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Nucleophilic Attack vs General Base Assisted Hydrolysis in the Reactions of Acetic Anhydride with Primary and Secondary Amines. pH–Yield Studies in the Recognition and Assessment of the Nucleophilic and General Base Reactions[1]

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The reaction of a set of primary and secondary amines with acetic anhydride in water at 25 °C gave variable yields of the *N*-substituted acetamide in seven of the eight amines studied. The yield of the amide as a function of pH revealed the incursion in most cases of a general base assisted hydrolysis of the acetic anhydride by the amine. From the pK_a's of the amines and k_w and k_{OH} for acetic anhydride (the specific rates for the reaction of the anhydride with water and hydroxide, respectively), both k_{DN} (for the formation of the acetamides) and k_{GB} (for the general base assisted hydrolysis) may be readily evaluated by fitting the pH–yield data to pH–yield or pH–product ratio profiles. The reactions of ethyl chloroformate with aniline and benzylamine in water also showed the presence of the general base assisted reaction. It is concluded that (a) pH–yield data provide a new way of showing the existence of a general base assisted hydrolysis in the presence of a direct nucleophilic displacement reaction, (b) the general base promoted reaction is sufficiently prevalent that it would be prudent to check specifically for its presence in any investigation of mechanisms of acyl transfer in water, and (c) until the extent of general base promoted hydrolysis can be predicted adequately, the possibility of such a reaction makes it difficult to predict yields of the products of the direct attack, and hence just how suitable a medium water may be for a particular preparative acyl transfer reaction.

We recently described[2] a simple procedure for estimating the optimal pH for carrying out reactions between a basic nucleophile (Nu) and a hydrolyzable electrophile (E) in water. We showed, for example, that Schotten–Baumann benzoylation of benzylamine at pH 10.4 using a 10% excess of benzoyl chloride gave a 98% yield of *N*-benzylbenzamide and that both higher and lower pH's gave lower yields. The optimal pH (i.e. pH_{max}) is given[2,3] by eq 1, which depends on two assumptions: (a) that the pseudo-first-order rate constant $k_{\psi o}$ for the hydrolysis of the electrophile is given by the following rate law, $k_{\psi o} = k_w + k_{OH}[OH^-]$, and (b) that the pseudo-first-order rate constant $k_{\psi N}$ for reaction of the nucleophile with the electrophile is given by $k_{\psi N} = k_{DN}[Nu]$, and hence the pseudo-first-order rate constant for the total consumption of E in the presence of Nu is given by eq 2. Equation 2 readily yields eq 1 and

$$\text{pH}_{\text{max}} = {}^1/_2(\log k_w/k_{OH} + \text{p}K_w + \text{p}K_a) \qquad (1)$$

$$k_{\psi T} = k_{\psi o} + k_{\psi N} = k_w + k_{OH}[OH^-] + k_{DN}[Nu] \qquad (2)$$

also eq 3, which describes the pH–yield profile, i.e. the (fractional) yield of the nucleophile–electrophile reaction product as a function of [H$^+$] (and hence pH) under pseudo-first-order conditions.

$$f_p = k_{\psi N}/k_{\psi T} = \frac{k_{DN}\text{Nu}_T K_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+] + k_{DN}\text{Nu}_T K_a/([H^+] + K_a)} \qquad (3)$$

All of the reactions described in the previous paper[2] conformed to eq 1, but not all with eq 3. Two in particular, namely the reaction of benzenesulfonyl chloride with aryloxides and that of acetic anhydride with amines, showed clear deviations ascribable to the consumption of a small portion (usually <10%) of the electrophile by hydrolysis assisted by the nucleophile acting as a general base.

This paper presents our results with the acetic anhydride–amine reactions and also describes a brief investigation of the reactions of ethyl chloroformate with amines in water, a reaction which also shows the general base assisted hydrolysis. This study (a) illustrates the usefulness of pH–yield profiles for identifying features of mechanism, (b) shows the generality and variability of general base catalysis under the conditions of acyl transfer in water, and (c) points up the importance of general base promoted reactions as a currently hard-to-predict feature that may limit the use of water as a solvent for such reactions.

Results and Discussion

Acetic Anhydride. The experimental pH–yield profile for the reaction of acetic anhydride with aniline in water at 25 °C is shown by the points in Figure 1. The broken lines are calculated from eq 3 using reported values[4] for k_w and k_{OH}, and two different values for k_{DN}. It is apparent that no value of k_{DN} with eq 3 will give a line in full accord with the experimental points, i.e. eq 3 and hence eq 2 do

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[•] Abstract published in *Advance ACS Abstracts*, February 1, 1994.

(1) Nucleophile-Electrophile Reactions in Aqueous Media. Part 2. Reference 2 is to be considered as part 1 in this series.

(2) King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3028–3033.

(3) Symbols (i) Rate constants: k_w hydrolysis of the electrophile (E) by water; k_{OH}, hydrolysis of E by hydroxide ion; k_{DN}, direct nucleophilic reaction of the nucleophile (Nu) with E to form the amide (or urethane); k_{GB}, hydrolysis of E with general base assistance from Nu; k_N, total reaction of E with Nu $(=k_{DN} + k_{GB})$; (ii) $K_w = [H^+][OH^-]$; K_a, acid dissociation constant of NuH$^+$ (the conjugate acid of Nu, $\text{Nu}_T = [\text{Nu}] + [\text{NuH}^+]$.

(4) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837–846. See also: Castro, C.; Castro, E. A. *J. Org. Chem.* **1981**, *46*, 2939–2943.

