NUCLEOPHILIC SUBSTITUTION IN THE AZINE SERIES (REVIEW)

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This review is devoted to a discussion of the quantitative characteristics of the reactivities and mechanisms of the reactions of substituted azines with nucleophilic reagents.

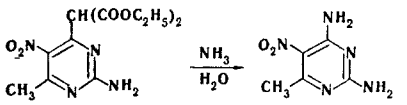
Nucleophilic substitution is very frequently used for the preparation of substituted azines, many of which have important practical value (amino, sulfamido, halo, and alkoxy derivatives, etc.). It is therefore not surprising that such great attention is directed to the study of nucleophilic substitution reactions in the azine series. Comprehensive material that generalizes the literature on this problem up to 1962-1963 is assembled in reviews [1, 2]. In 1971 a brief review on nucleophilic substitution in a number of azines [3] was published; only a few studies accomplished after 1963 were mentioned in this review, whereas a considerable number of new investigations directed toward the study of the quantitative aspects of the reactivities, an understanding of the role of the medium, and other factors that have a substantial effect on nucleophilic substitution reactions have appeared in the last decade.

It is not possible to comprehensively examine nucleophilic substitution reactions within the framework of a relatively brief review. Within the present review, we have not included the reactions of polyhaloazine and N-oxides of azines with nucleophiles, nor have we considered reactions that proceed via a hetarine nucleophilic substitution mechanism; the latter are discussed in a recently published review [4]. We deemed it expedient to direct primary attention to problems of the quantitative characteristics of the reactivities of azines in nucleophilic substitution reactions without striving to encompass all of the papers in which the use of nucleophilic substitution reactions for synthetic purposes are described.

Substitutable Groups and the "Element Effect" in Azines

In the last decade the relative reactivities of various substitutable groups in azines and the reactivities of substitutable groups as a function of their positions in the ring have been studied intensively.

In addition to the data presented in earlier reviews [1, 2], new nucleophilic substitution reactions have been found; thus it was shown that amination with cleavage of the C–C bond occurs on heating substituted (4-pyrimidyl)malonic esters of the I type with ammonium hydroxide [5].



I II

It has been established that it is possible to replace the trifluoromethyl group with cleavage of the C–C bond in the case of reactions of 2-(trifluoromethyl)pyridine, 2-(trifluoromethyl)quinoline, and 1-(trifluoromethyl)isoquinoline with sodium amide in liquid ammonia [6, 7]. Replacement of the trichloromethyl group was accomplished in a number of substituted pyrimidines (III) by reaction with primary and secondary aliphatic and cyclic amines [8]:

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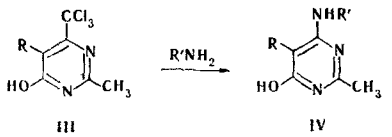


III IV

R = OCH_3; $COOCH_3$

It is interesting to note that the action of sodium methoxide on 3-(trifluoromethyl)quinoline [9] leads only to stepwise replacement of the fluorine atoms rather than replacement of the CF_3 group.

The hydrogen atom can, although with certain difficulties, also be replaced (for example, by Chichibabin amination of heterocycles [10] and by the action of CN^- and Hal^- on O-alkylated N-oxides of pyridines [11]) when a sufficiently strong nucleophile is used or there is additional activation of the azine ring (quaternization of the ring nitrogen atom or the use of azine N-oxides).

In investigations of the replacement of halogen atoms in haloazines, the reactivity of the chlorine atom has been studied most completely. A comparison of the labilities of fluorine and chlorine atoms in the reaction of 2-halo-5-nitropyridines with aniline and piperidine enabled Bamkole and Hirst [12] to note the characteristic (for aza-activated substrates) considerable decrease in the ratio of the rate constants for the reactions of the corresponding fluoro and chloro derivatives (k_F/k_{Cl}) as compared with halonitrobenzenes. A lower (than for nitro-activated substrates) k_F/k_{Cl} ratio was also observed in the reaction of 2-halopyridines, 2- and 4-haloquinolines, and 2-haloquinoxalines with sodium methoxide and piperidine [13] and of 2-halopyrimidines with piperidine in various solvents [14]. The low k_F/k_{Cl} ratio in the azine series in the case of proton-donor solvents is explained [13, 14] by the peculiarities of solvation effects in these compounds.

