KINETICS AND MECHANISM OF NUCLEOPHILIC HALOGEN EXCHANGE IN FURAN DERIVATIVES

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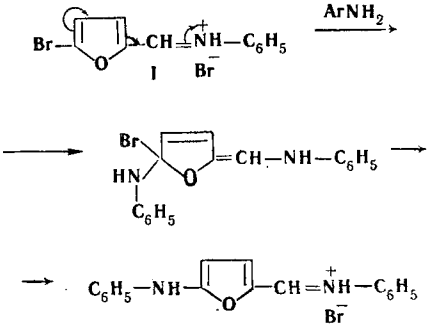
Studies are made of the reaction of 5-bromofurfurylidenaniline with aromatic amines (reaction 1), of the disproportionation of 5-bromofurfurylidenaniline (reaction 2), and of the reaction of 5-bromofurfurylidenaniline and 5-bromofurfural with saturated secondary amines (reaction 3). It is shown that these reactions are of the autocatalytic type (the catalyst being a reaction product, the hydrobromide of the amine), that addition of acid accelerates them, while they are retarded by addition of alkali. The hypothesis is advanced that in these reactions the active form of the substrate is the salt containing the fragment $\rangle C{=}\overset{+}{N}\langle$. The latter arises by protonation of the Schiff's base (reactions 1 and 2), or by quaternization of aminoacetals (which are products formed by addition of a secondary amine across the (double) bonds in $\rangle C{=}O$ or $\rangle C{=}N{-}$) through the action of the hydrohalide salt of the amine (reaction 3).

There are a large number of papers [1–13] dealing with the possibility of exchanging halogen in furan derivatives for nucleophilic groups. However, the traditional views regarding nucleophilic exchange at an unsaturated carbon atom do not always explain the peculiar qualitative regularities observed when running these reactions for preparative purposes. Hence, we decided to investigate some reactions of that class kinetically.

It has been shown [11–13] that the halogen in 5-halogenofurfurylidenanilines (Schiff's bases) is readily replaced by an aromatic amino group, to give almost quantitative yields of 5-N-arylaminofurfurylidenarylamines. It is difficult to explain this phenomenon, if one considers only the relatively minor effects of the electronegativity of the group C=N— of the substrate and the basicity of the reagent. We investigated the kinetics of the reaction of 5-bromofurfurilidenaniline with aromatic amines (aniline, methylaniline), and found that it was of the autocatalytic type (Fig. 1a, 3), as indicated by the induction period and the concentration acceleration in the first phase of the reaction. If measured quantities of acid are added, the induction period disappears and the reaction rate increases (Fig. 1a, 1,2). On the other hand addition of alkali metal hydroxide inhibits the reaction (obviously the inappreciable separation of Br^- ion is connected with SN_2 with exchange of halogen for an alkoxy group, previously demonstrated [12]). From these results it can be concluded that a necessary condition for the above reaction to proceed is protonation of the C=N– group of the Schiff's base. A molecule of the reagent attacks the mesocation at position 5 in the furan ring, followed by separation of halogen as an anion. The hydrogen halide functions as a protonating agent, being distributed at the moment of formation between all the bases in the reaction mixture in proportion to their pKs.



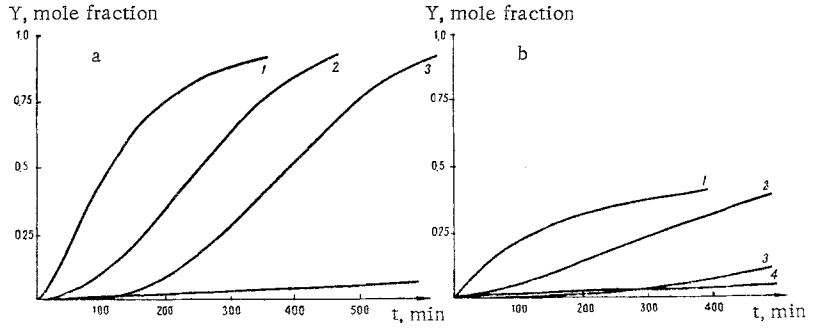


Fig. 1. Reaction kinetics: a) reaction of V with methylaniline; b) disproportionation of V for various starting concentrations of the hydrobromides of the relevant bases: 1) $c_{Br} = 0.02$ M; 2) 0.004 M; 3) traces of Br^-, undetectable analytically; 4) the same in the presence of KOH, c = 0.05 M (Y—reaction product yield).