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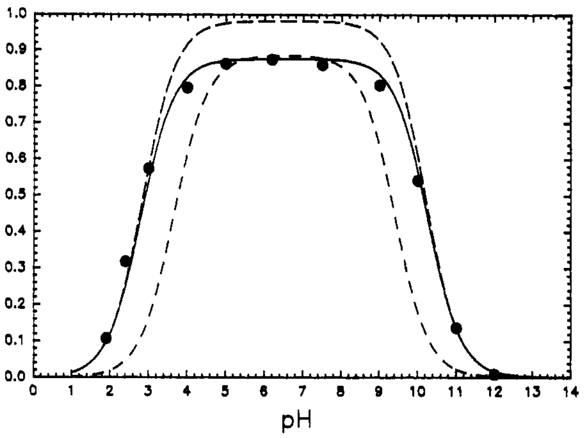

Figure 1. pH–yield profile for the reaction of acetic anhydride (C_o 0.001 M) with aniline (C_o 0.01 M) at room temperature: dashed lines, calculated from eq 3 (no general base catalysis) using k_w 2.80 × 10^{-3} s^{-1}, k_{OH} 970 M^{-1} s^{-1}, k_{DN} values of 15.0 and 2.1 M^{-1} s^{-1} (outer and inner curves, respectively); solid line, calculated from eq 5 with k_{DN} 15.0 and k_{GB} 2.1 M^{-1} s^{-1}; points, experimental yields.

Table 1. Rate Constants for the Reaction of Acetic Anhydride with Amines in Water

amine (pK_a)	$10^{-3}k_{DN}$[a] (M^{-1} s^{-1})	$10^{-3}k_{GB}$[a] (M^{-1} s^{-1})	$10^{-3}k_N$[b] (M^{-1} s^{-1})
$(CH_3)_2CHCH_2CH_2NH_2$ (10.6)	10.0	~0.4	10.4
$C_6H_5CH_2NH_2$ (9.34)	2.20	0.20	2.48
$C_6H_{11}NH_2$[c] (10.64)	2.10	0.17	2.25
$(CH_3)_3CNH_2$ (10.55)	0.056	0.014	0.068
$C_6H_5NH_2$ (4.6)	0.0155	0.0019	0.0179.
$(CH_2)_5NH$[d] (11.22)	51.6	≤0.25	51.7
$(C_2H_5)_2NH$ (10.98)	1.25	0.05	1.36
$[(CH_3)_2CH]_2NH$ (11.05)	≤0.01	(0.03)[b]	0.031

[a] k_{DN} and k_{GB} were obtained from a best fit of the pH–yield profile. [b] From rate measurements. [c] Cyclohexylamine. [d] Piperidine.

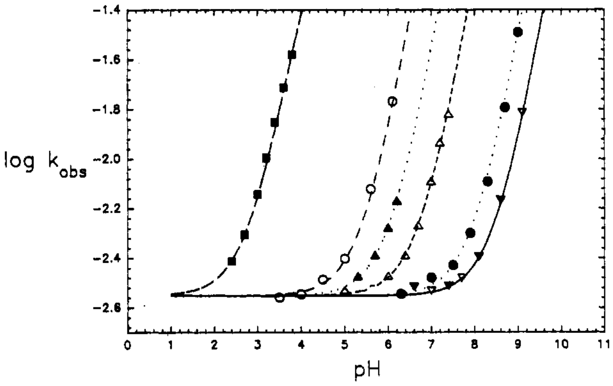

Figure 2. pH–rate profiles for the reaction of acetic anhydride with primary amines in 0.05 M KCl at 25.0 °C. Lines were calculated from eq 6 and the k_N values in Table 1. Symbols are as follows: points, experimental; squares, aniline; open circles, benzylamine; filled triangles, 3-methylbutylamine; open triangles, cyclohexylamine; filled circles, *tert*-butylamine; open inverted triangles, no added amine 0.001 M NaOAc added; filled inverted triangles, no added amine (0.05 M KCl only).

not adequately describe the acetic anhydride–aniline reaction. It should be noted, however, that eq 1 predicts pH_{max} in good agreement with observation.

General base promotion of hydrolysis of acyl transfer by nucleophiles in the medium has been recognized for many years,[5] although the number of carefully studied examples appears to be small. Addition to eq 2 of the term $k_{GB}[Nu]$ for a general base assisted hydrolysis of the electrophile gives eqs 4 and 5. From eq 5 we may readily

$$k_{\psi T} = k_w + k_{OH}[OH^-] + k_{GB}[Nu] + k_{DN}[Nu] \qquad (4)$$

$$f_p = k_{DN}[Nu]/k_{\psi T}$$

$$= \frac{k_{DN}Nu_TK_a/([H^+] + K_a)}{k_w + k_{OH}[OH^-] + (k_{GB} + k_{DN})Nu_TK_a/([H^+] + K_a)} \qquad (5)$$

find (e.g. by manual curve fitting) values for k_{GB} and k_{DN} that yield the solid line (in Figure 1) which fits the points within experimental uncertainty.

To test this proposal we turned to rate measurements. Using the pH-stat technique we found pseudo-first-order behavior (to >80% reaction) for the reaction of acetic anhydride in water with or without amines. The pH–rate profile calculated for the simple hydrolysis of acetic anhydride using the reported[4] k_w and k_{OH} values is shown by the solid line in Figure 2; the seven inverted triangles give values for runs carried out to ensure that (a) our measurements agreed with previous results and (b) the low concentration of acetate anion (which is produced in the reaction and which is known to show weak general base assistance to the hydrolysis[6]) had no detectable influence on the rate. The closed squares in Figure 2 are our experimental points for the reaction in the presence of aniline; the line through these points is obtained from the average of the values of k_N obtained from each of these points using eq 6. Obviously eqs 4 and 6 become identical

$$k_{obs} = k_w + k_{OH}[OH^-] + k_N[Nu] \qquad (6)$$

if $k_N = k_{GB} + k_{DN}$; as may been seen in Table 1, the k_N of 18 M^{-1} s^{-1} (as obtained from the rate data in Table 1) and $k_{GB} + k_{DN} = 1.9 + 15.5 = 17.4$ M^{-1} s^{-1}, (from the pH–yield profile) are in good accord; i.e. the rate measurements are quantitatively consistent with a 2-fold mode of action of aniline with acetic anhydride with the aniline acting both as a nucleophile and as general base assisting hydrolysis.

