EVIDENCE FOR GENERAL BASE CATALYSIS BY PROTIC SOLVENTS IN A KINETIC STUDY OF ALCOHOLYSES AND HYDROLYSES OF 1-(PHENOXYCARBONYL)PYRIDINIUM IONS UNDER BOTH SOLVOLYTIC AND NON-SOLVOLYTIC CONDITIONS

Dennis N. KEVILL[a1,*], Byoung-Chun PARK[a2] and Jin Burm KYONG[b]

[a] *Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115-2862, USA; e-mail: [1] dkevill@niu.edu, [2] sandooli@hanmail.net*

[b] *Department of Chemistry and Applied Chemistry, Hanyang University, Ansan-si, Gyeonggi-do 426-791, Korea; e-mail: jbkyong@hanyang.ac.kr*

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Dedicated to the memory of Professor Otto Exner in recognition of his outstanding contributions to physical organic chemistry and chemometrics.

The kinetics of nucleophilic substitution reactions of 1-(phenoxycarbonyl)pyridinium ions, prepared with the essentially non-nucleophilic/non-basic fluoroborate as the counterion, have been studied using up to 1.60 M methanol in acetonitrile as solvent and under solvolytic conditions in 2,2,2-trifluoroethan-1-ol (TFE) and its mixtures with water. Under the non-solvolytic conditions, the parent and three pyridine-ring-substituted derivatives were studied. Both second-order (first-order in methanol) and third-order (second-order in methanol) kinetic contributions were observed. In the solvolysis studies, since solvent ionizing power values were almost constant over the range of aqueous TFE studied, a Grunwald–Winstein equation treatment of the specific rates of solvolysis for the parent and the 4-methoxy derivative could be carried out in terms of variations in solvent nucleophilicity, and an appreciable sensitivity to changes in solvent nucleophilicity was found.

Keywords: Phenoxycarbonylpyridinium ions; Solvolysis; Alcoholysis; Kinetics; Grunwald–Winstein equation.

Amine catalysis of nucleophilic substitution reactions of acyl derivatives has been a recommended synthetic procedure for over a hundred years. Several reviews of the early investigations are available[1–4]. Pyridines have been found to be efficient catalysts (Eq. (*1*)) and recently there have been both synthetic[5–9] and mechanistic[9–13] studies of the highly efficient 4-(dimethylamino)pyridine (DMAP). This catalyst has been found to be espe-

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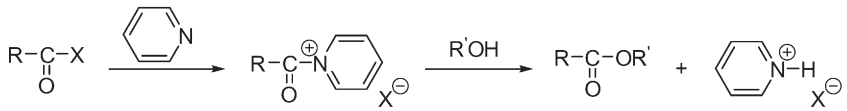
cially useful for the difficult reactions of sterically hindered alcohols with acid anhydrides or acyl halides.

Calculations, using a high level of theory, have been performed on the reaction of acetic anhydride with *tert*-butyl alcohol in the presence of DMAP [10]. The calculations indicate, in agreement with experimental mechanistic studies[10,13–19], that nucleophilic catalysis is involved (Eq. (*1*)). An initial formation of the acetylpyridinium ion[20] is followed by a general-base catalyzed nucleophilic attack by the alcohol. The liberated acetate ion was considered to be a prime candidate for the role of the catalyst, especially when preassociated within an ion-pair in solvents of low polarity. As regards this anionic general-base assistance to alcoholyses of the acylpyridinium ion, there is a close similarity to the reactions of acyl halides with alcohols in acetonitrile, where general base catalysis by halide ion, by a second molecule of alcohol, or by an acetonitrile molecule can be observed. However, a major difference to the pyridinium ion alcoholyses is that, for the catalysis by halide ion to be observed, a halide-ion containing salt needs to be added. In acetonitrile, the halide ion liberated during the alcoholyses of acyl halides exists as essentially unionized hydrogen chloride[21,22].



