Influence of solvents on the reaction of 5-nitro-2-furylvinyl-trimethylammonium bromide with piperidine*

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The kinetics of reactions of (E)-[β-(5-nitro-2-furyl)vinyl]trimethylammonium bromide, (E)-2-(β-bromovinyl)-5-nitrofuran, and 2-ethynyl-5--nitrofuran with piperidine in various solvents at 25 °C has been studied. The comparison of the obtained data has shown that despite the strongly electron-accepting nature of the ammonium group furylvinylammonium salts actually do not excel the corresponding vinyl halides and ethynylfurans in their reactivity. The reason for this lies in different manifestations of solvation effects of the medium in above reactions proceeding differently by their transition states nature. The influence of nonspecific and specific solvation of solvents on the rate of interaction between a furylvinyltrimethylammonium salt and piperidine has been investigated.

Исследована кинетика реакций бромида (E)-[β-(5-нитро-2-фурил)-винил]триметиламмония, (E)-2-(β-бромвинил)-5-нитрофурана и 2--этинил-5-нитрофурана с пиперидином в различных растворителях при 25 °C. Сравнение полученных данных говорит о том, что вопреки сильно электроноакцепторному характеру аммониевой группы, соли фурилвиниламмония не превосходят по своей реакционной способности соответствующих винилгалоидов и этинилфуранов. Причина этого заключается в различном проявлении сольватирующих эффектов среды в данных реакциях, протекающих через различные переходные состояния. Исследовано влияние неспецифической и специфической сольватации растворителями на скорость взаимодействия между солью фурилвинилтриметиламмония и пиперидином.

5-Nitro-2-furylvinylation of amines is of considerable interest for obtaining biologically active enamines related to 5-nitrofuran [1, 2]. Quaternary furyl-

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vinyltrialkylammonium salts are rather promising furylvinylating agents; the strong electron-accepting nature of the ammonium group is assumed to pro- mote enhancing their reactivity in comparison to vinyl halides and ethynylfurans [3]. The use of vinylammonium salts for obtaining aminovinyl derivatives is also advantageous since they are less toxic than the corresponding vinyl halides [3, 4] and yield the products of high purity [3]. So far, no quantitative data on the reactivity of [β-(5-nitro-2-furyl)vinyl]trialkylammonium salts with nucleophiles have been reported and therefore, optimal conditions for the synthesis of enami- nes had to be found (Scheme 1).
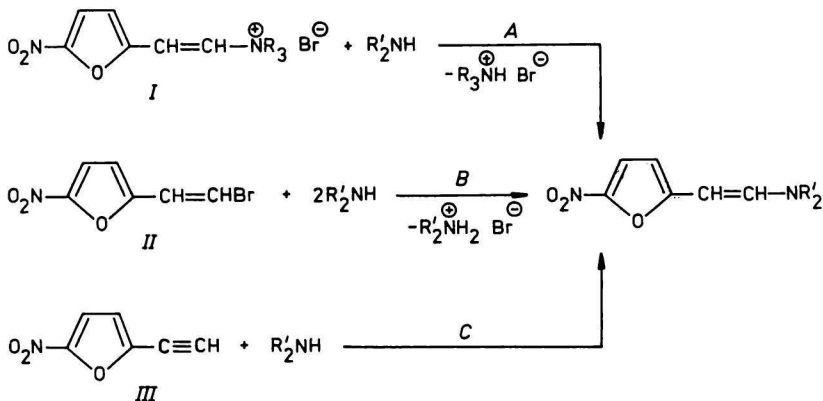
Scheme 1

To estimate the reactivity of 5-nitro-2-furylvinylating agents in reactions with amines the kinetics of reactions of (E)-[β-(5-nitro-2-furyl)vinyl]trimethylam- monium bromide (I), (E)-2-(β-bromovinyl)-5-nitrofuran (II), and 2-ethynyl-5- -nitrofuran (III) with piperidine (Scheme 1) was investigated in various solvents at 25 °C*. The second-order rate constants (first-order for each of the reactants) of the processes under consideration are given in Tables 1 and 2. As follows from the above-presented data and also from those obtained already earlier [7] 5-nitro-2-furylvinylation of amines proceeds most advantageously in high polar aprotic solvents as dimethylformamide, hexamethylphosphorotriamide, di- methyl sulfoxide, and acetonitrile (Table 2).

