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THE EFFECT OF ELECTRONIC FACTORS ON THE REACTIVITY OF HETEROAROMATIC N-OXIDES

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On the basis of an analysis of the reasons for the multiplicity of σ constants for substituents it has been concluded that they are variables, the absolute value and sign of which depend on the nature of the compounds being considered (in particular other substituents), the partner with which reaction occurs, and the medium (the aggregate state of participants of the interaction). The use of modifications of the Hammett equation is caused by the impossibility in principle of only varying the values and sign of ρ to describe universally linear functions of the dependence of rate (or equilibrium) constants of chemical processes from the algebraic sum of the electronic, steric, and other factors, which differ in their nature.

Keywords: heteroaromatic N-oxides, donor-acceptor complexes, metalloporphyrins, pyridine, Hammett and Taft equations.

At the present time empirical equations of the Hammett and Taft type ($\log(k/k_0) = \rho\sigma$) are widely used in organic chemistry in spite of the fact that the multiplicity of σ constants requires greater care in choosing them for making correlations, and the use for interpreting the structure of a transition state interferes with certain other resistant concepts [1-6]. Thus the Hammett equation is used for assessing the structure of a transition state (according to the size of $|\rho|$) among similar compounds by the variation of substituents and consequently by the change in reactivity. It is therefore assumed that ρ is a constant (but is dependent on the nature of the second reactant and the reaction conditions), i.e. the nature (σ) of a substituent does not affect the structure of the transition state. However according to the Hammond postulate [5] in rapid reactions the transition state is more like the reactants, but in slow reactions it is more like the reaction products, i.e. on changing the reaction rate the structure of the transition state must also be changed.

In the monograph [4] V. A. Palm notes that the problem of constructing a precise scale even for induction constants of substituents of the type of functional groups or containing functional groups has no solution. The assumption of even O. A. Reutov, A. L. Kurts, and K. P. Butin [5, Vol. 1, p. 288], that "ρ and σ are not independent parameters, as suggested, but are linked to one another, while a parameter linking ρ and σ is reduced in their product", does not only not clarify the situation, but also remains as an additional problem as to the nature of this parameter.

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In spite of (and also thanks to the fact that) the enormous quantity of studies devoted to the Hammett equation, consideration of the reasons for its nonuniversality, in our view, is urgent.

In the present paper, as model reactions for studying the effect of electronic and steric factors on the reactivity of nucleophiles/bases, we have considered the processes of complex formation of heteroaromatic N-oxides of the pyridine, quinoline, and acridine series with ν-acceptors (Lewis acids) of various Pearson hardness [H^+, BF_3, $ZnCl_2$, and Zn(II)tetraphenylporphin (Zn-TPP)]. Donor-acceptor interactions of the types mentioned with ligands are similar in many cases and enable the principles of coordination chemistry to be used for explaining kinetic and thermodynamic data of classic chemical reactions investigated in organic chemistry. The expediency and originality of such an approach is also caused by the fact that we have proposed a new scale of nucleophilicity/basicity based on parameters characterizing the formation of axial (*n*,ν-type) complexes of the Zn-TPP with ligands (bases/nucleophiles) [7], on using which the values of the stability constants of complexes, and the displacements of the maxima of the absorption bands of the metalloporphyrin in the electronic spectra, conform to the Hammett equation and correlate linearly with the rate constants of chemical reactions.

The Hammett equation may only be used under conditions of mutually proportional change of various types of electronic effects and in the absence of other, for example, steric effects. In just this way is the impossibility explained of using the usual σ constants in the presence of the "*ortho* effect" even taking into account the steric constants (E_s), because it strongly affects the mesomeric effect of substituents by breaking the conjugation between the reaction center and the functional group, and also the need to use σ^+ or σ^- constants in the presence of direct resonance conjugation with substituents, possessing already large +*M* or -*M* effects respectively. The disproportional change in inductive and mesomeric effects on displacing substituents from the *para* to *meta* position (absence of conjugation with the reaction center) compels the use of two types of Hammett constant, σ_{para} and σ_{meta}.

In addition, equations of the Hammett and Taft type in no way consider the fact that even in the gas phase one substituent may display donor and acceptor properties in the molecule, depending on the sign of the charge (aiding its delocalization) arising in the reaction center. In particular, an increase in the length of an alkyl group stabilizes both the anion on removal of proton from alcohols and carboxylic acids (acidity [8]) and also the cation on protonating them (basicity [9]). It is natural that this ability must be even more marked in readily polarizable conjugated systems, in aniline, phenol, and phenolate anion the benzene ring displays acceptor properties, and donor properties in chlorobenzene and the anilinium cation.

Dynamic polarization of a group (such as amino-, alkoxy-, nitro-) may also be effected under the action of a molecule of solvent (as a result of interaction with Bronsted–Lowry acids the acceptor properties of the NO_2 group are increased, but the donor properties of NH_2, OH and OR are reduced, or even, as in the case of acidifying a solution of aniline [3, p. 86], are reversed to acceptor properties).

