Electronic Structure and the Rate of Deuteroexchange in the Methyl Groups of Nitrogen Heterocycles and Their N-Oxides

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Abstract

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Electronic Structure and the Rate of Deuteroexchange in the Methyl Groups of Nitrogen Heterocycles and Their N-Oxides

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Nitrogen-containing methylated heterocyclic compounds are capable of exchanging the hydrogen of CH_3 groups for deuterium from an amphoteric solvent (ND_3, CH_3OD, C_2H_5OD) (^{1,2}).

The aim of the present work is to trace, using the reaction of hydrogen exchange of CH_3 groups with deuteroalcohol as an example, the change in reactivity in a series of methyl-substituted nitrogen heterocycles and their N-oxides as a function of the electronic structure of the molecules. The objects of study were chosen so that, from the mobility of hydrogen, it would be possible to estimate changes in reactivity in a series of α-methyl-substituted heterocycles as a function of the magnitude of the conjugation effect at a constant strength of inductive interaction. In addition, in α-, β-, and γ-picolines and their N-oxides, changes in hydrogen mobility caused by superposition, on the conjugation effect, of an unequal electronegative inductive effect were investigated.

Table 1 summarizes the experimental data for the unoxidized heterocyclic compounds. In addition to the rate constants for hydrogen exchange with deuteroethyl alcohol in the presence of potassium alcoholate, the activation parameters, $\lg A$ and E, found from the temperature dependence of the rate constants, and the values of $\lg k/k_0$, where k_0 is the exchange rate constant of α-picoline, are given here. The corresponding kinetic data for the N-oxides are given in Table 2 (k_0 is the exchange rate constant of α-picoline N-oxide). Because of the high reactivity of α-methyl-substituted N-oxides, comparison of the hydrogen mobility in them was carried out in the deuteroexchange reaction with methyl alcohol in the presence of triethylamine. Exchange under these conditions is strongly retarded (^{2}).

From comparison of the experimental data it is seen that the order of change in the reactivity of isomeric picolines is $\gamma > \alpha > \beta$, and of picoline N-oxides is $\alpha > \gamma > \beta$; the hydrogen mobility of α-methyl-substituted heterocycles increases in the series α-picoline < α-naphthoquinaldine < β-naphthoquinaldine < quinaldine < 9-methylphenanthridine; α-picoline N-oxide < quinaldine N-oxide < 9-methylphenanthridine N-oxide.

The results obtained can be interpreted semiquantitatively within the framework of the molecular-orbital method, if one introduces the usual assumption that the contributions of σ-electronic energies in the processes of activation of the molecules are constant for the case of the deuteroexchange reaction and assumes that the reaction proceeds according to the following scheme:

$$\mathrm{A} \quad \underset{\mathrm{ROH}}{\overset{\mathrm{RO^-}}{\rightleftarrows}} \quad \mathrm{B} \quad \xrightarrow{\mathrm{ROD}} \quad \text{deuterated product}$$

where the scheme shown corresponds to conversion of a methyl-substituted nitrogen heterocycle into a carbanion of type $-\mathrm{CH}_2^-$, followed by formation of the $-\mathrm{CH_2D}$ product.

Table 1

Kinetic characteristics of deuterium exchange in $\mathrm{C_2H_5OD} + 0.57\,N\,\mathrm{C_2H_5O^-}$ and indices of the electronic structure of non-oxidized heterocycles

Compound	T-range, °C	k_{exp}, $\mathrm{sec}^{-1} \cdot 10^5$	E, kcal/mol	$\lg A$	$\lg k/k_0$	$\delta_q = 1 - q_C(\mathrm{CH_3})$	ΔE_π, $\lvert\beta\rvert$	$P_{\mathrm{N=C(CH_3)}}$	Chem. shift (δ), ppm	k_D/k_T
α-Picoline	90	1.7	24.7	9.86	0	+0.0444	4.56	0.6435	1.04	1.7 (90°)
α-Picoline	105	6.5	24.7	9.86	0	+0.0444	4.56	0.6435	1.04	1.5 (105°)
α-Picoline	120	23.0	24.7	9.86	0	+0.0444	4.56	0.6435	1.04	
β-Picoline	100	0.037	31.0	11.73	−1.87	+0.0190	4.60			
β-Picoline	120	0.3	31.0	11.73	−1.87	+0.0190	4.60			1.0 (120°)
β-Picoline	140	2.1	31.0	11.73	−1.87	+0.0190	4.60			
γ-Picoline	45	0.57	20.3	8.66	1.05	+0.0507	4.56			
γ-Picoline	60	2.3	20.3	8.66	1.05	+0.0507	4.56			
γ-Picoline	70	5.9	20.3	8.66	1.05	+0.0507	4.56			
α-Naphthquinaldine	55	0.20	26.2	11.77	0.66	+0.0590	4.50	0.6740	1.24	
α-Naphthquinaldine	65	0.66	26.2	11.77	0.66	+0.0590	4.50	0.6740	1.24	

