CHARGE TRANSFER COMPLEXES IN THE CHEMISTRY OF AROMATIC *N*-OXIDES

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Abstract - Using nucleophilic substitution reactions in heteroaromatics (*N*-oxides) it was shown, that binding of substrate in donor-acceptor complex with appropriate acceptor decreases strongly the electron density in the nucleus of the starting compound, thus substantially facilitating the reactions with nucleophilic reagents. At the same time, the electrophilicity of heteroaromatic substrate increases owing to the partial electron density transfer to the π-acceptor molecule, which remains covalently unbound with donor in the course of the reaction.

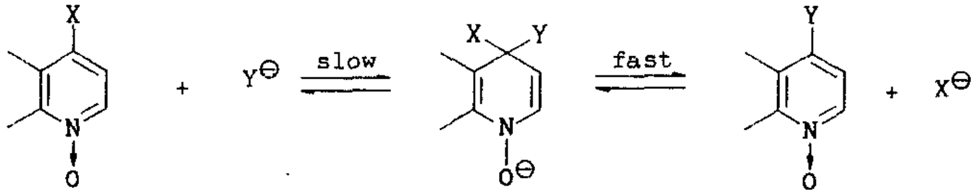
Introduction

It is well known[1] that the nucleophilic substitution reactions in the aromatic series proceed easily if substrate contains electron-acceptor substituents. Its classical example[1] may be the hydrolysis of picryl chloride, which takes place under very mild conditions in contrast with chlorobenzene hydrolysis. One can assume that electron density reduction in aromatic or heteroaromatic nucleus may be caused as well by means of "external" acceptor, which is not directly bound with starting compound. These effects are formally analogous to those of "internal" and "external" heavy atoms, assisting in singlet-triplet transfers and increasing long-living triplet states concentration. The analogy between π-acceptor action on starting aromatic substrate and metal-complex catalysis can be proposed too.

Nucleophilic substitution in the heteroaromatic *N*-oxides series

Electron-deficient aromatic heterocycles can undergo nucleophilic attack, and this process is facilitated in compounds with a positive charge on the heteroatom (in quaternary *N*-alkyl or *N*-acyl derivatives, pyrylium salts etc.). However, the aromatic *N*-oxides are the most appropriate compounds for studying such processes owing to their unique activity towards various reagents. At present the problem of the nucleophilic (and electrophilic) substitution in pyridine *N*-oxide and quinoline *N*-oxide derivatives is studied well enough.[2,3] This is one of the important parts of the azines chemistry.

In the series of heteroaromatics the bimolecular mechanism of nucleophlic substitution involving the first rate-determining step seems to be the most likely for the following nucleophilic substitutions:



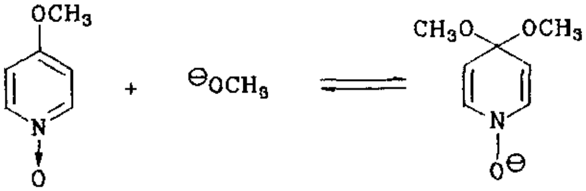
The following facts confirm this mechanism:

1. Ability of the functional groups (X) towards nucleophilic substitution increases with their electron-acceptor properties:

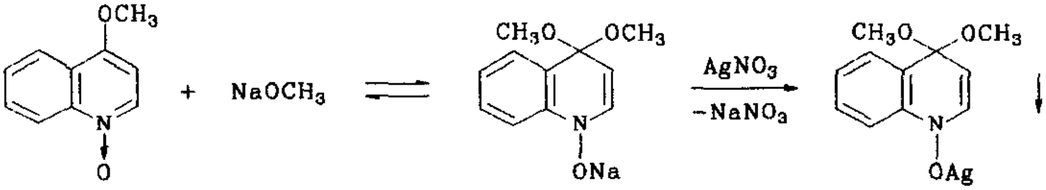
$$NO_2 > F > Cl > Br > OAr > OAlk.$$

In this connection the *N*-oxides of 4-nitropyridine and 4-nitroquinoline are of most value as the starting materials for the synthesis of 4-substituted *N*-oxides.[4]

