KINETICS AND MECHANISM OF REACTION OF 2-ANILINO-4,6-DICHLORO- AND -DIFLUORO-1,3,5-TRIAZINE WITH SUBSTITUTED ANILINES

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The title reaction has been studied in methanol, acetone and acetonitril media. The influences of substituents and solvents suggest that the rate-limiting step of the reaction of the fluoro derivative consists in decomposition of the intermediate, the structure of which is discussed.

Formation of the intermediate is the rate-limiting step of the reaction of chloronitrobenzenes with aniline and N-methylaniline, whereas decomposition of the intermediate is rate-limiting during the corresponding reactions of fluoronitrobenzenes (in aprotic and slightly polar solvents)[1]. The occurence of base catalysis is considered to be the main piece of evidence for the decomposition of the intermediate being the rate-limiting step[2]. However, this criterion sometimes fails, especially so in the case of *o*-nitrofluorobenzene derivatives[3-5]. In the activated complex the amino hydrogen is bound to the basic *o*-nitro group by a hydrogen bond, so that its transfer to an external base becomes unfavourable energetically, and it is not kinetically significant[4,5].

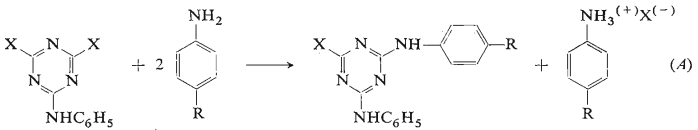
Nitrogen atoms of six-membered heterocycles facilitate an aromatic nucleophilic substitution to about the same extent as nitro groups. In contrast to nitro groups, however, these heteroatoms are much more basic and, therefore, the reactivity of heterocyclic halogeno derivatives is considerably increased in *e.g.* protic solvents, as the activated complex is stabilized by the bond being formed between proton and heterocyclic nitrogen atom[6,7]. The influence of this bond on the reaction course is rather similar to that of the abovementioned intramolecular hydrogen bond of an *o*-nitro derivative, and thus it cannot be excluded that the catalytic influence of the added bases will not make itself felt in the case of the heterocyclic fluoro derivatives, too.

In the present work we have studied the influence of medium and base concentration on the reactivity of 2-anilino-4,6-dichloro-1,3,5-triazine (*I*) and 2-anilino-4,6-difluoro-1,3,5-triazine (*II*). Its aim was to establish the rate-limiting step in the case of the fluoro derivative *II* and the occurence of base catalysis and to get some picture of the structure of the activated complexes from the study of the influence of medium.

RESULTS AND DISCUSSION

The kinetic experiments were carried out in methanol, acetone and acetonitril, using an excess of the halogeno derivative or aniline or a stoichiometric ratio of the both reactants (reaction (*A*). In all the cases the reaction was 1. order in either of the both

components and agreed with the stoichiometry of the reaction (*A*). The values of the bimolecular rate constants are given in Table I.



(*A*)

I, *II* *III*–*VI*

I, X = Cl
II, X = F

III, R = H
IV, R = CH_3O

V, R = CH_3
VI, R = Cl

From the kinetic experiments it follows that there is neither any general base catalysis (a higher order with respect to aniline) nor any acid autocatalysis during the reaction (*A*). The ratio of the rate constants k_F/k_{Cl} is within the limits 5 and 0·35, which suggests that the decomposition of the intermediate is rate-limiting in the case of the fluoro derivative *II* in all the three media. In the opposite case the fluoro derivative should react faster by at least two orders of magnitude. These results are similar to those of the reaction of 2,4-dinitrohalogenobenzenes (chloro-, fluoro-) with N-methylaniline in methanol and acetonitril. There also the second step was rate-limiting in the case of the fluoronitrobenzene ($k_F/k_{Cl}=1$ resp. 2) and no base catalysis was found[5]. This suggests that the amino hydrogen is bound to some of the nitrogen atoms of the ring in the activated complex so strongly that the catalytic effect of aniline does not make itself felt.

