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Relative Nucleophilic Reactivity of Pyridines and Pyridine *N*-Oxides (Supernucleophilicity of Pyridine *N*-Oxides)

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Abstract—Supernucleophilicity of pyridine *N*-oxides in acyl transfer reactions was rationalized for the first time on a theoretical level. Unlike pyridines, transition state derived from pyridine *N*-oxides is stabilized by direct conjugation between the nucleophilic and electrophilic components.

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It has long been known that oxygen-centered nucleophilic catalysts are more effective than nitrogen-centered nucleophiles in aprotic medium [1]. This difference is especially pronounced for pyridines and pyridine *N*-oxides, which stimulated systematic studies on nucleophilic reactivity of pyridines and pyridine *N*-oxides toward various electrophilic substrates (benzoyl chloride, diphenyl chlorophosphate, 4-toluenesulfonyl bromide, and methyl iodide in acetonitrile and methyl chloroformate in ethanol [2]), as well as in acetyl [3] and dimethylcarbamoyl [4] group transfer processes. Taking into account that factors responsible for different reactivities of the above classes of organic compounds remain so far unclear, in the present work analysis of published data on nucleophilic and basic properties of pyridines and pyridine *N*-oxides and experimental data on their complex formation with various *v*-acceptors made it possible to rationalize supernucleophilic properties of pyridine *N*-oxides in terms of $sp^2 \rightarrow sp^3$ rehybridization of the *N*-oxide oxygen atom, which depends on both nucleophile and substrate structures and other conditions.

Savelova et al. [2] compared the reactivities of pyridines and pyridine *N*-oxides in various reactions using Brønsted equation (1). The authors noted that higher sensitivity of the reaction rate to nucleophile basicity in the case of pyridine *N*-oxides (β_1 ratio ranges from 1.4 to 1.6) should inevitably lead to crossing of the corresponding plots at a certain pK_a value, where the reactivities of pyridines and pyridine *N*-oxides are equal (specific "isoparametric" point [5]); after that point, the reactivity is reversed.

$$\log k = \log k_o + \beta_1 \mathrm{p}K_a^{\mathrm{MeCN}}. \quad (1)$$

Here, $\mathrm{p}K_a^{\mathrm{MeCN}}$ is the basicity of nucleophile in acetonitrile.

However, the isoparametric points for the acylation of pyridines and pyridine *N*-oxides with benzoyl chloride, 4-toluenesulfonyl bromide, and methyl chloroformate fall out of the experimentally attainable region. Within the experimental $\mathrm{p}K_a^{\mathrm{MeCN}}$ range (5–15), the reactivity ratio of pyridine *N*-oxides and pyridines having equal basicities amounts to 10^3–10^6 in the reactions with benzoyl chloride and methyl chloroformate and 10^2–10^3 in the reactions with 4-toluenesulfonyl bromide and diphenyl chlorophosphate. Therefore, in these reactions pyridine *N*-oxides can formally be regarded as supernucleophiles. In the alkylation of pyridines and pyridine *N*-oxides with phenacyl bromide and methyl iodide, the isoparametric points appear within the experimental range of $\mathrm{p}K_a^{\mathrm{MeCN}}$ values, and reversal of their reactivity is actually observed at those points (Fig. 1). For example, substituted pyridine *N*-oxide having a $\mathrm{p}K_a^{\mathrm{MeCN}}$ value of 15 reacts with phenacyl bromide and methyl iodide more rapidly than does the corresponding substituted pyridine by a factor of 40 and 3, respectively, whereas the reaction rate of pyridine *N*-oxide with a $\mathrm{p}K_a^{\mathrm{MeCN}}$ value of 5 is smaller by a factor of 2 and 18, respectively, than the reaction rate of pyridine with the same basicity.

These data led the authors to conclude that supernucleophilicity of pyridine *N*-oxides is not determined by specificity of their electronic structure compared to pyridines since the appearance of their supernucleophilic properties depends on the nature of electrophilic partner. Therefore, the authors presumed that the existence of separate Brønsted correlations for pyridines

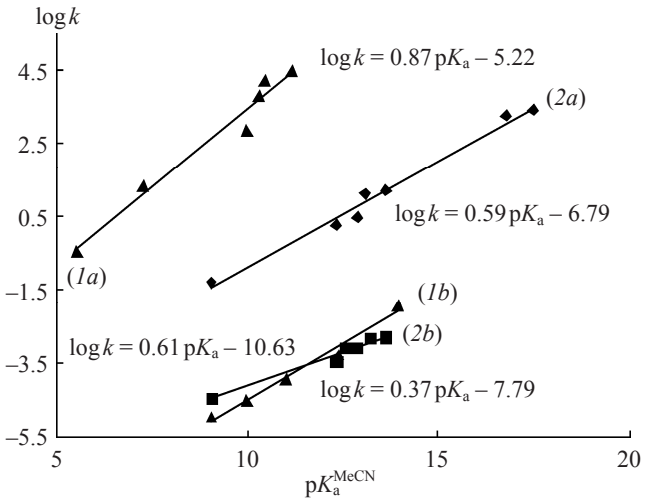


Fig. 1. Plots of $\log k$ for the reactions of (*1*) pyridine *N*-oxides and (*2*) pyridines with (*a*) benzoyl chloride and (*b*) methyl iodide in acetonitrile at 25°C versus pK_a of the nucleophiles in acetonitrile.

and pyridine *N*-oxides is related to different modes of stabilization of the corresponding transition states.