To test the generality of this picture, pH–yield and pH–rate profiles for four other representative primary amines and three secondary amines have been obtained similarly (see Figures 2–5); Table 1 summarizes the rate constants. With most of these amines both direct nucleophilic attack and general base terms were required to obtain satisfactory agreement between calculated curves and experimental points. With 3-methylbutylamine and piperidine, however, the curves calculated without the general base term

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(5) Reviews: (a) Satchell, D. P. N; Satchell, R. S. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; John Wiley and Sons, Ltd.: London, 1969; Chapter 9, pp 375–452. (b) Talbot, R. J. E. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Chapter 3, pp 209–293. (c) Satchell, D. P. N.; Satchell, R. S. In *Supplement B The Chemistry of Acid Derivatives*; Patai, S., Ed.; John Wiley and Sons, Ltd.: Chichester, England, 1992; Volume 2, Part 1, Chapter 13, pp 747–802.

(6) (a) Kilpatrick, M. *J. Am. Chem. Soc.* **1928**, *50*, 2891–2902. (b) Butler, A. R.; Gold, V. *J. Chem. Soc.* **1961**, 2305–2312. (c) Johnson, S. L. *J. Am. Chem. Soc.* **1962**, *84*, 1729–1734.

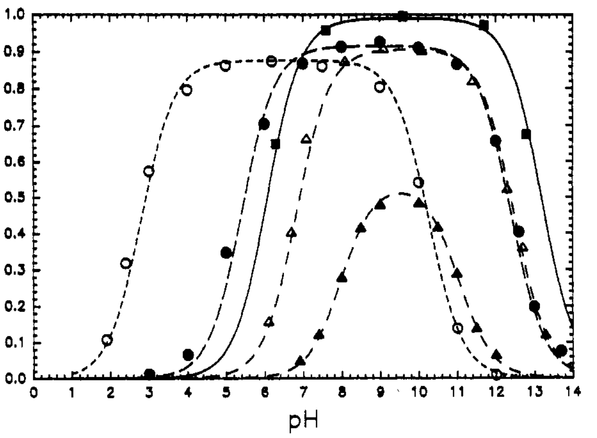

Figure 3. pH–yield profiles for the reaction of acetic anhydride (C_o 0.001 M) with primary amines (C_o 0.01 M): open circles, aniline; filled circles, benzylamine; squares, 3-methylbutylamine; open triangles, cyclohexylamine; filled triangles, *tert*-butylamine. Lines were calculated from eq 5 and rate constants in Table 1; points are experimental values.

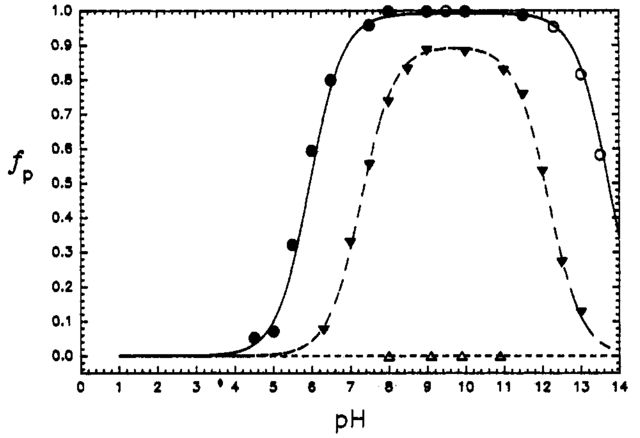

Figure 4. pH–yield profiles for the reaction of acetic anhydride (C_o 0.001 M) with secondary amines (C_o 0.01 M): circles, piperidine (open, Ac_2O added neat; closed, Ac_2O added in DME solution); inverted triangles, diethylamine; open triangles, *N*,*N*-diisopropylamine. Lines were calculated from eq 5 and rate constants in Table 1; points are experimental values.

(eq 3) gave a passable fit although this was improved if a relatively small k_{GB} term was included; it is clear that with these bases the intervention of general base promotion of hydrolysis is not certain and the values of k_{GB} given in Table 1 are highly approximate.

N,*N*-Diisopropylamine, on the other hand, gave no sign of formation of any *N*,*N*-diisopropylacetamide. An authentic sample was found to be stable to the conditions of reaction and workup, and we conclude that the direct nucleophilic attack of diisopropylamine on acetic anhydride in water under these conditions is simply too slow to compete detectably with the hydrolytic reactions. From the pH–rate profile *N*,*N*-diisopropylamine would appear to have a weak but definite catalytic effect on the consumption of acetic anhydride; this is assigned to a weak general base assistance of hydrolysis.

In summary, the eight amines in the present study range in their reaction patterns from (a) almost complete nucleophilic attack with little (or no) general base reaction, through (b) a combination of nucleophilic attack and general base assistance with the former predominating (the most common situation), to (c) exclusive, although sluggish, general base assisted hydrolysis.

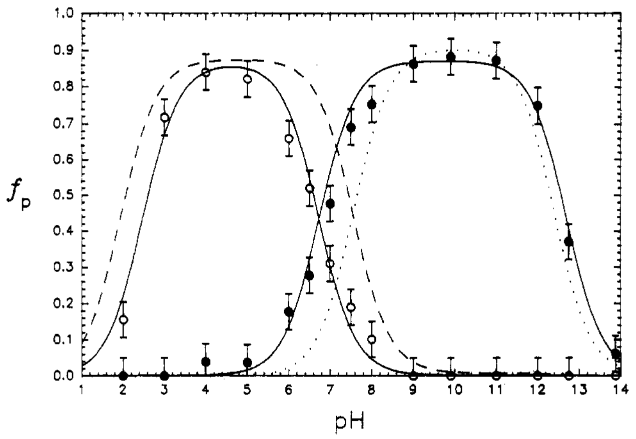

Figure 5. pH–yield profiles for the reactions of acetic anhydride (C_o 0.001 M) with (a) *p*-aminobenzylamine (**1**) (C_o 0.01 M) and (b) a model mixture of aniline and benzylamine (each C_o 0.01 M) (calculated yields): open circles, **1** → **2** (experimental values); filled circles **1** → **3** (experimental values); accompanying solid line calculated from versions of eqs 8 and 9 of ref 2 (expanded to include the k_{GB} terms), using $(k_{DN})_x$ 4.5 M^{-1} s^{-1}, $(k_{GB})_x$ 0.4 M^{-1} s^{-1}, $(k_{DN})_y$ 4.2 × 10^3 M^{-1} s^{-1}, $(k_{GB})_y$ 6.0 × 10^2 M^{-1} s^{-1}; dashed line, aniline → acetanilide and dotted line, benzylamine → *N*-benzylacetamide, both calculated similarly using the k_{DN} and k_{GB} values in Table 1.