(*1*)

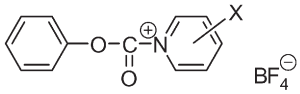
General base catalysis by the anion accompanying the acylpyridinium ion can be avoided by incorporation[20] of the essentially inert tetrafluoroborate ion (BF_4^-)[20,23]. The general base catalysis will then be by the alcohol reagent or by the solvent. Care must be taken to avoid contamination of the salt by traces of free pyridine, which, in the absence of a basic counterion, can give a fairly efficient general base catalysis to the alcoholysis of an acylpyridinium ion[4,9,14].

Phenyl chloroformate has been shown to solvolyze by an addition-elimination pathway, with the addition step rate-determining, over a wide range of solvents[24,25]. Analysis was conveniently carried out using an extended form of the Grunwald–Winstein equation (Eq. (*2*)).

$$\log (k/k_0) = lN_T + mY_{Cl} + c \qquad (2)$$

It was found that various subsets of solvents gave essentially identical l and m values, indicating the correlations to be very robust. In Eq. (*2*), k and k_0

are the specific rates of solvolysis of a substrate in a given solvent and in 80% ethanol, respectively, *l* is the sensitivity towards changes in solvent nucleophilicity (N_T)[26,27], *m* is the sensitivity towards changes in solvent ionizing power (Y_{Cl} when based on a chloride leaving group)[28,29], and *c* is a constant (residual) term. Chloroformate esters can be conveniently converted to a pyridinium salt using the procedure of King and Bryant and the synthesis and characterization of 1-(phenoxycarbonyl)pyridinium tetrafluoroborate (**1**) is described in their report[20]. We have studied the reactivity and alcoholysis kinetics of **1** and three pyridine-ring-substituted derivatives: 4-methoxy (**2**), 3-chloro (**3**), and 4-cyano (**4**) using methanol in acetonitrile and, for **1** and **2**, under solvolytic conditions, using 2,2,2-trifluoroethan-1-ol (TFE) and its mixtures with water.



(*2*)

1, X = H; **2**, X = 4-OMe; **3**, X = 3-Cl; **4**, X = 4-CN

EXPERIMENTAL

The 1-(phenoxycarbonyl)pyridinium tetrafluoroborate (**1**) and the derivatives **2**, **3**, and **4** were prepared by the general procedure developed by King and Bryant[20]. Three determinations of the decomposition points of samples of **1** gave values of approximately 147, 141, and 154 °C (ref.[20], 143–145 °C). Decomposition points for organic salts are notoriously dependent on the rate of heating[30]. All four compounds gave excellent C, H, and N elemental analyses and NMR and IR spectra consistent with the structures[20]. The analyses for the three new substrates are as follows: Compound **2**, for $C_{13}H_{12}NO_3$ calculated: 49.25% C, 3.82% H, 4.41% N; found: 49.22% C, 3.72% H, 4.39% N. Compound **3**, for $C_{12}H_9ClNO_2$ calculated: 44.84% C, 2.82% H, 4.36% N; found: 44.80% C, 2.82% H, 4.33% N. Compound **4**, for $C_{13}H_9N_2O$ calculated: 50.04% C, 2.91% H, 8.98% N; found: 50.00% C, 2.93% H, 9.05% N. The purifications of acetonitrile[21,31] and other solvents[26] and the kinetic runs under non-solvolytic[21] and solvolytic[26] conditions were carried out as previously described.

RESULTS

The methanolyses of **1**–**4** in acetonitrile have been studied over a range of methanol concentration of from 0.08 to 1.60 mol l^{-1}. The kinetics can be represented as in Eq. (*3*), where [salt] represents the concentration of **1**–**4**. To an acceptable degree of accuracy, the kinetic data can be treated in terms of experimental second-order rate coefficients. At low methanol concentrations, the first term of Eq. (*3*) will dominate and at the higher methanol concentrations,

$$\frac{d[PyrH^+]}{dt} = k_2[salt][MeOH] + k_3[salt][MeOH]^2 \qquad (3)$$

with at least a five-fold molar excess of methanol over the salt being studied, for each individual run the goodness of fit will be independent of the order in methanol that is incorporated. The experimental second-order rate coefficients are shown in Table I, calculated according to Eq. (*4*).