2. The kinetic and thermodynamic data were obtained for the reaction of 4-methoxypyridine-*N*-oxide with sodium methoxide:[5]

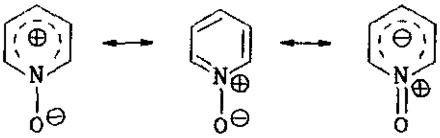


3. In continuation of our research in this field we obtained evidence for the formation of a σ-anionic Jackson-Meisenheimer complex in the system of 4-methoxyquinoline *N*-oxide and sodium methoxide. This complex was isolated by us in the form of silver salt:[6]

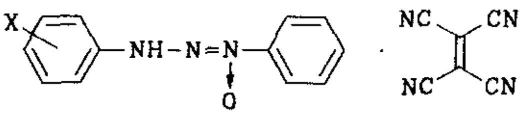


Probably, appearance of dark brown color in the interaction of aromatic *N*-oxides with metal alkoxides or aliphatic amines can be explained by the formation of such intermediates. One can assume that any change in the structure of heterocycles, which caused depletion of the electron density from the π-system, should enhance its reactivity towards nucleophiles.

In this connection we studied for a few years the possibility of "outside" π-acceptors application, which can activate an aromatic ring by the charge transfer complex (CTC) formation. These acceptors remain covalently unbound to aromatic system in the course of the reaction. It is possible to use this method to enlarge greatly the synthetic potential of nucleophilic substitution reactions in the chemistry of aromatic heterocycles. These CTCs of *N*-oxides have been found to be more suitable objects for the investigation of the reactions with π-acceptors than those of nonoxygenated heterocycles. Donor activity of *N*-oxides is significantly increased by means of p,π-conjugation of oxygen atom and aromatic ring:[7]



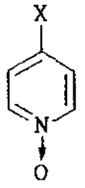
Many strong π-acceptors are also active as dipolarophiles. On the other hand, *N*-oxides may be represented as 1,3-dipoles with dipolar function included in aromatic ring.[8] We have established that CTC formation is more probable process than 1,3-dipolar cycloaddition reaction. The later process is only observed with dipolarophiles which are not active as π-acceptors.[9] Moreover, it was reported that even *N*-oxides of triazenes form CTCs with tetracyanoethylene (TCE), giving no cycloaddition products.[10]

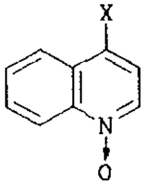


Aromatic *N*-oxides were studied as the ambident (n- or π-) donors in the reaction with π-acids starting from 80th years. The complexes of alkyl-substituted pyridine *N*-oxides with phenyl isocyanate[11] and TCE[12] will be described later. The complexes of aromatic *N*-oxides with π-acceptors exist only in solution in equilibrium with the original components. It was shown that the reactivity of the *N*-oxides correlates with the electronic properties of the substituents. For example, v-acceptors and σ-acceptors

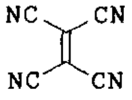
(BF_3, $AlCl_3$, I_2) react with the oxygen atom of *N*-oxides exclusively forming stable n,v- or n,σ-complexes. The question about donor center and complex nature in complexation with π-acceptors is not so evident. Formation of both n,π-(coordination through oxygen atom) complex and π,π-(coordination through aromatic ring) complex are apparently observed in these reactions. It should be noted that the former as a rule precedes the latter. Furthermore, *N*-oxides are capable to react with π-acceptors yielding the CTCs with various stoichiometric compositions. It is of interest that the 4-nitroquinoline *N*-oxide containing a strong electron-withdrawing group can also form CTCs with π-donors. The reaction of this *N*-oxide with phenols can be considered as a typical example.[13]

We have chosen some pyridine *N*-oxides (**1 a-e**) and quinoline *N*-oxides (**2 a-e**) for the detailed investigation of their CTCs with typical π-acceptors such as TCE (**3**) and *p*-benzoquinones (**4 a,b**). These complexes can be used in the nucleophilic substitution reactions:


