra with those of authentic specimens of **3** or **5**. The results are shown in Figure 2. In the selectivity experiment, the solution contained both **2** and **4** (each initially 0.010 M), and the relative amounts of the sulfonamides (**3** and **5**) were determined by ^{1}H NMR integration (signals at, respectively, 7.75 and 7.85 ppm); results: Figure 5.

(b) Benzoyl Chloride (6). The experiments with **6** were carried out in the same way as those with **1** except as noted below. (a) With piperidine, **6** (562 mg, 2 mmol, weighed into a vial) was added quantitatively over ~5 min (initially dropwise from a Pasteur pipette, followed by rinsing with the reaction mixture) to a solution of piperidine (3.406 g, 20.0 mmol) in water (1000 mL, in a 2-L beaker). (b) With benzylamine, **6** (141 mg, 0.50 mmol) was similarly added to **4** (536 mg, 5.00 mmol) in water (500 mL, in a 1-L beaker). (c) Reactions were run for 15 min after addition; workup included washing of the CH_2Cl_2 layer with saturated $NaHCO_3$ and water. The results are shown in Figure 3.

(c) Allyl Bromide. *N*-Methylmethanesulfonamide (1.2 g, 20 mmol) was dissolved in water (200 mL) in a three-necked 500-mL round-bottomed flask fitted with a rubber septum, a stopper, and pH electrode (as specified above), with each neck wrapped with Parafilm "M". Added by syringe through the septum were (a) concentrated aqueous NaOH dropwise until the desired pH was reached, (b) allyl bromide (242 mg, 2 mmol), and (c) NaOH dropwise to maintain the pH. After the specified reaction time, NaOH was added to give pH 13.8, and the mixture was extracted with CH_2Cl_2 (6 × 40 mL). The extracts were dried ($MgSO_4$), and the solvent was evaporated: ^{1}H NMR δ 5.75–5.58 (m, 1 H), 5.21–5.10 (m, 2 H), 3.18 (m, 2 H), 2.68 (s, 3 H), 2.67 (s, 3 H); ^{13}C NMR δ 132.0, 118.9, 52.3, 35.6, 33.8; pH, reaction time (h), and yield 10.0, 96, 69 mg (23%); 11.0, 84, 213 mg (71%); 12.0, 18, 267 mg (89%); 13.0, 18, 245 mg (82%); 13.8, 18, 147 mg (49%); pH_{max} 12.2, k_N 2.8×10^{-2} M^{-1} s^{-1} (from best fit).

Preparations under pH-Controlled Schotten–Baumann Conditions. (a) *N*-Benzoylpiperidine. Benzoyl chloride (**6**) (773 mg, 5.50 mmol) was added with vigorous magnetic stirring to a solution of piperidine (426 mg, 5.00 mmol) in water (500 mL, at 25 °C, in a 1-L beaker) previously set at pH 11.4 with 6 M HCl; during the addition and the subsequent 15 min of stirring, the pH of the reaction mixture was kept at pH 11.4 by careful addition of NaOH solution (1 M). The pH was then adjusted to 2 with HCl (6 M) and extracted with CH_2Cl_2 (3 × 60 mL); the extract was washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated, yielding a colorless oil (940 mg, 4.97 mmol, 99%) with ^{1}H and ^{13}C NMR spectra identical to those of an authentic specimen of *N*-benzoylpiperidine. Otherwise identical runs using 5.00 mmol of **6** and reaction times of, respectively, 15 and 30 min gave 924 and 926 mg (98%) of *N*-benzoylpiperidine.

(b) *N*-Benzylbenzamide. Benzoyl chloride (**6**) (5.50 mmol) and benzylamine (**4**) (536 mg, 5.0 mmol) under the same conditions except that (a) the pH was 10.45, (b) **6** was dissolved in DME (5 mL), and (c) the mixture was stirred for 30 min gave **5** as a white solid (1.024 g, 96.9%); use of 5.00 and 6.00 mmol of **6** led to, respectively, 0.914- (87%) and 1.040-g (99%) yields of **5**. At pH 13.0, 5.00 and 6.00 mmol of **6** gave, respectively, 0.412- (39%) and 0.509-g (48%) yields, while at pH 7.5, 5.00 and 6.00 mmol of **6** gave 0.557- (53%) and 0.579-g (55%) yields of **5**. In all runs, the product showed infrared, ^{1}H NMR and ^{13}C NMR spectra and melting points identical to those of an authentic specimen.

