THE PRINCIPLES OF HYDROGEN ISOTOPE EXCHANGE REACTIONS IN SOLUTION

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Introduction

ISOTOPE-EXCHANGE reactions are the reversible chemical processes by which two isotopes of the same element (^{l}Z, ^{m}Z) exchange places, *e.g.*,

$$X.^{l}Z + Y.^{m}Z \rightleftharpoons X.^{m}Z + Y.^{l}Z \quad . \quad . \quad . \quad (1)$$

Their possibility was first investigated by Hevesy [1] forty years ago. Because isotopically different molecules have certain distinguishable properties, namely, those directly dependent on mass or on nuclear structure (like the velocity of radioactive decay), these equilibria can be studied experimentally.

Among all groups of isotopes, those of hydrogen hold a special place since the relative disparity between the masses of protium (H or ^{1}H), deuterium (D or ^{2}H), and tritium (T or ^{3}H) is far greater than that in the isotopes of any other element, thus facilitating assay and exaggerating other differences dependent upon mass.[2] Moreover, deuterium was the first uncommon isotope to be concentrated [3] and separated in a pure form [4] in comparatively large amounts, and soon afterwards heavy water was used in the study of hydrogen isotope-exchange reactions.[5] These reactions have been found to take place both heterogeneously and homogeneously in gaseous and liquid systems under a wide variety of conditions.

A number of factors have combined to intensify interest in this field. Among these may be mentioned the widespread occurrence of hydrogen in chemical compounds, the special role which hydrogen plays in acid–base equilibria and consequently in solution chemistry as a whole, the industrial importance of catalysts whose ability to catalyse exchange reactions is connected with their catalysis of other processes,[6] and, by no means last in importance, the comparatively low cost of deuterium oxide and of equipment required for its analysis. The subject also derives some indirect importance from the widespread use of hydrogen-isotope labelling as a means of following the mechanisms of complex reactions of organic

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[1] G. von Hevesy and E. Róna, *Z. physikal. Chem.*, 1915, **89**, 294; G. von Hevesy and L. Zechmeister, *Ber.*, 1920, **53**, 410.

[2] H. C. Urey and G. K. Teal, *Rev. Mod. Phys.*, 1935, **7**, 34.

[3] H. C. Urey, F. C. Brickwedde, and G. M. Murphy, *Phys. Rev.*, 1932, **39**, 164; **40**, 1.

[4] G. N. Lewis, *J. Amer. Chem. Soc.*, 1933, **55**, 1297; G. N. Lewis and R. T. Macdonald, *ibid.*, pp. 2616, 3057; *J. Chem. Phys.*, 1933, **1**, 341.

[5] (*a*) G. N. Lewis, *J. Amer. Chem. Soc.*, 1933, **55**, 3502; (*b*) K. F. Bonhoeffer and G. W. Brown, *Z. physikal. Chem.*, 1933, *B*, **23**, 171.

[6] D. D. Eley, *Quart. Rev.*, 1949, **3**, 209; G. C. Bond, *ibid.*, 1954, **8**, 279.

molecules *in vitro* and particularly *in vivo*. It is essential in such cases t understand the exchange behaviour of the tracer hydrogen atoms under th experimental conditions of the reaction studied and during the subsequen separation of the labelled compound.

In the present Review attention will be restricted to solution reaction occurring without the intervention of heterogeneous catalysts. Most o the work described relates to deuterium, since tritium has not been availabl for chemical studies until recently.

General Remarks concerning Experimental Procedures

In favourable cases the exchange process can be observed by direc spectroscopic examination of the reaction mixture, but more usually it i necessary to isolate a representative sample of one or both of the reactin species and to subject it to isotopic analysis. In a two-phase system isolation is largely achieved by the separation of the phases, but for homogeneou systems an operation such as distillation, precipitation, or extraction b means of an immiscible solvent of one of the species involved is required It is always essential to check that the separation procedure is not itsel responsible for the occurrence of an exchange reaction or an isotope fractionation effect.

The methods of assaying isotopes have recently been reviewed in som detail.[7] For deuterium–protium analysis, the most straightforward an probably the most accurate method is to determine the density [7] of th water obtained from the reactants, either directly when it is one of them or indirectly by combustion or decomposition. The method suffers fro the disadvantage that relatively large samples are required, even for determinations on the micro-scale. It is, therefore, sometimes preferred t convert the sample into hydrogen [8] or ethane [9] and to analyse the gas b mass spectrometry.[7] Methods based on other manifestations of the difference in mass can sometimes be used with accuracy, *e.g.*, infrared spectra,[1] thermal conductivity,[7] and refractive-index differences.[7]

Tritium emits soft β-radiation and is usually assayed by introduction o the sample, as gas, into a counting tube.[11]

In the most commonly studied type of exchange experiment a substanc is dissolved in, or agitated with, an isotopically different medium, usuall isotopically enriched water often with the addition of acid or alkali Ethan[^{2}H]ol and dioxan–water mixtures have sometimes been used in orde to increase the solubility of organic substances. Work with non-hydroxyl

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[7] I. Kirshenbaum, " Physical Properties and Analysis of Heavy Water ", McGraw Hill Book Co. Inc., New York, 1951.

