Kinetic Isotope Effects in Hydrogen Exchange of Aromatic CH Bonds in Benzene, Fluorobenzene, and Nitrogen-containing Heterocycles with Solution of Alkali Metal Amide in Liquid Ammonia

I. F. Tupitsyn and N. N. Zatsepina

Prikladnaya Khimiya Russian Scientific Center, St. Petersburg, Russia

Received April 19, 2000

Abstract — The kinetic isotope effects in deuterium and tritium exchange in benzene, fluorobenzene, pyridine, pyridine *N*-oxide, and quinoline with a solution of an alkali metal amide in liquid ammonia $k_D^{NH_3}/k_T^{NH_3}$ were determined, where $k_D^{NH_3}$ and $k_T^{NH_3}$ are the experimental rate constants of protodedeuteration and protodetritation, respectively. The variation of the tritium exchange rates in benzene in going from NH₃ to ND₃ ($k_T^{NH_3}$ and $k_T^{ND_3}$) was evaluated. The deviation of the observed ratios $k_D^{NH_3}/k_T^{NH_3}$ and $k_T^{ND_3}/k_T^{ND_3}$ from the maximum possible values corresponding to the Swan–Shaad equation suggests the reaction mechanism in which both elementary stages, ionization of the CH acid and diffusion separation of the complex of the carbanion with the ammonia molecule, are partially limiting. A small decrease in the secondary isotope effect of the solvent, defined as $k_T^{ND_3}/k_T^{NH_3}$, as compared to the theoretical maximum of 2.4, is assumed to be due to similar structures of the transition state and the equilibrium carbanion. A theoretical explanation was given for the observed dependences of the primary isotope effect of the substrate on pK_a for deutero (tritio) derivatives of fluorobenzene [4D(t) < 3D(t) < 2D(t)], for reactions in the series pyridine-2D(t) < pyridine-3D(t) < quinoline3D(t), and for hydrogen exchange in pyridine-2D(t) *N*-oxide ($k_D^{NH_3}/k_T^{NH_3} \sim 1$).

The modern state of the mechanistic studies of hydrogen isotope exchange of CH bonds in organic molecules with basic reagents is contradictory. On the one hand, owing to the maximum possible use of kinetic isotope effects of various nature in combination with semiempirical correlations (like Brønsted or Hammett equations), there has been a considerable success in revealing the mechanism of reactions in hydroxyl-containing solvents. As shown in numerous studies, in these media the isotope exchange can be a convenient test reaction for such protolytic processes as enzymatic oxidation-reduction, E2 elimination, nucleophilic substitution of methane derivatives activated with nitro groups, etc. On the other hand, the mechanism of the reaction in strongly basic highly polar nonaqueous media such as solution of alkali metal amide in liquid ammonia (ε 26.7 at $-60^{\circ}C$ [1]) was practically beyond the scope of researchers' interest. At the same time, there are good grounds to expect that the hydrogen isotope exchange of organic compounds in this medium will show different features as compared to hydroxyl-containing media. Indeed, the features of liquid ammonia (high capability for solvation of metal cations as compared even with the most efficient dipolar aprotic solvents [1]

and weak solvation of anions) suggest that hydrogen isotope exchange in liquid ammonia, being an ionic process, would be relatively weakly affected by the medium and hence would be largely controlled by forces acting between isolated reactants. The higher protophilicity of amide ions dissolved in liquid ammonia as compared to hydroxide ions in water follows from simple comparison of their proton affinities in the gas phase, kcal mol⁻¹: 419 for NH₂⁻ and 384 for OH⁻.

An additional argument in favor of different reaction mechanisms in these reaction media is provided by elemental chemical reactions. For example, nucleophilic dehalogenation of halobenzenes [2], 3- and 4-chloropyridines [3], and 2-chloropyridine *N*-oxide [4] in a solution of potassium amide in liquid ammonia occurs chiefly by the aryne mechanism, whereas in an alcoholic solution the major pathway is addition of a nucleophile followed by elimination of the halide ion [5].

In view of these facts, the goal of this work was to reveal, as fully as possible, the features of the mechanism of deuterium and tritium exchange in a solution of potassium (or sodium) amide in liquid ammonia

Table 1. Rate constants of protodeduteration $(k_D^{\text{NH}_3})$ and protodetritiation $(k_T^{\text{NH}_3})$ and $k_D^{\text{NH}_3}/k_T^{\text{NH}_3}$ ratio for deuterium and tritium exchange of benzene-D(t) in a solution of potassium amide in liquid ammonia $(C_{\text{KNH}_3} \ 0.05 \ \text{M})^{\text{a}}$

Tempera- ture, °C	$k_{\rm D}^{\rm NH_3 \times 10^5},$	$k_{\rm T}^{\rm NH_3\times10^5},$	$k_{\mathrm{D}}^{\mathrm{NH}_3}/k_{\mathrm{T}}^{\mathrm{NH}_3}$		
0 25 40	$ \begin{array}{r} 1.1 \pm 0.1 \\ 11 \pm 2 \\ 92 \pm 2 \end{array} $	$\begin{array}{c} 0.57 \pm 0.02 \\ 6.1 \pm 0.6 \\ 48 \pm 3 \end{array}$	1.9 2.0 1.9		

^a Average values from 5-6 runs at each temperature.

with structurally related CH acids containing the same exchange center, aromatic CH bond [benzene-D(t), fluorobenzene-3D(t), fluorobenzene-4D(t), pyridine-2D(t), pyridine-3D(t), quinoline-2D(t), quinoline-3D(t), and pyridine-2D(t) N-oxide]. These compounds cover a relatively broad range of kinetic CH acidity and therefore are convenient objects for studying the specific features of the multistage mechanism and revealing the differences in the structures of the carbanionic transition states characterized by high localization of the excess negative charge. Among the chosen objects, the most convenient model compound is the simplest compound, benzene, whose hydrogen atoms are equivalent. Therefore, benzene was studied in most detail. We attempted to apply the modern theoretical concept, that explains the whole set of experimental data on the values and variations of the primary kinetic isotope effect and Brønsted coefficient α in isotope exchange reactions of OH, NH, and CH acids in hydroxyl-containing media [6, 7], to hydrogen isotope exchange of aromatic CH bonds in a solution of potassium amide in liquid ammonia. Most attention was given to the following problems: estimation of the contribution of the internal return effect described by the ratio of the rate constants of the competing stages k_{-1} and k_2 [scheme (1)]; evaluation of the extent of structural transformation of the initial CH acid in the carbanionic transition state when moving along the reaction coordinate; and study of the variation of the reaction mechanism depending on the molecular structure of the CH acid.

Primary kinetic effect of the substrate and internal return. The average rate constants of protodedeuteration $(k_D^{\text{NH}_3})$ and protodetritiation $(k_T^{\text{NH}_3})$ of benzeneD(t) and the kinetic isotope effect of the reaction $(k_D^{\text{NH}_3}/k_T^{\text{NH}_3})$ with a solution of potassium amide in liquid ammonia are listed in Table 1. Previously, in a paper on a similar problem [8], Shatenshtein *et al.* reported for the reaction of benzene-D(t) with a solution of potassium amide in liquid ammonia the ratio $k_{\rm D}/k_{\rm T} = 2.1 \pm 0.1$ (0°C, $C_{\rm KNH_2}$ 0.02 M). We obtained $k_{\rm D}/k_{\rm T} = 1.9 \pm 0.1$ (0°C, $C_{\rm KNH_2}$ 0.05 M). The reason for this small difference is unclear, but it is of no principal importance. Along with measurements of the primary kinetic isotope effect, for revealing the exchange mechanism it is important to study the kinetics of isotope exchange in the catalytic system C₆H₅–KND₂–ND₃(liquid) and to study the secondary isotope effect of the substrate defined as the ratio of the rates of deuterium exchange of separate isotopomers with the solvent in the same liquid ammonia solution [system C₆D₆–C₆H₅D–KNH₂–NH₃(liquid)]. These data are listed in Tables 2 and 3.

