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Investigation of Rapid Proton Exchange by Proton Magnetic Resonance

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The review presents a critical compilation and a general account of the published data on rapid proton exchange processes obtained by proton magnetic resonance (PMR). An attempt has been made to establish wherever possible the dependence of the rate and mechanism of the exchange on the chemical structure of the reactants, particularly on the properties of the hydrogen bonds formed by them.
The bibliography includes 163 references.

CONTENTS

I.	Introduction	875
II.	Proton exchange in OH groups	876
III.	Proton exchange in NH groups	881
IV,	Proton exchange in hydrogen fluoride	884
V.	Proton exchange in PH and SH groups	884
VI.	Exchange in CH groups	886
VII.	Certain general problems of proton exchange	887

I. INTRODUCTION

Many of the most important types of chemical reactions reduce to proton transfer between molecules or ions. This group includes, for example, the dissociation of acids and bases, neutralisation, acid–base catalysis, a number of cases of solvolysis, various tautomeric transformations, rapid isotope exchange of hydrogen, and other processes. One of the central problems of theoretical chemistry involves understanding the driving forces, kinetics, and mechanisms of such processes as a function of the structure of the reactants and the experimental conditions.

Advances in this field are due to the application of relaxation methods[1,2], which allow, in particular, the study of the kinetics of rapid protolytic reactions in ions of different charge types, and the PMR method. The latter proved particularly convenient in the investigation of the detailed mechanism of protolytic reactions and the role of solvation processes in them.

This review deals with studies on rapid proton exchange reactions by the PMR method. In order to supplement several review articles already available[3–8], the relevant literature is considered up to the end of 1968. Particular attention has been concentrated on the dependence of the rate and mechanism of exchange on the chemical structure of the reactants and especially on the properties of the hydrogen bonds formed by them. The role of these bonds in proton exchange was discussed in some studies (see, for example, Refs. 9–16), but has usually been underestimated in the treatment of the experimental data obtained by the PMR method.

We shall not consider in detail the theory of the nuclear magnetic resonance (NMR) method and its application in the study of rapid reactions; the treatment will be restricted to the formulation of certain concepts needed here, the description of the fundamental principles involved in calculating the rates of exchange, and the references to appropriate sources.

The application of the NMR method to problems of chemical kinetics is based on the study of the form of spectral lines. The multiplet structure of the spectrum and the width and intensity of the lines are partly determined by dynamic processes, which can be divided into two types: intermolecular exchange of atoms, groups of atoms, or electrons, and intramolecular processes, for example hindered rotation of atomic groups, inversion of configuration, and rearrangements. We shall examine here the exchange of protons between two molecules:

$$AH^* + BH \leftrightarrows AH + BH^* . \qquad (1)$$

When the exchange is very slow [the lifetimes of the proton in the molecules AH and BH (τ_A and τ_B) are greater than 1 second], the PMR spectrum of such a system shows two narrow resonance signals associated with the magnetic non-equivalence of the two hydrogen nuclei. With increase of the rate of exchange (decrease of τ_A and τ_B), the magnetic environment of the protons in the A–H and B–H bonds becomes averaged, the absorption lines therefore broaden and at a certain exchange frequency merge into a single signal, which becomes narrower on further acceleration of the exchange.

The first approximate relations between the change in line shape and the rate of exchange were proposed by Gutowsky and coworkers[17–19], who used a solution of the Bloch equations[20] in which the time variation of the nuclear magnetisation vector was taken into account by introducing an exponential multiplier, which depends on the lifetime of the proton in a given state. In these studies it was also shown that exchange processes whose frequency is comparable to the difference between the chemical shifts ($\Delta\nu = \nu_A - \nu_B$) of the protons undergoing exchange may be observed by the PMR method.

A more rigorous treatment was proposed by McConnell[21], who introduced into the Bloch equation a number of additional terms, characterising the exchange. The following assumptions were made: (a) proton exchange is a reversible process in which hydrogen nuclei are transferred from one electronic environment to another; (b) the lifetime of the protons in positions AH and BH is much greater than the time necessary for the transfer of protons from A to B and conversely; (c) the probability of finding the protons in the equilibrium positions P_A and P_B and the equilibrium exchange time τ are related to τ_A and τ_B as follows in accordance with the principle of detailed balance:

$$P_A = \frac{\tau_A}{\tau_A+\tau_B}; \; P_B = \frac{\tau_B}{\tau_A+\tau_B}; \; \tau = \frac{\tau_A \cdot \tau_B}{\tau_A+\tau_B} .$$

He also regards the quantities P_A and P_B as the statistical weight fractions of the protons in the corresponding positions. We shall consider in greater detail certain special cases of proton exchange.

1. Under conditions of "slow" exchange when τ_A and $\tau_B \gg \Delta\nu^{-1}$, PMR spectra show two separate signals. Their width Δ increases with decrease of τ (acceleration of exchange). These quantities are related by the equation[22]

$$\pi\Delta_A = T_{2A}^{-1} + \tau_A^{-1} ,$$

which allows the lifetime of the proton (duration of the exchange) τ_A to be determined from the width of the signal when exchange is absent ($T_{2A}^{-1} = \pi\Delta_0$).

2. In the case of "rapid" exchange, where τ_A and $\tau_B \ll \Delta\nu^{-1}$ the spectrum shows a single common signal, whose position depends on the ratio of P_A and P_B and whose width is related to τ_A and τ_B by the equation[23]

$$\pi\Delta = T_2^{-1} + P_A^2 P_B^2 (\tau_A + \tau_B) ,$$

from which τ is found. At very high rates of exchange the contribution of the second term to line width may be negligible and the above formula becomes unsuitable for the determination of τ. In these cases τ may be found from the change in the intensity of the combined signal[24].

3. In the region of intermediate rates of exchange where τ_A and τ_B are comparable to $\Delta\nu^{-1}$, τ may be determined in several ways. One of these consists in comparing the absorption curves calculated for different τ with the experimental spectra. The most general solution of this problem was obtained by Rogers and Woodbrey[25]. Gutowsky and Holm[19] obtained the following expression for the signal intensities q_ν on the assumption that $P_A = P_B$, $\tau_A = \tau_B = 2\tau$, and $T_{2A} = T_{2B} = \infty$ (in the absence of exchange the absorption lines are infinitely narrow):

$$q_\nu = \frac{K\tau\,(\nu_A - \nu_B)^2}{\left[\left(\frac{\nu_A + \nu_B}{2}\right) - \nu\right]^2 + 4\pi^2\tau^2\,(\nu_A - \nu)^2(\nu_B - \nu)^2} .$$

They also derived an equation for the more general case where $T_{2A} = T_{2B}$ is finite and $P_A \neq P_B$. The determination of the rate of exchange can be significantly simplified by obtaining a universal curve (suitable for any values of $\Delta\nu$ and T_2) which relates τ to line width at half the height or to the ratio of the maximum and minimum signal intensities. This problem has been solved for a doublet of lines of equal intensity[26,27] and for the case where $P_A \neq P_B$[28]. A method has also been developed for the determination of τ from the distance between the maxima ($\Delta\nu_{max}$) of the signals due to the states involved in the exchange[19]. The resulting equation is simplest for an infinitely narrow line ($T_{2A} = T_{2B} = \infty$):

$$\tau^{-1} = \sqrt{2}\,\pi\,(\Delta\nu^2 - \Delta\nu_{max}^2)^{\frac{1}{2}} .$$

It shows that the signals merge when $\tau^{-1} = \sqrt{2}\,\pi(\nu_A - \nu_B)$. Such merging is characteristic of these systems and may serve for the estimation of τ.

In contrast to the two-centre exchange described above, the derivation of analytical expressions for many-centre exchange is fairly complex and has been achieved only in the simplest cases[29-33]. The general expression for an n-centre exchange in the absence of spin–spin coupling between non-equivalent protons was obtained by Piette and Anderson[22].

When the absorption lines corresponding to the mobile protons in the molecules A–H and B–H have a multiplet structure due to spin–spin coupling, the exchange of protons (both equivalent and non-equivalent) leads to a broadening and merging of the components of the multiplet. The rate of exchange may be assessed from these changes. Thus Solomon and Bloembergen[34] solved the problem of the broadening of the lines of the multiplet in "rapid" exchange. Kaplan[35,36] developed a general theory which includes "rapid" and "slow" exchange as limiting cases. Kaplan's method was used by Alexander[37,38] for exchange between different molecules. General methods for the calculation with a spin doublet have been put forward[39-43]. Equations relating the rate of proton exchange to changes in the form of a triplet[29,30,44] and quartet[42] are also available.

More detailed information about the calculation of the rate of proton exchange from NMR spectra may be found in monographs by Pople et al.[45] and Emsley et al.[46]

The lifetime τ_A of the proton in the HA molecule is related to the rate constant k for proton exchange. Evidently the relation between τ_A, the concentration of the substance HA, and the rate of exchange is of the form

$$\tau_A = [HA] / -\frac{d[HA]}{dt} \quad \text{or} \quad \tau_A^{-1} = -[HA]^{-1} \cdot \frac{d[HA]}{dt} .$$

On the other hand,

$$-\frac{d[HA]}{dt} = k\,[HA]^m\,[HB]^n .$$

Consequently

$$R = \tau_A^{-1} = k\,[HA]^{m-1}\,[HB]^n ,$$

where R is the relative rate of proton exchange.

With the aid of NMR it is possible to measure τ in the range $1-10^{-4}$ s. When the values outside this range are encountered, the rate of exchange is altered by varying the concentration, temperature, or the solvent, in order to make it measurable.

The NMR method has advantages over other procedures for the investigation of rapid reactions—it permits a more detailed study of their mechanism and yields more accurate values of the rate constants. It is significant that, in contrast to relaxation methods, equilibrium in the test system is not displaced or hindered during the measurement. The disadvantages of the NMR method include low sensitivity, which makes it difficult to investigate dilute solutions or gases at a low pressure.

