JOC Notes

A Study of the OH^--Induced β-Elimination Reactions of 2-(4-Chloroethyl)pyridine, 2-(2-Chloroethyl)pyridine, 1-Methyl-2-(4-chloroethyl)pyridinium Iodide and 1-Methyl-2-(2-chloroethyl)pyridinium Iodide in Acetonitrile/Water

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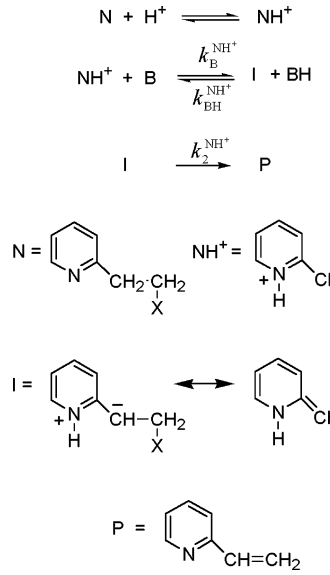
Abstract: Second-order rate constants have been determined for the title reactions in OH^-/H_2O and in $OH^-/(CH_3CN/H_2O)$ [30/70, 60/40, and 85/15 (v/v) mixtures]. A relatively small increase in reactivity is observed for the four substrates upon increasing the percentage of CH_3CN in the solvent mixture. The methyl activating factors ($k_{OH^-}^{NCH_3}/k_{OH^-}^{N}$) are also slightly affected by the solvent composition. On the other hand, the high acceleration of the reaction by methylation of the pyridine ring amounts to 10^4-10^6 according to an E1cb mechanism.

A strong proton catalysis in β-elimination reactions of substrates activated by a pyridine ring has been observed.[1−4] The proton-activating factor (PAF),[1,3,5−7] defined as the ratio of the rate constants of the nitrogen-protonated (NH^+) and unprotonated substrate (N), k^{NH^+}/k^N, for 2-(2-chloroethyl)pyridine (**2**), is 1.38×10^5 at 50 °C, $\mu = 1$ M (KCl) in acetohydroxamic acid/acetohydroxamate buffers.[2] This high rate increase for hydronium catalysis is in agreement with an E1cb mechanism (Scheme 1). In fact, the intermediate formed by carbon deprotonation from NH^+ is strongly stabilized by conjugation (Scheme 1).

A large rate increase upon methylation of the pyridine ring was also observed: MethylAF, defined as the ratio k^{NCH_3}/k^N, is 6.88×10^5 for **2** in OH^-/H_2O at 25 °C.[2] Several biological processes occur via the same type of catalysis;

SCHEME 1



one such example is the β-elimination of ammonia from L-histidine, catalyzed by the enzyme histidine ammonia lyase. [8] This process occurs by an E1cb mechanism, and the driving force for the C−H bond-breaking is provided by a protonated imidazole ring in the active site of the enzyme. The key intermediate carbanion in the enzymatic elimination reactions involving pyridoxal phosphate[9] as cofactor is similarly stabilized by resonance involving the quaternized nitrogen of the pyridine ring. A third example is the carbanion formed in the decarboxylation reaction of α-ketoacids in enzymatic reactions involving the thiamine pyrophosphate where the stability of the intermediate is also related to an enamine-type structure.[9]

In S_N2 reactions of methyl halides with chloride or acetate ion a rate enhancement between 10^3 and 10^6 on transfer from a protic to a dipolar aprotic solvent has been observed.[10] Moreover, the rate of elimination of dimethyl sulfide from 2-phenylethyldimethylsulfonium bromide promoted by OH^- exhibits[11] a 40- and a 1000-fold increase on adding to the aqueous medium 50% (v/v) or 70% (v/v) of DMSO, respectively. A similar increase has been observed[12] in the dehydrobromination of 2-phenylethyl bromide in solutions of *t*-BuO^-/(DMSO/*t*-BuOH).