In keeping with the extended Hammond–Leffler postulate [2, 6], the structure of transition state reflects structural specificity of the reagents and products. Therefore, it seems to be more appropriate and justified to compare the Gibbs energies of activation ($\Delta G^{\neq}$) or reactivities ($\log k$) with the Gibbs energy of reaction (ΔG^{o}) or equilibrium constant ($\log K_{eq}$) for the same process:

$$\log k = \log k^{o} + \alpha \log K_{eq}. \qquad (2)$$

Here, the coefficient α characterizes effective charge distribution over reaction centers in going from

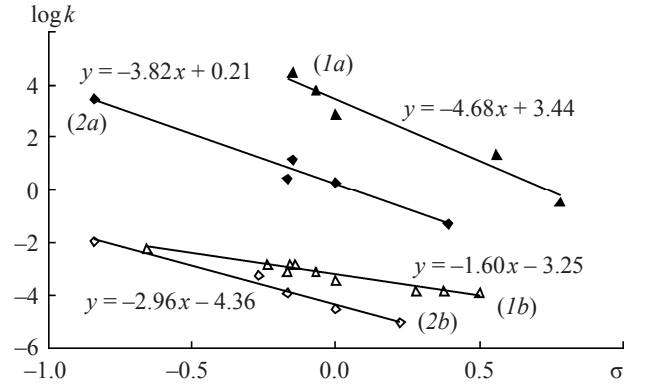


Fig. 2. Plots of $\log k$ for the reactions of (*1*) pyridine *N*-oxides and (*2*) pyridines with (*a*) benzoyl chloride and (*b*) methyl iodide in acetonitrile at 25°C versus Hammett constants σ.

initial to transition state; it is defined as the ratio of the Brønsted coefficients β_1 and β_2 in Eqs. (1) and (3).

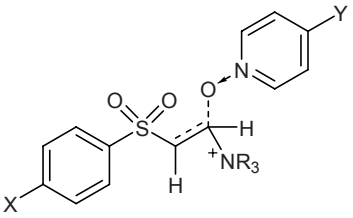
$$\log K_{eq} = \log K_{eq}^{o} + \beta_2 pK_a^{MeCN}. \qquad (3)$$

As shown in [2], the application of the Hammond–Leffler approach to the reaction of methyl iodide with pyridine *N*-oxides and pyridines in acetonitrile at 25°C does not give a common correlation, and the ratio of the coefficients α (2.14) increases even more strongly relative to the ratio of β_1 (1.57). This means that the reactivities of the above nucleophiles differ considerably despite equal thermodynamic stabilities of the products. The authors believed that more reactive pyridine *N*-oxides provide some additional stabilization of transition state and that no such stabilization effect exists in reactions with pyridines.

With a view to elucidate the nature of this effect, variation of the relative nucleophilicity of pyridines and pyridine *N*-oxides with reaction conditions should be considered in more detail. First of all, it should be noted that, regardless of the substrate nature (MeCOCl, $MeSO_3F$, $PhSO_2Cl$, $EtSO_3F$, RBr, MeI, EtI) and solvent (water, 2-nitropropane, nitromethane, nitrobenzene), the slopes of the $\log k$—pK_a [7] ($\log k$—σ) plots for 3- and 4-substituted pyridines remain almost constant at 25°C. In addition, the substrate nature affects the reactivity of pyridines to a much weaker extent as compared to pyridine *N*-oxides. For example, in the reactions of benzoyl chloride and methyl iodide with pyridines and pyridine *N*-oxides (pK_a^{MeCN} 11.0) at 25°C (Fig. 1), the rate constants differ by 3.5 and 8 orders of magnitude, respectively (4 and 7 orders of magnitude at σ = 0, Fig. 2). This means that the configuration of transition state in the reactions with pyridines depends on the electrophile nature to a lesser extent as compared to pyridine *N*-oxides and that the main factors affecting the reaction rate are variations in the charge on the reaction center and in its steric environment.

Thus the different reactivities of pyridines and pyridine *N*-oxides cannot result from sharp variation of properties of pyridines. However, if supernucleophilic properties were determined only by the nature of *N*-oxide, they would be reflected in all cases, regardless of the substrate. Moreover, supernucleophilicity cannot be related to variation of charge or substrate structure; otherwise, the same effect would be observed for both reaction series. Therefore, anomalously high nucleophilicity originates from a combination of properties of pyridine *N*-oxide and substrate (consistent interaction).

The fact that pyridine *N*-oxides having sp^2-hybridized oxygen atom act as supernucleophiles toward unsaturated substrates (activated vinyl halides, carboxylic acid halides, organic phosphorus and sulfur halides) in aprotic media suggests the existence of a single conjugation chain formed by nucleophile and substrate in the transition state which radically differs from the transition state formed by pyridines. Otherwise, change of hybridization of the reaction center in the substrate (sp^2-carbon atom in benzoyl chloride and sp^3-carbon atom in methyl iodide) should change the relative reactivity of pyridines and pyridine *N*-oxides so strongly that isoparametric point would be attainable experimentally in the reactions with alkyl halides and phenacyl bromide (Figs. 1–3). Only in this case some pyridine *N*-oxides having electron-withdrawing substituents become weaker nucleophiles than pyridines characterized by equal basicity. It should be specially emphasized that the reactivity of pyridine *N*-oxides in the replacement of trialkylammonium group in trialkyl(*trans*-arylsulfonylvinyl)ammonium salts (where the arylsulfonyl group is conjugated with the pyridine ring in the transition state) is higher by several orders of magnitude than in reactions with saturated alkyl halides [8]. On the other hand, trimethylamine *N*-oxide having no aromatic system reacts at the same rate as does pyridine *N*-oxide, although the basicity of the former is greater by four orders of magnitude.