Examination of the rate constants in Table 1 reveals further points. As expected, the highest values of k_{DN} are found with amines with the highest pK_a's, but it is also quickly apparent that basicity is not the only factor controlling reactivity; 3-methylbutylamine, cyclohexylamine, and *tert*-butylamine, with pK_a's of 10.6, 10.64, and 10.55, have k_{DN}'s of 1.0 × 10^4, 2.1 × 10^3, and 56 M^{-1} s^{-1}, respectively. It is reasonable to assign these differences to steric effects, i.e. slowing of the reaction by increased nonbonding interactions as the alkyl groups get bulkier.

It has long been a feature of discussions of nucleophilic vs general base promoted reactions that the former are regarded as much more sensitive to steric effects than the latter.[7] It is perhaps surprising to find that the k_{GB}'s for cyclohexylamine and *tert*-butylamine are 170 and 14 M^{-1} s^{-1}, respectively. The ratio (12.1) is less than that for the corresponding k_{DN}'s (37.5) but is still sizeable. It is tempting to suggest that the role of the amine in this case may be more than simply to assist in the removal of the proton from the attacking water molecule,[8] conceivably also, for example, by hydrogen bonding of the incipient $\delta-$ on the oxygen with the hydrogen on the nitrogen.

As was described in our previous paper[2] we have used the reaction of acetic anhydride with a diamine to demonstrate the value of pH control in achieving selective reaction at one electrophilic center or the other. The specific reaction was the conversion of *p*-aminobenzylamine (**1**) into either *p*-acetamidobenzylamine (**2**) at pH 4.15 (84% yield) or *N*-(*p*-aminobenzyl)acetamide (**3**) at pH 11.25 (85% yield). The pH yield profile for the reaction of **1** with acetic anhydride in water is shown in Figure 5. Again one notes that satisfactory agreement between calculated[9] and observed curves requires inclusion of k_{GB} terms of roughly 10–15% of the k_{DN} values.

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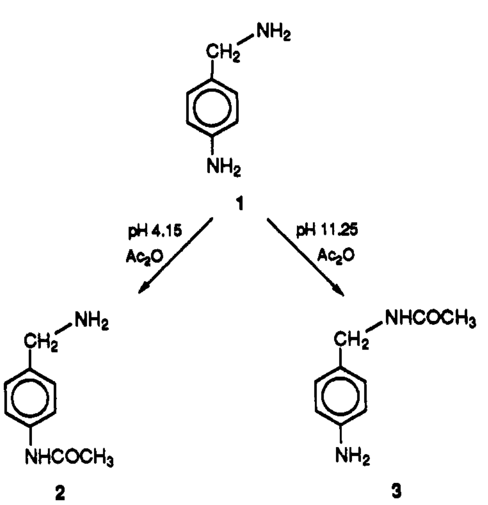
[7] See, for example: Johnson, S. L. *Adv. Phys. Org. Chem.* **1967**, *5*, 237–330 (see especially p 283).

[8] As has been suggested, for example, by Johnson.[6c]

[9] The lines were calculated using eqs 8 and 9 of ref 2 along with pK_a's of 3.74 and 9.70 for **1** (ref 2) and the k_{DN} and k_{GB} values shown in Figure 5 (from best fits to the curves).



Also shown in Figure 5 (broken lines) are the calculated pH–yield profiles for a simple model mixture of equimolar amounts of aniline and benzylamine reacting with acetic anhydride, obtained in the same way from the parameters in Table 1. The broken and solid curves are basically similar, indicating that the model system is a serviceable guide for synthetic experiments designed to prepare either of the monoacetylated derivatives of 1 by reaction with acetic anhydride. Perhaps the most notable difference between 1 and the model mixture is that the acetylation of the aromatic NH_2 in 1 has a narrower pH range and that of the aliphatic NH_2 a wider range than that of the model counterparts, aniline and benzylamine, respectively. This result would appear to reflect primarily the lower k_{DN} value for the conjugate acid of 1 ($^+NH_3CH_2C_6H_4NH_2$) relative to aniline (4.5 vs 15.5 $M^{-1}\ s^{-1}$) and the larger k_{DN} for the aliphatic NH_2 in 1 relative to benzylamine (4.2×10^3 vs $2.20 \times 10^3\ M^{-1}\ s^{-1}$); such a trend in k_{DN}'s appears reasonable in the light of the pK_a values: 3.74 for $^+NH_3CH_2C_6H_4NH_2$ vs 4.60 for aniline and 9.70 for 1 vs 9.34 for benzylamine.

Ethyl Chloroformate. The pH–rate profile for the hydrolysis of ethyl chloroformate in 0.05 M NaCl at 25 °C corresponded to the rate law $k_{\psi o} = k_w + k_{OH}[OH^-]$ with k_w $4.85 \times 10^{-1}\ s^{-1}$ and k_{OH} 40.6 $M^{-1}\ s^{-1}$. Reported values of k_w at 25 °C in water without added salts range[10] from 3.63×10^{-4} to $3.87 \times 10^{-4}\ s^{-1}$; there appear to be no previous reports of k_{OH} for ethyl chloroformate. Addition of aniline or benzylamine led to a rapid increase in the disappearance of ethyl chloroformate; the pseudo-first-order rate constants so obtained conformed to eq 6 with k_N values of, respectively, 17.6 and 137 $M^{-1}\ s^{-1}$.

The pH–yield profiles for the reactions with benzylamine and aniline are shown in Figure 6. In each case satisfactory agreement between the calculated curves and the observed points required inclusion of a minor contribution from the general base term. The best values of k_{DN} and k_{GB} so obtained 14.4 and 3.2 $M^{-1}\ s^{-1}$ for aniline and 123 and 14 $M^{-1}\ s^{-1}$ for benzylamine.