In this work, the second-order rate constants, $k_{OH^-}^N$, for β-elimination reactions of 2-(4-chloroethyl)pyridine (**1**) and 2-(2-chloroethyl)pyridine (**2**) and $k_{OH^-}^{NCH_3}$ for the β-e-

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(1) Alunni, S.; Conti, A.; Palmizio Errico, R. *J. Chem. Soc., Perkin Trans. 2* **2000**, 453.
(2) Alunni, S.; Busti, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 778.
(3) Alunni, S.; Laureti, V.; Ottavi, L.; Ruzziconi, R. *J. Org. Chem.* **2003**, *68*, 718.
(4) Alunni, S.; Conti, A.; Palmizio Errico, R. *Res. Chem. Intermed.* **2001**, *27*, 653.
(5) Stewart, R.; Srinivasan, R. *Acc. Chem. Res.* **1978**, *11*, 271.
(6) McCann, G. M.; More O'Ferrall, R. A.; Walsh, S. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2761.
(7) Eustace, S. J.; McCann, G. M.; More O'Ferrall, R. A.; Murphy, M. G.; Murray, B. A.; Walsh, S. M. *J. Phys. Org. Chem.* **1998**, *11*, 519.
(8) Langer, M.; Pauling, A.; Rétey J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1464.
(9) Abeles, R. H.; Frey, P. A.; Jencks, W. P. *Biochemistry*; Jones and Barlett Publishers: Boston, 1992.
(10) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.
(11) Cockerill, A. F.; Saunders: W. H., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4985.
(12) Cockerill, A. F.; Rottschaefer, S.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 901.

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TABLE 1. Second-Order Rate Constants for the OH^--Induced β-Elimination Reactions of 1 and 1a in H_2O or CH_3CN/H_2O Mixture at 25 °C

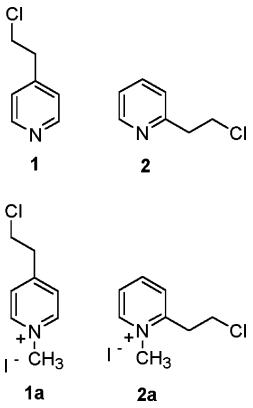
	isomer **1**		isomer **1a**		
solvents	$10^4\ k^N_{OH^-}$ ($M^{-1}\ s^{-1}$)	$k^N_{OH^-}$(mixture)/$k^N_{OH^-}(H_2O)$	$k^{NCH_3}_{OH^-}$ ($M^{-1}\ s^{-1}$)	$k^{NCH_3}_{OH^-}$(mixture)/$k^{NCH_3}_{OH^-}(H_2O)$	MethylAF $k^{NCH_3}_{OH^-}/k^N_{OH^-}$
H_2O	1.47	1.0	3.35	1.0	2.23×10^4
CH_3CN/H_2O (30/70)	2.84	1.9	8.70	2.6	3.06×10^4
CH_3CN/H_2O (60/40)	3.51	2.4	34.4	10	8.90×10^4
CH_3CN/H_2O (85/15)	32.4	22	408	122	12.6×10^4

TABLE 2. Second-Order Rate Constants for the OH^--Induced β-Elimination Reactions of 2 and 2a in H_2O or CH_3CN/H_2O Mixture at 25 °C

	isomer **2**		isomer **2a**		
solvents	$10^5\ k^N_{OH^-}$ ($M^{-1}\ s^{-1}$)	$k^N_{OH^-}$(mixture)/$k^N_{OH^-}(H_2O)$	$k^{NCH_3}_{OH^-}$ ($M^{-1}\ s^{-1}$)	$k^{NCH_3}_{OH^-}$ (mixture)/$k^{NCH_3}_{OH^-}(H_2O)$	MethylAF $k^{NCH_3}_{OH^-}/k^N_{OH^-}$
H_2O	3.20	1	39.0	1.0	1.22×10^6
CH_3CN/H_2O (30/70)	4.15	1.3	126	3.2	3.04×10^6
CH_3CN/H_2O (60/40)	5.57	1.7	857	22	15.4×10^6
CH_3CN/H_2O (85/15)	36.3	11	11500	295	32.7×10^6

limination reactions of 1-methyl-2-(4-chloroethyl)pyridinium iodide (**1a**) and 1-methyl-2-(2-chloroethyl)pyridinium iodide (**2a**) (Scheme 2) have been determined by following spectrophotometrically the formation of the corresponding alkenes at 25° C, in OH^-/H_2O or in $OH^-/(CH_3CN/H_2O)$ [30/70 (v/v), 60/40 and 85/15 (v/v)] in order to gain information on the effect of the medium on the reaction rate.