X = H, CH_3, Cl, O_2N; Y = H, Me, Et, Me_2N.

Anomalous behavior of heteroaromatic *N*-oxides in reactions with electrophilic substrates is commonly rationalized in terms of steric factor. However, much weaker basicity of pyridine *N*-oxides relative to pyridines cannot be compensated only by spatial accessibility of the oxygen atom, taking into account high electronegativity of the latter. Furthermore, conjugation with the heteroaromatic ring increases the double character of the N→O bond (see canonical structures **V**–**VII**).

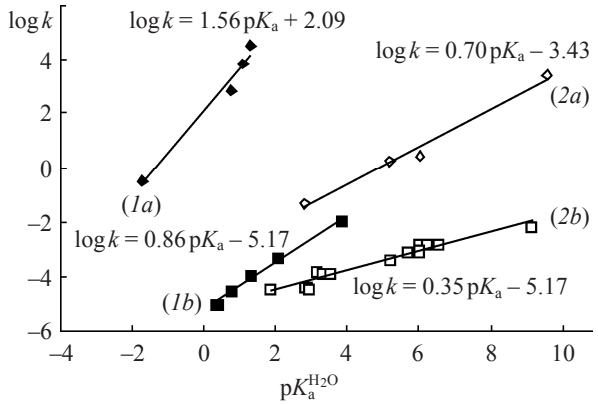


Fig. 3. Plots of $\log k$ for the reactions of (*1*) pyridine *N*-oxides and (*2*) pyridines with (*a*) benzoyl chloride and (*b*) methyl iodide in acetonitrile at 25°C versus pK_a of the nucleophiles in water.

It is known that double bonds are not only more accessible for attack by various reagents but also highly polarizable. Therefore, in the initial step reactions of electrophiles with heteroaromatic *N*-oxides could induce polarization of the N→O bond. By analogy with mechanisms of reactions involving double bonds, formation of a π-complex and then chemical bond with the oxygen atom cannot be ruled out. Thus the first step in reactions with electrophiles may be attack on the readily polarizable and spatially accessible electron pair occupying the unhybridized orbital which is conjugated with the heteroring rather than on sp^2-hybridized orbitals on the oxygen atom. This mode of N→O bond polarization could lead finally to transfer of electron pair from the oxygen atom to vacant orbital of electrophile.

In this context, it is important which orbital on the oxygen atom is overlapped by electrophile orbital in the transition state and in the final product. If the initial attack is directed at the oxygen atom, one of its sp^2 orbitals should be involved in the formation of new chemical bond. Provided that the initial process is polarization of the N→O bond, the oxygen atom may be forced out from conjugation with the heteroaromatic ring, followed by its rehybridization.

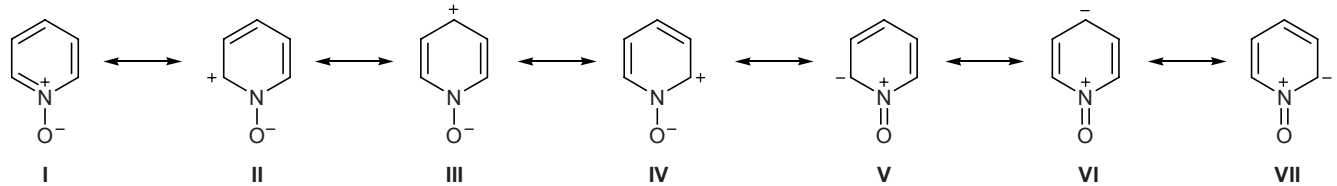


Table 1. ^{1}H NMR spectra of pyridine *N*-oxides, their molecular complexes with HCl and BF_3, and products of their reactions with methyl and ethyl iodides

Pyridine *N*-oxide	Electrophile	Chemical shifts δ, ppm						Solvent
		2-H	6-H	3-H	5-H	4-H	R	
$C_5H_5N\rightarrow O$	–	8.17 d		7.36 t		7.27 t	–	DMSO-d_6
	HCl	8.88 d		7.94 t		8.17 t	–	DMSO-d_6
	BF_3	8.53 d	8.86 d	8.01 t	8.38 t	7.70 t	–	DMSO-d_6
	MeI	9.61 d		8.61 t		8.32 t	4.66 s (NOMe)	$CDCl_3$
	EtI	9.58		8.71		8.28	4.80 (NOEt), 3.06 (NOEt)	$CDCl_3$
4-$MeC_5H_4N\rightarrow O$	–	8.29 d		7.42 d		–	2.47 s (4-Me)	DMSO-d_6
	HCl	8.94 d		7.96 d		–	2.74 s (4-Me)	DMSO-d_6
	BF_3	8.46 d 8.60 d	8.98 d 9.01 d	7.60 d 7.70 d	8.07 d 8.12 d	–	2.59 s (4-Me) 2.78 s (4-Me)	DMSO-d_6 DMSO-d_6–$CDCl_3$ (1 : 1)
	MeI	9.46 d		8.07 d		–	4.59 s (NOMe), 2.69 s (4-Me)	$CDCl_3$
	EtI	9.40 d		8.07 d		–	4.79 q (NOEt), 2.63 s (4-Me), 2.63 (NOEt)	$CDCl_3$
4-$MeOC_5H_4N\rightarrow O$	–	8.01 d		6.97 d		–	3.82 s (4-OMe)	DMSO-d_6
	BF_3	8.68 d		7.45 d		–	4.05 s (4-OMe)	DMSO-d_6
	MeI	9.33 d		7.66 d		–	4.50 s (NOMe), 4.17 s (4-OMe)	$CDCl_3$
	EtI	9.23 d		7.60 d		–	4.67 q (NOEt), 4.07 s (4-OMe), 3.08 (NOEt)	$CDCl_3$