It is evident that the polarization of groups, both on introducing other substituents or on a charge arising at the reaction center, must depend on their mutual position in the aromatic system and the nature of the latter. For example, a benzene ring is usually only a conductor (transmission ability $\pi' = 0.27$ [3]) of electronic effects, and the pyridine ring, displaying powerful acceptor properties, may even change the sign of the electronic effect of another electron-accepting group. Thus in [10, 11] it was shown that such substituents as NO_2 and CN (-*I*, -*M* effects) in certain cases display donor properties by a conjugation mechanism. This, in the opinion of the authors, explains the fact that pyridines containing a nitro or a cyano group in position 4 are more strongly basic (p*K*a 1.39 and 1.86 respectively) than analogs with substituents in position 3 (p*K*a 1.18 and 1.35).

However such a reversal of the sign of the electronic effect (as also the mutual effect of substituents) must become much less probable depending on the increase in size of the conjugated system (benzene < naphthalene < anthracene, pyridine < quinoline < acridine etc [12]) in view of the alleviation of the possibility of concurrent displacement of electron density from the condensed aromatic system. In particular, a quantitative assessment of the effect of substituents on acid–base properties (solvent ethanol–water, 1:1) of substituted 9-chloroacridines by the Hammett equation showed a good correlation of the following form:

$$\text{p}K\text{a} = (3.98 \pm 0.01) - (0.85 \pm 0.04)\sigma,$$
$$n = 11,\ S_0 = 0.01,\ r = 0.998$$

The small value of ρ (practically coinciding with ρ for protonation of substituted 9-hydrazinoacridines) indicates the low sensitivity of the heterocyclic nitrogen towards the effect of substituents in the 9-chloroacridine molecule [13].

Comparison of the reaction constants for protonation of pyridines (ρ 5.90), quinolines (ρ 5.42 for substituents in the pyridinium nucleus), acridines (ρ 0.88) show that the appearance of the benzene ring annelated with the pyridine ring, regularly leads to some reduction in the sensitivity of the reaction center. In the tricyclic system dibenzopyridine (acridine) itself ρ is reduced by approximately fivefold.

Heteroaromatic N-oxides arouse special interest in investigating the electronic effects of substituents. In these compounds the N→O group (usually displaying acceptor properties) in conjugation with a very strong acceptor (such as NO_2), unlike the nitrogen atom of its unoxidized analogs, may also be a donor of electrons.

According to the data of Table 1 functional groups (amino-, hydroxy-, alkoxy-, phenoxy-) in position 4 of the pyridine ring capable of displaying a +*M* effect (methyl – a hyperconjugation effect) have close σ_{PyO} (introduced for N-oxides of pyridine [15]) and σ^+ constants (significantly different from the Hammett σ constants). Even a chlorine reduces its acceptor properties somewhat (σ = +0.227; σ_{PyO} = +0.206), indicating that they are weaker than the these of N→O group. However for substituents with a -*M* effect the values of σ_{PyO} approach the values of the σ^- constant, indicating that the N-oxide group, being in conjugation with such powerful acceptor groups as COOMe, COOH, CN, NO_2, is forced to display donor properties. This is also confirmed by data of X-ray structural analysis, the molecules of 4-nitropyridine N-oxide in the crystalline state are found in the quinonoid form [15].

In order to clarify how strong the acceptor properties of the nitrogen atom of the pyridine ring are we have calculated the following equation based on the data of [10] for 32 pyridines with substituents in positions 3, 4, and 5:

$$pKa = -5.83\sigma + 5.46,\ r = 0.975$$

Since compounds with substituents with large +*M* and -*M* effects (pyridines containing COO^-, NH_2, NO_2, CN, COOMe, Ac, Bz, CHO, MeO groups in position 4) clearly show deviations from a straight line to the side of overestimating the basicity (p*K*a = -6.18 σ + 6.16, r = 0.990), we excluded them from the calculation and obtained the following equation.

$$pKa = -5.90\sigma + 5.24,\ r = 0.998,\ n = 23$$

Substituents: nothing or 3-Me; 4-Me; 4-Et; 4-*n*-Pr; 4-*i*-Pr; 3-MeO; 3-NH_2; 3-Cl; 4-Cl; 3-Br; 4-Br; 3-Bz; 3-CN; 3-NO_2; 4-Ph; 3-COOMe; 3-COO^-; 3,4-Me_2; 3,5-Me_2; 3,5-Cl_2; 3,5-Br_2; 3-Br, 5-MeO.

