Effective Charge on the Nucleophile and Leaving Group during the Stepwise Transfer of the Triazinyl Group between Pyridines in Aqueous Solution

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Abstract: Second-order rate constants (k_{xpy}) have been measured for the displacement reaction between substituted pyridines (xpy) and 1′-(2,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium ion in aqueous solution. The rate constants for the reverse reaction (k_{-xpy}) have also been measured for substituted pyridine leaving groups. The plots of log k_{xpy} and log k_{-xpy} against pK_a^{xpy} each consist of two intersecting linear correlations consistent with a two-step mechanism involving a Meisenheimer-like intermediate. The overall transfer of the triazin-2-yl group between substituted pyridines has a β_{eq} value of 1.25. There is negligible coupling between the bonding changes in both steps, and the substituent effects indicate that bond formation is half complete in the addition step. Reaction of substituted pyridines with 2,6-diphenoxy-1,3,5-triazin-2-yl chloride has a similar bonding change in the addition step. The 1′-triazin-2-ylpyridinium ion species exist in aqueous solution in equilibrium with the pseudobase formed by addition of water at the 2-position of the pyridinium ring.

Introduction

Relative timing of bond formation and fission is important in a reaction because it governs the reactivity and mechanism through its effect on charge development.[1] We have recently demonstrated that transfer of the triazin-2-yl group between phenolate ions involves a mechanism with a single transition state (eq 1) consistent with simultaneous bond formation and fission $(A_N D_N)^2$ in contrast to the stepwise process $(A_N + D_N)$ classical for these systems.[3]

[O4NP = 4-nitrophenoxy]
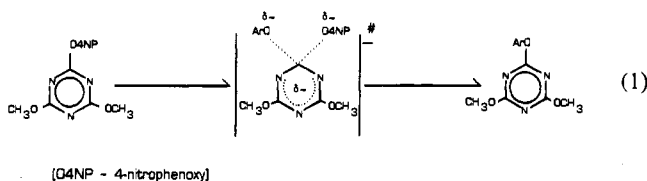
Substitution at trigonal carbon is receiving considerable scrutiny, and $A_N + D_N$ processes have been demonstrated in

reactions not hitherto investigated systematically such as nucleophilic displacements at vinyl centers. The concerted mechanism of nucleophilic displacement $(A_N D_N)^2$ is without experimental precedent for aromatic systems, and in view of contemporary interest in displacements at trigonal carbon[4] it is important to study its scope; we report here the results of an investigation of the quasi-symmetrical displacement reaction between pyridines and triazin-2-ylpyridinium ions **1a** (eq 2).
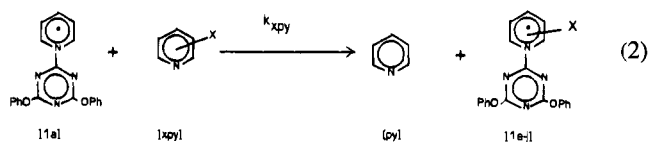
The study seeks to distinguish between a concerted and a stepwise process in a triazinyl system where the entering and leaving ligands have grossly different electronic structure from those in eq 1. The study aims to discover the effective charges[1a] at the reaction center through the reaction coordinate and to analyze these by measuring β_{eq} for the equilibrium constant of the overall reaction. The β_{eq} value would be useful in analyzing changes in effective charge in other reactions of pyridines in triazin-2-yl centers.

Experimental Section

Materials. The pyridines employed in this study were obtained commercially and were purified by redistillation. 3-Methoxypyridine and 4-methoxypyridine were prepared by the method of Prins.[5]

4,6-Diphenoxy-1,3,5-triazin-2-yl Chloride. This material was prepared by Schaefer's method;[6] a solution of phenol (9.4 g, 0.1 mol) and KOH (5.6 g, 0.1 mol) in water (50 mL) was slowly added to a stirred mixture of cyanuric chloride (9.22 g, 0.05 mol) and acetone

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Table 1. Analytical Results for 1'-(4,6-diphenoxy-1,3,5-triazin-2-yl)-Substituted Pyridinium Salts[a]

substituent	formula	mp/°C	% C	% H	% N
parent (**1a**)	$C_{20}H_{15}N_4O_2Cl(0.27H_2O)^e$	158−160	62.6 (62.6)	4.3 (4.1)	14.6 (14.6)
4-$CONH_2$ (**1b**)	$C_{21}H_{16}N_5O_3Cl^e$	205−207	59.6 (59.8)	3.7 (3.8)	16.7 (16.6)
3-Me (**1c**)	$C_{21}H_{17}N_4O_2Cl(0.70H_2O)^e$	120−125	62.2 (62.2)	4.5 (4.5)	13.6 (13.8)
3,5-Me_2 (**1d**)	$C_{22}H_{19}N_4O_2Cl(0.96H_2O)^e$	97−99	62.3 (62.3)	5.1 (5.0)	12.9 (13.2)
4-NH_2 (**1e**)	$C_{20}H_{16}N_5O_2Cl(1.41H_2O)^e$	127−131	57.3 (67.3)	4.4 (4.5)	18.0 (16.7)
3,4-Me_2 (**1f**)	$C_{22}H_{19}N_4ClO_2^e$	170−175	64.8 (65.0)	4.9 (4.7)	13.6 (13.8)
4-NMe_2 (**1g**)	$C_{22}H_{20}N_5ClO_2(1.52H_2O)^e$	210−212	58.8 (58.8)	4.9 (5.2)	15.8 (15.6)
3-Cl (**1h**)	$C_{20}H_{14}N_4Cl_2O_6^d$	207−211	50.5 (50.3)	2.8 (3.0)	11.9 (11.7)
3-MeO (**1i**)	$C_{21}H_{17}N_4ClO_7(4.79H_2O)^d$	127−129	45.1 (45.1)	2.9 (4.8)	10.0 (10.02)
4-MeO (**1j**)	$C_{21}H_{17}N_4ClO_7^d$	137−138	61.2 (61.7)	4.1 (4.2)	13.8 (13.7)
chloride[c]	$C_{15}H_{10}N_3ClO_2^e$	120−1[b]	60.1 (60.1)	3.1 (3.4)	14.0 (14.0)

