ANION-RADICAL MECHANISM OF BROMINE EXCHANGE BY IODINE IN FURAN DERIVATIVES

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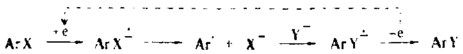
The kinetics of bromine exchange by iodine in furan derivatives were studied; it is shown that the reaction is reversible and inhibited by oxidizing agents. Chloro derivatives of furan do not undergo this reaction. A cryptoreductive mechanism is proposed; the first step of this mechanism consists of electron transfer to the halofuran molecule with subsequent reversible dissociation of the anion radical – inclusion of the iodide anion in the dissociation equilibrium leads to the substitution product.

The classical concepts regarding the mechanism of aromatic nucleophilic substitution in recent years have been expanded considerably due to the detection of a large number of diverse new mechanisms that include a step involving electron transfer [1-11]. A common feature of these mechanisms is the assumption of the formation of anion radicals $ArX^{\dot{-}}$ (which, in a number of cases, have been recorded by ESR, NMR, and electronic spectroscopy) as a result of electron transfer from the nucleophile to the aromatic molecule. The subsequent fate of the anion radical may vary – either rapid "in-cage" recombination of the radical pair to give the Meisenheimer complex [1, 2], or emergence of the anion radical from the reaction "cage" into solution with subsequent independent reaction of it, is assumed. A chain mechanism of the second type (symbolically designated as SRN1) has been detected by a number of researchers [5-8]:

Scheme 1



In the case of heteroaromatic nucleophilic substitution these ideas have been used by Wolfe and co-workers [10], who studied the kinetics of nucleophilic exchange of chlorine in 2-chloroquinoline, and also by Zoltewicz and Oestreih [11], who demonstrated that 3-bromoisoquinoline, depending on the nature of the nucleophile, may react both via the classical ionic mechanism and via an ion-radical chain mechanism of the SRN1 type.

In our preceding papers [12-15] we showed that the reaction of 5-halo-2-substituted furans with amines is subject to the principles characteristic of the traditional stepwise mechanism of the "addition–elimination" type. However, it was found that these principles undergo a complete "reversal" for bromine exchange by iodine, which, with respect to its stoichiometry, is also classified as "nucleophilic substitution":

Scheme 2

I-V I-Va

I Z = CHO; II Z = $COCH_3$; III Z = $CH{=}CH{-}COC_6H_5$; IV Z = $CH{=}CH{-}NO_2$; V Z = NO_2

Bromine exchange by iodine in furan derivatives, which has been known for ~ 20 years, is widely used in preparative practice (for example, see [16-18]), but its mechanism has not been investigated. The presence of oxygen has a substantial effect on the rate of the process, and we therefore initially investigated the reaction in a nitrogen atmosphere in the case of 5-bromofurfural. It follows from curves 1 and 2 (Fig. 1) that the reaction is reversible and that equilibrium is reached at 80% conversion. The same equilibrium position can be reached

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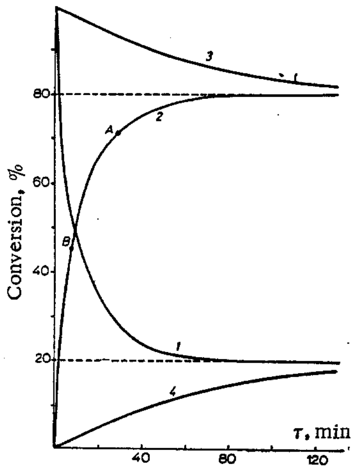


Fig. 1

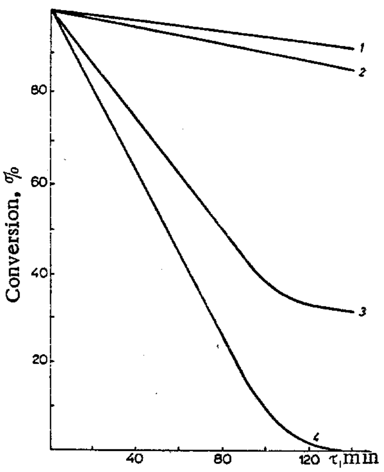


Fig. 2

Fig. 1. Kinetics of bromine exchange by iodine for 5-bromofurfural [1) iodine consumption; 2) accumulation of bromide ion] and iodine exchange by bromine for 5-iodofurfural [3) bromine consumption; 4) accumulation of iodide ion] in a nitrogen atmosphere.