SCHEME 2



A decrease in the polarity of the solvent could better[13] simulate the reaction environment at the active site of the enzyme or in membranes. The variation of PAF or methyl-activating factors (MethylAF) upon changing the solvent has not been previously studied, and this subject is also of considerable interest.

The values of $k^N_{OH^-}$, $k^{NCH_3}_{OH^-}$, and the MethylAFs for isomers **1** and **2** are reported in Tables 1 and 2, respectively.

As expected,[1,2] the quaternization of the pyridine nitrogen atom brings about a high activation for the β-elimination reaction particularly for isomer **2**. With regard to the mechanism of the reaction, an irreversible E1cb mechanism was previously [2] assigned for **2a** in OH^-/H_2O. The same mechanism can be assumed for **1a** owing to the parallel chemistry of the two isomers. The relatively higher activation observed for compounds **2a** with respect to compounds **1a** can be related to the different resonance energy and the closer proximity of the opposite charges in the zwitterionic intermediate of the former substrate. The mechanism for substrates **1** and **2** is uncertain as it could be E2 concerted, owing to the minor β-activation with respect to **1a** and **2a**, or E1cb irreversible. It is not clear whether the high values of MethylAF are related to the increase in the rate of the elimination reaction (due to methylation) within the same E1cb mechanism or they are associated with a change from a concerted E2 (isomers **1** and **2**) to an E1cb (isomer **1a** and **2a**) mechanism.

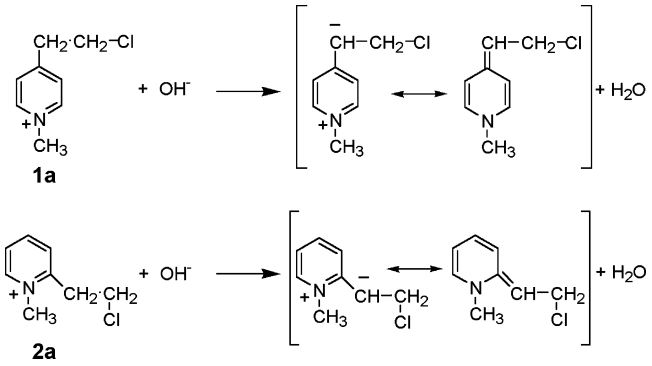
An increase in both $k^N_{OH^-}$ and $k^{NCH_3}_{OH^-}$ by increasing the percentage of CH_3CN in the solvent mixture has been observed. By changing the solvent from H_2O to 85% (v/v) CH_3CN, $k^N_{OH^-}$ increases 22 times (isomer **1**) and 11 times (isomer **2**); the same variation of solvent composition produces a 120- and a 300-fold increase of $k^{NCH_3}_{OH^-}$ for isomers **1a** and **2a**, respectively. It can be seen that the MethylAF values (and probably the PAF values too) in these systems are only slightly dependent on the increase of CH_3CN up to 85% (v/v). A possible interpretation[14] of the observed small variation of $k^{NCH_3}_{OH^-}$, when the percentage of CH_3CN in the solvent mixture is increased, is that the increased activity of OH^- is offset by a higher solvation of the methylated substrate. It is well-known[10] that large organic cations such as **1a** and **2a** are more solvated by dipolar aprotic solvents than by water. The differential solvations, in H_2O and in CH_3CN/H_2O, of the activated complexes leading to the intermediates of Scheme 3 could also play a role.[10]

A similar explanation can be put forward for the unmethylated substrates **1** and **2**; the dehydration of the OH^- anion might be offset by the increased solvation of the organic substrates and/or the desolvation of the corresponding activated complexes.

(13) Perutz, M. *Proc. R. Soc. B* **1967**, *167*, 349.

(14) Reichardt C. *Solvent and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1990.

