KINETICS OF DEUTERO EXCHANGE IN THE NH GROUPS OF PYRROLE, INDOLE, AND CARBAZOLE

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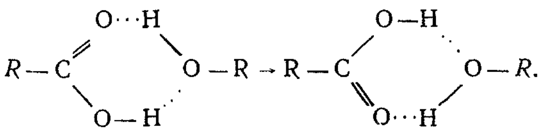
In [1] it was shown that the hydrogen of the NH group in pyrrole derivatives is replaced by the deuterium of heavy water within tens of minutes. The authors explained this by the existence of conjugation between the free pair of the nitrogen atom and the π electrons of the double bonds, which (according to the hypothesis put forward in [2]) should make the synchronous transfer of protons in the cyclic complex containing hydrogen bonds more difficult.

In recent years the development of the point of view held by A. I. Brodskii has been based on work using the NMR method. By measuring the rate constant of hydrogen exchange between the hydroxyl group of an alcohol and the carboxyl group of an acid, Grunwald and his collaborators [3, 4] proposed the following mechanism for the elementary event:



Here the cyclic complex includes one molecule of the alcohol in the presence of excess acid and two molecules of the alcohol in the presence of excess alcohol. The authors discuss two types of process, viz., a one-stage process where the motion of the protons along the hydrogen bonds takes place in step and a two-stage process where the first stage is the ionization of the acid to form an anion-cation pair and the second is the transfer of the proton to the anion.

In the present work we have investigated the kinetics of the isotope exchange of hydrogen between the hydroxyl group of the alcohol and the NH groups of pyrrole, indole, and carbazole in solutions in carbon tetrachloride, the molecules of which react weakly with the molecules of the reagents. Infrared spectroscopy was used to observe the course of the exchange reaction $RNH + CD_3OD \rightarrow RND + CD_3OH$. The reaction was carried out in glass cells 0.5, 1, 2, 5, and 15 mm thick with windows of fluorite. The pyrrole was distilled under vacuum, the indole and carbazole were recrystallized from ligroin, and the carbon tetrachloride was distilled and dried over zeolite. The work was carried out on a IKS-12 spectrometer with sodium chloride prism, a replica grating with 200 lines/mm, and an OAP-1 collector at the following bands for the monomeric molecules: ν(NH) pyrrole 3490, indole 3482, carbazole 3479; ν(ND) pyrrole 2580, indole and carbazole (doublet) 2607, 2588 [5]; ν(OH) 3640 and ν(OD) 2685 cm^{-1} for methanol.

The experiments showed that, with the reagent at a concentration of 0.2 mole/l, the half-exchange p periods for pyrrole and indole were in the order of hundreds of minutes, and it was therefore possible in the measurement of the kinetics to record the optical densities D of the four (and in some cases three) bands in succession and to plot kinetic curves for all the molecules participating in the exchange reaction (Figs. 1 and 2). According to [6], in isotope exchange reactions the variation of the concentration of each component obeys the exponential law:

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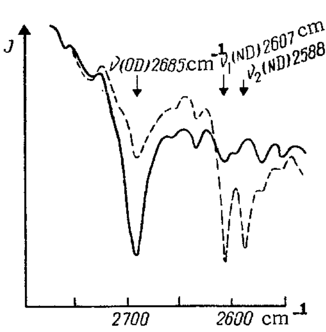


Fig. 1

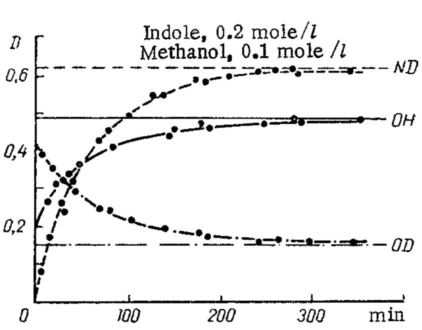


Fig. 2

Fig. 1. The absorption spectrum of solutions of 0.1 mole/l indole + 0.1 mole/l methanol-d in carbon tetrachloride before exchange (continuous curve) and after exchange (dotted curve).