According to the ^{1}H NMR [9] and X-ray diffraction data [10], $sp^2\rightarrow sp^3$ rehybridization of the oxygen atom in the N→O group is possible in reactions of heteroaromatic *N*-oxides with not only such hard Lewis acid as BF_3 but also milder acids, $ZnCl_2$, $CuCl_2$, and (tetraphenylporphyrinato)zinc(II) (Zn-TPP). The ^{1}H NMR data (Table 1) show that hybridization of the oxygen atom in complexes with boron trifluoride (at least in solution) is determined by the basicity of *N*-oxide. In the $C_5H_4NO\cdot BF_3$ and 4-$MeC_5H_4NO\cdot BF_3$ complexes in DMSO the O–B bond involves sp^2 orbital of the oxygen atom, while $sp^2\rightarrow sp^3$ rehybridization of the latter becomes possible only in BF_3 complexes with more basic *N*-oxides, such as 4-(4-dimethylaminostyryl)- and 4-methoxypyridine *N*-oxides [9].

I believe that the differences in the nucleophilicity/basicity of pyridines and pyridine *N*-oxides, which depend on the properties of electrophile (acid, acceptor), as well as configuration and stability of their alkylation and acylation products, can also be interpreted in terms of rehybridization of the *N*-oxide oxygen atom.

The basicity of pyridines [pK_a(MeCN) = –5.88σ + 12.01; $pK_a(H_2O)$ = –4.70σ + 5.19] and pyridine *N*-oxides [pK_a(MeCN) = –6.08σ + 10.50; $pK_a(H_2O)$ = –3.32σ + 1.06] in acetonitrile and water is strongly sensitive to the substituent nature. High negative ρ values suggest a large positive charge on the reaction center in the transition state formed in the reactions of pyridines and pyridine *N*-oxides with proton. In addition, the ρ values for pyridines and pyridine *N*-oxides in acetonitrile are fairly similar, indicating similar structures of the corresponding transition states. However, the ρ values in water are considerably lower than in acetonitrile, which is very consistent with donor–acceptor properties of these solvents. Hard Lewis acids (according to Pearson), such as proton and protonated pyridines and pyridine *N*-oxides, are solvated (in keeping with the Ingold–Hughes theory) by acetonitrile

(which is a mild Lewis base) much more poorly than by water. In addition, water molecules compete with the heterocyclic bases for proton. Therefore, as follows from the ρ values, the positive charge in the transition state formed in acetonitrile is greater than in water. Considerably smaller positive charge in the transition state formed by protonation of pyridine *N*-oxides in water, as compared to pyridines, is likely to result from better hydration of spatially more accessible $N–O^+–H$ fragment (which favors charge delocalization), as compared to the $N^+–H$ moiety in pyridinium ion. Transition states in the protonation of pyridines is formed with participation of the sp^2 orbital on the nitrogen atom, which is orthogonal to *p* orbitals of the aromatic ring, so that conjugation with the latter is impossible. Taking into account similar ρ values, formation of O–H bond in the protonation of pyridine *N*-oxides in acetonitrile is likely to involve sp^2 or sp^3 orbitals (rehybridization) of the oxygen atom, i.e., the transition state is not stabilized by conjugation. In this case, the relative stability (in terms of stability of the protonated species) is determined by electronegativities of the nitrogen and oxygen atoms. Therefore, pyridines are stronger bases than pyridine *N*-oxides. In going to water, hydration of the oxygen atom (with formation of *n*,*v*-complexes like $C_5H_5N→O\cdots H–O–H$ and $C_5H_5N→O\cdots 2H–O–H$ [11]) increases the probability for formation of π-complexes (as with alkenes) with participation of partially double N→O bond and proton. Polarization of the N→O bond could lead to rehybridization of the oxygen atom and formation of O–H bond involving *p* orbitals through a transition state in which conjugation between the oxygen atom and substituents in the heteroring still exists to an appreciable extent (much stronger than in acetonitrile).

The positive charge on the reaction center decreases in the following electrophile (Lewis acid) series H^+ > PhCOCl > MeI, and the absolute values of ρ change in parallel. However, the ρ value for the reaction of pyridine *N*-oxides with benzoyl chloride is higher (in absolute value, –4.7 and –3.8; $\alpha^{PyO}/\alpha^{Py} = 1.24$) and for the reaction with methyl iodide is lower (–1.6 and –3.0; $\alpha^{PyO}/\alpha^{Py} = 0.53$) than those found for the reactions with pyridines. Thus the reversal of nucleophilic reactivity of pyridines and pyridine *N*-oxides may be rationalized, on the one hand, by greater difference in the variation of charge in the transition states in going from one electrophile to another and, on the other, in terms of stabilization of transition state in the reaction of pyridine *N*-oxides with PhCOCl by both mesomeric and inductive substituent effects (electrophilic center is conjugated with the pyridine ring; in other cases the transition state is stabilized only by inductive effect).