To interpret the mechanistic features of the exchange reaction under consideration, we use a kinetic scheme taking into account the intermediate formation of the primary and secondary contact complexes [7]:

$$C-H + NL_{2}^{-} \xleftarrow{k_{1}}{k_{-1}} C^{-} \cdot HNL_{2} \xleftarrow{k_{2}}{C^{-}} \cdot LNLH$$
$$\xleftarrow{}{C-L} + NLH^{-}.$$
(1)

Here L = H, D, or T; the constants k_1 and k_{-1} characterize formation and decomposition of the primary contact complex; k_2 is the rate constant of the diffusion-controlled process of separation of the leaving solvent molecule from the primary complex and formation of the secondary contact complex.

In terms of scheme (1), the overall rate constant of deuterium exchange $k_{\rm D}$ is given by relation (2):

$$k_{\rm D} = \frac{k_1 k_2}{k_{-1} + k_2} \,. \tag{2}$$

The expected behavior of k_D can be different depending on the ratio of the constants of the elementary stages. If $k_2 \gg k_{-1}$, then $k_D = k_1$ and we deal with the reaction not complicated by internal return. On the contrary, if the intermediate primary contact complex is so reactive that it abstracts a proton from the solvent molecule and this process occurs faster than transformation into the secondary contact complex $(k_{-1} \gg k_2)$, then there is a simple correlation between the rate constant of the exchange reaction k_D and rate constant of ionization of the CH acid k_1 . The overall rate in this case is determined by the diffusion rate (rate constant k_2): $k_D = (k_1/k_{-1})k_2 = K_{preeq}k_2$.

Internal return seems to be an essentially dynamic process depending on many factors (structure of the CH acid and reacting base, viscosity of the reaction medium, temperature). Therefore, in many cases detection of internal return plays a decisive role in elucidation of the reaction mechanism.

Table 2. Conditions and results of experiments on deuterodeprotonation $(k_{\rm H}^{\rm ND_3})$ and deuterodetritiation $(k_{\rm T}^{\rm ND_3})$ of benzene-t in a solution of potassium amide in liquid deuterated ammonia (0°C, initial deuterium concentration 99 at. %, $C_{\rm KNH_2}$ 0.05 M)

Experi- ment	m_{a}^{\prime}	Relative intensity of indicated peak in mass spectrum, %							C _b , ^b at. %	$k_{\rm H}^{\rm ND_3 \times}$ 10 ⁵ ,	$S_b^0 \times 10^2$, c	$S_{b} \times 10^{2}$, c	$k_{\mathrm{T}}^{\mathrm{ND}_{3}} \times 10^{5},$
tion, h	m _s	78	79	80	81	82	83	84	D	s ⁻¹			s ⁻¹
1.5 3.0 4.0 6.0	82 87 76 87	3.0 _ _ _	15.8 0.5 - -	30.5 5.3 2.2 -	30.6 18.4 12.9 1.4	15.6 34.3 1.8 10.8	3.9 30.8 36.9 38.1	0.3 10.6 16.2 49.7	42.1 70.2 75.3 89.3	13 14 15.3 d	184 386 294	146 286 196	2.1 2.1 1.9

^a Here and hereinafter: (m_a, m_s) number of moles of the solvent and substrate, respectively. ^b (C_b) Concentration of deuterium atoms in benzene after the experiments. ^c (S_b^0, S_b) Activities of benzene samples before and after the experiments, respectively. ^d Equilibrium.

Table 3. Conditions and results of experiments on protodedeuteration of the isotope mixture C_6H_5D and C_6D_6 (1 : 1) in a solution of potassium amide in liquid ammonia [system $C_6H_5D + C_6D_6 + NH_3(liquid) + KNH_2$, C_{KNH_2} 0.05 M]^a

Run pera-	Experi- ment $m_{a'}$	m _a /	Relative intensity of indicated peak in mass spectrum, %					С _{С6} D6,	С _{С6} Н5D,	$\begin{bmatrix} k_{C_6D_6} \times \\ 10^5 \end{bmatrix}$	$k_{C_6H_5D} \times 10^5$	$k_{C_6H_5D'}$			
110.	no. ture, duration, m °C h	m _s	78	79	80	81	82	83	84	at. % D	at. % D at. % D	s ⁻¹	s ⁻¹ s ⁻¹	^r C ₆ D ₆	
_	_	_	_	11.8	88.2	_	_	3.0	19.5	77.5	95.8 ^b	14.7 ^b	_	_	
1	0	3.0	44.9	11.2	78.8	0.7	3.0	12.7	36.9	46.7	87.7	13.1	0.81	1.1	1.3
2	0	6.0	55.3	34.1	65.9	3.6	12.6	28.1	35.0	20.0	75.9	11.0	1.1	1.2	1.1
3	0	7.0	60.9	37.1	62.9	6.1	17.0	31.1	31.6	14.1	71.1	10.5	1.1	1.3	1.2
4	25	0.25	33.4	18.8	81.2	0.8	2.2	9.8	30.7	56.5	90.0	13.5	7.0	9.0	1.3
_	_	—	_	8.1	91.9	_	0.8	3.9	24.6	71.3	94.3 ^b	15.3 ^c	-	-	-
5	25	0.33	35.7	20.8	79.2	2.7	5.5	17.6	37.5	36.6	83.2	13.2	10.4	12.4	1.2
6	25	0.5	44.9	23.3	76.7	3.4	7.9	18.4	31.8	38.4	82.3	12.8	7.6	10.0	1.3

^a $(C_{C_6D_6})$ Concentration of deuterium atoms in "heavy" isotopomers $(C_6D_6, C_6D_5H, C_6D_4H_2)$; $(C_{C_6H_5D})$ concentration of deuterium atoms in "light" isotopomers present in the isotope mixture $(C_6H_4D_2, C_6H_5D, C_6H_6)$; $(k_{C_6D_6}, k_{C_6H_5D})$ rate constants of proto-dedeuteration of the corresponding isotopic species. ^b Concentration of deuterium atoms $C_{C_6D_6}$ and $C_{C_6H_5D}$ in the isotopic mixture taken for run nos. 1–4. ^d Concentration of deuterium atoms $C_{C_6D_6}$ and $C_{C_6H_5D}$ in the isotopic mixture taken for run nos. 5 and 6.

To find whether the isotope exchange of hydrogen in benzene-D(t) with an alkali metal amide in liquid ammonia is complicated by internal return, we estimated the deviation of the exponent in the Swan– Shaad equation from the maximal value $y_{max} = 3.34$ corresponding to the case when the stage with the rate constant k_1 fully limits the reaction rate [9]:

$$\log k_{\rm H}^{\rm ND_3/k_{\rm T}^{\rm ND_3}} = y_{\rm max} \log k_{\rm D}^{\rm NH_3/k_{\rm T}^{\rm NH_3}}.$$
 (3)

Assuming, as usual, that the influence of the solvent isotope effect on the primary kinetic isotope effect is negligible, we determined, following the above procedure, the exponent *y* for the isotope ex-

change in benzene-D(t) from the rate constants $k_D^{\rm NH_3}$, $k_T^{\rm NH_3}$, $k_H^{\rm ND_3}$, and $k_T^{\rm ND_3}$ (0°C) found in this work, where $k_D^{\rm NH_3}$ and $k_T^{\rm NH_3}$ are the rate constants of protodeductration and protodetritiation, respectively ("reverse" exchange); $k_H^{\rm ND_3}$ and $k_T^{\rm ND_3}$ are the rate constants of deuterodeprotonation and deuterodetritiation, respectively ("direct" exchange, with solvent as deuterium donor).

