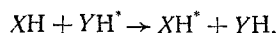


HYDROGEN BOND AND THE KINETICS OF HYDROGEN
ISOTOPE EXCHANGE IN NH, OH, AND SH GROUPS
IN SOLUTION*

G. S. Denisov and A. E. Semenova†

UDC 541.8:532.77

According to Brodskii [1] exchange reactions of the type

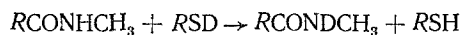
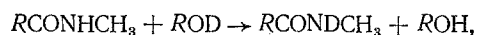


where the X and Y atoms, which may also be identical, possess unshared electron pairs, are usually characterized by fast hydrogen isotope exchange. Under certain conditions, however, such reactions may occur rather slowly. In particular, if the unshared pair participates in conjugation, the process slows down. In a water-dioxane medium hydrogen atom displacement of a pyrrolic NH group in deuterium oxide takes several hours [2]. In [3, 4] the kinetics of hydrogen exchange in the peptide group of N-methyl acetamide was studied in D₂O and in heavy-water-dioxane mixtures, the rate constants and activation energy of the process were determined, and the catalytic effect of some acids and bases was studied.

We employed IR spectroscopy for studying the kinetics of hydrogen isotope exchange of the NH group of N-methyl substituted amides and the hydroxyl group of alcohols, as well as the sulfhydryl group of mercaptans. Our aim was to elucidate the role of the hydrogen bond in fast hydrogen isotope exchange processes, determining the order and rate constant of the reaction in dilute solution and in such solvents the molecules of which interact with the dissolved substance but weakly. Carbon tetrachloride was chosen as such a solvent, as it is transparent throughout the absorption band of OH, OD, NH, ND, monomeric alcohols, and amides. The process was carried out in an absorption cuvette and the kinetics was followed by the change in the band intensity with time. The measurements were made on IKS-12, IKS-14, and UR-10 spectrophotometers. The solutions were prepared by weighing out the components, within an error of 5-15%. The reaction mixture was made up by mixing equal volumes of the component solutions. A CH₃OD preparation was used (96% deuterium enrichment) and isobutyl mercaptan exchanged with D₂O (7-80% enrichment). All the measurements were carried out at 18-22°C. As a rule, the rate constant in each experiment for the amide-CH₃OD system was determined by measuring the intensity of all four bands, for the amide-mercaptan system the amide ν (NH) and ν (ND) bands; the results were averaged.

The N-methyl formamide-methanol system was selected for determining the order of the exchange reaction. Preliminary experiments showed that at a concentration of the order of 0.02 mole/liter in CCl₄ the equilibrium distribution of deuterium is established in ten minutes. In the diethylamine-methanol system at the same concentration the exchange process is faster than ten seconds. This means that the participation of the unshared electron pair of the nitrogen of the amide in conjugation with the π electrons of the carbonyl group reduces the proton acceptor capability of the NH group.

Analysis of the results shows that the kinetics of the isotope exchange



* This work was presented at the 8th All-Union Conference on the Physics of the Liquid State, Kiev, May 1967.

† Deceased.

Leningrad State University Scientific-Research Institute of Physics. Leningrad State University Scientific-Research Institute of Chemistry. Translated from *Teoreticheskaya i Eksperimental'naya Khimiya*, Vol. 8, No. 6, pp. 822-825, November-December, 1972. Original article submitted October 21, 1971.

© 1974 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00.

follows an exponential law; i.e., the concentration of each component is described by the equation

$$C_t = C_\infty + (C_0 - C_\infty) e^{-rt},$$

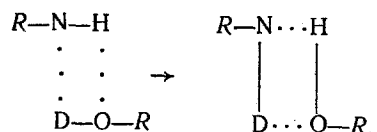
where C_∞ and C_0 are the equilibrium and initial concentration of each molecular form. The value of r is determined from the slope of the straight-line plot of $\ln(1-F)$ vs t , where F is the fraction of exchange [5]. Neglecting the isotope effect, the rate of hydrogen exchange R is related to r as [5, 6]

$$R = r \frac{AB}{A+B},$$

where A and B are the total concentrations of both isotopic forms of the amide and alcohol (mercaptan) molecules. The order of exchange reaction is found by determining the concentration dependence of R . Twenty-one experiments were carried out in which the concentration of methanol and *N*-methyl formamide were varied between the limits 0.01-0.12 and 0.002-0.023 mole/liter, respectively, while the concentration ratio of the alcohol to amide was varied from 0.5 to 50, and the results were treated by a statistical method. Using the least-square method the system of equations

$$\log R_t = \log k + \alpha \log A_t + \beta \log B_t$$

was solved for $\log k$, α , and β , where α and β are the reaction order with respect to amide and alcohol. The values obtained, $\alpha = 1.1 \pm 0.2$ and $\beta = 0.7 \pm 0.1$, are close to unity and the reaction is regarded to be bimolecular. The most natural mechanism for this reaction is a synchronous transfer of protons in a cyclic complex with hydrogen bonds, made up of two molecules,



The average value of the rate constant calculated assuming $\alpha = \beta = 1$ is $(3.5 \pm 1.5) \times 10^{-2}$ liter/mole·sec. This value differs greatly from that obtained for the reaction



in [4] in dioxane solution, $k = 3 \times 10^{-6}$ liter/mole·sec.