2. PROTON EXCHANGE IN OH GROUPS

The exchange in water has been investigated in several studies by Meiboom, Loewenstein, and their coworkers[23,47,48]. Oxygen contains a certain amount of the ^{17}O isotope, which has a nuclear spin. Spin–spin coupling with protons should lead to a multiplet structure of the PMR spectrum of water in the absence of exchange. However, the spectrum consists of a single line, which is explained by a rapid exchange reaction. Its rate increases in the presence of acid or alkali, which is evident from the narrowing of the line. These small changes in line form cannot be observed under the usual steady-state conditions. They have been measured by the spin-echo method[49] in water specimens enriched in oxygen-17 as a function of the pH and the rate constants for the processes leading to exchange have been found:

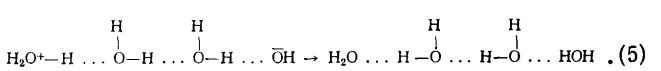
$$H_2O + OH^- \overset{k_1}{\rightleftarrows} HO^- + OH_2 , \qquad (2)$$

$$H_2O + H_3O^+ \overset{k_3}{\rightleftarrows} H_3O^+ + H_2O , \qquad (3)$$

$$H_2O + H_2^*O \overset{k_4}{\rightleftarrows} H_2^*O + H_2O . \qquad (4)$$

At 25°C they have the following values: $k_1 = 3.8 \times 10^9$ litre mole^{-1} s^{-1}, $k_3 = 10^{10}$ litre mole^{-1} s^{-1}, and $k_5 = 2.2 \times 10^5$ s^{-1}. The activation energies E and the preexponential factors A for the reactions were determined from the temperature variation of the rate of exchange in the range 20–80°C: $E_1 = 4.8$ kcal mole^{-1} and $E_3 = 2.6$ kcal mole^{-1}, $A_1 = 2 \times 10^{12}$ and $A_3 = 10^{12}$. The values of E were later revised[50] to $E_1 = 2.1$ kcal mole^{-1} and $E_3 = 2.4$ kcal mole^{-1}, which agree well with the values calculated from the anomalous mobility of these ions in water. It is of interest to compare these data with $k = 1.4 \times 10^{11}$ litre mole^{-1} s^{-1}, $E = 2$–3 kcal mole^{-1}, and $A = 9 \times 10^{12}$ found by Eigen and de Maeyer[51-53] by a relaxation method for proton transfer between H_3O^+ and OH^- ions.

The above results are important for the understanding of the mechanism of proton transfer and the anomalous mobility of the ions in water. The rate constants quoted agree with the values found from the anomalous mobilities of hydrogen and hydroxide ions based on electrical conductivity data. The rate constant for the reaction between H_3O^+ and OH^- corresponds to the value calculated for a process which is diffusion-controlled with a distance of approach of the ions of about 7 Å, which corresponds to their separation by 2–3 layers of water molecules. Hence it is concluded that, when the ions approach one another as a result of diffusion to this distance, the reaction occurs rapidly by the migration of protons along hydrogen bond chains:



(5)

An analogous mechanism accounts for the anomalous mobility of hydrogen ions in water. The reaction proceeds in two stages. The first consists in the formation of a chain of hydrogen bonds with a suitable orientation of the molecules achieved by their rotation. In the second protons are transferred along this chain. The rate is limited by that of the first step. Probably a mechanism of this type obtains in all rapid reactions with participation of H_3O^+ and OH^- ions†.

It is noteworthy that in alcohols (see below) the rate constants for proton exchange are smaller by several powers of ten than in water and the mobility of hydrogen ions is also much lower. Since the strength of hydrogen bonds in alcohols and in water is almost the same[55], which implies that the activation energy for proton exchange is also almost the same (see Section VII), it may be supposed that the rate of exchange in alcohols, as in water, is limited by the rate of formation of hydrogen bond chains of type (5), which is hindered by bulky hydrocarbon groups.

Data have been published on the rate of proton exchange between water molecules in various organic solvents[56]. The exchange proved to be slower the greater the electron-donating capacity of the solvent. These observations were explained by the fact that the solvent dissociates the hydrogen bond between water molecules and forms hydrogen bonds with the water protons, which reduces their mobility.

Rapid proton exchange in alcohols was discovered by Zimmerman and coworkers[57,58], but the first quantitative study was made by Arnold[29], who estimated the values of τ from the change in the form of the triplet due to the hydroxyl protons in ethanol as the pH was changed.

A detailed study of the exchange in ethanol and methanol has been made[59-61]. In neutral ethanol the reaction is slow and the PMR spectrum consists of a triplet due to CH_3, two overlapping quartets due to CH_2, and a triplet due to OH. When the ethanol contains water, the single signal due to the latter appears between the multiplets of the CH_2 and OH groups. In acidified alcohol or in the presence of alkali the signal due to methylene protons is converted into a simple quartet, the hydroxyl triplet is converted into a singlet, and the separate water peak is not observed. These changes in the spectrum are caused by a decrease in the lifetime of the proton in the hydroxy-group due to two consecutive processes.

In anhydrous alcohol only the protons of the OH group undergo exchange and the values of τ found from the analysis of the form of the CH_2 and OH signals are the same. On the other hand, when the alcohol contains water, two exchange reactions take place—between alcohol molecules and between alcohol and water. The rate of the overall process R was found from the change in the form of the methylene signals and the rate of exchange with water R_W from the width of the water line. The rate of the alcohol–alcohol exchange R_A was determined from the equation $R_A = R - R_W$. It was found that R_A and R_W depend linearly on the concentration of acid or alkali. The rate constants for the reactions leading to exchange were found from the slope of the straight line obtained and the equilibrium constants which determine the values of the ratios $[H_3O^+]/[ROH_2^+]$ and $[OH^-]/[RO^-]$:

$$\begin{gathered} ROH + OH^- \overset{k_1}{\underset{}{\rightleftarrows}} RO^- + H_2O \ , \\ ROH^* + HOH + RO^- \rightleftarrows RO^- + H^*OH + ROH \ , \end{gathered} \tag{6}$$

or

$$\begin{gathered} ROH + RO^- \overset{k_2}{\rightleftarrows} RO^- + ROH \ , \\ ROH + H_3O^+ \overset{k_2}{\rightleftarrows} ROH_2^+ + H_2O \ , \end{gathered} \tag{7}$$

or

$$ROH_2^+ + HOH^* + ROH \rightleftarrows ROH + HOH + RO^+HH^* , \tag{8}$$

$$ROH + RO^+H_2 \overset{k_4}{\rightleftarrows} RO^+H_2 + ROH \ , \tag{9}$$

$$ROH^* + HOH \overset{k_5}{\rightleftarrows} ROH + HOH^* . \tag{10}$$

We may note that in the system isopropyl alcohol–water[62] the mechanism of the exchange in an acid medium was found to depend on the relative amounts of the alcohol and water. The reaction takes place via mechanism (8) when the solvent is the alcohol and via the mechanism

$$H_3O^+ + ROH^* + OH_2 \rightleftarrows H_2O + ROH + H^*O^+H_2$$

when the solvent is water.

In contrast to ethanol, even in highly purified methanol the doublet due to the methyl protons and the quartet due to the hydroxyl are broadened. In aqueous solution the water line appears in the vicinity of the broadened quartet. The overall rate of exchange was found from the change in the form of the doublet and R_W from the broadening of the water line. The results proved to be analogous to those obtained for ethanol with the sole difference that in neutral anhydrous methanol the reaction

$$ROH^* + ROH \rightleftarrows ROH + ROH^* \ ,$$

which in ethanol is too slow to be investigated by the NMR method, makes an appreciable contribution to the overall rate of exchange. The activation energy for methanol proton exchange in an acid or alkaline medium is 2–3 kcal mole^{-1}, which corresponds to the activation energy for a diffusion process. There are data[63] showing an increased activation energy for the exchange in degassed methanol, compared with the alcohol saturated by oxygen.

† An analogous mechanism was recently proposed for the exchange between $H_2PO_4^-$ and HPO_4^{2-} ions in water[54].

The rate constants for the exchange reactions in ethanol and methanol and also in isopropyl and isobutyl alcohols [64] and in water are compared in Table 1.

The kinetics of proton exchange between various alcohols and water in a neutral solution have been investigated [64-66] as a function of the concentration of water; the rate of exchange decreases in the following sequence:

$$CH_3OH > C_2H_5OH > n\text{-}C_3H_7OH > n\text{-}C_4H_9OH > (CH_3)_2{-}CHCH_2OH > > \begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!CHOH > (CH_3)_2CHOH > (CH_3)_3COH \ .$$

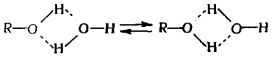
Table 1. Rate constants for proton exchange in alcohols and water.

R—OH	k_1	k_2	k_3	k_4	k_5
H—OH	$3.8\cdot10^{9}$*	—	$1.4\cdot10^{10}$*		$2.2\cdot10^{5}$*
CH_3—OH	$2.6\cdot10^{6}$	$7.4\cdot10^{8}$*	10^{8}	$3.5\cdot10^{9}$*	3
C_2H_5—OH	$2.8\cdot10^{6}$	$1.4\cdot10^{6}$	$2.8\cdot10^{6}$	$1\cdot10^{8}$	0.8
n-C_3H_7—OH	—	$0.6\cdot10^{6}$	—	$8\cdot10^{6}$	—
$(CH_3)_2CHCH_2$—OH	—	$2.7\cdot10^{6}$	—	$2\cdot10^{7}$	—

Note. The designations of the constants k (litre mole^{-1} s^{-1}) are the same as in Eqns. (2)–(4) and (6)–(10). The temperatures are 20° ± 2°C but 25°C for the values distinguished by an asterisk.

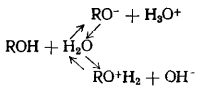
As already mentioned, the decrease of the rate of catalysed exchange in alcohols compared with water is due to the steric effect of the hydrocarbon residues, which hinder the orientation of the molecules and screen the hydroxy-group, and this inhibits the formation of complexes of type (5), the rate-limiting step in the exchange process. The data in Table 1 confirm this idea, since the rate decreases in the series of alcohols as the bulk of the hydrocarbon group increases. Possibly the decreased acidity of alcohols, which weakens the hydrogen bond formed by them, plays a certain role. This factor is probably not of decisive importance, since the changes in acidity (and in the strength of the hydrogen bond) are small compared with the changes in the rate of exchange. The above relation fails for isobutyl alcohol.