(c) *N*-Benzylbenzenesulfonamide. Benzenesulfonyl chloride (**1**) (1.35 mL, 10.5 mmol) was added dropwise with stirring to a solution of benzylamine (**4**) (1.10 mL, 10.0 mmol) in water (100 mL) set at pH 9.6; the pH was kept constant by manual addition of dilute NaOH. After being stirred for an additional 2 h, the solution was extracted with CH_2Cl_2, the extract washed with dilute H_2SO_4, and the solvent evaporated, leaving **3** as a white solid (2.467 g, 99.9%). Three experiments using **1** (10 mmol) and **4** (10.5 mmol) at pH 7.5 (8 h of stirring), 9.6 (1 h of stirring), and 12.0 (30 min of stirring) gave, respectively, 1.707- (69%), 2.370- (96%), and 2.159-g (87%) yields of **5**; addition of **1** in DME solution (5 mL) at pH 9.6 and 12.0 (stirring for 1 h in both runs) gave **5** in yields of 98% and 87%, respectively. In all runs, the ^{1}H and ^{13}C NMR spectra were identical to those of an authentic specimen.

Selective Monoacetylation of 4-Aminobenzylamine (14). The starting material (**14**) was prepared by a modified version of Amsel and Hofmann's[30] route: benzylamine → *N*-benzylacetamide → *N*-(4-nitrobenzyl)acetamide → *N*-(4-aminobenzyl)acetamide (**16**) → 4-aminobenzylamine (**14**). The acetylation (98%) was carried out at pH 9.1 with a 20% excess of acetic anhydride, the nitration (54%) with HNO_3/H_2SO_4 at 10–15 °C, the reduction to the amine (80%) with Sn/HCl at 90 °C for 20 min, and the hydrolysis (**16** → **14**) (86%) with 15% aqueous NaOH at reflux for 2.5 h; workup by extraction with CH_2Cl_2 followed by evaporation of the solvent gave **14** as a brown oil: IR ν_{max} 3353 (s), 3210 (s), 3023 (m), 2923 (m), 2859 (m), 1615 (s), 1516 (s), 1437 (m), 1385 (m), 1281 (s), 1179 (m) cm^{-1}; ^{1}H NMR δ 7.06 (d, 2 H, J = 8 Hz), 6.61 (d, 2 H, J = 8 Hz), 4.1 (br s, 4 H), 3.70 (s, 2 H); ^{13}C NMR δ 145.3, 133.3, 128.1, 115.1, 45.8; MS m/z 122.0840 (calcd for $C_7H_{10}N_2$ 122.0844). An aqueous solution of the brown oil was acidified to pH 2 with 3 M HCl and the water evaporated. The bishydrochloride so obtained was recrystallized from ethanol, with a second crop obtained after addition of ether, as orange crystals (19.3 g): mp >260 °C; IR ν_{max} 3434

(29) A referee informs us that he recalls "learning ... that it is sometimes possible to selectively label nucleophilic residues in proteins by working at a pH close to the pK_a for the target nucleophile". The equivalent statement in the notation of this paper would be $pH_{xmax} \approx pK_x$ and $pH_{ymax} \approx pK_y$. It may be readily seen that this is not *generally* identical to eqs 10 and 11, but does become so in the special cases in which $pK_x = pH_a$ and $pK_y = pH_b$; inspection of Figure 4, for example, shows that pH_{xmax} differs from pK_x and pH_{ymax} from pK_y by, respectively, 1.5 and 0.9 pH units. In practice, this rule provides an indication of where to start in the search for selective reaction, but since pH_{xmax} is sometimes above and sometimes below pK_x, it is our view that such a search, which must include experiments on both sides of pK_x, would be much less efficient than one based on eqs 10 and 11 with even the crudest set of k_x and k_y values.