[8] J. Bigeleisen, M. Perlman, and H. Prosser, *Analyt. Chem.*, 1952, **24,** 1356.

[9] L. Friedman and P. Irsa, *ibid.*, p. 876.

[10] V. Thornton and F. E. Condon, *ibid.*, 1950, **22,** 690 ; N. R. Trenner, R. W. Walke B. Arison, and C. Trumbauer, *ibid.*, 1951, **23,** 487 ; T. L. Brown and R. B. Bernstei *ibid.*, p. 673.

[11] G. B. Cook and J. F. Duncan, " Modern Radiochemical Practice ", Oxford, 195 p. 253.

solvents such as liquid ammonia [12] and hydrogen bromide [13] has been far less extensive. In most experiments the "solute" and "solvent" have been present in comparable proportions and the exchange has been measured by density changes in the solvent. Less often, isotope assays have been made on the solute. It is likely that, even where there is incomplete mutual solubility of the reagents, the reaction occurs in a liquid phase and not, in the main, at a phase boundary between them. Exchange reactions between two solutes in an inert solvent [14] have so far received little attention. Occasionally, exchange among the hydrogen atoms of a single chemical species is observed. For example, at 200° the deuterium atoms of phen[^{2}H]ol become distributed also among the *o*- and the *p*-position of the benzene nucleus.[15]

The duration of the exchange reactions has varied from seconds to months ; the lower limit to this is set by the time required for mixing and separating the reagents.

In general, the aim of the experiments has been confined to the establishment of the number and, if possible, the location of exchangeable hydrogen atoms under various conditions. These studies produced, within a few years of the discovery of deuterium, a large number of facts [16] so that, from the qualitative point of view, the general picture of the exchangeability of variously bound hydrogen atoms with hydroxylic solvents is fairly complete, and exchange reactions have become a recognised route in the preparation of substances labelled with hydrogen isotopes.[17]

Qualitative Results on Exchangeability

In the first detailed publication on this subject Bonhoeffer and Brown [5b] reported that all the hydrogen atoms in ammonium chloride and about half of those in sucrose exchanged with heavy water at an immeasurably great speed, whereas the other hydrogen atoms in sucrose—presumed to be those linked directly to carbon—were found not to exchange at all. The very rapid exchange of hydroxylic hydrogen atoms has since been confirmed, without any substantiated exception,[18] for a large number of different compounds. These include hydrogen peroxide [19] and various

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[12] (*a*) A. I. Shatenshtein and co-workers, *Doklady Akad. Nauk S.S.S.R.*, 1950, **60,** 1029 ; 1951, **79,** 479 ; 1952, **85,** 381 ; (*b*) W. K. Wilmarth and J. C. Dayton, *J. Amer. Chem. Soc.*, 1953, **75,** 4553.

[13] A. I. Shatenshtein and Ya. M. Varsharskii, *Doklady Akad. Nauk S.S.S.R.*, 1952, **85,** 157.

[14] L. Kaplan and K. E. Wilzbach, *J. Amer. Chem. Soc.*, 1954, **76,** 2593.

[15] A. I. Brodskii and I. I. Kukhtenko, *Dopovidi Akad. Nauk Ukrain R.S.R.*, 1950, 279.

[16] (Reviews) (*a*) C. K. Ingold and C. L. Wilson, *Z. Elektrochem.*, 1938, **44,** 62 ; (*b*) K. F. Bonhoeffer, *Trans. Faraday Soc.*, 1938, **34,** 252.

[17] H. R. V. Arnstein and R. Bentley, *Quart. Rev.*, 1950, **4,** 189 ; S. L. Thomas and S. H. Turner, *ibid.*, 1953, **7,** 411.

[18] (*a*) J. Hine and C. H. Thomas, *J. Amer. Chem. Soc.*, 1953, **75,** 739 ; (*b*) *idem, ibid.*, 1954, **76,** 612 ; H. Kwart, L. P. Kuhn, and E. L. Bannister, *ibid.*, p. 5998.