TABLE 1. Values of σ_{para}, σ_{PyO} , σ^+, and σ^- Constants of Substituents

X	σ_{para} [2]	σ_{PyO} [14]	σ^+ [2]	σ^- [14]
4-NMe_2	-0.84	-1.48	-1.7	—
4-NH_2	-0.66	-1.37	-1.3	—
4-OH	-0.37	-0.751	-0.92	—
4-OPh	-0.32	-0.574	-0.5	—
4-OMe	-0.268	-0.603	-0.778	—
4-Me	-0.170	-0.240	-0.311	—
4-Ph	-0.01	—	-0.179	—
H	0	0	0	0
4-F	+0.062	—	-0.073	—
4-SMe	0.00	—	-0.604	—
4-Cl	+0.227	+0.206	+0.114	—
4-C≡CH	+0.233	—	+0.179	—
4-COOMe	+0.32	+0.574	—	+0.64
4-COOH	+0.45	+0.608	—	+0.728
4-C≡N	+0.660	+0.94	—	+0.88 [3]
4-NO_2	+0.778	+1.19	+0.790 [3]	+1.27

TABLE 2. Basicity of Heteroaromatic N-Oxides in Water at 25°C

N-Oxide	p*K*a	N-Oxide	p*K*a
Pyridine [16-18]	0.79	4-Nitropyridine [16]	-1.7
2-Methylpyridine [19]	0.97	2-Methyl-4-nitropyridine [15]	-0.97
3-Methylpyridine [16, 20]	1.08	2,6-Dimethyl-4-nitropyridine [15]	-0.86
4-Methylpyridine [16]	1.29	3-Methyl-4-nitropyridine [18]	-0.97
2-Ethylpyridine [19]	1.17	4-Cyanopyridine [17]	-1.17
4-Ethylpyridine [19]	1.29	2-Methyl-4-cyanopyridine [15]	-0.674
2,6-Dimethylpyridine [15]	1.44	2,6-Dimethyl-4-cyanopyridine [15]	-0.61
2-Aminopyridine [20]	2.67	Quinoline [14]	0.86
2-Dimethylaminopyridine [20]	2.27	4-Methylquinoline [14]	1.44
3-Aminopyridine [16]	1.47	4-Chloroquinoline [14]	0.47
4-Aminopyridine [21]	3.65	4-Nitroquinoline [26]	-1.39
4-Methylaminopyridine [20]	3.85	Isoquinoline [16]	1.01
4-Dimethylaminopyridine [16] [17,20]	3.88 4.05	Acridine [22]	1.37

It is possible to draw the conclusion on the basis of these correlations that, unlike the N→O group the nitrogen atom of the pyridine ring significantly weakens the acceptor and enhances the donor properties of groups capable of strong polarization of π bonds.

Heteroaromatic N-oxides in water are far weaker bases (p*K*a ~1-2), than the corresponding heterocycles (p*K*a ~5) and aliphatic N-oxides (p*K*a ~4-5). However the p*K*a determined for them in the gas phase are close to the p*K*a values of the corresponding unoxidized bases, which is indicated by the significantly stronger interaction of water molecules with the protonated forms of the N-oxides compared with the unoxidized heterocycles.

Primarily the presence and character of the substituents and the structure of the heterocycle influence the basicity of the N-oxide. As is seen from Table 2 it increases in the series pyridine < quinoline < isoquinoline < acridine (for the unoxidized analogs it is changed in the sequence aniline (p*K*a 4.58) < quinoline (p*K*a 4.94) < isoquinoline (p*K*a 5.14) < pyridine (p*K*a 5.21) < acridine (p*K*a 5.60) [23]).

The dependence of the p*K*a of pyridine N-oxides on the character of the substituent in the pyridine ring is described far better by the Hammett correlation equations using σ_{PyO} (p*K*a = -3.32σ + 1.06, r = 0.957; p*K*a = -2.09σ_{PyO} + 0.79, r = 1.000 [14, 23]), while unlike the corresponding pyridines, the N-oxide of 4-nitropyridine (p*K*a 1.74) is a weaker base than the N-oxide of 3-nitropyridine (p*K*a 1.07) due to both the *-I* and *-M* effects of the nitro group. Analogous correlations of p*K*a for the Hammett σ constant were also detected for substituted N-oxides of quinoline (p*K*a = -2.95σ + 0,96, r = 0.995; p*K*a = -1.95σ_{PyO} + 0.91, r = 0.999 [14, 23]), but the effect of the functional groups in them was displayed somewhat more weakly.

As a result of the large spatial accessibility of the oxygen atom of the N→O group in comparison with the nitrogen atom in pyridines (and especially in anilines) the introduction of alkyl groups into position 2 of N-oxides not only does not reduce but even leads to an increase of the basicity (Table 2) of pyridine N-oxides (substituents are indicated).

$$2,6\text{-}Me_2 > 4\text{-}Et,\ 4\text{-}Me > 3\text{-}Me > 2\text{-}Et > 2\text{-}Me > H$$
$$2,6\text{-}Me_2\text{-}4\text{-}C{\equiv}N > 2\text{-}Me\text{-}4\text{-}C{\equiv}N > 4\text{-}C{\equiv}N$$
$$2,6\text{-}Me_2\text{-}4\text{-}NO_2 > 3\text{-}Me\text{-}4\text{-}NO_2,\ 2\text{-}Me\text{-}4\text{-}NO_2 > 4\text{-}NO_2$$

Paying attention to this fact we, attempted to assess σ_{PyO} for the methyl group in position 2 on the basis of the data in Tables 1 and 2. As is seen from Table 3, its value depends on the nature of the other substituents in the pyridine ring, and in the case of 2-methyl derivatives the electron-donating properties are higher than the