1 a–e


2 a – e

a) $X=NO_2$
b) $X=Cl$
c) $X=H$
d) $X=CH_3$
e) $X=OCH_3$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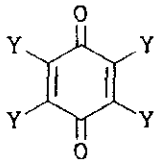

4 a,b

a) $Y=H$
b) $Y=Br$

It is well known[6,14] that electrochemical oxidation potentials ($E_{1/2}^{ox}$) of aromatic substances can be used for evaluation of their donor ability. These characteristics for some of pyridine *N*-oxides were determined earlier.[15] We have determined them for *N*-oxides of quinoline series (2

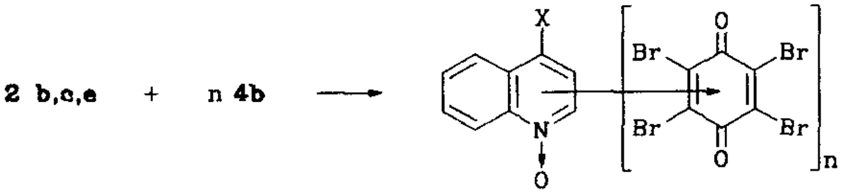
b,c,e) using polarographic method (Table 1). These data show that $E_{1/2}^{ox}$ values decrease from monocyclic *N*-oxides to polycyclic *N*-oxides. Therefore the investigation was carried out mainly with quinoline *N*-oxides.

Table 1. Oxidation potentials of some *N*-oxides as the function of substituent effect

Substituent in 4-position	Pyridine *N*-oxides, $E_{1/2}^{ox}$,v	Quinoline *N*-oxides, $E_{1/2}^{ox}$,v	σ_p^+ [16]
NO_2	2.130	-	+ 0.790
Cl	1.795	1.630	+ 0.114
H	1.802	1.537	0
CH_3	1.606	-	- 0.311
OCH_3	1.362	1.110	- 0.778

On the other hand, the π-acceptor activity is characterized by the values of the electrochemical reduction potentials.[6] For benzoquinone **(4a)**, bromanile **(4b)** and TCE **(3)** these values are -0.51v, 0.00v and 0.15v, respectively.

The process of molecular complexes formation of the most active *N*-oxides **(2 b-e)** with *p*-benzoquinone can be followed by electron spectroscopy method. The uv spectra show batochromic shifts of π-π* absorption bands of *N*-oxides and n-π* bands of *p*-benzoquinone. The value of the shifts correlate with the properties of the substituents in *N*-oxides. These complexes can exist only in solution in equilibrium with their components and can not be prepared in solid state. We managed to prepare the solid CTCs with a stronger π-acceptor, bromanile **(4b)**. These complexes can be precipitated from the saturated solutions of *N*-oxides and bromanile mixture in dioxane:



5 b,c,e

b) X=Cl; c) X=H; e) X=OCH_3

The compounds **(5 b,c,e)** are colored solid substances (Table 2). Uv spectra of these CTCs show that batochromic shift of *N*-oxides π-π* absorption bands of *N*-oxides and n-π* bands of bromanile are much greater than those in the spectra of CTCs with *p*-benzoquinone. The vibrations of N-O bond in the ir spectra of CTCs correspond to the vibrations of the same bonds in the *N*-oxides spectra. These facts show that the *N*-oxides are π-donors with respect to bromanile, affording π,π-complexes with the latter.

Table 2. *Solid CTCs of some N*-oxides with bromanile.

CTC	The precipitation time, h	Yield,%	mp °C	Stoichiometry *N*-oxide:bromanile
5 b	48	30	170-172	1 : 0.5
5 c	24	33	133-135	1 : 0.78
5 e	2	34	162-164	1 : 0.78

