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Dynamics of Molecular Hydrogen Exchange in Hydrogen-Bonded Systems*

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The kinetics of hydrogen exchange in molecular systems with H-bonds studied by kinetic IR spectroscopy and low-temperature NMR spectroscopy methods is critically reviewed. The experimental rate constants and activation energies obtained so far for molecules capable of forming H-bonds as both proton donors and proton acceptors are collected and analyzed from the point of view of the influence of H-bond formation ability of the molecules-partners. The evidence available testifies to a molecular mechanism of the H-exchange reactions in inert solvents and in the gas phase *via* the formation of cyclic, mostly bimolecular, intermediates. The different mechanisms of the molecular H-exchange process in inert media are discussed and the possible paths of experimental elucidation of reaction mechanism are offered.

Key words: hydrogen exchange, rate constants, kinetic IR spectroscopy, low-temperature NMR

Introduction

In this paper we shall discuss the results of the studies of molecular H-exchange kinetics with the special attention to review critically the experimental values of the kinetic characteristics of the reaction gathered so far (the rate constants k and the activation energies E_a) and to analyze the possible mechanisms of the process.

The traditional approach to hydrogen bonding (H-bonding) is the study of the static characteristics of complexes, such as the geometry, spectral changes under the H-bonded complex formation, electrooptical and thermodynamic parameters. In treating some static characteristics of complexes the question of dynamic properties of H-bonding already arises, the possible influence of fast exchange processes upon the shape of bands in optical and NMR spectra being of interest. The dynamics of systems with H-bonding is interesting in itself, since H-bonds play a decisive role in kinetics of a number of processes, in particular, the processes of proton transfer and proton exchange. By investigation of the kinetics of these processes we may gain information on the barriers, separating the minima on the potential energy surface. In the simplest case, the elementary step of hydrogen exchange (H-exchange) RAH +

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R′BH* ⇔ RAH* + R′BH is a cooperative proton transfer in a cyclic complex with two H-bonds (below we shall discuss the facts, which support this idea). The existence of a minimum on the potential surface of interaction between AH and BH, referring to a cyclic complex with two H-bonds AH…B and BH…A (A and B may be the same), indicates the existence of another minimum, which results from symmetry [1]. These two minima refer to two physically indistinguishable states of a complex, and the transfer from one state to the other requires some activation energy. Because of high rate of the reactions at room temperature, most of the problems referring to the kinetics of H-bonded systems depend, to a large extent, on the development of special techniques for the study of fast reactions.

Although the interest in H-bond dynamics has increased considerably in recent four decades, yet it is still not clear, how to approach these problems. Besides, most results have been obtained by studying concentrated solutions and pure liquids [2–5], in cases when the interaction with the surrounding medium, which influences the mechanism of the process qualitatively, not only cannot be excluded but becomes decisive. This fact makes investigation of the dynamics of H-bonded systems expedient under conditions of minimum interaction with the surroundings, *i.e.* in the gas phase, or at a low concentration in inert solvents, whose energy of interaction with the molecules under investigation is apparently lower than the energy of interaction between the partner molecules. The kinetic study of the H-exchange in solvents, whose molecules do not stimulate electrolytic dissociation, allows one to neglect consideration of acid-base catalysis and is of great interest for finding the mechanism of the initial interaction between the molecules concerned. Therefore, it would be desirable to carry out experiments under conditions, where it is possible to separate the influence of the surrounding medium from that of the partner molecules on the dynamics of H-bonding.

During recent decades the kinetic IR spectroscopy and dynamic NMR spectroscopy are the most informative and wide-used experimental methods for the study of H-exchange kinetics. It is clear that using the first method we have to study the isotopic effects and their influence on the kinetics of reaction.