TABLE I

Experimental second-order rate coefficients (k_2^{expt}) for the methanolyses of the 1-(phenoxycarbonyl)pyridinium ion and three pyridine-ring-substituted derivatives[a] in acetonitrile at 0.0 °C and calculated second-order (k_2) and third-order (k_3) rate coefficients

[MeOH], mol l^{-1}	$10^4\ k_2^{expt}$ (l mol^{-1} s^{-1})[b]			
	4-OMe[c] (**2**)	H (**1**)	3-Cl[c] (**3**)	4-CN[c] (**4**)
0.080	0.199 ± 0.013	2.31 ± 0.06	9.07 ± 0.13	19.7 ± 1.3
0.100	0.206 ± 0.016	2.44 ± 0.07	10.5 ± 0.4	21.8 ± 0.8
0.160	0.200 ± 0.010	3.17 ± 0.20	14.8 ± 0.4	32.3 ± 0.8
0.250	0.230 ± 0.007	4.26 ± 0.27	19.6 ± 0.8	45.1 ± 2.3
0.500	0.258 ± 0.007	5.60 ± 0.27	38.8 ± 1.5	95.0 ± 3.2
0.750	0.264 ± 0.010	5.76 ± 0.12	61.0 ± 3.8	137. ± 5
1.00	0.254 ± 0.008	8.43 ± 0.27	79.6 ± 2.3	–
1.15	0.260 ± 0.005	10.2 ± 0.5	102 ± 5	–
1.30	0.278 ± 0.010	11.9 ± 0.7	115 ± 6	–
1.45	0.250 ± 0.010	14.3 ± 0.8	123 ± 6	–
1.60	0.286 ± 0.011	16.3 ± 0.9	146 ± 10	–
$10^4\ k_2$ (l mol^{-1} s^{-1})[d]:	0.202 ± 0.010	2.14 ± 0.34	1.98 ± 0.81	3.85 ± 1.39
$10^4\ k_3$ (l^2 mol^{-2} s^{-1})[d]:	0.070 ± 0.017	5.99 ± 0.66	77.3 ± 1.5	178 ± 4
Correlation coefficient (*r*):	0.868	0.971	0.999	0.999

[a] Concentration of 0.0150 mol l^{-1} and with a tetrafluoroborate counterion. [b] With associated standard deviations. [c] Substituent within the pyridine ring of the substrate. [d] Calculated as intercept and slope of $k_2^{expt} = k_2 + k_3$[MeOH] and with associated standard errors, using values for ≤1.0 M methanol.

$$\frac{\mathrm{d[PyrH^+]}}{\mathrm{d}t} = k_2^{\mathrm{expt}}[\mathrm{salt}][\mathrm{MeOH}] \qquad (4)$$

Also shown in Table I are the second- and third-order rate coefficients calculated according to Eq. (*5*) using the k_2^{expt} values for methanol concentrations of ≤1.0 mol l^{-1}.

$$k_2^{\mathrm{expt}} = k_2 + k_3[\mathrm{MeOH}] \qquad (5)$$

$$\frac{\mathrm{d[PyrH^+]}}{\mathrm{d}t} = k_3^{\mathrm{expt}}[\mathrm{salt}][\mathrm{MeOH}]^2 \qquad (6)$$

The relevant plots for methanolyses of **1** and **3** are shown in Figs 1 and 2.

Third-order experimental rate coefficients, calculated according to Eq. (*6*) are presented in Table II for the methanolyses of **1**, **3**, and **4**. Since the k_2^{expt} values for **2** in Table I are close to constant, it would not be helpful to calculate k_3^{expt} values for this substrate.