Fig. 2. Kinetics of the oxidation of the iodide ion by air oxygen at 115°C (1, 2) and at 100°C (3, 4) [1) and 3) are the percentages of titrable iodide ion; 2) and 4) are its effective concentrations in the reaction mixture].

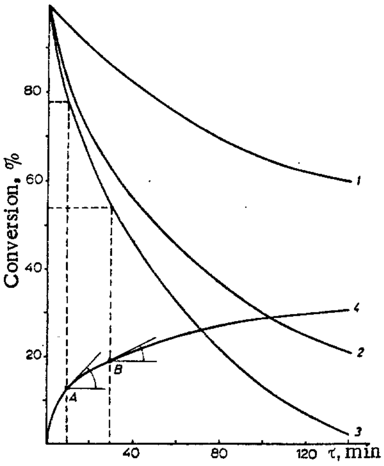


Fig. 3

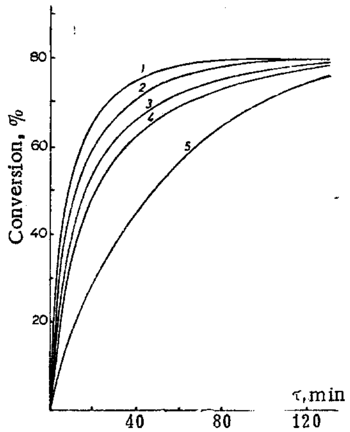


Fig. 4

Fig. 3. Kinetics of bromine exchange by iodine for 5-bromofurfural in an air atmosphere [1) iodide ion consumption in oxidation; 2) percentage of the titrable iodide ion; 3) effective concentration; 4) accumulation of bromide ion].

Fig. 4. Effect of inhibitors on the kinetics of bromine exchange by iodine for 5-bromofurfural in a nitrogen atmosphere [1) in the absence of an inhibitor; 2) in the presence of 1% p-nitrobenzaldehyde; 3) in the presence of 5% p-nitrobenzaldehyde; 4) in the presence of 1% p-aminophenol; 5) in the presence of 1% p-aminophenol].

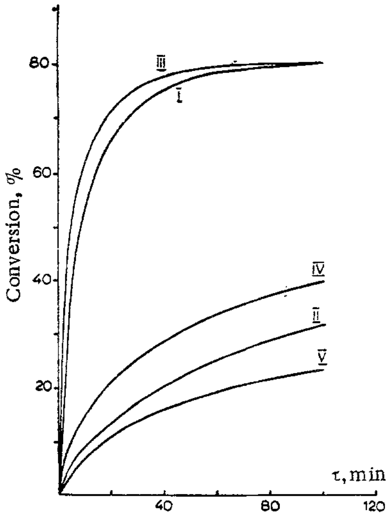


Fig. 5. Effect of functional groups on the kinetics of bromine exchange by iodine for 5-bromo-2-Z-substituted furans (the numbers on the curves correspond to the numbers of the compounds.

when an equimolar mixture of 5-iodofurfural (Ia) and potassium bromide (curves 3 and 4) is added to the reaction. An attempt to calculate the k_1 and k_{-1} constants within the framework of the equation [19]

$$-\frac{dC_I}{d\tau}=k_1[I][I^-]-k_{-1}[Ia][Br^-]$$

was unsuccessful: It was found that the reaction does not follow the equation for reversible bimolecular reactions.

