

KINETICS OF REACTION OF 4-SUBSTITUTED 2-NITROFLUOROBENZENES WITH PIPERIDINE IN BENZENE-ACETONITRILE MIXTURES

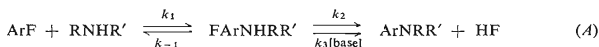
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The rate of the nucleophilic substitution reaction studied increases with polarity of medium. In accord with decreasing polarity of the respective activated complexes, the base-catalyzed decomposition of the intermediate into products is most accelerated and the formation of the intermediate is least accelerated. The values of the Hammett constants ρ of the individual steps depend on the change of the energy of the intramolecular hydrogen bond in the respective activated complexes. Water retards the formation of the intermediate by solvation of piperidine.

Nucleophilic substitution reaction of the activated aryl fluorides by primary and secondary amines takes the following course (Scheme (A)) and the rate is given by Eq. (1), where k' is given by Eq. (2).



$$v = k'[\text{ArF}][\text{RNHR}'] \quad (1)$$

$$k' = k_1(k_2 + k_3[\text{RNHR}'])/(k_{-1} + k_2 + k_3[\text{RNHR}']) \quad (2)$$

If $(k_2 + k_3[\text{RNHR}']) \gg k_{-1}$, then

$$k' = k_1 \quad (3)$$

and the formation of the intermediate is rate-limiting. At a sufficiently low amine concentration the expression $k_3[\text{RNHR}']$ becomes negligible as compared with the value k_2 , and k' is given by Eq. (4).

$$k' = k_1 k_2 / (k_{-1} + k_2) \quad (4)$$

In polar protic media facilitating the C—F bond cleavage the k_2 value increases to such an extent, that $k_2 \gg k_{-1}$. Thereby the expression (4) is simplified to Eq. (3) which expresses that the formation of the intermediate is rate-limiting. In contrast to it in aprotic less polar media, the value k_2 decreases to such an extent, that Eq. (5) holds for k' at small amine concentrations.

$$k' = k_1 k_2 / k_{-1} \quad (5)$$

This equation expresses a mechanism of nucleophilic aromatic substitution with antecedent equilibrium leading to formation of intermediate and its subsequent rate-limiting decomposition into products. With increasing amine concentration, an amine-catalyzed decomposition of the intermediate into products can make itself felt kinetically. The value k' is then defined by Eq. (6) derived from Eq. (2) under the assumption that $k_{-1} \gg (k_2 + k_3[\text{RNHR}'])$.

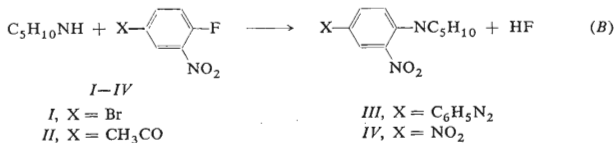
$$k' = k_1 k_2 / k_{-1} + k_1 k_3 [\text{RNHR}'] / k_{-1} \quad (6)$$

At a sufficiently high amine concentration^{1,2} the rate of decomposition of the intermediate into products becomes comparable with that of its reverse decomposition into starting substances, and the dependence of k' on the base concentration ceases to be linear. Further increasing of the amine concentration results in such an increase of the rate of the amine-catalyzed decomposition of the intermediate into products, that the reverse decomposition becomes practically negligible, and the formation of the intermediate is again rate-limiting (Eq. (3)).

In our previous works^{3,4} we studied the kinetics of the reactions of 2,4-dinitrofluorobenzene with substituted anilines and N-methylanilines in methanol and acetonitrile media. In the case of 2,4-dinitrofluorobenzene and aniline in methanol, the formation of the intermediate was rate-limiting. In the aprotic acetonitrile the reaction was base-catalyzed, the dependence of k' on the concentration was not linear in the whole concentration range studied, and it followed Eq. (2).