The range of solvolytic studies for **1**–**4** was limited by fast reactions in the conventional alcohols and their mixtures with water. The titration tech-

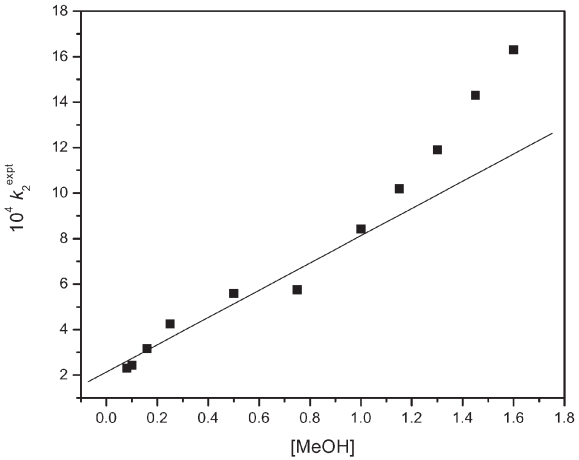


FIG. 1
Plot of the experimental second-order rate coefficients against the methanol concentration for methanolyses of **1** in acetonitrile

TABLE II

Experimental third-order rate coefficients (k_3^{expt}) for the methanolyses of the 1-(phenoxycarbonyl)pyridinium ion and two pyridine-ring-substituted derivatives[a] in acetonitrile at 0.0 °C

[MeOH], mol l^{-1}	$10^4\ k_3^{expt}$ ($l^2\ mol^{-2}\ s^{-1}$)[b]		
	H (**1**)	3-Cl[c] (**3**)	4-CN[c] (**4**)
0.080	28.9	113	246
0.100	24.4	105	218
0.160	19.8	93	202
0.250	17.0	78	180
0.500	11.2	78	190
0.750	7.7	82	183
1.00	8.4	80	–
1.15	8.9	89	–
1.30	9.2	88	–
1.45	9.9	85	–
1.60	10.2	91	–

[a] From the kinetic runs also analyzed in terms of second-order rate coefficients in Table I. [b] Average values of integrated rate coefficients; calculated for $d[PyrH^+]/dt = k_3[salt][MeOH]^2$. [c] Substituent within the pyridine ring of the substrate.

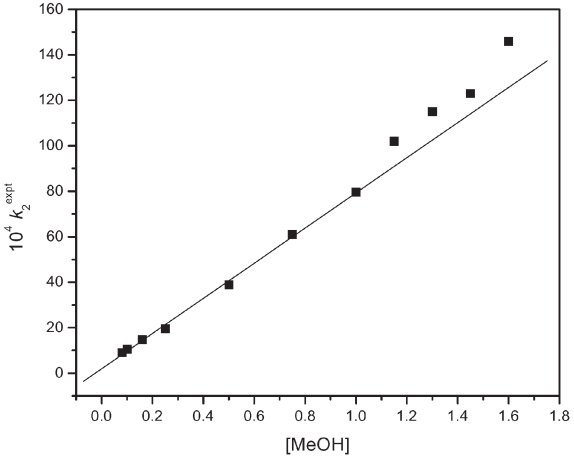


FIG. 2

Plot of the experimental second-order rate coefficients against the methanol concentration for methanolyses of **3** in acetonitrile

nique, after sampling, was suitable only for relatively non-nucleophilic solvents and measurements were made, for the slower reacting **1** and **2**, only in TFE and its mixtures with up to 30% water (w/w). The specific rates of solvolysis at 0.0 °C are presented in Table III. In the table are also listed the relevant N_T values[27,32], Y_{Cl} values[29,33], and Y^+ values[29,34], with the Y^+ values obtained with a dimethyl sulfide molecule leaving from the 1-adamantyldimethylsulfonium ion[34].

