KINETICS OF NUCLEOPHILIC HALOGEN EXCHANGE IN 1-ALKYL-2-(5'-HALO-2'-FURYL)BENZIMIDAZOLES

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The kinetics of the reaction of 1-alkyl-2-(5'-halo-2'-furyl)benzimidazoles and their corresponding quaternary salts with secondary aliphatic amines were studied. The effect on the activation parameters of this reaction of the nature of the halogen being replaced by the secondary amine residue, the presence of a positive charge on the imidazole ring, the character of the anion in the quaternary salts, and the remoteness of the reaction center from the activating grouping on the activation parameters of this reaction is discussed.

In recent years activated nucleophilic exchange at an aromatic carbon atom (S_N2) has been evoking the increasing interest of investigators. Reactions of this type proceed via a unique mechanism, whose details still remain unclear. A number of important results in this field were obtained in an investigation of nitrogen-containing heterocycles since the pyridine nitrogen atom in them can act as an activating group in S_N2 reactions. For example, the kinetics of nucleophilic halogen exchange in pyridine [1], benzothiazole [2-4] naphthothiazole [5], and benzimidazole [6-9] derivatives were studied.

In addition, it is known that 2-halofurans which contain activating substituents in the 5-position readily exchange halogen for nucleophilic groupings via an S_N2 mechanism [10, 11].

In this paper we have studied the kinetics of nucleophilic halogen exchange in the recently [12] synthesized 1-alkyl-2-(5'-halo-2'-furyl)benzimidazoles and their corresponding quaternary salts.

The peculiarity of nitrogen-containing heterocycles with respect to this reaction consists in the fact that the $>C=N-$ grouping can, as a result of proton exchange, be converted to a conjugated acid grouping ($>C=\overset{+}{N}H-$), whose activating effect in reactions of the S_N2 type is much greater than that of the corresponding base. Quite some time ago it was noted that acids catalyze the nucleophilic substitution of halogens in nitrogen-containing heterocycles [13]. An autocatalytic effect in the reaction of 4-chloropyridine and 4-chlorolutidine with benzylamine was revealed in [1]. It was recently shown [14] that the reaction of 1-methyl-2-chlorobenzimidazole (I) with aromatic amines proceeds via an autocatalytic mechanism and is accelerated by the addition of mineral acid. A similar mechanism was observed in the reaction of aromatic amines with 5-halofurfurylideneanilines [15]. It was natural to assume that a similar mechanism would be observed in 1-alkyl-2-(5'-halo-2'-furyl)benzimidazoles. However, the experimental results indicate just the opposite: 1-methyl-2-(5'-chloro-2'-furyl)benzimidazole (II) and 1-methyl-2-(5'-bromo-2'-furyl)benzimidazole (III) do not react with aniline in propanol at 100 deg C, regardless of the presence of acid in the reaction mixture.

The basicities of II and III, determined by potentiometric titration in 50% alcohol, are practically identical and quite high (pK_a 3.4), and the concentration of the protonated form of II and III in a reaction mixture containing acid will therefore exceed the corresponding concentration for I (pK_a 2.3). Despite this, the protonated form of II and III does not react with aniline. Its reactivity is apparently considerably lower

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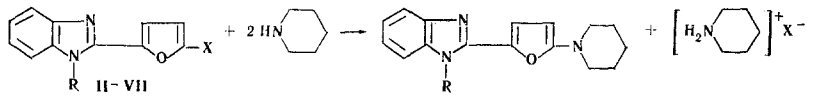
TABLE 1. Kinetic Parameters for the Reaction of II-VII with Piperidine in Dimethylformamide



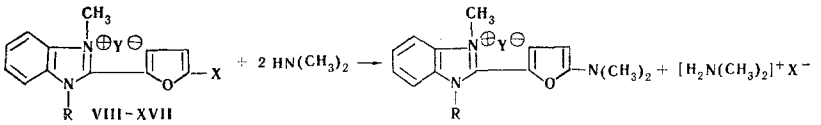
Compound	R	X	ΔG≠, kcal/mole	ΔH≠, kcal/mole	ΔS≠, cal/mole·deg
II	CH_3	Cl	32,03	43,92	26,44
III	CH_3	Br	31,82	30,26	−3,79
IV	CH_3	I	33,78	15,83	−45,85
V	$CH_2C_6H_5$	Cl	31,37	44,92	32,79
VI	$CH_2C_6H_5$	Br	32,03	33,91	4,56
VII	$CH_2C_6H_5$	I	33,50	16,58	−41,02

than that of the protonated form of I. However, the use of a stronger base (piperidine) in this reaction virtually excludes the possibility of protonation of compounds of the I-III type. As previously shown in [14], for I, in this case, the reaction proceeds via an S_N2 mechanism (the process is first-order in the presence of excess reagent). We observed a similar phenomenon during an investigation of the kinetics of the reaction of 1-alkyl-2-(5'-halo-2'-furyl)benzimidazoles with excess piperidine in dimethylformamide. The parameters of the Eyring equation [16], obtained on the basis of the temperature dependence of the second-order rate constant, are presented in Table 1.

