The aminolysis and hydrolysis of *N*-(4,6-diphenoxy-1,3,5-triazin-2-yl) substituted pyridinium salts: concerted displacement mechanism

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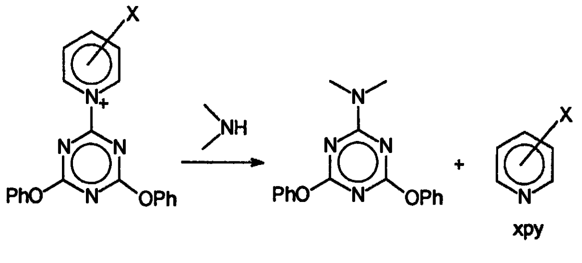
Reaction of the title pyridinium salts in aqueous buffers containing amines involves nucleophilic displacement of the pyridine by the amine nitrogen in addition to background hydrolysis. The second-order rate constants for attack of a series of unhindered primary amines on the (4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium cation obey a Brønsted-like equation with slope $\beta_{nuc} = 0.68$. Six-membered-ring cyclic secondary amines have a similar Brønsted selectivity but are approximately 10-fold more reactive than primary amines of similar pK_a.

The reactivity of ethanolamine against the title pyridinium salts obeys a Brønsted-like equation with $\beta_{lg} = -0.47$. In aminolysis of the triazinyl pyridinium salts the changes in bond fission and bond formation signalled by the polar substituent effects give Leffler α_{lg} and α_{nuc} values of 0.38 and 0.54, respectively, which indicate strong coupling between the bonding changes consistent with a concerted process for the displacement reaction. The adduct in the putative stepwise mechanism is considered too reactive to possess a significant barrier for it to exist as a discrete molecule.

Introduction

Recent interest in concerted displacement mechanisms (A_ND_N) at trigonal carbon centres has been extended to nucleophilic aromatic substitution reactions.[1–3] Although A_ND_N mechanisms have been considered theoretically unlikely for trigonal carbon[4] they have been demonstrated in carbonyl acyl group transfer reactions[5] and in displacements at the triazinyl function. The novelty of the discoveries of concerted mechanisms warrent further studies to investigate the scope of the A_ND_N process for aromatic substitution. Studies centre on the heteroaromatic systems as these offer good vehicles for the study of displacement reactions without complications attendant on nitro-activated aromatic systems.[6]

We are in a good position to employ polar substituent effects to investigate the advancement of bond formation and bond fission in displacements at the triazinyl group because previous work has determined the values of β_{eq} for the transfer to substituted pyridine[2] or phenoxide ion[1] nucleophiles. The present study is of the aminolysis of 4,6-diphenoxy-1,3,5-triazin-2-yl substituted pyridinium salts, eqn. (1), where the structures of both nucleophile and leaving group are varied. The application of Leffler α_{nuc} and α_{lg} values[7] determined from the Brønsted selectivities enables the comparison of the relative extents of bond formation and bond fission, respectively, and thus provides information about the extent of coupling between the two bonding processes, which is necessary for a fundamental understanding of a mechanism.



(1)