Assuming that Hammett constants σ reflect both inductive and mesomeric effects of substituents and that the unhybridized *p* orbital of the oxygen atom is completely or partially forced out (or not) from conjugation with the pyridine ring in the alkylation, acylation, or protonation transition state, the sensitivity of pyridine *N*-oxides to mesomeric constituent of electronic effects of substituents should depend on acceptor properties of electrophiles and spatial accessibility of reaction centers. For example, interaction with strong Lewis acids (such as BF_3) and increase in the size of substituent in the 2-position (or in positions *2* and *6*) of the pyridine ring could, respectively, hinder conjugation with the aromatic system or even promote $sp^2→sp^3$ rehybridization of the oxygen atom.

Obviously, methyl iodide is the weakest Lewis acid in the above electrophile series. Therefore, the initial step of the reaction of pyridine *N*-oxides with methyl iodide is most likely to involve one of the two accessible sp^2 orbitals rather than *p* orbital of the oxygen atom, which is conjugated with the pyridine ring. Further moving along the reaction coordinate may be accompanied by $sp^2→sp^3$ rehybridization of the *N*-oxide oxygen atom with formation of an equilibrium mixture containing the initial *N*-oxide, alkyl halide, and nucleophilic replacement product (in solution) or individual alkoxypyridinium salt (solid phase), as follows from the NMR (Table 1) and X-ray diffraction data [10]. If two strong electron-donating groups are present in the pyridine ring, the reaction in liquid phase could also produce alkoxypyridinium salt in almost quantitative yield.

The data in Table 1 show that the maximal shift of signals from protons in the pyridine ring (2-H/6-H and 3-H/5-H) is observed in the reactions of pyridine *N*-oxides with alkyl iodides rather than with BF_3 or HCl. The shift becomes smaller in the series C_5H_5NO > 4-MeC_5H_4NO > 4-$MeOC_5H_4NO$, in keeping with decrease in polarity and increase in strength of the newly formed O–C bond. If that bond were formed with participation of sp^2 orbitals on the oxygen atom, it would be even stronger than the corresponding O–B bond formed in the reaction of pyridine *N*-oxides with BF_3, and all protons in the pyridine ring would be nonequivalent. The observed equivalence of 2-H/6-H and 3-H/5-H indicates that the signals belong to alkoxypyridinium iodides in which conformational transformations about the O–C bond involving sp^3 orbitals of the oxygen atom are very fast.

Presumably, the formation of activated complex $[XC_5H_4N{\rightarrow}O^{\delta-}\cdots{}^{\delta+}CH_3\cdots I^{\delta-}]^{\neq}$ by methyl iodide and substituted pyridine *N*-oxide is an equilibrium process, and the corresponding equilibrium constant is determined by relative thermodynamic stability of the initial compounds and products, which depends in turn on the relative strength of the O–C and C–I bonds and relative nucleophilicity/basicity of pyridine *N*-oxide and iodide ion. Increase in the O–C bond strength, as well as in nucleophilicity and basicity of pyridine *N*-oxide, should enhance electron-donor and weaken electron-acceptor properties of the substituent X.

If pyridine *N*-oxide possesses a low basicity, methoxypyridinium salt $[XC_5H_4NOCH_3]^+I^-$ formed theoretically via overlap of sp^2 orbital of the oxygen atom which remains conjugated with the pyridine ring and sp^3 orbital of the methyl carbon atom may be sufficiently strong or capable of undergoing dissociation in solution, as is observed for molecular complexes of pyridine *N*-oxides with boron trifluoride. According to the ^{1}H NMR data, the complex $C_5H_5NO\cdot BF_3$ is unstable even in chloroform, whereas 4-$MeC_5H_4NO\cdot BF_3$ (sp^2-oxygen atom) and 4-$MeOC_5H_4NO\cdot BF_3$ (sp^3-oxygen atom) are stable in DMSO [9].

In fact, Popov et al. [12] reported that dissolution of preliminarily prepared methoxypyridinium iodide in acetonitrile leads to accumulation of pyridine *N*-oxide and methyl iodide and that the concentration of iodide ions decreases to the same value as in the formation of the initial salt from pyridine *N*-oxide and methyl iodide taken at appropriate concentrations. Addition of tetramethylammonium iodide to the reaction system after equilibration increases the concentration of methyl iodide (common-ion effect). The conversion in the reactions of unsubstituted pyridine *N*-oxide with methyl and ethyl iodides (initial reactant concentration 0.2–0.4 M, ratio 1 : 1) is ~30 and 80%, respectively. The ethyl group exhibits a stronger positive inductive effect (+*I*) as compared to methyl group and better stabilizes the O–C bond.

The presence of electron-donating groups in the heteroring of pyridine *N*-oxides should enhance the O–C bond formed by sp^2 orbital of the oxygen atom and probably induce rehybridization of the oxygen atom so that the O–C bond will involve sp^3 orbital of the oxygen atom. Therefore, the equilibrium with highly basic 4-methoxy- and 4-dimethylaminopyridine *N*-oxides is displaced almost completely toward alkoxypyridinium salts (Table 2).