Fig. 2. The variation of D with time for the ν(ND), ν(OH), and ν(OD) absorption bands of the 0.2 mole/l indole + 0.1 mole /l methanol-d system in carbon tetrachloride.

$$[XH]_t = [XH]_\infty + ([XH]_0 - [XH_\infty]) e^{-rt},$$

where r characterizes the rate of the establishment of an equilibrium distribution of the isotopes in the system and is determined from the experimental data on the slope of the straight line obtained against the coordinates ln $[(D_t - D_\infty)/(D_0 - D_\infty)]$ and t. In our case these relations did in fact give straight lines, and the r values determined on different bands differed by no more than 10-15%. The isotope exchange rate R was calculated from the equation [7]:

$$R = r/(A^{-1} + B^{-1}),$$

where A and B are the concentrations of the reagents. During the investigation of the concentration dependence of the reaction rate it was found that the random experimental error was extremely large; the r values determined at different times under standard conditions sometimes differed by two to three times. Therefore, in order to determine the rate constant k and the reaction orders α and β for the indole-methanol system the following set of equations was solved by the method of least squares:

$$\log R_i = \log k + \alpha \log A_i + \beta \log B_i.$$

The concentrations of indole A and methanol B were varied between 0.05 and 0.4 mole/l. Solution of the set of 14 equations gave the values $\alpha = 1.3 \pm 0.3$ and $\beta = 0.8 \pm 0.4$. The proximity of these values to unity makes it possible to take the process as bimolecular and to assume that $\alpha = \beta = 1$. The mean value of k calculated for $\alpha = \beta = 1$ in the indole-methanol system is $(4.5 \pm 1.7) \cdot 10^{-4}$ l/mole · sec.

Kinetic experiments on the exchange between pyrrole and methanol at concentrations between 0.05 and 0.4 mole/l showed that, with the reagents at identical concentrations, the half-exchange period for pyrrole was several times longer than that for indole. From the results of 13 experiments and on the assumption that the reaction was bimolecular we obtained the value $k = (1.2 \pm 0.5) \cdot 10^{-4}$ l/mole · sec. [A qualitative experiment at the γ (NH) bands of indole (605 cm^{-1}) and pyrrole (500 cm^{-1}) showed that in a solution containing indole, pyrrole, and methanol-d the intensity of the γ (NH) band for indole decreased appreciably more quickly as a result of the exchange than that of the band for pyrrole.]

In the NH group of carbazole the exchange reaction takes place several orders of magnitude more quickly than in indole and pyrrole. Owing to the low solubility of carbazole in carbon tetrachloride the concentration dependence of the exchange rate was not investigated. From the results of several experiments carried out with a carbazole concentration of about 0.004 mole/l and a methanol concentration of 0.05 mole/l we obtained $k = 0.3$ l/ mole · sec. Thus, the hydrogen exchange rate with methanol increases in the following order: Pyrrole < indole $\ll$ carbazole.

The effect of impurities of acidic and basic character on the exchange rate was checked in the indole-methanol system. With the components at a concentration of 0.1-0.2 mole/l the addition of $2 \cdot 10^{-4}$ mole /l

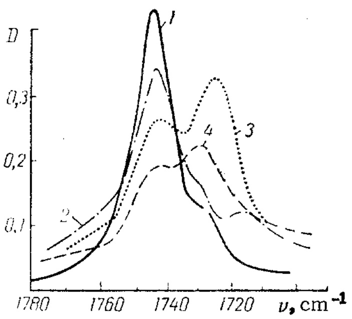


Fig. 3. The shift of ν (C=O) for butyl acetate during the formation of a hydrogen bond with carbazole (2), indole (3), and pyrrole (4) in carbon tetrachloride solution; 1) The absorption of a 0.02-mole/*l* solution of butyl acetate in carbon tetrachloride.

of triethylamine to the solution accelerated the reaction by more than an order of magnitude. Under the same conditions in the presence of trichloroacetic acid the exchange took place in less than 10 secs. It was also impossible to measure the exchange reaction rate when DC_3OD containing 0.1 N potassium methoxide was used. The addition of $2 \cdot 10^{-4}$ mole/*l* of tridecylammonium chloride does not have a noticeable effect on the process rate.