Experimental

Materials

Water used throughout the study was double distilled from glass and degassed before use. KCl, acetonitrile and buffers were of AR grade, and amine nucleophiles were obtained commercially and purified by recrystallization, redistillation or by sublimation. Dioxane was purified by passage of the AR-grade material through active alumina and the filtrate tested for peroxides by use of KI solution. (4,6-Diphenoxy-1,3,5-triazin-2-yl)pyridinium salts were synthesized as described previously.[2] 2-Piperidyl-4,6-diphenoxy-1,3,5-triazine was prepared by stirring a mixture of piperidine (0.85 g) and 2-chloro-4,6-diphenoxy-1,3,5-triazine (3.00 g) and triethylamine (1.40 ml) and chloroform (50 ml) for 2 h, filtering, washing the filtrate with water and evaporating the dried solution. The yield was not optimized and the material, recrystallized from methanol in prisms, had mp 128–129 (lit.,[8] 130–132 °C) (Found: C, 68.70; H, 5.70; N, 16.10%. Calc. for $C_{20}H_{20}N_4O_2$ C, 68.9; H, 5.8; N, 16.1%). 2-Hydroxy-4,6-diphenoxy-1,3,5-triazine was from a previous study[2] and the identities and purity of the substrates were confirmed by NMR spectroscopy and TLC. 2-Amino-4,6-diphenoxy-1,3,5-triazine was prepared according to the method of Thurston[9a] from 2-amino-4,6-dichloro-1,3,5-triazine;[9b] it had mp 180–182 (lit.,[9a] 181–182 °C) (Found: C, 64.1; H, 4.1; N, 20.1%. Calc. for $C_{15}H_{12}N_4O_2$: C, 64.3; H, 4.3; N, 20.0%).

Kinetic methods

Rates of aminolysis were measured at 25 °C with a solvent mixture of composition 20% ethanol–water (v/v) with the ionic strength maintained at 0.25 M with KCl. A series of solutions were prepared with the same pH, ionic strength and solvent composition but with varying concentrations of the amine by diluting stock buffer solution with solution at the same pH, which was lacking the amine. Stock solutions of buffers were prepared by adding the solution of amine, ethanol, trishydroxymethylaminomethane (Tris) buffer at 0.025 M, HCl (1 M) and water to produce solutions of the required pH. Stock solutions of the substrates (the triazinyl species) were prepared in dimethyl sulfoxide (perchlorates) or ethanol (chlorides) at a concentration between 10 and 15 mg ml^{-1}. The kinetics of the reactions were monitored at suitable wavelengths determined in preliminary experiments by repetitive scanning of the UV spectrum. The reactions were initiated by adding an aliquot (0.02 ml) of the stock triazine substrate solution to a silica cell containing the sample solution (2.5 ml) in the thermostatted cell compartment of a Unicam SP800 or Perkin-Elmer Lambda 5 spectrophotometer.

Data were fitted directly to theoretical equations for first-order kinetics by use of grid-search programs written in BASIC and using a BBC Master computer or an Opus VII desktop PC.

Product analysis

Piperidinolysis reactions were also carried out under the conditions of the kinetic experiments but with larger quantities of triazine reactant. The product solutions were evaporated to dryness *in vacuo* and extracted with acetone; the acetone extracts were then subjected to TLC on fluorescent Kieselgel 60 F_{254} DC-Alufolien sheets with benzene eluent. The spots were developed by UV and their positions compared with those for standard 2-piperidinyl-4,6-diphenoxy-1,3,5-triazine and the hydrolysis product, 2-hydroxy-4,6-diphenoxy-1,3,5-triazine. The products of the hydrolysis experiments were examined in a similar way and acetone extracts were subjected to TLC and the spot compared with those for the 2-hydroxy- and 2-amino-4,6-diphenoxy-1,3,5-triazine.

Results and discussion

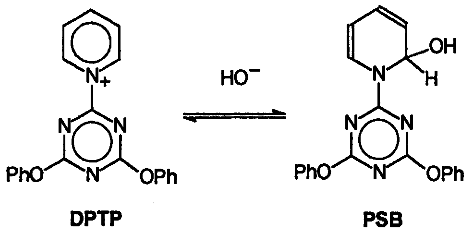
Aminolysis

The decomposition of the 1,3,5-triazin-2-ylpyridinium salts in amine buffers obeyed excellent pseudo-first-order kinetics up to 90–95% of the total reaction and product analysis studies with piperidine indicate that aminolysis rather than hydrolysis is occurring over the pH ranges employed. The rate constants are linearly dependent on the concentration of added amine, eqn. (2), and second-order rate constants, k_2, were obtained by

$$k_{\text{obs}} = k_{\text{int}} + k_2'[\text{amine}]_{\text{total}} = k_{\text{int}} + k_2[\text{free amine}] \quad (2)$$

dividing the slope (k_2') by FB, the fraction of amine present in its basic form.