It was preparatively demonstrated in [12] that fixation of a positive charge on the imidazole ring of compounds of the II-III type results in an increase in the lability of the halogen atom in the nucleophilic substitution reactions. The kinetic data confirm this conclusion. The results of a kinetic investigation of the reaction of the corresponding quaternary salts (VIII-XVIII) with dimethylamine (for XI, also with piperidine) in methanol are presented in Table 2.

A comparison of the data in Tables 1 and 2 indicates that quaternization of the pyridine nitrogen atom results in a decrease in the free energy of activation by an average of 8-10 kcal/mole. This occurs as a result of a sharp decrease in the enthalpy of activation (by an average of 10-20 kcal/mole), while the entropy of activation changes in a direction unfavorable for the reaction and partially compensates for the decrease in enthalpy. In our opinion, the increase in the negative value of the entropy of activation in this case is associated with partial removal of the furan ring from conjugation with the imidazole system when the latter contains two alkyl residues. A similar effect was observed [17] in a number of quaternary salts of 2-phenylbenzimidazole. Transfer of electrons to the activating grouping due to nucleophilic attack requires coplanarity of the imidazole and furan rings. The probability of such a configuration decreases when alkyl residues are introduced into the imidazole ring.

TABLE 2. Kinetic Parameters of the Reaction of VIII-XVIII with Dimethylamine in Methanol

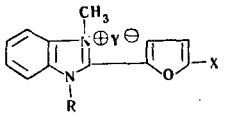


Compound	R	X	Y	ΔG≠, kcal/mole	ΔH≠, kcal/mole	ΔS≠, cal/mole·deg
VIII	CH_3	Br	F	24,13	13,90	−31,67
IX	CH_3	Br	Cl	25,19	10,35	−45,94
X	CH_3	Br	Br	25,11	11,24	−42,95
XI	CH_3	Br	I	24,40	13,98	−32,23
XII	CH_3	Br	NO_3	24,21	14,90	−28,85
XIII	CH_3	Cl	I	24,06	15,35	−26,97
XIV*	CH_3	I	I	25,96	7,13	−58,28
XV	$CH_2C_6H_5$	Cl	I	23,70	16,72	−21,59
XVI	$CH_2C_6H_5$	Br	I	23,99	15,81	−25,33
XVII †	$CH_2C_6H_5$	I	I	25,41	8,53	−52,26
XVIII	CH_3	I	I	26,32	4,76	−66,77

*For the reaction of XIV with piperidine, $\Delta G^{\neq} = 24.32$, $\Delta H^{\neq} = 14.93$, and $\Delta S^{\neq} = -29.68$.

†XVIII is 1-methyl-2-[β-(5'-iodo-2'-furyl)vinyl]benzimidazole methiodide.

TABLE 3. Spectral Characteristics of VIII-XII and XIX-XXIII



Compound	R	X	Y	λ_{max}, nm	lg ε
VIII	CH_3	Br	F	317	4,256
IX	CH_3	Br	Cl	315	4,361
X	CH_3	Br	Br	316	4,401
XI	CH_3	Br	I	319	4,421
XII	CH_3	Br	NO_3	320	4,299
XIX	CH_3	$N(CH_3)_2$	F	405	4,470
XX	CH_3	$N(CH_3)_2$	Cl	406	4,496
XXI	CH_3	$N(CH_3)_2$	Br	407	4,602
XXII	CH_3	$N(CH_3)_2$	I	410	4,789
XXIII	CH_3	$N(CH_3)_2$	NO_3	405	4,562

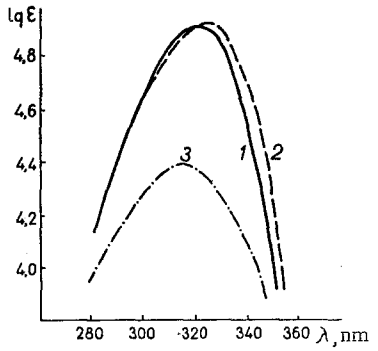


Fig. 1. UV spectra (in 0.1 N HBr in methanol): 1) 2-(5'-bromo-2'-furyl)benzimidazole; 2) 1-methyl-2-(5'-bromo-2'-furyl)benzimidazole; 3) 1-methyl-2-(5'-bromo-2'-furyl)benzimidazole methobromide.

The UV spectra of 2-(5'-bromo-2'-furyl)benzimidazole, III, and the corresponding quaternary salt of the latter (methobromide) in 0.1 N hydrogen bromide in methanol are presented in Fig. 1. This figure indicates that the introduction of one methyl group does not affect the intensity of the long-wave absorption band of the corresponding salt and induces only a slight bathochromic shift of this band. Steric hindrance to conjugation is not created in this case, as previously noted by Kipriyanov and Shulezhko [18], since the furan ring, in contrast to the benzene ring, is asymmetrical. However, the introduction of a second methyl group induces a sharp decrease in the intensity of this band and a considerable hypsochromic shift of it, which attests to partial removal of the furan ring from conjugation with the benzimidazole ring [17]. Thus, the spectrophotometric data are in agreement with the fact of the sharp increase in the negative value of the entropy of activation for nucleophilic halogen exchange in quaternary salts as compared with the bases corresponding to them.