An investigation of the relative labilities of chlorine, bromine, and iodine atoms in 2-halo-, 5-bromo-2-halo-, 2-halo-4,6-dimethyl-, and 4-halo-2,6-dimethylpyrimidines in reactions with isoamyl- or 1,4-dimethylpentylamine in media of the same amines showed [15] that the reactivities of the bromine atoms in each group of compounds are higher than the reactivity of chlorine, but the difference between them is small (by a factor of approximately 3). The reactivities of the iodine atoms in the same groups of compounds may be higher or lower than the reactivities of the chlorine atoms, depending on the amine used.

Thus, like halonitrobenzenes, the order of lability of the halogens in haloazines ($F \geq Br > I$) may vary as the nucleophile and solvent are changed. Additional interaction of the aza group with the solvents complicates this pattern even more.

Despite the fact that the amino group and substituted amino groups are categorized as difficult-to-remove substituents [2], the kinetics of hydrolytic deamination of 2- and 4-amino-5-bromopyrimidines, 4-aminoquinazoline [16], and melamine [17] by the action of dilute aqueous alkali solutions have been studied. Basic catalysis by the reagent shows up in concentrated alkali solutions [16].

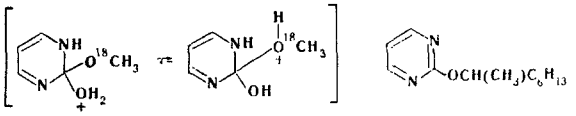
As previously shown [1, 2], the trimethylammonium group has high lability. Subsequent kinetic studies [18] made it possible to quantitatively estimate its reactivity. Barlin and Young [18] obtained various trimethylammonium derivatives of pyridine, nitropyridine, pyrimidine, nitropyrimidine, and purine and measured their rates of reaction with alkali in water. It was found that at 20°C (2-pyrimidyl)trimethylammonium chloride reacts faster by a factor of 700 than 2-chloropyrimidine and faster by a factor of 5 than 2-methylsulfonylpyrimidine.

The nitro group has a very high reactivity in azines. The relative rates of substitution at 50° for the 4-derivatives ($NO_2 : SO_2CH_3 : Cl = 7080 : 154 : 1$) and 2-isomers ($NO_2 : SO_2CH_3 : Cl = 5060 : 65 : 1$) were established [19] by comparison of the rate constants for substitution of the nitro group in 2- and 4-nitropyridines with sodium methoxide in methanol with the analogous constants for the corresponding methylsulfonyl and chloro derivatives of pyridine.

As in the study of the labilities of halogen in substituted pyrimidines [15], the aminolysis (in the case of reaction with butylamine) of 2- and 4-methoxy and 2- and 4-methylthiopyrimidines was investigated in [20]. Under these conditions, the alkoxy group proved to be more labile than the alkylthio groups, but both of these groups were less reactive than the chlorine atom in the corresponding chloropyrimidines. In the case of the alkoxy derivatives, aminolysis is accompanied by isomerization to give N-alkylated hydroxypyrimidines; Brown and Foster [20] took this into account by appropriate corrections.

This sort of isomerization complicates the study of the acid and alkaline hydrolysis of alkoxy derivatives of azines. The competitive isomerization and dealkylation of 2,4-dialkoxypyrimidines in aqueous and methanol media has been investigated [21]. Dealkylation predominates in strongly acid and strongly alkaline media and also when the concentration of the pyrimidine bases is very low; in this case, hydrolysis of the 2-methoxy group proceeds more readily in acid media, while hydrolysis of the 4-methoxy group proceeds more readily in alkaline media. In nonaqueous media, where dealkylation can proceed only through cleavage of the alkyl—oxygen bond, isomerization predominates.