[a] Numbers in parentheses denote the calculated percentages for the elemental analysis. [b] Literature value 120−1 °C.[6] [c] 4,6-Diphenoxy-1,3,5-triazin-2-yl chloride. [d] ClO_4 salts. [e] Cl salts.

(50 mL) at 15−20 °C. The resulting mixture was stirred for a further 90 min and then diluted with ice-cold water (100 mL). The product was isolated by filtration and dried in vacuo over silica. The dried product was taken up with dry hot benzene and filtered hot to separate the hydrolysis products and sufficient dry petroleum ether (bp 60−80 °C) added to cause the solution to become opaque. Keeping the mixture overnight gave recrystallized product which was isolated by filtration, washed with dry petroleum ether (bp 40−60 °C), and kept over wax turnings; an alternative recrystallization solvent is heptane. The material had a melting point of 120−1 °C (lit.[6] mp 120−1 °C).

1'-(4,6-Diphenoxy-1,3,5-triazin-2-yl)pyridinium Salts 1a−j. These were prepared by the following general procedure.[7] A solution of the appropriate pyridine (0.01 mol) in tetrahydrofuran (25 mL) was added dropwise over 15 min to a vigorously stirred solution of 4,6-diphenoxy-1,3,5-triazin-2-yl chloride (2 g, 0.01 mol) in tetrahydrofuran solvent (25 mL) at about 20 °C under nitrogen. A precipitate usually formed after the final addition was complete and the mixture was stirred for a further 4 h. The product was isolated by filtration and washed repeatedly with tetrahydrofuran and finally with petroleum ether (bp 40−60 °C). The product was kept over wax turnings and sent directly for ¹H NMR and elemental analysis. Attempts to recrystallize or to purify by exchanging the counterion of the materials usually ended in altered products. Analysis by TLC on Kieselgel (MeOH/toluene, 9:1) indicated a major spot with minor components identified as reactants.

The above method of preparation gave solid precipitates which had satisfactory analyses (after allowing for water incursion), but 3-chloropyridine and 3-methoxypyridine gave products which failed to precipitate. We modified the preparation for the addition of the last two pyridine ligands to include addition of anhydrous $NaClO_4$ (1.22 g, 0.01 mol) to the reaction solution after the initial addition step. A precipitate occurred after about 2 h of stirring at room temperature. The perchlorate salts were dissolved in $CHCl_3$/dimethyl sulfoxide (1:1, v/v) and added dropwise to a stirred mixture of ethyl acetate/hexane (1:1, v/v). The resultant precipitate was collected, and TLC analysis (petroleum ether (bp 40−60 °C)/ethyl acetate, 4:1, v/v) showed a single spot. The products were isolated and kept over wax turnings and silica gel before being sent for elemental analysis. Many of the triazinylpyridinium salts are hygroscopic, and the elemental analysis (Table 1) reveals varying proportions of water in most of the samples.

Other materials were of analytical reagent grade or were purified by recrystallization or redistillation from bench grade products. Dioxane and tetrahydrofuran were of "HPLC" grade and were purified by their passage through active alumina, and the filtrate was tested for peroxides by use of KI solution and starch indicator. Water used throughout was degassed and doubly distilled from glass.

TLC analyses were carried out with DC-Alufolien Kieselgel-60 F_{254} 0.2 mm plates using either MeOH/toluene (9:1, v/v) or petroleum ether (bp 40−60 °C)/ethyl acetate (4:1, v/v) as eluent. Melting points were determined with a Kofler "Thermospan" instrument, and ¹H NMR spectra were recorded with Jeol JNM 100 MHz and Jeol GX 270 MHz instruments (we are grateful to Mrs. M. Williamson and Dr. D. O. Smith for this service). Elemental analyses were carried out by Mr. A. J. Fassam of the University of Kent Analytical Laboratory using a Carlo Erba 1106 CHN analyzer.

The analytical and physical data (Table 1) for the materials prepared here and the NMR data were consistent with the proposed structures of the compounds.