It was established, that the interaction of *N*-oxides with TCE leads initially to the formation of intensely colored "weak" complexes, that exist only in solution in the equilibrium with the starting components. Uv spectra of these complexes show new "charge transfer" bands, but the positions of the absorption bands of the original substances remain unchanged. We found the equilibrium constants (Kx_i) for the formation of these complexes, the stoichiometry 1:1 being observed. The equilibrium constants of "weak" complexes formation show a linear correlation with σ_p^+-constants of the substituents (Table 3):

$$\lg Kx_i = \lg Ko + \sigma_p^+ \rho$$

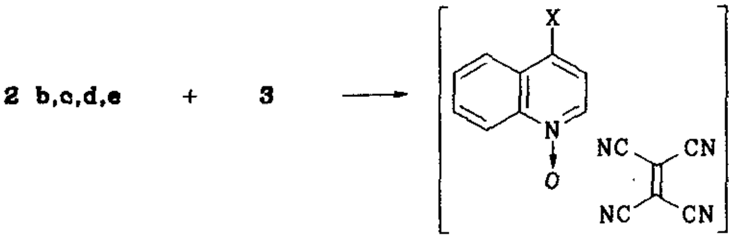
(Ko - equilibrium constant of the complex formation of quinoline *N*-oxide **(2c)** and TCE).

Table 3 lists the wavelengths of the "charge transfer" bands and equilibrium constants for the complexation reaction between the *N*-oxide **(2c)** and TCE in different solvents. CTC of *N*-oxide **(2a)** with TCE can be observed only in dioxane, no complexation being observed in methanol. These results indicate that the stability of the CTCs of *N*-oxides decreases with increasing of the solvent polarity.

Table 3. p,π-Complexes of aromatic *N*-oxides with TCE.

N-oxide	Solvent	Charge transfer band, nm	$K^{\rho}_{x_i}$, mol^{-1}	$\lg K^{\rho}_{x_i}$
1e	$CHCl_3$	425	-	-
2b	$CHCl_3$	490	2.38	0.377
2c	$CHCl_3$	498	2.84	0.453
2d	$CHCl_3$	504	3.35	0.453
2e	$CHCl_3$	522	6.15	0.789
2c	Et_2O	477	4.47	-
2c	CH_3CN	471, 517	low	-

The absence of the π-π* absorption shifts of the aromatic system of *N*-oxides on the stage of initial interaction with TCE and the results obtained earlier for simplest *N*-oxides,[17] point to formation of the n,π-type complexes. This means that the oxygen atoms of the *N*-oxides are the donors of electron pair in these CTCs:



n,π-Complexes should be evidently less stable than *N*-oxides in polar solvents due to reduction of negative charge on oxygen atom. The initial formation of n,π-complexes can apparently be explained by the open state of oxygen atom and by higher (as compared with aromatic π-system) degree of the negative charge localization.

Crystallization of solid nonstoichiometric CTCs in dioxane led to complete or partial decolorization. The uv spectra of these CTCs differ from those of the corresponding *N*-oxides. The π-π* absorption band maxima are shifted towards shorter wavelengths. The "charge transfer" bands, which are characteristic *of the n,π-complexes, are not displayed* by the corresponding solid CTC.

On the other hand, the CTCs of *N*-oxides **(1e and 2e)** are yellow, and their uv spectra display an additional bands in the 390-430 nm region. The positions of most of the absorption bands in the ir spectra of the CTCs are *practically the same as those in the corresponding N*-oxides, but the bands of the $C\equiv N$ bond in the CTCs spectra are shifted by an average value of 30-40 cm^{-1} towards longer wavelengths as compared with the spectrum of TCE (Table 4). This kind of relationship is observed when TCE is bound into a CTC.[18]

It is known that pyridine initially gives n,π-CTC with TCE.[19] This complex further transforms into the pyridine-TCE addition product, which was isolated in the solid state.[19] This adduct can also liberate one of the cyanogroups and add to one or two more molecules of TCE.

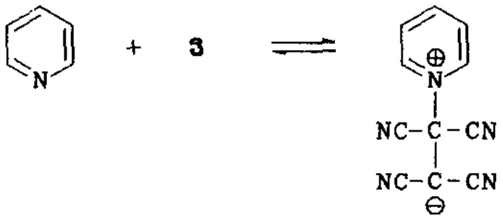
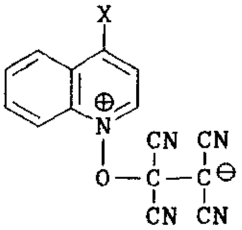


Table 4. Solid π,π -complexes of aromatic *N*-oxides with TCE.