In the case of the reaction of 2,4-dinitrofluorobenzene with N-methylaniline (secondary amine), the non-catalyzed decomposition of the intermediate into products was rate-limiting in the both media. This unexpected reaction course was explained by a formation of a hydrogen bond between the hydrogen atom of the secondary amine and *o*-nitro group in the intermediate. The base-catalyzed decomposition of the intermediate necessitates splitting of the hydrogen bond, which makes this step inasmuch unfavourable energetically, that it does not practically make itself felt.

In order that we might ascertain the influence of solvent and of substitution in position 4 of the substrate on the reaction rate values (and, hence, on the reaction mechanism, too), we have studied the reaction of 4-substituted 2-nitrofluorobenzenes I–IV with piperidine (B).



In the case of piperidine problem of the formation and cleavage of the hydrogen bond in the intermediate is the same as in the case of N-methylaniline. As piperidine is both a much stronger base and nucleophile than N-methylaniline, the relative importance of the reverse reaction (k_{-1}) is decreased, and the probability of base catalysis is

increased. The reaction (B) was studied in methanol⁵, and it was found that the formation of the intermediate is rate-limiting. Therefore, we have chosen acetonitrile and benzene resp. their mixtures for the reaction media. Besides a base catalysis we also expected that Eq. (6) would hold in an increasingly broader concentration range of the base with decreasing polarity of medium.

EXPERIMENTAL

2-Nitro-4-bromofluorobenzene (*I*) was prepared by thermal decomposition of 2-nitro-4-bromobenzenediazonium fluoroborate. The product was purified on an alumina column (Brockmann *II*; benzene elution) and vacuum distilled. Yield 20%, m.p. 17.5–19°C (ref.⁵). 3-Nitro-4-fluoroacetophenone (*II*) was prepared similarly with a 40% yield, m.p. 49–50°C (ref.⁵). 3-Nitro-4-fluoroazobenzene (*III*) was prepared by condensation of nitrosobenzene and 3-nitro-4-fluoroaniline in acetic acid medium according to a procedure described for the respective chloro derivative⁶; m.p. 135–136°C (ref.⁷ gives 136°C). 2,4-Dinitrofluorobenzene (*IV*) p.a. (Lachema, Brno) was distilled at the b.p. 151°C/8 Torr. Piperidine (p.a.) and acetonitrile (Apolda and Sojuzchimexport, Moscow) were purified as in our previous works^{6,3,4}. Benzene p.a. (Lachema, Brno) was dried over sodium and distilled.

Kinetic measurements. The kinetics was followed by measuring the concentration increase of the coloured N-phenylpiperidine derivative formed with the use of a spectrophotometer VSU-2P (Zeiss, Jena). The reaction solutions were placed in the cells thermostated at $20 \pm 0.2^\circ\text{C}$. The rate constant k was calculated graphically from Eq. (7)

$$kt = -2.3 \log (E_\infty - E_t) + \text{const.} \quad (7)$$

where E_t and E_∞ are the extinctions at a time t and $t = \infty$ (six half-lives), respectively.

RESULTS

The reaction (B) studied proceeded quantitatively in all the media, and no side products were found. The reaction was 1. order in the fluoro derivative *I–IV* and took a pseudomonomolecular course when the excess of piperidine was sufficient. The bimolecular rate constant k' obtained from the experimental rate constant k through dividing by the piperidine concentration (Eq. (7)) was plotted against the amine concentration (for a given derivative *I–IV* and given solvent).

In the benzene medium the values k' increased up to the highest piperidine concentration used (Fig. 1). In the region of the lowest amine concentrations this dependence was almost linear. Therefrom the values k_1k_2/k_{-1} and k_1k_3/k_{-1} were obtained by application of Eq. (6) (Table I). In the case of the fluoro derivatives *III* and *IV* the dependence of k' on the piperidine concentration was studied within a sufficient concentration range (Fig. 1), and the constant k_1 could be determined graphically from the Eq. (8) obtained by modification of Eq. (2)

$$((k_2/k_3) + [\text{RNHR}'])/k' = (k_{-1} + k_2)/k_1k_3 + [\text{RNHR}']/k_1. \quad (8)$$

TABLE I
Rate Constants Values ($l \text{ mol}^{-1} \text{ s}^{-1}$) of Reaction (B) in Benzene-Acetonitrile Mixture at 20°C