It is also necessary to correct for the pseudo-base equilibrium, eqn. (3),[2] by division of the second-order rate constant obtained above by FA, the fraction of the triazinyl pyridinium salt present in its pseudo-acid form (FA = $1/(1 + 10^{\text{pH}-\text{p}K_{\text{R}^+}})$.



DPTP PSB

(3)

Intercepts of the rate constants at zero amine concentration (k_{int}) due to hydrolysis were negligible at the pH values studied and are considered later. The rate constants for the piperazinolysis and aminolysis by the monocation of ethylenediamine were determined by studies of the rate constants over a pH range (see Table 1). The data for the piperazine case are illustrated by the pH-dependence (Fig. 1) and are fitted to eqn. (4)

$$k_2' = \frac{(k_aK_{a1}K_{a2} + k_bK_{a1}[\text{H}^+])(\text{FA})}{(K_{a1}K_{a2} + [\text{H}^+]K_{a1} + [\text{H}^+]^2)} \quad (4)$$

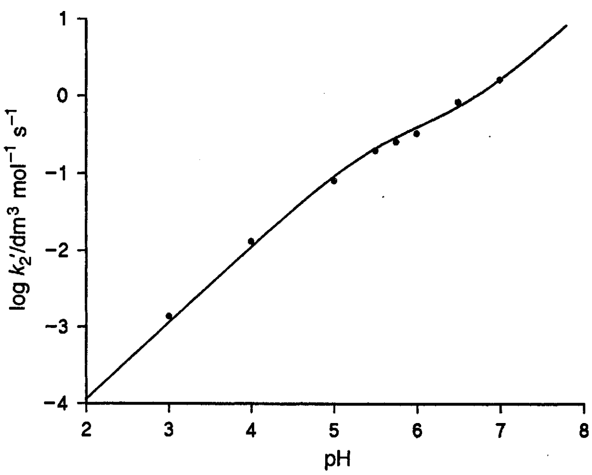


Fig. 1 Dependence on pH of the second-order rate constant for reaction of piperazine with 4,6-diphenoxy-1,3,5-triazin-2-ylpyridinium chloride with conditions as in Table 1; line is calculated from eqn. (4). The points are derived from data corrected for background hydrolysis.

where k_a and k_b are the rate constants for monocation and neutral amines, respectively, and pK_{a1} and pK_{a2} are the pK_a values for the respective di- and mono-cation. In the case of ethylenediamine a similar equation can be written but the reactivity of the diamino form is too high to allow it to be measured under the conditions of these experiments. At the lower pH values, where the fraction present as the neutral ethylenediamine is low, the bulk of the reaction flux goes through the monocation. The values of k_a and k_b were obtained for the diamines from the pH dependency from eqn. (4) by fitting the data using the known values of pK_{a1} and pK_{a2}.

The values for k_2' for attack of amines on the parent triazinyl pyridinium salt are recorded in Table 1 and those for attack of ethanolamine on *N*-triazin-2-yl substituted pyridinium salts in Table 2. The second-order rate constants for the six-membered secondary amines obey the Brønsted type eqn. (5) and those for unhindered primary amines obey eqn. (6). The reaction of ethanolamine with the triazinyl pyridines obeys eqn. (7) and the data from Table 1 are illustrated in Fig. 2.

$$\text{Secondary amines } \log k_2 = 0.71 \pm 0.07\text{p}K - 4.39 \pm 0.65\ (r = 0.9897) \quad (5)$$

$$\text{Primary amines } \log k_2 = 0.68 \pm 0.04\ \text{p}K - 5.15 \pm 0.39\ (r = 0.9877) \quad (6)$$

$$\text{Ethanolamine } \log k_2 = -0.47 \pm 0.03\ \text{p}K + 3.82 \pm 0.20\ (r = 0.9944) \quad (7)$$

