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Isotope Effects and Hydrogen Exchange Mechanism in Compounds Having Labile Aliphatic C–H Bonds in Basic Liquid Ammonia Solutions

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Abstract—Specific features of the stepwise hydrogen exchange mechanism and transition state structure in the systems acetophenone–liquid ammonia in the absence of foreign compounds and in the presence of bases and toluene–liquid ammonia in the presence of potassium amide were studied in terms of an approach based primary and secondary kinetic isotope effects of the substrate and the solvent. The mechanisms of reactions involving acetophenone and toluene were compared. In the first case, an elementary act of CH-acid ionization is contributed to a small extent by diffusion-controlled separation of the carbanion and ammonia molecule. hydrogen exchange in toluene is characterized by complete absence of the internal ion pair return effect. The ratio $k_D^{NH_3}/k_T^{NH_3}$ for hydrogen exchange in acetophenone tends to decrease on addition of bases (with simultaneous increase in its rate), which may be explained by formation of an adduct via interaction between the unshared electron pair on the heteroatom in the base molecule and the carbonyl carbon atom. The anomalous temperature dependence of $k_D^{NH_3}/k_T^{NH_3}$ for hydrogen exchange in toluene is interpreted as a result of contribution of side metalation of the C–H bond by potassium amide. The change in the solvent protophilicity due to replacement of the "light" solvent by deuterated one differently affects the kinetics and mechanism of hydrogen exchange in acetophenone and toluene. Measurements of the α-deuterium effect gave information on the mode of angular deformation of C–D bonds in the methyl group of toluene in the hydrogen exchange transition state.

We previously examined the effects of structural and solvation factors on the equilibrium and kinetic parameters of proton transfer in compounds characterized by different labilities of aliphatic C–H bonds [1]. We made an attempt to study the mechanism of hydrogen isotope exchange in some compounds in basic liquid ammonia solutions. Apart from the results obtained in [1], there are many published data on the effect of structural factors, solvent properties, and catalyst on the rate of H–D exchange in compounds belonging to different classes both in liquid ammonia in the absence of other bases and especially in the catalytic system KNH_2–liquid NH_3 [2–4]. Taken together, these results provide a good basis for drawing conclusions related to protolytic reactivity of CH acids, such as those concerning the order of variation of kinetic CH acidity in series of structurally similar substrates, dependence of the rate constant on the base protophilicity, degree of similarity of transition states to reagents and products, etc. However, little attention was given so far to fine details of the mechanism of hydrogen exchange between liquid ammonia and compounds having labile aliphatic C–H bonds. Therefore, some specific features of hydrogen exchange mechanism have not been interpreted unambiguously. In addition, we should note insufficient substantiation of the existing concepts of interrelation of the rate-determining elementary steps, poor data on specific linear and angular structure of the transition states, and scanty information on possible complications caused by solvent factors. The latter issue originates from both incomplete utilization of the available theoretical basis and shortage of experimental data on kinetic isotope effects in hydrogen exchange in liquid ammonia solution. In rare cases, where the mechanism of such reactions was studied, the specificity of intermediate steps was derived as a rule from only primary kinetic isotope effect which was measured at a single temperature (see, e.g., [5]). The results thus obtained could not provide a complete phenomenological pattern; they should be regarded as preliminary and requiring further exploration. In terms of the above stated, it should be noted that the situation with mechanisms of protolytic reactions in aqueous or alcoholic medium is quite different. Here, vast experimental data on primary and secondary isotope effects of substrate and solvent were collected and systematized, and criteria for determination of the mechanism were found on the basis of isotope effect measurements. Joint study of the above effects ensured quantitative description of all specific features intrinsic to such processes. Undoubtedly, the way of studying the reaction mechanism tested on hydroxyl-containing media can be applied to reactions occurring in liquid ammonia, the more so the degrees of similarity and specificity of the mechanisms of deuterium–tritium exchange in hydroxyl-containing and noaqueous basic polar media (ammonia being a typical representative of the latter) constitute an open problem.

In keeping with the above, in the present work we performed a detailed study of various aspects of hydrogen isotope exchange of typical compounds having aliphatic C−H bonds with liquid ammonia solutions. As subjects of the most detailed investigation we selected H–D exchange in the methyl group of acetophenone with pure liquid ammonia and its solutions containing basic substances and H–D exchange in the methyl roup of toluene with a solution of potassium amide in liquid ammonia. These media are polar and strongly basis; therefore, as a rule they do not give rise to ion association. The selected substrates are readily soluble therein even at low temperatures. However, the above media are capable of specifically interacting with various CH acids, so that interpretation of the mechanism of hydrogen exchange is not expected to be trivial. In some cases, a simple stepwise mechanism may be inappropriate, at least for some processes accompanying isotope exchange could lead to formation of by-products. There are data indicating side formation of an adduct via reaction of ammonia (through unshared electron pair on the nitrogen atom) at the electron-deficient center of acetophenone [4, 6] and coordination of potassium cation to CH acid (metalation of C−H bond in alkylaromatic hydrocarbons) in solutions of potassium amide in liquid ammonia [7].

Our study of the reaction mechanism included a number of techniques which ensured the maximum possible utilization of different kinetic isotope effects, analysis of the dependences of primary isotope effect of the substrate (k_D/k_T) on the temperature and proton-acceptor properties of added bases, and analysis of the behavior of the $k_D^{NH_3}/k_T^{NH_3}$ ratio on variation of CH acidity of the substrate in the presence of the same base.

MECHANISM OF HYDROGEN ISOTOPE EXCHANGE IN THE METHYL GROUP OF ACETOPHENONE

We performed two series of experiments. In the first series, the reaction medium was pure liquid ammonia which contained no compounds possessing basic properties. In the second series, the initial conditions were changed via variation of protophilic properties of the medium.

Primary substrate isotope effect in hydrogen isotope exchange between acetophenone and pure liquid ammonia. It seemed important to determine whether the rate of isotope exchange in the methyl group of acetophenone is limited by the stage of C−D (C−T) bond ionization (k_1) or it is an apparent quantity depending on the preequilibrium intermediate stage.

$$\text{C–L} + \text{NH}_3 \underset{k_{-1}^{\text{L}}}{\overset{k_1^{\text{L}}}{\rightleftarrows}} \text{C}^{\delta-},\ \text{NH}_3\text{L}^{\delta+} \xrightarrow{k_2} \text{C–H} + \text{NH}_2\text{L}. \quad (1)$$

Here, L = D or T; k_1^L and k_{-1}^L are the rate constants of formation and decomposition of intermediate contact complex; and k_2 is the rate constant of diffusion-controlled separation of a solvent molecule from the intermediate complex.