Studying H-exchange by NMR technique it is necessary to use special methods for calculations of line shapes for different molecular systems and different rates of exchange (see, for example, [6]) and to compare the theoretical contour with experimental data, providing the best agreement. As an illustration, Fig. 1 demonstrates an example of the H-exchange study for the 3,5-dimethylpyrazole+formic acid system at 120 K in solution in freon mixture CDF_3+CDF_2Cl+$CDFCl_2$ (1:4:1) [7]. The theoretical spectrum consists of a doublet of NH and an AX system of formyl and hydroxyl protons; as the proton transfer frequency is gradually increased, the spectrum is transformed as shown in Fig. 1b. The experimental NMR spectra are shown in Fig. 1a: the ^{1}H NMR spectrum (1) consists of a poorly resolved doublet of mobile protons and a triplet of formyl protons and coincides with theoretical spectra calculated at the frequency of proton migration $\tau_{H-H}^{-1} = 620 \pm 50$ s^{-1}; the frequency of degenerate transfer of two deuterons (see spectrum 2) was estimated from the ^{2}H spectra and was

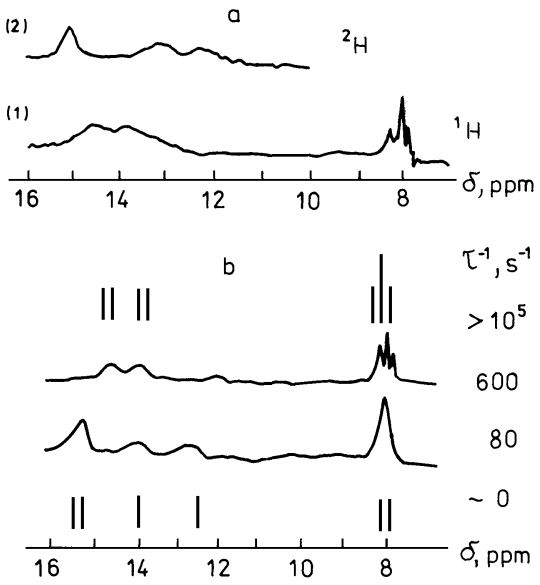

Figure 1. The experimental ^{1}H (1) and ^{2}H (2) NMR spectra of solutions of the 3,5-dimethylpyrazole – formic acid system in a mixture of freons at 120 K (a) and the evolution of the calculated spectrum of the same system (b) upon variation of the frequency of proton transfer: $\tau^{-1} = 0$ (1), 80 (2), 600 (3) and $>10^5$ s^{-1} (4).

found equal to 35 s^{-1}. The line shape analysis of the NMR spectra also gives an opportunity to study the influence of the temperature and solvent polarity on the rate of H-exchange [8].

As for the kinetic IR spectroscopy, the H-exchange process is followed by measuring the time dependence of the intensity at absorption maxima of AH(AD) or/and BH(BD) stretching vibration bands, which is proportional to the component concentration. These changes correspond to the redistribution of isotopes between the functional groups of molecules-partners till the equilibrium isotope distribution (as it is illustrated by Fig. 2a for the methanol–o–chlorophenol system [9]). Combined with stopped-flow method [10] developed by us for the IR spectral region, it permits the study of H-exchange in solutions with a half-exchange period as little as a few milliseconds (see Fig. 2b). For every system the values of specific reaction rate (non-dependent on time) R can be determined under different relative reactants' concentrations, and the rate constants k and the orders of reaction α and β with respect to every component were obtained. The Arrhenius activation energies E_a have been determined from the ln k *vs*. 1/T dependence:

$$[AH]_t = [AH]_\infty + ([AH]_0 - [AH]_\infty) \exp(-rt), \quad (1)$$

$$R = r[A][B]/([A] + [B]), \text{ where } [A] = [AH] + [AD], [B] = [BH] + [BD], \quad (2)$$

$$R = k[A]^\alpha[B]^\beta \quad (3), \qquad k = k_0 \exp(-E_a/R_0T). \quad (4)$$