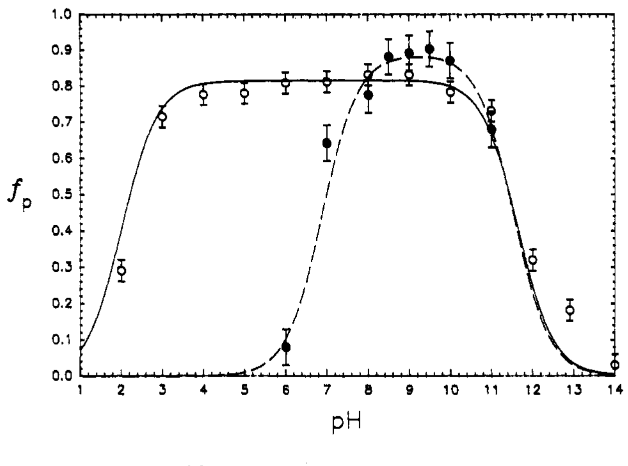


Figure 6. pH–yield profiles for the reactions of ethyl chloroformate (C_o 0.001 and 0.0001 M, respectively) with aniline (C_o 0.01 M) and benzylamine (C_o 0.001 M) at room temperature.

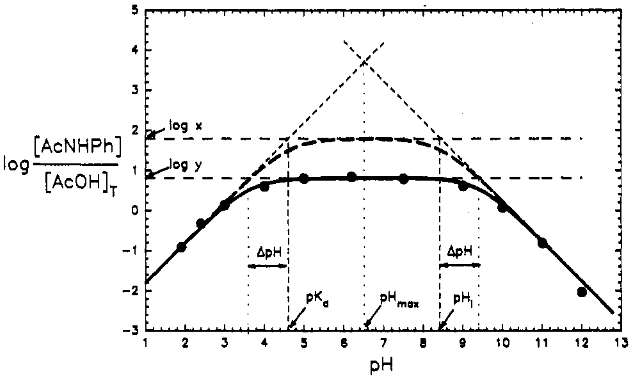


Figure 7. pH–product ratio profiles for the reaction of acetic anhydride with aniline with and without general base catalysis: heavy dashed line, (hypothetical) reaction without general base catalysis (calculated from eq 8, k_{DN} 15.0 $M^{-1}\ s^{-1}$); dotted line, (actual) reaction with general base catalysis (from eq 9, k_{DN} 15.0, k_{GB} 2.1 $M^{-1}\ s^{-1}$); light dashed lines: slope = 1, from $r = k_{DN}Nu_TK_a/k_w[H^+]$; upper horizontal line from $r = k_{DN}Nu_T/k_w$; slope = −1 line from $r = k_{DN}Nu_T[H^+]/k_{OH}K_w$; lower horizontal line from $r = k_{DN}Nu_T/(k_w + k_{GB}Nu_T)$; points, experimental (from $r = f_p/(1 - f_p)$); $[AcOH]_T = [AcOH] + [AcO^-]$.

Presentation of Yield Data by pH–Product Ratio Profiles. Up to this point we have used pH–yield profiles, i.e. plots of f_p (the yield of product in mole fractions) vs pH, to present the variation of product with pH. Among the general advantages of this form are (a) it represents the simplest, most direct presentation of data, (b) it is particularly readily comprehended, (c) the errors in the points tend to be comparable, thereby facilitating curve fitting, and (d) in cases in which more than one pathway yields the product, the yield of each pathway can be presented and the total found by the sum of the yields of the separate routes. It can also, however, be useful to express the yields in terms of the product ratio, r, defined by eq 7. Under pseudo-first-order conditions and in the

$$r = \frac{[\text{nucleophilic attack product}]}{[\text{hydrolysis product}]} = f_p/(1 - f_p) \qquad (7)$$

absence of the general base assisted hydrolysis, r is given by eq 8. A plot of log r vs pH takes the form shown in

$$r = \frac{k_{DN}Nu_TK_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+]} \qquad (8)$$

Figure 7 by the dashed line, which may be regarded as assembled from three lines of slopes 1, 0, and −1, respectively, with rounded off intersections (see Figure 7). It may be readily shown that the pH value of the two points of intersection of these (tangential) straight lines

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[10] Queen, A. *Can. J. Chem.* 1967, *45*, 1619–1629.

are at the pK_a (of NuH^+) and the pH_i (of E).[11] In the example shown in Figure 7, $pK_a < pH_i$ and hence it is the intersection at lower pH which corresponds to the pK_a and the intersection at higher pH which corresponds to pH_i. For those reactions in which $pK_a > pH_i$ this picture is reversed, and for the special case in which $pK_a = pH_i$ then log *r* takes the shape of a (rounded) inverted V with the point of intersection at pH = $pK_a = pH_i$.

When general base catalysis of hydrolysis by Nu is also present *r* is given by eq 9. The horizontal line is *lowered*

$$r = \frac{k_{DN}Nu_TK_a/([H^+] + K_a)}{k_w + k_{OH}K_w/[H^+] + k_{GB}Nu_TK_a/([H^+] + K_a)} \quad (9)$$

while the two sloped lines are unchanged; the result is the solid line in Figure 7. The basic shape is the same as the dashed line but the intersections are no longer at pK_a and pH_i. Instead the pH at the low pH intersection is lowered (by $|\Delta pH|$) and that at the high pH intersection raised (also by $|\Delta pH|$); in the plot of log *r* vs pH for the reaction of aniline with acetic anhydride shown in Figure 7, the intersections are at pH 3.62 and 9.42 rather than at the pK_a and pH_i values of 4.60 and 8.44, respectively.

A practical result of this mode of presentation is that a simple plot of log *r* vs pH will disclose the presence or absence of general base catalysis of the hydrolysis by Nu provided one knows *either* the pK_a of NuH^+ *or* the pH_i for E (and the reaction has the rate law given by eq 4).[13] No rate measurements are required.

Concluding Comments. The work described in this paper has its origins in the application of reaction mechanisms to organic synthesis. The results are relevant to both topics.