The acid hydrolysis of 2-methoxypyrimidine, as shown in the O^{18}-labeled compound, proceeds primarily via a nucleophilic substitition mechanism through intermediate ion V, since the methanol that is formed contains 90% of the label oxygen [22]. In contrast to the acid cleavage of 2-methoxypyrimidine, the acid hydrolysis of alkoxy derivative VI, in which the secondary carbon atom is bonded to the ether oxygen, proceeds by means of S_N1 heterolysis at the O—Alk bond [23] of the ring-protonated VI.



V VI

2-, 3-, and 4-Methoxypyridines on reaction with sodium methoxide in methanol readily form the corresponding hydroxy derivatives of pyridine and dimethyl ether [24]. In the opinion of Zoltewicz and Sale [24], cleavage of the C—O bond also proceeds at the saturated carbon atom of the methoxy group in this case.

Alkyl(aryl)sulfinyl- and alkyl(aryl)sulfonylazines, obtained by oxidation of the readily accessible alkyl-(aryl)thio derivatives, have high reactivities and recently have been frequently used in nucleophilic substitution reactions. The quantitative study of these reactions was systematized (up to 1967) in a review [25], in which investigations of the aminolysis of halo, alkoxy, and alkyl(aryl)thio derivatives of azines were also correlated and their reactivities were compared. Thus 2- and 4-methyl and 2- and 4-phenylsulfinyl as well as 2- and 4-methyl- and 2- and 4-phenylsulfonyl groups in the corresponding pyrimidines on reaction with amylamine in dimethyl sulfoxide (DMSO) are substituted at a somewhat higher rate than the chlorine atom and faster by a factor of $\sim 10^5$ than the alkylthio group [26]. The methylsulfonyl group in methylsulfonylpyridines, -pyridazines, -pyrazines and their benzo analogs is readily replaced by the action of sodium methoxide in methanol [27], while the methylsulfonyl group in the 3 position of pyridazine is more labile by a factor of 90 than the chlorine atom in 3-chloropyridazine; similarly, 2- and 4-methylsulfonylquinolines are more reactive by a factor of 40-100 than the corresponding chloroquinolines.

The rate of substitution of arylsulfinyl and arylsulfonyl groups depends on the nature of the substituent in the aryl portion of the molecule. A linear dependence of the reaction rate constants on the σ substituent constants is observed in the alkaline hydrolysis of 2-(arylsulfinyl)-and 2-(arylsulfonyl)pyrimidines [28]. In an investigation of the effect of an alkyl group in reactions of 2-alkylthio-, 2-alkylsulfinyl-, and 2-alkylsulfonylquinolines with sodium methoxide in methanol it was shown [29] that passing from the methyl to the tert-butyl derivative induces a decrease in the rate by a factor of 1.8, 140, and 24, respectively, for each pair of compounds. Barlin and Brown [29] explain this decrease in the reactivity by both the steric and electronic effects of the tert-butyl group.

It is apparent from the examined kinetic data that the alkyl(aryl)sulfonyl groups in azines are more labile in nucleophilic substitution reactions than the chlorine atom. The known examples of the preferred substitution by nucleophiles of the chlorine atom in azines that simultaneously contain alkyl(aryl)sulfonyl groups [30-32] are apparently associated with the mutual effect of these groups on one another and also with the effect of other substituents in the azines and with the nature of the nucleophile.

The potassium salts of various mono- and disubstituted pyrimidine-2- and -6-sulfonic acids [33] are readily hydrolyzed to the corresponding hydroxypyrimidines in alkaline and acid media.

The rates of substitution of various leaving groups are usually characterized by the "element effect" by comparing the rate constants of compounds that contain a substitutable group with the rate constants of the chloro derivatives, which are taken to be unity. As already noted, the nature of the reagents used, other substituents in the heterocyclic ring (activation of the substrate molecule), and the solvation effects of the solvents have a substantial effect on the rate of substitution of various groups. Since there is no comparison of all of the reaction conditions in most of the published studies, it is impossible to compare the overall order of the relative labilities of the substitutable groups and to consider the reasons for the changes in

their relative reactivities. On the basis of the available quantitative data, one can only note that the following order of labilities of the leaving groups is observed in most cases for unsubstituted azines: NO_2; $\overset{+}{N}(CH_3)_3$> SO_2R; F > Br ≥ Cl > OR > SR > NR_2.

