The Reactivity of Some Primary Amines in S_N2Ar Reactions with 2- and 4-Chloro-1-methylpyridinium Ions

Eugênia Cristina Souza Brenelli and Paulo José Samenho Moran *
Universidade Estadual de Campinas, Instituto de Química, 13081 Campinas, SP, Brasil

Rate constants for the S_N2Ar reactions of 2- and 4-chloro-1-methylpyridinium ions with butylamine, glycine, glycylglycine, and ethylenediamine monohydrochloride, in water at 1.0 mol dm^{-3} constant ionic strength and 25 °C have been determined. For all amines studied k_{obs} is found to be related to free-amine concentration, [A], as $k_{obs} = k_0 + k_1[A]$. The 2-isomer was always more reactive than the 4-isomer. The Brønsted β coefficients are 0.66 for the 2-isomer and 0.49 for the 4-isomer. These reactions seem to be charge-controlled. From the derived Edwards-equation results one could infer that the 2-isomer might tend to interact by way of its charge more than the 4-isomer.

Due to the presence of the quaternary nitrogen atom in the aromatic ring the 2- and 4-chloro-1-methylpyridinium ions are sufficiently activated to undergo nucleophilic aromatic substitution by an addition–elimination mechanism.[1] The mechanism of these reactions is strikingly similar to the mechanism of nucleophilic displacement of halonitrobenzenes.[2] In some reactions of pyridine derivatives Meisenheimer-type complexes have been isolated.[3]

In the initial studies of the reactivities of these ions, with the *p*-nitrophenoxide ion, the 2-isomer is found to be more reactive than the 4-isomer,[4] as is also found for the quantitative estimates of their reactivities with sodium methoxide in methanol.[5]

The alkaline hydrolysis[2,6] and the neutral methanolysis and hydrolysis[7] also exhibit the above order of reactivity. In these reactions the first transition state is found to be rate limiting, because of the halogen mobility order, F ≫ Cl, observed in the alkaline hydrolysis of 2- and 4-halo-1-methylpyridinium ions.[6]

A kinetic study of the displacement reactions towards half-neutralised piperidine in water indicated small differences in reactivity between the 2-isomer and the 4-isomer.[8] There are no reports concerning the reactivities of these ions with primary amines. The present paper reports the investigations of the reactivity of butylamine, glycine, glycylglycine, and ethylenediamine monohydrochloride, with these ions. Reasonably good Brønsted plots are obtained for these two substrates and an attempt is made to apply the Edwards equation to the present results.

Results and Discussion

For all studied reactions, the pseudo-first-order rate constant (k_{obs}) was found to be related to the concentration of free amine, [A], by equation (1), where k_0 is the rate of removal of substrate, independent of free-amine concentration.

$$k_{obs} = k_0 + k_1[A] \qquad (1)$$

For all amines, except butylamine, k_0 is *ca.* zero. Under the experimental conditions, pH = pK_a, the concentration of hydroxide ions was highest when butylamine was used and, in this case, the k_0 value was of the same order of magnitude as the product $k_{OH^-}[OH^-]$ which is calculated using the k_{OH^-} value, obtained previously.[6] Thus, the values determined for k_0 for the 2- and 4-isomers are 6.08×10^{-4} and 4.28×10^{-6} s^{-1}, respectively. From the activation parameters, previously reported,[6] the calculated values of the product $k_{OH^-}[OH^-]$ are 3.16×10^{-4} s^{-1} and 3.08×10^{-6} s^{-1}, respectively for the same substrates. Although there were differences in ionic-strength conditions, comparison of these results implies that k_{OH^-} could have been the principal component of k_0 when butylamine was used. Values of k_{obs} and k_1 are provided in Table 1.