The effect of the nature of alkyl group in alkyl halides on the rate of formation of alkoxypyridinium salts is considerably weaker than in the alkylation of pyridines [13], which is consistent with better spatial accessibility of the *N*-oxide oxygen atom. The rate constant ratio for the alkylation of pyridine *N*-oxide with methyl and isopropyl iodides in acetonitrile at 25°C is equal to 4.3, while the corresponding ratio for the alkylation of pyridine under the same conditions is much greater (392).

The rate of decomposition of alkoxypyridinium salts into the initial reactants in going from methoxy to ethoxy and isopropoxy derivatives decreases to an appreciably stronger extent than the rate of their formation. For example, the corresponding rate constant ratios for pyridine *N*-oxide are 428 : 7 : 1 and 4.3 : 2.2 : 1. On the basis of the data in Table 2 it was concluded [13] that introduction of methyl groups into positions *2* and *6* of the pyridine ring, as well as increase in the size of alkyl group on the oxygen atom in alkoxypyridinium salts, stabilizes the latter due to inductive effect and steric shielding of the reaction center (in reactions with halide ions); on the other hand, the same factors destabilize alkoxypyridinium salts owing to steric strains in the cation. The overall effect of the nature of alkyl radicals on the rates of the direct and reverse reactions makes *N*-ethoxypyridinium iodides the most stable among the examined salts.

At first glance, all the above conclusions are fairly reasonable. However, more detailed analysis of the results obtained in [13] could provide additional valuable information on the steric structure of alkoxypyridinium salts. Attention should be given to the fact that, according to the data in Table 2, variation in the stability of alkylation products in the series C_5H_5NO, 2-MeC_5H_4NO, and 2,6-$Me_2C_5H_3NO$ is anomalous. The expected reduction in the stability is observed only upon introduction of one methyl group into position *2* of the pyridine ring (cf. k_{-1} and K_{eq}), while introduction of the second substituent into the 6-position increases the stability, though the role of steric effect should be enhanced in this case. For example, *N*-methoxy- and *N*-ethoxy-2,6-dimethylpyridinium iodides and bromide are even more stable than their 2-methyl-substituted analogs, and only *N*-isopropoxy-2,6-dimethylpyridinium iodide is characterized by lower value of K_{eq}; furthermore, the rate of decomposition of the latter (k_{-1}) becomes equal to the rate of decomposition of *N*-ethoxy derivative. It should also be noted that the conclusion [13] that ethoxypyridinium iodides are the most stable seems to be inappropriate. In fact, only the equilibrium constant K_{eq} of *N*-isopropoxy-2,6-dimethylpyridinium iodide is lower than that of its *N*-ethoxy

Table 2. Rate constants for the formation ($k_1 \times 10^5$ l mol^{-1} s^{-1}) of *N*-alkoxypyridinium salts from pyridine *N*-oxides and alkyl halides, equilibrium constants (K_{eq}), and rate constants for decomposition ($k_{-1} \times 10^5$ l mol^{-1} s^{-1}) of *N*-alkoxypyridinium salts into the initial reactants in acetonitrile at 25°C [13]

Nucleophile (R_n in $R_nC_5H_{5-n}NO$)	MeI			EtI			*i*-PrI			MeBr		
	k_1	k_{-1}	K_{eq}	k_1	k_{-1}	K_{eq}	k_1	k_{-1}	K_{eq}	k_1	k_{-1}	K_{eq}
H	2.90	3.55	0.82	1.51	0.057	28	0.682	0.0083	82	1.36	5.60	0.24
4-Cl	1.00	–	–	–	–	–	–	–	–	0.41	–	–
4-Me	11.9	1.00	11.9	6.37	–	>100	2.01	–	>100	5.00	1.07	4.7
4-MeO	52.2	–	>100	23.5	–	>100	7.18	–	>100	24.4	0.43	57
4-Me_2N	1150	–	–	486	–	–	125	–	–	625	–	–
2-Me	2.20	4.70	0.47	0.821	0.076	11	0.255	0.022	12	1.00	5.14	0.19
2,6-Me_2	1.64	3.05	0.54	0.635	0.032	20	0.104	0.035	3.0	0.592	2.39	0.25

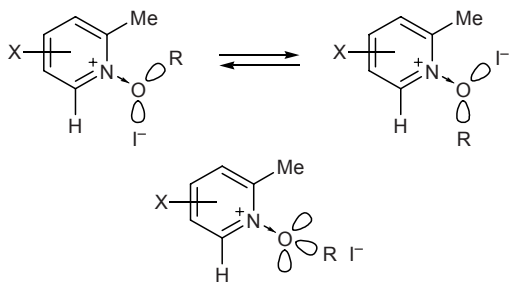
analog, whereas the corresponding k_{-1} values are almost similar.

Obviously, from the viewpoint of *+I* effect, introduction of methyl groups into position *2* and then *6* of pyridine *N*-oxide molecule, as well as increase in the size of alkyl group on the oxygen atom in the alkylation product, should stabilize the latter. On the other hand, concomitant increase in steric strain should facilitate its decomposition. Provided that hybridization of the oxygen atom remains unchanged, the behavior of *N*-alkoxy-2,6-dimethylpyridinum iodides contradicts the above conclusions. As follows from the data in Table 2, introduction of even one methyl group into position *2* of pyridine *N*-oxide, regardless of the alkyl group nature in alkyl iodide, accelerates decomposition of alkoxypyridinium salts (steric factors become predominating), stronger increase in the rate of decomposition being observed for 2-methyl-substituted derivatives with larger alkyl group on the oxygen atom. Introduction of the second methyl group into the 6-position should enhance the above tendency. However, the rate of decomposition of *N*-methoxy and *N*-ethoxy derivatives is even lower than those found for unsubstituted pyridine *N*-oxide derivatives. Only the rate constant k_{-1} for *N*-isopropoxy-2,6-dimethylpyridinium iodide approaches that found for *N*-ethoxy-2,6-dimethylpyridinium iodide (k_{-1} = 0.035 and 0.032×10^{-5}, respectively; Table 1), as if steric factor in this case is not so significant as electronic effect.