N-oxide	Crystallization time, h	mp °C	*N*-oxide:TCE ratio	C≡N, cm^{-1}	N-O, cm^{-1}	Yield, %
1 e	24	128	1:0.59	2207	1306	53-55
2 b	48	123	1:0.36	2230	1297	21-25
2 c	24	133-134	1:0.35	2220	1305	44-52
2 d	21	142-144	1:0.34	2218	1310	55-57
2 e	1	180-181	1:0.66	2210	1320	61-66

There is a question concerning the possibility of such covalent addition of TCE to an oxygen atom of *N*-oxide in the solid CTCs. We think that the adduct **(6)** of this type can hardly be obtained under these conditions.



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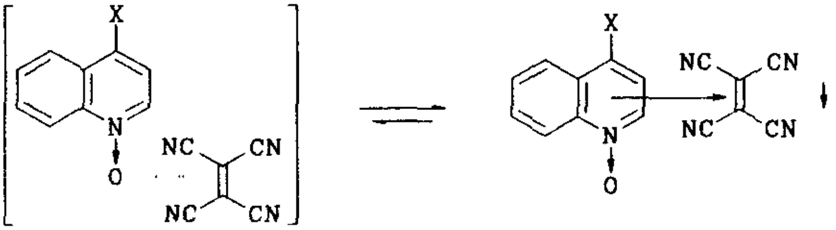
As it was discussed earlier, the ir spectra of CTCs of *N*-oxides and TCE show no shifts of the absorption band of N-O bond compared with the corresponding *N*-oxides. Uv spectra indicate the presence of p,π-conjugation of the oxygen atom of *N*-oxide group with aromatic ring in the CTCs. Moreover, the starting *N*-oxides can be regenerated from their CTCs with TCE by various methods, e.g. dissolution in polar solvents:[20]

$$\pi,\pi\text{-CTC} \rightleftharpoons n,\pi\text{-complex} \rightleftharpoons N\text{-oxide} + \text{TCE}$$

Thus, these facts show that the solid CTCs of aromatic *N*-oxides and TCE are π,π-complexes, their aromatic system being the donor center in this case.

The weak n,π-complexes of aromatic *N*-oxides initially formed with TCE, apparently, have to transform to stable solid π,π-complexes:

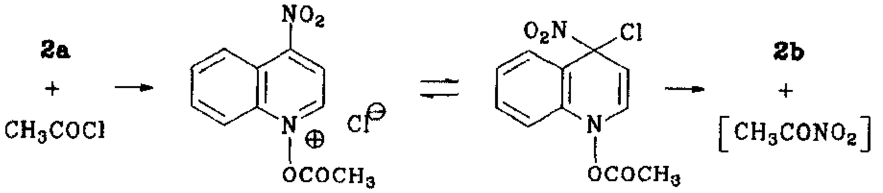


Electrom-withdrawing substituents decrease the donor ability of aromatic system of *N*-oxides. As a result the life time of n,π-complexes increases and its transformation to π,π-complexes proceeds slowly.

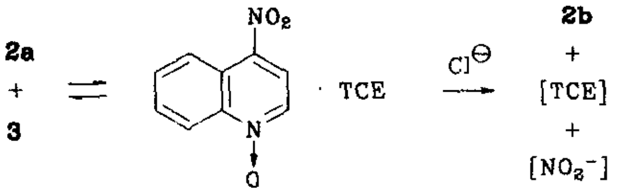
Electron-donating substituents exert a different influence: they increase the donor ability of *N*-oxides and accelerate the conversion of n,π-complexes to π,π-complexes.

The spectral characteristics of such CTCs indicate significant transfer of charge and, consequently, a high degree of electron deficiency in the aromatic π-system. It is of importance to determine to what extent the bonding of the heterocycles into molecular complexes facilitates nucleophilic substitution.