Mechanisms of Nucleophilic Substitution Reactions in the Azine Series

Concepts regarding the mechanisms of the reactions of heterocyclic compounds with nucleophilic reagents have been established primarily in analogy with the mechanisms of nucleophilic substitution in aromatic hydrocarbon derivatives. This approach to the study of nucleophilic substitution in azines is also currently used (thus, for example, the mechanism of the replacement of the 4-$\overset{+}{N}R_3$ group in the pyrimidine series [18] is considered). However, one should bear in mind that concepts regarding the mechanisms of nucleophilic substitution in the aromatic series have recently changed. Thus it has been assumed [34] that S_Nl Ar reactions proceed through a carbonium ion (Ar^+); recently, in the case of the decomposition of diazonium salts, it was proved that radical and ion-radical mechanisms may also occur [35-38].

In contrast to aromatic compounds, reactions with nucleophilic reagents in the azine series may proceed by a more complex path associated with opening of the heteroring and subsequent cyclization [1, 2, 39-43].

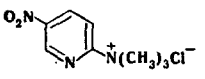
In investigations of the reactions of compounds of the aromatic series, principal attention is directed to the mechanisms of bimolecular substitution reactions. However, even up to the present there has been no proof that completely excludes the possibility of the occurrence of these reactions via a one-step synchronous mechanism [34, 44]. The most widespread concept is that of the two-step S_N2 Ar mechanism of bimolecular nucleophilic substitution reactions. The principal proofs of this mechanism are based on the detection and properties of intermediates (σ complexes) and also on the kinetic regularities of the occurrence of the reactions [34]. The structures and properties of σ complexes, including those of the heterocyclic series have been described in detail in a number of reviews [45-47]. Later other stable σ complexes were also obtained in reactions of azines with nucleophilic reagents [48-52].

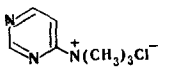
In addition to the classical two-step mechanism, concepts regarding a radical mechanism for nucleophilic substitution reactions have evolved in recent years [53-56]. The effect of light, oxygen, and inhibitors on the rate of reactions of halonitrobenzenes with nucleophilic reagents, which attests to a chain mechanism, has been observed [53, 55]. The possibility of this sort of mechanism in reactions of azines with nucleophiles has not been proven. One can only note that, like aromatic nitro compounds, azines readily form anion radicals during electrochemical reduction [57-59] and reaction with metals [60]; the effect of light and hydrogen peroxide [61, 62], just as in reactions of compounds of the benzene series, has been noted in reactions of azines with nucleophiles. These data make it possible to assume that a chain mechanism is also possible in nucleophilic substitution reactions in azines.

Aza Activation. Effect of Substituents in the Ring of Azines. Correlation Ratios in the Azine Series

The activating effect of the heterocyclic nitrogen atom (the aza group) and the nitro group is often compared to expose the peculiarities of reactions of azines, for which the relative values of activation by these groups is usually considered by comparing the ratios of the rate constants under identical conditions (k_{NO_2}/k_{aza}). This ratio varies within the limits of one order of magnitude [1]. As already noted, a number of factors – the medium, the group being substituted, the reagent, etc. [1, 2] – have a considerable effect on the rate of nucleophilic substitution reactions, and this effect may be substantially different for nitro- and aza-activated systems. It is therefore not surprising that the usual order of reactivity – NO_2 > aza or $k_{NO_2}/k_{aza} > 1$ – is reversed in some cases. This sort of phenomenon was noted [18] in a comparison of the rate constants of alkaline hydrolysis reactions in water of (5-nitro-2-pyridyl)trimethylammonium (VII) and (4-pyrimidyl)trimethylammonium (VIII) chlorides.