Kinetic Methods. Rates of reaction of the triazin-2-yl species were measured at 25 °C in a solvent mixture of 10% dioxan/water (v/v) with ionic strength maintained at 0.25 M with KCl. A series of solutions were prepared which had the same pH, ionic strength, and solvent composition but varying concentration of the substituted pyridine. Stock solutions of pyridine containing buffers were prepared by adding the solution of substituted pyridine, dioxane, buffer at 0.05 M (where necessary), HCl (1 M), and water to produce solutions of the appropriate pH. Stock solutions of the substrate triazin-2-yl species were prepared in dimethyl sulfoxide at a concentration between 10 and 15 mg/5 mL.

The kinetics of the reactions were monitored at a suitable wavelength determined in preliminary experiments by repetitive scanning of the UV spectrum. The reactions were initiated by adding an aliquot (0.02 mL) of the triazin-2-yl solution to a silica cell containing sample solution (2.5 mL) in the thermostated cell compartment of a spectrophotometer (Unicam SP800 or Perkin-Elmer Lambda 5 instrument). The rate constants were determined from the change of absorbance versus time fit directly to the theoretical first-order rate equations by grid search programs written in BASIC and using a BBC Master-128 computer or an Opus VII desktop PC. The pH values of the solutions were measured directly in the cell at the end of the reaction with a Radiometer Model PHM 62 instrument calibrated with EIL buffers. Results where changes in pH occurred differing by greater than ±0.05 units from that of the original solution were discarded.

Product Analysis. Products from the reactions of pyridines with the parent triazin-2-yl pyridinium salt were identified by comparing the UV spectrum at completion of the reaction with those of authentic samples of the anticipated products under similar conditions.

pH Dependence of the UV Absorbance of Aqueous Solutions of Triazin-2-ylpyridinium Ions. It was observed that the value of the initial absorbance (A_o) for solutions of the triazinylpyridinium salts changed as a function of the pH. Measurements were made of A_o as a funtion of pH in the absence of added pyridines by extrapolating the absorbance to zero time. Values of the ionic product, K_w, were determined for the solvent in question by the following technique. Solutions of HCl (after accurate dilution) were employed to calibrate the pH probe which measured the $[H^+]$ at defined concentrations of KOH. It is assumed that there is no interference from the K^+ ion at the concentrations of KOH employed.

Results

Pseudobase Formation in Aquesous Solutions of Triazin-2-ylpyridinium Salts.

The UV spectrum of the triazin-2-ylpyridinium ions without added pyridines changed with pH according to a titration equation (3a) (Figure 1) from which the parameter K_{R+}[8] could be determined for the formation of the pseudobase assumed to be formed (Scheme 1). The value K_{R+} fitted the Brønsted equation (3b); the parameters A_a and

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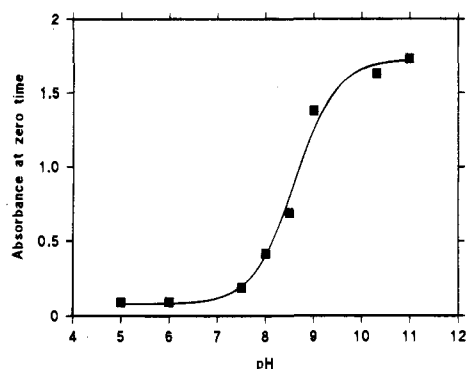(8) Bunting, J. W. *Adv. Heterocycl. Chem.* **1975**, 25, 1.

Figure 1. Dependence on pH of the absorbance of 1′-(2,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium chloride (**1a**) at 25 °C. The line is calculated from eq 3a using data from Table 2.
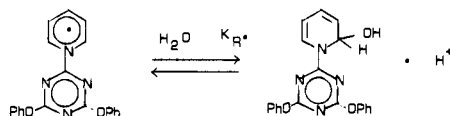
Scheme 1. Pseudobase Formation from **1a**

Table 2. Value of pK_{R+} for the Substituted Pyridinium Pseudoacids **1a,b,h,i**[a]

pyridinium cation	pK_a^{xpy} [b]	ΔpH[c]	λ^f/nm	N^d	pK_{R+}^{xpy} [e]
3-Cl (**1h**)	2.81	2.63–6.37	315	7	4.40
4-CONH$_2$ (**1b**)	3.50	2.20–9.80	315	7	4.88
3-MeO (**1l**)	4.91	6.83–9.36	315	6	8.10
parent (**1a**)	5.32	5.00–11.0	305	8	8.61

[a] Conditions: 25 °C, 0.25 M ionic strength maintained with KCl. Solvent composition: 9:1 water/dioxane (v/v). [b] pK_a of the substituted pyridine; values from Table 3. [c] pH range of the absorbance measurements. [d] Number of data points. [e] Errors no greater than ±0.05. [f] Wavelength of absorption measurement.