Hydrolysis

The hydrolysis of the parent pyridinium salt was studied in order to provide information on the intercepts in the aminolysis reactions. The intercepts obtained from the aminolysis kinetics are displayed in Fig. 3 and they are fitted to eqn. (8), which is obtained from analysis of reaction Scheme 1 and eqn. (9)

$$k_{\text{obs}} = \frac{(k[\text{H}^+] + k_{\text{OH}}K_{\text{w}} + k'_{\text{OH}}K_{\text{w}}K_{\text{R}^+})}{([\text{H}^+] + K_{\text{R}^+})} \quad (8)$$

$$\text{Rate} = k_{\text{obs}}[\text{total triazinylpyridinium salt}] = k[\text{DPTP}] + k_{\text{OH}}[\text{OH}][\text{DPTP}] + k'_{\text{OH}}[\text{OH}][\text{PSB}] \quad (9)$$

The parameter k is the rate constant for reaction of water with the pseudo acid (DPTP), k_{OH} is the rate constant for

Table 1 The reaction of amines with *N*-(4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium chloride[a]

Amine	pK_a	pH	Δk_{obs}/ 10^{-2} s^{-1} [g]	Δ[Amine]/ M[c]	N[d]	FB[e]	k_2/dm^3 mol^{-1} s^{-1} [b]	λ/nm[f]
Morpholine	8.33	6.00	0.120–1.20	0.025–0.120	9	0.004 66 [0.998]	21.4	275
Piperazine		3–7	0.014–13.3		16			275
Monocation	5.56						0.417 (k_a)[i,k]	
Neutral	9.83						865 (k_b)[i,k]	
Piperidine	11.1	8.30	1.34–5.30	0.0025–0.020	5	0.001 50 [0.670]	2250	305
Aminoacetonitrile	5.56	5.00	0.36–1.36	0.1–7.0	5	0.216 [0.999]	0.077 8	275
Ethylenediamine	7.49	5–8.5		0.07–0.13	16		0.360 (k_a)[j,k]	275
Ethyl glycinate	7.65	5.75	0.76–1.65	0.2–0.6	5	0.012 0 [0.999]	1.01	275
Glycylglycine	8.33	7.20	0.68–3.53	0.01–0.12	8	0.069 0 [0.963]	3.73	275
Ethanolamine	9.71	7.20	0.71–3.39	0.060–0.40	5	0.003 08 [0.963]	23.3	275
Glycine	9.80	7.20	0.49–0.91	0.020–0.060	5	0.002 50 [0.963]	41.2	275
Methylamine	11.0	7.40	0.36–0.76	0.01–0.06	4	0.000 251 [0.942]	335	275
Butylamine	10.77	8.00	0.80–1.5	0.020–0.060	5	0.001 70 [0.803]	128	305
Tris[h]	8.23	8.20	0.63–1.22	0.050–0.20	4	0.483 [0.720]	0.194	305
sec-Butylamine	10.67	8.00	0.54–1.8	0.10–0.60	4	0.002 13 [0.803]	14.3	305
tert-Butylamine	10.82	8.00	0.42–0.52	0.03–0.20	4	0.001 51 [0.803]	4.97	305

[a] 25 °C, ionic strength maintained at 0.25 M with KCl, 20% ethanol–water (v/v). [b] The uncertainties of the derived second-order rate constants, k_{nuc} are less than 10%. [c] Range of concentrations of the amine. [d] Number of data points not including duplicates. [e] Fraction of the amine present in its basic form. The value in square brackets refers to the fraction of the pyridinium species (FA) present in its pseudo acid form; where no figure is quoted the fraction of pseudo acid present is unity. Values of pK_{R^+} are from ref. 1. [f] Wavelength of the kinetic experiments. [g] Range of observed rate constants. [h] Trishydroxymethylaminomethane. [i] Values for the piperazine nucleophiles were calculated as described in the text. The rate constant intercepts at zero amine concentration (k_{int}) were negligible; some of the data are derived from measurements at single amine concentrations for which the value of k_{int} was shown to be negligible. [j] The rate constant was calculated assuming only the monocation is active under the pH conditions of the experiments. [k] The parameters k_a and k_b refer to k_2 for the monocation and neutral species, respectively.