TABLE 3. Values of σ_{PyO} (Methyl Group in Position 2 of Pyridine N-oxides, Calculated from the Equation p*K*a = -2.09Σσ_{PyO} + 0.79 [23] and σ (Methyl Group in Position 2 of Pyridines, Calculated According to the Equation p*K*a = -5.83σ + 5.46 [10])

N-Oxides of pyridines X–C_5H_4N→O (X)	σ_{PyO}	Pyridines X–C_5H_4N (X)	σ
2-Me	-0.086	2-Me	-0.108
2,6-Me_2	-0.156	2,6-Me_2	-0.106
2-Me-4-NO_2	-0.348	2-Me-4-NO_2*	—
2,6-Me_2-4-NO_2	-0.200	2,6-Me_2-4-NO_2	-0.189
2-Me-4-C≡N	-0.240	2-Me-4-C≡N*	—
2,6-Me_2-4-C≡N	-0.135	2,6-Me_2-4-C≡N	-0.175

*p*Ka values were not found in the literature.

stronger electron-withdrawing properties of the functional groups. Since in the N-oxide of 2-methylpyridine the σ_{PyO} of the Me group in position 2 is equal to -0.086 (i.e. hardly greater than σ_{meta} = -0.069 and σ_1 = -0.05 [2]), but in the N-oxide of 4-cyano-2-methylpyridine its value is close to (-0.240) or in the N-oxide of 2-methyl-4-nitropyridine even exceeds (-0.348) σ^+_{para} = -0.311 (σ_{PyO} for the methyl group in position 4 is equal to -0.240), the required is that in the N-oxide of 2-methylpyridine the methyl group mainly displays an inductive effect. In the presence of nitro and cyano groups the effect of hyperconjugation is sharply strengthened, seemingly thanks to conjugation with these substituents through the N→O group (cross-conjugation [3]).

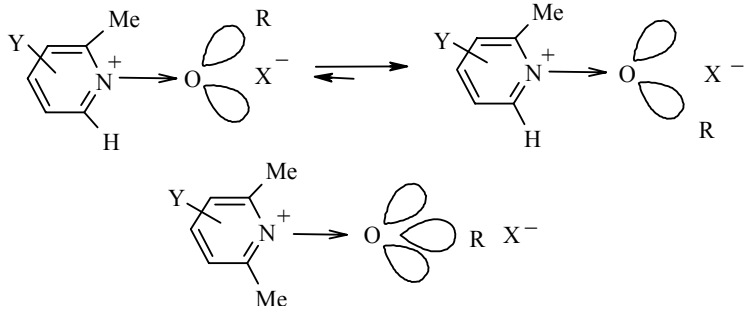


Fig. 1. Rehybridization ($sp^2 \rightarrow sp^3$) of the oxygen atom on interacting pyridine N-oxides with Bronsted–Lewis acids (R = H) and alkyl halides (R = Me, Et, *i*-Pr).

However on introducing a second methyl group into position 6 of 2-methylpyridine N-oxide its donor properties grew while in the 2,6-dimethyl-4-nitro and 4-cyano-2,6-dimethyl derivatives they were reduced.

Such an unusual behavior of the methyl group may be explained from the point of view of $sp^2 \rightarrow sp^3$ rehybridization of the oxygen atom of the N→O group, demonstrated by us by ^{1}H NMR methods previously in the processes of complex formation with boron trifluoride [24].

In accordance with Fig. 1 the protonation of the N-oxide of 2-methylpyridine (as also the interaction with BF_3 in [24]) must mainly be effected with the participation of the sp^2 hybrid orbital of the oxygen atom most removed from the methyl group and coplanar with the aromatic ring. Consequently the methyl group in this compound primarily displays an inductive effect. In the case of the N-oxide of 2,6-dimethylpyridine, due to steric hindrance from the direction of the two alkyl groups, protonation of a *p*-orbital of the oxygen atom proved to be more favorable (with its subsequent $sp^2 \rightarrow sp^3$ rehybridization), as it induces hyperconjugation of the

methyl groups capable of conjugation. According to ^{1}H NMR data [24] rehybridization of the oxygen atom in the case of the interaction of pyridine N-oxides with boron trifluoride is observed for compounds with p*K*a ≥ 1.4. In view of the fact that the N-oxide of 2,6-dimethylpyridine has p*K*a 1.44, and proton must be a stronger Lewis acid than BF_3, the hypotheses given above have foundation.

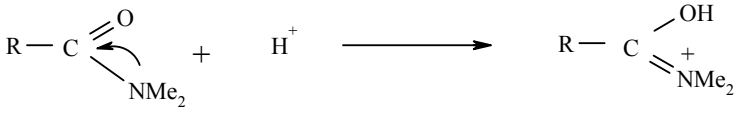
In the N-oxides of 4-cyano-2-methyl- and 2-methyl-4-nitropyridines (unlike the N-oxide of 2-methylpyridine) the methyl group is a similar or an even better electron donor than in position 4 (Table 1, 3). However these compounds, being very weak bases, like the N-oxide of 2-methylpyridine must be more effectively protonated at the sp^2 hybrid orbital of the oxygen atom, which is in no way conjugated with the substituents in position 2 of the pyridine ring. We assume that the effect of the methyl group is caused by a weakening of the interaction (in this case the inductive effect is more important) of cyano and nitro groups with N→O due to the partial saturation of their electron density through cross-hyperconjugation. This explains well the sharp increase in basicity of the indicated N-oxides compared with the unmethylated analogs. The introduction of a second methyl group into the nitro and cyano derivatives, as in the case of the N-oxide of 2,6-dimethylpyridine, must lead to protonation of the *p*-orbital and rehybridization of the oxygen atom. In this case the mutual conjugation of the two methyl groups and the N→O, NO_2, and CN groups leads to a still greater fall in the electron-accepting properties of the NO_2 and CN groups, and finally to such mutual weakening of electronic effects of all the substituents so that their behavior may then be described by the usual Hammett σ constants.