In contrast to the constants $k_D^{\text{NH}_3}$, $k_T^{\text{NH}_3}$, and $k_H^{\text{ND}_3}$, obtained from direct measurements (Table 1), the quantity $k_T^{\text{ND}_3}$ was estimated indirectly on the basis of the fact that the hydrogen isotope exchange in the same reaction mixture occurs by two opposite path-

ways (Table 2). The first pathway is incorporation of deuterium atoms from the solvent to the nondeuterated benzene molecule; it prevails at short reaction times (1.5 and 3 h, Table 2). In view of the large isotope effect of the solvent, the loss of the tritium content in the benzene molecule in this period can be neglected. As for the second pathway involving exchange of tritium in the benzene molecule with deuterium from the solvent, we monitored its kinetics during a period sufficient for the equilibrium in the back deuterium exchange reaction to be arrained (4-6 h):

$$C_6D_5t + ND_3(liquid) \longrightarrow C_6D_6 + ND_2t.$$
 (4)

Finally, the true deuterodetritiation rate constant $k_{\rm T}^{\rm ND_3}$ was determined by correcting the apparent constant $k_{\rm T}({\rm C}_6{\rm D}_5{\rm t}-{\rm ND}_3)$ for the secondary deuterium isotope effect: $k_{\rm D}({\rm C}_6{\rm H}_5{\rm D})/k_{\rm D}({\rm C}_6{\rm D}_6) = 1.2$ (Table 3). Then, $k_{\rm T}^{\rm ND_3} = k_{\rm T}({\rm C}_6{\rm D}_5{\rm t}-{\rm ND}_3)k_{\rm D}({\rm C}_6{\rm H}_5{\rm D})/k_{\rm D}({\rm C}_6{\rm D}_6) = 2 \times 1.2 \times 10^{-5} = 2.4 \times 10^{-5} {\rm s}^{-1}$. The exponent y = 2.86 determined by substituting the ratios $k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3}$ and $k_{\rm H}^{\rm ND_3}/k_{\rm T}^{\rm ND_3}$ in relation (3) is lower than the limiting value $y_{\rm max} = 3.34$ corresponding to the state when the stage with the constant k_1 in scheme (1), which is sensitive to isotope substitution, is fully rate-determining. In other words, the kinetics of hydrogen isotope exchange of benzene with a solution of potassium amide in liquid ammonia is complicated in part by the internal return.

An additional unambiguous evidence of the internal return is the zero temperature coefficient of the primary kinetic isotope effect in deuterium and tritium exchange of the aromatic CH bonds in benzene, found by us: $k_D^{\text{NH}_3}/k_T^{\text{NH}_3} = 1.9-2.0$ at 0, 25, and 40°C (Table 1). In this connection, we should note the following. Despite numerous data accumulated in the recent decades that the primary kinetic isotope effect in protolytic reactions can show no temperature dependence [7, 10], or even the ratio $k_{\rm D}/k_{\rm T}$ can increase with temperature [11], the views that the kinetic isotope effect should always monotonically decrease with increasing temperature still prevail in the literature. These views are based on the well-known theoretical concept that the major contribution to the observed isotope effect is made by the difference in the zero vibration energies of the CD and CT bonds cleaving in the course of the reaction. However, analysis shows that this conclusion is valid only for exchange processes fully limited by the stage with the rate constant k_1 [scheme (1)]. The internal return can be the only factor responsible for the abnormal behavior of the ratio $k_{\rm D}/k_{\rm T}$, observed in this and some other [8, 10] works. Indeed, the temperature coefficient of the kinetic isotope effect in stages with the constants k_1 and k_{-1} , irrespective of the mechanistic features, is approximately equal, because these stages involve cleavage of bonds with a similar strength: CD(T) and ND(T) [12]. Hence, the preequilibrium constant $K_{\text{preeq}} = k_1/k_{-1}$, similar to k_1 , tends to decrease with increasing temperature. As for the constant k_2 , its variation with temperature is governed by the close correlation between k_2 and the diffusion motion in relatively bulky molecular complexes. Generally, the lower the solution viscosity, the lower the potential barrier to escape of the emerging solvent molecule from the nearest environment of the carbanion and hence the higher k_2 . Naturally, variation with temperature of the kinetic isotope effect under the influence of the growing contribution of k_2 will have the opposite sign as compared to variation of $K_{\text{preeq}}^{\text{D}}/K_{\text{preeq}}^{\text{T}}$. The influence of temperature on k_2 should be especially significant in liquid ammonia which is characterized by a high viscosity at low temperatures and a strong temperature dependence of the viscosity [13]. Hence, the influence of two competing factors on the kinetic isotope effect of hydrogen isotope exchange of benzene with solution of potassium amide in liquid ammonia causes the above-noted abnormal independence of the $k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3}$ ratio from temperature. However, the relative contribution of the internal return to the reaction mechanism cannot be estimated from the temperature dependence of $k_D^{\text{NH}_3}/k_T^{\text{NH}_3}$. To estimate the parameter $\alpha_T = k_{-1}^T/k_2$ characterizing the extent of internel acture at the second internal return at tritium exchange, Streitwieser et al. [9] proposed the formula

$$[1 - a_{\rm T}(B^{1/y_{\rm max}} - 1)]^{y_{\rm max}} = A + a_{\rm T}(A - B), \quad (5)$$

where y = 2.86; $A = (k_D/k_T)^y/(k_H/k_T)$; $B = (k_D/k_T)^y \times K_{eq}^T$; K_{eq}^T is the equilibrium constant of the reaction $C_6H_5T + NH_3$ (liquid) $\iff C_6H_6 + NH_2T$; $K_{eq}^T \approx 1.2$ [14].

Unfortunately, Eq. (5) for determining $\alpha_{\rm T}$ cannot be solved analytically, and it was solved numerically by the iteration procedure. Knowing the extent of internal return in tritium exchange, we can calculate, without performing the experiment, the kinetic isotope effect in the stage of hydrogen transfer $(k_1^{\rm H}/k_1^{\rm T})$ and the parameter $\alpha_{\rm H}$ by Eqs. (6) and (7):

$$k_1^{\rm H}/k_1^{\rm T} = k_{\rm H}/k_{\rm T}[1 - a_{\rm T}(K_{\rm eq}^{\rm T}k_{\rm H}/k_{\rm T} - 1)]^{-1},$$
 (6)

$$a_{\rm H} = a_{\rm T} K_{\rm eq}^{\rm T} k_{\rm l}^{\rm H} / k_{\rm l}^{\rm T}.$$
 (7)

The extents of internal return of triton and proton, obtained by this procedure, are low: $\alpha_T = 0.058$ and $\alpha_H = 1.05$ (0°C). Thus, we deal with a situation already known for the hydrogen isotope exchange in normal CH acids with an alkaline aqueous or methanolic solution (see, e.g., [7]): none of the three stages

of scheme (1) is definitely limiting, with the rate constants of the elementary stages k_2 and k_{-1} being comparable; $k_{-1}^{\text{H}} > k_{-1}^{\text{D}} > k_{-1}^{\text{T}}$. It is notable that even a weak internal return effect has a significant influence on the multistage mechanism of hydrogen isotope exchange in benzene, decreasing the kinetic isotope effect in the stage of ionization of the CH acid $(k_1^{\rm H}/k_1^{\rm T})$ from the theoretically calculated value of 19 to 12 [estimation by formula (6)]. There is also another explanation for the decreased kinetic isotope effect, taking into account the asymmetry of the threecentered linear model of the transition state [15]. For better understanding of this problem, it was desirable to supplement the above data by studying of the secondary isotope effect of the solvent, characterizing the energy and position of the transition state on the reaction coordinate.