In the initial step of the study, we measured the rate constants of protodedeuteration $k_D^{NH_3}$ and protodetritiation $k_T^{NH_3}$ in the methyl group of α-D(T)-acetophenone with liquid ammonia and determined the ratio of these constants $k_D^{NH_3}/k_T^{NH_3}$. The latter varies from 2.2 to 2.3 throughout the examined temperature range (Table 1). Generally speaking, using the $k_D^{NH_3}/k_T^{NH_3}$ ratios, it is impossible to quantitatively estimate the contribution of each of the above stages to the observed primary kinetic isotope effect of the substrate for the whole reaction. The maximal information which can be derived from the measured $k_D^{NH_3}/k_T^{NH_3}$ values is that is some limiting version of the mechanism operative or not in the reaction under study. In fact, according to scheme (1), the overall protodedeuteration rate constant $k_D^{NH_3}$ or protodetritiation rate constant $k_T^{NH_3}$ is given by formula (2):

$$k_L^{NH3} = k_1^L \cdot k_2/(k_{-1}^L + k_2). \quad (2)$$

Equation (2) is simplified in the two opposite cases where the maximal or minimal primary isotope effect of the substrate is directly related to the ratios of the rate constants for elementary steps, k_1^L, k_{-1}^L, and k_2. If $k_2/k_{-1}^L \gg 1$, according to formula (2) we obtain $k_D^{NH_3}/k_T^{NH_3}$; k_1^D/k_1^T; i.e., we have the isotope difference between the rates of ionization, which reflects the “true” isotope effect. By contrast, if the intermediate contact complex is so strongly reactive that it abstracts proton from the solvent molecule (which participates in the protolytic process) at a higher rate than the rate

Table 1. Average rate constants for protodedeuteration ($k_D^{NH_3}$) and protodetritiation ($k_T^{NH_3}$) and $k_D^{NH_3}/k_T^{NH_3}$ ratios for hydrogen exchange in α-D(T)-acetophenone with liquid ammonia[a]

Temperature, °C	$k_D^{NH_3} \times 10^5$,[b] s^{-1}	$k_T^{NH_3} \times 10^5$, s^{-1}	$k_D^{NH_3}/k_T^{NH_3}$
0	1.0 ± 0.1	0.45 ± 0.05	2.3
15	2.3 ± 0.2	1.0 ± 0.1	2.3
25	5.8 ± 0.3	2.6 ± 0.2	2.2

[a] Mean values from the results of 8–12 experiments.

[b] Tentative values of the Arrhenius parameters: ΔE = 9.2 kcal/mol, $\log A$ = 2.3. A rough estimate of $k_D^{NH_3}$ at –40°C is 2.5×10^{-7} s^{-1}.

Table 2. Average rate constants for deuterodeprotonation $k_H^{ND_3}$ and tritiodeprotonation $k_T^{ND_3}$ and $k_H^{ND_3}/k_T^{ND_3}$ ratios for hydrogen exchange in α-H-acetophenone and α-T-acetophenone with liquid trideuteroammonia[a]

Temperature, °C	$k_H^{ND_3} \times 10^5$, s^{-1}	$k_T^{ND_3} \times 10^5$, s^{-1}	$k_H^{ND_3}/k_T^{ND_3}$
0	8.0 ± 0.7	–	–
15	17 ± 1	1.4 ± 0.1	12.1
25	40 ± 2	–	–

[a] Deuterium concentration in the initial ND_3 98% (of the theoretical value). Here, as well as in Tables 3, 4, and 6, average values from 5–6 experiments (at each temperature) are given.

of transfer of the latter into bulk solution ($k_{-1}^L/k_2 >> 1$), formula (2) is reduced to Eq. (3).

$$k_L = k_1^L/k_{-1}^L \cdot k_2 = K_{eq}^L \cdot k_2. \qquad (3)$$

Taking into account that the equilibrium isotope effect K_{eq}^D/K_{eq}^T is negligible [8] and that the stage described by the rate constant k_2 is insensitive to isotope substitution, kinetic isotope effect is not observed at all: $k_D^{NH_3}/k_T^{NH_3} = 1$.

Our experiments with a solution of α-D(T)-acetophenone in liquid ammonia gave $k_D^{NH_3}/k_T^{NH_3}$ values which correspond to neither theoretical maximum ($k_D^{NH_3}/k_T^{NH_3}$ = 2.6 at 25°C) nor total absence of isotope effect. Then, the primary substrate isotope effect is a complex function of the parameter $a_L = k_{-1}^L/k_2$ which characterizes the effect of internal ion pair return [3]. In other words, both elementary stages k_{-1} and k_2 partialy limit the reaction rate, leading to the observed decrease of isotope effect relative to the maximal value. Nevertheless, it is possible to estimate the partial rate constants k_1^L and k_{-1}^L and their isotope ratios if the experimental $k_D^{NH_3}$ and $k_T^{NH_3}$ values are supplemented by the corresponding values of deuterodeprotonation ($k_H^{ND_3}$) and tritiodeprotonation rate constants ($k_T^{ND_3}$), determined independently. Such experiments were performed for solutions of α-T-acetophenone and “light” α-H-acetophenone in liquid ND_3 (Table 2). The rate constants thus obtained were treated by a univesal procedure which utilizes several empirical formulas. The procedure makes it possible to deduce the true kinetic isotope effect which reflects isotope difference in the rates of dissociation of C–D (C–T) bond at the stage $k_1(k_1^D/k_1^T)$ and to estimate on a quantitative level the effect of internal ion pair return (k_{-1}^L/k_2) [9]. This approach was developed by Streitwieser and co-workers [9]. Its extension to hydrogen exchange in acetophenone with liquid ammonia requires the following to be made. Initially, it is necessary to identify on a qualitative level the possibility for contribution of internal ion pair return to the stage of C−H bond ionization or to make certain that such effect is absent. For this purpose, the empirical exponent in the Swain–Schaad formula was compared to the theoretical maximum y_{max} = 3.34. The latter corresponds to the case when the stage k_1^L in scheme (2) is fully rate-determining.

$$\log (k_H^{ND_3}/k_T^{ND_3}) = y_{max} \log (k_D^{NH_3}/k_T^{NH_3}). \qquad (4)$$

Substitution of the rate constants from Tables 1 and 2 (15°C) shows that the exponent y for the reaction under study differs from the maximal value (y = 3.0). Further on, using the experimental isotope effects $k_D^{NH_3}/k_T^{NH_3}$ and $k_H^{NH_3}/k_T^{NH_3}$ in combination with Eq. (4) and assuming the absence od isotope effect at the stage k_2, we can calculate the contribution of internal ion pair return in the tritium and protium exchange (a_T and a_H) and the true isotope effect at the ionization stage k_1^H/k_1^T according to Eqs. (5)–(7).

$$1 - a_T(B^{1/y} - 1)^{y_{max}} = A + a_T(A - B); \qquad (5)$$

$$\begin{aligned} k_1^H/k_1^T &= (k_H^{ND_3}/k_T^{ND_3}) \\ &\times \{[1 - a_T((K_{eq}^T/K_{eq}^H)(k_H^{ND_3}/k_T^{ND_3}) - 1)]\}^{-1}; \qquad (6) \end{aligned}$$

$$a_H = a_T(K_{eq}^T/K_{eq}^H)(k_1^H/k_1^T). \qquad (7)$$

Here, $A = (k_D^{NH_3}/k_T^{NH_3})^{y_{max}}/(k_H^{NH_3}/k_T^{NH_3})$; $B = (k_D^{NH_3}/k_T^{NH_3})^{y_{max}}/(K_{eq}^T/K_{eq}^H)$; K_{eq}^T/K_{eq}^H is the equilibrium constant.

$$\text{C–T} + NH_3(\text{liq.}) \rightleftarrows \text{C–H} + NH_2T(\text{liq.})$$

According to the data of [10], K_{eq}^T/K_{eq}^H = 1.1. The calculation of $a_T = k_{-1}^T/k_2$ by Eq. (5) involves some inconvenience, for Eq. (5) cannot be solved in an analytical form. Therefore, the solution was found by iteration, and a_T and a_H were estimated at 0.022 and 0.44, respectively (15°C). Thus, the noncatalytic hydrogen exchange in acetophenone can be classed with reactions characterized by a weak (a_T) but nevertheless perceptible (a_H) internal ion pair return. The latter does not hamper attainment of a high isotope effect at the stage of proton transfer from CH acid to base: $k_1^H/k_1^T = 18$. The k_1^H/k_1^T value thus obtained is very close to the theoretical value ($k_1^H/k_1^T = 19$ [11]). In keeping with the simplest version of the transition state theory, this result can be regarded as an evidence for symmetric structure of the transition state in the kinetically controlled C–H ionization stage, which is postulated by the three-center linear model.