4-Nitroquinoline *N*-oxide **(2a)** is most reactive towards nucleophiles among all *N*-oxides chosen. It reacts smoothly with alkoxides, phenols, mercaptanes, amines and hydrazines (in high yields). However, the substitution of nitro group with weak nucleophiles such as chloride-ion and nitrophenols requires more drastic conditions. Thus, the conversion of 4-nitroquinoline *N*-oxide **(2a)** into 4-chloroquinoline *N*-oxide **(2b)** is carried out usually by treatment with excess acetyl chloride.[4] This process proceed *via* the intermediate formation of the *N*-acetoxy derivative:

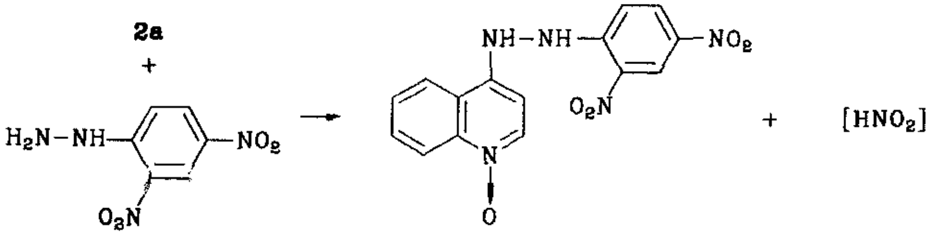


On the contrary we have established that *N*-oxide **(2a)** in the presence of TCE reacts with benzyltriethylammonium chloride in dioxane-acetonitrile mixture at room temperature:



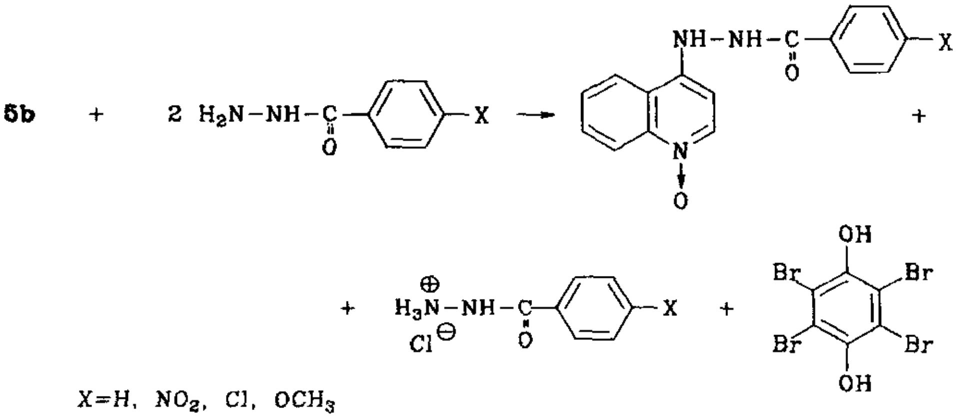
The reaction occurs through the formation of CTC of the *N*-oxide with TCE, which is detected by the uv spectroscopy, to yield *N*-oxide **(2b)**.

Similarly, the reaction of *N*-oxide **(2a)** with 2,4-dinitrophenylhydrazine in the presence of TCE can be carried out:



These data show that the use of CTC of **2a** *increases synthetic utility of* **2a** .

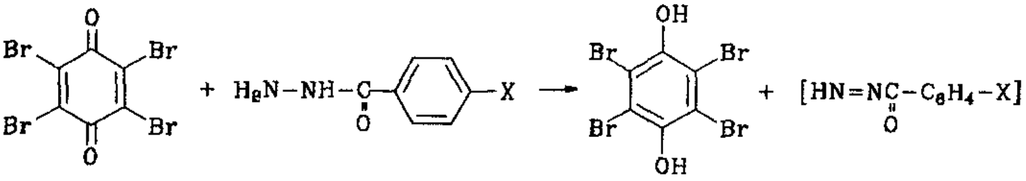
It is necessary to note that there are some obstacles for the wide use of CTCs for promotion of nucleophilic (and other types, probably) reactions. The main obstacle, in our opinion, is high lability of CTCs. The complex formation is a reversible process, and the starting constituents of these complex are presented in the solution as a result of their dissociation. Thus, the possibility of the side reactions between nucleophilic agent and acceptor should be taken into account. To avoid such interaction the introduction of less reactive acceptor or the use of the solid CTCs prepared in advance can be proposed. For example, the solid CTC **(5b)** of *N*-oxide **(2b)** and bromanile reacts with acylhydrazines:



X=H, NO_2, Cl, OCH_3

This reaction requires only 30 min at room temperature (or lower) giving good yield (about 60%). On the other hand, the *N*-oxide **(2b)** itself reacts with the *p*-substituted benzoylhydrazines only at 100°C for 3 h in 30% yield.