Fluoro derivative	By vol.% acetonitrile in benzene	$10^2 k_1$	$\frac{k_1 k_2}{k_{-1} + k_2}$	$\frac{10^2 k_1 k_2}{k_{-1}}$	$\frac{10^{-2} k_1 k_3}{k_{-1} + k_2}$	$\frac{10^{-2} k_1 k_3}{k_{-1}}$
<i>I</i>	50	3.75 ± 0.05	—	—	—	—
	25	2.50 ± 0.05	—	—	—	—
	0	—	—	0.35 ± 0.01	—	$10^{-4} \pm 3 \cdot 10^{-5}$
<i>II</i>	50	190 ± 5	1.5 ± 0.3	710 ± 50	7 ± 4	33 ± 18
	25	115 ± 5	0.8 ± 0.2	260 ± 30	4 ± 1	13 ± 5
	0	—	—	8.7 ± 0.2	—	0.08 ± 0.005
<i>III</i>	50	127 ± 3	0.8 ± 0.2	220 ± 40	11 ± 3	30 ± 13
	25	75 ± 3	0.4 ± 0.1	110 ± 20	4 ± 1.5	10 ± 4
	0	65 ± 2	—	3.7 ± 0.1	—	0.025 ± 0.002
<i>IV</i>	100	10 000	—	—	—	—
	50	$7\ 600 \pm 200$	42 ± 7	$9\ 400 \pm 1\ 500$	700 ± 200	$2\ 700 \pm 1\ 400$
	25	$5\ 300 \pm 200$	13 ± 5	$1\ 550 \pm 600$	800 ± 300	$1\ 030 \pm 500$
	0	$1\ 200 \pm 50$	—	125 ± 5	—	8 ± 0.3

TABLE II
Relative Values of Rate Constants of Reaction (B) in Benzene-Acetonitrile Mixture at 20°C^a

Fluoro derivative	By vol.% acetonitrile in benzene	k_3/k_2	k_{1rel}^b	k_{2rel}^b	k_{3rel}
<i>I</i>	50	—	1.5	—	—
	25	—	1.0	—	—
	0	3.0	—	—	—
<i>II</i>	50	470	1.65	82	430
	25	500	1	30	169
	0	88	—	1	1
<i>III</i>	50	1 350	2.0	57	1 200
	25	900	1.2	30	400
	0	66	1	1	1
<i>IV</i>	50	3 000	6.3	75	340
	25	6 000	4.4	12.4	130
	0	640	1	1	1

^a Experimental errors: in mixed solvents up to $\pm 50\%$, in benzene $\pm 5\%$ except for the derivative *I* ($\pm 30\%$). ^b The relative values of k for derivatives *I* and *II* are related to 25% acetonitrile.

The value k' was independent of the piperidine concentration and corresponded to k_1 for all the derivatives *I–IV* in benzene solutions containing 25 and 50% (by vol.) acetonitrile at the piperidine concentrations higher than $2\text{--}3 \cdot 10^{-3}$ mol/l (Table I). A greater decrease of k' was encountered first at the piperidine concentrations lower than 10^{-3} mol/l. Extrapolation of the k' values to zero concentration of piperidine gave the rate constants of the non-catalyzed reactions of the derivatives *II–IV*, and from the angular coefficient of the extrapolated curve at this concentration the rate constants of amine-catalyzed reaction could be determined. With respect to the fact that the extrapolation was not linear and the last experimental points were obtained at very low piperidine concentrations ($5 \cdot 10^{-5}$ mol/l), the values of the rate constants obtained in the abovementioned way are subject to a considerable experimental error (up to $\pm 50\%$). In the case of the bromo derivative *I* at the piperidine concentrations lower than 10^{-3} mol/l, the reaction rates were so small, that it was impossible to obtain reliable experimental values k' for extrapolation.

