HYDROGEN-EXCHANGE REACTION OF METHYL-SUBSTITUTED *N*-AMINO- AND *N*-METHYL-QUINOLINIUM IONS

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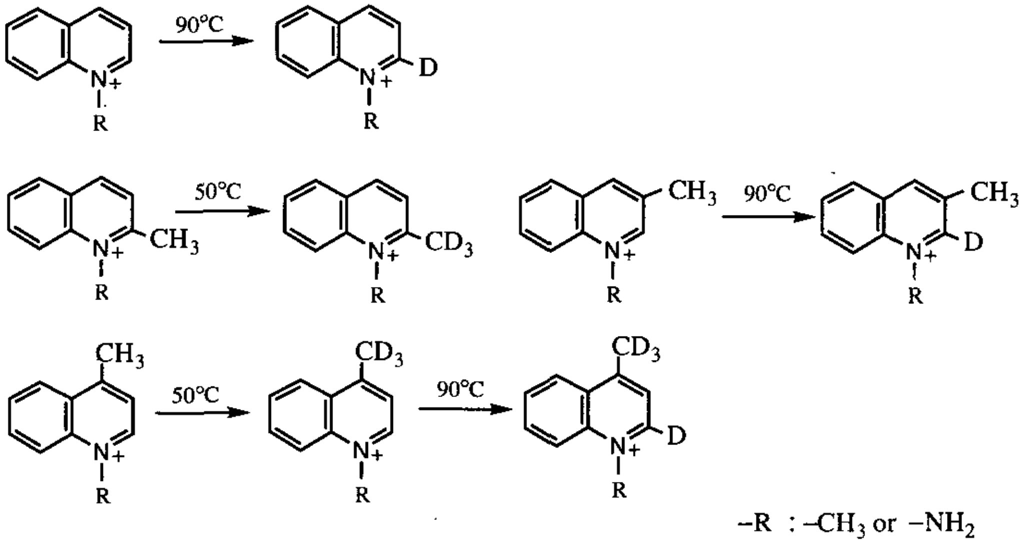
Abstract — H-D Exchange rates of the hydrogens of methyl-substituted *N*-amino-quinolinium ions were compared with those of the corresponding *N*-methylquinolinium derivatives. In treatment carried out below 90°C in phosphate-buffered D_2O solvents at pD's ranging from 3.4 to 11.7, only the ring α-hydrogen and the α- and γ-methyl hydrogens underwent H-D exchange. The *N*-amino group facilitated exchanges of the ring α-hydrogen several tens of times more than did the *N*-methyl group, whereas the former facilitated the exchange of substituent methyl hydrogens only several times more than the latter. The pD-dependence of the exchange reactions are described.

It is known that hydrogens of methyl substituents at positions-α and -γ to the cationic ring nitrogen of pyridinium ions are readily exchanged with deuterons by heating in D_2O solvents within a certain range of pD.[1,2] The ring hydrogen at position-α to the cationic ring nitrogen is also exchanged with a deuteron under more drastic reaction conditions than those for the methyl-hydrogen exchange.[2-4] It is considered that such exchanges proceed by a base-catalyzed process through stabilization of a fully or partially deprotonated transition state due to the cationic nataure of the ring nitrogen of pyridinium ions.[4,5] In the present study, H-D exchange rates of the hydrogens of methyl-substituted N-aminoquinolinium ions were compared with those of the corresponding *N*-methyl derivatives. Dependence of the exchange rate on the pD of the reaction mixture was also examined. The exchange reactions were carried out below 90°C in buffered D_2O solvents at a pD range of 3.4 to 11.7. The compounds examined were the chloride salts of *N*-aminated 2-, 3-, and 4-methylquinolinium ions, abbreviated as *N*-NH_2-2Me-Q^+, *N*-NH_2-3Me-Q^+, and *N*-NH_2-4Me-Q^+, respectively, and those of the corresponding *N*-methylated derivatives abbreviated as *N*-CH_3-2Me-Q^+, *N*-CH_3-3Me-Q^+, and *N*-CH_3-4Me-Q^+, respectively. The reaction conditions described in this study might be useful for selective labeling of these compounds with deuterium or tritium.

