PROTON-TRANSFER REACTIONS IN AZOLES

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The kinetics of proton transfer in solutions of diazoles were investigated by ^1H and ^{13}C NMR spectroscopy. The kinetic data are explained by means of quantum-mechanical representations of the elementary act of proton transfer. It is concluded that proton transfer has substantial collective character. It was established that a small number of coordination centers (transition metal ions) have a dramatic effect on proton transfer owing to extraspheral complexing.

Proton transfer plays an important role in many biochemical processes in which nitrogen heterocycles and their metal complexes participate (in point mutations [1], the conductivity of biological membranes [2], and in enzymatic catalysis [3]). There is growing interest in reactions involving the transfer of NH protons in diazoles and triazoles, which have been found to be convenient models for the study of these processes.

Diazoles and triazoles exist in solutions in the form of self-associates via hydrogen bonds between the amino and imino groupings [4-6]. Proton transfer occurs intermolecularly within the framework of the hydrogen bonds, during which the system is converted from one associated state to another. Although data on the geometry of N-H···N bridges in solution of diazoles are currently unavailable, one should expect that the geometry does not differ markedly from that of the corresponding fragments in crystals. Thus, it may be assumed that the N···N distance in the bridge bonds does not exceed 3.2-3.5 Å [7, 8]. In this case the proton in the elementary act of proton transfer should migrate no more than 0.6-0.8 Å. This means that at low temperatures the length of the de Broglie proton wave corresponding to the vibrational motion is comparable to the length of the classically forbidden region, and one should expect the manifestation of the quantum properties of the proton.

The most rigorous description of the elementary act of proton transfer in molecular systems has been given by Dogonadze and Kuznetsov [9]. Following the concept developed by them, we will divide our system into classical ($h \ll kT$) and quantum ($h \gg kT$) subsystems. The first subsystem includes the nuclei of the atoms of the azole rings, and the second subsystem includes the protons and electrons. The change in position of the classical subsystem determines the activation energy of the process, whereas the quantum subsystem determines the magnitude of the transmission coefficient. The effect of the classical subsystem is diminished at low temperatures at which the amplitudes of the thermal motion of the heavy nuclei decrease, and the quantum-mechanical tunneling of the proton is manifested kinetically, i.e., the activation energy decreases. Thus, we are dealing with elimination of the masking effect of the classical subsystem at low temperatures.

Despite the fact that there have been many investigations devoted to the study of proton-transfer phenomena and the formation of H bonds in diazoles [10-13], up until now no one has been able to observe fixed tautomeric forms in imidazole and pyrazole solutions by NMR spectroscopy (this has, however, been accomplished for benzotriazole [14]). The rate of prototropic rearrangements in these heterocycles is so high that the molecules (within the range of ^1H NMR frequencies) retain effective C_{2v} symmetry over a wide range of temperatures. The rearrangement has degenerative character, i.e., the limiting tautomeric forms are equivalent. The 4,5 and 3,5 positions in imidazole and pyrazole, respectively, are isochromic and leads to A_2X PMR spectra. The considerably wider range of ^{13}C chemical shifts enabled us to study the kinetics of proton transfer in these heterocycles [15, 16]. However, in this

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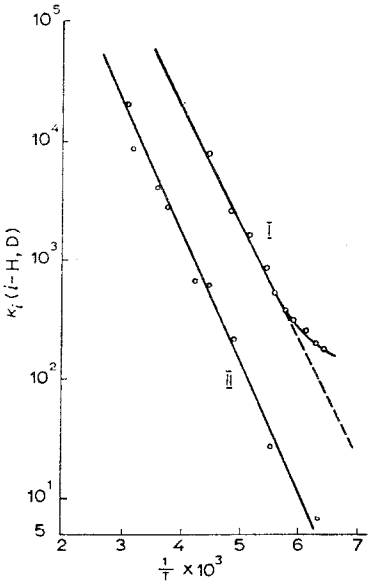

Fig. 1. Temperature dependence of the logarithm of the rate constant for tautomeric rearrangement in pyrazole (I) and d_1-pyrazole (II).