Taking into account the structure-dependent nature of isotope effect, we presume that $k_D^{NH_3}/k_T^{NH_3}$ should decrease in going from acetophenone to other analogous CH acids. Indeed, according to the modern concepts, the dependence of k_D/k_T upon CH acidity for structurally similar substrates consists of two branches, ascending and descending, with a maximum at $\Delta pK_a = 0$, where $\Delta pK_a = pK_a$(substrate) – pK_a (autoprotolysis constant of the solvent); in a few cases, the maximum is displaced toward positive or negative ΔpK_a values [12]. The ascending branch of the $(k_D/k_T)_{max}$—pK_a curve corresponds to early transition states which are structurally more similar to the initial state, and the descending branch corresponds to late transition states. A typical example in support of the theoretical views is hydrogen exchange in a series of thiazolium ions in aqueous medium [13]. In the series under consideration, the k_D/k_T ratio attains the maximal value when the difference ΔpK_a for two acids, one of which is a CH acid participating in the reaction and the other is an acid conjugate to a common organic base, is equal to zero. This means that the linear three-center model is valid [13]. An analogous relation between k_D/k_T and ΔpK_a was observed for exchange reactions of fluorene derivatives in a solution of potassium methoxide in methanol [14]. On the basis of available experimental data it is impossible to trace consistently substrate influence on the isotope effect in hydrogen exchange between acetophenone and liquid ammonia. Indene and fluorene are the only hydrocarbons studied, which are structurally related to acetophenone. Their relative inertness suggests that the mechanism of H–D exchange is not complicated. As was shown in [5], the average rate constants and $k_D^{NH_3}/k_T^{NH_3}$ ratios for tritium exchange in indene are $25 \times 10^{-5} \pm 0.1$ s^{-1} and $k_D^{NH_3}/k_T^{NH_3} = 2.0$ at 0°C, i.e., a 25-fold increase in the reaction rate relative to acetophenone corresponds to decrease of the isotope effect from 2.3 to 2.0. This is consistent with the greater (by 4.5 log unit) thermodynamic CH acidity of indene in DMSO (pK_a 20.1) than that of acetophenone (pK_a 24.6). Likewise, the ratio $k_D^{NH_3}/k_T^{NH_3}$ equal to 2.2 at 25°C for hydrogen exchange in acetophenone is smaller than the corresponding value for the more acidic fluorene: $k_D^{NH_3}/k_T^{NH_3} = 1.9$ at 25°C ($pK_a = 22.4$, $k_D^{NH_3} = 16 \times 10^{-5}$ s^{-1} [5]).

Thus, increase in CH acidity leads to a slightly increased asymmetry of the transition state. Unfortunately, the lack of kinetic data for a weaker CH acid than acetophenone does not allow us to speak about attainment of the theoretical maximum of isotope effect in the reactions under comparison.

An additional information on the ratio of partial rate constants k_1, k_{-1}, and k_2 can be derived from analysis of the temperature dependences of the isotope effect. We believe that the number of measurements and their accuracy are sufficient to differentiate $k_D^{NH_3}/k_T^{NH_3}$ values obtained at 0 and 25°C. The data in Table 1 indicate that $k_D^{NH_3}/k_T^{NH_3}$ does not tend to decrease in the temperature range from 0 to 25°C: $k_D^{NH_3}/k_T^{NH_3}$ = 2.3, 2.3, and 2.2 at 0, 15, and 25°C, respectively. This contradicts the commonly accepted view, according to which $k_D^{NH_3}/k_T^{NH_3} = \exp[h(\nu_{CD} - \nu_{CT})/kT]$ on the assumption that the corresponding preexponential factors are similar ($A_D = A_T$). The decrease in the isotope effect in the temperature range 0–25°C attains 10%, if k_D/k_T is taken equal to 2.7.

Unfortunately, published data on the temperature dependence of isotope effect in hydrogen exchange between compounds having a labile aliphatic C–H bond and liquid ammonia are very scanty. The experimental temperature dependence of $k_D^{NH_3}/k_T^{NH_3}$ was obtained only for indene [5]. According to [5], the ratio $k_D^{NH_3}/k_T^{NH_3}$ is 2.3 at –30°C and 2.0 at 0°C. In this case, the temperature dependence of isotope effect is similar to that predicted by the conventional theory for processes in which $k_D^{NH_3}/k_T^{NH_3}$ decreases due to variation of the degree of asymmetry of the three-center transition state at the stage of C–H bond ionization (k_1) [15]. As applied to processes involving internal ion pair return, the temperature dependence of $k_D^{NH_3}/k_T^{NH_3}$ should be different, for the effect of temperature on the constant k_2 [see scheme (1)] should also be taken into account. In this case, the temperature gradient of the experimentally measured $k_D^{NH_3}/k_T^{NH_3}$ ratio can be divided arbitrarily into two parts, one of which characterizes change of isotope effect at the k_1 stage, and the other, its variation due to temperature contribution of internal ion pair return (k_2). The latter contribution has the opposite sign, and it acts to increase the overall istope effect as the temperature rises. This increase directly follows from the close relation between the numerical value of k_2 and diffusion motion which is known to increase with rise in temperature. Insofar as hydrogen exchange in acetophenone involves two concurrent stages, k_1 and k_2, either zero temperature gradient of $k_D^{NH_3}/k_T^{NH_3}$ or even its positive value could be expected. An analogous pattern was observed in [13, 16]. Thus the results of studying temperature dependence of the kinetic isotope effect in hydrogen exchange in acetophenone are consistent with the occurrence of internal ion pair return in this reaction.

Secondary isotope effect of the solvent in hydrogen exchange between acetophenone and liquid ammonia. Further study of the mechanism of hydrogen exchange in acetophenone in liquid ammonia requires fine structure of the transition state to be known. One of the ways to elucidate this problem consists of estimation of the Brønsted coefficient α. Our previous study [1] of the Brønsted relation for hydrogen exchange in liquid ammonia was performed with CH acids belonging to two structural classes: (1) compounds possessing a labile aliphatic C–H bond and giving rise to delocalized carbanions and (2) quasiaromatic compounds (isomeric carboranes). Despite differences between these classes, the relation between the Gibbs activation energy of hydrogen exchange in liquid ammonia ($\log k_D$) and pK_a was found to be linear. The Brønsted coefficient α of the corresponding equation was used to evaluate the degree of structural and energetic similarity of the transition state to products of proton transfer. Although the Brønsted equation is helpful in explaining the mechanism of hydrogen transfer, the results obtained therewith are not always consistent with those derived from the kinetic isotope effects.

An independent way of elucidating the structure of transition state may be determination of α on the basis of the secondary isotope effect of the solvent, i.e., of the ratio of rate constant for tritium exchange in the same substrate with deuterated and and nondeuterated solvent ($k_T^{ND_3}/k_T^{NH_3}$). A theory of secondary isotope effects of a solvent has been developed [17], which is valid for protolytic reactions in water or alcohol [17]. The theory establishes relations between the experimental isotope effect k_T^{OD}/k_T^{OH}, on the one hand, and Brønsted coefficient α and maximum attainable ratio $(k_T^{OD}/k_T^{OH})_{max}$ = 2.4, on the other.

$$k_T^{OD}/k_T^{OH} = (k_T^{OD}/k_T^{OH})^{\alpha}_{max} = 2.4^{\alpha}. \qquad (8)$$