RESULTS

H-D Exchange Rate of Ring α-Hydrogens of Quinolinium Ions

H-D Exchange of the ring α-hydrogen of quinolinium ions was carried out at 90°C in buffered D_2O solvents at various pD's (3.5 to 9.5) Pseudo-first order rate constants (h^{-1}) on a logarithmic scale (log k_{obs} at 90°C) were linearly proportional to pD values for all the compounds examined. Correlation coefficients (r^2) between log k_{obs} and pD fell within a range of 0.992 to 0.998. The results are summarized in Table I and illustrated in Scheme 1.



Scheme 1 *H-D Exchange in D_2O at pD 3.4 - 11.7*

Accuracy in the rate measurements is exemplifed by plottings for *N*-amino-4-methylquinolinium and *N*-methyl-4-methylquinolinium derivatives in Figure 1, including the dependence of their k_{obs}'s on pD. All other ring hydrogens except for the α-hydrogen were not exchanged under the reaction conditions employed in this study. These results seem to

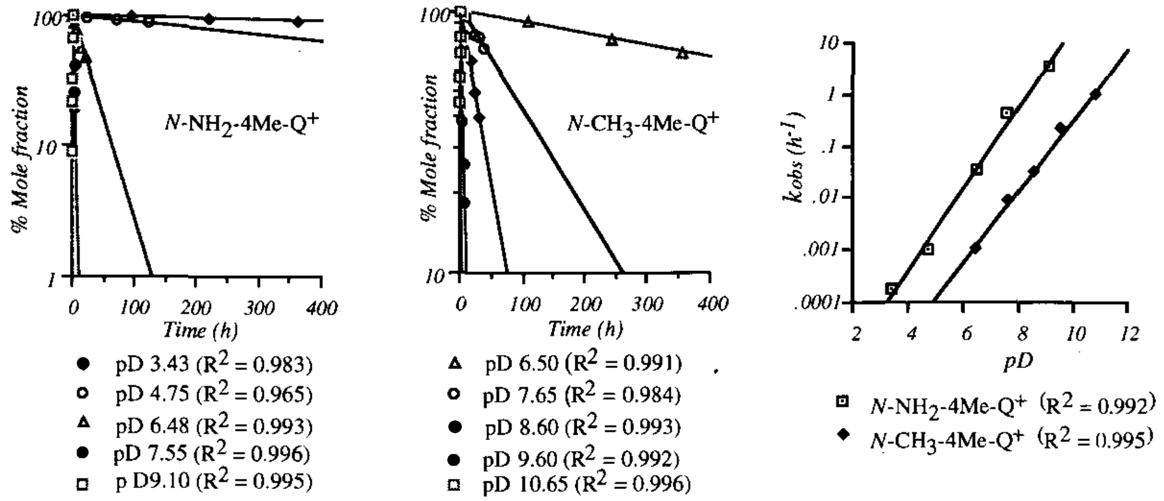


Figure 1 *Examples of Experimental Data for H-D Exchange of the Ring α-Hydrogen*

support the previously proposal of a mechanism involving an ylide intermediate which is formed by an OD^- attack. However, the proportionality constants of the $\log k_{obs}$ *vs.* pD equations were significantly smaller than unity:

$$\log k_{obs} = 0.73 \cdot pD + \text{constant} \qquad (SD: \pm 0.10;\ n = 6)$$

It is questionable whether the rate is governed by the 0.7th order with regard to [OD^-]. Deviation from unity seems difficult to explain in terms of inaccuracies in quantitative analysis by nmr spectroscopy or of inadequacy in estimation of the pD values, as described in the Experimental section.