A_b are the absorbances due to pseudoacid and pseudobase, respectively.

$$A_o = A_a/(1 + K_{R+}/[H^+]) + A_b/(1 + [H^+]/K_{R+}) \quad (3a)$$

$$pK_{R+} = (1.85 \pm 0.21)pK_a^{xpy} - 1.12 \pm 0.88 \quad (r = 0.9875) \quad (3b)$$

The determined values of pK_{R+} (Table 2) may be used to estimate the proportion of the triazinylpyridinium ions in solution at a given pH. Slight yellow color was observed if solutions of the pyridinium salts were kept at pH 10–12 (the pyridinolysis reactions were not followed at such high pH values); this is considered to be consistent with pyridinium ring fission to yield the 2-aminotriazine.[9]

Reaction of Pyridines with Triazin-2-ylpyridinium Chloride. Triazin-2-yl-substituted pyridinium salts are subject to hydrolysis, and plots of rate constants against buffer concentration for reactions with pyridines showed intercepts at zero pyridine concentration at the higher pH values employed here. The pH values of the experiments were kept as low as possible, consistent with sufficient free pyridine base, so that the rate constant intercepts due to background hydrolysis were only a minor proportion of the total change over the concentration range of pyridine. The principal final products of the reaction of 1′-(4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium chloride with 4-aminopyridine and isonicotinamide were identified as the substi-
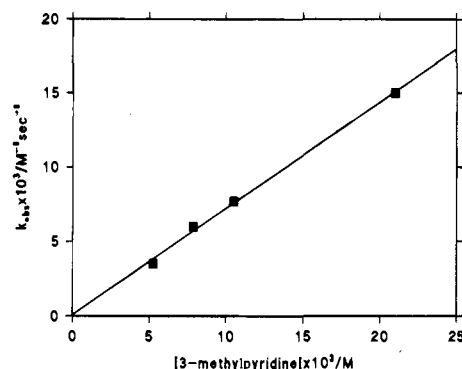
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Figure 2. Pseudo-first-order rate constants for the decomposition of **1a** in buffer solution at pH 5.70 as a function of total 3-methylpyridine concentration. The line is calculated according to eq 4 with the k_{xpy} parameter from Table 3 and a negligible k_{int}.

tution products at the triazine 2-position by comparison of the UV spectra with those of synthesized samples. The reactions exhibited excellent pseudo-first-order kinetics over at least 90% of their total progress curves, and the derived rate constants were linearly dependent on the concentration of the added pyridine (eq 4; see Figure 2 for an illustration). The intercept

$$k_{obs} = k_{int} + k_2'[x{-}pyridine] \quad (4)$$

at zero pyridine concentration (k_{int}) was never a substantial component of the reactions and agreed with the hydrolytic rate constants at the given pH in the absence of pyridine buffer.

Second-order rate constants were obtained for both forward (k_{xpy}) and reverse (k_{-xpy}) reactions from the pseudo-second-order rate constant, k_2', using eq 5. A correction is necessary

$$k_{xpy} = k_2'/(1 + K_a^{xpy}/[H^+]) \quad (5)$$

in the results for k_{-xpy} (the rate constant for attack of pyridine on the triazin-2-ylpyridinium salts) in the runs at those pH values where the substrate is in equilibrium with a significant proportion of pseudobase (Scheme 1). Such a correction is not needed for the forward reaction (k_{xpy}) because the studies were all at pH values where the the pseudobase of the parent **1a** is a neglible component. The correction to be employed is given by eq 6 where K_{R+} is the thermodynamic dissociation constant

$$k_{-xpy} = \{k_2'/(1 + K_a^{xpy}/[H^+])\}(1 + K_{R+}/[H^+]) \quad (6)$$

of the pseudoacid. Values of k_{xpy} and k_{-xpy}, respectively, are collected in Tables 3 and 4.

If the mechanism were stepwise (eq 7), the parameters k_{xpy}
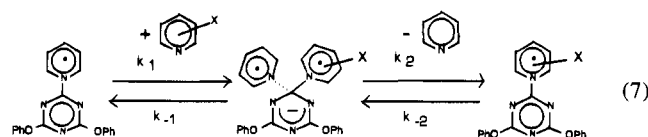
for attack of substituted pyridines on 1′-triazin-2-ylpyridinium salt (Table 3) should fit a theoretical law (eq 8) and the

$$k_{xpy} = k_{py} \times 10^{\beta_1 \Delta pK_a}/(1 + 10^{-\Delta\beta\Delta pK_a}) \quad (8)$$

parameters for the reverse reaction (k_{-xpy}, Table 3) should fit the analogous eq 9. The parameter $\Delta\beta$ is $\beta_2 - \beta_{-1}$, $\Delta pK_a =$

$$k_{-xpy} = k_{py} \times 10^{-\beta_{-2}\Delta pK_a}/(1 + 10^{\Delta\beta\Delta pK_a}) \quad (9)$$

pK_a^{xpy} − pK_a^{py}, and k_{py} is the identity rate constant, namely,

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Table 3. Kinetic Data for the Reactions of Substituted Pyridines with 1'-(4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium Chloride[a]

x[b]	pK_a^{xpy} [c]	$k_{xpy}^e/$ $(M^{-1}s^{-1})$	pH[f]	$[xpy]^g/$ mM	k_{obs}^h $(10^{-3}s^{-1})$	N^i	$\lambda/$nm[j]
3-Cl	2.98[d]	0.000633	3.60	40–140	0.08–0.12	4	332
3-MeOCO	3.25	0.00246	4.00	30–100	0.15–0.30	5	325
3-Ac	3.43	0.00341	4.23	30–140	0.16–0.46	4	370
4-CONH₂	3.55	0.011	3.65	50–150	0.46–1.09	5	320
3-MeO	4.94	0.208	5.45	9–50	4.88–11.23	5	325
3-Me	5.82	1.66	5.70	5–20	3.50–15.00	5	290
3,5-Me₂	6.14	3.12	6.20	5–20	9.10–34.50	4	300
4-MeO	6.71	5.01	6.55	6–17	19.1–39.0	4	280
4-MPk	8.63[d]	72.7	7.95	1–3	20.0–38.0	5	330
4-NH₂	9.21	96.3	8.55	0.8–3	12.6–39.1	4	305
4-NMe₂	9.68	192	9.10	5–20	15.0–34.0	4	300