TABLE III
Specific rates of solvolysis (k) of 0.015 M solutions of 1-phenoxycarbonyl)pyridinium (**1**) and 4-methoxy-1-(phenoxycarbonyl)pyridinium (**2**) ions in 2,2,2-trifluoroethan-1-ol (TFE)–water mixures at 0.0 °C and a comparison with the corresponding values (k(Cl)) for phenyl chloroformate[a]

TFE, %[b]	$10^4\ k$, s^{-1} [c]		k(**1**)/k(Cl)	N_T[d]	Y_{Cl}[e]	Y^+ [f]
	1	**2**				
100	3.05 ± 0.16	2.62 ± 0.15	23×10^4	–3.93	2.81	0.46
97	9.26 ± 0.37	10.3 ± 0.3	1.7×10^4	–3.30	2.83	0.39
90	53.0 ±1.8	35.6 ± 1.7	0.46×10^4	–2.55	2.85	0.37
80	196 ± 9	76.8 ± 4.2	0.28×10^4	–2.19	2.90	0.35
70	–	109 ± 7	–	–1.98	2.96	0.34
l value[g]	1.02 ±0.10	0.82 ± 0.02				

[a] Estimated from values at 25.0 °C (see the text). [b] w/w. [c] With associated standard deviations, using integrated first-order rate coefficients (specific rates) from duplicate runs. [d] From ref.[27] [e] From listing in ref.[29] (largely from ref.[28]). [f] From ref.[34] [g] Calculated using log $k = lN_T + c$.

DISCUSSION

Early studies involved the in situ generation of an 1-acylpyridinium ion by reaction of the pyridine with an anhydride[17–19,23,35,36] or a chloroformate ester[14,37,38]. For example, for the pyridine catalyzed hydrolysis of acetic anhydride, the scheme was expressed[35] as in Eq. (*7*), with $PyrAc^+$ representing the unstable intermediate.

$$\begin{aligned} Ac_2O + Pyr &\rightleftharpoons PyrAc^+ + OAc^- \\ PyrAc^+ + H_2O &\longrightarrow AcOH + PyrH^+ \end{aligned} \qquad (7)$$

Initially, the first step was considered to be rate-determining[35]. However, a large solvent isotope effect, with the slower reaction being in deuterium oxide, strongly indicated[19] that it is the second step which is rate-determining. It was suggested that the large value resulted from a general base catalysis by a second H_2O or D_2O molecule to the nucleophilic attack at the acyl carbon[14]. Moodie and coworkers[14] obtained values for k_{H2O}/k_{D2O}, at 25.0 °C, of 2.87 for the 3-chloro-1-(methoxycarbonyl)pyridinium ion and 3.53 when a 4-(dimethylamino) replaced the 3-chloro substituent. These values were nicely consistent with previous values of 2.5 for the 1-acetylimidazolium ion[39] and 3.4 for 1-acetylpyrazole[40] hydrolysis. These values are somewhat higher than the corresponding value of 1.89 for the hydrolysis of methyl chloroformate[41], with ejection of a chloride instead of the pyridine molecule, suggesting that the proton (deuteron) transfer to the general base is more advanced at the transition state for reactions of the pyridinium ions.

When the intermediate 1-acylpyridinium ion is formed in situ (Eq. (*1*)), the rate-determining step of the catalyzed substitution reaction can be either the formation or subsequent reaction of the intermediate[2,17,38]. The use of a very basic pyridine, such as DMAP favors a relatively rapid formation of a resonance-stabilized intermediate, which then undergoes a relatively slow further reaction, such that a kinetic study gives information concerning the attack upon the 1-acylpyridinium ion. Indeed several of the intermediates formed by attack of DMAP (or related derivatives using a cyclic amino group in position 4 of the pyridine[42]) can be isolated, even with relatively nucleophilic counterions[2].

In preparative experiments, acylations in the presence of DMAP usually use the acetic anhydride as the acylating agent (so as to generate the acetate counterion, which then functions as a good general-base) in a nonpolar solvent, such as dichloromethane, and in the presence of an auxiliary base, such as triethylamine (TEA)[2]. In this way even highly hindered tertiary alcohols can be esterified[43].

The computational study[10] suggesting general base catalysis only by acetate ion, when the intermediate is generated using acetic anhydride, without general base catalysis by either DMAP or auxiliary base (such as TEA) has been given strong support from kinetic studies in dichloromethane using the more reactive cyclohexanol as the alcohol component[10]. The rate law contained two terms, corresponding to uncatalyzed and catalyzed (by DMAP) reaction. There was no indication of general base catalysis by DMAP or by the TEA, present as the auxiliary base.