Compound	T-range, °C	k_{exp}, sec$^{-1}\cdot 10^5$	E, kcal/mol	lg A	lg k/k_0	$\delta_q = 1 - q_C(\text{CH}_3)$	ΔE_π, $\lvert\beta\rvert$	$P_{\text{N=C(CH}_3)}$	Chem. shift (δ), ppm	k_D/k_T
α-Naphthquinaldine	75	2.0	26.2	11.77	0.66	+0.0590	4.50	0.6740	1.24	
α-Naphthquinaldine	85	5.8	26.2	11.77	0.66	+0.0590	4.50	0.6740	1.24	
β-Naphthquinaldine	60	2.2	22.5	10.07	1.46	+0.0616	4.50	0.6782	1.22	
β-Naphthquinaldine	70	5.8	22.5	10.07	1.46	+0.0616	4.50	0.6782	1.22	1.8 (50°)
Quinaldine	25	0.19	20.8	9.77	2.0	+0.0698	4.48	0.6952	1.23	
Quinaldine	40	0.95	20.8	9.77	2.0	+0.0698	4.48	0.6952	1.23	2.2 (40°)
Quinaldine	55	4.4	20.8	9.77	2.0	+0.0698	4.48	0.6952	1.23	
9-Methylphenanthridine	25	0.70	20.9	10.19	2.57	+0.0946	4.40	0.7429	1.40	
9-Methylphenanthridine	35	2.2	20.9	10.19	2.57	+0.0946	4.40	0.7429	1.40	1.9 (45°)
9-Methylphenanthridine	45	6.4	20.9	10.19	2.57	+0.0946	4.40	0.7429	1.40	

In such a model the transition complex of the reaction—the carbanion (B)—is a conjugated system with a greater degree of delocalization of the π-electrons than the initial heteroaromatic molecule (A). The extracyclic carbon atom in the carbanion is sp^2-hybridized. In this case the change in the π-electronic activation energy ΔE_π, equal to the difference between the π-electronic energies of the carbanion and the initial molecule, may serve as a measure of the reactivity of the compound in the deuterium-exchange reaction. As another characteristic of reactivity we attempted to use the magnitude of the π-electron charge $q_{C(\text{CH}_3)}$ on the carbon atom of the ring bonded to the methyl group. The starting premise for this was the concepts of qualitative electronic theory (^{3}). Indeed, the lower the value of the π-electron charge $q_{C(\text{CH}_3)}$, the larger the fraction of the electron cloud of the CH_3 group that will be displaced toward the ring, and the higher the mobility of the hydrogen should be. To test these assumptions, we carried out calculations by the simple LCAO MO method for the quantities ΔE_π and $q_{C(\text{CH}_3)}$. For α-substituted heterocycles the bond orders $P_{\text{N=C(CH}_3)}$ were also calculated, on which, according to the concepts of qualitative electronic theory, the degree of transmission of the conjugation effect of the nitrogen atom depends (^{4}). In the calculations for non-oxidized heterocyclic compounds, the values of the Coulomb and resonance integrals adopted in work (^{5}) were used:

$\alpha_N = \alpha + \frac{1}{2}\beta, \quad \alpha_{C(\mathrm{H}_3)} = \alpha - 0.1\beta, \quad \alpha_{H_3} = \alpha - 0.3\beta, \quad \beta_{C-\mathrm{CH}_3} = 0.8\beta, \quad \beta_{C\equiv H_3} = 2.8\beta.$