From the temperature dependence of the isotope exchange rate we obtained tentative values for the activation enthalpy and entropy of the process. The reactions of indole and pyrrole with methanol were investigated between 23 and 50°C. The reaction commenced at room temperature, the exchange continued to ~50% of equilibrium, and the cell was then placed in a jacket connected to a thermostat and heated to the required temperature. The reaction with carbazole was investigated between 10 and 23°C. The following values were obtained for the activation energies: Pyrrole 8 ± 2; indole 11 ± 2; carbazole 14 ± 2 kcal/mole.

The proton-donating ability, determined from the pK_a value, increases in magnitude from pyrrole to indole [8]; there are no data for carbazole. As a rule, the shift of the band for a standard acceptor during the formation of a hydrogen bond with the XH group varies in the same direction as the acidity of donors of the same type [9, 10]. This shift can be used as a comparative measure of the acidity of the XH group in a series of donors. Such experiments were carried out on the ν (C=O) band for a solution of butyl acetate in carbon tetrachloride (0.02 mole/*l*). In the presence of 0.2-1.0 mole/*l* of pyrrole the decrease in the ν(C=O) frequency during the formation of the hydrogen bond was 15 cm^{-1}, for indole the decrease was 20 cm^{-1}, and in a saturated solution of carbazole the decrease was 25 cm^{-1} (Fig. 3). Consequently, the proton-donating ability increases in the following order: Pyrrole < indole < carbazole. The acidity can also be estimated fairly reliably from the shift of the ν(NH) band during reaction with a standard proton acceptor. According to data in [11], during their reactions with pyridine and triethylphosphine oxide the ν (NH) shift does in fact increase in the order: Pyrrole < indole < carbazole.

The proton-acceptor ability, determined from the pK_B value, decreases from pyrrole to indole [12]. In order to determine the basicities of these molecules spectroscopically [13] we measured the shifts of the ν (OH) band for methanol due to the formation of the OH. . .N hydrogen bond. In spite of the fact that the ν (OH) band of the complex lies close to the ν (NH) band it is possible to identify it. The Δν (OH) value decreases in the order pyrrole > indole > carbazole (97, 72, and 52 cm^{-1}), and the basicity consequently decreases in this order.

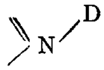
The extremely small differences in the acidic and basic characteristics of the two participants in the exchange reaction make it possible to propose two mechanisms for the reactions between the alcohol and the heterocyclic amines. According to the first of these, in the course of the exchange process the proton of the NH group is removed (or the NH bond is extended) by the hydroxyl group of the alcohol molecule, and a deuteron is then transferred from the alcohol molecule to the pyrrolate anion (i.e., the heteroaromatic substrate behaves as an acid). In addition it is possible to postulate another mechanism where the role of the acid is fulfilled by the alcohol molecule and ionization (or extension) of the OD bond occurs in the first stage to form an intermediate complex, in which the deuteron adds to the pyrrole; in the second stage the proton is transferred to the methoxide ion.

The choice between the above-mentioned types of mechanism for the investigated reaction can be approached in different ways. It is possible, for example, to attempt to compare the change in the proton–donor and proton–acceptor characteristics on passing from pyrrole to carbazole with the corresponding changes in the exchange rate constants and to judge the mechanism from the presence of a linear relation between ln k and pK_a or pK_B. However, since the range over which the acidity varies is small and in the given case it is only possible to speak of agreement between log k and pK_a, it is not possible to choose between the two mechanisms by examining the protolytic characteristics of the given compounds. A more conclusive answer can be obtained from an analysis of the changes in the activation parameters. As seen from the table, the main increase of the exchange rate in the pyrrole–indole–carbazole series takes place

TABLE 1. The Kinetic Characteristics of the Deutero Exchange Reactions of Amines with Methanol-d and the Quantum-Chemical Reactivity Indices