Taking into account an almost complete identity of factors which (in keeping with the theoretical concepts) are responsible for the appearance of secondary isotope effect of the solvent for reactions in water and liquid ammonia [similar deuterium partition coefficients in both liquid media and similar deuterium isotope effects (which are reflected in the ionic products of the solvents)], we used Eq. (8) to estimate the Brønsted coefficient α for the reaction under study. The value of α was thus found to be 0.47 at 15°C. This value can serve as an “internal” criterion of the validity of the previous [1] conclusion on the structure of transition state for hydrogen exchange in liquid ammonia, which (as noted above) was derived from direct comparison of $\log k_D^{NH_3}$ and pK_a. According to [1], the Brønsted coefficient α is 0.74 at 25°C and 0.6 at 120°C. The disagreement between the values of α determined by different methods may be explained by the fact that two different kinds of CH acids were included in a single reaction series. First of all, this applies to isomeric carboranes which give rise to hard intermediate carbanions (i.e., the latter are characterized by a high degree of electron density localization). Therefore, in keeping with the Leffler–Grunwald postulate, inclusion of carboranes should lead to approaching of the transition state structure to that of the final carbanion. Outwardly, this corresponds to some overestimation of α relative to the true Brønsted coefficient for hydrogen exchange in the methyl group of acetophenone. According to the latest concepts, the transition state for hydrogen exchange in acetophenone should approach completely symmetric one with respect to both the magnitude of charge and its distribution. On the whole, the Brønsted coefficient α is consistent with the conclusion drawn in the previous section, i.e., that the transition state in the reaction under study has a symmetric structure.

Effect of bases on the kinetics and mechanism of hydrogen exchange in acetophenone. In the next step of our study we made an attempt to estimate the effect of substances capable of acting as proton acceptors on the kinetics and mechanism of hydrogen exchange in acetophenone. The advantage of this technique is that macroscopic parameters of the system (primarily, its dielectric permittivity) remain unchanged, for the concentration of the base added is small. However, the degree of protophilicity of the solution is expected to change in going from one base to another, so that favorable conditions are created for detalization of the role of bases in the mechanism of the process. Preliminary experiments with various bases showed that a positive catalytic effect is produced by addition of an organic base, piperidine, poorly soluble sodium amide, and an inorganic compound, calcium nitrate. Triethylamine was also among the examined bases; its basicity is similar to the basicity of piperidine. The rate constants were

Table 3. Average rate constants of deuterodeprotonation ($k_D^{NH_3}$) and tritiodeprotonation ($k_T^{NH_3}$) and $k_D^{NH_3}/k_T^{NH_3}$ ratios for hydrogen exchange in α-D(T)-acetophenone with liquid ammonia in the presence of bases[a]

Added base	Concentration, M	Temperature, °C	$k_D^{NH_3} \times 10^5$, s^{-1}	$k_T^{NH_3} \times 10^5$, s^{-1}	$k_D^{NH_3}/k_T^{NH_3}$
Piperidine	0.11	15	15 ± 1	6.7 ± 0.6	2.2
	0.22	15	22 ± 1	–	–
	0.58	15	24 ± 1	–	–
	0.67	15	30 ± 2	–	–
Sodium amide	(0.02)[a]	–40	220 ± 15	157 ± 12	1.4
Calcium nitrate	3.9	0	3.6 ± 0.2	2.1 ± 0.1	1.7
	3.9	15	11 ± 2	7.9 ± 0.5	1.4
	3.9	25	20 ± 2	17 ± 2	1.1

[a] Molar ratio sodium amide : acetophenone 1.4; molar ratio solvent : acetophenone 140–150.

Table 4. Average rate constants of deuterodeprotonation ($k_H^{ND_3}$) and protodedeuteration ($k_D^{NH_3}$) of acetophenone, toluene, and benzene with liquid ammonia containing basic substances

Catalytic system[a]	Temperature, °C	Base concentration, M	$k_H^{ND_3} \times 10^5$, s^{-1}	$k_D^{NH_3} \times 10^5$, s^{-1}	$k_H^{ND_3}/k_D^{NH_3}$
$C_6H_5COCH_2L$ + NL_3(liq.)	15	–	17 ± 2	2.3 ± 0.1	7.4
$S_6H_5COCH_2L$ + NL(liq.) + piperidine	15	0.11	16 ± 2	15 ± 1	~1
$C_6H_5COCH_2L$ + NL_3(liq.) + triethylamine	15	0.09	14 ± 1	–	–
$C_6H_5COCH_2L$ + NL_3(liq.) + triethylamine	15	0.18	5.5 ± 0.5	–	–
$C_5H_5CONH_2L$ + NL_3 + $Ca(NO_3)_2$	15	3.9	85 ± 10	11 ± 2	7.7
$C_6H_5CH_2L$ + NL_3 + KNL_2	–35	0.05	69 ± 5	5.6 ± 0.7	12
C_6H_5L + L + KNL_2	0	0.05	14 ± 1	1.1 ± 0.1	13

[a] L = H or D. Deuterium concentration in NL_3 (L = D) 98% of the theoretical value.

measured at several concentrations of the base added. The kinetic data are collected in Tables 3 and 4. The following facts should be noted:

(1) The data in Tables 1 and 3 indicate that the rate of deuterium exchange in α-D-acetophenone with liquid ammonia at –40°C in the absence of bases is lower by a factor of ~10^4 than in the presence of sodium amide (a suspension; c_{NH_2} = 0.02 M);

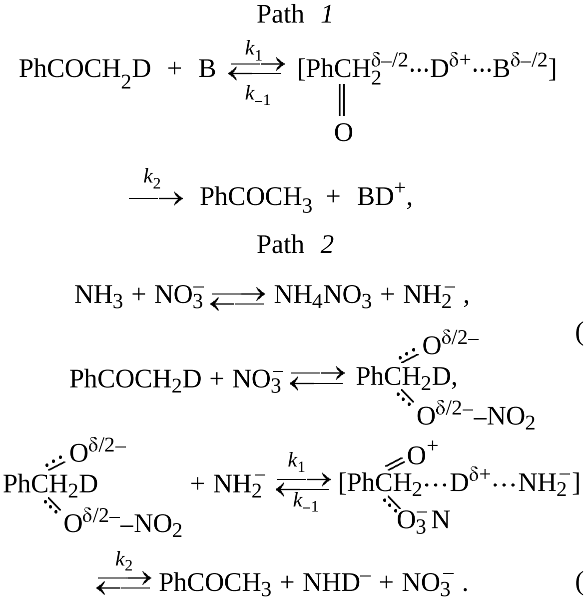
(2) Addition to a solution of acetophenone in liquid ammonia of piperidine, which is a stronger base than ammonia, induces a positive catalytic effect. The latter increases as the concentration of piperidine rises (general base catalysis: the rate constant increases by a factor of 13 as the concentration of piperidine rises from 0 to 0.67 M);

(3) A specific feature of triethylamine as base additive to liquid ammonia is that the rate constant $k_D^{NH_3}$ for deuterium exchange in acetophenone changes insignificantly upon variation of triethylamine concentration. Moreover, the rate of deuterium exchange tends to slightly decrease as the concentration of triethylamine rises (Table 4);

(4) The effect of salts on the rate of hydrogen exchange was studied using calcium nitrate. Nitrate ions act as proton acceptors, though the acceleration effect is weak: At an NO_3^- concentration of 3.9 M, the rate constant of deuterium exchange increases by a factor of 4–5 at 15°C and by a factor of 3 at 25°C.