Table 2

Kinetic characteristics of deuterium exchange and indices of the electronic structure of N-oxides

Compound	T-ure, °C	$k_{\mathrm{exch}} \cdot 10^5$, sec^{-1}	E, kcal/mole	$\lg A$	$\lg k/k_0$	$\delta q = 1 - q_C(\mathrm{CH}_3)$	$\Delta E_{\pi} \mid \beta \mid$	$P_{\mathrm{N=C(CH_3)}}$	Chem. shift (δ), ppm	k_D/k_T	Exchange conditions
N-oxide of α-picoline	−10	0.75	19.9	11.05	0	+0.0588	4.41			2.2 (−10°)	
N-oxide of α-picoline	0	2.1	19.9	11.05	0	+0.0588	4.41			2.2 (−10°)	
N-oxide of α-picoline	10	6.6	19.9	11.05	0	+0.0588	4.41			2.2 (−10°)	
N-oxide of β-picoline	30	2.6	22.5	11.30	−1.564	+0.0014	4.66			1.0 (30°)	C_2H_5OD+ 0.57 N $C_2H_5O^-$
N-oxide of β-picoline	40	8.6	22.5	11.30	−1.564	+0.0014	4.66			1.0 (30°)	C_2H_5OD+ 0.57 N $C_2H_5O^-$
N-oxide of β-picoline	50	26.0	22.5	11.30	−1.564	+0.0014	4.66			1.0 (30°)	C_2H_5OD+ 0.57 N $C_2H_5O^-$

Compound	T-ure, °C	$k_{exch} \cdot 10^5$, sec^{-1}	E, kcal/mole	lg A	lg k/k_0	$\delta q = 1 - q_C(CH_3)$	$\Delta E_\pi \mid \beta \mid$	$P_{N=C(CH_3)}$	Chem. shift (δ), ppm	k_D/k_T	Exchange conditions
N-oxide of γ-picoline	0	1.3	15.8	7.80	−0.245	+0.0568	1.45				
N-oxide of γ-picoline	10	3.8	15.8	7.80	−0.245	+0.0568	1.45				
N-oxide of γ-picoline	20	9.6	15.8	7.80	−0.245	+0.0568	1.45				
N-oxide of α-picoline	120	0.048	22.6	6.31	0	+0.0588	1.41	0.5600	1.11		
N-oxide of α-picoline	140	0.20	22.6	6.31	0	+0.0588	1.41	0.5600	1.11		
N-oxide of α-picoline	160	0.69	22.6	6.31	0	+0.0588	1.41	0.5600	1.11		
N-oxide of quinaldine	90	0.60	16.1	4.68	1.67	+0.0927	1.32	0.7006	1.29		CH_3OD+ 0.08 N $(C_2H_5)_3N$
N-oxide of quinaldine	110	1.7	16.1	4.68	1.67	+0.0927	1.32	0.7006	1.29		CH_3OD+ 0.08 N $(C_2H_5)_3N$

Compound	T-ure, °C	$k_{\text{exch}} \cdot 10^5$, sec^{-1}	E, kcal/mole	$\lg A$	$\lg k/k_0$	$\delta q = 1 - q_C(\text{CH}_3)$	$\Delta E_\pi \mid \beta \mid$	$P_{\text{N=C(CH}_3)}$	Chem. shift (δ), ppm	k_D/k_T	Exchange conditions
N-oxide of quinaldine	130	4.6	16.1	4.68	1.67	+0.0927	1.32	0.7006	1.29		CH_3OD+ 0.08 N $(\text{C}_2\text{H}_5)_3\text{N}$
N-oxide of 9-methylphenanthridine	55	0.88	13.9	4.20	2.67	+0.1209	4.22	0.7413	1.55		
N-oxide of 9-methylphenanthridine	70	2.3	13.9	4.20	2.67	+0.1209	4.22	0.7413	1.55		
N-oxide of 9-methylphenanthridine	85	5.3	13.9	4.20	2.67	+0.1209	4.22	0.7413	1.55		

In addition, the parameter

$$h' = \frac{\alpha_{\text{C(N)}} - \alpha}{\beta} = 0.085$$

was introduced into the calculation, taking into account the inductive influence of nitrogen on the carbon atoms nearest to it (^{6}).