[19] F. Fehér, *Z. Elektrochem.*, 1937, **43,** 663.

inorganic and carboxylic acids (such as boric acid [20] and benzoic acid [21]), alcohols,[18] phenols,[22] and carbohydrates.[5b] There is not much experimental evidence concerning the analogous thio-compounds in which the hydrogen of an S–H group is being replaced. It has, however, been reported that at very low temperatures the velocity of the exchange reaction between liquid hydrogen sulphide and an alcohol is measurably slow.[23]

Hydrogen atoms directly bound to nitrogen in primary [18b] and secondary [24, 25] aliphatic and aromatic amines, pyrrole,[26] acid amides,[27] amino-acids,[28] and similar compounds exchange with hydroxyl groups or other amines within the time necessary for mixing and recovering the reagents. However, it is well established that for metal ammines,[29] such as $Co(NH_3)_6(NO_3)_3$, exchange is measurably slow under appropriate conditions. It has also been reported that the hydrogen atoms of the ammonium ion and of alkylammonium ions exchange at a measurable velocity with an alcohol in organic solvents [14, 30a] or with aqueous acid.[30b]

Slow exchange reactions have been established for P–H bonds in neutral solutions of hypophosphite ions [31a] and for phosphine in acid or alkaline solution,[31b] and for H–H bonds in alkali.[32] The B–H bonds in sodium borohydride do not exchange in water,[33] nor do those of diborane in liquid ammonia.[34] Triethylmonosilane ($SiHEt_3$) does not undergo an exchange reaction in water or ethanol either alone or in the presence of acids or bases.[35]

Most of the work on exchangeability concerns C–H bonds, for which a wide range of behaviour has been found, as is the case for other substitution reactions involving these bonds. With the notable exception of certain

[20] E. Ogawa, *Bull. Chem. Soc. Japan*, 1936, **11**, 310.

[21] H. B. Erlenmeyer, A. Epprecht, H. Lobeck, and H. Gärtner, *Helv. Chim. Acta*, 1936, **19**, 354.

[22] (*a*) C. K. Ingold, C. G. Raisin, and C. L. Wilson, *J.*, 1936, 1637; (*b*) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, 1938, **13**, 681.

[23] K. H. Geib, *Z. Elektrochem.*, 1939, **45**, 648; A. Tananger, *Tids. Kjemi, Berg.*, 1943, **3**, 44.

[24] P. Goldfinger and W. Lasareff, *Compt. rend.*, 1935, **200**, 1671.

[25] W. G. Brown, M. S. Kharasch, and W. R. Sprowls, *J. Org. Chem.*, 1939, **4**, 442.

[26] M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, 1937, **12**, 107.

[27] O. Reitz, *Z. Elektrochem.*, 1938, **44**, 693.

[28] J. A. Stebol and W. H. Hamill, *J. Biol. Chem.*, 1937, **120**, 531.

[29] J. S. Anderson, H. V. A. Briscoe, and N. L. Spoor, *J.*, 1943, 361; J. S. Anderson, H. V. A. Briscoe, L. H. Cobb, and N. L. Spoor, *ibid.*, p. 367.

[30] (*a*) C. G. Swain, J. T. McKnight, M. M. Labes, and V. P. Kreiter, *J. Amer. Chem. Soc.*, 1954, **76**, 4243; (*b*) A. I. Brodskii and L. V. Sulima, *Doklady Akad. Nauk S.S.S.R.*, 1950, **74**, 513.

[31] (*a*) H. B. Erlenmeyer, W. Schoenauer, and G. Schwarzenbach, *Helv. Chim. Acta*, 1937, **20**, 732; W. A. Jenkins and D. M. Yost, *J. Chem. Phys.*, 1952, **20**, 538; G. P. Miklukhin and A. F. Rekasheva, *Doklady Akad. Nauk S.S.S.R.*, 1952, **85**, 827; (*b*) R. E. Weston and J. Bigeleisen, *J. Amer. Chem. Soc.*, 1954, **76**, 3074.

[32] (*a*) K. Wirtz and K. F. Bonhoeffer, *Z. physikal. Chem.*, 1936, *A*, **177**, 1; (*b*) W. K. Wilmarth, J. C. Dayton, and J. M. Flournoy, *J. Amer. Chem. Soc.*, 1953, **75**, 4549.

[33] P. R. Girardot and R. W. Parry, *ibid.*, 1951, **73**, 2368.

[34] A. B. Burg, *ibid.*, 1947, **69**, 747.

[35] A. I. Brodskii and I. G. Khaskin, *Doklady Akad. Nauk S.S.S.R.*, 1950, **74**, 299.

atoms in paraffin chains, exchange has been effected in a large number of cases and often at speeds amenable to measurement.