[a] General conditions: 25 °C, 0.25 M ionic strength maintained with KCl. Solvent composition: 9:1 water/dioxane. The pH was maintained with each substituted pyridine acting as its own buffer except for 4-amino- and (4-dimethylamino)pyridines where 0.05 M carbonate buffer was used. [b] Substituent(s) in the nucleophilic pyridine. [c] pK_a values from ref 10c. [d] pK_a values from ref 11a. [e] Error range not more than 10% of the quoted value. [f] Average pH for all the runs. [g] Concentration range of the pyridine. [h] Range of the observed pseudo-first-order rate constants. [i] Number of data points not including duplicates. [j] Wavelength used for the kinetic study. [k] N-Pyrid-4-ylmorpholine.

that for attack of pyridine on **1a**. The numerical subscript for the β refers to the single reaction step of the same number which is assumed reasonably to obey a linear Brønsted plot. The data for the parameters k_{xpy} and k_{-xpy} can be fit to these equations by a grid search program which recognizes that k_{py} and $\Delta\beta$ are parameters common to both equations. The fit is illustrated in Figure 3 where the solid lines represent fits of the two equations globally and the dashed lines indicate fits of k_{xpy} and k_{-xpy} separately to eqs 8 and 9, respectively. The derived global parameters are recorded in the legend of Figure 3. A graphical indication of the goodness of fit, apart from consideration of the correlation coefficients and uncertainties, is the similarity of the lines obtained from the "forced global" fit and the "free running" fit of each set of rate constants to its own equation (eq 8 or 9; Figure 3). The free running fit does not take into account the common values of k_{py} and $\Delta\beta$ in both equations, and it is not surprising, in view of the limited data, that these values from both equations are not equal in this analysis. The experimentally determined value of each parameter is close to that obtained via the preferred global fit within the uncertainty limits.

The equilibrium constants obtained by division of forward by reverse rate constants (Table 4) fit a linear Brønsted equation (10), and this is illustrated in Figure 4. The Brønsted exponent

$$\log K_{eq} = (-1.19 \pm 0.04)pK_a^{xpy} + 6.35 \pm 0.23$$
$$(r = 0.9979) \quad (10)$$

for eq 10 should be the same as that obtained by summation of β_1, $\Delta\beta$, and $-\beta_{-2}$ obtained from the global fitting of eqs 8 and 9 (1.25 ± 0.13), and this equality (within the uncertainty limits) gives further confidence in the self-consistency of the above analysis.

Reaction of Pyridines with Triazin-2-yl Chloride. The reactions of pyridines with 4,6-diphenoxy-1,3,5-triazin-2-yl chloride obey the rate law of eq 4, and the second-order rate constants, collected in Table 5, were obtained as for the transfer reaction from triazinylpyridinium ions by use of eq 5. The second-order rate constants (k_{xpy}^{Cl}) fit a linear Brønsted equation (11) which is illustrated in Figure 5.

$$\log k_{xpy}^{Cl} = (0.51 \pm 0.041)pK_a^{xpy} - 3.35 \pm 0.25$$
$$(r = 0.9878) \quad (11)$$

Discussion

Reaction between Pyridines and 1'-(2,6-Diphenoxy-1,3,5-triazin-2-yl)pyridinium Cations. The Brønsted type plots for reactions of substituted pyridines with the triazinylpyridinium cation (k_{xpy}) and for the reverse reaction (k_{-xpy}) are illustrated in Figure 3, and they both exhibit breaks at the pK_a of the parent pyridine; this provides excellent evidence for a two-step process (eq 7). We shall employ the parameters obtained from the global fitting procedure, including the β_{eq} determined from them (1.25), in determining effective charges for the reaction. The mechanism of eq 7 would have been expected[3] prior to the discovery of an A_ND_N process, but the result is nevertheless important because the position of the break point may be unequivocally predicted. There are very few kinetic demonstrations of Meisenheimer-like intermediates, and their existence in displacement reactions in both heteroaromatic and aromatic systems rests largely on analogy with the cases where such intermediates are stable enough to have been isolated.[3] The observation of a break point at an unequivocally predicted value of a parameter has never been made for any system utilizing quasi-symmetrical reactions as probes of "timing" in group transfer reactions.[10] Moreover, to our knowledge, no previous demonstrations of reactive intermediates by use of intersecting linear free energy correlations possess *a-priori* predictable break points.