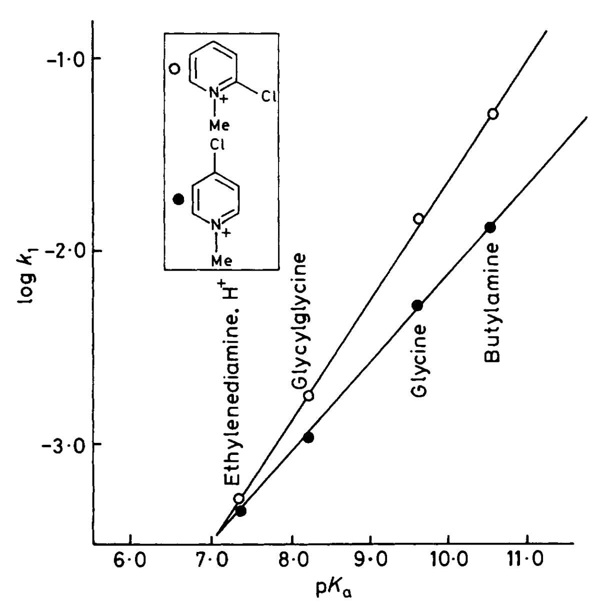

Figure 1. Brønsted plots for the reactions S_N2Ar of 2- and 4-chloro-1-methylpyridinium iodides with the amines at μ = 1.0 mol dm^{-3} and at 25.0 °C in water.

The Brønsted relationship is generally applicable to all combinations of nucleophiles and electrophiles.[9] It has been successfully applied to S_NAr reactions of nitro-activated homoaromatic substrates with primary amines.[10] The Brønsted plots (Figure 1) for the amines studied here exhibited nearly perfect linear relationships, for each substrate, which was shown by the very high values of the coefficients of correlation (*R*). The value of β in the following equation, was determined by least-squares analysis. For 2-chloro-1-methylpyridinium β was 0.66

$$\log k = C + \beta pK_a \qquad (2)$$

(*R* = 0.9999), and for 4-chloro-1-methylpyridinium, β = 0.49 (*R* = 0.9998).

Table 1. Experimental kinetic data for reactions of the corresponding primary amines with 2- and 4-chloro-1-methylpyridinium iodides in water at 25 °C and ionic strength 1 mol dm^{-3}.

Substrate	Amine	$k_{obs}{}^{a}/10^{-4}$ s^{-1}	$k_1/10^{-3}$ dm^3 mol^{-1} s^{-1}	S.d. (R)^b	λ^c/nm
2-chloro-1-methylpyridinium	Butylamine (pK_a = 10.5)	172(0.2979); 186(0.2979); 120(0.2016); 123(0.2015); 72.6(0.1190); 72.0(0.1190); 25.0(0.0299); 25.1(0.0299)	57.6	±2.8% (0.9975)	310
	Glycine (pK_a = 9.63)	62.3(0.4118); 64.9(0.4118); 63.1(0.4118); 62.0(0.4118); 44.4(0.2998); 42.7(0.2990); 25.8(0.1919); 26.4(0.1919); 9.90(0.0800); 10.3(0.0800)	16.1	±2.0% (0.9984)	300
	Glycylglycine (pK_a = 8.25)	7.40(0.3998); 7.00(0.3998); 3.98(0.2218); 3.91(0.2218); 2.45(0.1414); 2.45(0.1414); 2.48(0.1414); 1.27(0.080 95); 1.29(0.080 95); 0.900(0.0594); 1.02(0.0594)	1.84	±1.4% (0.9989)	305
	Ethylenediamine monohydrochloride (pK_a = 7.42)	1.19(0.2297); 1.18(0.2297); 0.833(0.1637); 0.780(0.1637); 0.429(0.089 03); 0.430(0.089 03)	0.535	±3.0% (0.9981)	310
4-chloro-1-methylpyridinium	Butylamine	60.1(0.3807); 52.3(0.3807); 38.4(0.2650); 38.6(0.2650); 22.6(0.1530); 23.2(0.1530); 5.62(0.0392; 5.81(0.0392)	14.7	±4.3% (0.9944)	280
	Glycine	23.2(0.4201); 23.2(0.4201); 17.0 (0.3084); 16.7(0.3084); 10.2(0.1982); 10.4(0.1982); 4.15(0.0849); 4.18(0.0849); 4.03(0.0849)	5.71	±0.9% (0.9997)	275
	Glycylglycine	2.46(0.2218); 2.33(0.2218); 1.60(0.1414); 1.37(0.1414); 5.48(0.060 43); 5.15(0.060 43); 5.73(0.05940)	1.14	±4.2% (0.9956)	280
	Ethylenediamine monohydrochloride	1.09(0.2235); 1.08(0.2235); 0.671(0.1385); 0.652(0.1385); 0.354(0.068 75); 0.324(0.068 75)	0.482	±2.0% (0.9992)	280

[a] Amine concentrations in parentheses. Standard deviation found to obtain k_{obs} was less than 3% and the correlation coefficient was not less than 0.9980. [b] Standard deviation found to obtain k_1. Values of R are the correlation coefficients. [c] Wavelength values used for the kinetic experiments.

