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Abstract

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ON THE SIGNIFICANCE OF THE KINETIC ISOTOPE EFFECT FOR THE THEORY OF HYDROGEN SUBSTITUTION IN AROMATIC SYSTEMS

In studying the mechanism of substitution in aromatic compounds, we have found contradictions between kinetic and isotope data in the iodination and bromination of benzene derivatives. It turned out, in particular, that the removal of a proton in the stage limiting the reaction rate and the appearance of a proton acceptor in the kinetic equation are not always associated with a kinetic isotope effect.

This applies to the iodination with iodine of ions of *m*- and *n*-dimethylaminobenzenesulfonic acids and of *m*-dimethylaminobenzoic acid, to the bromination of the *m*-anisolsulfonate ion with hydrobromous acid, and probably to various other cases.

Thus, it has been shown that the kinetic equation for the iodination of tertiary aromatic amines has the form:

$$-\frac{d(\mathrm{J})}{dt} = k \cdot M[\mathrm{J}^+] \cdot B + k' M[\mathrm{J}_2]B,$$

where (J) is the analytical concentration of iodine, M and B are the concentrations of the aromatic amine and of the basic component of the buffer mixture ([1,2]). Although this equation is equally applicable to all the tertiary amines studied, the kinetic isotope effect, $i = k_\mathrm{H}/k_\mathrm{D}$, is different: for dimethylaniline $i = 3$, for the *m*-dimethylbenzoate ion i, under different conditions, varies from 1.8 to 1; in the iodination of dimethylaminobenzenesulfonates the isotope effect is absent (or very small).

The bromination of the *m*-anisolsulfonate ion with hydrobromous acid is not associated with an isotope effect, although the concentration of base enters into the kinetic equation.

Analyzing these relations, we were at first inclined to assume that the base B is part of the iodinating complex ([2,3]) and that, consequently, an approximate scheme of the reaction has the form:

Fig. 1

Figure 1: Fig. 1

$$(B\cdots J^+)+R_2NC_6H_6+H_2O \longrightarrow \left(\begin{array}{c}\text{aromatic complex with } NR_2,\\ B\cdots J,\ H\cdots OH_2\end{array}\right)^+ \longrightarrow B+\text{iodinated aromatic product}+H_3$$

Under this assumption, the presence or absence of a kinetic isotope effect depends on the stage of proton elimination by water molecules and is not connected with the empirical kinetic equation of the reaction.

However, continuing our investigation, we obtained evidence that the base B acts in the reaction as a proton acceptor, and not as a participant in the iodinating complex. Namely, by introducing various buffer salts into the mixture, we established that the rate of iodination increases with an increase in the basicity and concentration of the basic component of the buffer.

solution. This also applies to the case when there is an isotope effect (aniline) and when $i = 1$ (N,N-dimethylanilinium ion). For the iodination of the dimethylanilinium ion, these data are presented in Fig. 1 (k_1 is the constant in the equation $d(\mathrm{J})/dt = k_1(\mathrm{J})$).

From theoretical considerations it follows that the strength of the halogenating agent is the greater, the less basic the donor component of the active complex. Therefore ($\mathrm{J}^+ \ldots \mathrm{CO}_3^{2-}$) should be weaker than ($\mathrm{J}^+ \ldots \mathrm{HCO}_3^-$). In the pH interval indicated in the caption to Fig. 1, $[\mathrm{HCO}_3^-] \gg [\mathrm{CO}_3^{2-}]$, but the reaction proceeds through the CO_3^{2-} ion, and not through the HCO_3^- ion. This relation, as well as the decrease in the isotope effect with increasing concentration of the CO_3^{2-} ion, indicate the role of a proton acceptor for the base according to the scheme:

$$\mathrm{J}+\mathrm{R}_2\mathrm{NC}_6\mathrm{H}+B \longrightarrow (\text{cyclohexadienyl complex bearing } \mathrm{NR}_2,\ \mathrm{J},\ \mathrm{H})^+ + B \longrightarrow (\text{cyclohexadienyl complex bearing}$$

Obviously, proton abstraction constitutes the rate-limiting stage of the reaction. As for the isotope effect, it is present in some cases and absent in others*.