SCHEME 3



Experimental Section

Materials. Glass-distilled and freshly boiled water was used throughout. Reagent grade 4-(2-hydroxyethyl)pyridine, 2-vinylpyridine, and CH_3CN were used without further purification. 4-Vinylpyridine (commercial) was purified by column chromatography on silica gel using diethyl ether as the eluent. 2-(2-Chloroethyl)pyridine (**2**) and 1-methyl-2-(2-chloroethyl)pyridinium iodide (**2a**), 1-methyl-4-vinylpyridinium iodide, and 1-methyl-2-vinylpyridinium iodide were prepared according to a previously described procedure.[2,3]

4-(2-Chloroethyl)pyridine (1). A mixture of 4-(2-hydroxyethyl)pyridine (0.83 g, 6.76 mmol), $P(Ph)_3$ (2.14 g, 8.2 mmol), and CCl_4 (4 mL) was allowed to react at room temperature for 72 h. The solution was poured into water, neutralized, and extracted with $CHCl_3$. The solvent was removed by rotary evaporation and the residue treated with *n*-hexane. The mixture was filtered, the solution taken to dryness, and the residue treated again with *n*-hexane. After solvent evaporation, chromatography of the crude product on silica gel (eluent: diethyl ether) allowed **1** to be collected (0.21 g, 22%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.56 (dd, J = 4.4, 1.6 Hz, 2 H), 7.17 (dd, J = 4.4, 1.6 Hz, 2 H), 3.76 (t, J = 7 Hz, 2 H), 3.08 (t, J = 7 Hz, 2 H); MS (70 eV) m/z 143 ($M^+ + 2$, 36), 141 (M^+, 100), 106 (62), 92 (92), 77 (16), 65 (38), 51 (28).

1-Methyl-4-(2-chloroethyl)pyridinium Iodide (1a). A solution of **1** (0.040 g, 0.28 mmol) and CH_3I (0.114 g, 0.8 mmol) in acetone (1 mL) was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure, and the solid residue was washed with Et_2O, dried under reduced pressure, and recrystallized from EtOH−Et_2O to obtain pure **1a** (0.040 g, 50%): mp 96−99 °C; ^{1}H NMR (D_2O, 200 MHz) δ 8.45 (d, J = 6.4 Hz, 2 H), 7.73 (d, J = 6.4 Hz, 2 H), 4.12 (s, 3 H), 3.76 (t, J = 6.2 Hz, 2 H), 3.18 (t, J = 6.2 Hz, 2 H). Anal. Calcd for $C_8H_{11}NClI$: C, 33.89; H, 3.91; N, 4.94. Found: C, 33.80; H, 3.93; N, 4.91.

Kinetics Measurements. The second-order rate constants $k^{N}_{OH^-}$, M^{-1} s^{-1}, and $k^{NCH_3}_{OH^-}$, $M^{-1}s^{-1}$, for the elimination reaction of **1**, **2** ($k^{N}_{OH^-}$) and **1a**, **2a** ($k^{NCH_3}_{OH^-}$) were measured in the presence of an excess of [OH^-] in H_2O or in a CH_3CN/H_2O mixture [30/70 (v/v) or 60/40 (v/v) or 85/15 (v/v)] by following the formation of the corresponding alkenes at 25 °C (to completion for **1**, **1a**, and **2a** or by the method of initial rate [2] for **2**). The molar absorptivities were independent of the solvent composition up to 60/40 of CH_3CN/H_2O mixture: ϵ = 12 200 (±60) M^{-1} cm^{-1} at λ = 243 nm for 4-vinylpyridine, ϵ = 18 390 (± 70) M^{-1} cm^{-1} at λ = 268 nm for 1-methyl-4-vinylpyridinium iodide, ϵ = 5800 (± 100) M^{-1} cm^{-1} at λ = 277 nm for 2-vinylpyridine and ϵ = 9040 (± 90) M^{-1} cm^{-1} at λ = 286 nm for 1-methyl-2-vinylpyridinium iodide. In CH_3CN/H_2O 85/15, molar absorptivities were as follows: ϵ = 13 490 M^{-1} cm^{-1} at λ = 243 nm for 4-vinylpyridine, ϵ = 15 774 M^{-1} cm^{-1} at λ = 268 nm for 1-methyl-4-vinylpyridinium iodide, ϵ = 5491 M^{-1} cm^{-1} at λ = 277 nm for 2-vinylpyridine and ϵ = 8777 M^{-1} cm^{-1} at λ = 286 nm for 1-methyl-2-vinylpyridinium iodide. The kinetics of the methylated substrates (**1a** and **2a**) were similarly followed using a stopped-flow technique.

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