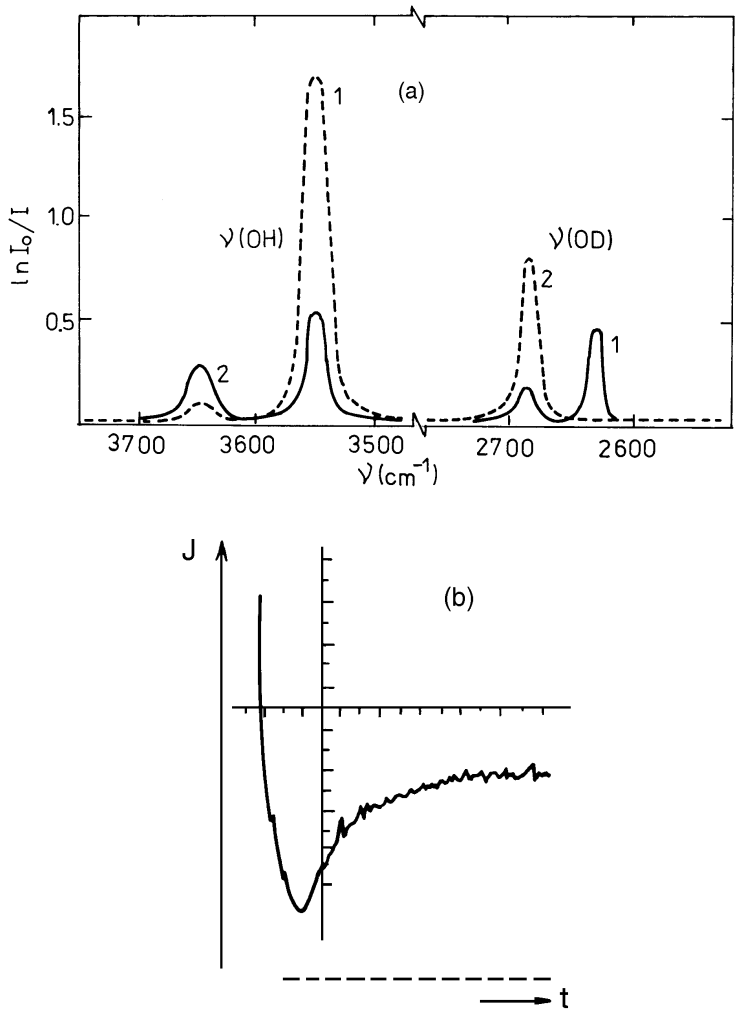

Figure 2. a – IR spectra of the 0.05 M CH_3OD – 0.02 M *o*-ClC_6H_4OH system before (dotted line) and after (solid line) H-exchange in CCl_4, 1 – bands of phenol, 2 – bands of alcohol; b – the kinetic curve recorded on ν OD band for H-exchange between 0.2 mol/l C_2H_5OD and 0.075 mol/l $(C_2H_5)_2NH$ at 30°C, time scale is 20 ms per line.

The role of hydrogen bonding in reaction kinetics

Nowadays, the information available on the kinetics of H-exchange processes embraces practically all classes of molecules capable of forming H-bonds: the carboxylic acids, alcohols, phenols, water, amines, amides and other nitrogen-containing compounds, thiols, and so on. In Table 1 we collected the known values of experimentally obtained kinetic characteristics of the H-exchange processes for the

main classes of molecules capable to form H-bonds. In spite of the broad variety of physical and chemical properties of the molecules studied, and the wide range of characteristic times of H-exchange (from some milliseconds to several hours), one may conclude from the available experimental data that the ability of a molecule to form a hydrogen bond determines the kinetic characteristics of the exchange process with its participation. Comparing different classes of compounds, it will be obvious that the exchange of the proton of thiohydrilic group of thiols with all the partners studied (See Table 2) is accomplished much more slowly than the exchange of the proton of hydroxylic group of similar alcohols. The ability of the SH group to form H-bonds as a proton donor and a proton acceptor is considerably lower than that of the OH group. Since the acidity of thiols is greater than that of alcohols, one may conclude that, in this case, H-exchange rate is determined by the ability of the molecule to form H-bonds rather than by its acidic properties.

Experimental data have shown that the maximum values of the rate constants of H-exchange with alcohols or thiols (see Table 2) were found for carboxylic acids. The reaction becomes slower for phenol, still slower when water or alcohols are used, and is further retarded for secondary amines, amides, and thiols. As a rule, the sequence of decreasing proton donor ability in a series of compounds is the same. A similar dependence has been obtained for the gas phase, when we studied the H-exchange between thiol and alcohols and amines [11,12]. The same regularity was observed in studying the influence of proton donor ability on the rate of H-exchange in a series of compounds of one class. As a rule, an increase in the proton donor ability of the AH group in such a series (see, for example, Table 1, carboxylic acids) results in an increase of the rate constant. In a series of RAH molecules, the proton donor and proton acceptor abilities are changed in different directions by variation of the substituent R.

Table 1. Kinetic characteristics of H-exchange processes in diluted CCl_4 solutions at 293 K.