To investigate the effect of the solvent on the rate of hydrogen exchange in the reaction of *N*-methyl formamide with methanol the kinetics was studied in carbon tetrachloride containing dioxane, 5 and 10% by volume. In the presence of 5% dioxane the rate constant was found to be 1.8×10^{-2} liter/mole·sec and in the presence of 10% dioxane 0.5×10^{-2} liter/mole·sec. According to the results of four parallel experiments carried out at the same time in pure carbon tetrachloride $k = 2.8 \times 10^{-2}$ liter/mole·sec. Thus the difference in the rate constants obtained in [4] and in this work may be attributed mainly to the effect of the solvent. Because of the stable hydrogen bonds that the amide and methanol form with dioxane, the concentration of the mixed amide-alcohol complex in which the elementary step of hydrogen exchange occurs is considerably lower in dioxane than in carbon tetrachloride, and this leads to much reduced rate constants for the exchange reaction.

To study the effect of the electronic structure of the NH group on the ability of the hydrogen atom of this group to exchange, the reaction rate was determined in a series of amides, $RCONHCH_3$, with methanol and isobutyl mercaptan in carbon tetrachloride. The results obtained are shown in Table 1, from which it is seen that the rate constant of the exchange of amides with alcohols is higher by an order of magnitude than with mercaptan. This is in agreement with the greater stability of the hydrogen bond formed by the OH group both as oxygen and as hydrogen, in comparison with the sulfhydryl group [7].

For amides, increasing the electronegativity of R in the series $C(CH_3)_3$, $n-C_4H_9$, $n-C_3H_7$, CH_3 , H leads to a corresponding increase of the rate constant of the reaction with methanol and mercaptan. However, for CCl_3 the rate constant decreases sharply. This can be interpreted in the following way within the frame of the proposed exchange mechanism. In the cyclic complex

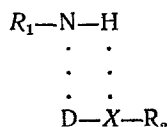


TABLE 1

R	CH ₃ OD		iso-C ₄ H ₉ SD		CH ₃ OD	iso-C ₄ H ₉ SD	No. of expts.	
	amide	alcohol	amide	mercap.	k · 10 ³ , liter/ mole · sec	k · 10 ³ , liter/ mole · sec	CH ₃ - OD	iso-C ₄ H ₉ SD
	conc., mole/liter							
C(CH ₃) ₃	—	—	0,05	0,10	—	0,4 ± 0,1	—	3
n-C ₄ H ₉	0,01	0,02	0,05	0,10	0,6 ± 0,1	0,8 ± 0,2	4	4
n-C ₈ H ₁₇	0,01—0,02	0,02	0,05	0,10	0,54 ± 0,03	0,46 ± 0,05	6	4
CH ₃	0,01	0,02	0,05	0,10	2,6 ± 0,1	3,3 ± 0,5	3	3
H	0,002—0,023	0,01—0,12	0,05	0,10	3,5 ± 1,5	2,8 ± 0,5	21	4
CCl ₃	0,01	0,02—0,05	0,05	0,1—0,5	0,23 ± 0,03	0,05 ± 0,02	3	5

the stability of the hydrogen bond NH...X increases as the electronegativity of R₁ increases and at the same time the stability of the XD...N bond decreases because of the diminished electron density on the nitrogen atom. In the case of CCl₃CONHCH₃ this decrease is apparently so significant that it becomes the main factor in determining the reaction rate, despite the high activity of the proton of the NH group.

The authors thank Yu. M. Boyarchuk and B. V. Ioffe for providing the amide samples and N. G. Bakhshiev for his interest in this work.

LITERATURE CITED

1. A. I. Brodskii, Chemistry of Isotopes [in Russian], Izd. Akad. Nauk SSSR, Moscow (1957).
2. D. N. Kursanov, Z. N. Parnes, and R. G. Kononova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 1493 (1958).
3. I. M. Klotz and B. H. Frank, J. Am. Chem. Soc., **84**, 3461 (1962).
4. I. M. Klotz and B. H. Frank, J. Am. Chem. Soc., **87**, 2721 (1965).
5. S. Z. Roginskii, Theoretical Foundations of Isotopic Methods of Studying Chemical Reactions [in Russian], Izd. Akad. Nauk SSSR, Moscow (1956).
6. C. G. Swain and M. M. Labes, J. Am. Chem. Soc., **79**, 1084 (1957).
7. G. S. Denisov, É. M. Kazakova, and E. V. Ryl'tsev, ZhPS, **8**, 690 (1968).