Table 2. Values of $[\log(k^2/k_0^2)]/H$ and $[\log(k^4/k_0^4)]/H$ relative to the corresponding amine at 25.0 °C.

Amine	$[\log(k^2/k_0^2)]/H$	$[\log(k^4/k_0^4)]/H$
Ethylenediamine monohydrochloride	0.792	0.882
Glycylglycine	0.780	0.841
Glycine	0.768	0.805
Butylamine	0.759	0.781

Since the β values are generally positively associated with the degree of bond formation in the transition state,[10–13] the reaction of 2-chloro-1-methylpyridinium shows a greater degree of bond formation than that of 4-chloro-1-methylpyridinium in the transition state. The Edwards equation (3) was to some

$$\log(k/k_0) = \alpha E + \beta H \qquad (3)$$

extent, idealized for correction of deviations from the Brønsted equation.[14] In fact as α tends to zero the Brønsted equation becomes a particular case of the Edwards equation. Also, to a certain degree, the ratio α/β reflects the tendency of the reaction to be frontier- or charge-controlled,[15] large values of the ratio α/β indicate the process to be frontier controlled and small values indicate charge control.

The α values for the reactions considered can be inferred to be very small (since a good fit is observed for the Brønsted plots), thus the ratio α/β is small and therefore these reactions seem to be charge controlled. To characterize comparatively the tendency of the reactions to occur it is necessary to estimate the ratio α/β for each substrate. If values of E for the amines studied were known then the pair (α,β) could be estimated by a multiple-regression technique. Unfortunately the E values, $E = E_0 + 2.60$, where E_0 is the electrode potential for oxidative dimerization, are known only for a relative small number of nucleophiles which limits the use of this equation.

One way to circumvent this problem is to manipulate simultaneously the Edwards equation for these two substrates as in equations (4), (5), and (6). In equation (5) it is taken into consideration that E is only dependent on the nucleophile. The

$$E = \frac{\log(k/k_0) - \beta H}{\alpha} \qquad (4)$$

$$\frac{\log(k^2/k_0^2) - \beta^2 H}{\alpha^2} = \frac{\log(k^4/k_0^4) - \beta^4 H}{\alpha^4} \qquad (5)$$

$$\frac{\log(k^2/k_0^2)}{H} = \frac{\alpha^2}{\alpha^4}\frac{\log(k^4/k_0^4)}{H} - \frac{\alpha^2\beta^4}{\alpha^4} + \beta^2 \qquad (6)$$

superscripts 2 and 4 refer to the 2- or 4-isomer and H is dependent on the nucleophile ($H = 1.74 + pK_a$). Equation (6) is now seen as a linear equation relating the left-hand side to the analogous quantity with the 4-isomer, where the ratio α^2/α^4 is identified as the slope and $-\alpha^2/\alpha^4\beta^4 + \beta^2$ as the intercept (which is itself a linear combination of the slope).

Determination of the slope and intercept in equation (6) was carried out by least-squares analysis and is illustrated graphically in Figure 2. Numerical values of $[\log(k^2/k_0^2)]/H$ and $[\log(k^4/k_0^4)]/H$ were used, from predetermined values[7] of k_0^2 and k_0^4, and are provided in Table 2. The resulting estimates of the slope and intercept were 0.32 and 0.52, respectively (R = 0.9985). The aforementioned estimates are consistent with the results obtained independently by the Brønsted equation, indeed substitution of β^2 and β^4 into the intercept expression yields an absolute difference from 0.52 of 2%.