Under these conditions, nitro compound VII is less reactive than substituted pyrimidine VIII ($k_{NO_2}/k_{aza} \approx 0.4$). A greater activating effect of the aza group as compared with the nitro group was also pre-


VII


VIII

viously observed in the case of reactions with piperidine of 4-chloro-6-methylpyrimidine and 2-chloro-4-methyl-5-nitropyridine in ethanol [63, 64]. It should be noted that in all of these cases the reactions were carried out in proton-donor solvents. A comparison of the rate constants for the dechlorination of 2- and 4-chloro-1-nitronaphthalenes and 2- and 4-chloroquinolines with piperidine in various solvents demonstrated [65] that specific solvation by proton-donor solvents (hydrogen bonding) accelerates the nucleophilic reactions of halo azines considerably more than those of halonitronaphthalenes. In the opinion of Illuminati and co-workers [65], this difference in the effects of specific solvation is also the reason for the observed $k_{NO_2}/k_{aza} < 1$ ratios.

The aza group, like the nitro group, activates the α and γ positions considerably more strongly than the β position in the ring of azines. The widespread opinion regarding the relative reactivity of the α and γ positions in azines is that $\gamma > \alpha$ (i.e., p > o) predominates while activation of the nitrogen atoms in combination, (o, p) > (o, o), prevails in diazines. However, as seen from the data in Table 1, the relative reactivities of the α and γ positions of azines depend substantially on the structure of the substrate, the type of reagent, and the solvent (see the section "Solvation Effects in Reactions of Substituted Azines with Nucleophilic Reagents").

In examining the effect of substituents in various positions of the heteroring on the reactivity, one should bear in mind that the presence in azines of nitrogen atoms, the basicity of which varies as substituents are introduced, may complicate this effect and in some cases even change it to the opposite of the usual effect. For example, the effect is anomalous (electron-acceptor substituents such as NO_2 and Cl lead to deactivation of the substrate) in the noncatalytic reaction of substituted 2- and 4-chloroquinolines with p-thiocresol in methanol [66], although the reaction follows second-order kinetics. Illuminati and co-workers [66] have shown that in this case reaction of the substrate with p-thiocresol at the heterocyclic nitrogen atom [Eq. (1)] precedes nucleophilic substitution of chlorine [Eq. (2)]:

$$\mathrm{ArSH(solv.)} + \mathrm{QCl(solv.)} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{ArS(solv.)^-} + \mathrm{HQCl(solv.)^+} \quad (1)$$

$$\mathrm{ArS(solv.)^-} + \mathrm{HQCl(solv.)^+} \xrightarrow{k_2} \mathrm{HQSAr(solv.)^+} + \mathrm{Cl(solv.)^-} \quad (2)$$

Q — quinoline residue

The presence of a fast preequilibrium (1) explains the observed action of substituents in the reaction with p-thiocresol, which has a quite acidic proton.

The appearance of secondary steric effects on the part of substituents in the ortho position relative to the activating aza group because of hindrance to its solvation by a proton-donor solvent [67] may serve as an example of another complication of the effect of substituents. As noted by Calligaris and co-workers [67], these effects in azines, in contrast to nitro-activated systems, become significant only in the case of very bulky groups and for reactions carried out in protic polar solvents. In most of the other cases, the substituents affect the reactivity mainly through their electronic effects.

However, the problem of the quantitative allowance for the polar interaction of the substituent and the reaction center in the azine series is also complicated in cases in which interactions of the heteroatoms with the reagents, solvent, etc., are excluded (see the review [68] on the use of the Hammett equation for heterocyclic compounds). These complications are caused by interaction of both the reaction center and the substituent with the heteroatom. Kholodov [69] has expressed the opinion that the interaction of the reaction center with the heteroatom is approximately constant for the entire series (for any substituents R); in correlation analysis, the magnitude of this interaction will enter into the log k_0 value and will be reflected in the ρ value. However, the interaction of substituent R with the heteroatom, which is specific for each type of substituent, will be expressed in a deviation from the Hammett equation.