The observation of a stepwise process is of further significance in view of the concerted mechanism of transfer between phenoxide ions (eq 1).[2] Other transfer systems, namely, those of carbonyl,[11] phosphoryl[12] and sulfuryl,[13] have been shown to involve concerted displacement mechanisms when the leaving group and nucleophile are either pyridines or phenoxide ions. The putative tetrahedral adducts for transfer of the carbonyl group between either pyridines[11a] or phenoxide ions[11b] have insufficient stabilities to support the stepwise process against a concerted one although Moodie and Castro have shown that tetrahedral adducts involving both pyridine and oxygen ligands can be discrete intermediates.[14] In triazinyl group transfer the corresponding adduct with phenoxide ion ligands is unstable[2] whereas that with pyridine ligands is relatively stable. The explanation of the difference between the systems is not apparent to us but may be due to the greater delocalization of the negative charge by the triazinyl ring in the putative Meisenheimer-like adduct compared with the more localized oxyanion in the tetrahedral intermediate in carbonyl group transfer. If this were the case, then the Meisenheimer-like adduct would be relatively more stable than the tetrahedral adduct, bringing its energy closer to that for a borderline region between stepwise and concerted mechanisms. Relatively small energy changes, which would be difficult to attribute, could therefore cause changes in mechanism.

(10) (a) The first applications of this technique employing quasi-symmetrical reactions were reported by the groups of Williams[10b,c,f,g] and Jencks.[10d,e] (b) Bourne, N; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 3357. (c) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 7591. (d) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 3356. (e) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 7597. (f) Bourne, N.; Hopkins, A. R.; Williams, A. *J. Am. Chem. Soc.* **1993**, *105*, 3358. (g) Bourne, N.; Hopkins, A. R.; Williams, A. *J. Am. Chem. Soc.* **1985**, *107*, 4327.

(11) (a) Chrystiuk, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040. (b) Ba-Saif, S. A.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 6362. (c) Ba-Saif, S. A.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1989**, *111*, 2647.

(12) Ba-Saif, S. A.; Waring, M. A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1653.

(13) D'Rozario, P. D.; Smyth, R. L.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 5027.

(14) (a) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 828. (b) Castro, E. A.; Ibanez, F.; Lagos, S.; Schick, M.; Santos, J. G. *J. Org. Chem.* **1992**, *57*, 2691.

Table 4. Kinetic Data for the Reaction of Pyridine upon 1'-(4,6- Diphenoxy-1,3,5-triazin-2-yl)-x-pyridinium Chlorides[g]

x[a]	$pK_a^{xpy\ b}$	k_{-xpy}^{c}/(M^{-1} s^{-1})	pH[d]	[py][e]/mM	k_{obs}^{f}/(10^{-3} s^{-1})	N[g]	λ^{h}/nm	K_{eq}
4-CONH₂	3.55	1.86	3.63	19—96	1.3—6.68	5	300	169
3-Me	5.82	0.292	5.65	1—50	1.86—10.64	5	290	0.176
3,5-Me₂	6.14	0.206	5.43	8—41	0.94—4.85	5	285	6.60 × 10^{-2}
4-NH₂	9.21	0.00367	5.90	30—150	0.18—0.52	4	330	3.81 × 10^{-5}
3-Cl	2.98	0.535	5.25	6—30	1.0—7.6	5	325	845
parent	5.32	0.95[h]						1.0

[a] Substituent(s) in the nucleofugal pyridine. [b] pK_a values from Table 3. [c] Error range not more than 10% of the quoted value. [d] Average pH for all the runs. [e] Concentration range of pyridine. [f] Range of the observed pseudo-first-order rate constants. [g] General conditions: 25 °C, 0.25 M ionic strength maintained with KCl. Solvent composition: 9:1 water/dioxane. The pH was maintained with pyridine acting as its own buffer. [h] Value determined from the global fit; see the text and legend to Figure 3. [i] $K_{eq} = k_{-xpy}/k_{xpy}$.
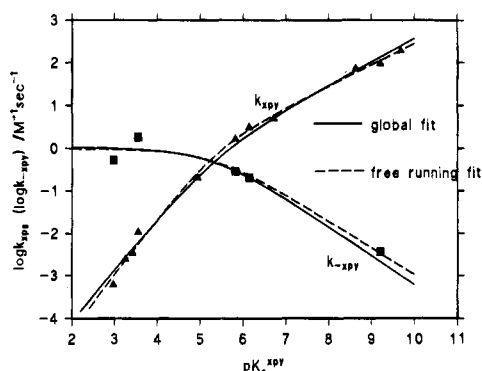

Figure 3. log k_{xpy} and log k_{-xpy} versus pK_a^{xpy}. The data and conditions are from Tables 3 and 4. The solid lines are calculated from eqs 8 and 9 using the parameters $k_{py} = 0.95 \pm 0.15$ M^{-1} s^{-1}, $\beta_1 = 0.56 \pm 0.03$, $\Delta\beta = 0.67 \pm 0.05$, $\beta_{-2} = 0.02 \pm 0.05$. The dashed lines are calculated from eq 8 using $k_{py} = 1.27 \pm 0.24$ M^{-1} s^{-1}, $\beta_1 = 0.50 \pm 0.03$, and $\Delta\beta = 0.82 \pm 0.08$ and from eq 9 using $k_{py} = 0.99 \pm 0.48$ M^{-1} s^{-1}, $\Delta\beta = 0.64 \pm 0.21$, $\beta_{-2} = 0.00 \pm 0.14$.