In order to compare the effect of a CH_3 group on the protonation of N-oxides and the unoxidized analogs, we calculated (Table 3) the value of σ (-0.11) in 2-methyl- (p*K*a 6.11 [25]) and 2,6-dimethylpyridine (p*K*a 6.72 [25]). The values of σ in 2-methyl- and 2,6-dimethylpyridine and σ_{PyO} for the N-oxide of 2-methylpyridine were close, which confirms the similarity of the mechanism of protonation (sp^2 hybrid orbitals of the heteroatoms). The high donor properties of the methyl group (Table 3) in 4-cyano-2,6-dimethyl- (p*K*a = 3.68 [26], σ = -0.175) and 2,6-dimethyl-4-nitropyridine (p*K*a = 3.15 [26], σ = -0.189), approaching those of the corresponding N-oxides, rather indicate the reduction of general acceptor properties of the cyano and nitro groups, since in the case of these pyridines protonation may also be effected only at the sp^2 hybrid orbital of the nitrogen atom.

In both substituted pyridines and N-oxides the functional groups mutually influence their electronic effects, which are expressed in the values of the σ constants. However this influence is stronger than the large effects of the conjugation these groups possess. Subsequently we propose to investigate this phenomenon in detail.

When other *p*-donor groups in addition to the N→O group are present in the molecule the place of protonation depends on the relative availability of the electron pair and the presence or absence of conjugation between complex-forming centers plays an important role.

It is known that if the nitrogen atom is bonded directly to a group displaying a large -*M* effect then its unshared electron pair is far strongly displaced in the direction of the electronegative atom so that the latter becomes more basic.



On protonating such compounds the nitrogen atom is converted into the onium state [3]. In particular, the interaction of ureas with HNO_3 is effected just at the oxygen atom of the carbonyl group [27].

The first protonation of the mono-N-oxides of pyrazine and quinoxaline occurs at the unoxidized nitrogen atom [28, 29], the unshared electron pair of which is not included in the conjugation chain (however the interaction of pyrazine mono-N-oxide with iodine proceeds at the oxygen atom of the N-oxide group [30]).

In the case of the N-oxides of 2- and 4-aminopyridines, also containing two potential electron-donating centers but found in conjugation, the oxygen atom of the N→O group is protonated first [20, 31-33] (in the unoxidized analogs, the nitrogen atom of the heterocycle is first). In the absence of conjugation between the N→O and amino groups in the N-oxide of 3-aminopyridine [20] protonation is effected at the oxygen atom, and in the N-oxide of 3-dimethylaminopyridine [34] at the nitrogen atom of the NMe_2 group, i.e. the introduction of two methyl groups possessing a *+I* effect leads to reversal of the relative basicity of the two donor centers. Special mention is made of the N-oxide of 4-(4-dimethylaminostyryl)pyridine, which contains two potential coordination centers (the N→O group (p*K*a 1.46) and NMe_2 (p*K*a 4.30) separated by the styryl fragment [35]). In organic solvents it interacts with Bronsted–Lowry and Lewis acids at the oxygen atom of the N-oxide group, but in water it is protonated at the amino group [36].

In this way, even the description of acid-base interactions involving such a small particle as a proton is not always possible on the basis of σ constants to assess correctly the distribution of electron density in a molecule. If the acid-base interactions are considered in the wider sense (from the position of Lewis, nucleophile – base, electrophile – acid), then interpretation of the Hammett equation meets further difficulties since the effect of steric factors becomes far more significant.

In [37], data known up to that time on the behavior of 3,4, 3,5, and 3,4,5 derivatives in 33 reactions were analyzed and it was established that the electronic influence of substituents is additive, i.e. the following relationship is fulfilled:

$$\lg k/k_0 = \rho\Sigma\sigma,$$

but Hancock and Westmoreland [38] discovered that the equation

$$\lg k = -0.1089 - 1.620\Sigma\sigma_D + 2.37\Sigma\sigma_B$$

was applicable in 46 cases of reactions of *m*- and *p*-substituted benzoic acids (σ_D) with *m*- and *p*-substituted diphenyldiazomethanes (σ_B) [1].