Table I *H-D Exchange of the ring α-hydrogen and the substituent methyl hydrogens at pD 8.0*

Compound	Rate of ring α-hydrogen at 90°C		Rate of methyl hydrogens at 50°C	
	k_{obs} (h^{-1})	$T_{1/2}$ (h)	k_{obs} (h^{-1})	$T_{1/2}$ (h)
N-NH_2-Q^+	1.12×10^{0}	6.19×10^{-1}		
N-NH_2-2Me-Q^+			7.83×10^{0}	8.85×10^{-2}
N-NH_2-3Me-Q^+	9.92×10^{-1}	6.99×10^{-1}	not exchanged	
N-NH_2-4Me-Q^+	6.01×10^{-1}	1.15×10^{0}	1.32×10^{-2}	$5.25 \times 10^{+1}$
N-Me-Q^+	4.16×10^{-2}	1.67×10^{1}		
N-Me-2Me-Q^+			6.41×10^{0}	1.08×10^{-1}
N-Me-3Me-Q^+	2.48×10^{-2}	2.79×10^{1}	not exchanged	
N-Me-4Me-Q^+	1.32×10^{-2}	5.25×10^{1}	1.14×10^{-2}	$6.08 \times 10^{+1}$

Therefore, apart from consideration of the second-order rate constant, the structural dependence of the exchange rates was investigated in terms of the k_{obs} value of each derivative at a pD of 8.0. It is noteworthy that the exchange rates for α-hydrogen of *N*-amino derivatives were several tens of times faster than those of the corresponding *N*-methyl derivatives. This suggests that an ylide-like transition state might be more stabilized by the *N*-amino group than by the *N*-methyl group, probably because of an electron-withdrawing inductive effect of NH_2 group. Methyl-substitution at position-4 decreased the rate to one half or one third of those of the respective parent quinolinium ions (without a methyl substituent) in both the *N*-amino and *N*-methyl series. The 4-methyl group located at the γ-position to the cationic ring nitrogen might partly neutralize the cationic charge on the ring nitrogen through electron-donating hyperconjugation.

H-D Exchange Rate of Hydrogens of Substituent Methyl Groups

H-D Exchange rates of hydrogens of substituent-methyl groups were measured at 50°C over a pD range of 3.4 to 11.7. The results are summarized in Table I and illustrated in Scheme 1. Hydrogens of the 2- and 4-methyl groups were much more exchangeable than the ring α-hydrogen of quinolinium ions, whereas 3-methyl hydrogens, as well as *N*-methyl hydrogens, were not exchangeable at 50°C or even at 90°C. 2-Methyl hydrogens were more readily exchanged than 4-methyl hydrogens in both *N*-amino and *N*-methylquinolinium ions. Methyl hydrogens of the *N*-amino derivatives were more readily exchanged than those of the corresponding *N*-methyl derivatives regardless of the location of the methyl group, i.e., the 2- or 4-position. Hence, it appears that the *N*-amino group might be more effective in stabilizing

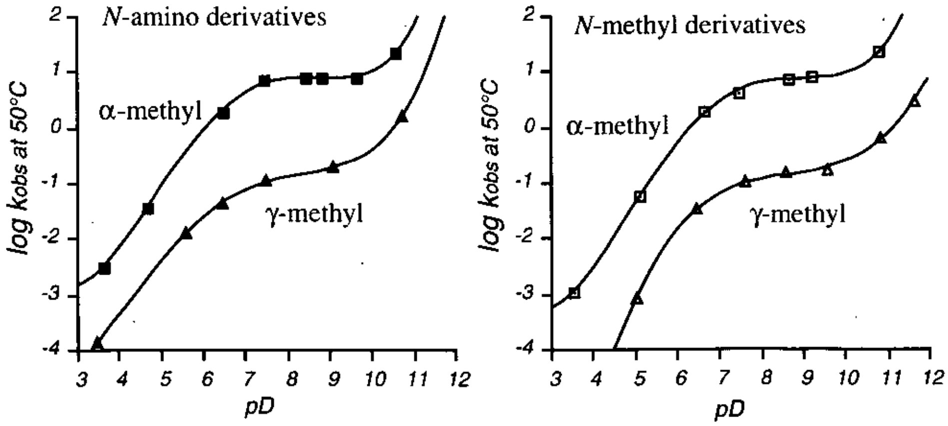
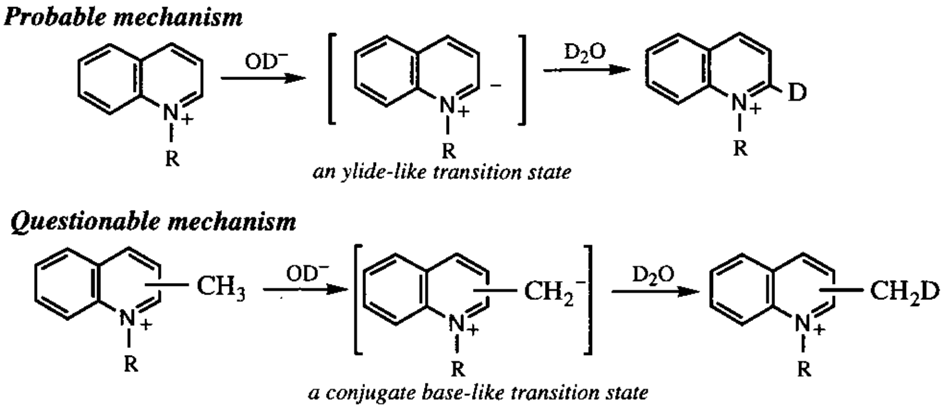