case also it was necessary to reach temperatures below −100°C to slow down the prototropic rearrangements. In this connection we used a mixture of solvents [ether and tetrahydrofuran (THF)]. In our case ether solvents can form N-H···O hydrogen bonds, but we worked with concentrated solutions (1- and 2-M sample concentrations). Under these conditions the diazoles evidently exist primarily in the form of cyclic trimers (pyrazole) and linear oligomers (imidazole) [17, 18]. In this case, therefore, one can, without disrupting the general character, disregard the effect of ligand transfer on the kinetics of proton transfer, i.e., one can disregard reactions leading to the formation (cleavage) of H complexes. Below we will examine cases in which these processes play a substantial role.

Having studied the temperature dependence of the ^{13}C resonance signal [3, 5], we calculated the rate constants of proton transfer at various temperatures. The most remarkable result of these calculations was the non-Arrhenius relationship between the logarithms of the rate constant for proton transfer and the temperature (Fig. 1). In the general case the nonlinearity of this function may be associated with a number of factors (a change in the mechanism of the reaction, the temperature dependence of the enthalpy of the reaction, the peculiarities of the dielectric relaxation of the solvent, etc.). However, the specific character of the systems under consideration — the degenerate character of the reaction, the absence of labile protons in the solvent molecules, and the invariability of the macroscopic mechanism of the reaction — make it possible to disregard alternative hypotheses in this case and to link the deviation from linearity with the manifestation of the tunneling effect in the elementary act of proton transfer. We suppose that, commencing at −105°, activationless tunnel infiltration is manifested more appreciably in the kinetics of the entire process. The decrease in the activation energy (from 4.8 to 1.65 kcal/mole) and its absolute value at low temperatures (below the activation energy of the diffusion-controlled reactions, 2.5-4.0 kcal/mole [19]) also provide evidence in favor of this.

Since the probability of the tunneling effect decreases as the mass of the tunneling particle increases, to obtain a definitive answer we studied the temperature dependence of the ^{13}C NMR spectrum of d_1-pyrazole [20]. The observable isotope effect proved to be extremely significant: the low-temperature limiting spectrum was obtained at −70° (at −138° in the case of pyrazole), and the coalescence temperature was found to be −80° (−105° for pyrazole). The dependence of log k on 1/T has the usual Arrhenius character (Fig. 1). The isotope effect was also manifested in the anomalous ratio of the frequency factors $A_D/A_H \cong 10^3$ (usually less than 10) at low temperatures.* All of these anomalies arise owing to the lower probability of tunneling of a deuteron as compared with a proton in the case of an invariable general reaction mechanism.

*In a study of the vibrational spectra of crystalline imidazole, Brikmann and Zimmermann [21] analyzed the complex structure of the bands in terms of inversion splitting because of tunneling in the static potential [21]. However, it was subsequently found that this is associated with the solid state effect and the anharmonicity of the vibrations [22].

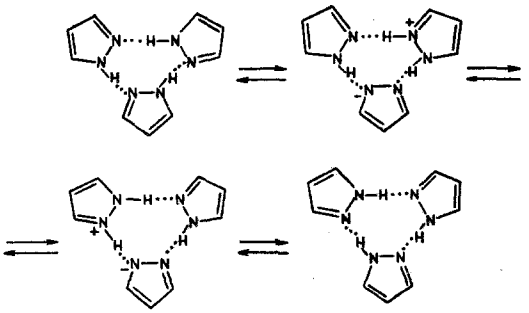

Fig. 2. Diagram of proton transfer in pyrazole.

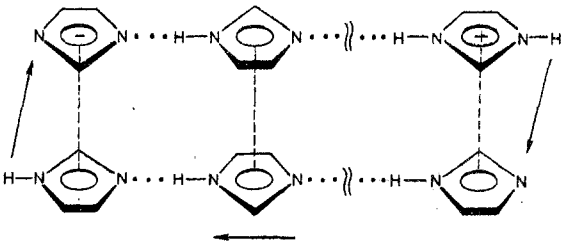

Fig. 3. Diagram of proton transfer in imidazole.