Secondary isotope effect of the solvent. Structure and energy of the transition state of the reaction. The goal of this part of our study was to apply the semiquantitative interpretation of the secondary isotope effect of the solvent, developed previously only for protolytic processes in water or alcohol [7, 16, 17], to isotope exchange of hydrogen in benzene with a solution of potassium amide in liquid ammonia. One of the main results of this approach was revealing a direct correlation of the secondary isotope effect of the solvent, defined as the ratio k_{OD}^T/k_{OH}^T , with the coefficient α in the Brønsted equation and with the maximum attaniable value of this ratio, $(k_{OD}^T/k_{OH}^T)_{max}$. The latter, in turn, is determined as the product of the deuterium fractionation factor in aqueous alkaline solution 1 by the deuterium isotope effect manifested in the ionic product of water, K_{water}^H/K_{water}^D . Then, we obtain [7]

$$k_{\rm OD}^{\rm T}/k_{\rm OH}^{\rm T} = (k_{\rm OD}^{\rm T}/k_{\rm OH}^{\rm T})_{\rm max}^{\alpha} = 2.4^{\alpha}.$$
 (8)

Relationship (8) was frequently used to evaluate the extent of structural and energetic similarity between the transition state and the products of proton transfer [7]. With data on the secondary isotope effect of the solvent, this relationship reproduces, as a rule, the values of α that were determined from usual correlation between the activation free energies (log K_D) and pK_a . In the limiting case of $\alpha = 0$, the CH bond remains intact in the transition state, whereas in the opposite limiting case ($\alpha = 1$) the transition state is actually a carbanion.

In this work we proceeded from an apparent assumption that the secondary isotope effect of the solvent in the reaction of tritium exchange in a solution of potassium amide in liquid ammonia is due to the same factor as in the similar reaction in water

(OD/OH secondary isotope effect). Namely, the $ND_2^$ ion in deuterated liquid ammonia is a stronger base than the NH_2^- ion in nondeuterated liquid ammonia (Table 2), and the OD^- ion in D_2O is a stronger base than the OH^- ion in H₂O. Although the media being compared differ significantly from each other in the protophilic properties, the statistical thermodynamic calculations taking into account small differences in the vibrational frequencies of H₂O and D₂O, as compared to NH₃ and ND₃, give similar values of 1 and K_{eq}^{D}/K_{eq}^{H} . Therefore, we believe that relationship (8) can be used to estimate the location on the reaction coordinate of the transition state of hydrogen isotope exchange of benzene with a solution of potassium amide in liquid ammonia, and to evaluate the properties of this transition state. Knowing the ratio of the rate constants of tritium exchange in a solution of potassium amide in deuterated and "light" liquid ammonia, $k_{\rm T}^{\rm ND_3/k_{\rm T}^{\rm NH_3}} = (1.9 \times 10^{-5})/(0.9 \times 10^{-5}) = 2.1 (0^{\circ}\text{C}, C_{\rm KNH_2} 0.05 \text{ M})$ (Table 2), we estimated by Eq. (8) the coefficient α for this reaction: $\alpha = 0.85$. This value is close to that ($\alpha \ge 0.8$) obtained usually for reactions in which the negative charge in the forming carbanions is localized and its stabilization is due to the s-orbital effect of the carbon atom of the reaction center and the electrostatic interaction with the other atoms of the molecule, including substituents (see, e.g., [18-22]). A characteristic feature of the reaction in question, and also of similar reactions of other normal CH acids, is also partial preservation of the solvation of the reactants in the transition state, which minimizes the contribution of the energy of reorganization of the polar medium to the activation energy.

Variation of the primary kinetic isotope effect of hydrogen isotope exchange of aromatic CH bonds as influenced by the CH acidity of the substrates. When discussing the results of this section, we used a relatively versatile Eigen's method for qualitative or semiquantitative description of variation of the mechanism of hydrogen isotope exchange in aqueous solutions as influenced by the reactant structure [6]. By analogy with OH and NH acids, Eigen subdivided all the CH acids into two groups: normal acids and pseudo-acids. The important distinctive feature of the normal CH acids is that, when $\log k_{\rm D}$ of their reactions is correlated with pK_a , the so-called Eigen's curves are obtained, each of which can be approximated by linear sections with the coefficients α equal to unity and zero. In an Eigen's curve there is a sharp break in going from the section with $\alpha = 1$ (relatively narrow region where the difference $\Delta p K_a$ between $p K_a$ of the CH acids under consideration and pK_a of water autoprotolysis differs from zero) to the section with $\alpha = 0$ (a narrow region in the vicinity of $\Delta p K_a = 0$).

Table 4. Mean values of the rate constants of protodedeuteration $(k_D^{\rm NH_3})$ and protodetritiation $(k_T^{\rm NH_3})$ and the ratios $k_D^{\rm NH_3}/k_T^{\rm NH_3}$ for deuterium and tritium exchange in isotopically substituted fluorobenzenes in a solution of sodium amide in liquid ammonia $(m_{\rm Na}/m_{\rm s} = 0.2)^{\rm a}$

Compound	Compound Tem- pera- ture, °C		$k_{\mathrm{T}}^{\mathrm{NH}_{3} \times 10^{5}}, \mathrm{s}^{-1}$	f^{b}	$k_{\mathrm{D}}^{\mathrm{NH}_{3}/}$ $k_{\mathrm{T}}^{\mathrm{NH}_{3}}$	
Fluoro- benzene-	-10 0	7.6±0.2 16±2	2.9 ± 0.1 6.3 ± 0.2	17	2.6	
3D(t)	0	11101	051000		2.0	
Fluoro-	0	1.1 ± 0.1	0.5 ± 0.02	1 1	2.0	
4D(t)	15	4.1±0.2	2.1 ± 0.2	1.1	2.0	
	25	9.6 ± 0.5	4.5 ± 0.2		2.1	
Benzene- D(t)	0	0.9 ± 0.1	_	1.0	_	

^a Here and hereinafter, m_{Na} is the number of moles of sodium amide. ^b (f) Factor of the partial rate of deuterium exchange.

As for pseudo-CH acids, they exhibit a wide linear correlation between $\log K_{\rm D}$ and $pK_{\rm a}$ with the coefficient α ranging from 0 to 1. Let us briefly discuss the mechanistic features of deuterium exchange of normal Eigen's CH acids. It is believed at present that variations of α are due to a change in the limiting stage of the overall reaction mechanism. In particular, when the Brønsted coefficient α is equal to unity, two stages partially determine the reaction rate: diffusion separation of the contact complexes (k_2) and ionization of the CH acid (k_1) [scheme (1)] [7, 22]. In contrast, the value $\alpha = 0$ corresponds to the mechanism in which formation of the primary "contact" complex >CH \cdot B⁻ is a fully equilibrium process, and the rate-determining stage is separation of the primary and secondary contact complexes.