Figure 2 *pD-Dependence of k_{obs} (h^{-1}) for H-D Exchange of Methyl Hydrogens at the α- and γ-Positions*

the transition state which has a fully or partially deprotonated structure, in other words, the *N*-amino group is more effective in electron-withdrawal than is the *N*-methyl group. The time-course of decreases in the signal intensity of methyl hydrogens indicated that the H-D exchange proceeded with first-order reaction kinetics. Pseudo-first order rate constants (h^{-1}) on a logarithmic scale measured at 50°C in buffered D_2O solvents *versus* pD values are plotted in Figure 2. Within a pD range of 3 to 6, k_{obs} is almost proportional to pD with a slope approaching unity, suggesting that the rate is linearly proportional to [OD^-]. In contrast, k_{obs} values for each compound did not change much over a pD 7.0 to 9.5. Then, k_{obs} tends to increase with increases in the pD value of over 10. On first consideration, it appeared that expression of the exchange rate should have included an equilibrium constant to allow for certain structural changes which are dependent on pD or pOD, just as was seen in H-D exchange of the 8-H of purine derivatives.[4] However, this is not the case here, because the uv spectra of these derivatives were unaffected over all pD range examined.

DISCUSSION

Presuming that the two types of hydrogen exchanges studied here proceed *via* the mechanisms described in Scheme 2, the transition state resembles the deprotonated form; an ylide-like structure for the ring-α-hydrogen exchange[5] and a conjugate base-like structure for the methyl hydrogen exchange. It is, therefore, expected that the relative rates among the compounds examined here are semiquantitatively correlated with differences in the potential energy ("energy gain") between the derivative in question and its deprotonated structure. The total energy (sum of electronic energy and core-core repulsion) was then calculated by the semiempirical molecular orbital MOPAC 93 PM3 method. In Figure 3, the observed k_{obs} values are plotted *versus* the energy gain on a semi-log scale since the rate constant should be exponentially proportional to the activation energy. The ring α-hydrogen exchange seems to be correlated with these values, supporting the likelihood of the mechanism involving an ylide-like transition state, as illustrated in Scheme 2.[5] However, there is definitely no correlation with respect to the exchange of methyl hydrogens. Taking into account the complex dependence of the k_{obs} on pD observed in this study, a simple deprotonation mechanism involving a conjugate base-like transition state cannot adequately account for the methyl hydrogen exchange. The actual mechanism involved on pD is open to further investigation.