Table 2 The reaction of ethanolamine with *N*-(4,6-diphenoxy-1,3,5-triazin-2-yl) substituted pyridinium salts[a]

Amine	pK_a	pH	Δk_{obs}/ 10^{-2} s^{-1} [g]	Δ[Ethanolamine]/ M[c]	N[d]	FB[e]	k_{nuc}/M^{-1} s^{-1} [b]	λ/nm[f]
4-Dimethylamino	9.71	9.00	0.380–1.90	0.1–0.6	5	0.163	0.185	335
Parent	5.25	7.20	0.712–3.39	0.06–0.4	5	0.003 08 [0.963]	22.4	275
3,5-Dimethyl	6.15	7.40	1.97–4.17	0.2–0.5	4	0.004 87	15.4	295
4-Amino	9.14	8.90	0.785–1.57	0.1–0.3	3	0.121	0.324	310
4-Carboxamido	3.51	6.30	0.115–0.200	0.2–0.8	4	0.000 389 [0.0366]	120	315

Footnotes as in Table 1.

reaction of hydroxide ion with the pseudo acid (DPTP), k'_{OH} is the rate constant for hydroxide ion attack on the pseudo base (PSB), K_{R^+} is the equilibrium constant for the formation of the pseudo base and K_w is the ionic product for water ($10^{-14.15}$) under the conditions of the experiment. The value of K_{R^+} has already been determined ($10^{-8.61}$). The fit of the data to eqn. (8) (pK_w = 14.15) without assuming a value of K_{R^+} gives the following parameters: k, $(7.75 \pm 0.65)10^{-5}$; k_{OH}, 958 ± 107; k_{OH}', 1.09 ± 0.11; pK_{R^+} = 8.80 ± 0.08 (r = 0.9986). When the value of pK_{R^+} is fixed at the previously determined value the parameters do not markedly differ and the fit is illustrated in Fig. 3.

Discussion

Aminolysis

Product analysis of the reaction of (4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium salts with piperidine indicates the formation of the corresponding piperidyltriazine species. General base catalysis of hydrolysis in the reaction with amines is excluded by the absence of detectable hydrolysis product (2-hydroxy-4,6-diphenoxy-1,3,5-triazine) and by the observation that hindered amines have significantly reduced reactivity (Fig. 2). The observation that six-membered secondary amines possess a greater reactivity at a given pK_a compared with that of primary amines is consistent with nucleophilic substitution rather than general base-catalysed hydrolysis.

The reactivity of the amines studied here follows a pattern expected for aminolysis reactions; secondary amines are known to react faster than primary amines in reactions involving nucleophilic attack.[10]

Proton transfer in aminolysis of the triazines is subsequent to the bond-formation step as confirmed by the absence of general base catalysis of the reactions; a similar observation has been made for aminolyses of triazinyl species where the leaving group is an aryl oxide ion.[3] Rate-limiting proton