The involvement of the acetate counterion can lead to kinetic complications. Nucleophilic attack with early establishment of an equilibrium is averted by use of DMAP as the catalyst but, at high alcohol concentrations (above about 1 mol l^{-1}), a reduction in the rate coefficient for the catalyzed reaction is observed. This was rationalized[10] in terms of increased solvent polarity, but an important feature will be the partial deactivation of the acetate by increased solvation, which will moderate its ability to function as a general-base towards the nucleophilic addition. Such an effect was observed and studied in detail in the chloride catalyzed methanolysis of 4-nitrobenzoyl chloride in acetonitrile[21].

Pathways involving interaction by the counterion can be avoided by incorporation of a non-nucleophilic/non-basic counterion, such as tetrafluoroborate or tetraphenylborate. These salts can be isolated in very pure form[20] and added to the solvent either directly or as a concentrated solution in a relatively inert solvent, avoiding the requirement of in situ production. We chose the tetrafluoroborate ion, for which the procedure for the preparation of **1** has been presented in detail by King and Bryant[20]. It is necessary to use a very pure material and, in particular, to avoid the free pyridine, which, in the absence of a basic anion, can serve as the general base catalyst for an appreciable proportion of the overall product formation.

Our kinetic study of the methanolyses of **1**–**4** in acetonitrile is reported in Table I in terms of the experimental second-order rate coefficients (Eq. (*4*)) and in Table II in terms of the experimental third-order rate coefficients (Eq. (*6*)).

The very small increase in k_2^{expt} values for **2** as the methanol concentration increases results in a very small k_3 value when Eq. (*5*) is applied to the data. Further, a part of this increase could represent a solvent effect upon the k_2 value. Such a solvent effect was shown to be especially important at above about 1 M methanol in a kinetic study of the methanolysis of 4-nitrobenzoyl chloride[21]. In contrast, for **3** and **4**, it is the third-order rate coefficients which are approximately constant (Table II), at a value only very slightly higher than the calculated k_3 values of Table I, indicating the third-order component to be the dominant contribution (Eq. (*5*)) above ca. 0.16 M methanol. The methanolyses of **1**, under these conditions, represents a delicate balance between second- and third-order contributions, with the third-order contribution dominant above ca. 0.5 M methanol.

As with earlier acyl halide studies[21,44], the term which is first-order in methanol probably involves the acetonitrile solvent functioning as the general base. The contribution from the overall third-order term (methanol as general base) is dominant at the higher methanol concentrations. Support

for acetonitrile as a general base came from the observation of only an overall third-order term for the methanolysis of 4-nitrobenzoyl chloride when the solvent was changed from acetonitrile to nitromethane[21]. The variation in the k_3/k_2 ratio, using values from Table I (from 0.4 l mol^{-1} for **2**, 2.8 l mol^{-1} for **1**, 39 l mol^{-1} for **3**, and 46 l mol^{-1} for **4**) can be rationalized in terms of the general base catalysis by methanol, relative to that by acetonitrile, becoming increasingly favored as one moves to more electron-withdrawing substituents in the pyridine ring.

The lower reactivity for **2** is consistent with the conclusions of Fersht and Jencks[18] that the 4-methoxypyridine-catalyzed hydrolysis of acetic anhydride has a high equilibrium concentration of the acetylpyridinium ion and a low rate of subsequent reaction of this intermediate due to the resonance interaction when the 4-methoxy substituent is present (Eq. (*8*)). It is readily seen that, since there is appreciable driving force for further reaction from the interactions of the positive nitrogen with the directly adjacent positive dipole of the carbonyl group, the resonance leads to a partial separation of the interacting positive charges, with a reduced driving force. In DMAP catalysis, the same effect will operate and the consequences will be enhanced due to a larger resonance effect from a dimethylamino group than from a methoxy group[45].