No.	Molecular system	k (l/mol·s)	E_a (kJ/mol)	Ref.
	1. Carboxylic acids			
1.	$CF_3COOH - C_2H_5OH$	51000	18	[13]
2.	$CCl_3COOH - C_2H_5OH$	37000	20	[13]
3.	$CHCl_2COOH - C_2H_5OH$	26000	14	[13]
4.	$CH_2ClCOOH - C_2H_5OH$	6800	8	[13]
5.	$CH_3COOH - CH_3OH$	4800	24	[8]
6.	$CH_3COOH - C_2H_5OH$	1300	19	[13]
7.	$CH_3COOH - o\text{-}NO_2C_6H_4OH$	16	21	[14]
8.	$HCOOH - C_2H_5OH$	3300	21	[13]
9.	$(CH_3)_3CCOOH - C_2H_5OH$	1000	24	[13]
10.	$iso\text{-}C_3H_7COOH - iso\text{-}C_4H_9SH$	2.1	55	[24]
11.	$CH_3COOH - iso\text{-}C_4H_9SH$	2.5	–	[25]

Table 1 (continuation)

	2. Phenols and their derivatives			
12.	*p*-ClC_6H_4OH – CH_3OH	320	8.4	[9]
13.	C_6H_5OH – CH_3OH	240	9	[9]
14.	*o*-$NO_2C_6H_4OH$ – CH_3OH	110	28	[26]
15.	*o*-$NO_2C_6H_4OH$ – tert-C_4H_9OH	70	29	[14]
16.	*o*-$NO_2C_6H_4OH$ – $(C_6H_5)_2NH$	2.4	29	[14]
17.	*o*-ClC_6H_4OH – CH_3OH	65	14	[9]
18.	2,4,6-$Cl_3C_6H_2OH$ – CH_3OH	37	13	[9]
19.	Guaiacol – CH_3OH	40	29	[14]
20.	Salicylic aldehyde – CH_3OH	20	36	[15]
21.	Ethyl-3-nitrosalicylate – CH_3OH	4	38	[15]
22.	*p*-$NO_2C_6H_4OH$ – C_4H_9SH	0.21	13	[27]
23.	*p*-ClC_6H_4OH – C_4H_9SH	0.13	18	[27]
24.	C_6H_5OH – C_4H_9SH	0.10	19	[28]
25.	*p*-$CH_3C_6H_4OH$ – C_4H_9SH	0.023	21	[27]
26.	α-naphthol – C_4H_9SH	0.12	17	[27]
27.	β-naphthol – C_4H_9SH	0.09	18	[27]
	(see also System 7)			
	3. Alcohols			
28.	CH_3OH – tert-C_4H_9OH	850	7.5	[29]
29.	CH_3OH – CH_3OH	380	6.3	[30]
30.	CH_3OH – H_2O	270	7.1	[31]
31.	C_2H_5OH – H_2O	240	8.0	[22]
32.	C_2H_5OH – $(C_2H_5)_2NH$	150	5.9	[10]
33.	C_4H_9OH – $(C_2H_5)_2NH$	85	12	[32]
34.	CF_3CH_2OH – tert-C_4H_9SH	$3\cdot10^{-2}$	–	[29]
35.	CH_3OH – tert-C_4H_9SH	$3\cdot10^{-2}$	–	[29]
36.	C_2H_5OH – tert-C_4H_9SH	$2.2\cdot10^{-2}$	21	[29]
37.	tert-C_4H_9OH – tert-C_4H_9SH	$0.4\cdot10^{-2}$	21	[29]
38.	CH_3OH – diazoaminobenzene	2200	26.3	[33]
39.	iso-C_3H_7OH – diazoaminobenzene	3800	20.9	[33]
40.	tert-C_4H_9OH – diazoaminobenzene	1500	20.1	[33]
41.	iso-C_3H_7OH – diphenylacetamidine	4300	–	[34]
42.	tert-C_4H_9OH – diphenylacetamidine	2800	–	[34]
	(see also systems 1–6, 8–9, 12–15, 17–21, 43–45, 54–56, 61–63)			
	4. Amines and nitrogen-containing heterocycles			
43.	$C_6H_5NHCH_3$ – C_2H_5OH	240	7.5	[28]
44.	$(C_3H_7)_2NH$ – C_2H_5OH	100	–	[32]
45.	$(iso\text{-}C_4H_9)_2NH$ – C_2H_5OH	80	13	[32]
46.	$(C_6H_5CH_2)_2NH$ – tert-C_4H_9SH	$2.2\cdot10^{-2}$	–	[28]
47.	$(C_2H_5)_2NH$ – tert-C_4H_9SH	$1.1\cdot10^{-2}$	25	[29]
48.	$(C_3H_7)_2NH$ – tert-C_4H_9SH	$0.8\cdot10^{-2}$	34	[28]