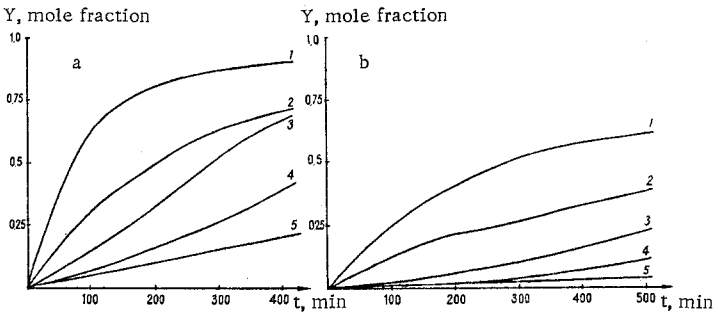
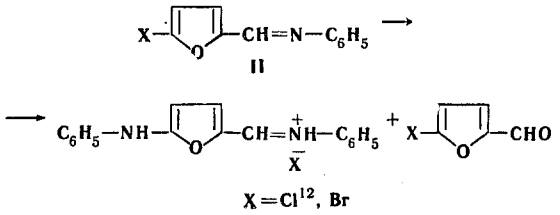


Fig. 2. Kinetics of the reaction of: a) 5-bromofurfural; b) V, with secondary amines for various initial concentrations of the hydrobromides of the respective amines: 1) Dimethylamine, $c_{Br} = 0.05$ M; 2) piperidine, $c_{Br} = 0.05$ M; 3) dimethylamine, traces of Br^- analytically undetectable; 4) piperidine, traces of Br^- not detectable analytically; 5) the same in the presence of KOH, c = 0.05 M (Y—yield of reaction product).

Application of this reaction mechanism to the disproportionation of 5-halogenofurfurylidenanilines, which takes place readily in ethanol solution, and which was discovered in [12], gives

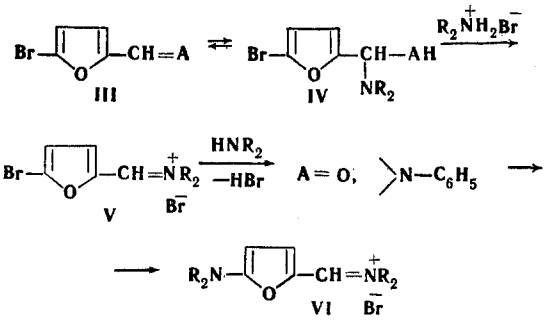


II

X=Cl[12], Br

We showed that this reaction is completely inhibited by alkali, and is accelerated by adding acid (Fig. 1b). Obviously the substrate in this particular nucleophilic reaction is the protonated form of the Schiff's base I, and the reactant is the amine formed by partial or complete alcoholysis of the group $\rangle C{=}N-$ of base II. It is important to note that furan Schiff's bases not containing halogen can react in acid medium with amine by a mechanism closely resembling that given above, opening of the furan taking place with formation of Stenhouse salts [14].

The reaction of 5-halogenofurfural and 5-halogenofurfurlidenanilines (III, A = 0, $\rangle N-C_6H_5$) with excess secondary aliphatic amine (dimethylamine, piperidine, morpholine, reaction 3), which we have investigated, proceeds by another mechanism.* Here too addition of a protonating substance has an accelerating effect, while addition of alkali inhibits the reaction. The structure of the end product VI [6] in conjunction with the kinetic data (Fig. 2) gave grounds for supposing that here amine hydrohalide reacts with IV to give quaternary salt V, which is the active exchange form. At low amine salt concentration the reaction is initially accelerated. Special addition of amine salt leads to rapid accumulation of the exchange form V:



III IV V VI

The latter subsequently splits up with increasing velocity (due to a concentration effect) (Fig. 2, 1,2).

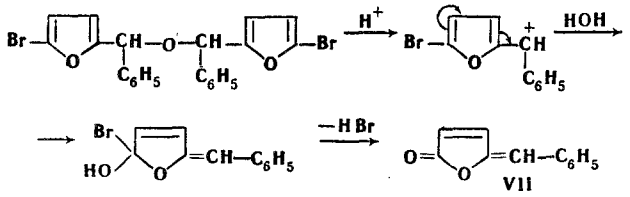
The mechanism put forward above is confirmed by literature data [15] on the ease of formation of type V quaternary salts by reaction of carbonyl compounds (among them furfural) with salts of secondary amines. When investigating the reactions of furfural and furylacrolein with dimethylamine in the presence of acids, König [16] also observed formation of type V quaternary salts, further attacked at ring position 5 by the amine, with subsequent ring opening. Our results show that with 5-halogenofuran derivatives, this reaction gives the nucleophilic metathesis exchange VI.

Dimethylamine undergoes this reaction more rapidly than piperidine and this may be due to steric strain accompanying $sp^3 \rightarrow sp^2$ nitrogen rehybridization in the piperidine ring.

A general characteristic of the observed mechanisms is that electrophilic attack of the substituent at position 2, accompanied by formation of an electrophilic reaction product, precedes nucleophilic attack on the furan ring at position 5. A reaction investigated by Gilman et al., [17] can be considered to be of that type. It is the reaction of 5-halogenofurfurylcarbinols

*[6] evaluates this reaction preparatively.

and their ethers with acid reagents to give type VII lactones.



Unsubstituted furfurylcarbinols react with acids by a similar mechanism, but in the last stage the furan ring is opened to give homologs of levulinic acid [18, 19].

EXPERIMENTAL

The reaction kinetics were investigated in ethanol at 25° using a 0.1 M substrate concentration; the concentration of reactant was chosen in accordance with the stoichiometric ratio; in the series shown in Fig. 1a it is 0.1 M, in Fig. 2, 0.2 M.

Reaction was quenched by diluting the sample with water; halogen was determined by potentiometric titration with 0.1 N $AgNO_3$. Before the estimation the sample was acidified with nitric acid. The indicating electrode was a silver one, the reference electrode a calomel one.

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