In a neutral medium the rate constants for the exchange are lower by many powers of ten than when catalysed by an acid or alkali. Bearing in mind that the rates of formation of the reaction complex in the neutral alcohol and in catalysis by an acid or alkali should be similar, one may suppose that the rate of neutral exchange is limited by the migration of protons along the hydrogen bonds in the complex. A synchronous mechanism of exchange in the cyclic association complex



(11)

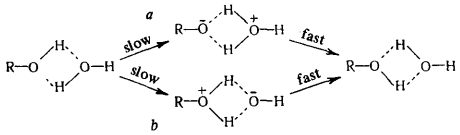
or a mechanism including slow dissociation into ion pairs and their rapid recombination,



(12)

have been proposed for this case [65].

The second mechanism is unlikely because of the high energy expenditure on the separation of the ions. The formation of "close" ion pairs linked by hydrogen bridges is more acceptable:



(13)

Among the pathways described, only pathway *a* accounts for the observed acceleration of exchange with increasing acidity of the alcohol. It is difficult to reconcile this acceleration with mechanism (11), according to which the rate should be independent of the acidity of the alcohol. We may also note that the formation of four-centre complexes assumed in mechanisms (11) and (13) is unlikely. It is unfavourable on energetic grounds [13-15] and has not been confirmed by determinations of the reaction order.

We have already noted that in the PMR spectrum of pure neutral methanol both multiplets are broadened. It has been found [67] that the addition of acetone to alcohols leads to a narrowing of the lines of the multiplet due to localisation of the hydroxyl proton in the hydrogen-bonded alcohol–acetone complex. This localisation hinders the exchange between the alcohol molecules, distorting the form of the spectrum. Such an effect of complex formation on the rate of proton exchange has already been noted in the discussion of studies on water. As will be shown below, it is of general importance.

We may refer to two studies on proton exchange in hydrated acetaldehyde [68] and its hemiacetal [69], in which a rapid exchange between the hydrogen atoms of the OH groups of the hydrate, hemiacetal, alcohol, and water is observed.

Proton exchange between hydrogen peroxide and water has been investigated [70]. The spectrum of a mixture of these substances consisted at room temperature of a single line whose width depended on the hydrogen peroxide concentration and the pH. In the pH range 2.5–4 the rate of exchange was proportional to the concentration of H_3O^+ ions and at 27°C $k = 1.6 \times 10^7$ litre mole^{-1} s^{-1}. The rate-limiting stage is probably

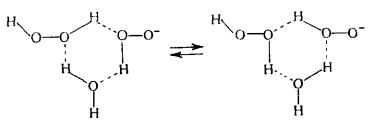
$$H_2O_2 + H_3O^+ \rightleftarrows H_3O_2^+ + H_2O \ . \qquad (14)$$

At pH 5.0–6.5 the rate proved to be proportional to the concentration of OH^- and the peroxide and was determined by the rate of the reaction

$$HO_2H + H^*OH + HO_2^- \rightleftarrows HO_2^- + HOH + H^*O_2H \qquad (15)$$

with $k = 7.3 \times 10^7$ litre mole^{-1} s^{-1} at 27°C.

Since the collision of three molecules is improbable and cannot lead to rapid reactions, it was assumed [70] that the process proceeds via a stage of complex formation between the peroxide or the HO_2^- ion and water and occurs in a cyclic activated complex:



(16)

We note that the rate of exchange between hydrogen peroxide and water is lower by several powers of ten than in water itself but is close to the rate of exchange in alcohols.

The exchange between t-butyl hydroperoxide and water has been investigated [71]. In an acid medium a mechanism

analogous to mechanism (14) was established and it was found that the rate of reaction is virtually the same as for hydrogen peroxide: $k = 1.1 \times 10^7$ litre mole^{-1} s^{-1} at 23°C. On the other hand, in an alkaline medium the mechanism proved to be different. The relative rate no longer depended on the concentration of the peroxide and was proportional to the concentration of alkali alone ($k = 6.5 \times 10^6$ litre mole^{-1} s^{-1} at 23°C). The observed change in the mechanism may be due to the fact that the hydroperoxide cannot form a cyclic complex of type (16).

A series of studies have been made on the proton exchange in phenols. The exchange between phenol and water catalysed by sodium phenoxide[72] is characterised by a rate constant $k_B = 7.1 \times 10^8$ litre mole^{-1} s^{-1} at 25°C and an activation energy $E_B = 4.2$ kcal mole^{-1}. The rate of reaction is proportional to the concentration of phenol and alkali; the equation for the exchange reaction includes one or several water molecules:

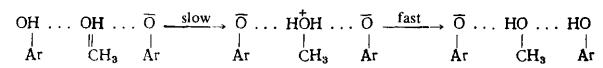
$$PhOH + (H_2O)_n + \overline{O}Ph \rightleftarrows Ph\overline{O} + (H_2O)_n + PhOH \quad . \qquad (17)$$

Grunwald and Puar[73] studied the exchange between phenols and water catalysed by acids and alkalis. Somewhat different characteristics are obtained for reaction (17): $k_B = 5.7 \times 10^8$ litre mole^{-1} s^{-1} at 25°C. $E_B = 3.2$ kcal mole^{-1} and it was shown that one water molecule is involved. The following mechanism was proposed for an acid medium:

$$H_3O^+ + PhOH + H_2O \rightleftarrows H_2O + PhOH + H_3O^+ \quad , \qquad (18)$$

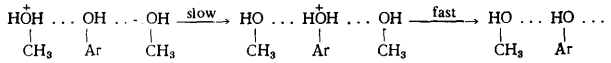
where $k_A = 1.5 \times 10^7$ litre mole^{-1} s^{-1} at 25°C and $E_A = 5.5$ kcal mole^{-1}.

Studies on the exchange between substituted phenols and methanol[74,75] led to a more profound understanding of the mechanism of processes of type (17) and (18). It was found that in an alkaline medium the rate of reaction for a series of phenols varies in parallel with their acidity. These data were explained by an exchange process involving a dissociative mechanism in a trimolecular complex. The proton is transferred from the phenol to the alcohol in the slow stage:



(19)

In the acid-catalysed process the rate varies inversely with the acidity of the phenols. Consequently the slow stage in the exchange is protonation of the phenol:



(20)

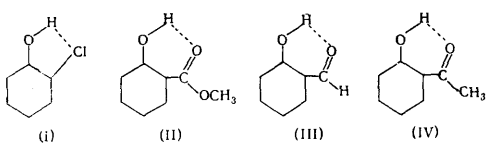
Analogous results were obtained[76] for the reactions of a series of other phenols with water in dioxan or dimethyl sulphoxide solutions. It was noted[75] that the rate of exchange between phenols and methanol in an acid medium is lower the greater is the bulk of the substituents in the *ortho*-position in the phenol molecule. This observation may be explained by steric hindrance to the transfer of protons to the phenol in the slow stage of process (20) due to the substituent. Such interpretation is consistent with the results of studies on the hydrogen bond in sterically hindered phenols[77-82]. We may note that a less marked steric effect of substituents may be expected for exchange in an alkaline medium, since steric hindrance has a smaller effect on the acid dissociation of phenols, the rate-limiting stage in process (19), than on the protonation of phenols in reaction (20). The effect of steric hindrance on the exchange between 2,6-disubstituted phenols and methanol in a neutral medium has been investigated[82]. The rate of exchange decreases in the following series of substituents: H > CH_3 > $(CH_3)_2CH$ > $(CH_3)_3C$; since the activation energy is constant, this was explained by an increase in the entropy of activation in the above series.

The study of association in and the proton exchange between a series of *para*-substituted phenols and ethanol showed[83] that the activation energy for the exchange is lower the stronger is the hydrogen bond in the association complex of the phenol and alcohol. This provided one of the first experimental proofs of the predicted relation[14] between the height of the potential barrier to the exchange and the energy of the hydrogen bond in the reaction complex.

An intramolecular hydrogen bond has a significant influence on the rate of proton exchange in phenols. Thus the uncatalysed exchange between *o*-chlorophenol (I) and methanol is much slower than the exchange between phenol and the same alcohol. Probably the rate is determined by the stage involving the formation of an ion pair:

$$PhOH + CH_3OH \rightarrow PhO^- + CH_3O^+H_2 \quad .$$

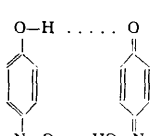
The rate constant is 9×10^2 s^{-1} and the activation energy is 4.6 kcal mole^{-1}. The relatively low rate of exchange is explained by the fact that, despite its low energy ($\Delta H = -2.4$ kcal mole^{-1}), the intramolecular hydrogen bond OH...Cl lowers significantly the capacity of compound (I) to form intermolecular-hydrogen bonds. This interpretation was confirmed by the fact that methyl salicylate (II), salicylaldehyde (III), and *o*-hydroxyacetophenone (IV),



(I) (II) (III) (IV)

which form stronger intermolecular hydrogen bonds, undergo exchange at a much lower rate than compound (I)[84]. Compounds (III) and (IV) were investigated in greater detail[85]. It was found that (III) undergoes exchange faster than (IV), because the latter has a stronger intramolecular hydrogen bond by virtue of the electron-donating effect of the methyl group.

The interesting case of proton exchange between tautomeric forms of *p*-nitrosophenol has been studied[86]. The relative rate of reaction in a neutral medium is proportional to the concentration and therefore two molecules, probably the molecules of both tautomeric forms, are involved in the elementary step. It is natural to suppose that the exchange takes place in hydrogen-bonded complexes, for example:



In the presence of acids or bases the rate of exchange increases. Catalysis by bases has been explained by the ionisation of the substrate:

$$HOC_6H_4NO + [OC_6H_4NO]^- \rightleftarrows [OC_6H_4NO]^- + OC_6H_4NOH \quad ,$$
$$OC_6H_4NOH + [OC_6H_4NO]^- \rightleftarrows [OC_6H_4NO]^- + HOC_6H_4NO \quad .$$

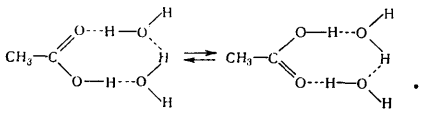
The catalysed reaction takes place with a lower activation energy than the uncatalysed reaction.