Table 1 (continuation)

49.	$(C_4H_9)_2NH$ – tert-C_4H_9SH	$0.5\cdot10^{-2}$	–	[28]
50.	$(iso\text{-}C_4H_9)_2NH$ – tert-C_4H_9SH	$0.4\cdot10^{-2}$	34	[29]
51.	$(C_6H_5)_2NH$ – tert-C_4H_9SH	$0.1\cdot10^{-2}$	25	[29]
52.	$C_6H_5NHCH_3$ – tert-C_4H_9SH	0.1	34	[1]
53.	$C_6H_5NHC_2H_5$ – tert-C_4H_9SH	0.08	34	[1]
54.	Pyrrole – CH_3OH	$1.2\cdot10^{-4}$	34	[35]
55.	Indole – CH_3OH	$4.5\cdot10^{-4}$	46	[35]
56.	Carbazole – CH_3OH	0.3	59	[35]
57.	Diazoaminobenzene – dimethylpyrazole	14000	–	[36]
	(see also systems 16, 32–33, 38–42)			
	5. Amides			
58.	$HCONHCH_3$ – iso-C_4H_9SH	$2.8\cdot10^{-3}$	–	[37]
59.	$(CH_3)_3CCONHCH_3$ – iso-C_4H_9SH	$0.4\cdot10^{-3}$	–	[37]
60.	$Cl_3CCONHCH_3$ – iso-C_4H_9SH	$0.05\cdot10^{-3}$	–	[37]
	6. Mercaptans			
61.	iso-C_4H_9SH – iso-C_3H_7OH	$0.4\cdot10^{-2}$	–	[29]
62.	tert-C_4H_9SH – iso-C_3H_7OH	$0.9\cdot10^{-2}$	23	[29]
63.	tert-C_4H_9SH – CH_3OH	$7.0\cdot10^{-2}$	13	[29]
	(see also systems 10–11, 15, 22–27, 34–37, 46–53, 58–60)			

Therefore, if the H-exchange takes place in cyclic complexes, formed by the BH molecule with a number of partners RAH, an increase in the strength of one H-bond will have to be accompanied by a decrease in the strength of the other. That is why there are deviations from the dependence described above (see Table 1). For example, the *k* value for H-exchange in the trifluoroethanol–butanethiol system is equal to *k* for the reaction between methanol and butanethiol, although the proton donor ability of fluorinated alcohol is considerably greater than that of CH_3OH, since it contains strong electronegative substituents. A decrease in *k* was observed on the transfer from alkylanilines to diphenylamine, a still stronger proton donor. Even for carboxylic acids, we have observed a retardation of the increase of *k* values [13] with the rise of acidity. These facts may be considered as an indication of the influence of decrease in proton acceptor ability of the A atom in the AH group, and of the cyclic structure of H-exchange intermediates.

Table 2. Rate constants *k* (l/mol·s) for some molecular systems in CCl_4 at 293 K.

Partners:	CH_3OH	C_4H_9SH
CH_3COOH	4800	2.5
C_6H_5OH	240	0.1
$(C_6H_5)_2NH$	150	0.011
$CH_3CONHCH_3$	0.026	0.0033

That is why it has been of great interest to study the situation, when the molecule studied as a partner in H-exchange reaction can lose its proton donor or proton acceptor ability in intermolecular interaction. The first situation can be realized by the study of the H-exchange kinetics with the participation of molecules with intramolecular H-bond, where the proton of AH group is already included into a H-bond with a proton-acceptor center of the same molecule. In the H-exchange of phenol derivatives with methanol [14,15], the reaction was retarded as proton donor ability of the molecule increases (see Table 1). The results obtained testify to the fact (Table 3) that formation of an intramolecular H-bond by the AH group proton is accompanied by a considerable decrease in the rate of H-exchange. It would be added that the values of activation energy are close to the estimates of the intramolecular H-bond energies for the molecule under investigation. The dependence of H-exchange rate on the formation of intramolecular H-bonds by the proton donor functional AH groups can be used effectively in biochemical studies of biopolymers' structure. It has been shown recently that short strong H-bonds play important role in the fermentative catalysis (such as in acidic and basic catalysis), and the considerable decrease (some orders of magnitude) of the H-exchange rate of the bridge proton with solvent in the ferment-substrate complex has been recognized as one of the criteria of such bonding [16–18].