As in the H–D exchange in pure liquid ammonia, sufficient information on the reaction mechanism can be obtained by simultaneously considering both kinetic and thermodynamic aspects of the catalytic reaction. Therefore, let us analyze variations of the reaction rate, caused by addition of the above-listed substances, in terms of homogeneous base catalysis. For this purpose, the rate constants should be brought into correlation with the equilibrium parameter of the added bases. Although pK_a values in water for all the bases used are now available, we believe it unreasonable to treat them as basicity criteria in liquid ammonia. Unlike water or alcohol, liquid ammonia weakly solvates and stabilizes both the bases themselves (B) and their conjugate acids (BH^+) via hydrogen bonding, for its ability to form such bonds is insignificant (as compared to water). A more appropriate basicity parameter in liquid ammonia may be the basicity in the gas phase (or proton affinity). The proton affinities of the selected bases are greater than that of ammonia (207 kcal/mol) but smaller than of amide ion (419 kcal/mol). The data in Table 3 indicate that increase in the reaction rate in going from pure liquid ammonia to its solutions containing piperidine and amide ion is consistent with the corresponding proton affinity order in the gas phase (207, 232, and 419 kcal/mol, respectively [18]). The absence of catalytic effect in the presence of triethylamine, whose gas-phase proton affinity (236 kcal/mol [18]) approaches that of piperidine, is not surprising. Presumably, this is the result of steric shielding of the unshared electron pair on the nitrogen atom by bulky ethyl groups. An analogous pattern was observed previously while studying the kinetics and thermodynamics of proton transfer in the gase phase [19]. Meot-Ner and Smith [19] found that there exist considerable differences between unhindered and sterically hindered basic centers: The rates of proton transfer in such systems differ by more than 20 orders of magnitude.

It is most difficult to interpret the disagreement between the difference in the proton affinities of piperidine (232 kcal/mol) and nitrate ion (318 kcal/mol [20]) and appreciably smaller increase in the rate of H–D exchange under catalysis by the latter. No plausible explanation may be given to the observed anomaly on the basis of the experimental data presented in Table 3. Some clarity can be introduced by analysis of published data. There are both direct and indirect indications that chemical reactions of ketones, including acetophenone, with bases involve intermediate formation of an adduct via attack by unshared electron pair of the base on the carbonyl carbon atom. The new bond is considered to be covalent [6]. Alikhanov *et al.* [4] advanced a similar hypothesis, according to which H–D exchange of acetophenone with liquid ammonia slows down due to establishing of an equilibrium between the above adduct and its decomposition products. Therefore, we cannot rule out a mechanism where hydrogen exchange is preceded by formation in solution of a molecular complex with either ammonia or added base. Obviuously, this process should affect in one or another way the subsequent exchange reaction. In other words, the formation of an adduct is equivalent to complication of the reaction mechanism. The existence of a correlation between the rate of H–D exchange and the gas-phase basicity of the reagent supports the assumption that the overall reaction mechanism is contributed to a greater extent by deuteron transfer from the C–D bond of unperturbed acetophenone molecule to the base (path *1*) rather than by the process involving intermediate complex. By contrast, initial formation of a solvate complex by CH acid and basic reagent could slow the reaction down (path *2*). Both tendencies *a priori* make the overall rate of H–D exchange dependent on the contributions of the two paths on addition of bases. The above stated may be illustrated by the following scheme.



Path *1*

$$\mathrm{PhCOCH_2D} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [\mathrm{Ph}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{H_2^{\delta-/2}\cdots D^{\delta+}\cdots B^{\delta-/2}}]$$

$$\xrightarrow{k_2} \mathrm{PhCOCH_3} + \mathrm{BD^+}, \qquad (9)$$

Path *2*

$$\mathrm{NH_3} + \mathrm{NO_3^-} \rightleftarrows \mathrm{NH_4NO_3} + \mathrm{NH_2^-},$$

$$\mathrm{PhCOCH_2D} + \mathrm{NO_3^-} \rightleftarrows \mathrm{Ph}\overset{\cdot\cdot\, \mathrm{O}^{\delta/2-}}{\underset{\cdot\cdot\, \mathrm{O}^{\delta/2-}\text{–}\mathrm{NO_2}}{\mathrm{C}}}\mathrm{H_2D}, \qquad (10)$$

$$\mathrm{Ph}\overset{\cdot\cdot\, \mathrm{O}^{\delta/2-}}{\underset{\cdot\cdot\, \mathrm{O}^{\delta/2-}\text{–}\mathrm{NO_2}}{\mathrm{C}}}\mathrm{H_2D} + \mathrm{NH_2^-} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [\mathrm{Ph}\overset{\mathrm{=O^+}}{\underset{\cdot\cdot\, \mathrm{O_3^-N}}{\mathrm{C}}}\mathrm{H_2\cdots D^{\delta+}\cdots NH_2^-}]$$

$$\overset{k_2}{\rightleftarrows} \mathrm{PhCOCH_3} + \mathrm{NHD^-} + \mathrm{NO_3^-}. \qquad (11)$$

It is readily seen that our attempt to correlate the order of variation of the rate constants of hydrogen exchange in acetophenone with gas-phase proton affinities of the corresponding bases gives a reasonable result. Path *1* is more significant for the series of active bases such as ammonia, piperidine, and sodium amide. On the other hand, catalysis of hydrogen exchange by calcium nitrate is favorable for stronger (than in the other catalytic systems) interaction between the anion and the positively charged carbonyl carbon atom. Addition of nitrate ion (through unshared electron pair on its oxygen atom) to the α-carbon atom of acetophenone neutralizes the positive charge on the latter, thus reducing proton mobility of the methyl hydrogen atoms. Despite such inhibitory effect, the reaction along path *2* provides a slightly higher rate of H–D exchange than the reaction rate in the pure solvent, presumably as a result of generation of excess amide ions in solution. Thus, an appreciable catalytic effect of nitrate ions may be explained by a simultaneously occurring reversible reaction between ammonia and nitrate ions. The assumption that an additional amount of NH_2^- ions is generated by reaction (10) seems to be justified if we take into account the following data. As shown in [21], addition of potassium nitrate to a solution of some structurally related CH acids (such as 3-methylpyridine and 2-methylnaphthalene) in liquid ammonia containing potassium amide leads to increase in the intensity of the long-wave carbanion band. Extra NH_2^- ions formed by reaction (10) cause the equilibrium between the molecular form of the substrate and its carbanion to shift toward the latter.

Changes of the reaction path and transition state structure, postulated above as a result of addition of basic compounds, could lead to variation of primary substrate isotope effect $k_D^{NH_3}/k_T^{NH_3}$ which is an experimentally measured parameter of the transition state. The experimental results are given in Table 3. The isotope effect in hydrogen exchange between α-D(T)-acetophenone and liquid ammonia in the presence of piperidine remains almost the same as in the absence of catalyst (Table 1). In experiments on "reverse" exchange in α-D(T)-acetophenone with addition of sodium amide, the ratio $k_D^{NH_3}/k_T^{NH_3}$ sharply decreases (1.4 at –40°C).

A specific feature of the catalytic system containing $Ca(NO_3)_2$ (3.9 M) is sharply reduced primary substrate isotope effect ($k_D^{NH_3}/k_T^{NH_3}$ = 1.1 at 25°C and 1.4 at 15°C). According to the data in Tables 1 and 3, hydrogen exchange in α-D(T)-acetophenone with pure liquid ammonia is characterized by the maximal isotope effect. It decreases as the basicity of the reagent increases: $NH_3 \approx$ piperidine $\gg$ sodium amide. Unfortunately, the difference in the isotope effects in going from ammonia to sodium amide can be estimated only roughly, for kinetic experiments with different bases cannot be performed at the same temperature. Nevertheless, taking into account antiparallel variations of the isotope effect $k_D^{NH_3}/k_T^{NH_3}$ and the basicity of the catalyst for the same CH acid (acetophenone), we can state that the position of the transition states on the reaction coordinate corresponds to the descending part of the curve (except for the reaction in the presence of nitrate ions). Upon addition of nitrate ions, a small increase in k_D is accompanied by sharp decrease of $k_D^{NH_3}/k_T^{NH_3}$, which contradicts the Leffler–Grunwald postulate. Presumably, the formation of a solvate complex with equivalent $C\cdots O$ bonds leads to disappearance of positive charge and appearance of a negative charge on the carbonyl carbon atom. As a result, the transition state moves from the product-like region (descending branch of the $k_D^{NH_3}/k_T^{NH_3}$–pK_a curve) through the maximum of the $k_D^{NH_3}/k_T^{NH_3}$–pK_a dependence to the reagent-like region (ascending branch). In other words, the transition states in the reactions under comparison are located at different parts of the reaction path, each being characterized by a high degree of asymmetry.