Amine	t° C	k, l/mole·sec	$\Delta S^{\neq}$, eu	$\Delta H^{\neq}$, kcal/mole	ΔE_{π}^{loc}	ΔE_{π}^{loc}	ΔE_{π}^{deloc}	q_N for neutral molecule
q_N for anion	23	$(1{,}2\pm0{,}5)\,10^{-4}$	—49±5	8±2	0,533	—1,188	1,519	0,813
	48	$(3{,}5\pm1{,}0)\,10^{-4}$						
Indole	23	$(4{,}4\pm1{,}7)\,10^{-4}$	—38±5	11±2	3,626	—1,234	1,573	0,823
	48	$(1{,}9\pm0{,}4)\,10^{-3}$						
Carbazole	23	$(0{,}3\pm0{,}05)$	—14±5	14±2	6,300	—0,975	1,631	0,866
	10	$(0{,}1\pm0{,}03)$						

through an abrupt decrease in the absolute value of the negative activation entropy (from −49 to −14 eu), which compensates the small increase in the activation energy. Such behavior in the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values is consistent with the idea that the main part in the acceleration of the process is played by the solvation component of the activation free energy, and in the donor−acceptor process the heterocyclic amines fulfill the function of the base and the methanol molecules fulfill the function of the acid.

The considerable negative value of $\Delta S^{\neq}$ during the exchange of the most basic heterocycle, pyrrole, is evidently explained by a large separation of the charges at the OH bond in a transition state of the type  $\ldots H^{+} \ldots O^{-}\, CH_3$. Owing to the small volume of the CH_3O^- ion which is produced and its great ability to form hydrogen bonds with the alcohol strong solvation of the system, accompanied by ordering of the neutral molcules of the proton donors around the CH_3O^- ion, occurs on passing from the initial reaction state to the activated complex. In addition to the difficulties created by the entropy factors in the deutero exchange process the formation of such a highly polar activated complex reduces the activation energy The increase in $\Delta S^{\neq}$ which occurs with weakening of the basic (proton−acceptor) characteristics of the substrate on passing to indole and carbazole may be due to a decrease in the negative charge generated on the oxygen atom in the transition state.

The similarity in the acid-base characteristics of the alcohol molecules ($pK_a = 16.5$) and the substrate makes it possible for the type of mechanism of the exchange reaction to change in the presence of acidic and basic additions. Under the conditions of our experiments the hydrogen of the NH group of the substrate can either be removed during general or specific catalysis by bases [under the influence of $(C_2H_5)_3N$ or the CH_3O^- ion respectively] or the substrate, by acting as base, can add the proton of the alcohol molecule [which evidently takes place in the presence of CCl_3COOH and, possibly, also $(C_2H_5)N_3$ additions].

In connection with the suggestion that the transfer of the proton from the neutral molecule of the alcohol to the substrate is a significant moment determining the reactivity of the five-membered heterocycles in the deutero exchange of the NH bonds it was interesting to compare the changes in the rate constants with the quantum-chemical reactivity indices. The necessary calculations were carried out in the Hückel approximation with the usual h_N, h_{N^+}, and β_{CN} values for the neutral and ionic forms of the heterocycle [14]. It was assumed that protonation of the hetero atom leads to the complete exclusion of the two neighboring bonds from the region of conjugation of the π electrons. The results from calculations of the excess electron density q_N at the nitrogen atom in the neutral molecule and in the anion, the π-electron delocalization energies $\Delta E_{\pi}^{deloc} = E_{\pi}^{an} - E_{\pi}^{in}$, and the π-electron localization energies during the protonation of the heterocycle $\Delta E_{\pi}^{loc} = E_{\pi}^{cat} - E_{\pi}^{in}$ are given in the table. The best agreement is found in the comparison of the the electrophilic reactivity indices q_N and ΔE_{π}^{loc} with the change in log k. On the other hand, there is no correlation between log k and the ΔE_{π}^{deloc} values, which characterize the proton-donor ability of the investigated heterocycles.

The results make it possible to suppose that the mechanism involving the intermediate addition of a hydrogen atom from the CH_3OH molecule to the substrate molecule is the most likely.

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