Proton exchange in organic acids was investigated in a number of cases. Thus Luz and Meiboom[87] studied the

system acetic acid–water enriched in oxygen-17. The rate proved to be too high to be accounted for by the dissociation of acid:

$$CH_3COOH + H_2O \rightleftarrows CH_3COO^- + H_3O^+ .$$

The limiting rate of dissociation may be calculated from the dissociation constant and the rate of reaction between the ions CH_3COO^- and H_3O^+, which cannot exceed the limit set by diffusion. The upper limit to the rate of dissociation found in this way proved to be below the observed rate of exchange by several powers of ten. For this reason, a synchronous cyclic reaction mechanism was proposed:

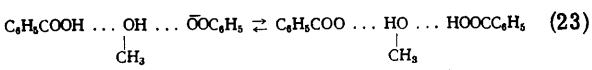


(21)

The exchange of benzoic acid and a series of substituted benzoic acids (HA) with methanol was investigated by Grunwald and coworkers[88-90], who found that the expression for the rate of reaction in an alkaline medium includes two terms corresponding to an uncatalysed and a catalysed process:

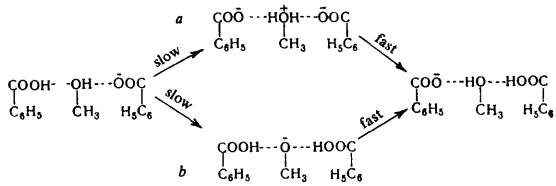
$$R = k_1 + k_B[A^-] . \quad (22)$$

The values of k_1 and k_B for benzoic acid proved to be 1.3×10^5 s^{-1} and 1.2×10^8 litre mole^{-1} s^{-1} at 24.8°C. It was established that in the uncatalysed process two alcohol molecules participate together with an acid molecule and in the catalysed process the reactants are an acid and an alcohol molecule and an acid anion. The rate of the first reaction is much higher than the limiting value which could be accounted for by the dissociation of the acid and has a negative entropy of activation. Therefore the authors proposed a mechanism analogous to that given in equation (21). The displacement of protons in this complex can take place both synchronously and asynchronously with formation of "close" ion pairs in the slow stage. In the catalysis by alkali the exchange in the open-chain trimolecular complex can also take place via mechanisms of two types—a synchronous mechanism:



(23)

or an ionisation mechanism:

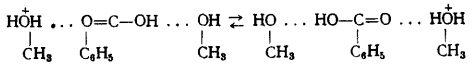


(24)

The rate of reaction by these mechanisms should depend in different ways on the acidity of HA. The ratio $d \lg k/d.\lg K_A$, which Grunwald and coworkers used to infer the mechanism, is a measure of the sensitivity of the rate to changes in acid strength. The ratio should be +1 if the rate is limited by acid dissociation [mechanism (24 a)] and −1 when it is determined by the protonation of the base [mechanism (24 b)]. In the synchronous mechanism the ratio should be independent of acid strength, since an increase in the acidity of HA is fully compensated by a decrease in the basicity of A^-. It was found that $d \lg k_1/d.\lg K_A = 0.53$ and $d \lg k_B/d \lg K_A = 0.26$. Therefore it was concluded that the uncatalysed and base-catalysed exchange involves both synchronous and ionisation mechanisms [formula (24 a)]. We believe that these conclusions have little justification, since they do not take into account a number of factors which influence the exchange. We may point, for example, to the fact that a change in acidity alters the strength of hydrogen bonds in complexes of types (21) and (23), on which depends not only the ease of migration of protons in the complexes but also their concentration. Other criteria whereby synchronous and ionisation mechanism may be distinguished are formulated below (see Section V).

Results analogous to those presented above were obtained in a study of the base-catalysed exchange between neopentyl alcohol and acetic, cyanoacetic, and trichloroacetic acids[91]. In this case the ratio $d \lg k_1/d \lg K_A$ proved to be 0.55. However, the authors concluded that a synchronous exchange mechanism of type (23) operates, since they did not observe a variation of the ratio $d \lg k/d.\lg K_A$ with the dielectric constant of the solvent, which would have been expected for a mechanism of type (24 a).

Grunwald and Jumper[90] obtained a rate constant $k_A = 2.52 \times 10^8$ litre mole^{-1} s^{-1} for the exchange between benzoic acid and methanol in an acid medium and proposed a termolecular reaction complex:



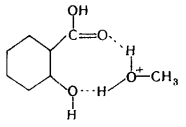
(25)

but the reaction order with respect to the alcohol was not determined.

The effect of the intramolecular hydrogen bond in salicylic acid on the rate of proton exchange between carboxy- and hydroxy-groups on the one hand and methanol on the other in an acid medium at −80°C was studied by Puar and Grunwald[92]. The following kinetic equations were derived:

$$R_{COOH} = k_1 + k_A[HCl]\text{ and }R_{OH} = k'_A[HCl]$$

with $k_1 = 440$ s^{-1}, $k_A = 1.35 \times 10^5$ litre mole^{-1} s^{-1}, and $k'_A = 5.8 \times 10^3$ litre mole^{-1} s^{-1}. These equations are analogous to the expressions describing the exchange between benzoic acids and phenols on the one hand and acidified methanol on the other. Therefore mechanisms of types (21) and (25) were proposed for the reaction involving the carboxyl and mechanism (20) for the exchange involving the hydroxyl. The constant k_1 for salicylic acid is much higher than for benzoic acid, because the former is a stronger acid and the intramolecular hydrogen bonds in salicylic acid dissolved in methanol are probably disrupted and do not interfere with the formation of complexes of type (21). On the other hand, the constants k_A and k'_A are lower than for benzoic and phenols, which was explained by the stability of the complex



whose formation lowers the concentration of termolecular complexes and thereby retards the reactions via mechanism (20) and (25).

The exchange of protons between the OH and COOH groups of *p*-hydroxybenzoic acid was studied in various solvents[27]. The reaction was found to be retarded on passing from acetone to dimethylformamide and dimethyl sulphoxide. This is due to the increased electron-donating capacity of the solvent and the stability of its association complexes with the acid. Association with the solvent hinders the formation of acid dimers in which the exchange takes place.

In a series of isomeric hydroxybenzoic acids the rate of the uncatalysed reaction in dimethyl sulphoxide solution increased in the *ortho* > *para* > *meta* series. The exchange of *m*-hydroxybenzoic acid was studied in greater detail in a later investigation [93].

III. PROTON EXCHANGE IN NH GROUPS

The study of proton exchange in NH groups was begun by Ogg [94,95] using ammonia. The PMR spectrum of thoroughly dried liquid or gaseous ammonia consists of a triplet with a splitting of about 46 Hz. It arises as a result of spin–spin coupling between the proton and the ^{14}N nucleus, the spin of which is unity. In the presence of traces of water in liquid ammonia the triplet merges into a singlet owing to the rapid reaction

$$NH_3 + H_2O \rightleftarrows NH_4^+ + OH^- .$$

This conclusion contradicts the results of other investigations [96–98], in which separate NH and OH peaks were observed ("slow" exchange) for solutions containing less than 50% of water. The explanation offered for the discrepancy [98] is that Ogg observed a reaction catalysed by traces of ammonium ions generated in the reaction between ammonia and the protons adsorbed on glass. The exchange in liquid ammonia is also catalysed by potassamide. The following reaction probably occurs:

$$NH_3 + NH_2^- \rightleftarrows NH_2^- + NH_3 .$$

Its rate constant is close to 10^9 litre mole^{-1} s^{-1}. In the gas phase the form of the spectrum is independent of the presence of water vapour and therefore the rapid reaction with water does not take place.

The exchange between ammonium salts and water was investigated in a large series of studies. We shall consider these studies using methylammonium chloride as an example [41,99–101]. In an acid medium (pH ~ 1) the rate of exchange is low and the spectrum shows a quartet due to the methyl protons, arising by virtue of the spin–spin coupling with the protons of the NH_3^+ group, a triplet due to the NH_3^+ protons generated by coupling with ^{14}N, and a singlet corresponding to water. With increase of the pH, the rate of exchange rises. The peaks of the methyl quartet are broadened and merge into a single broad line, which then becomes narrower, while the NH_3^+ triplet continues to become broader and finally disappears.

Both these effects may serve as a measure of the average lifetime of the protons in NH_3^+. The water singlet broadens, merges with the signal due to the NH protons, and the combined peak becomes narrower. A study of the above spectral changes provided evidence for the following exchange reactions:

$$R_3NH^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R_3N + H_3O^+ , \quad (26)$$

$$R_3NH^+ + OH^- \overset{k_2}{\rightleftarrows} R_3N + H_2O , \quad (27)$$

$$R_3NH^+ + R_3N \overset{k_3}{\rightleftarrows} R_3N + R_3NH^+ , \quad (28)$$

$$R_3\overset{H}{\overset{|}{N}}H^+ + OH + NR_3 \overset{k_4}{\rightleftarrows} R_3N + HO\overset{H}{\overset{|}{N}}HR_3 , \quad (29)$$

and made possible the determination of the corresponding rate constants. The overall rate of exchange is determined by the relation

$$R = k_1 + \frac{1}{[H^+]}\{k_2 K_w + (k_3 + k_4) \cdot K_A [R_3\overset{+}{N}H]\} ,$$

where K_W is the ionic product of water and K_A is the acid dissociation constant of R_3NH^+. The constants k_1, k_2, and $k_3 + k_4$ were determined from the relation between R (calculated from the change in the form of the CH_3 quartet) and the pH and the R_3NH^+ concentration. The individual values of k_3 and k_4 were obtained by analysing the broadening of the water line. It was found that at a low pH the contribution by reactions (26) and (27) to the overall rate is low and that k_4 for any ratios of the reactant concentrations is approximately 1.5 times greater than k_3. In a later study [99] the rate constants were revised to allow for changes in the viscosity. The results are listed in Table 2.

Table 2. Rate constants for the proton exchange of ammonium salts in water at 22°C*.

R_3NH^+	k_1	$k_{-1}\cdot10^{-10}$	$k_2\cdot10^{-11}$	$k_3\cdot10^{-8}$	$k_4\cdot10^{-8}$	$K_A\cdot10^{10}$
NH_4^+	25	4.4	10	11.7	0.9	5.68
$CH_3NH_3^+$	—	—	1	4.0	5.3	0.242
$(CH_3)_2NH_2^+$	—	—	1	0.5	9.0	0.168
$(CH_3)_3NH^+$	4.7	3.0	1	0.3	3.4	1.57
$(C_2H_5)_3NH^+$ **	0.31	2.0	0.17	—	1.8	0.155
$CH_3\overset{+}{N}H_2CH_2COOH$	1.10	3.2	—	—	—	30

* The units of k_1 are s^{-1} and of k_{-1} and k_2–k_4 are litre mole^{-1} s^{-1} respectively.
** Temperature 25–30°C.