In the field of mechanisms we show how pH–yield information, either in the form of pH–yield profiles or pH–product ratio profiles may be used to ascertain the presence or absence of general base assistance of hydrolysis by the nucleophile (Nu), provided one knows (minimally) either the pK_a (of NuH^+) or pH_i (for E). Where k_w and k_{OH} for the hydrolysis of E and the pK_a are known, the pH–yield data readily give k_{DN} and k_{GB} without any rate measurements involving the nucleophile being needed, although where these are readily obtained they would be useful in verifying the pH–yield results. The method is, of course, restricted to nucleophile–electrophile reactions which give products so constituted that the total amount may be quantitatively determined, either by simple extraction from the final reaction mixture, as in the examples described here, or by some other procedure.[14]

We have found general base assisted hydrolysis with both of the electrophiles studied in this investigation and have previously noted it also in the reactions of benzenesulfonyl chloride with aryloxides.[2,15] On the other hand, the reactions of benzoyl chloride with benzylamine or piperidine[2] and of benzenesulfonyl chloride with aniline, benzylamine, diethylamine, or *tert*-butylamine[16] show no sign of the general base promoted hydrolysis. Taken altogether, however, these results suggest that any investigation of the mechanism of the reaction of a nucleophile with a hydrolyzable electrophile in water must simply be regarded as incomplete if it lacks a quantitative determination of the product composition to assign the role (if any) of the general base assisted hydrolysis.

Looked at from the viewpoint of organic synthesis, the present results point to a factor that may seriously affect yields of nucleophile–electrophile reactions in water. When one seeks to maximize the yield of the product from the Nu–E process, any general base assisted hydrolysis simply wastes the electrophile. Where the latter is acetic anhydride, which is relatively cheap, the problem may often be readily solved by adding an appropriate excess of the electrophile, but with other electrophiles the answer may not be as simple and the intervention of the general base reaction may preclude the use of water as a practically useful solvent. A method for predicting when the general base assisted hydrolysis will or will not manifest itself would be a valuable asset for predicting the outcome of synthetic reactions in aqueous media.

Experimental Section

General. Instrumentation and general procedures have been described elsewhere.[2,17] The amines were commercial materials distilled from CaH, except for the piperidine used in the kinetic experiments, which was purified as described below. Commercial Ac_2O was refluxed over Mg turnings and fractionally distilled, the fraction collected at 140–141 °C being used. Commercial EtOCOCl was fractionally distilled.

Authentic Specimens. The various acetamides (with physical properties in accord literature values) were prepared by pH-controlled Schotten–Baumann reactions of Ac_2O and the amines at pH's prescribed by eq 1; yields (except for CH_3CONH-*t*-Bu, 80%, and CH_3CON-*i*-Pr_2, 0%) varied from 94 to 99.8%; details are given elsewhere.[18] *N,N*-Diisopropylacetamide was prepared in 98% yield by the reaction of *N,N*-diisopropylamine (30 mmol), Et_3N (36 mmol), and CH_3COCl (36 mmol) in ether (20 mL) at room temperature. The ethyl phenyl- and benzylcarbamates were prepared from the amines and EtOCOCl in H_2O–THF (80:20) buffered, respectively, with potassium hydrogen phthalate and Na_2CO_3 (98 and 97% yields); ^1H and ^{13}C NMR and IR spectra and exact mass values were in accord with the structures.

pH–Product Ratio Measurements: (a) Acetic Anhydride with Monoamines. Ac_2O was injected from a 1-mL syringe into a solution of amine in water (1000 mL) at 25 °C which had previously been set at the specified pH value with aqueous HCl or NaOH (6 M). The reaction was allowed to run to completion with monitoring of the pH with a Sargent-Welch pH 6000 digital

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[11] The pH_i of an electrophile is defined as the pH at which the rates of the uncatalyzed and hydroxide promoted hydrolyses are equal;[2] one may readily show that $pH_i = \log k_w/k_{OH} + pK_w$. In the present context pH_i is a useful intrinsic property of the electrophile, which, along with the pK_a of the nucleophile, determines (a) pH_{max} [which equals $^1/_2(pH_i + pK_a)$], as well as (b) the shape of the log *r* vs pH curve, as discussed at this point. A table giving pH_i values of 25 representative electrophiles may be found in ref 2. More (denoted as I_{NB} values) are given by Mabey and Mill,[12] who point to their utility in estimating the effect of pH change on the persistence of hydrolyzable compounds in the environment.

[12] Mabey, W.; Mill, T. *J. Phys. Chem. Ref. Data* **1978**, *7*, 383–415.

[13] If one knows K_a, k_w, and k_{OH} it is a simple matter to calculate k_{DN} and k_{GB}. Knowing only K_a, it is still possible to find k_{DN}/k_{GB}, which is given by $xy/(x - y)$ where x and y are the "plateau" (or "intersection") values of *r* for the reactions without and with general base catalysis, respectively (see Figure 7). To obtain x one extends each sloped line of the log *r* vs pH plot and finds the (lower) point of intersection with a vertical line drawn at pH = pK_a. Alternatively one may use $k_{DN}/k_{GB} = y/(1 - y/x)$ where $y/x = 10^{-|\Delta pH|}$; ($|\Delta pH|$ is defined in the text and shown in Figure 7).

[14] Palling and Jencks, for example, describe the determination of total acetylpyridinium ion in the reaction of acetyl chloride with pyridine in water by trapping with inorganic phosphate and subsequently converting the acetyl phosphate with hydroxylamine to the hydroxamic acid and assaying by addition of $FeCl_3$ (Palling, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 4869–4876).

[15] Lam, J. Y. L. Ph.D. Thesis, University of Western Ontario, 1993.

[16] King, J. F.; Gill, M. S. Unpublished observations. It was observed, however, that the products of the reaction of $PhSO_2Cl$ with either piperidine or morpholine are consistent with the incursion of a small amount (<10%) of the general base (k_{GB}) reaction.

[17] King, J. F.; Lam, J. Y. L.; Ferrazzi, G. *J. Org. Chem.* **1993**, *58*, 1128–1135.