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* Preparation of the necessary reactants [3, 5, 6] and solvents [7, 8] as well as taking kinetic measurements [7, 9] has been carried out by known methods.
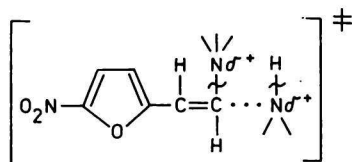
Table 1

Numerical values of rate constants ($10^4 . k/(\mathrm{dm^3\,mol^{-1}\,s^{-1}})$) of 5-nitro-2-furylvinylation of piperidine by compounds *I—III* in various solvents at 25 °C

Solvent	*I*	*II*	*III*
Acetonitrile	6.37 ± 0.07	329 ± 3	166 ± 4
Dimethylformamide	3030 ± 30	1090 ± 20	434 ± 6
Methanol	46.3 ± 1.6	79.0 ± 4.7	5.82 [9]
2-Propanol	11.4 ± 0.3	62.3 ± 1.1	9.63 ± 0.17

As found (Table 1), furylvinyltrialkylammonium salts are rather effective furylvinylating agents but they actually do not excel the corresponding vinyl halides and ethynylfurans in their reactivity as expected in [3].

We believe that the reason for this phenomenon lies in different manifestations of medium solvation effects in reactions *A*, *B*, and *C* (Scheme 1) proceeding differently by their transition states nature. Thus, in reactions of 2-ethynyl-5-nitrofuran and 2-(*β*-halovinyl)-5-nitrofurans with amines the transition state is more polar than the original reactants [7, 12]. Yet in the reaction with the participation of furylvinyltrialkylammonium salt both the original and the transition states are similarly charged; however, in the transition state the positive charge is delocalized.

So the solvent nature may exert significant influence on the correlation of the rate constants of the above-mentioned processes, which is clearly illustrated by the data of dimethylformamide and acetonitrile (Table 1). Thus, for example, in acetonitrile interacting with the reaction participants predominantly according to the nonspecific solvation mechanism, due to the reasons mentioned above, a high ε_r will promote the acceleration of piperidine reactions with 2-(*β*-bromovinyl)-5-nitrofuran and 2-ethynyl-5-nitrofuran and impede the reaction with the participation of 5-nitro-2-furylvinyltrimethylammonium bromide. This will result in 25—50 times lower rate of the last reaction compared to the rates of reactions *B—C*. In dimethylformamide which is similar in polarity to acetonitrile but interacts with the reactants and the transition state by both mechanisms

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Table 2

Rate constants of the reaction of 5-nitro-2-furylvinyltrimethylammonium bromide with piperidine in various solvents at 25 °C

No.	Solvent	ε_r (20 °C) [10]	D [11]	$10^4 \cdot k/(dm^3 \, mol^{-1} \, s^{-1})$
1	Tetrachloromethane	2.238	—	30.1 ± 1.7
2	Chloroform	4.806	—	27.9 ± 5
3	Dichloromethane	9.08	—	24.4 ± 2
4	1,2-Dichloroethane	10.36	—	51.4 ± 9
5	Chlorobenzene + acetonitrile (volume ratio $\varphi' = 4:1$)	11.63*	—	108.1 ± 13
6	Chlorobenzene + acetonitrile (volume ratio $\varphi' = 2:1$)	15.14*	—	62.8 ± 1.3
7	Chlorobenzene + acetonitrile (volume ratio $\varphi' = 1:1$)	20.50*	—	13.6 ± 0.3
8	Nitrobenzene	34.82	4.4	9.95 ± 0.23
9	Acetonitrile	37.50	14.1	6.37 ± 0.07
10	Acetone	20.74	17.0	55.5 ± 1.6
11	Tetrahydrofuran	7.39	20.0	116.0 ± 2
12	Dimethyl sulfoxide	48.90	29.8	76.7 ± 2.3
13	Dimethylformamide	36.70	30.9	3030.0 ± 30
14	Hexamethylphosphorotriamide	29.6	38.8	1050.0 ± 60
15	2-Propanol	18.3	—	11.4 ± 0.3
16	Methanol	32.65	—	46.3 ± 1.6