The examples given above are merely illustrative and are not intended to be a comprehensive list of the very large number of systems studied, since full bibliographies [36] of this field are available. Despite the qualitative nature of many of the investigations, they have sometimes revealed differences in exchangeability of non-equivalent hydrogen atoms in the same molecule; *e.g.*, there are three distinguishable rates of exchange for the hydrogen atoms of indole.[37] Accurate studies of exchange kinetics, which demand a greater refinement in the experimental conditions, are less numerous. The special requirements of such experiments will be mentioned on p. 64.

Equilibrium Constants of Exchange Reactions

The equilibrium constant for a gas-phase exchange reaction can be expressed in terms of the partition functions of the molecules involved:

$$K = \prod^{\text{Products}} Q \Big/ \prod^{\text{Reactants}} Q \quad . \quad . \quad . \quad . \quad (2)$$

Q is the partition function for unit volume when the energy of the molecule is relative to the hypothetical vibrationless state of the molecule with no zero-point energy, and the product is taken over all reactant or product molecules. For the reaction

$$x\mathrm{XH}_y + y\mathrm{YD}_x \rightleftharpoons y\mathrm{YH}_x + x\mathrm{XD}_y \quad . \quad . \quad . \quad (3)$$

the expression becomes

$$K = \left(\frac{Q_{\mathrm{XD}_y}}{Q_{\mathrm{XH}_y}}\right)^x \Big/ \left(\frac{Q_{\mathrm{YD}_x}}{Q_{\mathrm{YH}_x}}\right)^y \quad . \quad . \quad . \quad . \quad (4)$$

or, denoting the chemical species XH_y and YH_x by subscripts 1 and 2, respectively, and indicating the deuterated molecules by primed symbols,

$$K = \left(\frac{Q'_1}{Q_1}\right)^x \Big/ \left(\frac{Q'_2}{Q_2}\right)^y \quad . \quad . \quad . \quad . \quad (5)$$

which contains only the *ratios* of partition functions of isotopically different (but otherwise identical) molecules and may therefore be considerably simplified.[38–41] The detailed procedure for the theoretical calculation of K depends on the extent of the spectroscopic data available for the particular molecules concerned. In this discussion we shall make the approximation, which is necessary at any rate for most polyatomic molecules, that the

[36] (*a*) Up to 1946: A. H. Kimball, "Bibliography of Research on Heavy Hydrogen Compounds", McGraw-Hill Book Co. Inc., New York, 1951; (*b*) Since 1946: "A Review of the Properties of Deuterium Compounds. Annual Bibliography", U.S. Dept. of Commerce, National Bureau of Standards, Washington, D.C.

[37] M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, 1938, **13**, 307.

[38] H. C. Urey and D. Rittenberg, *J. Chem. Phys.*, 1933, **1**, 137.

[39] A. Farkas and L. Farkas, *Proc. Roy. Soc.*, 1934, *A*, **144**, 467.

[40] J. Bigeleisen and M. G. Mayer, *J. Chem. Phys.*, 1947, **15**, 261.

[41] H. C. Urey, *J.*, 1947, 562.

various forms of molecular energy are independent. Q then becomes a product of nuclear spin, electronic, translational, rotational, and vibrational factors. Of these, the nuclear spin terms will always cancel out. In general, the first excited electronic level is so high that its population may be neglected and the electronic factor becomes equal to the degeneracy, which will also cancel out in the expression for K. However, a small isotope effect on the electronic levels of protium and deuterium atoms has been observed, which means that in their compounds also there will probably be what might be called an electronic zero-point energy difference. Since this difference may not be the same for different molecules, it may not cancel completely in the expression for K, leaving a slight uncertainty in the calculation. This effect will probably be greater for protium–tritium exchanges.[41] The translational and rotational factors have the values $(2\pi \boldsymbol{k}MT)^{3/2}/\boldsymbol{h}^3$ and $8\pi^2(8\pi^3XYZ)^{1/2}(\boldsymbol{k}T)^{3/2}/\sigma \boldsymbol{h}^3$ (or $8\pi^2 I\boldsymbol{k}T/\boldsymbol{h}^2$ for a diatomic molecule) respectively, the rotation being assumed to be classical. This will be a valid assumption except for reactions involving hydrogen molecules or reactions at very low temperatures, for which a correction has to be applied.[42] The vibrational factor is a product over the $3N - 6$ vibrational degrees of freedom ($3N - 5$ for linear molecules) and has the value

$$\prod \frac{\exp(-\boldsymbol{h}\nu_i/2\boldsymbol{k}T)}{1 - \exp(-\boldsymbol{h}\nu_i/\boldsymbol{k}T)}$$

if the anharmonicity is assumed to be negligible. For accurate work with simple molecules this assumption need not be made.[43] In these expressions, T is the absolute temperature, and $\boldsymbol{k}$ and $\boldsymbol{h}$ are Boltzmann's and Planck's constants, respectively. M is the mass of the molecule, X, Y, Z its principal moments of inertia (I is the moment of inertia for a diatomic molecule), ν_i is the classical vibration frequency for its ith mode of vibration, and σ is the symmetry number, *i.e.*, the number of equivalent orientations in space which the molecule can take up as the result of simple rotation.