[18] Guo, Z. R. Ph.D Thesis, University of Western Ontario, 1994.

display meter equipped with a Fisher all-range (pH 1–14) combination electrode and manual addition of aqueous NaOH (1.0 M). The solution was stirred rapidly for a further 0.5 h with the pH of the solution kept constant. The mixture was acidified to pH 2 with aqueous HCl (6.0 M) and extracted with CH_2Cl_2 (5 × 70 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (50 mL) and water (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product dried to a constant weight under vacuum. In all cases the amide product was shown by ^1H and ^{13}C NMR (and, where relevant, melting point) to be identical to the authentic specimen. The runs with 3-methylbutylamine were carried out in 400 mL at the same concentrations. The reaction of *N,N*-diisopropylamine was also carried out with $[Ac_2O] = 0.12$ M and $[\text{amine}] = 0.1$ M at pH 9.8; workup yielded no sign of the amide; the authentic amide specimen was found to stable to both sets of reaction conditions. Control experiments showed that some of the acetamides were not fully recovered from aqueous solution by the extraction procedure used. Accordingly a recovery plot was obtained by weighing a known quantity of each amide, adding it to water (1000 mL) stirring for 0.5 h, acidifying to pH 2 with 6 M HCl, and extracting as above. A plot of the recovered vs initially added amide from a series of such runs gave straight lines of the form $y = ax$ (in which x = weight of initially added amide and y = weight of recovered amide) with "a values" as follows: *N,N*-diethylacetamide 0.94, *N-tert*-butylacetamide 0.886, *N*-acetylpiperidine 0.93; to estimate the amount of each of these amides in the pH–yield runs, the weight of the isolated was divided by the appropriate "a value". Recovery of the other amides was sufficiently quantitative (≥99%) that the isolated yields were used directly. The results are shown in Figures 1, 3, and 4.

(b) *p*-Aminobenzylamine with Acetic Anhydride. In a 200–mL beaker equipped with a stir bar and combined pH electrode the dihydrochloride of *p*-aminobenzylamine (**1**) (pK_a's 3.74, 9.70)[2] (0.2075–0.2080 g, 1.06 mmol), an aqueous sodium methanesulfonate solution (25.00 mL, 4.241×10^{-3} M, 0.106 mmol, added from a volumetric pipet) and water (81.0 mL) were mixed. The aqueous solution was adjusted to the appropriate pH by addition of NaOH or, in the case of the run at pH 2.0, by addition of aqueous HCl (3 M). Freshly distilled Ac_2O (10 μL, 10.8 mg, 0.106 mmol) was added to the rapidly stirring solution. The pH was maintained by dropwise addition of NaOH solution (0.05 M) from a buret. When the pH remained stable, the solution was acidified to pH 2.5 and the water was evaporated. In all cases a brown powder was obtained. This was taken up in D_2O and the ^1H NMR spectrum was recorded; the products of reaction were the hydrochlorides of *N*-(*p*-aminobenzyl)acetamide (**3**) and *p*-acetamidobenzylamine (**2**), which were identified by addition of authentic specimens to the NMR sample tubes. No diacetamide product was apparent in any of the mixtures. Product yields are based on total Ac_2O and were obtained by integration of the acetyl methyl singlets relative to added anhydrous $CH_3SO_3^-Na^+$ (1 equiv) standard. For the runs from pH 5.0 to 9.0, Na_2HPO_4 (0.075 g, 0.005 M) was added to help maintain constant pH in this relatively unbuffered region. The yields (mole fractions) of the two acetamide products (**2** and **3**) at various pH values are shown in Figure 5. The curves were calculated by fitting rate constants of k_{DN} (4.5 M^{-1} s^{-1}) and k_{GB} (0.4 M^{-1} s^{-1}) for reaction of the arylamino moiety and k_{DN} (4200 M^{-1} s^{-1}) and k_{GB} (600 M^{-1} s^{-1}) for reaction of the alkylamino portion with the literature values[4] of k_w and k_{OH} (2.8×10^{-3} s^{-1} and 980 M^{-1} s^{-1}) for Ac_2O.

(c) Ethyl Chloroformate with Amines. Solutions of aniline hydrochloride (0.7835–0.7840 g, 6.05 mmol) in distilled water (605 mL) were made up in a 1-L beaker and were adjusted to the appropriate pH with NaOH. EtOCOCl (57 μL, 0.0647 g, 0.60 mmol) was added from a 100-μL syringe to the rapidly stirring solution while the pH was maintained by dropwise addition of NaOH titrant (0.05 M) from a buret. When the pH remained stable the solution was acidified to pH 2 with H_2SO_4 and was extracted with CH_2Cl_2 (5 × 50 mL). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated to give ethyl phenylcarbamate identified by ^1H NMR comparison with an authentic sample. The yields (mole fractions) are based on EtOCOCl (theoretical yield = 0.0985 g) and are shown in Figure 6. The curve was calculated by fitting rate constants (with the help of a computer spreadsheet program) for k_{DN} and k_{GB} to the experimental data using the previously determined rate constants for the hydrolysis of EtOCOCl and k_N for reaction of the amine with EtOCOCl. The reaction with $PhCH_2NH_2$ followed the same procedure with the following modifications. $PhCH_2NH_3^+Cl^-$ (0.400–0.401 g, 2.79 mmol) was dissolved in water (2.80 L) in a 3-L beaker. EtOCOCl (27.0 μL, 0.0365 g, 0.282 mmol) was added from a 50-μL syringe and after the reaction was complete the solution was acidified and extracted with CH_2Cl_2 (5 × 200 mL). The yields (mole fractions) are based on added EtOCOCl (theoretical yield = 0.0506 g). The rate constants so obtained for $PhNH_2$ and $PhCH_2NH_2$ are, respectively, k_{DN} 14.4 and 123 M^{-1} s^{-1}, and k_{GB} 3.2 and 14 M^{-1} s^{-1}).