Table 5. Reaction of Substituted Pyridines with 4,6-Diphenoxy-1,3,5-triazin-2-yl Chloride[a]

sub-stituent	$pK_a^{xpy\ b}$	$k_{xpy}^{Cl\ c}$/(M^{-1} s^{-1})	pH[d]	[xpy]/mM[e]	k_{obs}^{f}/(10^{-3} s^{-1})	N[g]	λ^{h}/nm
4-CONH₂	3.55	0.021	4.23	20—100	0.28—0.61	4	320
parent	5.32	0.29	5.43	10—50	2.64—9.23	5	275
3-Me	5.82	0.53	6.53	4—19	1.79—8.51	5	295
3,5-Me₂	6.14	1.04	6.35	4—21	2.67—13.4	5	300
4-MeO	6.71	0.60	6.73	3—15	0.86—4.6	5	295
4-NH₂	9.21	18.7	8.40	0.8—4	2.12—10.7	5	325
4-NMe₂	9.68	41.2	8.80	1—7	4.99—29.6	5	350

[a] General conditions: 25 °C, 0.25 M ionic strength maintained with KCl. Solvent composition: water/dioxane (9:1 v/v). The pH was maintained with each substituted pyridine acting as its own buffer except for the 4-amino- and (4-dimethylamino)pyridines where 0.05 M carbonate buffer was employed. [b] Values of pK_a^{xpy} from Table 3. [c] Error range not more than 10% of the quoted value. [d] Average pH for all the runs. [e] Concentration range of the pyridine. [f] Range of the observed pseudo-first-order rate constants. [g] Number of data points, not including duplicates. [h] Wavelength employed for the kinetic study.
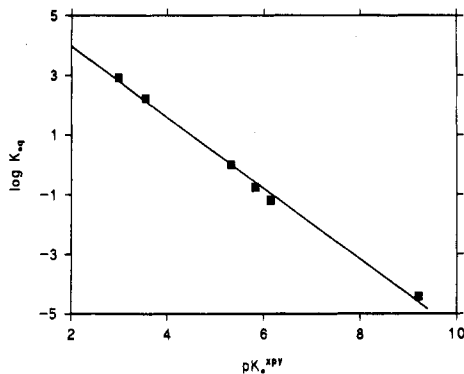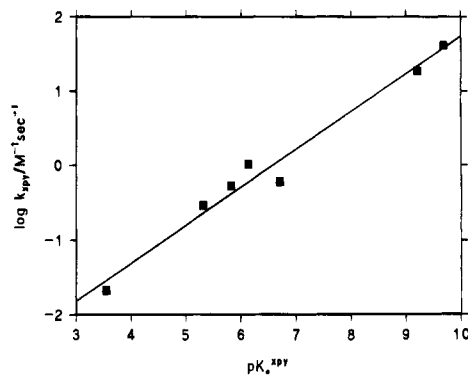

Figure 4. Brønsted type plot for the equilibrium constants for the transfer of 2,6-diphenoxy-1,3,5-triazin-2-yl between pyridine and substituted pyridines. The data and conditions are from Table 4, and the line is calculated from eq 10.

Figure 5. Brønsted dependence of log k_{xpy}^{Cl} versus the pK_a of the attacking pyridine for 2,6-diphenoxy-1,3,5-triazin-2-yl chloride. The data and conditions are from Table 5; the line is calculated from eq 11.

Changes in Effective Charge During the Transfer Reactions.

Scheme 2 and Chart 1 illustrate the full effective charge map for the transfer of the 2,6-diphenoxy-1,3,5-triazin-2-yl group between pyridine nucleophiles. The value of β_{eq} for the overall transfer of the triazin-2-yl group (1.25) is a little less than that for transfer of the triazinyl group between aryl oxide ions (1.48). This comparison is in the same direction as that for the transfer of the acetyl group between pyridines and between phenoxide ions (1.6 and 1.7, respectively), but in both cases the difference is not remarkable. The value of β_{eq} for the transfer can be added to the list of β_{eq} values for other transfer processes.[1a] The effectiveness of the triazin-2-yl group in inducing pseudobase formation in the pyridinium nucleus is consistent with its electron-withdrawing character as identified by the value of β_{eq}.

It is interesting that the value of $\beta_{eq(1)}$ for the bond formation step between the triazine and substituted pyridines (1.21) is within uncertainty limits the same as the overall β_{eq} value. The value for $\beta_{eq(2)}$, as that for β_{-2} and β_2, is uncertain. However, the ratio of $\beta_{-2}/(\beta_{-2} + \beta_2)$ is not uncertain and is known as accurately as the corresponding ratio for the k_1 step although the experimental values of the individual parameters are zero within the error limits; the value quoted for $\beta_{eq(2)}$ is thus an upper limit. The bond fission step has a $\beta_{eq(2)}$ (0.04) less than 5% of that for the addition step. These results are consistent with a reaction coordinate passing along the edges of a More—O'Ferrall—Jencks diagram (Figure 6).