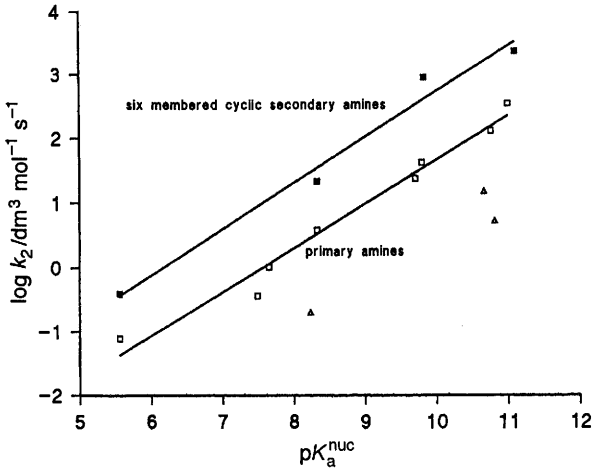


Fig. 2 Brønsted plot for the aminolysis of 4,6-diphenoxy-1,3,5-triazin-2-ylpyridinium chloride by six-membered cyclic secondary amines ■, primary amines □ and hindered amines △ (Tris, *sec*-butylamine and *tert*-butylamine). The data and conditions are from Table 1 and the lines are drawn from eqns. (5) and (6) for secondary and primary amines, respectively.

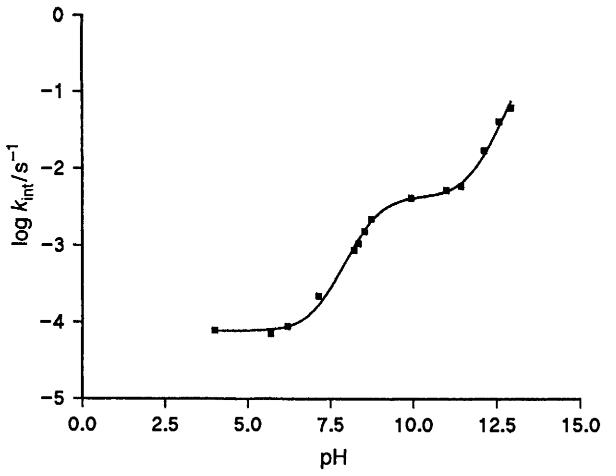
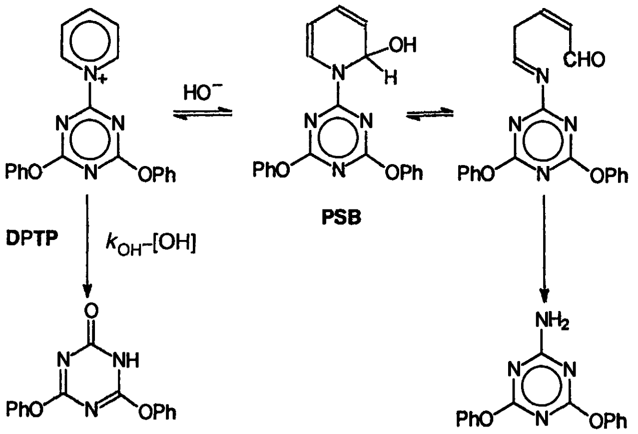


Fig. 3 The hydrolysis of (4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium ions as a function of pH. Line is calculated from eqn. (8) using the parameters given in the text. Conditions as in Table 1 except that the solvent composition is 20% dioxane–water (v/v).



Scheme 1 The hydrolysis of *N*-(4,6-diphenoxy-1,3,5-triazin-2-yl)pyridinium salt

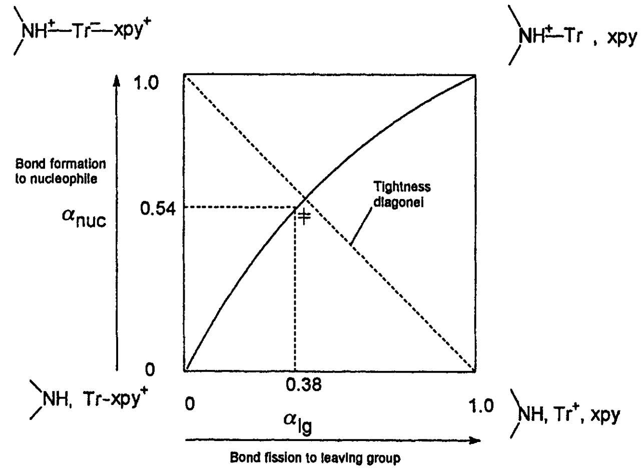
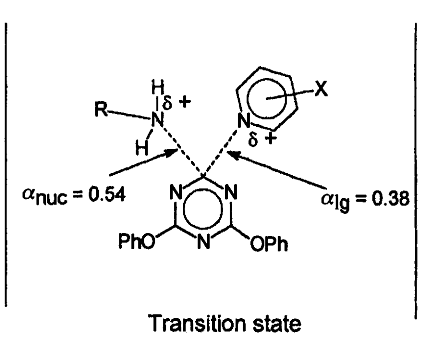