Contact of the reaction mixture with air oxygen leads to slowing down of the reaction. It is known that oxygen reacts with potassium iodide dissolved in glacial acetic acid at a rather high rate [20, 21]. Tying up of oxygen by the reaction mixture also occurs under the conditions of the reaction under consideration. For example, the kinetics of iodide ion consumption in the oxidation reactions ($3I^- \rightarrow I_3^-$) when halofuran is absent is shown in Fig. 2. The I_3^- complex ion can be determined in the reaction mixture spectrophotometrically from the change in the optical density in the region of the absorption maxima [λ_{max} 290 nm (log ε 4.74) and λ_{max} 360 nm (log ε 4.52)]. However, during potentiometric determination of the iodide ion in an aqueous acidic medium the complex is hydrolyzed, thereby giving a higher concentration of titrable halide ion (curves 1 and 3) than its effective concentration in the reaction mixture (curves 2 and 4). The kinetics of oxidation at 100° have diffusion character up to ~ 90% conversion (curve 4) and only then enter into the kinetic region. At 115° (which is close to the boiling point of acetic acid) the reaction rate decreases sharply (evidently because of a decrease in the oxygen concentration on the surface), and the kinetics have diffusion character over the entire investigated segment (curve 2).

The kinetic curves of the reaction of 5-bromofurfural with potassium iodide at 100° in an air atmosphere (Fig. 3) show that in this case there is a superimposition of parallel processes — reversible bromine exchange by iodine and irreversible oxidation of iodide ion. However, the decrease in the observed rates of debromination (in comparison with the corresponding reaction in a nitrogen atmosphere) cannot be explained only by formally kinetic inhibition due to partial tying up of the reagent. For example, for $\tau = 10$ min (curve 4, point A) the iodide ion concentration in the reaction mixture is 78%, as compared with an I concentration of 87%. However, the observed reaction rate in this case is low and corresponds to the rate at a substrate and reagent concentration of 29% for the reactions occurring in nitrogen (point A, curve 2, Fig. 1). For $\tau = 30$ min (point B, curve 4, Fig. 3) the observed rate of elimination of bromine is lower by a factor of 10 than the rate of the same reaction in nitrogen at equal iodide ion concentrations (54%) and a higher substrate concentration — 82 and 54%, respectively (point B on curve 2, Fig. 1).

Thus, in the presence of air oxygen the observed reaction rate decreases not only due to partial oxidation of the reagent but also due to truly kinetic inhibition of the reaction by oxygen. It was also established that aromatic nitro compounds, particularly p-nitrobenzaldehyde (Fig. 4), have an appreciable inhibiting effect. p-Aminophenol was found to be a strong inhibitor, although hydroquinone, with properties similar to it, does not effect the reaction; when p-aminophenol is added to the reaction mixture, it reacts with I to give the corresponding Schiff base (which can be detected photometrically from the appearance of a lemon-yellow color), which is probably a true reaction inhibitor. The effect of oxidizing agents (oxygen, p-nitrobenzaldehyde, and the Schiff base) on the reaction seemed unusual from the point of view of traditional concepts regarding the ionic SN2Ar mech-

TABLE 1. Polarographic Properties of I-V

Z	$-CH=CH-COC_6H_5$	CHO	$COCH_3$	$CH=CH-NO_2$	NO_2
$-E^{1/2}$, V	0.369	0.982	1.221	0.314	0.475

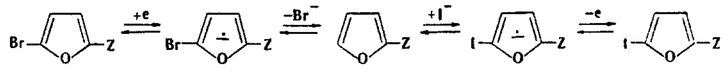
anism and more likely indicated its cryptoreductive radical character. A similar effect of oxidizing agents on the rate of a process was advanced in [7-11] as the main proof in favor of an SRN1 chain mechanism, on the basis of which we adopted this mechanism as a hypothetical mechanism also in the reaction that we examined.