The reactions of both *I* and *II* are fastest in methanol. The influences of acetone

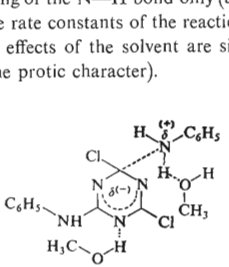
TABLE I

Values of Rate Constants k (l mol^{-1} min^{-1}) of Reaction (*A*) in Methanol, Acetone and Acetonitril at 20°C

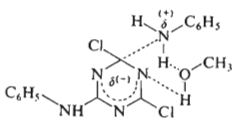
Aniline	k in methanol for	
	I	*II*
III	2·0 ± 0·2[a]	6·5 ± 0·5[b]
IV	7·0 ± 0·4	130 ± 5
V	6·0 ± 0·4	35 ± 2
VI	0·60 ± 0·02	0·68 ± 0·03

[a] Potentiometrically 2·4 ± 0·2 l mol^{-1} min^{-1}; in acetone 0·08 ± 0·01 l mol^{-1} min^{-1}; and in acetonitril 0·086 ± 0·01 l mol^{-1} min^{-1}; [b] potentiometrically 5 ± 1 l mol^{-1} min^{-1}; in acetone 1·05 ± 0·2 l mol^{-1} min^{-1}; and in acetonitril 0·031 ± 0·005 l mol^{-1} min^{-1}.

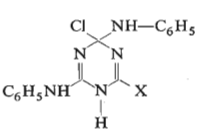
and acetonitril on the reaction rate are comparable in the case of the chloro derivative *I*, whereas the fluoro derivative *II* reacts 30 times more slowly in acetonitril than in acetone. The activated complex of the chloro derivative *I* (formula *A*) can be stabilized by a hydrogen bond to the basic atom of the solvent molecule[8] and also by formation of a hydrogen bond between the basic heteroatom and acid hydrogen atom of the solvent molecule. All the three solvents used have comparable dielectric constants and comparable molecular size. They differ only in their specific solvation effects, *i.e.* in their ability to form hydrogen bonds with protondonors and -acceptors. Methanol can form strong hydrogen bonds both with protondonors and -acceptors, aceton only can form them with protondonors, and acetonitril, which is a very weak base, forms only weak hydrogen bonds with protondonors. From the results in Table I it can be seen that the protic solvent had a great influence (a bond to heteroatom), whereas the basic character of the solvent did not make itself felt. In the case of methanol it is possible to consider even such a structure of activated complex *B*, where one methanol molecule acts both as an acid and base at the same time. On the basis of the results obtained until now and the structures of intermediates considered it can be presumed that the hydrogen atom is bound to one of the three nitrogen hetero atoms in the intermediate (*e.g.* the structure *C*). When the intermediate is transformed into products, both the C—X and N—H bonds of the heterocycle are split. Methanol, being both protic and basic solvent, facilitates the splitting of the both bonds (C—X, N—H) by formation of hydrogen bonds. Acetone, being a basic solvent, facilitates the splitting of the N—H bond only (acetonitril has similar but far weaker influence). From the rate constants of the reaction of the fluoro derivative II it is obvious that the both effects of the solvent are significant (the basicity effect being even stronger than the protic character).



A



B



C

The second activated complex is closer in its energy to the intermediate than to the final products, and hence also its structure will more resemble that of the intermediate[9]. It means that both the N—H bond splitting and the bond formation between hydrogen atom and base proceeded to a small extent only. In such a case the base concentration (not its strength expressed *e.g.* by its pK_a value) becomes decisive[8]. By other words it means that the value of the Brönsted coefficient β is small for this reaction. As the aniline concentration was lower than that of the solvent by several orders of magnitude in all the cases, the base catalysis of aniline did not make itself felt practically even in acetonitril.

An important contribution to mechanistic studies can often be made by investigation of the substituent effects on reaction rates expressed quantitatively by the Hammett reaction constant ϱ. In the case of aromatic nucleophilic substitution with rate-limiting formation of the intermediate the effect of a substituent acts till the moment of formation of the first activated complex, and the ϱ values of the reactions of substituted anilines and N-methylanilines are $-2{\cdot}5$ to -3 (ref.[10]). In the reaction of 2,4-dinitrofluorobenzene with the substituted N-methylanilines the decomposition of the intermediate is rate-limiting. A substituent having a positive (a negative) values of σ constant facilitates (hinders) both the formation of the intermediate and its decomposition into products, which results in a high negative value of ϱ constant ($-6{\cdot}5$ in the mentioned case[5]).