Scheme 2 *Possible mechanisms involved*

$-R : -CH_3$ or $-NH_2$

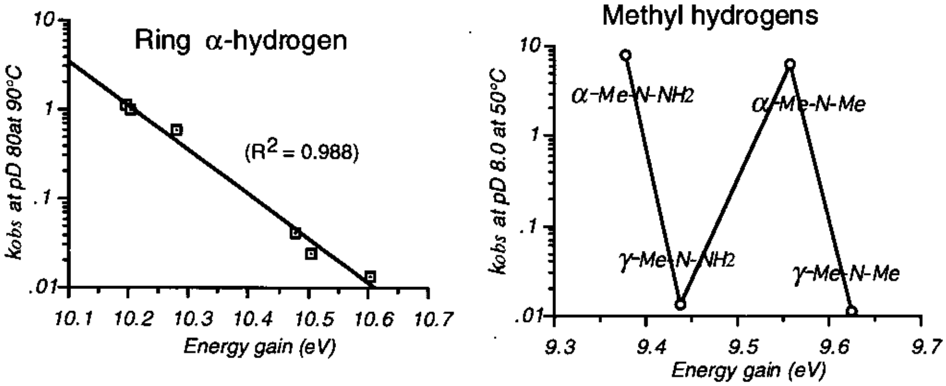


Figure 3 *Correlation of k_{obs} (h^{-1}) with the Energy Gain by Deprotonation Calculated by MOPAC-PM3*

EXPERIMENTAL

Materials Methyl-substituted *N*-methylquinolinium salts were prepared by treating methylquinolines with methyl iodide.[6] Methyl-substituted *N*-aminoquinolinium salts[7] were prepared by treating methylquinolines with *O*-(2,4-dinitrophenyl)hydroxylamine. All salts were converted to their chloride forms by passage through an ion-exchange resin column. The structure and purity of the preparations were confirmed by ^{1}H-nmr spectroscopy. Heavy water (D_2O) of 99.8% isotope purity was purchased from Merck and Co. Inc. (Rahway, NJ).

Preparation of buffered D_2O solvents The D_2O buffers at a pD range 5 to 10 were prepared by mixing appropriate volumes of 1/10 M KH_2PO_4 and 1/10 M Na_2HPO_4 (50 ml in total). These were lyophilized, dissolved in a small amount of D_2O, and lyophilized again. After one more cycle of dissolution and lyophilization, the residual solid was redissolved in 50 ml D_2O. Reaction solvents below pD 4 were dil. D_2SO_4 in D_2O and those above pD 10 were dil. NaOD in D_2O. The buffers thus prepared were subjected to pD measurement using a regular pH meter and pH readings were converted to pD's as follows:

$$\text{pD (in } D_2O) = \text{pH (read on pH-meter)} + 0.4.^{8}$$

For the $[OD^-]$ calculation, the pK_{DW} (ion product of heavy water) at 50°C and 90°C amounted to 14.18 and 13.26, respectively. For estimation of the ion products of heavy and light water, pK_{DW} and pK_{HW}, respectively, at desired temperatures, the following equations were employed, the parameters of which were obtained by computerized parameter-fittings using Cricket Graph and pK_{DW} and pK_{HW} values which were reported by Clever.[9]

$$pK_{HW} = 15.960 - 4.568\times10^{-2}(T^{\circ}C) + 2.374\times10^{-4}(T^{\circ}C)^2 - 6.971\times10^{-7}(T^{\circ}C)^3 \qquad (r^2=1.000)$$

$$pK_{W} = 14.947 - 4.285\times10^{-2}(T^{\circ}C) + 2.042\times10^{-4}(T^{\circ}C)^2 - 4.374\times10^{-7}(T^{\circ}C)^3 \qquad (r^2=1.000)$$

Measurement of H-D Exchange Rates The rate was estimated by measuring areal intensities of ^{1}H-nmr signals of the test compound (ca. 3.6 mg/ml) sealed in a tube in reference to the internal standard signal of methyl protons of $CH_3SO_3^- K^+$ dissolved in the test solution.

MO Calculation The molecular orbital calculations were carried out using MOPAC93 revision 2 (Stewart, J. J. P. JCPE PO81, JCPE Newsletter, 1995, 6(4), 76), The calculation program used was PM3 (Stewart, J. J. P. J. Comput. Chem., 1989, 10, 209).

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