The observed variation in the stability of alkylation products of pyridine *N*-oxides may be rationalized in terms of rehybridization of the oxygen atom provided that it leads to less strained structure. This is consistent with the data on rehybridization of molecular complexes of pyridine *N*-oxides with boron trifluoride even in the course of crystallization process [10]. Presumably, the formation of O–C bond in the alkylation of 2-methylpyridine *N*-oxide involves initially sp^2 orbitals of the oxygen atom to give an equilibrium mixture in which the fraction of conformer with the maximal distance between the alkyl group increases in parallel with the size of hydrocarbon radical in alkyl halide (Scheme 1). It is important that, in keeping with the data of [13], alkoxypyridinium salts undergo decomposition only as ion pairs where the halide ion (the effect of larger iodide ion should be stronger than the effect of bromide ion) creates stronger strain upon substitu-tion at positions *2* and *6* of the pyridine ring. In the alkylation of 2,6-dimethylpyridine *N*-oxide, conformers with sp^2-hybridized oxygen atom become so strained that rehybridization of the oxygen atom appears to be favorable, and the O–C bond is formed in the plane orthogonal to the pyridine ring with participation of sp^3 orbital. In this case, electrostatic repulsion between electron shells of the alkyl groups is reduced, and the stability of alkoxypyridinium salt increases.

An additional factor should be noted while considering reactions of pyridine *N*-oxides with substrates

Scheme 1.



R = Me, Et, *i*-Pr.

in which the reaction center is capable of being involved in conjugation with the *N*-oxide oxygen atom. This factor not only stabilizes the transition state but also ensures free rotation about the N–O bond without change of hybridization of the oxygen atom. The *p* orbital of the oxygen atom, which is partly overlapped in the transition state by *p* orbitals of the nitrogen atom and reaction center, may lose conjugation with the pyridine ring but become a part of conjugation chain in the substrate moiety. In this case, free rotation about the single N–O bond is possible even when the substituent R is large (Fig. 4), and the molecule can adopt most favorable conformation with mutually orthogonal pyridine and benzene rings. According to the ^{1}H NMR data, this possibility is realized for 1-dimethylcarbamoyloxy-4-(4-methoxystyryl)pyridinium tetraphenylborate [4] (protons in positions *2* and *6* of the pyridine ring are equivalent).

It should be noted that the stability of *O*-acyl and *O*-alkoxy derivatives of pyridine *N*-oxides in solution depends on donor–acceptor properties of substituents in the pyridine ring and on the oxygen atom, as well as on the nature (nucleophilicity and basicity) of the anion. For example, 1-dimethylcarbamoyloxy-4-(4-methoxystyryl)pyridinium tetraphenylborate is stable in aprotic solvents (tetraphenylborate is a very weak nucleophile), whereas anhydrous crystalline product of the reaction of pyridine *N*-oxide with benzoyl chloride (nucleophile Cl^-) decomposes almost completely into the initial reactants upon dissolution in benzene [1].

Like molecular complexes of pyridine *N*-oxides with BF_3 [10], crystalline *N*-alkoxy-, *N*-aroxy-, and *N*-hetaryloxypyridinium salts whose structure was determined by X-ray analysis [14] (CSD refcodes: CANTIU, SIRWUL, TAJPUP, etc.) contain sp^3-hybridized oxygen atom: the NOC fragment lies in the plane orthogonal to the pyridine ring, thus completely

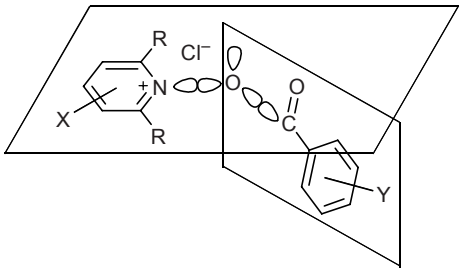


Fig. 4. A probable conformation (rotation about the N–O bond) of reaction products of pyridine *N*-oxides and substituted benzoyl chloride, in which *p* orbital of the sp^2-hybridized oxygen atom is conjugated only with the benzoyl fragment.

preventing conjugation between the latter and the oxygen atom.

Complex formation of Zn-TPP with pyridines and pyridine *N*-oxides was found [10, 15] to follow the same general relations as those typical of nucleophilic substitution processes, and the sensitivity of the stability constants to electronic properties of substituents in the pyridine ring was almost the same for both series of ligands ($\log K^{Py} = -1.11\sigma + 3.61$; $\log K^{PyO} = -1.15\sigma + 3.08$) but lower than in the alkylation or acylation. These findings suggest that Zn-TPP is even a weaker *v*-acceptor (at least in the transition state) than methyl iodide.

Unlike nucleophilic replacement, conjugation of the ligand with the zinc atom in the transition state formed in complex formation of pyridine *N*-oxides with Zn-TPP is improbable; nevertheless, pyridine *N*-oxides remain stronger nucleophiles than pyridines characterized by the same basicity ($\log K^{Py} = 0.23\,pK_a + 2.41$; $\log K^{PyO} = 0.32\,pK_a + 2.77$).