On the other hand McCullough and coworkers [39, 40] showed that for the process

$$(XC_6H_4)(YC_6H_4)Se{\cdot}Br_2 \rightleftharpoons (XC_6H_4)(YC_6H_4)Se + Br_2$$

the influence of the presence of substituents in both benzene rings was well described in the following form:

$$\lg K/K_0 = \rho(\sigma_1 + \sigma_2),$$

where *K* is the dissociation constant of complexes of diphenyl selenide with bromine (σ_1 refers to the substituent in one benzene ring and σ_2 in the other).

However such simple correlations are not always fulfilled. If the steric interactions between substituents in neighboring positions are significant this may lead to disturbance of the conjugation with the aromatic ring (reduction of the mesomeric effect of groups) and consequently with the reaction center. For example, Westheimer and Metcalf [41] established that for this reason the specific rate of alkaline hydrolysis of the ethyl ester of 4-dimethylamino-3,5-dimethylbenzoic acid was an order of magnitude greater than that predicted by the additivity rule. Wheland, Brownell, and Mayo [42] also found that for 3,5-dimethyl-4-nitrophenol the p*K*a was 8.25, i.e. significantly higher than the value of 7.35 calculated according to the additivity rule [1]. In addition, accumulation of benzene and other aromatic rings at one atom as a result of interaction of hydrogen atoms in the *ortho* position leads to their "wresting" out of the plane and disturbance of mutual conjugation. As an example, triphenylmethyl carbocation (trityl cation) and tetraphenyl porphin have a propeller-shaped structure [3].

According to our data [35], on complex formation of Zn-TPP with N-oxides of pyridines there was a certain deviation from the linear relationships log*K* – σ and Δλ – σ (where *K* is the stability constant of the complex in chloroform, Δλ is the displacement of the absorption bands of metalloporphyrin (MP) in the electronic spectra on interaction with ligand) in the case of the N-oxide of 3-methyl-4-nitropyridine, which is

also explained by "wresting" the nitro group and as a result of this by a reduction of its conjugation with the aromatic system of the N-oxide. In reality, according to data of X-ray structural analysis, the angle between the planes passing through the atoms of the nitro group and the pyridine ring in the N-oxide of 3-methyl-4-nitropyridine was 14.68° [43] (31.98° in the case of its complex with $ZnBr_2$ [44]).

However the N-oxide of 2-methyl-4-nitropyridine, in spite of the presence of the methyl group in position 2 of the pyridine ring, complied well with the linear correlation indicated above, which was in poor agreement with the behavior of reactants containing substituents in the *ortho* position of the benzene (position 2 of pyridine or quinoline) ring in relation to the reaction center due to the superposition of steric interactions onto electronic factors. It is evident that the methyl group shows only an electronic effect on the reactivity of this compound. On the basis of the value of $K = 269 \pm 20$ obtained by us for the complex of Zn-TPP with the N-oxide of 2-methyl-4-nitropyridine in chloroform we calculated σ_{PyO} for the methyl group in position 2 from the equation $\log K = -0.71\sigma_{PyO} + 3.03$ [35]. This value (-0.35) proved to be far greater in absolute value than for a methyl group in position 4 (-0.24) and especially in position 3 (-0.139) of the pyridine ring and agreed with that calculated by us on the basis of the p*K*a in water for the N-oxide of 2-methyl-4-nitropyridine. The effect of hyperconjugation in this case therefore influences to the same extent such different processes as protonation of the N-oxide in water and its interaction with metalloporphyrin in chloroform, which shows the dominant role of electronic factors in these processes. The presence of two methyl groups in the N-oxide of 2,6-dimethyl-4-nitropyridine seemingly leads to such a sharp increase in steric hindrance on complex formation with Zn-TPP that it was not possible to define $\Delta\lambda$ (due to the low concentration of complex) or to estimate a value of *K*.

From this point of view the absence of steric hindrance on complex formation of Zn-TPP with the N-oxide of 2-methyl-4-nitropyridine (as in the case of protonation) is explained by the fact that the formation of a new bond may begin on account of the more remote sp^3 hybrid orbital of the CH_3 group (or even a *p*-orbital found in conjugation with the pyridine ring) with the possible transfer of an oxygen atom in the final count into the sp^3 hybrid state [23]. At the same time in the presence of two CH_3 groups simultaneously in positions 2 and 6 of the N-oxide, the $sp^2 \rightarrow sp^3$ rehybridization of the oxygen atom should have been even more advantageous, since it should lead to the least steric interaction between the participants of complex formation. The fact that Zn-TPP does not form a molecular complex shows the low availability of the oxygen atom for the formation of a Zn–O donor–acceptor bond.

In the case of pyridines, which are far stronger bases than the corresponding N-oxides but with the nitrogen atom as a sterically less available reaction center, a somewhat different picture is observed. The stability constants determined by electronic and fluorescent spectroscopy (they agree within the limits of error of the experiment) in toluene for the complexes Zn-TPP and zinc(II)octaethylporphyrin (Zn-OEP) fall in the series 4-methylpyridine > 3-methylpyridine > pyridine >> 2-methylpyridine > 2,6-dimethylpyridine [25]. Unlike the N-oxides, as might have been expected, the introduction of even the first methyl group into position 2 of the pyridine ring causes so strong steric hindrance to complex formation that the second substituent in position 6 has little effect. Such a sharply discriminating steric influence of substituents on the reactivity of pyridines and the corresponding N-oxides is readily explained from the point of view of steric availability of the unshared electron pairs of the sp^2 hybrid orbitals of the nitrogen and oxygen atoms for the formation of new bonds with ν-acceptors.