Fig. 4 More O'Ferrall–Jencks diagram for the displacement of pyridines by amines from 4,6-diphenoxy-1,3,5-triazin-2-yl substituted pyridinium salts



transfer is observed in aminolyses of heteroaromatic chlorides in non-aqueous solvents[11] and in the aromatic series the observations of general base-catalysed aminolyses have been employed to demonstrate the Meisenheimer-like intermediate.[4,6,12] When the *N*-protonated product is relatively stable it is likely that proton transfer is not necessary to promote expulsion of the nucleofuge in either a stepwise or concerted process.

Comparison of the value of β_{nuc} for attack by primary amines (0.68) with a standard β_{eq} value for the overall reaction indicates that there is substantial bond formation in the transition structure. Since proton transfer is subsequent to bond formation the reaction in question involves the formation of the cationic species from the triazinyl donor and the amine R_2NH. It is reasonable to assume that that the value of β_{eq} for transfer of triazin-2-yl group between substituted pyridines and a standard nucleophile is the same as that for transfer between substituted primary amines given the absence of steric interaction in either case.[13a] The value of Leffler's α_{nuc} ($\alpha_{nuc} = \beta_{nuc}/\beta_{eq}$) is then calculated to be 0.54 for the attack of primary amines to give the protonated transfer product R_2NH^+–Tr (Tr is the 4,6-diphenoxy-1,3,5-triazin-2-yl group).

The effect of changing the leaving group structure on the second-order rate constant indicates that the bond-fission step in aminolysis of primary amines is also substantially advanced in the displacement reaction. The Brønsted dependencies are linear over the range of pK_a values studied and there is no evidence that the data for the ethanolaminolysis reaction and those for the other aminolyses refer to different rate-limiting steps. The value of β_{lg} for ethanolaminolysis, −0.47, yields a Leffler α_{lg} of 0.38 assuming that β_{eq} is close to that for pyridinolysis (1.25). The substantial values of both α_{lg} and α_{nuc} are consistent with a concerted process; the ratio of α_{nuc}/α_{lg} is 1.42 indicating substantial coupling between bond formation and bond fission and a transition structure which lies near to the tightness diagonal[14] (Fig. 4). The β_{nuc} for the secondary amines is close to that of the primary amines indicating that the conclusion is probably valid for aminolysis in general.

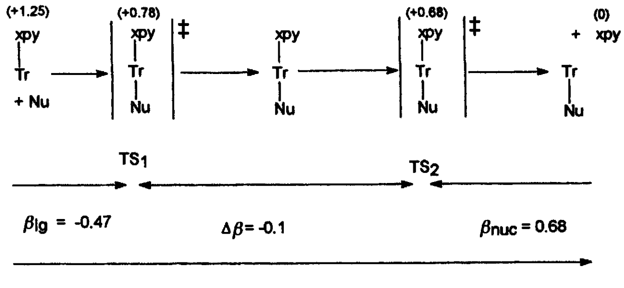


Fig. 5 Effective charge map for the putative stepwise aminolysis process. The values in parentheses refer to the effective charge on the pyridine nitrogen.