* As determined in [7].

of nonspecific and specific solvations, the accelerating effect of the specific solvation is more strongly manifested for the reaction of a furylvinylammonium salt (in a dipolar solvent the transition state is stabilized better than the original state). In the result, compound I in dimethylformamide will be a more reactive furylvinylating agent than the corresponding halovinyl and acetylene derivatives (Table 1).

It has been of interest to qualitatively estimate the influence of the medium polar characteristics on the rate of interaction of *trans*-5-nitro-2-furylvinyl-trimethylammonium bromide with piperidine as far as such data enable one to make definite conclusions on the nature of the transition state [13]. As it can be seen from the data on their influence over the rate of the above process given in Table 2, the solvents interacting with the reaction participants by a nonspecific solvation mechanism (No. *1* to *9*, Table 2) may be divided into two groups. In low polar mildly solvating media ($\varepsilon_r \le 10$, No. *1* to *4*, Table 2) the reaction rate constants in fact hardly differ within the experimental error. In the other group of solvents ($\varepsilon_r > 10$, No. *5* to *9*, Table 2) the rate constants noticeably decrease with the increase of medium polarity. The observed differences in the influence of these two groups of solvents on the reaction rate are caused, from our point of view, by the following reasons. In the low polar mildly solvating media furylvinyltrialkylammonium salt I is apparently present in the form of ion pairs. Relative permittivity rising the extent of dissociation of ion pairs into free ions increases with the nature of the solvent, and for high polar ones as *e.g.* acetonitrile by analogy with other quaternary ammonium salts [14] one should actually expect complete dissociation of the furylvinyltrialkylammonium salts into ions. Free ions are, however, more solvated than the ion pairs. That is why with medium polarity rising solvation is to decrease the ion reactivity as molecules of the reactant and the solvent will compete for the coordinating ion shell [11]. On the other hand, the comparison of the obtained data with the polarity of the solvents shows that in the narrow range of changing relative permittivities (from 11.63 for the mixture chlorobenzene + acetonitrile (volume ratio $\varphi' = 4:1$) up to 37.4 in acetonitrile) they follow the equation

$$\log\{k\} = \log\{k_0\} + yY \qquad (1)$$

where k and k_0 are the process rate constants in the medium with the relative permittivity ε_r and in the gaseous phase ($\varepsilon_r = 1$), respectively, $Y = (\varepsilon_r - 1)/(2\varepsilon_r + 1)$, and y is the reaction sensitivity to medium polarity depending on differences in the polarity of the transition state and of the reactants.

For the reaction under consideration (by the data in Table 2, No. *5* to *9*) eqn (2) is transformed as follows

$$\log\{k\} = (10.7 \pm 2.0) - (28.7 \pm 4.3)Y$$
$$(s = 0.15, r = 0.968) \qquad (2)$$

Low negative value of the coefficient y (28.7 ± 4.3) indicates that the transition state polarity in the reaction under investigation is considerably lower at this point than the total polarity of the original reactants. Accordingly, with rising medium polarity the transition state must be stabilized less than the reactants. This is the reason why the transition state will be shifting to the side of the final products of the reaction, *i.e.* it will become more product-like. A shift of this kind must be accompanied by a relative increase in the transition state Gibbs energy [15] and, therefore, by the decrease in the reaction rate which we have observed (Table 2).

Thus, the observed nature of varying the furylvinyltrimethylammonium bromide *I* reactivity in low polar and polar media has been brought about both by the different solvation extent of the original substrate in the form of different aggregates (ion pairs and ions), and by the variation of the transition state solvation in the process under investigation with the solvents changing.