Thus, the assumed change of the reaction mechanism, induced by addition of calcium nitrate, is indirectly supported by analysis of the kinetic isotope effects.

Effect of the protophilicity of solutions of acetophenone in liquid ammonia on the kinetics and mechanism of hydrogen exchange. The procedure utilizing addition of basic reagents gives helpful information on the mechanism of hydrogen exchange in acetophenone. However, it remains unclear whether a proton-abstracting species may be identified with the added base or it is common for different catalytic systems. For example, such a species may be amide ion generated by reaction (10). In the further treatment, we will try to substantiate an approach to determination of the nature of protophilic species, which implies examination of the differentiating effect on the kinetic CH acidity of acetophenone in each particular case in going from light liquid ammonia to its deuterated analog having similar properties. It is reasonable to presume that such a transition, as well as addition of a base, will result in a minimal change of polar properties of the medium (dielectric constant and dipole moment), while the main contribution to variation of the reaction rate will be that arising from change in the solvent protophilicity. The results of experiments carried out with both acetophenone and hydrocarbon CH acids (benzene and toluene) are given in Table 4. The data for benzene and toluene were included in order to elucidate how does the same base (amide ion) change the rate of deuterium exchange in aliphatic and aromatic C–H bonds on replacement of liquid ammonia by its deuterated analog. As follows from Table 4, the examined bases exert different accelerating effects on deuterium exchange in going from NH_3 to ND_3, other conditions being equal. The strongest accelaration is observed for potassium amide: it gives rise to the maximal difference (by a factor of 11–12) between the rate constants of deuterium exchange in each of the above listed hydrocarbons in going from the system NH_3(liq.) + KNH_2 to ND_3(liq.) + KND_2. Nitrate ion and ammonia occupy an intermediate place (the reaction with acetophenone is accelerated by a factor of 7.5). Piperidine turned out to be the least active (no acceleration was observed). These results can be explained on the assumption that the thermodynamic basicity of ND_2^- ion in deuterated liquid ammonia is greater than the basicity of NH_2^- ion in liquid NH_3, like OD^- ion in D_2O is a stronger base (by a factor of 1.47) [22, 23] than OH^- ion in H_2O.

It should be emphasized that there is a close analogy between the pattern of variation of deuterium exchange rates in going from H_2O to D_2O and the observed more pronounced catalytic effect of amide ions on the rate of hydrogen exchange in the above hydrocarbons in liquid deuterated ammonia compared to NH_3. Namely, the rate constant of ionization of deuteroacetone in water ($CD_3COCD_3 + H_2O + OH^-$) is lower by a factor of 11 than the rate of the reverse reaction of nondeuterated acetone in heavy water containing alkali [22].

The considerable acceleration of the reaction by the action of ND_2^- or OD^- ions in going from nondeuterated solvent to deuterated one and the absence of acceleration in the reaction catalyzed by piperidine lead us to conclude that the accelerating effect is a specific property of ions (ND_2^-, OD^-). As concerns the effect of organic bases on the rate of deuterium exchange in going from a light solvent to heavy, their contribution to the overall acceleration is a matter of discussion. In terms of the above stated, the intermediate degree of acceleration of hydrogen exchange by $Ca(NO_3)_2$ in liquid ammonia should be treated as the result of superposition of two reaction paths (*1* and *2*), when protophilic species are simultaneously the neutral base and NH_2^- ion.

We thus conclude that the difference in the rates of hydrogen exchange in different CH acids on variation of isotope composition of the solvent does not originate from change of the reaction mechanism but reflect specific features of thermodynamic interaction between CH acids and basic reagents.

MECHANISM OF HYDROGEN ISOTOPE EXCHANGE IN THE METHYL GROUP OF TOLUENE

Primary substrate isotope effect in hydrogen exchange in toluene with a solution of potassium amide in liquid ammonia. This section describes the relation between the structure of CH acid, specifically the nearest environment of the labile methyl group (with acetophenone and toluene as examples), and fine details of the hydrogen exchange mechanism in liquid ammonia solution.

Toluene is a fairly weak CH acid (pK_a 43), which determines its kinetic behavior. Hydrogen isotope exchange in the methyl group of toluene occurs at a kinetically measurable rate at reduced temperature and only in the presence of a very strong proton acceptor, amide ion [5]. The kinetics of isotope exchange in toluene containing deuterium and tritium in the methyl group with a solution of potassium amide in liquid ammonia were studied in [5], and the kinetic isotope effect at 0°C was measured. However, the contribution of internal ion pair return to the rate of hydrogen exchange was not estimated quantitatively (see above). More accurate results can be obtained by performing experiments on joint determination of both the rate constants of protodedeuteration $k_D^{NH_3}$) and protodetritiation ($k_T^{NH_3}$) (reverse exchange) and the rate constants of deuterodeprotonation ($k_H^{ND_3}$) and tritiodeprotonation ($k_T^{ND_3}$) (direct exchange where the solvent acts as a donor of heavy isotope). In order to determine the whole set of rate constants related to different temperatures, as well as the ratios of these constants), we used various H/D and H/T isotopomers of toluene and ammonia. The conditions and results of experiments are collected in Tables 5 and 6. Some comments should be given to the value of $k_T^{ND_3}$ presented in Table 6. Because of difficulties in the synthesis of the initial $C_6H_5CD_2T$ isotopomer we failed to perform kinetic measurements in the system $C_6H_5CD_2T + ND_2^- + ND_3$(liq.). Instead, an approximate value of the corresponding rate constant was determined for the system $C_6H_5CH_2T + ND_2^- + ND_3$(liq.). Here, the process involving decrease of the tritium concentration in the initial toluene is accompanied by deuterium transfer from the solvent to toluene molecule. The resulting secondary isotope effect of the substrate somewhat distorts the $k_T^{ND_3}$ value corresponding to tritium exchange in the system $C_6H_5CD_2T + ND_2^- + ND_3$(liq.). As noted above, the set of $k_D^{NH_3}/k_T^{NH_3}$ and $k_H^{ND_3}/k_T^{ND_3}$ values is required for calculations by Eq. (4) which gives a rough estimate of the deviation of y from the maximal value y_{max} = 3.34, when the k_1 stage of scheme (1) (which is sensitive to isotope replacement) is fully rate-controlling. Substituting the values of $k_D^{NH_3}$, $k_T^{NH_3}$, $k_H^{ND_3}$, and $k_T^{ND_3}$ for hydrogen exchange in toluene into formula (4) gives y = 3.3 (–25°C). Taking into account errors in the determination of rate constant, as well as the approximate character of Eq. (4), the difference between the experimental exponent y and the theoretical value (y_{max}) is negligible. This indicates that internal ion pair return does not affect the reaction under study. The absence of a diffusion limit of the reaction rate (a_L = 0) makes it possible to estimate the true kinetic isotope effect for hydrogen exchange in toluene using formula (6): k_1^H/k_1^T = 21. This value approaches the theoretical maximum, indicating a symmetric structure of the transition state.