Ammonium [102–104], dimethyl- and trimethyl-ammonium [42,105–107], triethylammonium [108], and $CH_3\overset{+}{N}H_2CH_2COOH$ [109] ions were investigated similarly and their exchange was explained by the same mechanisms (26)–(29). The rate constants obtained are compiled in Table 2, which shows that, as was to be expected, the constants k_1 vary in parallel with the acidity of the ammonium ions. The rate constants for the reverse reaction k_{-1} have values characteristic of processes whose rate is limited by diffusion and which apparently occur in almost every collision.

The values of k_1 proved to be sensitive to the presence of neutral salts and the pH. They decrease on addition of salts and strong acids [103–105,110]. The study of the effect of the acidity of the medium made it possible to refine the mechanism of reaction (26). The new mechanism [110] includes two stages: reversible ionisation in which the amine molecule does not initially lose its bond with the proton being eliminated:

$$R_3NH^+ \ldots (HOH)_n \underset{k_-}{\overset{k_+}{\rightleftarrows}} R_3N \ldots (HOH)_m + H^+(OH_2)_{n-m} \quad (26a)$$

and the exchange of water molecules between the hydration shell of the amine and the bulk of the solvent:

$$HOH \ldots NR_3 + H\overset{*}{O}H \overset{k_H}{\rightarrow} HOH + R_3N \ldots H\overset{*}{O}H . \quad (26b)$$

Reaction (26a) alone does not lead to the exchange of protons bound to the nitrogen as long as reaction (26b) does not occur. In an acid medium the first reaction plays the role of a pre-equilibrium stage and the rate of exchange is determined by stage (26b). The kinetic equation for the overall process is of the form [104]:

$$R = k_+ [R_3NH^+] \frac{k_H}{k_H + k_- [H^+]} .$$

When the acidity is fairly high, $k_H \ll k_-[H^+]$ and

$$R = \frac{k_+ k_H [R_3NH^+]}{k_- [H^+]} = \frac{K_A k_H [R_3NH^+]}{[H^+]} \quad (26c)$$

i.e. under certain conditions the rate of exchange is inversely proportional to the concentration of hydrogen ions. The consistency of the exchange kinetics with the equations quoted above implies that in very acid media the amine remains hydrated. When allowance is made for the hydration of the proton, it becomes clear that not less than two water molecules participate in reaction (26a)[110].

The values of k_H which can be found by Eqn. (26c) are of great interest, since these are the rate constants for the dissociation of the hydrogen bond between amines and water. They are listed in Table 3 together with the reciprocal quantities (τ_H), which define the average lifetime of the hydrogen bonds. The data in Table 3 suggest that τ_H is not determined by the basicity of the amine alone but also by steric factors on which depends the ease of the mutual approach of the amine and water and also other characteristics of the structure of the amines.

Table 3. Dissociation rate constants (k_H) and average lifetimes (τ_H) of the hydrogen bonds $R_3N...HOH$ at 25°C.

R_3N	$k_H \cdot 10^{-10}$, s^{-1}	$\tau_H \cdot 10^{11}$, s	$K_A \cdot 10^{10}$
NH_3	50	0.2	5.68
CH_3NH_2	8	1.25	0.242
$(CH_3)_3N$	1.1	9	1.57
$(C_2H_5)_3N$	0.38	26.3	0.155
CH_3NHCH_2COOH	0.8	12.5	30

In contrast to the values of K_A, k_3 (Table 2) decreases steadily from ammonium to trimethylammonium ions, which Loewenstein and Meiboom[42] suggest is caused mainly by steric hindrance. The ratio k_4/k_3 decreases steadily in the same series. The constants k_4 are correlated with K_A: the rate of reaction (29) increases as the acidity of the ammonium ions falls. This relation breaks down only for trimethylammonium ions, probably due to steric hindrance. The mechanism of reaction (29) was examined in detail by Grunwald and Kromhout[99]. Table 2 shows that reactions (26) are so slow that proton transfer from ammonium ions to water cannot ensure the occurrence of the rapid reactions (29). Therefore it was suggested that the rate is limited by proton transfer from the water in the hydration shell of the alkylammonium ions to the amine molecules in the hydrogen-bonded complexes:

$$R_3NH^+ \ldots OH \ldots NR_3 \xrightarrow{\text{slow}} R_3NH^+ \ldots \underset{H}{\overset{|}{O}} \ldots \overset{+}{H}NR_3 \xrightarrow{\text{fast}} \rightarrow R_3N \ldots \underset{H}{\overset{|}{HO}} \ldots \overset{+}{H}NR_3 \quad (30)$$

The electrostatic field of the cation promotes the slow stage of reaction (30), since it increases the acidity of water by several powers of ten. The field is almost identical for different ammonium ions. Therefore, when the substituents are not unduly bulky, the rate of reaction is determined by the basicity of the amine, which explains the experimental data.

Meiboom[26] revised mechanism (30). He investigated the kinetics of proton exchange in the system trimethylammonium chloride–trimethylamine–water enriched in oxygen-17 as a function of the concentration of water and showed that reaction (30) involves only one water molecule. Water molecules may participate also in reactions of type (27).

The temperature variation of the rate of exchange between ammonium salts and water has been investigated by several workers[100,105,106,110]. In the first study it was found for NH_4^+ and $(CH_3)_3NH^+$ ions that the activation energies of reactions (28) and (29) are close to zero. This result appears to be doubtful, since the activation energy for the reaction between the H_3O^+ and OH^- ions, whose rate is limited by diffusion, is 2–3 kcal $mole^{-1}$.[51,52]

In a later investigation[105] the plausible value $E = 3.3$ kcal $mole^{-1}$ was obtained for the exchange involving $(CH_3)_3NH^+$ via mechanism (29). The activation energy for reaction (26) with NH_4^+ ions proved to be $E = 12.2$ kcal $mole^{-1}$. Since the enthalpy change is 12.4 kcal $mole^{-1}$, one must assume that the activation energy for the reverse process

$$NH_3 + H_3O^+ \rightarrow NH_4^+ + H_2O$$

is close to zero, which is consistent with its very high rate (see above).

Several studies have been made of proton exchange between aminoacids and polypeptides on the one hand and water on the other in an acid medium. The mechanisms of the exchange processes involving glycine[111], sarcosine[109], glycylglycine[112], triglycine[113], and ammonium salts proved to be similar.

In contrast with acetamidinium salts[114] only the reaction of type (27) is significant. This was explained by the low acid dissociation constant of the ion $[CH_3C(NH_2)_2]^+$ which keeps the concentration of the amidine so low that reactions of type (28) and (29) scarcely occur.

Interesting results were obtained by comparing the proton exchange of ammonium salts in water and other solvents[115]. The changes in the kinetics and mechanism of the exchange could be observed as a function of the properties of the solvents and the structure of the salts. These data are of general importance in understanding the effect of the solvent on the mechanism of protolytic reactions.

In methanol[116–119], which like water has a high dielectric constant ($D = 33.7$ at 20°C), the mechanism of the exchange is similar to mechanism (26)–(29) and the mechanisms of the individual processes are only slightly different from those in water, as can be seen from a comparison of the data in Tables 2 and 4.

In contrast, in t-butyl alcohol, which has a much lower dielectric constant ($D = 12.5$ at 25°C), the mechanism of the exchange is different and the rate of the process is much lower[120–122]. The reason for the differences is that in this solvent ammonium salts exist in the form of ion pairs[123] and not free (solvated) ions. Under these conditions, processes of type (29) play the main role in the exchange, but they involve ion pairs and not free ions:

$$R_3N\overset{+}{H}X^- + \underset{C(CH_3)_3}{\overset{|}{OH}} + NR_3 \overset{k_5}{\rightleftarrows} R_3N + \underset{C(CH_3)_3}{\overset{|}{HO}} + \overset{+}{H}NR_3 \quad (29a)$$

Table 5 presents the experimental data and the ratios of the rate constants for reactions (29) and (29a). It shows that methylammonium salts differ sharply from trimethylammonium salts. The ratio k_4/k_5 for the former is close to 25 and depends little on the nature of the X^- anion, while for the latter the ratio varies from

several thousand to several hundred and depends significantly on X^-. The difference is probably due to the fact that the single hydrogen atom at the nitrogen in $(CH_3)_3N^+HX^-$ molecules is linked to the anion by a strong hydrogen bond, which lowers the rate of exchange by mechanism (29a) and to a greater extent with increasing strength of this bond. In $CH_3NH_3^+X^-$ only one hydrogen atom is linked to the anion and the other two form hydrogen bonds with the solvent and undergo exchange at a much higher rate, which depends little on the nature of the anion.

Table 4. Rate constants for the proton exchange of ammonium salts in methanol at 24°C.

Ammonium ion	k_1, s^{-1}	$k_{-1} \times 10^{-10}$, litre mole^{-1} s^{-1}	$k_4 \times 10^{-8}$, litre mole^{-1} s^{-1}	$K_A^* \cdot 10^{10}$
p-$CH_6H_4NH_3^+$	$2.9 \cdot 10^3$	1.04	0.81	2800
$(CH_3)_3NH^+$	0.6	0.5	3.25	1.2
2-Picoline.H^+	$9.1 \cdot 10^3$	1.2	2.89	7580
4-Picoline.H^+	$10.6 \cdot 10^3$	1.2	3.44	8830
2,4-Lutidine.H^+	$1.32 \cdot 10^3$	0.97	2.97	1360
2,6-Lutidine.H^+	$1.15 \cdot 10^3$	0.75	0.85	1530

* K_A was measured in methanol at 25°C.

In anhydrous acetic acid solution (D = 6.2 at 25°C) ammonium salts also form ion pairs and not free ions. The exchange reactions probably take place in two stages of type (26a) and (26b):

$$R_3N\overset{+}{H}\overset{-}{O}Ac \rightleftarrows R_3N \ldots HOAc \quad , \tag{26d}$$

$$AcOH \ldots NR_3 + H\overset{*}{O}Ac \overset{k_5}{\rightleftarrows} AcOH + R_3N \ldots H\overset{*}{O}Ac \quad , \tag{26e}$$

where reaction (26d) differs from (26a) in that the proton transfer takes place within an ion pair. The analogy with the dissociation and exchange processes in water is confirmed by a parallelism between the enthalpies and entropies of acid dissociation of ammonium ions in water and the corresponding activation parameters for proton exchange between ammonium salts and acetic acid. The experimental data [124-126] are presented in Table 6.