The data above are consistent with the supposition that the process involves cooperative (or, in some papers, concerted) proton transfer in the cyclic intermediate. For such a complex to form, the A atom and the B atom must have lone pairs of electrons. The NMR study of amine–dinitroethane systems has shown that the proton transfer in them is rapid, while the rate of proton exchange is very low [1]. This fact is naturally related to the electronic structure of the carbon acid molecule. We have obtained another remarkable result in studying H-exchange involving the (3-aminopropyl)dibutylborane molecule by kinetic IR spectroscopy [19]. This molecule possesses proton donor ability comparable with that of aliphatic alcohols, but, on account of a lone pair of the N atom involved in coordination to the boron atom, it loses its proton acceptor function completely. So (see above), we have the second situation of interest. While the k values for alcohol–alcohol and alcohol–amine systems in CCl_4 are of the order of 100–400 l/mol·s, the rate constants for the H-exchange between aminoborane and methanol, or secondary amines, in the same solvent are 3–4 orders of magnitude lower. Such a result points to a cyclic rather than a linear structure for the intermediate.

The experimental data available confirm the conclusion that the rate of the molecular H-exchange processes of the type considered is determined by the same peculiarities of electronic structure, which control the hydrogen bonding ability of the functional groups of the molecules and the reaction takes place *via* cyclic intermediate complex, formed by H-bonds between the functional groups of the molecules-partners.

Table 3. Influence of the intramolecular H-bonding on the kinetic parameters of H-exchange.

No.	Second partner	k, l/mol·s	E_a, kJ/mol	ΔH^{intra}, kJ/mol
(a) Methanol +				
1.	Ethyl-5-nitrosalicylate	5.1	42.0	
2.	Ethyl-3-nitrosalicylate	4.6	36.4	
3.	Salicylic aldehyde	20.0	35.6	33.5
4.	2-Nitrophenol	120.0	27	26
5.	2-Methoxyphenol	40.0	19	17.2
(b) 2-Nitrophenol +				
1.	CD_3COOH	16	22	
2.	$(CH_3)_3COH$	70	27	26
3.	$(C_6H_5)_2NH$	2.4	29	

The importance of H-bonding in H-exchange kinetics is supported also by the study of the influence on the kinetics of the process of solvents, capable of forming H-bonded complexes with the molecules concerned. This influence is seen clearly by comparing the results of the H-exchange study in alcohol-water systems in dilute CCl_4 solutions [22] and in a binary mixture [23]. In the latter case, the k values are smaller by two orders of magnitude, while E_a is markedly higher than in the case of H-exchange at component concentrations of 10^{-2}–10^{-3} M in non-polar solvent. This can be attributed to the effect of a network of H-bonds in the binary mixtures, hampering the formation of cyclic intermediate complexes between alcohol and water molecules.

The structure of intermediate complex and the mechanism of non-catalyzed hydrogen exchange

Experimental measurements of the order of reaction with respect to each component (see (3)) show that, in all cases of H-exchange in solution, the reaction order is close to unity. Hence, the process can be seen as bimolecular, *i.e*. the first step of the process takes place in the cyclic complex formed by two H-bonded molecules. That the reaction proceeds in the cyclic bimolecular intermediates has been accepted also in [20,21].