In fact, when a small set of substituents of the same type is used in, for example, reactions of substituted chloropyridines [70] and chloro-sym-triazines with nucleophiles [71, 72], linear dependences of log k on the σ substituent constants are found. The observance of a linear dependence between these values was also established for a definite relative orientation of the substituents (both donors and acceptors), ring heteroatoms, and reaction center. For example, in a series of 6-substituted 3-chloropyridazines [73] and 4-substituted 1-chlorophthalazines [74], in which the ring heteroatoms are not in the para position relative to either R or the reaction center, a linear correlation between log k and the σ substituent constants is observed. Large deviations from the correlation line are noted [75, 76] when a large set of substituents of different types are used in the correlations. In these cases, the ring nitrogen atoms, which can be considered to be unique groups, in turn transmit the effect of variable substituent R to the reaction center and have a different effect on the lability of the group being substituted, depending on

TABLE 1. Relative Reactivities of α- and γ-Chloroazines

Azines	Nucleophiles	Solvents	Temp, °C	k_γ/k_α	Literature
Chloropyridines					
4-Cl/2-Cl	Piperidine	Piperidine	122—125	0,45	1
4-Cl/2-Cl	Piperidine	Methanol	80	11	90
4-Cl/2-Cl	Sodium p-nitrophenoxide	Methanol	50	27	91
4-Cl/2-Cl	Sodium ethoxide	Ethanol	20	39	2, 92, 93
Chloroquinolines					
4-Cl/2-Cl	Piperidine	Toluene	86,5	0,01	83
4-Cl/2-Cl		Ethyl acetate	86,5	0,06	83
4-Cl/2-Cl		Piperidine	86,5	0,03	83
4-Cl/2-Cl		Methanol	86,5	0,98	83
4-Cl/2-Cl		DMSO	86,5	0,4	83
4-Cl/2-Cl	Sodium ethoxide	Ethanol	20	1,0	1
2,4-Dichloroquinolines					
4-Cl/2-Cl	Dimethylamine	Toluene	75,2	0,07	94
4-Cl/2-Cl	Dimethylamine	Methanol	75,2	2,6	94
4-Cl/2-Cl	Sodium methoxide	Methanol	75,2	1,9	95
Chloropyrimidines					
4-Cl/2-Cl	Piperidine	Isooctane	60	0,3	96
4-Cl/2-Cl		Benzene	60	1,6	87, 88
4-Cl/2-Cl		Methanol	60	11	87, 88
4-Cl/2-Cl		DMF	60	7,3	87, 88
4-Cl/2-Cl	Sodium p-nitrophenoxide	Methanol	50	0,017	91
2,4-Dichloropyrimidine					
4-Cl/2-Cl	Piperidine	Isooctane	60	0,5	96
Chloroquinazolines					
4-Cl/2-Cl	Piperidine	Ethanol	20	$6,5 \cdot 10^3$	2

the type of substituent. This sort of path for the transmission of the effect of R was earlier widely discussed at the qualitative level [2], but its quantitative evaluation is possible by two paths [77]. One of these paths assumes the introduction of new σ substituent constants that differ not only from the corresponding substituent constants of the benzene series but are also different for different positions of each azine. The other path is the use of the substituent constants found in the benzene series by means of the multiparameter correlation. The second path is probably more promising, since it provides a possibility for using the available σ constant values. Correlation of the rate constants of the reactions of substituted chloropyrimidines with piperidine in isooctane with the Taft and Lewis σ_i and σ_c substituent constants of the benzene series [78] may serve as an example of this sort of appraoch. A comparison of the ρ_i and ρ_c coefficients in the equations for the examined compounds of the pyrimidine series with the analogous coefficients of the equations for substituted chlorobenzenes showed that the relative conductivity of the electronic effects in the pyrimidine ring, expressed in the form of transmission factors, is higher than in the benzene series, and the differences in the transmission of the conjugation effects are the most substantial ones.

Solvation Effects in Reactions of Substituted Azines with Nucleophilic Reagents

Solvents within which chemical reactions take place determine not only their rates but often also the direction (orientation) and mechanism. A study of the effect of the properties of the medium on the reaction of organic compounds is therefore currently one of the most important problems in organic chemistry.