It follows from Fig. 5 that the effect of the nature of functional group Z of the halofuran on the reaction rate does not correspond to the activating force of the indicated grouping in reactions that take place via an addition–elimination mechanism. Substituents Z are arranged in the following order of decreasing rates: $CH=CHCO \cdot C_6H_5 > CHO > COCH_3 > CH=CH-NO_2 > NO_2$. At the same time, the substituents are arranged in the following order in the reaction of 5-halo-2-carbonyl compounds with secondary amines [15]: $CHO > COCH_3 \gg CH=CH \cdot COC_6H_5$; the nitro group is the strongest of all of the investigated activators of nucleophilic halogen exchange in the furan ring, surpassing its analogous effect in the benzene ring [14]. At the same time, a polarographic study of I-V* (Table 1) showed that the half-wave potentials for related groups of compounds correlate with their reactivities. In the case of carbonyl compounds the ease of polarographic reduction decreases in the order $CH=CHCOC_6H_5 > CHO > COCH_3$, as does the rate of bromine exchange by iodine.

The electrode process for these compounds consists of two-electron reduction of the halogen atom, as is observed for 5-bromo-2-acetylthiophene [22]. An analysis of the polarograms obtained for IV and V showed that the halogen and the nitro group are reduced at close potentials and that the half-wave potentials (see Table 1) correspond in this case to a four-electron process. The anomalously low rate of iododebromination for these compounds is possibly due to the "self-inhibiting" activity of the substrate: The functional group itself, which undergoes partial reduction, will act as a reaction inhibitor. It is known that nitrofurans form sufficiently stable anion radicals [23]. The biological action of nitrofurans is due to their inhibiting activity in the bacterial transport of electrons and correlates directly with the particular ease of their polarographic reduction [24]. This specificity of nitrofurans is apparently also manifested in the reactions studied in this research.

A mechanism of bromine exchange by iodine, including reversible electron transfer from the reductive background created by iodide ions to the halofuran molecule with subsequent elimination of a halide ion from the resulting ion radical, has been proposed to explain the facts set for the above [25]:

Scheme 3



The furyl radical obtained in this case reacts with one of the halide ions of the reaction mixture to give either the starting material or the final product. The equilibrium established in this reaction, which corresponds to 80% conversion, does not depend on the nature of functional group Z but, on the whole, is determined by the reactivity of the intermediate furyl radical with respect to the reaction with bromide and iodide ions.

The scheme presented above does not contradict data on the electrochemical reduction of activated halo derivatives. It is known, for example, that p-iodonitrobenzene during one-electron reduction gives an anion radical that dissociates reversibly to give iodide ion and the p-nitrophenyl radical. An increase in the iodide concentration shifts the dissociation equilibrium to favor the anion radical [26].

We have found that chlorofurans do not react with potassium iodide under the indicated conditions, whereas chloro derivatives of furan react with amines at the highest rate in the halogen series [13, 14]. This serves as yet another argument in favor of the ion radical character of the reaction under consideration: It is known that the C–X bond in aromatic anion radicals is much more stable with respect to ionization when X = Cl than when X = Br [27].

The investigated reaction undoubtedly has cryptoreductive character and passes through a step involving one-electron transfer with the formation of an anion radical. At the same time, the possibility that scheme 3 does not exactly reflect its true mechanism cannot be excluded. It may be assumed that the furyl radical is not formed in this reaction as a kinetically independent particle: Without emerging from the reaction "cage," it re-

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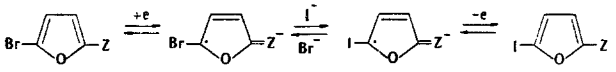
*The polarographic properties of the compounds were studied in the All-Union Scientific-Research and Design Institute of Monomers (Tula) by I. M. Sosonkin and G. L. Kalb, to whom the authors extend their sincere thanks.

acts with a second anion, which is also included in the activated complex. In the limiting case, synchronous mutual exchange of the halogens in the anion radicals (depicted in scheme 4 in the meso form with separation of the radical and ionic fragments) is possible here – in the spirit of the terminology of Bunnett and co-workers [5-7] this mechanism can be designated by the symbol SRN2:

Scheme 4



The data currently available are inadequate for a substantiated choice between scheme 3 and 4 and require additional studies.