Substituting these values for the partition functions in equation (5), we obtain

$$K = \frac{\left(\left[\frac{\sigma_1}{\sigma'_1}\left(\frac{X'_1Y'_1Z'_1}{X_1Y_1Z_1}\right)^{1/2}\left(\frac{M'_1}{M_1}\right)^{3/2}\prod_i \frac{1-\exp(-u_{i1})}{1-\exp(-u'_{i1})}\right]\prod_i \frac{\exp(-u'_{i1}/2)}{\exp(-u_{i1}/2)}\right)^x}{\left(\left[\frac{\sigma_2}{\sigma'_2}\left(\frac{X'_2Y'_2Z'_2}{X_2Y_2Z_2}\right)^{1/2}\left(\frac{M'_2}{M_2}\right)^{3/2}\prod_i \frac{1-\exp(-u_{i2})}{1-\exp(-u'_{i2})}\right]\prod_i \frac{\exp(-u'_{i2}/2)}{\exp(-u_{i2}/2)}\right)^y} \quad . \quad . \quad . \quad (6)$$

where $u_i = \boldsymbol{h}\nu_i/\boldsymbol{k}T$. Since $\frac{1}{2}\boldsymbol{h}\nu_i$ constitutes the zero-point energy of the ith vibration, this expression may also be written

$$K = \frac{[\ .\ .\ .\ ]^x}{[\ .\ .\ .\ ]^y}.\exp(-\Delta E^0/\boldsymbol{k}T) \quad . \quad . \quad . \quad (7)$$

where ΔE^0 is the net difference in zero-point energy between the two sides

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[42] L. S. Kassel, *Chem. Rev.*, 1936, **18**, 277.

[43] W. F. Libby, *J. Chem. Phys.*, 1943, **11**, 101.

of equation (3). Equation (6) may be considerably simplified [41] by applying Teller and Redlich's product theorem,[44] according to which

$$\left(\frac{X'Y'Z'}{XYZ}\right)^{1/2}\left(\frac{M'}{M}\right)^{3/2} = \left(\frac{m'}{m}\right)^{3n/2}\prod_i \frac{u'_i}{u_i} \qquad . \quad . \quad (8)$$

if the potential functions of isotopic molecules may be assumed to be identical ; m and m' are the atomic weights of the pair of isotopes considered, and n is the number of isotopic atoms exchanged [*i.e.*, x and y for the species of equation (3)]. Substitution in equation (6) eliminates the moments of inertia and the equation becomes

$$K = \frac{\left(\dfrac{\sigma_1}{\sigma'_1}\prod_i \dfrac{u'_{i1}}{u_{i1}}\cdot\dfrac{\exp\left(-\frac{1}{2}u'_{i1}\right)}{\exp\left(-\frac{1}{2}u_{i1}\right)}\cdot\dfrac{1-\exp\left(-u_{i1}\right)}{1-\exp\left(-u'_{i1}\right)}\right)^x}{\left(\dfrac{\sigma_2}{\sigma'_2}\prod_i \dfrac{u'_{i2}}{u_{i2}}\cdot\dfrac{\exp\left(-\frac{1}{2}u'_{i2}\right)}{\exp\left(-\frac{1}{2}u_{i2}\right)}\cdot\dfrac{1-\exp\left(-u_{i2}\right)}{1-\exp\left(-u'_{i2}\right)}\right)^y} \qquad . \quad . \quad (9)$$

This function involves only the vibration frequencies and symmetry numbers of the species in equation (3). Although the formal dependence on the moments of inertia has been eliminated by this procedure, their values will normally, but not inevitably, be required for the calculation of the product of the vibrational frequencies involved.[45]

Moments of inertia and molecular zero-point energies are little affected by isotopic replacement involving a heavy element. Therefore, in these cases, equations (7) and (9) can be greatly simplified [40, 41, 46] and K will scarcely differ from the ratio of the products of the symmetry numbers. However, significant departures from this ratio occur for the hydrogen isotopes and in calculations concerning them the full expression must be used. Careful comparison between the results of such calculations and the experimental values of the gas-phase equilibrium constants have been made in a few cases, with excellent agreement.[7, 41]