(30) Amsel, H.; Hofmann, A. W. *Ber.* **1886**, *19*, 1284–1290.

(br m), 2990 (br s), 2872 (br s), 2570 (m), 1595 (m), 1524 (m), 1482 (s), 1391 (m), 1266 (m), 1200 (m), 1103 (m), 1094 (m) cm^{-1}; ^1H NMR (D_2O) δ 7.65 (d, 2 H, J = 9 Hz), 7.52 (d, 2 H, J = 9 Hz), 4.28 (s, 2 H); ^{13}C NMR (D_2O) δ 136.4, 133.3 (2C), 126.5, 45.1; pK_a 3.74 and 9.70, by the method of Parke and Davis.[31]

4-Acetamidobenzylamine (15). Acetic anhydride (314 mg, 3.07 mmol, in 10 × 29-μL portions each injected quickly) was added to a rapidly stirred solution (26 mL) of **14** (501 mg, 2.57 mmol, of the bishydrochloride) in water adjusted to pH 4.15 with NaOH; after each addition, the pH was brought to pH 4.15 with 1.5 M NaOH. The solution was acidified to pH 2.5 and the solvent stripped under reduced pressure with warming. The brownish residue was digested with portions of boiling ethanol until the residual NaCl was white; the ethanol was evaporated, yielding a beige powder shown by ^1H NMR (in D_2O, integration of signals at 4.18 and 4.34, and 2.18 and 2.04 ppm) to be a 95:5 mixture of **15** and **16**. Recrystallization from methanol/2-propanol gave the hydrochloride of **15** (1st crop, 366 mg, mp 237–244 °C, 2nd crop by addition of ether, 64 mg, mp 227–234 °C, with NMR spectra identical to those of the first crop (these spectra showed no sign, i.e., <1%, of **16** in either crop); total 430 mg, 84%). A further recrystallization gave white crystals melting at 242–245 °C: IR (KBr) ν_{max} 3278 (m), 2959 (br s), 2602 (m), 1694 (s), 1665 (s), 1603 (s), 1536 (s), 1418 (m), 1370 (m), 1321 (s), 1260 (m), 831 (m) cm^{-1}; ^1H NMR (D_2O) δ 7.48 (m, 4 H), 4.18 (s, 2 H), 2.18 (s, 3 H); ^{13}C NMR (D_2O) δ 175.7, 140.4, 132.5, 132.1, 124.9, 45.4, 25.6; MS m/z 164.0946 (calcd for $C_9H_{12}N_2O$ 164.0949). To confirm the structure, a sample of the hydrochloride of **15** was converted to the diacetate by treating an aqueous solution at pH 9 with excess acetic anhydride; extraction with CH_2Cl_2 gave *N*-(4-acetamidobenzyl)acetamide, as pale yellow crystals melting at 210–211 °C (after recrystallization from cyclohexane): reported[32] mp 209–210 °C; IR ν_{max} δ 3291 (s), 3202 (m), 3137 (m), 3082 (m), 1647 (s), 1613 (s), 1545 (s), 1516 (s), 1462 (m), 1414 (m), 1372 (m), 1325 (m), 1283 (m), 1270 (m), 831 (m), 741 (m) cm^{-1}; ^1H NMR (D_2O) δ 7.34 ("q", 4 H), 4.34 (s, 2 H), 2.15 (s, 3 H), 2.03 (s, 3 H), (DMSO-d_6) δ 9.97 (br s, 1 H), 8.32 (br t, 1 H, J = 6 Hz), 7.53 (d, 2 H, J = 9 Hz), 7.16 (d, 2 H, J = 9 Hz), 4.18 (d, 2 H, J = 6 Hz), 1.93 (s, 3 H), 1.74 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 169.0, 168.1, 137.9, 134.0, 127.5, 118.8, 50.8, 23.84, 22.47; MS m/z 206.1051 (calcd for $C_{11}H_{14}N_2O_2$ 206.1055).