We found that, in the iodination of some (but not all) compounds, the isotope effect can be reduced and even eliminated by increasing the concentration and basicity of B, and, conversely, enhanced by increasing the acidity of the solution. The decrease of the isotope effect upon increasing the basicity of the medium could be associated with acceleration of the proton-abstraction stage; however, it must be borne in mind that in all cases B enters into the kinetic equation as an obligatory component and, consequently, proton removal limits the overall rate of the reaction.

Fig. 1. Rate of iodination of the *m*-dimethylaminobenzoate ion as a function of the concentration of the CO_3^{2-} ion in the pH interval 8.4—8.8 (30°). Concentrations in mol/l: $(J)_0$ 0.005, KJ 0.3, M 0.01, $([HCO_3^-] + [CO_3^{2-}]) : a$ —1.05, b —0.777.

According to the general principle, the indicated relations can be explained by the superposition of equilibrium and kinetic dependencies acting in opposite directions ([4,5]). However, these correlations do not obey simple and unambiguous regularities. Thus, in the iodination of aromatic amines we found a kinetic isotope effect, with a magnitude from 3 to 4.8, both for extremely active and for rather inert compounds. On the other hand, a kinetic isotope effect is not observed for some amines of intermediate activity ([2]). It may be noted that primary amines substituted with deuterium in quinoid positions are iodinated 3—4 times more slowly than analogous light compounds, whereas in iodination ···of tertiary amino compounds, the isotope effect is absent. However, this rule too is violated in the case of dimethylaniline ($i = 3$).

The kinetic isotope effect is not directly related to the activity of the halogenating agent either. We verified this by brominating the *m*-anisolesulfonate ion with reagents of different strength ([6]).

Agent	Br^+	Br_2	BrOH
Relative activity	> 1400	1	0.0015
i	1	2.6	1

Thus, the kinetic isotope effect is absent when both the strongest of the brominating agents, Br^+, and the weakest, BrOH, take part in the reaction. The isotope effect appears under the action of an agent of intermediate strength—elemental bromine.

These peculiar relationships are undoubtedly connected with the different states and displacements of hydrogen atoms during the reaction, and from this standpoint the kinetic isotope effect represents an interesting subject for study. However, as the data of the present work show, determinations of i give ambiguous results and do not always lead to the goal when they are applied as a method for establishing the mechanism of substitution in aromatic systems in the usual

[*] One could assume that the isotope effect disappears because proton abstraction occurs in two stages: first, relatively slowly, a complex $(Ar \ldots H \ldots CO_3^{2-})$ is formed; then, relatively rapidly, the proton is removed in the form of HCO_3^-. However, this is contradicted by the fact that the tendency toward a decrease of i increases with increasing basicity of B. It would seem that the opposite relation should be expected. In addition, there are grounds to suppose that deuterated compounds should form complexes with B more difficultly than their hydrogen analogues.

sense of the word. In particular, the absence of an isotope effect apparently does not permit any reliable conclusion to be drawn regarding the sequence and significance of the stages of the substitution process in an aromatic compound.

From this point of view, it may be noted that the results of the well-known experiments of Melander on the isotope effect in the nitration and bromination of aromatic compounds (7) ($k_H/k_T = 1$) do not by themselves prove categorically that proton detachment does not limit the reaction rate. Moreover, it had already been pointed out earlier that Melander' s experiments admit an interpretation different (8) from that given them by the author.

Experimental data (with the participation of E. I. Tomilenko). The sodium salt of *m*-dimethylaminobenzoic acid was obtained from *m*-nitrobenzoic acid by simultaneous reduction and methylation (9). *m*-Dimethylmetanilate was prepared by sulfonating dimethylaniline (10). To obtain *m*-anisolesulfonate, *m*-phenolsulfonic salt was methylated with dimethyl sulfate, and the product was purified through the acid chloride of *m*-anisolesulfonic acid (11).

2,4,6-Trideutero-*m*-dimethylmetanilic acid was obtained by exchange of the light amino compound with a 15-17% solution of DCl prepared from 98-99% D_2O and $SOCl_2$. In obtaining 2,4,6-trideutero-*m*-anisolesulfonate and 2,4,6-trideutero-*m*-dimethylaminobenzoic acid, it is not possible to make use of exchange of the light preparations with D_2O, since on prolonged heating in an acid medium they undergo some side reactions. They were therefore prepared from previously deuterated *m*-phenolsulfonate and *m*-aminobenzoic acid. The determination of D in the water from combustion of deuterium compounds was carried out by the drop method (12).