Study in this respect of variations of the kinetic isotope effect of various protolytic processes in water showed that, with a normal CH acid whose pK_a is considerably greater than that of water autoprotolysis, the ratio k_D/k_T takes relatively low values (1.5 < $k_D/k_T < 2.2$). In going to related CH acids whose pK_a differs from that of water autoprotolysis to a lesser extent, the ratio k_D/k_T gradually increases, with the ionization of the CH acids remaining a partially limiting stage. Fiinally, if pK_a of the CH acid is close to that of the conjugated acid of the reacting base, the ratio k_D/k_T decreases jumpwise, becoming close to unity ($1 < k_D/k_T < 1.1$). In the latter case the limiting stage is the diffusion-controlled transition from the primary to the secondary contact complex.

Available data for verifying the validity of the above relationships as applied to variations of the kinetic isotope effect of hydrogen isotope exchange in benzene and its derivatives with solutions of amides $(NH_2^- \text{ or } C_6H_{11}NH^-)$ in nonaqueous solutions are extremely scarce. Nevertheless, it is possible to explain in terms of the Eigen's theory the data on the kinetic isotope effect in deuterium and tritium exchange of a limited set of compounds (benzene and its fluorinated derivatives) with cyclohexylamine, catalyzed with lithium cyclohexylamide. The Brønsted coefficient α for this reaction is close to unity [23], and hence we deal with normal CH acids. If, using data in [24, 25], we consider the trend in variation of $k_{\rm D}/k_{\rm T}$ depending on pK_a or the partial rate factor $f = k_D(C_6H_5X)/k_D(C_6H_6)$ (X is a substituent), we see that the kinetic isotope effect increases with decreasing pK_a or with increasing log f in the following order: benzene-D(t) (k_D/k_T 1.6, p K_a 43, log f 0), fluorobenzene-4D(t) $(k_D/k_T 1.9, pK_a 41.9, \log f 0.03)$, fluorobenzene-3D(t) $(k_{\rm D}/k_{\rm T} 2.0, \, {\rm p}K_{\rm a} \, 40, \, \log f \, 1.95)$, trifluoromethylbenzene-3D(t) ($k_{\rm D}/k_{\rm T}$ 2.4, no data on p $K_{\rm a}$, log f 2.59), and fluorobenzene-2D(t) ($k_{\rm D}/k_{\rm T}$ 3.0, p $K_{\rm a}$ 37.3, $\log f$ 5.43). Streitwieser and Mares [24] have not revealed a sharp decrease in the kinetic isotope effect in the range of pK_a values in which the exchange rate is determined not by the stage of ionization of the CH bond but by another stage insensitive to the isotope substitution of hydrogen in the substrate. According to the theory, this pK_a range should be located in the vicinity of pK_a of cyclohexylamine autoprotolysis, 40.3 [26].

The influence of substituents and heteroatoms on the kinetic isotope effect of deuterium exchange of aromatic CH bonds in benzene with a solution of potassium amide in liquid ammonia was not studied at all. Shapiro *et al.* [27] compared, however, the relative kinetic acidities in this catalytic system with previously published [24] data on the relative kinetic acidity of systems that strongly differ in the protophilic power and are characterized by $\alpha = 1$. The close coincidence of the ratios $f = [k_D(C_6H_5X)/k_D(C_6H_6)]$ suggests that the behavior of benzene and its derivatives in this reaction corresponds to the behavior of normal Eigen's CH acids.

To find whether the trends in variation of the kinetic isotope effect in hydrogen isotope exchange of aromatic CH bonds with a solution of potassium (or sodium) amide in liquid ammonia are consistent with the Eigen's theory developed for aqueous solutions, we measured the variations of the isotope effect of the reaction in benzene as influenced by the fluorine substituent and its position in the ring. When studying

the hydrogen isotope exchange of fluorobenzene-3D(t)and fluorobenzene-4D(t), which is very fast, we used as catalyst not potassium amide but less soluble (solubility 0.012 M at 20°C) sodium amide. The results are listed in Table 4. Their comparison with the above data shows that the kinetic isotope effects of the hydrogen isotope exchange in benzene and deutero derivatives of fluorobenzene with solutions of alkali metal amide in liquid ammonia and of lithium cyclohexylamide in cyclohexylamine vary similarly: $(k_{\rm D}/k_{\rm T})_{ortho}$ > $(k_{\rm D}/k_{\rm T})_{meta} > (k_{\rm D}/k_{\rm T})_{para} \approx (k_{\rm D}/k_{\rm T})_{\rm C_6H_6}$. This fact seems natural, because with respect to the protophilic properties the latter catalytic system is close to solutions of amide ions in liquid ammonia. A note should be made, however, about the isotope exchange of the o-hydrogen atoms in fluorobenzene. The rate of this reaction in the system NH₂⁻-NH₃(liquid) is too high, and we could not determine the ratio $(k_D^{NH_3}/k_T^{NH_3})_{ortho}$. As seen from Tables 1 and 4, in both reaction series the ratio $k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3}$ tends to increase with increasing relative kinetic acidity characterized by the factor f. There can be two reasons for the observed increase in the kinetic isotope effect: influence of F either on the mechanism of isotope exchange, decreasing the internal return, or on the structure of the transition state. To choose between these two alternatives, we used the models involving the basic physics of proton transfer in solution [18]. Indeed, previously the set of data on this problem were obtained with these models according to which the constant k_{-1} [scheme (1)] is mainly related to the effective (statistical mean) vibrational frequency of the nuclei in the solvent and reactant molecules (ω_{eff}). Since the solvent molecules prevail, they make the major contribution to ω_{eff} . Therefore, for protolytic processes in the same catalytic system, k_{-1} is practically the same for different reactions. Thus, we can conclude that the above-noted influence of the strength of the CH acids on the kinetic isotope effect is mainly due to the fact that the extremely asymmetrical structure of the transition state in the case of benzene becomes less asymmetrical in going to the reactions of *m*- and *o*-H atoms in fluorobenzene.

Additional information on the mechanistic features of hydrogen isotope exchange of aromatic CH bonds can be, generally speaking, derived from the comparison of the influence of heteroatoms (N, NO) in the aromatic ring on the kinetic CH acidity and kinetic isotope effect with that of fluorine substituent. However, such a comparison involves methodical problems. First, the rates of hydrogen isotope exchange in pyridine-3D(t) and pyridine-2D(t) *N*-oxide were kinetically measurable only at low temperatures (from -50 to -25° C) in the presence of sodium amide, i.e., under

conditions when the exchange kinetics of the other compounds of the reaction series could not be studied by common procedures. Furthermore, to evaluate the kinetic isotope effect, it was necessary to estimate preliminarily what part of the dissolved alkali metal amide can be spent in side reactions. It was found in [28] that the color in the reaction mixtures originates from reversible addition of amide ions to the substrate molecules. To elucidate the influence of this side process on the kinetics of isotope exchange, we performed special experiments involving simultaneous measurement of the rate constants for the heterocycle being tested and an indicator compound chemically inert toward amide ions under the reaction conditions. As such indicator we chose fluorobenzene-3D. The conditions and results of experiments on concurrent exchange of pyridine-2D and pyridine-3D with the indicator are listed in Table 5. Comparison of Tables 4 and 5 shows that the exchange rate constants of both CH acids are equal, within the experimental error, to the values obtained for these compounds in control experiments under the same conditions. Thus, the potentially possible addition of amide ion to the aromatic ring has no effect on the kinetics of deuterium exchange in pyridine.