Assuming that the mechanism involves a putative stepwise process with the intervention of a Meisenheimer-like intermediate then an effective charge map can be constructed as shown (Fig. 5) for aminolysis by primary amines. It is possible to compare effective charges because the standard calibrating equilibria are similar. The formation of TS$_1$ from common nucleophile and varying pyridine leaving group has a β_{lg} of -0.47 corresponding to an increase in effective charge on the nucleofuge of -0.47 units. The value of β_{nuc} (0.68) refers to the formation of TS$_2$ from the product with a common leaving group (ethanolamine) and a variant nucleophile (the substituted pyridine). The value of $\Delta\beta$, the difference in effective charge on the leaving group nitrogen in the pyridine in the two transition structures, is determined from the values of β_{nuc}, β_{lg} and β_{eq} (given the assumptions made above). The value of $\Delta\beta$ (0.1) means that the difference in charge on the leaving nitrogen between putative intermediate and either TS$_1$ or TS$_2$ must be less than half of 0.1 which is only some 5% of the total change in effective charge suffered by this atom. An intermediate with a charge distribution close to that of the transition structures for its decomposition would be considered to be too reactive to possess a significant barrier for its existence as a discrete molecule. It is reasonable to expect that $\alpha_{nuc} \cong 1$ and $\beta_{lg} \cong 0$ for an $A_N + D_N$ mechanism for aminolysis with a rate-limiting transition structure (TS$_1$) close to that of the adduct.

Previous work indicates that the Meisenheimer-like adduct in the pyridinolysis of triazin-2-ylpyridinium ions is stable enough to exist as a discrete entity[2] whereas that in the phenolysis of phenoxytriazines is not.[1] It is possible that the reactivity of the intermediate in the aminolysis described here is due to the increased localization of charge on the amine nitrogen compared with an attacking pyridine where the charge would be spread over the ring atoms. It is perhaps significant that the methylene dipyridinium salt ($^+$py–CH$_2$–py$^+$ 2Br$^-$) is stable enough to be readily isolated.[15]

Nucleophilic aromatic displacement reactions do not seem to have any current major biological analogues although formation of Meisenheimer-like adducts is very important in some areas such as redox reactions with NAD$^+$ coenzymes. The study of biological aromatic dehalogenation is becoming important especially regarding detoxification mechanisms of microorganisms growing in waste spill sites. Recently, 4-chlorobenzoyl CoA dehalogenase has been studied and there is evidence that it acts *via* formation of an aryl-enzyme intermediate whereby a carboxylate group displaces the halide ion.[16] It was proposed that this mechanism is stepwise but the present and previous studies[1,3] demand that the concerted mechanism be considered especially since the nucleophile and leaving groups are excellent nucleofuges.

Hydrolysis

The hydrolysis of the parent species (Fig. 3) follows the rate law of eqn. (6) consistent with the mechanism given in the scheme. The pH-dependence exhibits three regions, which may be interpreted as follows. The plateau region up to about pH 6 arises from water attack on the 2-position of the triazine nucleus. The region of pH between pH 6 and 11 corresponds to the attack of hydroxide ion on the 2-position of the triazine; the levelling off of the rate is due to the formation of pseudo base, which has little reactivity against the hydroxide ion at the concentrations prevailing at the pH values in question. Above pH 12 the increased concentration of hydroxide ion is sufficient to react with the pseudo base. The spectra of the solutions in the alkaline region show marked visible absorptions (400–500 nm) and this is due to the fission of the pyridine ring. Product analysis is consistent with the above conclusions because at high pH the 2-amino-4,6-diphenoxy-1,3,5-triazine is formed whereas at low pH the 2-hydroxy species is the major product.

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7 The Leffler α values are defined as $\alpha_{nuc} = \beta_{nuc}/\beta_{eq}$ and $\alpha_{lg} = \beta_{lg}/\beta_{eq}$.[5] Since the β values are measured in the same reaction direction the α values are always positive and refer to the extent of bond formation and fission, respectively.

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