In the kinetic experiments, iodination of amines was carried out in solutions of iodine in potassium iodide, without additives or in the presence of buffer salts, at 25° or 35° (±0.05°). The analytical concentration of iodine was determined by titrating samples with thiosulfate solution in small volumes. Control experiments showed that, over the pH range used, the iodate-formation reaction is not significant.

The concentrations of the CO_3^{2-} ion indicated in Fig. 1 were calculated from the total concentration of carbonate salts in the experiment, using the second electrolytic dissociation constant of carbonic acid, equal to $1.5 \cdot 10^{-10}$ at the average ionic strength of our solutions (13). The hydrogen-ion concentration required for the calculation was found in the experimental mixture with the aid of a glass–

electrode. In the pH interval 8.4–8.8 the concentration of the HCO_3^- ion is almost equal to the total concentration of carbonic acid salts in the solution, and the reaction rate can be related by a proportionality relation both to $[CO_3^{2-}]$ and to $[OH^-]$. However, measurements carried out at constant concentration of the CO_3^{2-} ion at different pH values showed that the hydroxyl-ion concentration is of no significance in the reaction mechanism. In parallel experiments, at the same concentrations of the components, the 2,4,6-trideutero and ordinary *m*-dimethylaminobenzoate ions were iodinated equally rapidly. In the analogous bromination reaction of the *m*-anisolesulfonate ion with bromohypobromous acid, the rate constant (at 0°) increases from 0.177 in the absence of additives to $0.41\ \mathrm{l} \cdot \mathrm{mol}^{-1} \cdot \mathrm{min}^{-1}$ in the presence of carbonic acid salt at its concentration 0.5 M and solution pH 8.5. In both cases $i = 1$.

Table 1

y	k_1, min^{-1}	$\frac{k}{y}$
0.0825	0.0368	0.447
0.133	0.0622	0.467
0.165	0.0783	0.474
		0.46

In parallel experiments $i = 3.4$

In Table 1 are given the values of the rate constants for iodination of aniline at pH 9.6–9.7 and different concentrations of carbonic acid salt. The concentrations of the remaining reagents, in mol/l, are: (J) 0.005, KJ 0.4, aniline 0.025; y denotes the sum $[\mathrm{HCO}_3^-] + [\mathrm{CO}_3^{2-}]$. Table 1 shows that the reaction rate is proportional to the content of the buffer salt (in essence, of course, to the content of its more basic component).

Table 2 presents data on the change in the value of i during iodination of amines as a function of the pH of the medium.

Table 2

Compound	% substitution of H by D, %	M, mol/l	Buffer, mol/l	pH	i
m-Dimethylaminobenzoate ion	98	0.01	Acetate, 0.16	4.5	1.8
m-Dimethylaminobenzoate ion	98	0.02	–	(8-5)	1.3
m-Dimethylaminobenzoate ion	98	0.01	Phosphate, 0.35	8	1.2

Compound	% substitution of H by D, %	M, mol/l	Buffer, mol/l	pH	i
m-Dimethylaminobenzoate ion	98	0.01	Carbonate, 1.6	8.8	1.0
m-Dimethylamino-sulfonate ion	97.2	0.06	HCl, 50% neutralization	3.5	1.2
m-Dimethylamino-sulfonate ion	97.2	0.01	–	(7-5)	1.0
m-Dimethylamino-sulfonate ion	97.2	0.01	Phosphate, 0.3	8	1.0
Aniline	96.6	0.02	–	(8-5)	3.5
Aniline	96.6	0.04	Phosphate, 0.38	7.0	3.4
Aniline	96.6	0.012	Carbonate, 1.0	9.4	3.4

The deutero analogs of the compounds indicated in Table 2 contained D in the 2, 4, and 6 positions; $(J)_0 = 0.005\ M$, temperature 25° or 30°.

The isotope-effect values obtained under different conditions are well reproduced in repeated experiments.

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