It is apparent from Tables 1 and 2 that the positive value of the entropy of activation decreases with an increase in the atomic weight of the halogen being substituted. This phenomenon can be explained by the shielding action of the substituent, which increases with increasing covalent radius of the halogen.

It is also interesting to compare the kinetic parameters of nucleophilic exchange for I and II* (reaction with piperidine in dimethylformamide). The following $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ parameters are taken for these compounds: 29.01 and 32.03 kcal/mole, 12.15 and 43.92 kcal/mole, and −45.2 and 26.44 kcal/mole-deg. The sharp increase in the enthalpy of activation on passing from I to II can be explained by the decrease in the partial positive charge on the reaction center due to its greater distance from the activating group (which agrees with the above data on the basicity of the indicated compounds).

Attention is directed to the fact of the considerable change in the entropy of activation, which reaches a large negative value. This is apparently associated with the peculiarities of the structure of heterocyclic compounds of the I type. With respect to the reaction under consideration, their reaction center is simultaneously an activating grouping. Transition to an activated state is therefore associated with considerable steric hindrance caused by the shielding effect of the neighboring 1-alkyl group and the unshared electron pair of nitrogen.

Thus, steric effects have an appreciable influence on the kinetics of nucleophilic exchange, to a significant degree changing the entropy components of the free energy of activation. On the basis of the data in Table 1 it can be concluded that the rate constant and the free energy of activation change slightly on changing the various parameters (halogens in the ring and substituents in the 1-position) while these changes are not subject to any definite regularity. On the other hand, the enthalpy and entropy of activation change regularly in the indicated series of compounds.

* The data for I were obtained jointly with I. A. Sidorenko.

The spectral characteristics of VIII-XII, which contain different anions, and of the products of substitution of the halogen atom in the furan ring of these compounds by a dimethylamino group (XIX-XXIII) are presented in Table 3. These data attest to the fact that the character of the anion has a substantial effect on both the kinetic parameters of the reaction and on the spectral characteristics of the quaternary salts. It is important to note that the free energy of activation changes insignificantly on varying the anion and remains within the limits of 23 to 26 kcal/mole, while both $\Delta H^{\neq}$ and $\Delta S^{\neq}$ change extremely sharply; thus, these changes are mutually compensating. In the case under consideration, the quaternary salt which contains a fluorine anion (VIII) deviates from the series of salts which contain other halide ions, both with respect to reactivity and UV absorption spectra. On the other hand, in the series of salts which contain Cl, Br, and I anions (IX-XI) one observes definite regularity – the enthalpy of activation increases in parallel with an increase in the intensity and bathochromic shift of the long-wave band. The reason for this phenomenon is still not clear. It is possible that in this case the polarizability of the anions and their capacity for solvation by solvent molecules play a role; however, additional investigations are necessary for the final clarification of this problem.

EXPERIMENTAL

Two methods were used to determine the rate constants of the exchange reactions of the halogen atom in the furan ring by a dialkylamino group.

A) The rate constants for halogen exchange in II-VII were determined at 110, 120, and 130 deg. The course of the reaction was monitored from the percentage of ionic halogen in the reaction mixture, which was determined by potentiometric titration by the usual method [15]. (The substrate concentration was 0.05 mole/liter, and the reagent concentration was 1.5 mole/liter.) The second-order rate constant was calculated from the equation $K_2 = K_1/C_2$, where C_2 is the amine concentration. The applicability of the equation for the calculation of K_2 was checked by varying C_2, which indicated that the reaction is first-order in amine.

B) The rate constants for halogen exchange in VIII-XVIII were determined at 30, 40, and 50 deg in a thermostated cuvette. The course of the reaction was monitored spectrophotometrically, and the optical density at λ_{max} of the final product served as the measurable parameter. The substrate concentration (C_1) was 0.01 mole/liter, and the reagent concentration (C_2) was 0.435 mole/liter. The indicated concentrations were selected in such a way as to ensure a pseudo zero-order reaction. The pseudo zero-order rate constant was determined from the formula $K_0 = D/\varepsilon\tau$, where D is the optical density, ε is the molar extinction coefficient (both values are for λ_{max} of the reaction product), and τ is the time.

The second-order rate constant was calculated from the formula $K_2 = K_0/C_1C_2$. The applicability of this equation for the calculation of K_2 was verified by varying C_1 and C_2, which indicated that the reaction is first-order in each of the reagents. As in case A, a correction for the change in the concentration due to volume expansion of the solvent was introduced into the calculation of the rate constant. The parameters of the Eyring equation (as in case A) were calculated via the method described in [16]. The ionization constants of I and II were determined by the potentiometric titration and with LPU-01 potentiometer.

The UV spectra were obtained with an SF-4a spectrophotometer.

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