Table 5. Rate constants for the proton exchange between ammonium salts and t-butyl alcohol at 35°C.

R_3NH^+	X^-	$k_5 \times 10^{-5}$, litre mole^{-1} s^{-1}	k_4/k_5
$(CH_3)_3NH^+$	Cl^-	1.1	3500
$(CH_3)_3NH^+$	Br^-	5.3	740
$(CH_3)_3NH^+$	$CH_3C_6H_4SO_3^-$	7.0	560
$CH_3NH_3^+$	Cl^-	260	23
$CH_3NH_3^+$	$CH_3C_6H_4SO_3^-$	240	25

These data show that the values of k_6 for acetate salts depend on the acid dissociation constants of ammonium ions in water (K_A). They are almost proportional to the K_A, in accordance with the above exchange mechanism which includes an ionisation stage. Of its two stages, stage (26e) is probably rate-limiting [124,125]. Table 6 shows that the rate of exchange greatly depends on the anion. In accordance with mechanism (26d)–(26e), the rate for salts with the same cation proved to be proportional to the basicity of the anion in acetic acid. Similar results were obtained in a study on the proton exchange of *NN*-dialkylanilinium salts in acetic acid [127].

In some cases the solvent alters the rate of exchange, while the mechanism and the components undergoing exchange remains the same. Thus the reaction between NH_4^+, H_2O, and NH_3 in water is faster by two powers of ten than in liquid ammonia, probably because water has a lower dielectric constant [98].

Table 6. Rate constants for the proton exchange between ammonium salts and acetic acid at 25°C.

R_3NH^+	X^-	k_6, s^{-1}	$K_A \cdot 10^{10}$
NH_4^+	CH_3COO^-	6080	5.69
$CH_3NH_3^+$	CH_3COO^-	230	0.238
$(CH_3)_3NH^+$	CH_3COO^-	945	1.58
$(HOCH_2)_3CNH_3^+$	CH_3COO^-	41000	84.0
NH_4^+	$C_6H_2(NO_2)_3O^-$	30	
NH_4^+	CCl_3COO^-	2	
NH_4^+	Cl^-	too low for measurement by NMR method	
$CH_3NH_3^+$	Cl^-		
$(CH_3)_3NH^+$	Cl^-		

In several studies the kinetics and mechanisms of protolytic reactions with participation of carboxylic acid hydrazides [128] and amides [43,129] were investigated. For example, it was established that in an aqueous solution of *N*-methylacetamide at pH 5 the PMR spectrum consists of a singlet due to *C*-methyl protons, a doublet due to *N*-methyl protons, a singlet due to water, and a broad line due to the amide hydrogen. It was found from the form of the doublet that the half-life of the exchange exceeds 1 s. On increasing or decreasing the pH, the *N*-methyl doublet is converted into a single line and the water singlet becomes broader, which is evidence that both acids and alkalis catalyse the exchange. The following reaction mechanisms have been proposed:

$$CH_3{-}CONHCH_3 + OH^- \overset{k_1}{\rightleftarrows} (CH_3{-}CON{-}CH_3)^- + H_2O \quad ,$$

$$CH_3{-}CONHCH_3 + H_3O^+ \overset{k_2}{\rightleftarrows} (CH_3{-}CONH_2CH_3)^+ + H_2O \quad ; \tag{31}$$

$k_1 = 5.2 \times 10^6$ litre mole^{-1} s^{-1} at 21°C and $k_2 = 3.8 \times 10^2$ litre mole^{-1} s^{-1} at 23°C. The activation energy for the acid-catalysed exchange is in the range 14–16 kcal mole^{-1}. [130,131]

In a strongly acid solution the doublet structure of the signal due to the *N*-methyl protons persists in the presence of dioxan which retards the exchange. This observation shows that protonation involves mainly the oxygen atom, since the protonation of the nitrogen atom would convert the signal of the *N*-methyl protons into a triplet. The competition of reaction (31) with the protonation of the oxygen atom accounts for the relatively small value of k_2.

The protonation of amides at the oxygen atom was confirmed in a number of studies [132-134]. In the first of these the reaction of formamide, acetamide, and their *NN*-dimethyl derivatives with fluorosulphonic acid was investigated and it was found that at low temperatures a new line due to the =C$\overset{+}{O}$H group appears in the spectrum.

Thioamides and sulphonamides are also protonated at the sulphur or oxygen atom. Thiourea and *N*-methylthiourea in fluorosulphonic acid give rise to diprotonated forms[135]. Data have been obtained from the protonation of sodium sulphamate[136].

It is noteworthy that NMR is the only reliable procedure for the investigation of the mode of protonation of acid amides and their analogues.

IV. PROTON EXCHANGE IN HYDROGEN FLUORIDE

Liquid hydrogen fluoride contains the ions HF_2^- and H^+ which are formed by the mechanism

$$2\,HF \rightleftarrows HF_2^- + H^+ .$$

The concentration of protons increases in the presence of BF_3 and when the system contains water, H_3O^+ ions appear:

$$HF + H_2O + BF_3 \rightleftarrows H_3O^+ + BF_4^- .$$

In this case the PMR spectrum consists of a single peak at room temperature and two peaks, due to HF and H_3O^+, below $-50°C$. The merging of the peaks on warming was explained[137] by the following proton exchange reaction:

$$H_3O^+ + HF_2^- \rightleftarrows H_2O + 2\,HF .$$

Its rate constant proved to be close to 10^{11} litre mole^{-1} s^{-1} and the temperature coefficient was found to be small. In view of the closeness of the above values to the diffusion-limited rate constant for the reaction of hydrogen and hydroxide ions in water, it was suggested that there is an analogy also between the exchange mechanisms, the following scheme being suggested:

$$H_2\overset{+}{O}H \ldots FH \ldots F^- \rightarrow H_2O \ldots HF \ldots HF .$$

Possibly not one but several hydrogen fluoride molecules are involved in this reaction.

V. PROTON EXCHANGE IN PH AND SH GROUPS

We have emphasised more than once the effect of the acidity of the reactants in protolytic reactions and of the strength of the hydrogen bonds formed by them on the rate of proton transfer. However, so far, it has been impossible to separate the roles of these factors, since for many compounds of a particular type they vary in parallel. Such an estimate can be made by comparing the rates of proton exchange in a series of analogous nitrogen- and phosphorus-containing compounds and hydroxy- and mercapto-derivatives, since the replacement of nitrogen by phosphorus and of oxygen by sulphur increases the acidity but lowers the strength of hydrogen bonds. Therefore the study of exchange in PH and SH groups is of particular interest. The available data are fairly scanty, but they nevertheless allow certain definite conclusions.

A detailed study has been made of proton transfer from PH bonds in aqueous solutions of trimethylphosphonium ions[138]. In an acid medium (pH < 6) the rate of exchange is low and the PMR spectrum consists of a septet due to the hydrogen atom in PH, a double doublet due to methyl hydrogen atoms, resulting from spin–spin coupling with the PH proton and with ^{31}P, and a single line due to water. With increase of the pH, the rate of reaction rises and the septet merges into a very broad singlet, the signal due to the methyl protons is converted into a broadened doublet, and the water line is also slightly broadened. Analysis of the form of the methyl signal led to the determination of the overall rate of exchange involving trimethylphosphonium ions and the rate of the processes with participation of water could be found from the width of the water signal. Reaction mechanisms analogous to those adopted for ammonium salts were proposed:

$$(CH_3)_3PH^+ + H_2O \overset{k_1}{\rightleftarrows} (CH_3)_3P + H_3O^+ , \quad (32)$$

$$(CH_3)_3PH^+ + OH^- \overset{k_2}{\rightleftarrows} (CH_3)_3P + H_2O , \quad (33)$$

$$(CH_3)_3PH^+ + P(CH_3)_3 \overset{k_3}{\rightleftarrows} (CH_3)_3P + HP^+(CH_3)_3 , \quad (34)$$

$$(CH_3)_3PH^+ + \underset{\underset{H}{|}}{OH} + P(CH_3)_3 \overset{k_4}{\rightleftarrows} (CH_3)_3P + \underset{\underset{H}{|}}{HO} + HP^+(CH_3)_3 , \quad (35)$$

but the values of k_3 and k_4 were not determined separately.

Table 7. Rate constants for the proton exchange of $(CH_3)_3\overset{+}{N}H$ and $(CH_3)_3\overset{+}{P}H$ in water at 22°C.

$(CH_3)_3\overset{+}{X}H$	k_1, s^{-1}	k_2, litre mole^{-1} s^{-1}	(k_3+k_4) litre mole^{-1} s^{-1}	pK_A
$(CH_3)_3\overset{+}{P}H$	7.9	$4.6\cdot10^7$	$1.2\cdot10^2$	8.8
$(CH_3)_3\overset{+}{N}H$	4.7	$<10^{11}$	$3.4\cdot10^8$	9.8

The corresponding exchange rate constants for trimethylammonium and trimethylphosphonium ions in water are compared in Table 7. These data cannot be explained in terms of the acid–base properties of the ions undergoing exchange. Thus the higher value of k_1 for $(CH_3)_3PH^+$ is consistent with its higher acidity, but it remains obscure why k_2 for this species is a thousand times lower than for $(CH_3)_3NH^+$ although trimethylphosphonium ions behave as proton donors also in reaction (33). The authors accounted for the relative values of the combined constants $k_3 + k_4$ by the fact that in reaction (35), as in reaction (29), the rate is limited by proton transfer from water to the phosphine. However, it is still not clear why a difference between the basicities of the amine and phosphine by only one power of ten causes an enormous change in $k_3 + k_4$ (by six powers of ten).

On the other hand, the data in Table 7 can be explained if it is postulated that the ratio of the rates under consideration is determined by the ratio of the strengths of the hydrogen bonds. For phosphorus, these bonds are much weaker than for nitrogen and one must suppose that they are particularly weak in those cases where the phosphorus atom behaves as a proton acceptor. This in fact accounts for the lowering of k_2 and the even greater lowering of $k_3 + k_4$ on passing from ammonium to phosphonium ions. However it still remains obscure why k_1 increases slightly under these conditions.