The initial act of proton transfer leads to the formation of an ionic structure. The development of charges stimulates further migration of the proton in the chain. This circumstance explains the absence of long-lived charged samples in solutions of pyrazole, the associates of which have a cyclic form (Fig. 2). In any case, if the charged samples also develop, their lifetime is less than 10^{-13} sec [12]. However, some additional relaxation mechanism by means of which the self-associates rid themselves of ionic structures must be specified for transfer in imidazole. This may be either a mechanism of reorientation of the imidazole molecules relative to the second order pseudoaxis [23] or a process with participation of adjacent chains in which proton transfer is actually realized within the framework of quasi-closed systems (Fig. 3). It is known that interplanar interactions (the stacking effect) leading to additional association even in DMSO occurs in imidazole solutions [24]. It should be noted that the stacking effect is generally a characteristic type of intermolecular interaction for aromatic nitrogen bases (particularly in the double helixes of nucleic acids [25]). In addition, it is known that interchain proton transfer evidently occurs in experiments on the study of proton conductivity in imidazole crystals. In any case it was established that, in addition to considerable proton conductivity in the direction of the chains of the molecules, there is also a small amount of conductivity in the direction of the axis perpendicular to the orientation of the chains [29]. A relaxation mechanism in which proton transfer occurs between the chains within the framework of hypercyclic structures therefore seems more likely to us. Thus the charges that develop as a result of the primary act of proton transfer are separated still farther by successive shifts (the Grotthuss mechanism) until compensation of the charges occurs during return of the proton. The fact that isochronicity of the 4,5 and 3,5 positions in imidazole and pyrazole, respectively, is experimentally observed also indicates the cooperative character of transfer. If transfer were to occur in an isolated manner in the bridges, these signals, although they would change with temperature, would remain anisochronic.

The coordination of a metal with the diazole molecule, which leads to the formation of a localized nonlabile σ bond between the metal atom and the imino grouping, excludes the possibility of the occurrence of the usual rearrangement of the NH protons. Thus, prototropic migration of an NH proton does not occur in tetracarbonyl complexes of iron with diazoles [26]. In addition, if the metal-ligand bond is sufficiently labile for ligand exchange to occur, prototropic transfer may also occur in the course of this exchange [27]. The natural question that arises is how will ligand exchange affect the mechanism of proton transfer if these reactions proceed at comparable rates? According to the dada in [28], the exchange reactions of diazoles with bis(acetylacetonato)nickel(II) [$Ni(acac)_2$] occur at sufficiently high rates. When a large excess of the heterocycle is present, one can disregard the concentration of the pentacoordinated samples and examine only the tetragonal bipyramidal 2:1 complexes [29]. It is known that these compounds with diazoles are paramagnetic and have two unpaired electrons. We therefore studied proton transfer in pyrazole under conditions of reaction of the latter with small amounts of added $Ni(acac)_2$ [30]. The width of the lines under these conditions is determined by shortening of the lifetime in a definite magnetic environment because of chemical exchange (both ligand exchange and proton transfer) and by relaxation in the field of the unpaired electron. The Swift–Connick expressions [31] are usually employed for the analysis of the changes in the line width and changes in the chemical shift. Calculation showed that the proton-transfer reactions begin to show up as a substantial mechanism of nuclear magnetic relaxation in the 3,5 positions of the pyrazole ring at temperatures below −60° [30]. At these temperatures the rate of exchange of ligands in the first coordination sphere becomes so low that the paramagnetic centers no longer have an effect on relaxation of the nuclei in solution.