Even when the complete assignment of vibration frequencies is not available a very approximate calculation may be possible. This arises from the following circumstances. First, it can be shown that, apart from symmetry considerations and except in the case of very light molecules, the dominant effect of isotopic substitution is on the terms involving the zero-point energies [*i.e.*, on the exponentials $e^{-u/2}$ in equation (9)]. Secondly, the zero-point energy change caused by isotopic replacement is most marked in the stretching vibration of the X–H bonds undergoing exchange. Bending and twisting modes have lower frequencies, and consequently their zero-point energies and zero-point energy changes are less important. For example, for MeOH and MeOD [47] the isotopic frequency shift for O–H

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[44] E. Teller, quoted by C. K. Ingold *et al.*, *J.*, 1936, 971 ; O. Redlich, *Z. physikal. Chem.*, 1935, *B*, **28**, 371.

[45] L. Melander, *Arkiv Kemi*, 1950, **2**, 232.

[46] L. Waldman, *Naturwiss.*, 1943, **31**, 205.

[47] G. Herzberg, " Infrared and Raman Spectra of Polyatomic Molecules ", D. Van Nostrand Co. Inc., New York, 1945, p. 335.

stretching is 962 cm.$^{-1}$, that for C—O—H bending 477 cm.$^{-1}$, and the sum for all other modes of vibration amounts to 107 cm.$^{-1}$.

In the first approximation the reductions in zero-point energy caused by the replacement of protium by deuterium and tritium are, for a stretching vibration, $\frac{1}{2}h\nu(1 - 1/\sqrt{2})$ and $\frac{1}{2}h\nu(1 - 1/\sqrt{3})$ respectively [since the zero-point energy E_0 for a simple harmonic vibration of force constant k is given by $E_0 = (h/4\pi)\sqrt{k/\mu}$, where μ is the reduced mass for the particular vibration], *i.e.*, the reductions are proportional to the frequencies. An assumption that a qualitative result may be derived from a consideration of the X–H and X–D stretching frequencies alone, thus leads to the rule that at equilibrium in the gas phase the heavier isotope will be most highly concentrated in the tightest X–H bond, *i.e.*, the bond with the largest stretching force constant. This trend may be seen in the liquid-phase constants (Table 1) to which the majority of experimental results lead.

The theoretical calculation of the equilibrium constant in the condensed phase is less straightforward. If in the equilibrium (3) the molecules XH_y and XD_y are in one liquid phase (indicated by a single bar) and the molecules YH_x and YD_x in another liquid phase (indicated by a double bar), then the reaction can be written as

$$x\overline{XH_y} + y\overline{\overline{YD_x}} \rightleftharpoons x\overline{XD_y} + y\overline{\overline{YH_x}} \qquad . \quad . \quad (10)$$

If we consider a hypothetical path *via* the gas phase

$$x\overline{XH_y} + y\overline{\overline{YD_x}} \overset{K_1}{\rightleftharpoons} xXH_y + yYD_x \overset{K_2}{\rightleftharpoons} yYH_x + xXD_y \overset{K_3}{\rightleftharpoons} x\overline{XD_y} + y\overline{\overline{YH_x}} \qquad . \quad . \quad . \quad (11)$$

then $K_s = K_1K_2K_3$, where K_s is the liquid-phase equilibrium constant, K_2 is the gas-phase equilibrium constant given by equation (9), K_1 is the constant for the formation of x molecules of gaseous XH_y and of y molecules of gaseous YD_x from the respective liquid phases, and K_3 is the reciprocal of the corresponding constant for XD_y and YH_x. K_1 and K_3 can be written in terms of the ratios of the partial vapour pressures to the mole fractions in the liquid phase for the species concerned, *i.e.*,

$$K_1 = \left(\frac{p_1}{N_1}\right)^x\left(\frac{p'_2}{N'_2}\right)^y \quad \text{and} \quad K_3 = \left(\frac{N'_1}{p'_1}\right)^x\left(\frac{N_2}{p_2}\right)^y$$

When the liquid phases considered each consist only of the isotopic species of a single compound, Raoult's law, $p_1/N_1 = p_1^0$, may be assumed to hold and hence

$$K_1 = (p_1^0)^x(p_2^{0\prime})^y \quad \text{and} \quad K_3 = 1/(p_1^{0\prime})^x(p_2^0)^y$$

and hence

$$K_s = K_2\left(\frac{p_1^0}{p_1^{0\prime}}\right)^x\left(\frac{p_2^{0\prime}}{p_2^0}\right)^y \qquad . \quad . \quad . \quad . \quad (12)$$

where p^0 denotes the vapour pressure of a pure liquid isotopic species at the same temperature as the equilibrium constant.