***N*-(4-Aminobenzyl)acetamide (16).** Acetic anhydride (292 mg, 2.86 mmol, in 10 × 27-μL portions) was added to a solution (26 mL) of the bishydrochloride of **14** (507 mg, 2.60 mmol) in water previously set at pH 11.25, as in the pH 4.15 run, above. The same workup gave as the crude product a beige solid shown by ^1H NMR (in CD_3OD, integration of signals at 4.41 and 4.35, and 2.07 and 2.14 ppm) to be a 9:1 mixture of the hydrochloride of **16** and the diacetate; recrystallization from ethanol/ether gave the hydrochloride of **16** as beige crystals (444 mg, 85%): mp 173–177 °C, IR ν_{max} 3289 (s), 2892 (br s), 2606 (s), 1642 (s), 1603 (s), 1563 (s), 1514 (s), 1424 (m), 1374 (m), 1032 (m) cm^{-1}; ^1H NMR (D_2O) δ 7.41 (m, 4 H), 4.41 (s, 2 H), 2.05 (s, 3 H) (no sign (<1%) of either **15** or the diacetate); ^{13}C NMR (D_2O) δ 176.9, 141.9, 131.4 (2C), 125.9, 45.2, 24.6; MS m/z 164.0948 (calcd for $C_9H_{12}N_2O$ 164.0949). The structure was confirmed by adding a portion of this hydrochloride to an NMR tube containing an authentic specimen of **16** (from the reduction of 4-nitrobenzylamine in the original preparation of **14**) in D_2O/DCl; all ^1H NMR shifts and relative intensities were unchanged by the addition.

C-Allylation of Acidic Ketones. Preparative allylations were carried out at room temperature using the same procedure as that described above for the pH–yield runs with allyl bromide and *N*-methylmethanesulfonamide, except that (a) the reaction mixture was adjusted to pH 7 before extraction with CH_2Cl_2 and (b) in one run, as noted, pH was controlled by pH-stat. The pK_a's of **18**, **20**, and **21** (Scheme III) were determined by potentiometric titration; that of **12** (Scheme I) was estimated from the reported[33] value of 11.11 in 50% ethanol, taken with a solvent correction of ~0.6 pK units estimated from the following pK_a's: **20**, 9.45 (H_2O) and 10.09 (50% EtOH[31]); $CH_3COCH_2SO_2CH_3$, 9.90 (H_2O[33]) and 10.48 (50% EtOH[33]). Materials: **9** and **11**, by the Stork enamine procedure;[34] **12**, mp 87–88 °C, reported[35] mp 87 °C, from PCC oxidation of *trans*-2-(phenylsulfonyl)cyclohexanol, obtained from cyclohexene and benzenesulfenyl chloride following the procedure reported[36] for the methylsulfonyl analogue; **20**, from sodium benzenesulfinate and chloroacetone, mp 57 °C, reported[37] mp 56–57 °C; **17** and **22**, from Aldrich Chemical Co., the former redistilled before use.

(a) 2-Acetyl-2-allylcyclohexanone (10). 2-Acetylcyclohexanone (**9**) (1.75 g, 12.5 mmol) in water (250 mL) at pH 10.8 with allyl bromide (3.03 g, 25 mmol) for 2 h gave a colorless oil shown by its ^1H and ^{13}C NMR spectra to consist of **10**, 2-allylcyclohexanone (**11**), and unreacted (**9**) in the ratio 93:5:2, total yield 2.2 g (99%): ^1H NMR δ **10** 5.58–5.35 (m, 1 H), 4.88 (m, 2 H), 2.06 (s, 3 H), 2.52–1.30 (m, 10 H); ^{13}C NMR δ **10** 209.4, 206.1, 132.7, 118.1, 67.1, 41.2, 38.2, 33.6, 26.6, 25.8, 21.6, **11** 211.8, 136.2, 115.7, 49.6, 41.4, 33.2, 32.8, 27.3, 24.3. Three other runs with changes only as noted gave the following results: (a) reaction time of 1 h, with either the same or doubled concentrations of reactants, gave **10** with about 20% of unreacted **9** plus a trace of **11**; (b) reaction time of 48 h with Na_2CO_3 (2.5 g) buffering gave only **11** (1.7 g, 99%).