An opposite result was obtained in concurrent exchange in mixtures of pyridine-2D *N*-oxide and benzene-D (indicator) and of pyridine-2D *N*-oxide and naphthalene-1D (indicator). The reaction of the indicator hydrocarbon under the reaction conditions (25° C, C_{KNH_2} 0.1 M) is fully suppressed, whereas in the *N*-oxide the deuterium exchange is so fast that its kinetics cannot be measured. This fact indicates that under the reaction conditions potassium amide strongly interacts with the molecules of the aromatic heterocycle and that pyridine *N*-oxide is capable of active hydrogen isotope exchange with the solvent even in the presence of very low concentrations of amide ions.

The above experiments have not allowed determination of the true concentration of the NH₂⁻ ions in solution. To estimate, at least approximately, the factor of the partial exchange rate, we compared the exchange kinetics in benzene-D and pyridine-2D *N*-oxide. In the latter compound the rate of deuterium exchange could be measured by common procedures only at low temperature (-37°C, Table 6). For deuterium exchange in benzene-D as reference, $k_D^{\rm NH_3}$ was determined by calculation from the experimental activation energy E_a 15.7±0.2 kcal mol⁻¹ and the preexponential factor log *A* 7.8. For the exchange rate constant of benzene we obtained thus the value $k_D^{\rm NH_3}$ 3 × 10^{-7} s⁻¹, and for pyridine-2D *N*-oxide the exchange factor *f* was greater than 4300.

Run	Tempe-	Experiment	Experiment	Experiment duration.	Experiment duration	$m_{\rm a}/(m_{\rm s}$ +		$I_{\rm rel}^{\rm i},^{\rm b}$ %		$k_{\mathrm{D}}^{\mathrm{NH}_3 \times 10^5}$,		<i>I</i> ^h _{rel} , ^b %		$k_{\rm D}^{\rm NH_3} \times 10^5$,
no.	°C	h	m _i)	96	97	98	s ⁻¹	79	80	81	s ⁻¹			
1	0	2.0	102.2	79.9	20.1	_	15.1	42.2	54.3	3.5	2.1			
2		3.0	96.7	86.8	12.9	0.3	13.7	47.7	50.1	2.2	1.6			
3	-25	1.5	98.0	22.5	77.5	_	1.4	75.0	24.8	0.1	26			
4		3.0	89.9	27.5	72.5		1.3	90.5	9.5	_	22			

Table 5. Conditions and results of experiments on protodedeuteration of a mixture of pyridine-D₁ with fluorobenzene-3D $(m_s: m_i = 1: 1)$ in a solution of sodium amide in liquid ammonia^a

^a (m_i) Number of moles of the indicator compound. For run nos. 1 and 2: the heterocycle is pyridine-2D (initial relative intensity of the peaks in the mass spectrum: 79, 37.0; 80, 61.0; 81, 2.0) and the indicator compound is fluorobenzene-3D (initial relative intensity of the peaks: 96, 40.7; 97, 59.2; 98, 0.1); for run nos. 3 and 4: heterocycle pyridine-3D (79, 4.9; 80, 90.5; 81, 4.6) and indicator fluorobenzene-3D (96, 16.4; 97, 85.5; 98, 0.1). ^b (I_{rel}^i , I_{rel}^h) Relative intensities of the peaks of the indicator compound and heterocycle in the mass spectrum, respectively.

Table 6. Conditions and results of experiments on protoded euteration $(k_D^{NH_3})$ of pyridine-2D *N*-oxide in a solution of sodium amide in liquid ammonia (-37°C)

Run no.	Experiment	m_{a}/m_{s}	m_{Na}/m_s	Relativ	$k_{\rm D} \times 10^5$,			
	duration, n			95	96	97	98	S -
		Initial sa	Imple	15.4	79.6	3.6	1.4	_
1	0.2	86	0.18	52.6	46.9	0.5	-	1100
2	0.25	129	0.22	71.8	21.8	6.3	_	1400

To estimate the partial rate factors of deuterium exchange in quinolines-2D and -3D, it was appropriate to compare the exchange rates of quinolines-6D and -8D with those of naphthalenes-1D and -2D. These results are listed in Table 7. It seems from their comparison that the cyclic nitrogen atom strongly deactivates the 6 and 8 positions of the ring with respect to the hydrogen exchange of the aromatic CH bond: In going from naphthalene-1D to quinoline-8D (or from naphthalene-2D to quinoline-6D), the rate constant decreases by 2-3 orders of magnitude. However, actually this is not the case. According to published data, the pyridine ring of quinoline has a very weak effect on the reactivity of the annelated benzene ring [29]. The drastic decrease in the deuterium exchange rate is due to formation of addition complexes of quinoline with amide ions in solution, resulting in disappearance of free amide ions. Assuming that the exchange in the 6 position of quinoline should occur at almost the same rate as in the 2 position of naphthalene and that the rate of deuterium exchange is approximately proportional to the catalyst concentra-tion, we found that actually to $k_{\rm D}^{\rm NH_3}$ of quinoline-6D corresponds the concentration of amide ions $C_{\rm KNH_2}$ 2.2×10^{-4} M. Based on these data on the true concentration of amide ions and on the results of comparative kinetic studies of deuterum exchange in quinoline-2D, quinoline-3D, and naphthalene-2D, we calculated the relative exchange rates of heterocyclic compounds, with the rate of hydrogen isotope exchange in benzene at the same temperature and the same concentration of amide ions taken as unity (Table 7). The average rate constants of deuterium and tritium exchange in some aromatic nitrogen-containing heterocycles, the corresponding partial rate factors, and the kinetic isotope effects required for subsequent discussion are given in Table 8.

However, before discussing data in Table 8, we should examine the possibility of constructing the general series including the deutero derivatives of both fluorobenzene and heterocycles, as the structural similarity of the compounds of these classes is not evident. We believe that the general consideration of the electronic interactions in substituted benzenes and heteroaromatic compounds can be based on the traditional $\sigma\rho$ analysis. In terms of this approach, various types of electronic effects were distinguished and vari-

ous σ constants were obtained for the pyridine nitrogen atom and the *N*-oxide group as local structural elements of the molecules [30]. Previously [31–33], using these σ constants, the kinetic data on hydrogen isotope exchange in substituted benzenes and the heterocycles under consideration with alkali metal amide in liquid ammonia were treated by correlation analysis. In particular, a correlation was constructed between the partial rate factors of *o*-substituents in the benzene rings and the σ_I constants [32, 33]:

$$\log f_{ortho} = 12.3\sigma_I - 0.37; r 0.991, s 0.3, n 8.$$
 (9)

The influence of the *N*-oxide group on the acidity of the adjacent aromatic CH bond follows relation (9) with the induction constant of this group $\sigma_I(NO)$ 1.0, following the conclusions in [30]. The correlation of log f_{meta} with the σ_{meta} constants is somewhat worse:

$$\log f_{meta} = 8.85\sigma_{meta} - 0.16; \ r \ 0.964, \ s \ 0.4, \ n \ 7.$$
(10)

The point for pyridine-3D lies on the regression line if the action of the induction effect of the N atom is characterized by the value $\sigma_{meta}(3 - N=) = 0.45$ [30]. Note that the choice of the σ_I and σ_{meta} constants for analysis of this reaction series is governed by the fact that the negative charge arising on the hydrogen atom in the transition state cannot efficiently interact with the π system, and the resonance effects appear to be much less important than the inductive effect.