If the liquid phase is a solution of the compound, Raoult's law will not in general be valid, and we must write

$$K_1 = (p_1^0f_1)^x(p_2^{0\prime}f'_2)^y \qquad . \quad . \quad . \quad . \quad (13)$$

where f is the activity coefficient denoting the departure from Raoult's law. Making the reasonable assumption that activity coefficients of isotopically different but otherwise identical molecules are the same, *i.e.*, $f_1 = f'_1$ and $f_2 = f'_2$, we again obtain the result of equation (12). This result also holds when there is only one condensed phase as, for instance, in the exchange between a solute and water.

The relevant vapour-pressure measurements have been carried out in only a few cases. The values for the isotopic water molecules are known accurately,[7] and therefore the equilibrium constants for the exchange of gaseous hydrogen compounds with liquid water can easily be obtained from the gas-phase values. A comparison of the theoretical and experimental equilibrium constants in the liquid phase giving good agreement has been made for the deuterium exchange with water in the cases of ethanethiol and amyl alcohol,[48] where the vapour-pressure ratios $p^{0\prime}/p^{0}$ were found to be 0·911 and 0·855, respectively. However, in the vast majority of cases the vapour pressures are not known and therefore accurate comparison with theory is impossible.

Most of these experimental results refer to aqueous solution and to equilibria of the type

$$\text{HOD} + \text{RH}_x \rightleftharpoons \text{RDH}_{x-1} + \text{HOH} \quad . \quad . \quad . \quad (14)$$

only small concentrations of deuterium having been used in the solvent. The results are usually quoted in terms of the distribution coefficient, α, given by

$$\alpha = (\text{D/H})_{\text{solute}}/(\text{D/H})_{\text{solvent}} \quad . \quad . \quad . \quad (15)$$

This represents the ratio of deuterium to protium atoms in the exchangeable hydrogen of the solute divided by the same ratio for the solvent. If the product of the symmetry numbers of the reactant species is the same as that of the products, α will approach the value of the equilibrium constant as the concentration of the isotopic species approaches zero. If there is a change in the product of the symmetry numbers during the reaction, α will differ from K_s. For instance, for the reaction of equation (14)

$$K_s = [\text{RDH}_{x-1}][\text{HOH}]/[\text{RH}_x]\,[\text{DOH}] \quad . \quad . \quad . \quad (16)$$

and, if only one atom is exchangeable,

$$\alpha = \frac{[\text{RDH}_{x-1}]\{[\text{DOH}] + 2[\text{HOH}]\}}{[\text{RH}_x]\{[\text{DOH}] + 2[\text{DOD}]\}} \quad . \quad . \quad . \quad (17)$$

As the proportion of deuterium in the system tends to zero (so that $[\text{H}_2\text{O}] \gg [\text{DOH}]$ and $[\text{DOH}] \gg [\text{D}_2\text{O}]$), $\alpha \rightarrow 2K_s$ or, more generally,

$$\alpha \rightarrow \left(\prod^{\text{Products}} \sigma \Big/ \prod^{\text{Reactants}} \sigma \right) K_s.$$

Many determinations of the distribution coefficient have been made using water with a low deuterium concentration, and the corresponding equilibrium constants are therefore known. In cases where the amount of deuterium in the system is sufficiently high for an appreciable concentration

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[48] F. W. Hobden, E. F. Johnston, L. H. P. Weldon, and C. L. Wilson, *J.*, 1939, **61**.

of the species D_2O to be present in solution, the use of equations (16) and (17) allows the conversion of distribution coefficients into equilibrium constants—the relative abundance of the isotopic species H_2O, HOD, and D_2O being controlled by the constant for the equilibrium

$$H_2O + D_2O \rightleftharpoons 2HOD \quad . \quad . \quad . \quad . \quad (18)$$

which is accurately known.[7] If the exchanging solute has two equivalent hydrogen atoms and the value of the equilibrium constant for

$$XH_2 + DOH \rightleftharpoons XHD + H_2O \quad . \quad . \quad . \quad (19)$$

is required, it is similarly necessary to know the equilibrium constant for the reaction

$$XH_2 + XD_2 \rightleftharpoons 2XHD \quad . \quad . \quad . \quad . \quad (20)$$

in order to allow for the presence of XD_2. In heavy molecules it is sufficiently accurate to assume that this constant is equal to the statistical factor 4, *i.e.*, to the ratio $\sigma_{XH_2} . \sigma_{XD_2}/\sigma^2_{XDH}$. Similar considerations apply to cases where there are more than two equivalent exchanging hydrogen atoms.