For the sake of verification of the reaction mechanism and the intermediate structures suggested we have studied the influence of substituents on the reaction rate and expressed it quantitatively by the Hammett equation. The ϱ value $-2{\cdot}5$ of the chloro derivative *I* corresponds to the reaction mechanism with rate-limiting formation of the intermediate. The decomposition of the intermediate is rate-limiting in the case of the reaction of the fluoro derivative *II*. However, in contrast to the reaction of 2,4-dinitrofluorobenzene with N-methylanilines, we suppose that the amino hydrogen atom is transferred to heterocyclic nitrogen atom (structure *C*) during formation of the intermediate. The influence of substituents on this reaction step is, however, opposite to their influence on the bond formation between the nucleophile and the substrate and on the C—F bond splitting. The ϱ value of this reaction step would probably be within $+2$ and $+3$. If the ϱ value found for the reaction of N-methylanilines with 2,4-dinitrofluorobenzene[5] ($-6{\cdot}5$), is used in our case for addition of the nucleophile and F—C bond splitting, the overall ϱ value of this reaction would be $-3{\cdot}5$ to $-4{\cdot}5$. This agree with the experimental ϱ value $-4{\cdot}2$ of the reaction of the fluoro derivative *II*.

EXPERIMENTAL

2-Anilino-4,6-dichloro-1,3,5-triazine (*I*) was prepared from aniline and cyanuric chloride by a method described previously[11]. 2-Anilino-4,6-difluoro-1,3,5-triazine (*II*) was prepared from aniline and cyanuric fluoride in diethyl ether medium[12]. Aniline (*III*) and its 4-substituted derivatives *IV*—*VI* were commercial samples and were purified by crystallization or distillation. Methanol, acetone and acetonitril (p.a. chemicals Lachema, Brno) were dried[4] and distilled.

Kinetic measurements. The reaction was followed by measuring the concentration change of aniline photometrically after its transformation into the respective Schif's base with 4-dimethylaminobenzaldehyde[11]. Further, the concentration of chloride and fluoride ions was measured potentiometrically in methanol, using a selective chloride ion electrode Crytur type 17—17 resp. fluoride electrode type 09—17 and a reference calomel electrode Radiometer type K 401. The potential was measured by means of a Precision pH-meter OP 205 apparatus (Radelkis). The apparatus was calibrated with the 10^{-1}—10^{-6} mol/l solutions of potassium chloride resp. fluoride. The calibration was checked during kinetic measurements. The electrodes maintained stable potential in the course of one month. Bimolecular rate constants (Table I) were calculated from the reaction half-lives, measured in the cases where there was at least a tenfold excess of one of the reactants, or from Eq. (*1*) (in experiments using stoichiometric ratio of the reactants)

$$2kt = (1/(a - x)) - 1/a \qquad (1)$$

where a stands for the initial concentration of the halogenotriazine *I* or *II*, which was always half that of aniline *III*—*VI*; x is the decrease of the halogeno derivative at a time t, and k is the rate constant to be found.

REFERENCES

1. Pietra F.: Quart. Rev. *23*, 504 (1969).
2. Bunnet J. F., Garst R. H.: J. Am. Chem. Soc. *87*, 3879 (1965).
3. Pietra F., Del Cima F.: Tetrahedron Letters *46*, 4573 (1967).
4. Kaválek J., Haasová J., Štěrba V.: This Journal *37*, 3333 (1972).
5. Kaválek J., Kubias J., Štěrba V.: This Journal, *37*, 4041 (1972).
6. Illuminati G., Sleiter G., Speranza M.: J. Org. Chem. *36*, 1723 (1971).
7. Illuminati G., Marino G., Sleiter G.: J. Am. Chem. Soc. *89*, 3510 (1967).
8. Ross S. D.: Tetrahedron *25*, 4427 (1969).
9. Hammond G. S.: J. Am. Chem. Soc. *77*, 334 (1955).
10. Miller J.: *Nucleophilic Aromatic Substitution.* Elsevier, New York 1968.
11. Tran Minh Chinh, Kaválek J., Večeřa M.: This Journal *37*, 832 (1972).
12. Tran Minh Chinh, Kaválek J., Večeřa M.: This Journal *37*, 3328 (1972).

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