Speaking of intermediate cyclic structures, it should be clearly understood that the cyclic model of the binary complex, formed by two non-linear H-bonds between bifunctional groups AH and BH, is less expedient than the linear structures, in terms of energy and entropy. For the molecules with two different functional groups (carboxylic acids, pyrazoles, amidines, triazenes), the formation of cyclic complexes with linear H-bonds is real and has been realized for some molecular systems studied [7,8,13,39,40]. Although so far there is no direct experimental evidence to support the existence of four-membered cyclic H-bonded dimers, still the results of quantum chemical calculations (see, for example, [41]) show that such a complex does possess energy considerably exceeding the thermal energy, and is stable under the variations

of geometrical parameters. Recently, some interesting quantum chemical calculations of the kinetic characteristics for the concerted mechanism of proton migration along the H-bonds in cyclic dimers and oligomers were published. The kinetic parameters of H-exchange calculated for the cyclic complex with two H-bonds, formed by the acetic acid and methanol molecules [42] are in good agreement with experimental studies. Studying the cyclic trimers and tetramers of water, the authors found [43] that the lower calculation level used (B3LYP/6-31+*G*(*d*)) is in surprisingly good agreement with the higher level MP2/6-311++*G*(*3pd,3df*) results; especially the barrier height is nearly identical, being equal to 26.99 kcal/mol from both methods for trimer and 23.20÷23.29 kcal/mol for $(H_2O)_4$. The rate constants at 300 K have been found equal to $3.4 \cdot 10^{-4}$ s^{-1} (with large curvature tunnelling corrections) for trimer and 0.44 s^{-1} for tetramer (in latter case it means that the exchange takes place about one per second at 300 K!). The MP2/6-311++*G(3df,3pd)*///PM3-SRP calculations of the reaction rate constants for the concerted proton transfer in cyclic hydrogen fluoride pentamers [44] gave $2.86 \cdot 10^{9}$ s^{-1} at 300 K, which is similar to carboxylic acid dimers, whose experimental $k^{300\ K}$ values lie near 10^{10} s^{-1} [45].

As to the possible mechanism of molecular H-exchange process, the first assumption of synchronous transfer of two protons (or proton and deuteron) in the cyclic complex was made 50 years ago [38]. The mechanism of such cooperative (or concerted) process may be represented by the scheme (5):

H H
/ • • \
AH + BH* ⇔ A B ⇔ A B ⇔ AH* + BH. (5)
• / \ •
H* H*

In solutions other reaction mechanisms via binary complexes are possible [2]. An alternative mechanism is a sequential transfer of two protons in a linear complex, where the intermediate has to be the form of a cyclic ionic pair with two equal H-bonds:

H
• \
AH + BH* ⇔ AH…BH* ⇔ A^{-} ^{+}B ⇔ AH*…BH ⇔ AH* + BH. (6)
• /
H*

Such a process would not involve the stage of breaking of the ionic pair (the electrolytic dissociation) and, therefore, could proceed in an inert medium.

A study of the influence of the polar properties of medium (the dielectric permeability of a solvent, for example) on the rate of H-exchange process may be a help in choosing between mechanisms (5) and (6). Our results indicated that, as $\varepsilon_{solv.}$ increases, the rate of H-exchange (determined by the dynamic NMR spectroscopy) in water [46] or in alcohol–alcohol system [8] decreases, while, for alcohol–acetic acid system, the rate of reaction rises considerably. We explained this dependence by the cooperative synchronous mechanism (5) in the former case, and by the ion-pair mechanism (6) in the latter. On formation of the transition state of mechanism (6), a great increase of the dipole moment, as compared to the initial state, must follow. Therefore, when $\varepsilon_{solv.}$ increases, the rate of exchange must also increase. However, on formation of the transitional state of the cooperative mechanism (5), which resembles in structure the symmetrical cyclic complex, the dipole moment decreases, and this would result in the opposite effect. This strong dependence has been observed experimentally. It is possible to use another way for the change of dielectric properties of the medium. The influence of strong external electric field (up to 10^7 V/m) on the rate constants of H-exchange of methanol with acetic acid, phenol and dinitro-*p*-cresol in CCl_4 by kinetic IR spectroscopy and stopped-flow method [47] allowed to determine different mechanisms of the process for these molecular systems: (6) for the first system and (5) for two other ones.

The other path for the choice between the above-mentioned H-exchange mechanisms is the comparison of the kinetic characteristics of a molecular system in solution and in gaseous phase. The results of the study of proton exchange in gaseous dimethylamine and methanol-dimethylamine system and in the solutions [48] showed (Table 4) the decrease of k and the increase of the activation energies E_a for the both systems under the transition from gas to solution in deuterocyclohexane. This retardation of the reaction has been explained by the stronger solvation of molecules studied in solution in comparison with the cyclic symmetric transition complex exhibiting a smaller dipole moment.