An examination of solvation effects in nucleophilic substitution reactions in azines [1, 2] is also usually carried out in analogy with the approaches adopted in investigations of these reactions in compounds of the benzene series, in which piperidine is most often used as the model reagent [79-81].

Most solvents in reactions of aromatic halo derivatives with piperidine have an effect on the reaction rates as a result of nonspecific (ionizing strength of the medium) and specific (homogeneous catalysis) solvation. The latter is accomplished via general base, general acid, general acid—base, and bifunctional mechanisms, as a function of the nature of the solvent and the atom or group undergoing substitution [82].

The investigation of the effect of the nature of the solvents on the rates of nucleophilic substitution reactions in the azine series has made it possible not only to expose all of the above-indicated forms of catalysis but also to detect different forms of specific solvation that are characteristic for nitrogen-containing heterocyclic compounds [1, 2, 12-14, 25, 65-67, 83-89]. On passing from nonpolar to polar protic and dipolar aprotic solvents, the rate constants of the reactions of 2- and 4-chloroquinolines with piperidine

increase [83, 84], and this increase is much smaller than for the analogous reactions of substituted halonitrobenzenes. Illuminati and co-workers [83, 84] note the larger effect of the medium in the case of 4-chloroquinoline than in the case of the 2-isomer. This sort of decrease in sensitivity to a change in solvent in the case of 2-chloroquinoline was explained by the manifestation of the α-aza effect, in the understanding of which was included the interaction of the α-situated reaction center with the heterocyclic nitrogen atom.

Some data on the comparison of the reactivity of other α- and γ-chloroazines with nucleophiles in different solvents are presented in Table 1 (k_γ/k_α are the ratios of the rate constants of the corresponding 4- and 2-chloro derivatives of azines).

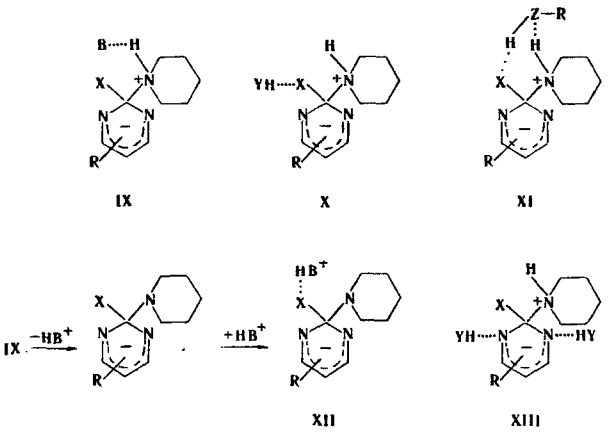
It is seen from the data in Table 1 that the k_γ/k_α ratio, in addition to its dependence on the type of substrate, nucleophile, and temperature, changes substantially as the solvent changes, and one should note that it basically increases with increasing polarity and proton-donor properties of the solvent. This sort of increase in the k_γ/k_α ratio apparently is also associated with the manifestation of the α-aza effect. However, this interesting phenomenon, which in many ways determines the specifics of heteroaromatic nitrogen-containing compounds in reactions with nucleophilic reagents, is not yet understood. One cannot exclude the possibility that the unraveling of the nature of the α-aza effect will make it possible to detect the fine mechanisms of the reactions specific for heterocyclic aza-activated systems.

In an investigation of the effect of solvents on the rates of reactions of substituted 2- and 4-chloropyrimidines, Mamaev and co-workers [14, 87-89] noted the change in the orders of reactivities of substituted chloropyrimidines as the nature of the solvents changed. This phenomenon was explained by the fact that the substituents in the pyrimidine ring have an effect on the ring heteroatoms in that they change the basicity of chloropyrimidines and, consequently, their capacity for solvation. In addition, it is noted that chloropyrimidines react with piperidine in benzene solution appreciably more rapidly than in isooctane. This sort of effect of benzene, in the opinion of Mamaev and co-workers [87, 89], is explained by both the greater contribution of nonspecific solvation due to the high polarizability and to the specific solvation of basic character. The accelerating effect of solvents that have basic properties, such as dioxane, dimethylformamide, piperidine, and N-methylpyrrolidone, is also explained by the manifestation of basic catalysis [89].