Kinetic Measurements. (a) Acetic Anhydride. Ac_2O (4.8 μL, 5.0 mg) was injected from a 10–μL syringe into a solution of amine (total initial concentration 0.01 M) in 50 mL of 0.1 M aqueous KCl which had been previously adjusted to the desired pH value with aqueous HCl (1 M) or NaOH (1 M) at 25.0 °C. The solution was stirred rapidly and the pH of solution kept constant with aqueous NaOH (0.1 M). The rate of the nucleophilic reaction was monitored by recording the volume (milliliters) of titrant (NaOH) delivered with time (seconds). The pseudo-first-order rate constants were obtained from the slopes of the best least squares lines from plots of $-\ln(V_\infty - V_t)$ versus time; k_{obs} values are listed in Table S1 (and shown for primary amines in Figure 2); average k_N values calculated from eq 6 are given in Table 1.

In a set of runs without amines Ac_2O (9.6 μL, 10.0 mg) was injected into water (50 mL) adjusted to the desired pH and the above procedure carried out; for some runs NaOAc (8.0 mg, 0.1 mmol) was added. The k_{obs} values are shown in Figure 2. Preliminary measurements of the rate of reaction of Ac_2O with piperidine which had been purified by distillation from CaH gave inconsistent results; the UV spectrum of the piperidine showed absorption at 257 nm consistent with the presence of pyridine. The piperidine was purified through *N*-(ethoxycarbonyl)piperidine as follows. A mixture of piperidine (17.22 g, 0.202 mol) and EtOCOCl (26.34 g, 0.243 mol) in CH_2Cl_2 (200 mL) was stirred for 30 min at room temperature. Water (50 mL) was added, and the two layers were separated. The organic layer was washed with HCl (0.5 M, 30 mL), saturated $NaHCO_3$ (30 mL), and water (30 mL). The organic layer was dried, and the solvent was removed to give a colorless liquid (27.75 g, 0.177 mol, 87.6% yield). The pure *N*-(ethoxycarbonyl)piperidine was obtained by distillation under reduced pressure, bp 57 °C (1 Torr) [lit.[19] bp 56 °C (1 Torr)]; IR (neat) ν_{max} 2982 (m), 2936 (s), 2857 (s), 1701 (s), 1431 (s), 1264 (s), 1235 (s), 1171 (s), 1149 (s), 1096 (s), 1032 (s), 855 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3H), 1.44 (m, 6H), 3.32 (t, 4H), 4.02 (q, 2H); ^{13}C NMR ($CDCl_3$) δ 15.5, 25.2, 26.5, 45.5, 61.8, 156.3. The *N*-(ethoxycarbonyl)piperidine was converted back to piperidine by refluxing a mixture of *N*-(ethoxycarbonyl)piperidine (15.0 g, 95.4 mmol) and KOH (15.0 g, 267 mmol) in water–DME (150 mL, 1:1, v/v) 2 h. The mixture was extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was dried, and the solvent was removed by distillation to give a colorless liquid (6.86 g, 80.6 mmol, 84.5% yield) which showed no sign of pyridine in the UV. Distillation under reduced pressure gave a clean product which gave satisfactory rate measurements.

(b) Ethyl Chloroformate (in 0.05 M NaCl, 25.0 °C). (i) Without Added Nucleophiles. In each kinetic run dry NaCl (0.146–0.147 g, 2.51 mmol) and distilled water were combined in the reaction vessel, and the temperature was brought to 25.0 °C. The solution was adjusted to the appropriate pH with NaOH solution. An aliquot (50 μL) of an EtOCOCl (0.5023 g, 4.629 mmol) solution in dry CH_3CN (5.00 mL, 0.926 M) was added from a 100-μL syringe to the rapidly stirring solution, $[EtOCOCl]_o = 0.001$ M. The solution was maintained at the chosen pH by addition of standard NaOH solution (0.124 M) from a calibrated syringe reservoir with the volumes of added titrant recorded at regular time intervals to allow the data to be treated according to the method of Guggenheim. Rate constants were obtained from the slopes determined from linear least squares fits of the data (plotted to at least two half-lives) and are listed in Table S2.

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(19) Kometani, T.; Shiotani, S.; Mitsuhashi, K. *Chem. Pharm Bull.* 1976, *24*, 342–349.

(ii) With Benzylamine. A solution of $PhCH_2NH_3^+Cl^-$ (0.0365 g, 0.2541 mmol) and dry NaCl (0.7300 g, 12.49 mmol) was made up to the mark with distilled water in a 250-mL volumetric flask to provide solution A ($[BnNH_3^+Cl^-] = 0.001$ M, $[NaCl] = 0.05$ M). Solution B was made up of EtOCOCl (0.0284 g, 0.2617 mmol) and dry CH_3CN (5.00 mL) in a 5-mL volumetric ampule ($[EtOCOCl] = 0.0523$ M). Kinetic determinations were performed using aliquots of solution A (50.0 mL) as the reaction medium which were maintained at 25.0 °C. The solution was adjusted to the appropriate pH with NaOH and solution B (100 μL, 5.23×10^{-6} mol) was added to the rapidly stirring solution from a 100-μL syringe, $[EtOCOCl]_0 = 0.0001$ M; rate constants were obtained as described for the hydrolysis of EtOCOCl. The pH's and corresponding $10^3 k_{obs}$ values were as follows: 7.00, 1.06; 7.50, 2.11; 7.70, 3.85; 7.85, 5.29; 8.00, 6.12.

(iii) With Aniline. Two kinetics runs at pH 7.0 were carried out as described for the reaction with $PhCH_2NH_2$. In the first the initial kinetic concentrations were $[PhNH_3^+Cl^-] = 0.001$ M, $[NaCl] = 0.05$ M, and $[EtOCOCl] = 0.0001$ M, in the second, $[PhNH_3^+Cl^-] = 0.0005$ M, $[NaCl] = 0.05$ M, and $[EtOCOCl] = 0.00005$ M. The data were treated in the same manner as above to give the following observed rate constants: at $[PhNH_3^+Cl^-] = 0.001$ M, 1.56×10^{-2} s^{-1} and at $[PhNH_3^+Cl^-] = 0.0005$ M, 9.74×10^{-3} s^{-1}; the speed of the reactions is estimated to limit the accuracy to ±25%.

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Supplementary Material Available: Tables of rate constants for the reactions of monoamines with acetic anhydride in aqueous medium and for the hydrolysis of ethyl chloroformate (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.