If the CTC of the *N*-oxide **(2b)** and bromanile is prepared in solution *"in situ"* the reaction of bromanile with acylhydrazines occurs in contrast with solid CTC **(5b)**:

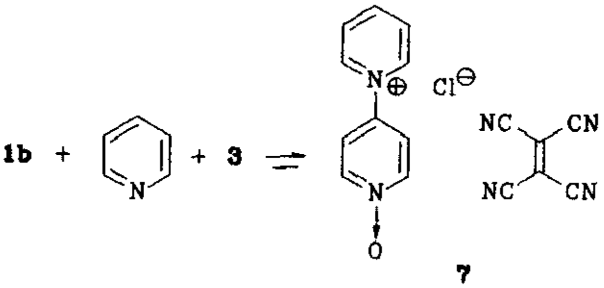


Moreover, substitution reaction can not be realized if the solid CTC of the *N*-oxide (**2b**) with TCE is used instead of CTC with bromanile, because TCE reacts also with nucleophiles and *N*-oxide (**2b**) is not changed:

Such processes can occur between TCE reacts and the most of reactive nucleophiles.[21] The reaction with the participation of CTC is evidently possible when nucleophile is chemically inactive towards acceptor or gives less stable CTC with the latter.

The selection of the counterparts of this process can be made based on such characteristics as the oxidation potentials of donors or reduction potentials of acceptors.

In continuation of our previous work we have established that the CTC of 4-chlorpyridine *N*-oxide (**1b**) and TCE, which exists only in solution, reacts with pyridine yielding the precipitate of molecular complex of *N*-(1-oxido-4-pyridyl)pyridinium chloride with TCE:[22]



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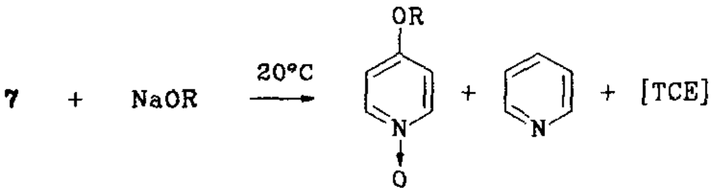
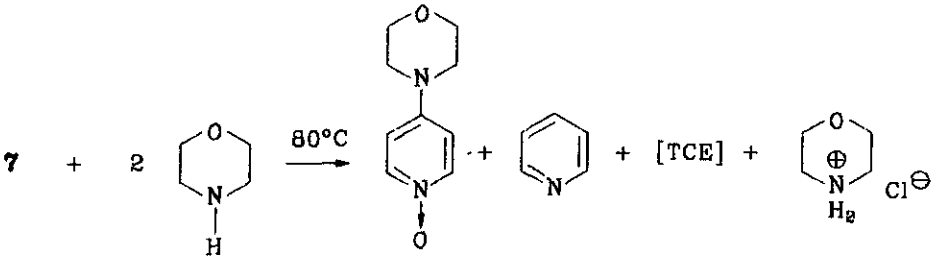
The structure of reaction product **(7)** has been established from the data of the elemental analysis, ^1H and ^{13}C nmr, uv and ir spectroscopies. The equilibrium constant of the complexation (K=1.06, 19°C) and stoichiometry of the molecular complex (1:1) were determined. In the CTC of **1b** with TCE the mobility of the chlorine atom is greatly increased. For this reason it is smoothly substituted with nuclear nitrogen of pyridine. We demonstrated that the *N*-oxide **(1b)** itself does not react with pyridine in the absence of catalysts even after prolonged heating (12 h) in *m*-xylene. In terms of the bimolecular nucleophilic substitution mechanism the role of the TCE involves increase of the electron deficiency in the initial π-system, and this promotes the attack by pyridine. At the same time, it cannot be considered as classical catalytic process, on account of the fact that the TCE is not regenerated in the reaction process. All attempts to obtain product salt without TCE have failed because of its decomposition to the starting substances.