Using the k_1^H/k_1^T values for the two CH acids, toluene and acetophenone, we can consider the effect of pK_a of CH acids on the mechanism of hydrogen exchange. It is seen that, contrary to expectations, change of pK_a by 17 units in going from one CH acid

Table 5. Average rate constants of protodedeuteration ($k_D^{NH_3}$) and protodetritiation ($k_T^{NH_3}$) and $k_D^{NH_3}/k_T^{NH_3}$ ratios for hydrogen exchange between α-D(T)-toluene and a solution of potassium amide in liquid ammonia[a]

Temperature, °C	$k_D^{NH_3} \times 10^5$,[b] s^{-1}	$k_T^{NH_3} \times 10^5$, s^{-1}	$k_D^{NH_3}/k_T^{NH_3}$ [c]
–25	7.8 ± 0.4	3.1 ± 0.2	2.5
–12	18 ± 2	6.4 ± 0.3	2.8
0	61 ± 3	23 ± 2	2.7

[a] Concentration of potassium amide 0.05 M. [b] Tentative parameters of the Arrhenius equation: ΔE = 8.0 kcal/mol, $\log A$ = 3; the value of $k_D^{NH_3}$ derived therefrom (–35°C) is 5×10^{-5} s^{-1}. [c] Average values from 8–12 runs at each temperature.

Table 6. Average rate constants of deuterodeprotonation ($k_H^{ND_3}$) and tritiodeprotonation ($k_T^{ND_3}$) and $k_H^{ND_3}/k_T^{ND_3}$ ratios for hydrogen exchange in light toluene and α-T-toluene in a solution of potassium amide in liquid ammonia[a]

Temperature, °C	$k_H^{ND_3} \times 10^5$,[b] s^{-1}	$k_T^{ND_3} \times 10^5$,[b] s^{-1}	$k_H^{ND_3}/k_T^{ND_3}$
–45	18 ± 1	–	–
–35	69 ± 3	–	–
–25	110 ± 10	5.0 ± 0.2	22

[a] Concentration of potassium amide 0.05 M.
[b] Deuterium concentration in the initial deuterated ammonia 98% of the theoretical value.

to the other is not accompanied by the corresponding change of the transition state structure. The observed insensitivity of k_1^H/k_1^T to CH acidity may be understood on the assumption that hydrogen exchange in acetophenone and toluene involves protophilic species of different natures, namely these may be ammonia molecule and amide ion, respectively. Presumably, the high degree of symmetry of the transition states in both reactions reflects similarity in electron density distribution over the three-center transition bridge $C^{\delta/2-}\cdots H^{\delta+}\cdots N^{\delta/2-}$ formed, on the one hand, by a medium-strength CH acid (acetophenone) and a relatively weak base (ammonia) and, on the other, by a very weak CH acid (toluene) and a powerful proton acceptor (NH_2^- ion).

We have no possibilities for applying the set of the above described techniques to analogous detailed study of the mechanism of hydrogen exchange in alike substrates differing from toluene by a smaller number of pK_a units. Therefore, in order to estimate the sensitivity of isotope effect in the reaction in a solution of potassium amide in liquid ammonia we confined ourselves to measurement of the rate constants $k_D^{NH_3}$ and $k_T^{NH_3}$ and their ratios $k_D^{NH_3}/k_T^{NH_3}$ for the reaction of 2-methylpyridine with a solution of potassium amide in liquid ammonia. 2-Methylpyridine is a stronger CH acid than toluene [pK_a(THF) = 34] [24], and it more readily reacts with liquid ammonia in the presence of potassium amide. The values of $k_D^{NH_3}$, $k_T^{NH_3}$, and $k_D^{NH_3}/k_T^{NH_3}$ for hydrogen exchange in α-D(T)-2-methylpyridine with potassium amide–liquid ammonia (c_{KNH_2} = 0.05 M) at –35°C are as follows: 1.6×10^{-5}, 0.56×10^{-5} s^{-1}, and 2.85. The ratio $k_D^{NH_3}/k_T^{NH_3}$ almost does not differ from the corresponding value for toluene, especially if we take into account that hydrogen exhange in 2-methylpyridine was examined at a higher temperature: $k_D^{NH_3}/k_T^{NH_3}$ = 2.6 ± 0.1 and 2.9 ± 0.1 at –25 and –12°C, respectively. Comparison of the data for the pair toluene–2-methylpyridine shows a very weak tendency for $k_D^{NH_3}/k_T^{NH_3}$ to vary as the CH acidity of the substrate rises (unless the lack of such tendency). Presumably, in our case the maximum on the $k_D^{NH_3}/k_T^{NH_3}$–pK_a curve is so fuzzy that no conclusion on the degree of symmetry of the transition state can be drawn on the basis of this dependence [25]. Streitwieser *et al.* [26] also noted the absence of sensitivity of k_D/k_T to pK_a in going from toluene (pK_a = 43) to triphenylmethane (pK_a = 30.6) while studying hydrogen exchange in a solution of lithium cyclohexylamide in cyclohexylamine (k_D/k_T = 2.8 ± 0.15 at 25°C). Also, the insensitivity of isotope effect in hydrogen exchange in the same solution to the CH acidity of toluene and some its derivatives having substituents in the benzene ring was reported [27].

Analysis of the mechanism of hydrogen exchange in toluene is not limited to comparison of the data on structural effects on the kinetic isotope effect with those found for acetophenone and other related CH acids. We also examined the temperature dependence of $k_D^{NH_3}/k_T^{NH_3}$ for hydrogen exchange in toluene. According to the data in Table 5, in the temperature range from –25 to 0°C, the ratio $k_D^{NH_3}/k_T^{NH_3}$ slightly increases as the temperature rises: The values of $k_D^{NH_3}/k_T^{NH_3}$ are 2.5, 2.8, and 2.7 at –25, –12, and 0°C, respectively. Measurements of the isotope effects were repeated for 8–12 times at each temperature; the differences in the resulting $k_D^{NH_3}/k_T^{NH_3}$ values were so large that they should be regarded as real. An analogous weak sensitivity of the isotope effect to temperature was observed for hydrogen exchange in acetophenone. Using the temperature dependence of $k_D^{NH_3}/k_T^{NH_3}$ we have substantiated the influence of internal ion pair return on the process. It was assumed that the normal course of the process implies gradual

Table 7. Conditions and results of protodedeuteration of α-D_3-toluene in liquid ammonia in the presence of NH_2^- ions (c_{KNH_2} = 0.05 M)

Run no.	Temperature, °C	Time, h	Relative intensity of ion peaks in the mass spectrum,[a] %				$k_D^{NH_3} \times 10^5$, s^{-1}
			m/z = 92	m/z = 93	m/z = 94	m/z = 95	
1	–25	1.5	51.0	3.3	7.9	37.8	2.6
2	–25	5	8.1	29.4	39.1	23.4	2.8
3	–25	8	19.1	29.7	37.5	13.7	2.4
4	–15	3	19.3	37.8	30.5	12.4	7.3

[a] Initial intensity, I_{rel}, %: run no. 1: m/z = 92, 49.5; m/z = 93, 0.5; m/z = 94, 0.0; m/z = 95, 50.5; run nos. 2–4: m/z = 92, 0.0; m/z = 93, 1.6; m/z = 94, 1.8; m/z = 95, 96.6.

decrease of $k_D^{NH_3}/k_T^{NH_3}$ as the temperature rises. There are published data on other examples of a nonclassical temperature dependence of isotope effect in protolytic reactions; here, variation of the isotope effect is assigned to variable temperature contribution of internal ion-pair return to the ratio $k_D^{NH_3}/k_T^{NH_3}$ [13, 16].