From comparison of the results of calculations of the electronic-structure indices presented in Table 1 with the values of $\lg k/k_0$, it follows that a decrease in the π-electron charges $q_{\text{C(CH}_3)}$ and an increase in the bond orders $P_{\text{N=C(CH}_3)}$ correspond to an approximately proportional increase in the proton mobility of the compounds studied. The differences in ΔE_π for individual molecules are less distinct; however, in this case as well it may be asserted that, within the series of compounds, there is a correlation in the changes of the quantities ΔE_π and of the exchange rate.

The results of studying the mobility of hydrogen atoms in the CH_3 groups of N-oxide molecules (Table 2) show that N-oxides exchange more rapidly than unoxidized heterocycles; that is, if the proposed interpretation is correct, the

π-electron charges $q_{\mathrm{C(CH_3)}}$ in N-oxides must be smaller than in the initial bases. Reasonable orders of reactivity for the reaction under study can be obtained if one uses the values of the Coulomb and resonance integrals taken from work (^{7}). Calculation with these values leads to agreement with the observed nucleophilic reactivity of pyridine N-oxide. As is evident from the data in Table 2, the orders of reactivity predicted from the values of $q_{\mathrm{C(CH_3)}}$, $P_{\mathrm{N-C(CH_3)}}$, and ΔE_π in the series of α-methyl-substituted N-oxides are in qualitative agreement with experiment. The theoretical conclusion concerning the increased activity of the hydrogen of the methyl groups in N-oxide of α-picoline as compared with N-oxides of γ- and β-picolines is also consistent with the facts.

In connection with our conclusions regarding the dependence of the reaction rate on the magnitude of the π-electron charge $q_{\mathrm{C(CH_3)}}$, experimental data on the distribution of electron density at the reaction-

center.* The latter can be obtained by means of high-resolution NMR spectroscopy. We measured the values of the chemical shifts of the protons of the $\mathrm{CH_3}$ groups of all α-substituted heterocycles and their N-oxides studied in the present work. The solvent was carbon tetrachloride in measurements of the heterocyclic bases and deuterochloroform in measurements of the N-oxides. The values of the chemical shifts were calculated relative to cyclohexane, taken as an internal standard, and interpolated to infinite dilution. The data of Tables 1 and 2 show that the chemical shifts in the series α-picoline—quinaldine—9-methylphenanthridine and in their N-oxides vary linearly with the values of $q_{C(CH3)}$ and $P_{\mathrm{N=C(CH_3)}}$. The deviations from linearity found for α- and β-naphthoquinaldines can readily be explained within the framework of the ring-current model (^{8}).

For the purpose of further experimental substantiation of the carbanion mechanism of hydrogen exchange of methyl groups, kinetic isotope effects (KIE) were determined in the deutero-tritium counter-exchange reaction for some of the compounds studied. The KIE in α-picoline N-oxide was studied in the forward and reverse exchange reactions. The average KIE values given in Tables 1 and 2 are reproduced in repeated experiments with an accuracy of ±0.2. The value obtained for k_D/k_T may be regarded as normal for a reaction in which the C—D or C—T bond is broken in the rate-determining step of the reaction. The certain decrease in the KIE observed in exchange in α-picoline is probably due to the temperature factor. The absence of a KIE in the exchange of β-picoline and β-picoline N-oxide is apparently associated with the low stability of the intermediate anion, which, unlike the α- and γ-isomers, is not stabilized by conjugation with the nitrogen of the aromatic ring. In this case the rate of the overall reaction is controlled by the diffusion process of neutralization of the anion by a deuteron from the solvent. Similar ideas concerning the role of the stability of intermediate ions in estimating KIE values were substantiated in (^{9}).

Thus, the experimental kinetic data on isotope exchange, the magnitudes of the chemical shifts in the NMR spectra, and the consistent results of molecular calculations by the LCAO MO method confirm the correctness of the view that delocalization energies, π-electron charges on the carbon attached to the CH_3 group, and C—N bond orders are expedient characteristics of reactivity for the deuterium-exchange reaction.

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Note: Figure translations are in progress. See original paper for figures.