Since α can be related to the magnitude of the frontier-control component and β to the availability of the charge on the electrophile,[15] one could infer from the obtained values of the

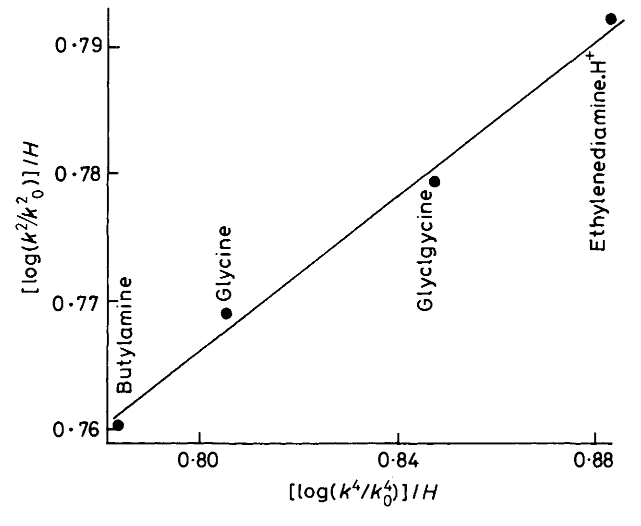

Figure 2. Plot of [log(k^2/k_0^2)]/H *vs.* [log(k^4/k_0^4)]/H.

ratios, $\alpha^2/\alpha^4 = 0.32$ and $\beta^2/\beta^4 = 1.3$, that if a hard nucleophile is used and charge control is attained, the 2-isomer will be more reactive than the 4-isomer, as was found for the present amines. However, if a soft nucleophile is used and frontier control is attained the 4-isomer should be more reactive than the 2-isomer. The ratio $(\alpha^2/\beta^2)/(\alpha^4/\beta^4) = 0.25$, taken as a measure of the relative tendency of the reactions to occur, reveals that the amines interact more by way of charge with the 2-isomer than with the 4-isomer.

There is further evidence to corroborate this conclusion. Firstly, for the pyridinium cation the charge density at C-2 is greater than at C-4, however, for the LUMO, the square of the coefficients of the atomic orbitals for C-4 is greater than for C-2,[16] which implies that hard nucleophiles will react in position 2 (charge control) and soft nucleophiles in position 4 (frontier control) in the nucleophilic additions.[16] Secondly, from the polyelectronic perturbation theory results for the nucleophilic addition of hard nucleophiles to the pyridinium ion, the harder the nucleophiles the more difference between these two positions is expected to be.[16] This indeed does occur as shown in Figure 1. The 2-isomer is always more reactive than the 4-isomer. The ratio of reactivity 2-/4-isomer varies from 1.1 to 3.9 corresponding, respectively, to the ethylenediamine monohydrochloride and the more basic butylamine.

For more basic nucleophiles such as methoxide and hydroxide ions, the corresponding values of these ratios were 30 and 77,[4–6] which is not surprising if their hardness is considered. There is also the claim that there is a stronger attraction between the cationic substrate and the anionic nucleophile for the 2-isomer.[6]

The result presented in this paper is based on a ratio of the values of α/β (corresponding to two substrates reacting with the same class of nucleophiles) which appeared to be suitable for comparing the relative tendency of the reactions to be frontier or charge controlled. It circumvents the necessity of knowing the E values in the Edwards equation. In this sense it is a general procedure which can be applied to co-ordination of substrates dependent on the degree of hardness or softness only when the same type of nucleophiles are used. Further work is being conducted in this direction.

Experimental

Materials.—The 2- and 4-chloro-1-methylpyridinium iodides were prepared by methylation of the corresponding chloropyridines with methyl iodide without solvent at a temperature of 0 °C. The recrystallization of products with methanol–ether gave crystals of m.p. 209–210 °C (lit.,[4] 207 °C) for the 2-isomer and 156–159 °C (lit.,[17] 161–163 °C) for the 4-chloro-1-methylpyridinium iodide. Glycylglycine (Sigma), glycine (Fisher) and potassium chloride (Merck) were used without further purification. The amines butylamine RPE (Carlo Erba) b.p. 76 °C (lit.,[18a] 77.8 °C, ethylenediamine (Riedel–de Haen) b.p. 115 °C (lit.,[18b] 116.5 °C), and water were distilled before use.