A comparison, similar to that carried out above, cannot be made for dimethylphenylphosphonium ions in methanol[116], since their nitrogen-containing analogue has not been investigated. One can only assert that reactions of types (34) and (35) are much slower with these ions than

with ammonium salts, which is consistent with the much weaker proton-accepting character of phosphorus in hydrogen bonds.

The exchange in SH bonds has been investigated on a somewhat larger scale. The study of phenylmethanethiol showed[139] that the rate of reaction is proportional to the concentration of the alkaline or acid catalyst. On this basis, the following mechanisms have been proposed for the exchange:

$$C_6H_5CH_2SH_2^+ + C_6H_5CH_2SH \overset{k_1}{\rightleftarrows} C_6H_5CH_2SH + C_6H_5CH_2SH_2^+ , \quad (36)$$

$$C_6H_5CH_2SH + C_6H_5CH_2S^- \overset{k_2}{\rightleftarrows} C_6H_5CH_2S^- + C_6H_5CH_2SH ; \quad (37)$$

$k_1 = 1.35 \times 10^2$ litre mole^{-1} s^{-1} and $k_2 = 6 \times 10^5$ litre mole^{-1} s^{-1}. The uncatalysed process is so slow that its rate cannot be determined by the NMR method.

The rate of exchange of protons in the SH group of 2-mercaptoethanol has been studied[140]. The PMR spectrum of a solution of this substance in carbon tetrachloride consists of a triplet due to the thiol hydrogen, a quartet due to S–CH_2, a triplet due to O–CH_2, and a singlet due to OH. The spectrum retains the same form in an acidified aqueous medium, but in a neutral solution or solutions made alkaline with sodium acetate the SH triplet and the OH singlet merge into a common signal. Analysis of these changes as a function of the catalyst concentration, taking into account the acid–base equilibrium constants in the system, made it possible to determine (at 27°C) the rate constants for the uncatalysed exchange ($k_0 = 32$ s^{-1}) and the reactions catalysed by acetate ions ($k = 2 \times 10^3$ litre mole^{-1} s^{-1}). The equilibrium constant for the reaction

$$HOCH_2CH_2SH + CH_3COO^- \rightleftarrows HOCH_2CH_2S^- + CH_3COOH$$

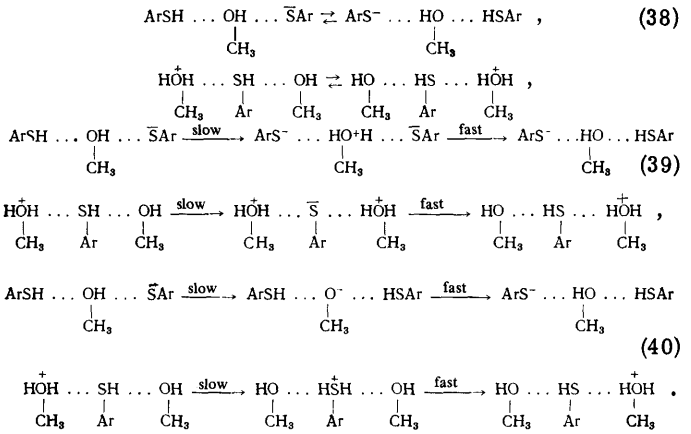
was found and the rate constant for the process

$$HOCH_2CH_2S^- + CH_3COOH \rightarrow HOCH_2CH_2SH + CH_3COO^- ,$$

was calculated to be 10^8 litre mole^{-1} s^{-1}. The absence of the acid catalysed proton exchange in the SH group of 2-mercaptoethanol was explained by the low basicity of the thiol group.

It is interesting to compare the above data with the results for alcohols, for example it is instructive to compare k_1 and k_2 from Eqns. (36) and (37) with k_4 and k_2 from Eqns. (9) and (7) (Table 1). The comparison shows that the rate of exchange in SH groups is smaller by several powers of ten than in OH. We explained this difference by the lower strength of SH...S hydrogen bonds compared with OH...O. This interpretation was confirmed in the present author's studies[141,142] of proton exchange of thiophenols.

A study was made of the exchange between a series of thiophenols and methanol catalysed by hydrogen chloride or sodium methoxide. The rate of reaction was found to be proportional to the concentration of the thiophenol, alcohol, and the catalyst. It increased (and the activation energy fell) in parallel with the acidity on introducing electron accepting substituents into the thiophenol nucleus. For *para*- and *meta*-substituted compounds, a linear relation was observed between the activation energy and the logarithm of the rate constants for the exchange in alkaline and acid media (E_B, E_A, $\lg k_B$, and $\lg k_A$), on the one hand, and Hammett's σ constants, on the other, the values of ρ in the correlation equations proving virtually identical in both series. These data confirmed the exchange mechanism. Three most probable mechanisms were considered, in which the reactants were combined by hydrogen bonds into a single reaction complex:



(38)

(39)

(40)

The data showing the acceleration of the exchange with increasing acidity of thiophenols contradict mechanism (40), which requires the opposite relation, but are consistent with mechanism (39). The choice between the latter and mechanism (38) was made on the basis that only reactions (39) explain the observed equality of the values of ρ in the correlation equations, since only in mechanism (39) is the slow exchange stage the same in both alkaline and acid media, namely proton transfer via the hydrogen bond in the SH...OH dimers. Hence it was concluded that there should be a quantitative relation between the kinetic parameters of the exchange and the thermodynamic characteristics of the hydrogen bond. Such a relation does indeed exist.

Table 8. Kinetic parameters of the proton exchange between thiophenols and methanol and the thermodynamic parameters of the hydrogen bonds between thiophenols and acetone.

ArSH	Proton exchange				Hydrogen bond		
	k_B (27°), litre mole^{-1} s^{-1}	k_A (27°) litre mole^{-1} s^{-1}	E_B, kcal mole^{-1}	E_A, kcal mole^{-1}	K (27°), mole fraction^{-1}	$-\Delta H$, kcal mole^{-1}	$-\Delta S$, e.u.
p-Methoxythiophenol	$4.2 \cdot 10^3$	$1.2 \cdot 10^2$	9.0	12.5	2.3	2.6	7.1
p-Thioxylenol	$3.3 \cdot 10^3$	—	8.3	—	2.1	2.9	8.2
Tetraline-2-thiol	$5.5 \cdot 10^3$	—	8.5	—	2.6	2.8	7.8
p-Thiocresol	$5.8 \cdot 10^3$	$1.7 \cdot 10^2$	8.2	12.0	2.6	2.9	7.8
Thiophenol	$14.0 \cdot 10^3$	$2.8 \cdot 10^2$	7.5	11.0	2.9	3.2	8.6
p-Chlorothiophenol	$28.3 \cdot 10^3$	$7.8 \cdot 10^2$	6.3	10.0	3.3	3.8	10.0
3,4-Dichlorothiophenol	$112.0 \cdot 10^3$	$33.3 \cdot 10^2$	5.5	8.5	4.5	4.1	10.4

We used NMR to investigate[143] the thermodynamics of hydrogen bond formation between acetone and the same series of thiophenols for which the exchange had been investigated and found a linear relation between E_B and E_A, on the one hand, and the enthalpy of formation of the hydrogen bond ΔH, on the other, and also between k_B and k_A, on the one hand, and the association constants K, on the other. It is significant that this relation holds also for *ortho*-substituted thiophenols. The kinetic and thermodynamic data obtained in these studies are compiled in Table 8.

The total set of results shows that the characteristics of the hydrogen bond formed by sulphur play a decisive role in the kinetics and mechanism of proton exchange of thiophenols. The weakness of these bonds explains, in particular, the relatively high activation energies and the low rates of exchange (much lower than in the phenols–methanol systems[75]). The proton-accepting power of sulphur is apparently much weaker. This hypothesis accounts for the observation that the exchange involving thiophenol in an acid medium does not take place by mechanism (40) in which sulphur serves as a proton acceptor, in contrast to the exchange involving phenols, which takes place by reaction (20), analogous to mechanism (40). We may recall that in the case of hydrogen bonds formed by phosphorus the proton-accepting character of phosphorus is apparently much weaker than that of nitrogen.

VI. EXCHANGE IN C–H GROUPS.

Rapid proton exchange in C–H bonds of hydrocarbons and their derivatives takes place only in catalysis by bases and only in those cases where the acidity of the hydrogen is particularly enhanced. Like the other exchange processes examined here, these reactions probably take place in hydrogen-bonded complexes. Hydrogen bonds are less typical for carbon, which explains the rare occurrence of rapid exchange in C–H groups.

Several studies have been made on substituted acetylenes $R-C\equiv CH$.[144,145] It was found that with R = C_6H_5, CH_2CH_2OH, CH_2OCH_3, $C(CH_3)_2OCH_3$, $C(CH_3)_2OH$, and $CH(OC_2H_5)_2$ the rate of base-catalysed exchange with aqueous t-butyl alcohol is proportional to the concentrations of the substrate and the catalyst; the logarithm of the rate constants varies linearly with σ^*. The mechanism can be represented as follows:

$$R-C\equiv CH + OH^- \rightleftarrows R-C\equiv C^- + H_2O \ .$$

A study was also made of the exchange in compounds with R = $SC(CH_3)_3$, OCH_3, $C(CH_3)_3$, $SCH=CH_2$ and $OCH=CH_2$ catalysed by $(CH_3)_4NOH$.[146] The rate proved to be a maximum for sulphur-containing substances and a minimum for t-butylacetylene, and is lower the higher the dielectric constant of the solvent. These data were explained by the fact that only in compounds containing sulphur is there conjugation of the type

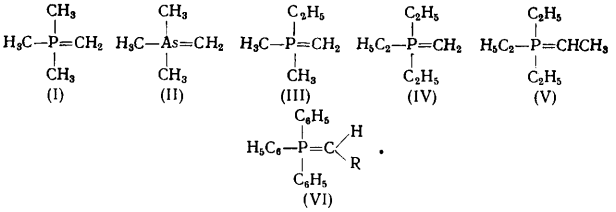
$$\bar{C}\equiv C-SR \leftrightarrow :C=C=\bar{S}R \ ,$$

which stabilises the anion, lowers the energy of the transition state for the reaction, $R-C\equiv C^{-\delta}\ldots H\ldots OH^{-\delta}$, and increases the rate of exchange. The transition state is less solvated than OH^- ions, which in fact explains the decrease of the exchange rate with increasing dielectric constant of the solvent.