While continuing analysis of the influence of methyl groups on the nucleophilic properties of pyridine N-oxides we paid attention to the fact that, according to literature data (Table 4), "strange" changes occurred (not noticed by the authors of [45]) in the stability of the series of products of alkylation of pyridine N-oxides, 2-methylpyridine to 2,6-dimethylpyridine, that is causing no surprise the reduction on introducing the first methyl group into position 2 of the pyridine ring (see k_{-1} and k_p), and contradictory to strengthening of the role of steric effects on introducing the second substituent into position 6. For example, the stability of methoxy- and ethoxy-2,6-dimethylpyridinium iodides grows even in comparison with the 2-methyl derivatives (see k_{-1} and k_p) and only for isopropyloxy-2,6-dimethylpyridinium iodide was k_p reduced, while the rate of decomposition (k_{-1}) of this salt became the same as for the ethoxy derivative.

TABLE 4. Rate constants [$k_1 \cdot 10^5$ l/mol·sec] and Equilibrium Constants [k_p] for the Formation of N-Alkoxypyridinium Salts from N-Oxides of Pyridines and Alkyl Halides, and Rate Constants of their Decomposition [$k_{-1} \cdot 10^5$ sec^{-1}] into the Initial Reactants in Acetonitrile at 25°C [45]

Nucleophile (X)	k_1	k_{-1}	k_p	k_1	k_{-1}	k_p	k_1	k_{-1}	k_p
	Substrate								
	MeI			EtI			*i*-PrI		
H	2.90	3.55	0.82	1.51	0.057	28	0.682	0.0083	82
4-Cl	1.00	—	—	–	—	—	—	—	—
4-Me	11.9	1.00	11.9	6.37	—	>100	2.01	—	>100
4-MeO	52.2	—	>100	23.5	—	>100	7.18	—	>100
4-NMe_2	1150	—	—	486	—	—	125	—	—
2-Me	2.20	4.70	0.47	0.821	0.076	11	0.255	0.022	12
2,6-Me_2	1.64	3.05	0.54	0.635	0.032	20	0.104	0.035	3.0

It is evident that on the one hand, the introduction into the pyridine N-oxide molecule of methyl groups into the second and then into the sixth position, and also an increase in the size of the alkyl group on the oxygen atom in the alkylation product, from the point of view of the *+I* effect must stabilize the salt even more, but on the other hand, due to the increase of steric hindrance, gradually accelerate its decomposition. However (if the oxygen atom retains the same type of hybridization) the behavior of the alkoxy-2,6-dimethylpyridinium iodides does not fit into this reasoning. According to the data of Table 4 the introduction of just the first methyl group into position 2 of the pyridine N-oxide leads to the fact that, independent of the alkyl iodide used, steric factors begin to play a dominant role, the decomposition rate of alkoxy-2-methylpyridinium iodides in comparison with derivatives of pyridine N-oxide is increased to a larger extent than the larger size of the alkyl group on the oxygen atom. The introduction of a second methyl group into position 6 should strengthen this tendency still more. However the decomposition rate of salts containing methyl and ethyl groups at the oxygen atom becomes even less than in the case of derivatives of pyridine N-oxide, and only in the presence of an isopropyl group does it increase and become the same as in the case of ethoxy-2,6-dimethylpyridinium iodide (Table 4; $k_{-1} \cdot 10^5$ sec^{-1} - 0.035 and 0.032), as if in this case the steric factor becomes less essential than the electronic influence.

Such a change in the stability of the alkylation products of the N-oxides may be explained by the change in hybridization of the oxygen atom in those cases when this leads to a less strained state of the molecule, which is in agreement with the data obtained by us on the rehybridization of molecular complexes of pyridine N-oxides with boron trifluoride even in the process of crystallization [23]. Probably the formation of a C–O bond on alkylation of 2-methylpyridine N-oxide in the initial stage of the reaction is effected through sp^2-hybrid orbitals of the oxygen atom leading to an equilibrium mixture in which the portion with a conformation with maximum distance between the alkyl groups increases with the increase in size of the radical in the alkyl halide (Fig. 1). In the case of alkylation of 2,6-dimethylpyridine N-oxide the conformation with oxygen in the sp^2 hybridization state becomes already so strained that rehybridization of the oxygen atom is favorable and the O–C bond (in the plane perpendicular to the pyridine ring) is formed through an sp^3 hybrid orbital (Fig. 1) thereby reducing the electrostatic repulsion between the electron clouds of the alkyl groups and increasing the stability of the salt.

The significantly stronger displacement towards low field in the ^1H NMR spectra (Table 5) of the signals of the pyridine ring protons, particularly H(2) and H(6), (reduced depending on the increase of electron-donating properties of the groups in position 4 and in the alkyl group of the iodide) in the products of O-alkylation of the N-oxides in comparison with the complexes with boron trifluoride and hydrogen chloride, probably indicates the removal of the oxygen atom from conjugation with the aromatic ring, and the pair equivalence of the H(2), H(6) and H(3), H(5) protons indicates sp^3 hybridization (free rotation relative to the N–O single bond) of the oxygen atom in the salt state.