Apparatus.—M.p.s were determined on Mettler FP5 apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. ^{1}H N.m.r. spectra were recorded on Bruker AW-80 spectrometer (3% solution in D_2O, with sodium 3-trimethylsilylpropane-1-sulphonate as an internal standard). U.v. spectra were recorded on a DMS-100 Intralab spectrophotometer and kinetics were followed using a Carl Zeiss PMQII-M4QIII spectrophotometer equipped with thermostated cell holders which maintained constant temperature of the reaction solution to ± 0.1 °C.

The products of some reactions were isolated using almost identical reaction conditions as were used in the kinetic studies. In this case the ratio of the concentration values of the free amine and the substrate was 2.2 times greater. After 10 half-lives the reaction product was precipitated with addition of picric acid at the pH of the reaction solution adjusted to the isoelectric pH of the amine correspondent.

2-(N-*Glycino*)-1-*methylpyridinium Picrate.*—Yield 99%, recrystallized from acetone–ether; m.p. 162–168 °C; ^{1}H n.m.r. δ(80 MHz; D_2O) 3.9 (3 H, s, CH_3), 4.3 (2 H, s, CH_2CO_2), 7.1 (2 H, m, aromatic protons at C-3 and C-5), 8.0 (2 H, m, aromatic protons at C-4 and C-6), and 8.9 (2 H, s, picrate protons); ν_{max}(KBr) 3 420, 3 240, 3 090, 2 910, 2 840, 1 630, and 1 590 cm^{-1}.

4-(N-*Glycino*)-1-*methylpyridinium Picrate.*—Yield 45%, recrystallized from acetone–ether; m.p. 225–228 °C (decomp.); δ(80 MHz; D_2O) 3.9 (3 H, s, CH_3), 4.1 (2 H, s, CH_2CO_2), 6.8 (2 H, m, aromatic protons at C-3 and C-5), 8.0 (2 H, m, aromatic protons at C-2 and C-6), and 8.9 (2 H, s, picrate protons); ν_{max}(KBr) 3 290, 3 070, 1 740, 1 655, 1 630, and 1 615 cm^{-1}.

2-(N-*Glycylglycino*)-1-*methylpyridinium Picrate.*—Yield 87%, recrystallized from acetone–ether; m.p. 149.1 °C; n.m.r. δ(80 MHz; D_2O) 3.9 (3 H, s, CH_3), 4.0 (2 H, s, CH_2CON), 4.3 (2 H, s, CH_2CO_2), 7.0 (2 H, m, aromatic protons at C-3 and C-5), 8.0 (2 H, m, aromatic protons at C-4 and C-6), and 8.9 (2 H, s, picrate protons); ν_{max}(KBr) 3 260, 3 070, 1 720, 1 650, 1 640, and 1 625 cm^{-1}.

4-(N-*Glycylglycino*)-1-*methylpyridinium Chloride.*—This product was extracted with methanol–acetone (1:1) from the evaporated reaction mixture. Yield 43%, recrystallized from water–acetone; m.p. 279 °C (decomp.); δ(80 MHz; D_2O) 3.9 (2 H, s, CH_2CON), 4.0 (3 H, s, CH_3), 4.3 (2 H, s, CH_2CO_2), 6.9 (2 H, m, aromatic protons at C-3 and C-5), and 8.1 (2 H, m, aromatic protons at C-2 and C-6; ν_{max}(KBr) 3 300, 3 060, 2 940, 1 670, 1 650, and 1 590 cm^{-1}.

Kinetics.—All reactions were performed in water, where the concentration of free amine was more than ten times the concentration of the 2- or 4-chloro-1-methylpyridinium iodides so that the pseudo-first-order conditions were followed. The ionic strength was maintained constant at a value of 1.0 mol dm^{-3}, with addition of KCl. The pH of reaction solution was made equal to the pK_a of the amine by addition of 0.5 equiv. of HCl to the free amine or by addition of 0.5 equiv. of KOH to the amine hydrochloride. The temperature employed for all kinetic runs was 25.0 ± 0.1 °C. The reactions were followed for several half-lives and the observed rate constants were determined by the method of Guggenheim[19] where the δ value was allowed to be greater than one half-life as recommended.[20] The reactions were followed by monitoring the appearance of a u.v. absorbance band in the region of λ 275–310 nm.

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