The values of the non-catalyzed reaction determined from the intercept at the y-axis are maximum four times smaller than the corresponding k_1 values. Therefrom it follows that the rate constants of the decomposition of the intermediate in the both directions (k_{-1} , k_2) are comparable and Eq. (4) holds for k' . These rate constants were multiplied by the expression $k_1/(k_1 - k_1k_2/(k_{-1} + k_2))$, and thus the

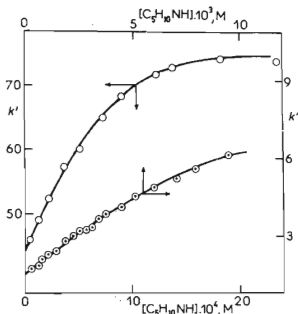


FIG. 1
Dependence of Rate Constant Values k' ($l \text{ mol}^{-1} \text{ s}^{-1}$) on Piperidine Concentration for Reaction of Fluoro Derivative *IV* in Benzene (\odot) and Benzene–Acetonitrile Mixture 1 : 1 (\square)

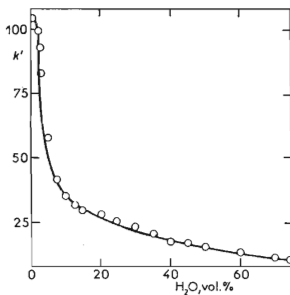


FIG. 2
Rate Constant Values k' ($l \text{ mol}^{-1} \text{ s}^{-1}$) of Reaction (*B*) of Fluoro Derivative *IV* in Acetonitrile–Water Medium

constants defined by Eq. (5) were determined. In the same way the experimentally obtained values for the base-catalyzed reaction were computed, too (Table I).

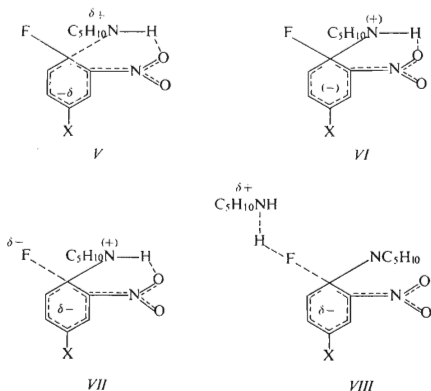
The influence of the added water on the reaction of the dinitroderivative *IV* with piperidine was studied in the medium of pure acetonitrile (Fig. 2). Such a piperidine concentration was chosen ($1.65 \cdot 10^{-3}$ mol/l), that the reaction rate was not too high and, at the same time, k' did not depend on it.

DISCUSSION

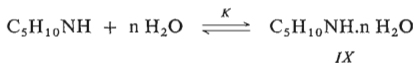
Influence of polarity of medium on reaction rate and mechanism. The structure of the activated complex *V* (leading to the intermediate *VI*) and those of the activated complexes *VII* and *VIII* (for non-catalyzed and amine-catalyzed reaction (*B*)) differ in the polarities, the order being $V < VI < VII < VIII$. Stability of the individual complexes and, hence, the values of rate constants k_1 , k_1k_2/k_{-1} and k_1k_3/k_{-1} increase with increasing polarity of medium in the same order, too (Table I). In accord to this, the relative values k_1 , k_2 (when going from benzene to benzene-acetonitrile mixture 1 : 1) and k_3 increase in this order (Table II). These changes are the same, within experimental error, for all the fluoro derivatives *I-IV*. As the change of the medium from benzene to benzene-acetonitrile mixture causes a many times greater increase in k_3 than in k_1 , the constant value of k' (Eq. (3)) is attained in the mixed solvent at a far lower piperidine concentration than in benzene (Fig. 1). As the polarity of the intermediate *VI* is greater than that of the activated complex *V*, the value of the rate constant k_{-1} decreases (with increasing polarity) and becomes comparable with the value k_2 . Therefore, the rate constants k' determined for the non-catalyzed reaction in the mixed solvent are defined by Eq. (4). (The same applies for the catalyzed reaction, too; Table I).