(b) 2-Allyl-2-(phenylsulfonyl)cyclohexanone (13). The same procedure with 2-(phenylsulfonyl)cyclohexanone (**12**) (1.785 g, 7.5 mmol) and allyl bromide (1.82 g, 15 mmol) in water (150 mL) at pH 12.0 for 10 h gave **13** as white crystals: mp 133–134 °C (1.98 g, 95%); ^1H NMR δ 7.57–7.49 (m, 5 H), 5.58–5.35 (m, 1 H), 5.18 (m, 2 H), 3.15 (m, 2 H), 2.81–1.58 (m, 8 H); ^{13}C NMR δ 205.3, 135.3, 134.3, 131.6, 130.3, 128.9, 120.6, 75.23, 41.4, 37.9, 29.6, 25.0, 21.2; MS m/z 278.0975 (calcd for $C_{15}H_{18}O_3S$ 278.0977). The same reaction, except for lack of pH control after the start of the reaction and a reaction time of 75 h, gave a product consisting of 75% of **13** with 25% unreacted **12**.

(c) 3-(2-Propenyl)-2,4-pentanedione (18). Acetylacetone (**17**) (1 g, 10 mmol) and allyl bromide (2.4 g, 20 mmol) in water (40 mL) at pH 8.0 gave a liquid product shown by NMR to consist of **18** (85%), the diallylated product (**19**) (5%), and unreacted **17** (10%): ^1H NMR δ **18** (keto form) 5.8–4.8 (m, 3 H), 3.59 (t, 1 H), 2.44 (m, 2 H), 2.01 (s, 6 H), **18** (enol) 5.0–4.8 (m, 3 H), 3.63 (m, 2 H), 1.92 (s, 6 H); ^{13}C NMR δ **18** (keto form) 203.2, 134.0, 117.0, 67.4, 31.9, 29.0, **18** (enol) 191.1, 135.5, 114.5, 106.8, 30.8, 22.5; **19** 205.1, 131.8, 118.8, 69.8, 34.7, 26.8; MS m/z 140.0839 (calcd for $C_8H_{12}O_2$ 140.0837).

(d) 3-(Phenylsulfonyl)hexen-2-one (21). (Phenylsulfonyl)acetone (**20**) (3.96 g, 20 mmol) and allyl bromide (4.84 g, 40 mmol) in water (200 mL) at pH 10.0 for 16 h (in the pH–stat apparatus) gave **21** as an oil (4.52 g, 95%): ^1H NMR δ 7.9–7.48 (m, 5 H), 5.55 (m, 1 H), 5.00 (m, 2 H), 4.15 (t, 1 H), 2.60 (m, 2 H), 2.32 (s, 3 H); ^{13}C NMR δ 199.5, 136.3, 134.4, 131.6, 129.2, 129.1, 119.0, 74.8, 31.8, 30.9; MS m/z 238.0666 (calcd for $C_{12}H_{14}O_3S$ 238.0664). When the reaction was carried out for 44 h with no pH control after the start of the reaction, the product was an 80:20 mixture of **21** and **20**.

(e) *tert*-Butyl 2-Acetyl-4-pentenoate (23). *tert*-Butyl acetoacetate (**22**) (3.16 g, 20 mmol) and allyl bromide (4.84 g, 40 mmol) in water (200 mL) buffered with Na_2CO_3 and $NaHCO_3$ (2 g each) at pH 10.5 for 5 h with pH control and an additional 5 h without gave **23** as an oil (3.8 g, 96%): ^1H NMR δ 5.84–5.64 (m, 1 H), 5.15–5.0 (m, 2 H), 3.42 (t, 1 H), 2.53 (m, 2 H), 2.22 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR δ 202.5, 168.2, 134.3, 116.9, 81.7, 60.0, 32.0, 28.8, 27.7; MS m/z 198.1252 (calcd for $C_{11}H_{18}O_3$ 198.1256).

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