Table 4. Kinetic characteristics of H-exchange in dimethylamine and in dimethylamine–methanol system for gaseous phase and solutions in C_6H_{12}.

	NH-NH		NH-OH	
	gas	solution	gas	solution
α_{NH}	1.9±0.1	2.0±0.1	1.0±0.3	1.0±0.1
β_{OH}	–	–	1.1±0.2	1.1±0.1
$k^{303\,K}$, $l \cdot mol^{-1} \cdot s^{-1}$	87±7	47±6	260±30	140±20
E_a, kJ/mol^{-1}	5.9±2.5	8.4±1.7	4.2±1.2	7.5±1.7

At last, the study of the kinetic isotope effects (KIE) for proton exchange kinetics may be useful for this choice [26,31,49]. The investigation of KIE is of great importance for the determination of isotope distribution coefficients for hydrogen and deuterium. It is known that H/D isotopic fractionation between different proton donor sites is mainly caused by zero-point energy changes between the sites. The measure-

ment of fractionation factors using a variety of methods is, therefore, an established tool of isotopic research. Especially strong deviations from normal statistic distribution are observed for the systems with H-bonds: hydrogen has a tendency to be concentrated at the positions with the strongest H-bonds. The systematic study of the H/D exchange between the active groups of biopolymers and solvent molecules (water or water-organic mixtures) permitted to determine the main regularities, which connect the fractionation factor and the strength of the H-bridge formed by proton donor group [50–54]. This is an indirect criterion for the estimation of H-bond energy in the complex biological systems.

Apparently, the most strong deviations from the statistically averaged distribution of isotopes have been recorded in [55]. Here, it has been shown that the concentrations of hydrogen OHO and deuterium ODO bonds for the solutions of the $H_5O_2^+$ ion in freon at 90 K (under 95% deuterium content) are equal practically, *i.e*. the content of deuterium in ODO fragment is four time less in comparison with the statistically average value.

The equilibrium constants of the isotopic redistribution for the substituted biphenolates and bicarboxylates systems have been studied in [56]. It has been shown that if the system is characterized by double-minimum potential curves, calculated fractionation factors decrease with simultaneous decrease of the potential barrier. And under the transition to the case of one-minimum potential, the situation changed qualitatively: the fractionation factors began to rise. It means that these factors can serve as a criterion of potential curve type.

On the other hand, fractionation factors theory constitutes the classical theory of kinetic H/D isotope effects of proton migration reactions. For example, the isotopic fractionation factors K between the acid-base complexes AHB+Ph_3COD…B $\leftrightarrow$ ADB+PhCOH…B, where AH represents the variety of acids and B represents pyridine-^{15}N, were measured by NMR around 110 K, using the mixture of liquefied $CDClF_2$-CDF_3 (2:1) as solvent [57]. The low-temperature NMR technique may permit to determine K directly by integration of appropriate proton NMR signals as the slow H-bond exchange regime can be reached. Measuring the experimental fractionation factors as a function of the ^{1}H chemical shifts, we found that K is an almost linear function of $\delta(^1H)$, exhibiting, however, a different slope on both sides of the quasi-symmetric complex, characterized by the lowest K and the largest $\delta(^1H)$. The slopes are different, depending on whether the proton is closer to oxygen or nitrogen. Thus, $\delta(^1H)$ can be a qualitative measure not only of the A…B distance but also of the fractionation factors, and can give interesting information about zero-point energy changes along the reaction pathways of proton transfer.

Conclusions

Summing up, one can say that there is little doubt that the ability of exchanging molecules to form H-bonds influences the kinetic characteristics of the H-exchange process. The evidence available testifies to a molecular mechanism *via* formation of cyclic intermediates (mostly, bimolecular ones) in an inert medium. The cooperative

mechanism of proton transfer is the simplest model of the reaction. Its realization in a pure form is most probable in systems with symmetrical intermediates. If the H-bond forming abilities of component molecules differ greatly, then the step-like mechanism *via* formation of the H-bonded ion pair may be correct. In nature, a whole variety of intermediate reaction paths may exist for different molecular systems. A better insight into the mechanism of H-exchange molecular processes may be obtained by a further spectroscopic study of the cyclic complexes, determination of their lifetimes, investigation of the dynamics of successive steps of the process by various physical and chemical methods and techniques, and by high-level theoretical calculations of the potential surfaces of the interaction.

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