Influence of substituents on values of rate constants. The values of the rate constants of the reaction (*B*) studied increase with the increasing electron-attracting ability of substituents (expressed quantitatively by the values of the Hammett σ_p^- constants^{5,8}). Correlation of logarithms of the rate constants k_1 , k_1k_2/k_{-1} and k_1k_3/k_{-1} with these σ constants gave the following values of the reaction constants ρ : 3 to 3.5, about 2.5 and 4.5 to 5 respectively. We suppose that the energy of the hydrogen bond to the oxygen atom of *o*-nitro group in individual activated complexes, *V*, *VII* and *VIII* has a decisive influence on these differences in ρ values. The stronger the hydrogen bond is, the more it stabilizes the activated complex and, hence, increases the value of the rate constant. An increasing value of σ_p^- increases the partial negative charge on the substituent and, thereby, the strength of the hydrogen bond decreases⁹. This effect acts against the main activating effect of the substituent and thus decreases the value of ρ constant. This influence is most important in the non-catalyzed decomposition of the intermediate where there is the strongest hydro-

gen bond in the respective activated complex *VII*. As the hydrogen bond is only just being formed in the complex *V*, the influence of substituents is smaller. In the complex *VIII* there is no hydrogen bond to *o*-nitro group, so that the antagonistic effects of substituents diminishing the ρ value do not make themselves felt at all. Besides in the calculated ρ values, this influence can be observed directly in the ratio of the rate constants k_3/k_2 (Table II). The increase of this ratio with increasing polarity of the medium is caused by the abovementioned influence on stability of the activated complexes *VII* and *VIII*.



Influence of water concentration on overall reaction rate. We have studied the influence of water on the reaction rate using dinitro derivative *IV* and such a concentration of piperidine that k' equalled k_1 . It was found with the benzene-acetonitrile mixture that the influence of polarity of medium on the k_1 value is comparatively small. From the k_1 values measured (Table I) and $k_1 = 1 \cdot 10^2 \text{ l mol}^{-1} \text{ s}^{-1}$ (in pure acetonitrile) we can estimate the increase of the k_1 value (due to the polarity increase caused by water addition) to be maximum two fold. Water, as a protic oxygen-containing solvent, can act both as a donor and as an acceptor of hydrogen bonds and, thereby, affect the reaction rate, too. From Fig. 2 it follows that the presence of water causes a considerable decrease of the reaction rate (by about 1 order of magnitude). The shape of the curve in this picture can be explained as follows: there is a reversible reaction between piperidine and water which is defined by the equilibrium constant K (Eq. (9)). There is a relation (Eq. (10)) between the rate constant k'_1 found in acetonitrile-water mixture and k_1 found in pure acetonitrile.



$$K = [\text{C}_5\text{H}_{10}\text{NH}\cdot n \text{H}_2\text{O}]/[\text{C}_5\text{H}_{10}\text{NH}][\text{H}_2\text{O}]^n \quad (9)$$

$$k'_1 = k_1[\text{C}_5\text{H}_{10}\text{NH}]/([\text{C}_5\text{H}_{10}\text{NH}] + [\text{IX}]) = k_1/(1 + K[\text{H}_2\text{O}]^n) \quad (10)$$

Eq. (10) does not involve the influence of the change of polarity of medium on k'_1 , because from the results it follows that it is smaller than the influence of the piperidine solvation by about one order of magnitude. At low water concentrations the expression $K[\text{H}_2\text{O}]^n$ is smaller than unity, and k'_1 decreases more slowly than the water concentration increases. At higher water concentrations $K[\text{H}_2\text{O}]^n > 1$, and k'_1 becomes inversely proportional to $[\text{H}_2\text{O}]^n$. A steady decrease of k'_1 stands in accord with the theoretical presumption that the non-hydrated piperidine is the only reacting nucleophile. The number n of solvating water molecules was determined graphically from Eq. (11) obtained by modification of Eqs (9) and (10).

$$\log (1/k'_1 - 1/k_1) = \log (K/k_1) + n \log [\text{H}_2\text{O}] \quad (11)$$

The dependence is practically linear (the greatest deviations being encountered at the lowest water concentrations) with the slope $n = 0.8 \pm 0.1$. Therefrom it follows that a piperidine molecule is solvated by one water molecule.

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