The data on the effect of the specifically solvating solvents for the reaction rate of 5-nitrofurylvinyltrimethylammonium bromide with piperidine (Table 2, No. *10* to *16*) indicate that in the process under investigation an important part is also played by the effects due to the specific interactions of reacting molecules with the solvent and to the nonspecific solvation. The latter is manifested, for instance, by the fact that the reaction rate in tetrahydrofuran is noticeably higher than in dichloromethane which resembles it by its polarity (*cf.* No. *3* and *11*, Table 2). The rates in the solvents such as methanol, dimethylformamide, and acetonitrile which are practically equal by their polarities, also considerably differ (No. *16*, *13*, and *9*, Table 2).

In aprotic dipolar solvents in which the solvating effect is determined first and foremost by their ability to form donor-acceptor complexes (electron-donating ability) transition state with the delocalized positive charge will be better stabilized than the original state in which the charge is concentrated. Therefore, the reactivity of furylvinyltrimethylammonium salt in them is maximal and varies generally symbatically with the variation of Gutman donor number of the solvent (Table 2).

In alcohols, *i.e.* hard proton solvents, the transition state stabilization will be poorer than in mild dipolar solvents; they will also better solvate the original state, whilst the reaction rate noticeably slows down in them (*cf.* No. *15*, *16*, and *10* to *14*, Table 2).

We have tried to quantify the impact of all solvent effects on the rate of interaction of 5-nitrofurylvinyltrimethylammonium bromide with piperidine using the Koppel—Palm equation [6]

$$\log\{k\} = \log\{k_0\} + yY + pP + eE + bB \qquad (3)$$

where Y, P, E, and B are constants characterizing the polarity, polarizability, electrophility, and nucleophility of the solvent, respectively, and y, p, e, and b denote the sensitivity of the reaction to these effects.

Processing of the obtained data (except the rate constants in binary solvents, for which there is no complete set of constants Y, P, E, and B) by eqn (3) leads to the following result

$$\log\{k\} = -(2.28 \pm 1.68) - (3.10 \pm 2.22)Y + (1.89 \pm 4.44)P + $$
$$+ (0.0024 \pm 0.0045)E + (0.0036 \pm 0.0010)B \qquad (4)$$
$$n = 14, \quad s = 0.67, \quad r = 0.691$$

The fact that there is no correlational dependence of type (3) is accounted for, as it has been mentioned above, by different structures of the original and the transition states in polar and nonpolar media. Though there is no said correlation for the total set of the solvents under investigation (see statistic indices of eqn (4)) still it is fulfilled quite satisfactorily for the set of solvents mostly with low ε_r in which transition complexes are apparently of similar structure

$$\log\{k\} = -(0.774 \pm 0.476) - (1.75 \pm 0.65)Y - (3.58 \pm 1.36)P - $$
$$- (0.015 \pm 0.012)E + (0.00238 \pm 0.00039)B \qquad (5)$$
$$n = 8 \ (\text{No. } 1\text{—}4, \ 8, \ 10\text{—}12, \ \text{Table 2}), \ s = 0.11, \ r = 0.976$$

The analysis of the coefficients obtained shows that the conclusions derivable from them completely correspond to those expounded above on the basis of comparing the rates of the reactions A, B, and C in solvents of various nature and quantitative regularities of medium polarity influence on the rate of interaction of furylvinyltrimethylammonium bromide with piperidine (see eqn (3)). Thus, the increase in medium polarity slows down the process rate (the value y is negative). The same refers to the polarizability effect ($\varrho = -3.58 \pm 1.36$), yet nucleophilic solvation accelerates the process ($b > 0$). It is difficult to make any definite conclusions concerning the influence of electrophilic solvation due to a great error ($\approx 100\ \%$) in determining the coefficient e. The fact that the influence of polarity here is relatively poor ($b = -1.75 \pm 0.65$), though it is very strong in polar media (cf. with $y = -28.7 \pm 4.3$ in eqn (2)), is also compatible with the assumption that the quaternary furylvinyltrialkylammonium salt is considerably dissociated in media with a high ε_r.

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