TABLE 5. ^{1}H NMR Spectra of Pyridine N-oxides, their Molecular Complexes with HCl and BF_3 [24], and Products of O-Alkylation

$XC_5H_4N\rightarrow O$ (X)	Electro-phile	Chemical shifts, δ, ppm (*J*, Hz)						Solvent
		H-2	H-6	H-3	H-5	H-4	R	
H	—	8.17 (2H, d, *J* = 5.2)		7.36 (2H, t, *J* = 6.4)		7.27 (t, *J* = 7.6)	—	DMCO-d_6
	HCl	8.88 (2H, d, *J* = 6.0)		7.94 (2H, t, *J* = 7.0)		8.17 (t, *J* = 7.6)	—	DMCO-d_6
	BF_3	8.53 (d, *J* = 4.4)	8.86 (d, *J* = 4.4)	8.01 (t, *J* = 6.4)	8.38 (t, *J* = 7.2)	7.70 (t, *J* = 6.0)	—	DMCO-d_6
	MeI	9.61 (2H, d, *J* = 6.0)		8.62 (2H, t, *J* = 7.6)		8.32 (t, *J* = 7.4)	4.66 (s, $NOCH_3$)	$CDCl_3$
	EtI	9.58 (2H, d, *J* = 7.2)		8.71 (2H, t, *J* = 7.8)		8.28 (t, *J* = 7.4)	4.80 (q, *J* = 7.0, $NOC\underline{H}_2CH_3$), 1.37 (t, *J* = 7.0, $NOCH_2C\underline{H}_3$)	$CDCl_3$
4-Me	—	8.06 (2H, d, *J* = 6.8)		7.06 (2H, d, *J* = 6.8)		—	2.28 (s, 4-CH_3)	DMCO-d_6
	HCl	8.94 (2H, d, *J* = 6.0)		7.96 (2H, d, *J* = 7.0)		—	2.74 (s, 4-CH_3)	DMCO-d_6
	BF_3	8.46 (d, *J* = 6.5)	8.98 (d, *J* = 6.6)	7.60 (d, *J* = 8.5)	8.07 (d, *J* = 7.8)	—	2.59 (s, 4-CH_3)	DMCO-d_6
	MeI	9.46 (2H, d, *J* = 6.8)		8.07 (2H, d, *J* = 6.8)		—	4.59 (s, $NOCH_3$), 2.69 (s, 4-CH_3)	$CDCl_3$
	EtI	9.40 (2H, d, *J* = 6.8)		8.07 (2H, d, *J* = 6.8)		—	4.79 (q, *J* = 7.1, $NOC\underline{H}_2CH_3$), 2.63 (s, 4-CH_3), 1.41 (t, *J* = 7.1, $NOCH_2C\underline{H}_3$)	$CDCl_3$
4-MeO	—	8.01 (2H, d, *J* = 6.8)		6.97 (2H, d, *J* = 6.8)		—	3.82 (s, 4-OCH_3)	DMCO-d_6
	BF_3	8.68 (2H, d, *J* = 7.0)		7.45 (2H, d, *J* = 7.0)		—	4.05 (s, 4-OCH_3)	DMCO-d_6
	MeI	9.33 (2H, d, *J* = 7.6)		7.66 (2H, d, *J* = 7.6)		—	4.50 (s, N–OCH_3), 4.17 (s, 4-OCH_3)	$CDCl_3$

It should be emphasized that in the solid state (similar to the molecular complex of pyridine N-oxides with BF_3 [23]), all 6 salts of N-alkoxy-, N-aryloxy-, and N-heteryloxypyridinium, for which structures were solved by X-ray structural analysis [46] (CSD reference code CANTIU, SIRWUL, TAJPUP, etc), contain an oxygen atom in the sp^3 hybridization state since in their conformations the atoms of the N–O–C fragment are in a plane perpendicular to the plane of the pyridine ring, excluding completely the possibility of conjugation between it and the oxygen atom.

In spite of the compliance of an enormous number of chemical processes with the Hammett equation, in the classic variant it is applicable only to a proportional change of all types of electronic effects of substituents in a definite ("proportional") range of polarizability (static and dynamic) of the molecule. Otherwise the equation is complicated and other constants must be introduced, depending on the actual conditions of polarization.

EXPERIMENTAL

The ^1H NMR spectra of hydrochlorides and adducts of heteroaromatic N-oxides with BF_3 in DMSO-d_6, and also of reaction mixtures containing N-oxide and alkyl iodide in a ratio of 1:2, in $CDCl_3$, were taken on a Bruker WM-400 (400 MHz) instrument at room temperature, internal standard was TMS. Electronic spectra were taken on a SF 2000-02 instrument. The stability constants of Zn-TPP with pyridines in chloroform were determined as described in [35].

The heteroaromatic N-oxides and their molecular complexes with BF_3 and HCl were synthesized as described in [15].

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