Pyridine *N*-oxides are classed with α-nucleophiles [1, 2]. It is also known that α-effect has no common nature. However, as noted in [1], molecule of a nucleophile should possess the following unique properties to suppress α-effect: (1) nucleophilic center should be a negatively charged atom belonging to the IInd Period of the Periodic Table and there should be no nearby substituents hampering attack on electrophilic center in a substrate for steric reasons; (2) nucleophile molecule should contain catalytically active centers or groups capable of stabilizing transition state; (3) the α-position should be occupied by an electronegative atom possessing unshared electron pairs (or one pair), which destabilize the initial state and stabilize the transition state. In addition, the magnitude of α-effect depends on the solvent and substrate nature and probably on other factors. For example, replacement of methyl group in some nucleophiles by dodecyl may increase the reactivity by 2–3 orders of magnitude provided that their concentration exceeds the critical micelle concentration. The reason is micellar catalysis [1].

An additional stabilizing factor responsible for supernucleophilicity of pyridine *N*-oxides in the complex formation with Zn-TPP may be π–π interaction between the aromatic systems of the reactants, which is impossible when the pyridine ring is oriented orthogonally to the porphyrin macroring plane [14]. According to the X-ray diffraction data [10], the dihedral angle between the macroring and ligand planes in the

crystalline 1:1 molecular complex of Zn-TPP with isoquinoline *N*-oxide is 24.34°.

The following conclusion can be drawn on the basis of the above stated. Supernucleophilic properties of pyridine *N*-oxides compared to more basic pyridines in nucleophilic substitution processes originate mainly from additional stabilization of the transition state due to conjugation between the *N*-oxide oxygen atom, reaction center in the electrophile molecule, and π system of the heteroring. It should also be taken into account that oxygen atom in the N→O group of pyridine *N*-oxides is spatially much more accessible than nitrogen atom in the pyridine ring.

EXPERIMENTAL

The ^{1}H NMR spectra of heteroaromatic *N*-oxide hydrochlorides and their adducts with BF_3, as well as of reaction mixtures containing *N*-oxides and alkyl iodide at a ratio of 1:2, were recorded at room temperature on a Bruker WM 400 spectrometer from solutions in DMSO-d_6 using tetramethylsilane as internal reference. Molecular complexes of heteroaromatic *N*-oxides with BF_3 and HCl were synthesized as described in [16].

REFERENCES

1. Litvinenko, L.M. and Oleinik, N.M., *Mekhanizmy deistviya organicheskikh katalizatorov. Osnovnyi i nukleofil'nyi kataliz* (Mechanisms of Action of Organic Catalysts. Base and Nucleophilic Catalysis), Kiev: Naukova Dumka, 1984.
2. Savelova, V.A., Popov, A.F., Solomoichenko, T.N., Sadovskii, Yu.S., Piskunova, Zh.P., and Lobanova, O.V., *Russ. J. Org. Chem*., 2000, vol. 36, p. 1465.
3. Rybachenko, V.I., Chotii, K.Yu., Kovalenko, V.V., and Schroeder, H., *Russ. J. Gen. Chem*., 2001, vol. 71, p. 786.
4. Schroeder, H., Rybachenko, V.I., Chotii, K.Yu., Kovalenko, V.V., Grebenyuk, L.V., Lenska, B., and Eitner, K., *Russ. J. Gen. Chem*., 2003, vol. 73, p. 455.
5. Pal'm, V.A., *Osnovy kolichestvennoi teorii organicheskikh reaktsii* (Principles of the Quantitative Theory of Organic Reactions), Leningrad: Khimiya, 1977.
6. Leffler, J.E. and Grunwald, E., *Rates and Equilibria of Organic Reactions as Treated by Statistical, Thermodynamic, and Extrathermodynamic Methods*, New York: Wiley, 1963.
7. Arnett, E.V. and Reich, R., *J. Am. Chem. Soc*., 1980, vol. 102, p. 5892.
8. Kravchenko, V.V. and Popov, A.F., *Zh. Org. Khim*., 1993, vol. 29, p. 2422.
9. Andreev, V.P. and Nizhnik, Ya.P., *Kord. Khim*., 2007, vol. 33, p. 703.
10. Andreev, V.P., *Doctoral (Chem.) Dissertation*, Petrozavodsk, 2007.
11. Gubarev, Yu.A., Lebedeva, N.Sh., Andreev, V.P., Nizhnik, Ya.P., and V'yugin, A.I., *Russ. J. Gen. Chem*., 2007, vol. 77, p. 1093.
12. Popov, A.F., Matveev, A.A., Koblik, I.V., Savelova, V.A., and Matvienko, V.N., *Russ. J. Org. Chem*., 1996, vol. 32, p. 587.
13. Matveev, A.A., Koblik, I.V., Popov, A.F., Savelova, V.A., and Matvienko, V.N., *Russ. J. Org. Chem*., 1998, vol. 34, p. 271.
14. *Cambridge Structural Database. Version 5.26*, 2004.
15. Andreev, V.P., Nizhnik, Ya.P., Bezruchko, D.G., and Morozov, A.K., *Russ. J. Gen. Chem*., 2005, vol. 75, p. 1309.
16. Ochiai, E., *Aromatic Amine Oxides*, Amsterdam: Elsevier, 1967.