Since substituted benzenes and aromatic nitrogencontaining heterocycles can be covered by general correlations only when the reaction mechanism does not change cardinally in going from one compound to another, it is appropriate to discuss the kinetic isotope effect in both groups of compounds from a common viewpoint. In this connection, it should be noted first that, whereas variations of the factor f and kinetic isotope effect in deuterated fluorobenzenes are corre-

Table 7. Average rate constants of protoded euteration $(k_D^{\text{NH}_3})$ of monodeutero-substituted naphthalenes and quinolines in a solution of potassium amide in liquid ammonia $(C_{\text{KNH}_2} \ 0.1 \ \text{M})^{\text{a}}$

^a 5–6 runs at each temperature. ^b The true constant $k_D^{\text{NH}_3}$ at C_{KNH_2} 0.1 M, 25°C is 8.6 × 10⁻³ s⁻¹, f 50; for naphthalene-2D the factor f was taken equal to 6. ^c The true constant $k_D^{\text{NH}_3}$ at C_{KNH_2} 0.1 M, 0°C is 7.2 × 10⁻³ s⁻¹, and at 25°C, 9 × 10⁻² s⁻¹; f 840 and 2700, respectively.

lated, with aromatic heterocycles this is not always the case. For example, although the accelerating effect of replacement of the 3-CH bond in the benzene molecule by a nitrogen atom (Table 8) is significant (f 120), the number and accuracy of measurements are insufficient to reliably differentiate the kinetic isotope effect of hydrogen exchange in both compounds (1.9 and 2.1, respectively). With hydrogen exchange in quinoline-3D(t), the pattern is somewhat different. The kinetic isotope effect increases to a considerably greater ex-

Table 8. Average rate constants of protodedeuteration $(k_D^{NH_3})$, protodetritiation $(k_T^{NH_3})$, and the ratio $k_D^{NH_3}/k_T^{NH_3}$ for deuterium and tritium exchange of some aromatic nitrogen-containing heterocycles in a solution of alkali metal amide in liquid ammonia^a

Гетрега- ture, °С	Alkali metal amide	$k_{\rm D}^{\rm NH_3 \times 10^5}$, s ⁻¹	$k_{\rm T}^{\rm NH_3 \times 10^5}$, s ⁻¹	f	$k_{\mathrm{D}}^{\mathrm{NH}_3/k_{\mathrm{T}}^{\mathrm{NH}_3}$
0 -10	NaNH ₂	2.1 ± 0.1 4.7 ± 0.2	1.5 ± 0.1 4.0 ± 0.1	2.2	1.3 1.2
-37	NaNH ₂	3.7 ± 0.1	1.8 ± 0.2	120	2.1
-37	$NaNH_2$	$1400\pm\!70$	1300 ± 70	4300	1.1
40	KNH ₂	26 ± 2^{b}	18 ± 2^{b}	50	1.4
15	KNH ₂	8.1 ± 0.6^{b}	3.0 ± 0.1^{b}	1800 ± 900	2.7
ſ	empera- ure, °C 0 -10 -37 -37 40 15	$\begin{array}{c c} empera-ure, \ ^{\circ}C & Alkali \ metal \\ amide \\ \hline 0 & NaNH_2 \\ -10 \\ -37 & NaNH_2 \\ -37 & NaNH_2 \\ 40 & KNH_2 \\ 15 & KNH_2 \\ \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

^a 5-6 runs at each temperature. ^b Apparent rate constants, without taking into account the loss of amide ions from solution as a result of interaction.

tent as compared to benzene or pyridine-3D(t). An increase in f by a factor of ~1800 is accompanied by the same increase in the ratio $k_D^{NH_3}/k_T^{NH_3}$ as that observed in going from benzene-D(t) to fluorobenzene-3D(t) (*f* 17). Despite the lower sensitivity of the kinetic isotope effect to increase in the rate in the case of pyridine-3D(t) and quinoline-3D(t), we conclude that, similar to 3-F substituent in benzene, incorporation of the cyclic nitrogen atom into the aromatic system of the ring (1 position) does not alter the mechanism of hydrogen isotope exchange in quinoline-3D but only shifts the position of the transition state at the same reaction mechanism.

Certain problems arise in interpretation of the abnormal decreases in both the rate and the ratio $k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3}$ for hydrogen isotope exchange in pyridine-2D(t) and quinoline-2D(t) (Table 8). The factors f and the ratios $k_D^{\text{NH}_3}/k_T^{\text{NH}_3} \approx 1.1-1.4$ for these compounds deviate from data obtained for the other examined compounds. As the σ_I constant of the cyclic nitrogen atom is relatively large (σ_1 0.45 [30]), the behavior of pyridine-2D(t) in hydrogen isotope exchange cannot be described in terms of the existing views on the electron-acceptor inductive effect of nitrogen on the adjacent reaction center. Nevertheless, the low values of f and $k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3}$, which are difficult to explain in terms of a purely inductive effect, can be interpreted assuming that in the examined compounds the kinetic isotope effect in the course of rearrangement of the intramolecular structure is determined by superposition of the inductive effect and an effect of the opposite sign originating from direct interaction of the lone electron pairs of the nitrogen atom and the anionic carbon atom in the adjacent position of the ring [30]. The latter effect is manifested not only in the kinetics of deuterium exchange or in the $k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3}$ values but also in variations of various physical quantities [intensities of stretching vibrations of aromatic CH bonds in the IR spectra, resonance frequencies $v(^{35}Cl)$ in the NQR spectra, etc.], i.e., in cases when the indicator center lies in the aromatic ring plane. Judging from the partial rate factor of deuterium exchange in quinoline-2D, the α effect of the lone electron pair is considerably weakened relative to that in pyridine- $2D_1$ (Table 8). Nevertheless, the kinetic isotope effect in this reaction remains low as compared to the hydrogen exchange in benzene.

As already noted, the regular increase in the rate of the hydrogen isotope exchange in pyridine-2D(t) *N*oxide exhibiting the highest σ_I constant among all the examined CH acids confirms the assumed common induction mechanism of activation of the reaction center. At the same time, the isotope effect in isotope exchange with pyridine-2D(t) *N*-oxide is the lowest or is totally lacking $(k_{\rm D}^{\rm NH_3}/k_{\rm T}^{\rm NH_3} \leq 1.1)$ (Table 8). The fact that introduction of the NO group considerably enhances the CH acidity and simultaneously drastically decreases the kinetic isotope effect strongly suggests that the above anomaly is due to the Eigen's condition according to which in the point $\Delta p K_a$ the isotope effect is close to unity. To check this assumption, it is necessary, however, to estimate pK_a of pyridine-2D N-oxide as CH acid. The difficulty of determining this quantity is due to the lack of reliable estimates for the factor f of deuterium exchange in pyridine-2D(t) N-oxide (see above). Therefore, we restricted our task to estimating the order of magnitude of pK_a rather than determining its value. For this purpose, we applied to the case of the acid-base equilibrium in liquid ammonia the approach used previously [23, 24] for calculating pK_a of mono- and polyfluorinated benzenes in a solution of cesium cyclohexylamide in cyclohexylamine. Streitwieser et al. [23, 24] proceeded from the fact that the coefficient α of the Brønsted relationship in this catalytic system is 1, and pK_a of the parent compound, benzene, is 43. This fact allowed calculation of pK_a of each particular compound belonging to the examined reaction series using a simple formula $pK_a(C_6H_5X) = pK_a(C_6H_6) - pK_a(C_6H_6)$ log f. Since the relative kinetic acidities of the aromatic CH bonds in benzene and its derivatives do not change in going from the above system to a solution of potassium amide in liquid ammonia [27], we estimated the upper level of pK_a of pyridine-2D N-oxide: $pK_a \leq 38$. The latter value is close to pK_a of autoprotolysis of liquid ammonia (pK_a 35). Hence, in the case of pyridine-2D N-oxide the reaction mechanism can be different, with the diffusion-controlled separation of the primary and secondary contact complexes (rate constant k_2) becoming the limiting stage.