(*8*)

In previous studies of in situ generated 1-(methoxycarbonyl)pyridinium ion it was shown[14] that the hydrolysis proceeded with involvement of two water molecules, one as a nucleophile and one as a general base. Parallel behavior was proposed for solvolysis of methyl chloroformate[46]. The destabilization due to adjacent positively charged atoms favors a faster reaction for **1**–**4** relative to phenyl chloroformate. In Table III, four specific rates for solvolysis of **1** in TFE and aqueous-TFE solvents are compared to the corresponding specific rates for phenyl chloroformate solvolysis. The values for phenyl chloroformate reported[24,25] at 25.0 °C were approximately adjusted to 0.0 °C by assuming that the exactly ten-fold reduction for hydrolysis in 100% H_2O [41] also applies in TFE–H_2O mixtures. The ratios (k(**1**)/k(Cl)) vary from 23 × 10^4 in 100% TFE to 0.28 × 10^4 in 80% TFE. The specific rates for both substrates increase as the water content increases but those for the chloroformate show the larger increase. Over the range of solvents studied, variations in both Y_{Cl} [28,29,47] and Y^+ scales[29,34], are very

small (relevant values listed in Table III) and the major source of solvent-induced changes in specific rate will be the variations in the N_T solvent nucleophilicity values[26,27].

Since variation in the Y scales, and hence in the mY contribution, is negligible, the Grunwald–Winstein treatment for the four or five solvents was using Eq. (*9*). This incorporates

$$\log k = lN_T + c \qquad (9)$$

the, unavailable, log k_0 term within the c value. Values were obtained for **1** (4 solvents) of 1.02 ± 0.10 for l, 0.43 ± 0.30 for c, 0.991 for the correlation coefficient (r), and 109 for the F-test value. For **2** (5 solvents), the values obtained were 0.82 ± 0.02 for l, –0.33 ± 0.07 for c, 0.999 for r, and 1252 for the F-test value. The l values indicate appreciable nucleophilic participation by the solvent in the rate-determining step, comparable to that for the standard SN2 solvolyses of the *S*-methyldibenzothiophenium ion (l = 1, by definition)[26,27,48]. The l values are considerably lower that the l value of 1.66 ± 0.08 obtained from an analysis[25], using Eq. (2), of 49 specific rates of solvolysis of phenyl chloroformate. This suggests an earlier transition state for the nucleophilic attack at the pyridinium ion but, with data available only for four or five rather similar solvents, one must be careful not to over-interpret the l values obtained in the present study.

The large k(**1**)/k(Cl) ratios observed (Table III) can be compared to corresponding ratios for a pyridine molecule or a chloride ion being replaced at a saturated (sp^3-hybridized) carbon. The 1-(1-adamantyl)pyridinium ion, which due to the bridgehead substitution follows the SN1 mechanism, reacts extremely slowly[49] in 100% TFE: at 190 °C, the specific rate is 1.2 × 10^{-4}. Since both Y^+ and Y_{Cl} values are similar for 100 and 97% TFE, specific rates for SNl reactions being expected to be essentially the same in these two solvents. For comparison, a very approximate value of 1.1 s^{-1} can be obtained for the solvolysis in 97% TFE of 1-adamantyl chloride, from a long extrapolation of values measured[28] at 25–75 °C, leading to a $k(Pyr^+)/k(Cl)$ ratio of 1.1 × 10^{-4} at 190 °C. The eight orders of magnitude difference in the magnitude of the ratio for the reactions at the carbonyl carbon (1.6 × 10^4 s^{-1} at 0.0 °C) and the sp^3-hybridized carbon is consistent with the destabilizing influence of the juxtaposition of positive charge in the substrate for the reaction at the carbonyl group, as discussed earlier.

A more relevant comparison would involve SN2 reaction at an sp^3-hybridized carbon. Data are not available for a direct comparison but the difference between the values for the ratios is reduced by four orders of

magnitude for the situation where several bimolecular reactions of benzylpyridinium ions and benzyl chloride are found to have about equal leaving-group abilities for pyridine and chloride ion[50].

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