EXPERIMENTAL

Chemically-pure-grade potassium iodide was dried at 100° and stored in a desiccator over sulfuric acid. Chemically-pure-grade glacial acetic acid was rendered anhydrous by repeated freezing out and was freed of dissolved oxygen by refluxing in a stream of nitrogen. The acid was stored under nitrogen and was selected for the experiments in a stream of nitrogen. The nitrogen from the cylinder was freed of oxygen by bubbling through two successively connected 1-m-high columns filled with a copper–ammonia complex, after which it was freed of ammonia and moisture by the usual methods.

The reaction was carried out with an equimolar ratio of reagents at a concentration of 0.025 M. Where necessary, the charging of the reactor with the reagents and the solvent and the selection of samples were accomplished in a stream of nitrogen. The reaction was stopped by the addition of water; the bromide and iodide ions were determined potentiometrically by the method in [12].

The polarograms of the compounds were recorded with a dropping mercury electrode by the method in [28] with an LP-7 polarograph at 20° in a solution of glacial acetic acid; 0.5 N Bu_4NClO_4 was used as the base electrolyte, and a standard calomel electrode was used as the comparison electrode.

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POLAROGRAPHY OF 5-ARYLFURFURALS IN AQUEOUS ALCOHOL MEDIA

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The reduction of 5-arylfurfurals on a dropping mercury electrode in aqueous alcohol media proceeds via the same mechanism as the reduction of unsubstituted furfural; the reduction wave of the anion radical of 5-arylfurfurals was detected for the first time. The $E_{1/2}$ values correlate with the σ constants of the substituents in the para position of the phenyl ring, and the correlation coefficient depends on the pH of the medium; this is determined by the different contributions of the protonation reactions after transfer of the first electron for compounds of the investigated series.

Of the rather large number of papers devoted to the polarographic study of furfural and its derivatives, the mechanism of the reduction of furfural on a dropping mercury electrode has been examined in greatest detail in [1-3], in which it was established that carbonyl compounds of the furan series are reduced in aqueous alcohol buffer media in conformity with the principles established for aromatic carbonyl compounds [4].

In order to study the effect of an aryl substituent, in the present research we investigated the reduction of 5-(p-R-phenyl)furfurals (R = Cl, Br, H, OCH_3, and CH_3) on a dropping mercury electrode in 50% aqueous ethanol buffered and unbuffered media.

One polarographic wave, the height of which corresponds to transfer of one electron, is observed in strongly acidic solutions at $pH < 2$ for all of the compounds. In this case the second wave is hidden by the discharge current of the base electrolyte. At pH 3-7 the polarograms contain two one-electron reduction waves. As in the case of furfural [1], the first wave is shifted to negative potentials as the pH increases, while $E_{1/2}$ of the second wave is independent of the pH. This leads to merging of both waves at pH 7 to give one two-electron reduction wave.

At pH 9-14 the two-electron wave is halved (Fig. 1). Thus in the reduction of 5-arylfurfurals in acidic media the protonation step precedes the electrode reaction, and the ketyl radical formed in the first step is reduced with greater difficulty than the protonated complex of 5-arylfurfurals. In addition, the electron affinity of the ketyl radical is higher than that of the starting depolarizer, and the second wave of 5-arylfurfurals in acidic media is therefore found at higher positive potentials than the two-electron wave due to the reduction of 5-arylfurfurals in the unprotonated form (Fig. 2).

Just as in the case of furfural, the $E_{1/2}$ value of the starting depolarizer is -1.35 V, whereas the $E_{1/2}$ value of the corresponding ketyl radical is -1.30 V [3].

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