Thus, in this work, with quite a different kinetic material as compared to [7, 20–22] and with a strongly protophilic medium, we confirmed the applicability of the Eigen's theory to the mechanism of hydrogen isotope exchange of aromatic CH bonds.

EXPERIMENTAL

Manipulations with solutions of alkali metal amides in liquid ammonia were performed in special apparatus resistant to high pressures and preventing access of moisture and oxygen. Commercial deuterated organic compounds were used; they were purified and dried before experiments. Tritium-labeled deuterated compounds were prepared via the corresponding organomagnesium derivatives which were hydrolyzed with deuterium and tritium oxide. Also, the majority of nitrogen-containing heterocycles-D,t were prepared from the corresponding halo derivatives by reduction with zinc dust in deutero(tritio)sulfuric acid. Quinoline-2D(t) was prepared by decarboxylation of quinaldic acid. Anhydrous liquid ammonia and deuteroammonia (94–99 at. %) were used.

The rates of deuterium and tritium exchange were measured in solutions containing usually 100–150 mol of a solvent per mole of an organic compound. The deuterium concentration was determined with an MI-1201 mass spectrometer at an ionizing electron energy of 12–14 eV. The tritium activity was measured using a scintillation counter with two coaxial photomultipliers operating in the coincidence mode. The scintillation procedure was used in two versions: (a) samples of organic compound before and after experiments were introduced directly into the scintillation solution; (b) tritium-labeled ammonia was burned over CuO, and the resulting water was dissolved in the scintillator. The measurement conditions were strictly fixed.

The rate constants of deuterium and tritium exchange, calculated by a first-order equation, had stable values in all the systems studied.

REFERENCES

- 1. Malykhin, E.V. and Shteingarts, V.D., *Zh. Ross. Khim. O*-*va*, 1999, vol. 43, no. 1, pp. 49–56.
- Huisgen, R., Mack, W., Herbig, K., and Ott, N., Chem. Ber., 1960, vol. 93, no. 2, pp. 412–424.
- Hertog, H.J., Pieterse, M.J., and Burman, D., *Recl. Trav. Chim. Pays-Bas*, 1963, vol. 82, no. 12, pp. 1173–1178.
- 4. Martens, P.J. and Hertog, H.J., *Recl. Trav. Chim. Pays-Bas*, 1964, vol. 83, no. 6, pp. 621–630.
- 5. Illuminatti, N., *Adv. Heterocycl. Chem.*, 1965, vol. 4, pp. 285–314.
- Eigen, M., Angew. Chem. Int. Ed. Engl., 1964, vol. 3, no. 1, pp. 1–19.
- Washabaugh, M.W. and Jencks, W.P., J. Am. Chem. Soc., 1989, vol. 111, no. 2, pp. 683–692.
- Shatenshtein, A.I., Yakushin, F.S., and Arshinova, M.I., *Kinet. Katal.*, 1964, vol. 5, no. 6, pp. 1000– 1007.
- Streitwieser, A., Hollyhead, W.B., Pudjaatmaka, A.H., and Owens, P.H., J. Am. Chem. Soc., 1971, vol. 93, no. 20, pp. 5088–5096.
- 10. Thibbin, A., Onicido, I., and Ahlberg, P., *Chem. Scripta*, 1982, vol. 19, no. 3, pp. 145–148.
- Shapiro, I.O., Ranneva, Yu.I., and Shatenshtein, A.I., *Zh. Org. Khim.*, 1986, vol. 22, no. 6, pp. 1332–1333.
- Bell, R.P., *The Proton in Chemistry*, Ithaca: Cornell Univ. Press, 1973, 2nd ed. Translated under the title *Proton v khimii*, Moscow: Mir, 1974, pp. 291, 297.
- 13. Teplofizicheskie svoistva ammiaka: Spravochnik

(Thermal Properties of Ammonia: Handbook), Moscow: Izd. Standartov, 1978, p. 143.

- Tupitsyn, I.F., Semenova, N.K., and Avdulov, G.I., in Radioisotopes in the Physical Sciences and Industry, Vienna: IAEA, 1962, pp. 255–257.
- 15. Westheimer, F.H., *Chem. Rev.*, 1961, vol. 61, no. 3, pp. 265–273.
- 16. Steffa, L.J. and Thornton, E.R., J. Am. Chem. Soc., 1967, vol. 89, no. 23, pp. 6149–6156.
- Gold, V. and Grist, S., J. Chem. Soc., Perkin Trans. 2, 1972, no. 1, pp. 89–95.
- Shapiro, I.O., *Fizicheskaya khimiya. Sovremennye problemy* (Physical Chemistry. Modern Problems), Moscow: Khimiya, 1987, pp. 129–164.
- Lin, A.C., Chang, A.C., Dahlberg, Y., and Kresge, A.J., J. Am. Chem. Soc., 1983, vol. 105, no. 16, pp. 5380– 5386.
- Aroella, T., Arrowsmith, C.H., Hojatti, M., and Kresge, A.J., *J. Am. Chem. Soc.*, 1987, vol. 109, no. 23, pp. 7198–7199.
- 21. Kresge, A.J. and Powell, M.F., J. Org. Chem., 1986, vol. 51, no. 6, pp. 819–822.
- 22. Argyrou, A. and Washabaugh, N.W., J. Am. Chem. Soc., 1999, vol. 121, no. 51, pp. 12054–12062.
- Streitwieser, A., Scannon, P.J., and Niemeyer, K., J. Am. Chem. Soc., 1972, vol. 94, no. 22, pp. 7936– 7937.
- 24. Streitwieser, A. and Mares, F., J. Am. Chem. Soc., 1968, vol. 90, no. 3, pp. 644-648.
- 25. Stratakis, M., Wang, P.J., and Streitwieser, A., J. Org. Chem., 1996, vol. 61, no. 9, pp. 3145–3150.
- 26. Streitwieser, A. and Guibe, B., J. Am. Chem. Soc., 1978, vol. 100, no. 14, pp. 4523-4534.
- Shapiro, I.O., Ranneva, Yu.I., and Shatenshtein, A.I., *Zh. Obshch. Khim.*, 1979, vol. 49, no. 9, pp. 2030– 2036.
- 28. Kane, A.A. and Tupitsyn, I.F., in *Khimiya i tekhnologiya izotopov* (Chemistry and Technology of Isotopes), Leningrad: Khimiya, 1967, pp. 232–236.
- 29. *Heterocyclic Compounds*, Elderfield, R.C., Ed., New York: Chapman and Hall, 1950. Translated under the title *Geterotsiklicheskie soedineniya*, Moscow: Inostrannaya Literatura, 1955, vol. 4, pp. 83–96.
- Zatsepina, I.F., Kirova, A.V., and Tupitsyn, I.F., *Reakts. Sposobn. Org. Soedin.*, 1968, vol. 5, no. 1, pp. 70–87.
- Tupitsyn, I.F., Zatsepina, N.N., Kirova, A.V., and Kapustin, Yu.M., *Reakts. Sposobn. Org. Soedin.*, 1968, vol. 5, no. 3, pp. 601–611.
- Ranneva, Yu.I. and Shatenshtein, A.I., in *Korrelya-tsionnye uravneniya v organicheskoi khimii* (Correlation Equations in Organic Chemistry), Tartu: Tartusk. Gos. Univ., 1962, vol. 1, pp. 136–149.
- Kamrad, A.G., *Reakts. Sposobn. Org. Soedin.*, 1968, vol. 5, no. 3, pp. 701–710.