The change in effective charge on the attacking nucleophile is, within experimental error, taken wholly by the addition step. There appears to be no coupling between the substituents in the nucleophile in the bond-forming step and the bond undergoing fission. Such a coupling occurs in the transfer of the triazinyl group between phenoxide ions in good agreement with

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Scheme 2. Effective Charge Map of the Transfer of the Triazin-2-yl Group between Pyridine Nucleophiles (See Text for Accuracy of the Parameters for Step 2) (2,6-Diphenoxy Groups Omitted for Clarity)
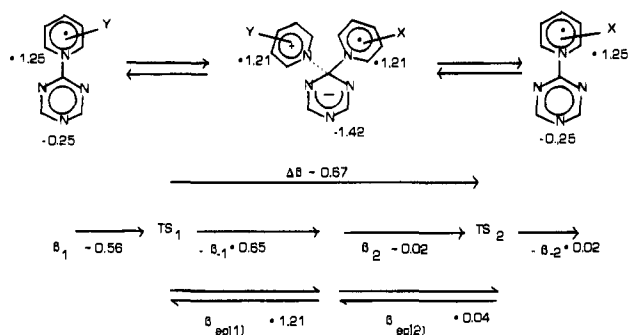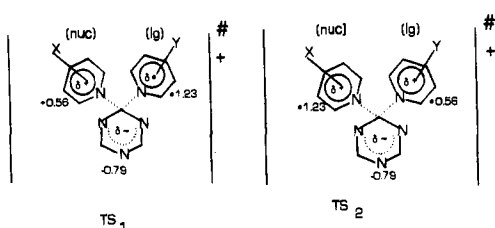

Figure 6. More−O'Ferrall−Jencks diagram for the transfer of triazin-2-yl between pyridine and substituted pyridines.

Chart 1. Detailed Structures for the Transition States TS_1 and TS_2 from Scheme 2

the concerted nature of the latter reaction. It is reasonable to assume that a stepwise transfer between phenolate ions would exhibit a similar absence of coupling. An absence of coupling would be reasonably expected between formation and fission steps in the case of most stepwise group transfer reactions, but to our knowledge there are no definitive reports where the effective charge map has been fully characterized for a stepwise $A_N + D_N$ process;[15] the present results are therefore of great importance in interpreting effective charge changes in stepwise processes in general.

Reaction of Substituted Pyridines with Triazin-2-yl Chloride. Knowledge of β_{eq} enables the interpretation of most Brønsted selectivities (β) for reaction of triazines with pyridines as either a nucleophile or a leaving group. Recent work on triazin-2-yl group transfer equilibria between phenoxide ion nucleophiles[2] enables a similar situation *vis-a-vis* reactions involving the phenolate ion ligand. The linear Brønsted plot (Figure 4) indicates that there is no change in the rate-limiting step over the range of substituents for displacement of chloride

ion from the triazin-2-yl chloride by substituted pyridine nucleophiles. It is probable that the mechanism is stepwise with a rate-limiting addition step; if the second step were rate-limiting, then the β_{nuc} would be on the order of 1.21 because formation of the Meisenheimer-like intermediate is likely to involve a value of $\beta_{eq(1)}$ similar to that when pyridine is the leaving group. The value of the Leffler α^{1a} of $0.51/1.25 = 0.41$ indicates a level of bond formation similar to that in the case where pyridine is displaced, which is consistent with the lack of connectivity between electronic effects in bond formation and bond fission.

Pseudobase Formation. The base hydrolysis of triazin-2-ylpyridinium species often yields a 2-aminotriazine as well as the 2-hydroxy product (strictly the 2-oxo).[9] This phenomenon is due to attack at the pyridine ring followed by ring opening and hydrolysis of the resultant imino species. The present results indicate that the pseudobase is often formed in stoichiometric amount and can be observed for suitable triazinylpyridinium salts in the UV−vis spectrum at zero time prior to the degradation by ring opening or by attack at the triazinyl center. Bunting[8] observed that this type of system could be analyzed according to Scheme 1. The values of pK_{R+} appear to be lower than those for the methylpyridinium ion ($pK_{R+} > 16$); it is probable that an arylpyridinium ion would have a similar high value. The triazinyl ring must be acting as a substantial electron-withdrawing group, and this would be consistent with the presence of the two ring aza groups adjacent to the C-2 atom attached to the pyridinium nitrogen. The very large Brønsted β parameter for the pK_{R+} of 1.85 is consistent with substantial charge change registered between the substituents and the reaction center, which would be expected for pseudobase formation due to the destruction of the heteroaromaticity.

(15) (a) Full effective charge maps have been constructed for $A_N D_N$ reactions[1a] and for stepwise processes involving proton transfer[15b] but not for $A_N + D_N$ processes. (b) Hill, S. V.; Thea, S.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 437; *J. C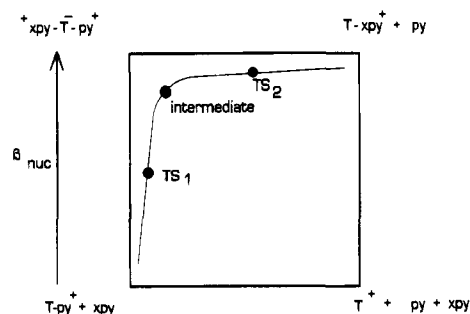hem. Soc., Chem. Commun.* **1982**, 547.