The reaction of the CTC of *N*-oxide **(2b)** and TCE with quinoline takes place similarly, leading to the molecular complex of the chloride of *N*-quinolinioquinoline *N*-oxide with TCE.

The complex **(7)** contains the good leaving group. Thus, we can suggest that this method is versatile for the synthesis of 4-substituted nitrogen-containing heterocycles. For example, we have shown that treating this complex with sodium alkoxides, hydroxide, phenoxide or morpholine under mild conditions results in the formation of the corresponding 4-substituted pyridine *N*-oxides:





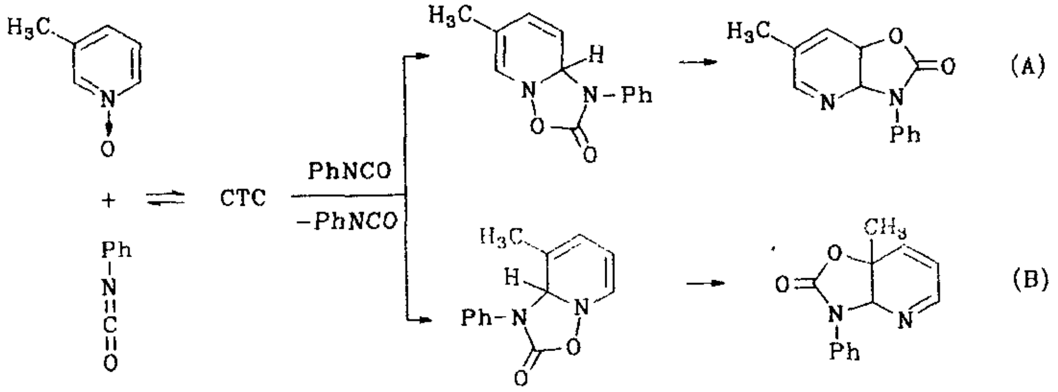
On the other hand, the *N*-oxide **(1b)** itself reacts with morpholine in usual manner[4] only at 135°C during 3 h in a closed system. In this case treatment of the mixture of *N*-oxides **(1b, 2b)** with TCE (for their activation) with sodium alkoxides or aliphatic amines has failed to give the nucleophilic substitution products. Only decomposition of CTCs was observed and starting *N*-oxides were regenerated.

<u>The donor-acceptor complexes in the 1,3-cycloaddition reactions</u>

It is known that cycloaddition reactions are very sensitive to electronic factors in both components, therefore even a slight electronic density redistribution in one of the reagent can have a great importance for the successful process.[8] It is also the case for the 1,3-dipolar cycloaddition reactions.[8,23]

In the aromatic *N*-oxide series there are a few examples concerning the role of CTCs in this process. Thus, pyridine *N*-oxides form CTCs with phenyl isocyanate, which precede cycloaddition reaction, and give oxazolo[4,5-*b*]pyridines. It should be pointed out that these CTCs exist only in solution. Moreover, this complex determines the direction of the reaction.[11]

If only steric control is operative, the adduct (A) should be formed predominantly. However, the observed product ratios were not consistent with this assumption. In a proposed explanation, the secondary orbital interaction between the hydrogen atoms of the methyl group and phenyl ring of the isocyanate in the CTC can contribute to stabilization of the transition state of the direction (B):



The similar results were obtained later for the reaction of methyl-substituted pyridine *N*-oxides with *N*-substituted maleimides.[24]

Conclusions

Thus, both literature and our results show that charge transfer interaction can effect on the reactions of heteroaromatic *N*-oxides and it proves a significance of this investigation.

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We have chosen for discussion the problem of nucleophilic substitution, mainly for the reason, that the first research works of Prof. Rolf Huisgen were dedicated to the same questions.

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