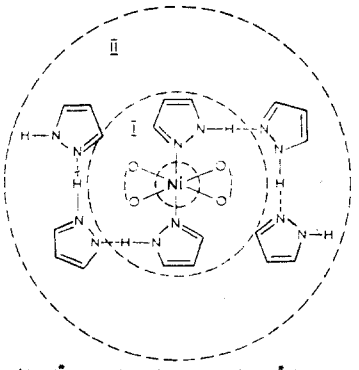

Fig. 4. Coordination sphere of nickel in a solution of pyrazole.

$$(Pz)_3\,Ni(Pz)_3^*(acac)_2 \rightleftarrows (Pz)_3 + Ni(Pz)_3^*(acac)_2 \quad (1)$$

$$(Pz)_3\,Ni(Pz)_3^*(acac) \rightleftarrows Pz + (Pz)_2Ni(Pz)_3^*(acac) \quad (2)$$

In addition, exchange of the ligands in the second coordination sphere, as before, occurs at sufficiently high rates. It was found that under these conditions the temperature dependence of the rate constant for proton transfer in Arrhenius coordinates has linear character. Thus the addition of $Ni(acac)_2$ to a solution of pyrazole does not prohibit proton transfer, but the rate constant for proton transfer in this case decreases considerably in absolute value, and, in addition, manifestations of proton tunneling are absent. It is important to once again emphasize that the $Ni(acac)_2$ concentration is by a factor of 100 lower than the pyrazole concentration, but $Ni(acac)_2$ nevertheless affects proton transfer in pyrazole at temperatures below −60°, at which the rate of exchange of the ligands in the first coordination sphere is already low and does not affect the relaxation processes in solution. We therefore examined a model of exchange processes based on the concept of extraspheral ligand exchange.

Since a trimer is the principal form of pyrazole self-associate, we assume that all of the associate enters into the coordination sphere of nickel (open ring), during which two molecules held by hydrogen bonds formulate the outer coordination sphere (Fig. 4). In coordinated associates of this type proton transfer either does not occur at all or may occur at low rates. Ligand exchange takes place at room temperature at sufficiently high rates in both the outer and inner coordination spheres. Moreover, in reaction (1) in Fig. 4 exchange of the entire block of self-associated molecules occurs, whereas only the composition of the second coordination sphere is transformed in reaction (2). Since the Ni-N bond is cleaved in the first case and N-H···N bond is cleaved in the second, these reactions have different activation characteristics. A decrease in the temperature therefore primarily slows down exchange reaction (1) and has little effect on reaction (2) at −60 to −100° [30].

The consequence of exchange processes of the (2) type will be the formation, at considerable rates, of different noncyclic associates of pyrazole with, generally speaking, a linear configuration of the hydrogen bridge bonds. In order for the proton transfer reactions to occur in the usual manner (i.e., as in free pyrazole), the perturbed (by extraspheral ligand exchange) system of self-associates should undergo relaxation to the equilibrium state. The relaxation process should evidently include ligand exchange between different self-associates for the formation of favorable trimeric systems, ring closing of the associates, and equilization of the configuration of the hydrogen bridge bonds. All of these, although rapid (evidently determined by the rate of diffusion), processes are, of course, activation processes. As a result, it turns out that the kinetics of the proton transfer reactions even at low temperatures are determined by the diffusion motion of the classical subsystem, and this masks the quantum character of proton tunneling.

The above assumption concerning the role of ligand exchange in the second coordination sphere is confirmed by an analysis of the widths of the lines of the ^1H NMR spectrum at low temperatures, i.e., below −90° [30]. In this case we observed broadening of the 4-H signal and simultaneous splitting of the 3,5-H line into two signals with different widths. These changes in the spectrum are explained within the framework of our model by the following reasons. While the exchange process in the first coordination sphere (1) becomes so slow that it does not make a contribution to the line width, intraspheral exchange reactions of the (2) type are so fast that the conditions of high-speed exchange between the pyrazole molecules in the volume and in the outer coordination sphere are satisfied [30]. In addition, at these temperatures the rate of prototropic rearrangement also becomes low, and the

3-H and 5-H state no longer interferes. In this case the line width is determined by relaxation in the second coordination sphere. The principal relaxation mechanism therefore becomes dipole–dipole interaction between the nucleus and the unpaired electron, and the line width of the resonating nucleus depends on the distance to the paramagnetic ion [32] as a function of r^{-6}, which also leads to different line widths of the aromatic protons of the pyrazole ring [30].