Many papers [1, 2, 13, 67, 83, 84] have been devoted to an investigation of the effect of alcohols and other protic solvents on the rates of reactions of haloazines with piperidine and other nucleophilic reagents. In them, the presence of catalysis by methanol and other protic solvents at the aza group in reactions of various heterocyclic systems, particularly quinolines [1, 2, 83, 84], pyridines [13], and pyrimidines [67], is noted. In the case of reactions of alkyl-substituted chloropyrimidines and chloroquinolines with piperidine in various solvents [67, 85] and of chloroquinolines with sodium methoxide in methanol [85], the steric effect of substituents in the ortho position relative to the aza group on the catalytic effect of protic solvents is investigated. Calligaris and co-workers [67, 85] note that bulky substituents decrease the solvation effect of methanol. A more detailed investigation of the effect of the nature and composition of solvents on the rate constants of the reactions of substituted 2- and 4-chloropyrimidines was carried out using binary solvent mixtures [89]. In this investigation, the action of specific and nonspecific solvation on the rates of the reactions under consideration was compared. It was confirmed that specific solvation of basic character increases the reaction rates. Proton-donor solvents also have a substantial effect on the reaction rates, and the direction and magnitude of this effect depend on the character of the substituent in the pyrimidine ring.

The rate constants of reactions of chloro and fluoro derivatives of pyridines [12, 13], quinolines, quinoxalines [13], and pyrimidines [14, 89] were compared in order to expose the general acid catalysis at the atom undergoing substitution. As already mentioned, fluoro derivatives usually react at higher rates than the corresponding chloro derivatives ($k_F/k_{Cl} > 1$), but the magnitude of this ratio is relatively low in the case of azines and becomes less than one for other cases [12]. Bamkole and Hirst [12] link the k_F/k_{Cl} ratios with the basicity of the reagent and assume that it increases with increasing basicity of the reagent and with the degree of activation of the substrate. A comparison of the rates of reactions of haloazines and halonitrobenzenes with the same nucleophile shows that the k_F/k_{Cl} ratio also depends substantially on specific solvation by the solvents, especially in the case of proton-donor solvents [13, 14].

On the basis of the available experimental data and the analogy with nucleophilic substitution in reactions of aromatic compounds [79-82], specific solvation (homogeneous catalysis) in the reactions of azines with nucleophilic reagents can be represented in the following manner (in the case of the reaction of 2-halopyrimidines with piperidine):



X is the group being replaced, B is the base, YH is the proton-containing solvent, and RZH is a bifunctional solvent of the piperidine or methanol type.

General base catalysis consists in splitting out by a basic solvent (B) of a proton from the NH group of piperidine in σ complex IX, while general acid catalysis consists in tying up of the atom or group (X) undergoing substitution or of the heteroatom (XIII) by proton-containing solvent YH. In the general case, the mechanism of the specific effect of the solvents that have basic properties can be represented as general base–acid catalysis (IX and XII). When splitting out of a proton and of a replaceable group are simultaneously possible, bifunctional catalysis (XI) is realized.

Since relatively few studies have appeared in which the effect of the nature of the nucleophile on nucleophilic substitution reactions in azines is discussed in addition to the previous reviews [1, 2], this problem is not touched upon in the present review. One should only note that, judging from the investigation of aromatic nucleophilic substitution, the effect of the nature of the nucleophile is intimately interrelated to the solvation effects of the medium, the nature of the group being replaced, and the nature of the substrate [79-81].

Thus, despite the considerable advances in the study of nucleophilic substitution reactions, up to now many of the aspects of these reactions have not been clarified. There is no doubt that a deep understanding of the peculiarities of the occurrence of nucleophilic substitution in the azine series promotes the exposure of the specifics of heterocyclic compounds and aids synthetic chemists in the selection of rational means for the production of new compounds.

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