In certain systems a rapid exchange was observed between the hydrogen in C–H groups and carbanions. Thus it has been established[147] that the rate constants for the reaction between dimethyl sulphoxide and Na^+ or $Li^+CH_3SOCH_2^-$ (determined from the change in the form of the ^{13}C satellites of the signal due to the CH_3 group) are 12 and 7 litre mole^{-1} s^{-1} respectively at 37°C.

In another study[148] it was shown by a double resonance method that the rate of exchange between fluorene and 9-fluorenyl-lithium in dimethyl sulphoxide solutions at 38°C is characterised by the constant k = 0.5 litre mole^{-1} s^{-1}. These results are inconsistent with the much higher rate of exchange in the analogous system comprising 9-methylfluorene and the 4,5-methylenephenanthryl anion[149] observed in a very dilute dimethyl sulphoxide solution by the stop-flow method. The difference is probably due to self-association of the organometallic compound in concentrated solution.

Rapid proton exchange was observed recently in phosphoranes and their analogues. Thus at room temperature the PMR spectra of the pure compound (I) or its benzene solution show doublets due to the methyl and methylene protons (the splitting is caused by interaction with the ^{31}P nuclei), but the rapid exchange induced by heating deprives the hydrogen atoms of their individual characteristics, which leads to a broadening of the signals, smearing out of the doublet structure, and merging of the signals into a singlet at a temperature above 100°C. In the presence of proton-donating compounds, for example traces of an alcohol, the singlet is observed even at room temperature[150,151]. A similar behaviour was noted for compounds (II)[152] and (III)–(V)[153]. In the latter compounds only the α-hydrogen atoms become indistinguishable. Variation of the form of the signal of the $\equiv P=CHR$ group with temperature was observed also for compounds having the general formula (VI) with R = H, CN, $CO(CH_2)_2C_6H_5$, $COCH_3$, $COOCH_3$, or CHO,[154] it too was explained by rapid proton exchange



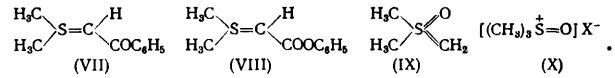
(I) (II) (III) (IV) (V) (VI)

The mechanisms of the above processes were investigated in several studies[154–156], the authors concluded that the exchange takes place between phosphoranes and catalytic amounts of phosphonium salts present in the solutions and formed by the interaction of the phosphorane with proton-donating molecules:

$$\begin{aligned} &(a) \quad R_3\overset{+}{P}-\bar{C}R_2 + HX \rightarrow [R_3\overset{+}{P}-CR_2H]\,X^- \ , \\ &(b) \quad R_3\overset{+}{P}-\bar{C}R_2 + [R_3\overset{+}{P}-CR_2H]\,X^- \rightleftarrows [R_3\overset{+}{P}-CR_2H]\,X^- + R_3P^+-\bar{C}R_2 \ . \end{aligned} \qquad (41)$$

This mechanism explains the catalysis of the exchange by proton-donating compounds mentioned above. It is confirmed by the inhibition of the reaction by bases, which decompose the phosphonium salts.

The rapid exchange by mechanism (41) probably explains the broadening of the signal due to the methylidyne hydrogen in the PMR spectra of the sulphoranes (VII) and (VIII)[156]:



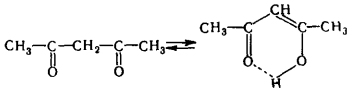
(VII) (VIII) (IX) (X)

Recently rapid exchange was observed in dimethyloxosulphonium methylide (IX).[157] It makes all the hydrogen atoms in this substance indistinguishable in solutions even at a temperature as low as –30°C. The exchange is probably catalysed by impurities. One cannot exclude the possibility that it proceeds by a mechanism analogous to mechanism (41) and is catalysed by compounds of type (X). This hypothesis is confirmed indirectly by data[158] for the rapid proton exchange of compounds of type (X) in aqueous alkaline solutions.

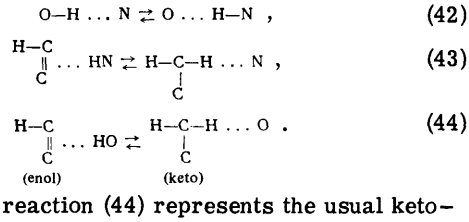
We may note that reactions of type (41b) constitute acid–base interactions. Their rate is high because the ylide structure of phosphorane and their analogues leads to high basicity of the methylene hydrogen and the positive

charge at the phosphorus, arsenic, or sulphur atom increases the acidity at the hydrogen at the adjacent carbon atom.

An interesting case of proton exchange in CH groups associated with the tautomerism of acetylacetone has been investigated[159,160]. The PMR spectrum of pure acetylacetone shows individual signals corresponding to the enol and keto-forms; however, in the presence of diethylamine the equilibrium



is displaced towards the formation of the enol and a common signal for the protons in OH, NH, and =CH– appears in the spectrum. To explain the involvement of the enolic methylidine hydrogen in the proton exchange, mechanisms were proposed with the intermediate participation of the keto-tautomer (only the atoms or groups between which protons migrate are indicated):



(42)

(43)

(44)

(enol) (keto)

We may note that reaction (44) represents the usual keto–enol transformation.

Special experiments showed that the exchange in =CH– is much slower than in OH and NH. This is consistent with the finding that the hydrogen-bond bridges with participation of π-bond electrons are usually weaker than those formed with participation of unshared electron pairs.

VII. CERTAIN GENERAL PROBLEMS OF PROTON EXCHANGE

In this section we shall give a general account of the role of hydrogen bonds in the mechanism of proton exchange and of the nature of the reaction complexes by which the exchange takes place; we will also examine certain considerations concerning the acidity of compounds with SH and PH bonds, which we proposed when comparing the data for the rate and mechanism of proton exchange.

The entire information presented in the review and probably all other published data are consistent with the hypothesis that in rapid exchange reactions the protons always migrate along hydrogen bonds and the ease of such migration is greater the stronger the bonds. Some time ago this hypothesis enabled Brodskii[161] to give a general treatment of the vast experimental data for hydrogen isotope exchange, to devise a classification for such data which has since been generally adopted, and to explain why hydrogen bound to atoms with non-bonding electron pairs is involved in the exchange. Using this hypothesis, Miklukhin[162,163] predicted the variation of the rate of hydrogen isotope exchange (and proton exchange) with the strength of the hydrogen bonds in reaction complexes. These predictions were later confirmed experimentally (see Section V). The hypothesis explains the usually observed parallel variation of the rate of exchange and the acidity of the protons being exchanged by the fact that the acidity and the strength of the hydrogen bonds vary in the same sense in series of related compounds. It also explains the higher rates of exchange between ions of opposite sign, frequently noted above, compared with the exchange between an ion and a molecule, or between neutral molecules, since the hydrogen bonds between ions of different signs are stronger than in the other two cases. It can also explain the rapid exchange in C–H bonds (see Section VI). This exchange is observed only in the system comprising compounds with highly acid hydrogen atoms and a strong base (X) with unshared electron pairs or π electrons. Probably isotope exchange in such systems takes place via hydrogen bonds of the type C–H...X. We may recall finally that in certain cases (see Sections II and V) a linear relation was established between the activation energy for proton exchange and the strength of hydrogen bonds. Thus, there are good reasons for the belief that rapid proton exchange always takes place via hydrogen-bonded reaction complexes.

The nature of these complexes was investigated only in rare cases and as a rule remains unknown. Thus the cyclic structures for these complexes proposed in many investigations of uncatalysed exchange processes are usually unsupported by any evidence. The number of members of the ring (4, 6, 8 and above) is also chosen arbitrarily since in the majority of cases the number of molecules participating in the slow reaction step is unknown.

In the interpretation of the mechanisms of reactions of different types cyclic complexes are sometimes preferred to open-chain complexes because the former can ensure a higher rate of reaction (see, for example, Syrkin[15]). We may note, however, that, for the formation of hydrogen-bonded cyclic complexes in the rapid exchange processes in which we are interested, it is necessary that each molecule forming part of the complex should be capable of behaving simultaneously as a hydrogen donor and acceptor. This condition does not as a rule hold in catalysed exchange, since the acid catalyst blocks the free electron pairs and frequently leads to the loss of acceptor capacity by the molecule, while the base usually leads to the conversion of molecules into ions, which lack labile hydrogen. Thus many of the very rapid catalysed proton exchange reactions undoubtedly involve open-chain complexes. We suggest that one cannot exclude the possibility that many uncatalysed exchange reactions also proceed via open-chain complexes.

In Section V it was already stated that the low rate and the relatively high activation energy of proton exchange in the PH and SH groups compared with NH and OH can be accounted for by the low strength of the hydrogen bond formed by phosphorus and sulphur. Generalising the findings, one can postulate, following Miklukhin[163], that the exchange in AsH, SbH, SeH, and TeH should be even slower and the activation energy should be still higher.

We have also noted (see Section V) that the properties of the hydrogen bond formed by sulphur and phosphorus determine the mechanism of the exchange involving mercapto-compounds and phosphonium salts and that the proton-accepting functions of sulphur and phosphorus are probably even weaker (compared with oxygen and nitrogen) than their proton-donating functions. We suggest that these characteristics of the hydrogen bond are responsible also for the acid properties of mercapto-compounds and phosphonium salts. The greater weakness of hydrogen bonds formed by sulphur and phosphorus compared with oxygen and nitrogen usually results in the retardation of both the forward and reverse reactions in the acid–base equilibrium of the type

$$X{-}H \ldots B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} X^- \ldots HB^+ .$$

This is because, as already stated above, the proton-accepting functions of sulphur and phosphorus are very much weaker. As a result, the acid dissociation constants $K = k_1/k_{-1}$ prove to be higher than for the corresponding oxygen- and nitrogen-containing substances.

This treatment is probably of general validity. It explains, for example, the higher acidity of phosphines compared with amines and the increase of the acidity in the series

$$H_2O < H_2S < H_2Se < H_2Te \text{ and } HF < HCl < HBr < HI .$$

Evidently this approach to the problem of acidity is applicable only in those cases where the hydrogen in the X–H bonds has partial positive charge sufficient for the formation of the hydrogen bond X–H...B.

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