The results given in Table 5 do not allow us to interpret the observed temperature anomaly in terms of the same approach, for our analysis of the relations between elementary steps of hydrogen exchange in toluene indicates the absence of internal ion pair return effect. We believe that the anomalous temperature dependence of isotope effect in the system under study should be treated as originating from an additional thermodynamic isotope effect intrinsic to metalation of the methyl C–H bond with potassium amide. This effect is concomitant to the kinetic isotope effect on proton transfer from CH acid to base. It is still impossible to separate the contributions of thermodynamic and kinetic factors to the observed $k_D^{NH_3}/k_T^{NH_3}$ value. Nevertheless, it seems to be improbable that the isotope effects would be similar for the two processes and that they would show similar temperature dependences. This assumption is supported by the fact that some structuraly related compouds, which are not considerably stronger CH acids than toluene, react with potassium amide in liquid ammonia to give alkaline–organic derivatives. The latter are detected by the appearance of carbanion bands in the electronic spectra and IR spectra of solutions of potassium amide in liquid ammonia containing compounds with both activated (2-methylpyridine, fluorene, etc.), and nonactivated methyl or methylene group (1-methylnaphthalene, diphenylmethane, 3-methylpyridine) [21]. The reason for the anomalous temperature dependence of primary isotope effect in hydrogen exchange in toluene requires further study.

Utilization of α-deuterium isotope effect for studying the transition state structure. A model of transition state for hydrogen exchange in toluene is characterized by two structural parameters. One of these is linear; it is defined as the drift along the reaction coordinate relative to the position of proton in the symmetric model which corresponds to the maximal isotope effect. The second parameter is angular; it is related to rehybridization of the methyl carbon atom during the reaction from sp^3 to near-sp^2. The above results make it possible to estimate on a qualitative level only the first parameter. To get a deeper insight into the mechanism of hydrogen exchange we should consider angular deformations of the C–D (C–H) bonds at the carbanionic center in the transition state. For this purpose, we determined the secondary α-deuterium substrate isotope effect by comparing the rates of deuterium exchange in α-D-toluene and α-D_3-toluene with a solution of potassium amide under similar conditions. It should be kept in mind that the proposed approach is applicable only when the relative degree of exchange is low, i.e., when the overall rate constant of the reaction in the methyl group of α-D_3-toluene can be equated to k_{III}.

$$C_6H_5CD_3 \overset{k_{III}}{\rightleftarrows} C_6H_5CD_2H \overset{k_{II}}{\rightleftarrows} C_6H_5CDH_2 \overset{k_I}{\rightleftarrows} C_6H_5CH_3. \qquad (12)$$

At a moderate degree of exchange, the rate constant measured experimentally (Table 7) is an apparent quantity which characterize at least two steps of the complex reaction (k_{III} and k_{II}). This means that the experimental rate constant ratio should be regarded only as a lower limit of the α-deuterium effect given by the ratio $k_D(C_6H_5CH_2D)/k_D(C_6H_5CD_3)$. According to the data in Tables 5 and 7, the ratio $k_D(C_6H_5CH_2D)/k_D^{NH_3}(C_6H_5CD_3)$ is equal to 3 at –25°C. Using the approximate formula $k_I/k_{II} = k_{II}/k_{III}$, we can readily calculate the "intermediate" rate constant $k_{II} \equiv k_D(C_6H_5CD_2H) = 4.5 \times 10^{-5}$ s^{-1} and hence the α-deuterium effect due to replacement of two H atoms by D. Such a “unit” α-deuterium effect $k_{\mathbf{I}}/k_{\mathbf{II}}$ = $k(C_6H_5CH_2D)/k(C_6H_5CD_2H)$ is equal to 1.7. The experimental value of $k(C_6H_5CH_2D)/k(C_6H_5CD_2H)$ is anomalously high. In keeping with the theoretical views, according to which the main contribution to α-deuterium effect is the difference in zero-point vibrations corresponding to deformation of carbon–hydrogen bonds with respective isotopes in the initial molecules and transition states, the maximal unit α-deuterium effect in going from the sp^3-hybridized the methyl carbon atom in toluene to the sp^2-hybridized carbon atom in the benzyl carbanion should approach a value of 1.4 [28]. According to our data, the α-deuterium effect caused by replacement of one H atom by D (except for the atom subjected to isotope substitution) exceeds not only the theoretical limit but also the experimental value 1.3 obtained for hydrogen exchange in toluene with a solution of lithium cyclohexylamide in cyclohexylamine [29]. In order to interpret the above disagreements, we presume simultaneous action of two different factors (vibrational and inductive) which are responsible for the value of α-deuterium effect. The inductive factor arising from a slightly stronger electron-donor effect of deuterium as compared to protium upon abstraction from toluene molecule does not depend on the mode of coordination of the anionic part of the transition state to the counterion. Unlike the inductive factor, the influence of the vibrational factor on isotope effect strongly depends on the polarity of the medium. Presumably, in a weakly polar solvent such as cyclohexylamine (ε = 4.7), the carbanionic transition state occurs as an ion pair with lithium cation. The electrostatic interaction therein is sufficiently strong to fix sp^3-like bond configuration at the anionic carbon atom [29]. Thus, the low value of α-deuterium effect relative to the theoretical limit corresponding to the vibrational approximation is explained by a combination of the two factors: (1) The degree of orbital rehybridization in the transition state is far from the limiting one (which corresponds to its planar structure) and (2) the inductive effect of deuterium is weak. By contrast, the role of counterion in the formation of transition state for deuterium exchange in a strongly polar solution of alkali metal amide in liquid ammonia is likely to be insignificant. The absence of interionic coordination favors transition to a state characterized by a greater *s*-order of hybridized orbitals than in the reaction in cyclohexylamine. This is due to greater delocalization of *p* electron on the anionic carbon atom via conjugation with the aromatic π-electron system. Such structural variation of the transition state leads to increased contribution of the vibrational factor to α-deuterium effect, while the inductive contribution remains unchanged regardless of the nature of the medium. Therefore, hydrogen exchange in the methyl group of toluene with a solution of potassium amide in liquid ammonia is characterized by increased overall α-deuterium isotope effect as compared with the analogous reaction in cyclohexylamine.

EXPERIMENTAL

α-D- and α-D_3-Toluene isotopomers and deuterated liquid ammonia were obtained from the pilot plant at the *Prikladnaya khimiya* Research Center. Samples of α-D,T-toluene were prepared by decomposition of benzylmagnesium bromide with water containing both deuterium (95 at %) and tritium. α-D,T-Acetophenone was synthesized by exchange of commercial acetophenone (preliminarily distilled under reduced pressure) with heavy water containing an indicator amount of HTO under catalysis by KOD (12 h, 100°C, c_{KOD} = 0.2 M). The procedures for preparation of KNH_2 solutions in liquid ammonia and kinetic measurements were described in [1]. The purity of all the compounds was checked by gas chromatography. In all experiments, the amount of solvent was 100–150 mol per mole of acetophenone; in experiments with toluene, the amount of solvent was 70 mol or more per mole of toluene. The rate constants did not change on variation of the solvent amount by a factor of 1.5–2. The position of deuterium in samples of acetophenone obtained in experiments with ND_3 was determined from increase in the intensity of vibration bands of aliphatic C–D bonds in the IR spectra (2200 cm^{-1}). Mass spectrometric analysis of benzoic acid prepared by oxidation of toluene with potassium permanganate showed the absence of deuterium in the aromatic ring of toluene samples obtained in “direct-exchange” experiments. The concentration of deuterium in the methyl groups of toluene and acetophenone was determined by low-voltage mass spectrometry using an MI-1301 instrument. The concentration of tritium in water obtained by combustion of substances before and after exchange was determined using a scintillation counter (in a solution of liquid scintillator). The rate constants of hydrogen isotope exchange were calculated by the first-order equation using average values from 5–6 runs. In the determination of the temperature dependence of $k_{\mathrm{D}}^{\mathrm{NH_3}}/k_{\mathrm{T}}^{\mathrm{NH_3}}$ 8–12 parallel experiments were run.

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