LITERATURE CITED

1. P. O. Lowdin, Advances in Quantum Chemistry, Vol. 2 (1965), p. 213.
2. H. Zundel, Hydration and Intermolecular Interaction [Russian translation], Mir, Moscow (1972).
3. T. Bruce and S. Benkowicz, Mechanisms of Bioorganic Reactions [Russian translation], Mir, Moscow (1970).
4. V. I. Minkin, O. A. Osipov, A. D. Garnovskii, and A. M. Simonov, Zh. Fiz. Khim., 36, 469 (1962).
5. O. A. Osipov, A. M. Simonov, V. I. Minkin, and A. D. Garnovskii, Dokl. Akad. Nauk SSSR, 137, 1374 (1961).
6. N. E. White and M. Kilpatrick, J. Phys. Chem., 59, 1044 (1955).
7. F. K. Larsen, M. S. Lehmann, I. Sötofte, and S. E. Rasmussen, Acta Chem. Scand., 24, 3248 (1970).
8. S. Martinez-Correra, Acta Cryst., 20, 783 (1966).
9. R. R. Dogonadze and A. M. Kuznetsov, Kinetics of Chemical Reactions in Polar Solvents [in Russian], VINITI, Moscow (1972).
10. H. A. Staab and A. Mannschreck, Tetrahedron Lett., No. 20, 913 (1962).
11. M. L. Roumestant, P. Viallefont, J. Elguero, and R. Jacquier, Tetrahedron Lett., No. 6, 495 (1969).
12. G. Zundel and J. Muelinghaus, Z. Naturf., 26B, 546 (1971).
13. N. Joop and H. Zimmermann, Z. Electrochem., 66, 440 (1962).
14. A. N. Nesmeyanov, V. N. Babin, L. A. Fedorov, M. I. Rybinskaya, and E. I. Fedin, Tetrahedron, 25, 4667 (1969).
15. A. N. Nesmeyanov, E. B. Zavelovich, V. N. Babin, N. S. Kochetkova, and E. I. Fedin, Tetrahedron, 31, 1461 (1975).
16. A. N. Nesmeyanov, E. B. Zavelovich, V. N. Babin, N. S. Kochetkova, and E. I. Fedin, Tetrahedron, 31, 1463 (1975).
17. D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, J. Chem. Soc., No. 1, 140 (1961).
18. D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, J. Chem. Soc., No. 9, 4201 (1961).
19. E. V. Grunwald, in: New Problems in Physical Organic Chemistry [Russian translation], Mir, Moscow (1969), p. 207.
20. A. N. Nesmeyanov, V. N. Babin, E. B. Zavelovich, and N. S. Kochetkova, Chem. Phys. Lett, 37, 184 (1976).
21. J. Brikmann and H. Zimmermann, Ber. Buns. Phys. Chem., 71, 160 (1967).
22. L. Glasser, Chem. Rev., 75, 21 (1975).
23. A. Cawada, A. R. McGhie, and M. M. Labes, J. Chem. Phys., 52, 3121 (1970).
24. Yu. V. Teterin and L. N. Nikolaenko, Dokl. Akad. Nauk SSSR, 210, 1382 (1972).
25. A. A. Bogdanov and R. N. Ledneva, Molecular Biology. Advances in Science and Technology [in Russian], Vo.. 5, Moscow (1975).
26. A. N. Nesmeyanov, V. N. Babin, N. S. Kochetkov, and Yu. S. Nekrasov, Dokl. Akad. Nauk SSSR, 200, 601 (1970).
27. A. Fratiello, R. E. Schuster, and M. Geisel, Inorg. Chem., 11, 11 (1972).
28. B. S. Tovrog and R. S. Drago, J. Amer. Chem. Soc., 96, 2743 (1974).
29. M. K. Misra and D. V. R. Rao, J. Inorg. Nucl. Chem., 31, 3875 (1969).
30. V. N. Babin, E. B. Zavelovich, and E. I. Fedin, Z. Naturf., 31C, 353 (1976).
31. T. Swift and R. Connick, J. Chem. Phys., 37, 307 (1962).
32. N. Bloembergen and L. O. Morgan, J. Chem. Phys., 34, 842 (1961).