Some values of the liquid-phase equilibrium constant [as defined by equations (14) and (16)] are given in Table 1. With the exception of the

TABLE 1. *Equilibrium constants for the liquid-phase exchange reaction*

$$HOD + RH_x \rightleftharpoons RDH_{x-1} + H_2O$$

	RH_x	Temp.	K_s	Ref.
O–H bonds . .	Methanol	80°	0·48	49*a*
	n-Amyl alcohol	25	0·55	48
	Benzyl alcohol	30—300	0·55 (average)	49*b*
	Phenol	25	0·54	49*b*, 85*a*
	p-Nitrophenol	100	0·54	49*c*
	Benzoic acid	30—300	0·52 (average)	49*b*
S–H bonds . .	Ethanethiol	25	0·22	48
N–H bonds . .	Aniline	0	0·55	49*b*
	Pyrrole	30	0·44	49*b*, 49*d*
	3-Methylindole	105	0·54	49*d*
	2 : 3-Dimethylindole	60	0·52	49*d*
	Indole	60	0·54	49*d*
C–H bonds . .	Acetylene	0	0·365	81*a*, *b*
		25	0·45	
		100	0·51	
	Nitromethane	83	0·39	68
	Indene	100	0·32	49*e*
	1-Methylindole (3-CH bonds)	60	0·38	49*d*
	Phenol (average of *o*- and *p*-positions)	100	0·45	85*a*, 49*f*

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[49] (*a*) J. O. Halford and B. Pecherer, *J. Chem. Phys.*, 1938, **6,** 571; (*b*) M. Harada and T. Titani, *Bull. Chem. Soc. Japan*, 1935, **10,** 554; 1936, **11,** 465; (*c*) M. Koizumi and T. Titani, *ibid.*, 1938, **13,** 318; (*d*) M. Koizumi, *ibid.*, 1939, **14,** 453; (*e*) *idem*, *ibid.*, 1939 **14,** 491; (*f*) M. Koizumi and T. Titani, *ibid.*, 1938, **13,** 681.

S–H bond the distribution coefficient α ($\sim 2K_s$) has a value near unity. This circumstance allowed correct conclusions concerning the number of exchangeable atoms to be drawn from simple exchange experiments at a time when the exact values of equilibrium constants were unknown.

The Isotope Effect on Reaction Rates and the Establishment of Exchange Equilibrium

According to the theory of absolute reaction rates [50] the velocity constant for a reaction

$$\mathrm{XH} + \mathrm{B} \longrightarrow \text{Products} \quad . \quad . \quad . \quad (21)$$

is given by

$$k = \chi . \frac{Q_{\ddagger}}{Q_1 . Q_{\mathrm{B}}} . \left(\frac{kT}{2\pi m^*} \right)^{1/2} . \frac{1}{\delta} \quad . \quad . \quad . \quad (22)$$

where χ is the transmission coefficient, Q the complete partition function for unit volume, m^* the effective mass of the complex along the co-ordinate of decomposition, and δ the arbitrarily chosen width of the top of the potential barrier which the complex traverses. The subscripts 1 and $\ddagger$ refer to the chemical species XH and the transition state, respectively. The partition functions are referred to a zero on the energy scale corresponding to the minimum in the potential-energy curve for the molecules XH and B, and the saddle point of the potential energy surface for the transition state TS.

The velocity constant of the same reaction involving the isotopic molecule XD

$$\mathrm{XD} + \mathrm{B} \longrightarrow \text{Products} \quad . \quad . \quad . \quad . \quad (21a)$$

is given by the analogous expression

$$k' = \chi' . \frac{Q'_{\ddagger}}{Q'_1 . Q_{\mathrm{B}}} . \left(\frac{kT}{2\pi m^{*\prime}} \right)^{1/2} . \frac{1}{\delta'} \quad . \quad . \quad . \quad (22a)$$

Taking δ and δ' to be equal, and assuming that $\chi = \chi'$, we can express the isotope effect on the reaction velocity [51] as

$$\frac{k'}{k} = \frac{Q'_{\ddagger} . Q_1}{Q_{\ddagger} . Q'_1} . \left(\frac{m^*}{m^{*\prime}} \right)^{1/2} \quad . \quad . \quad . \quad . \quad (23)$$

The ratio of partition functions occurring in equation (23) may be thought of as the equilibrium constant for the exchange reaction

$$\mathrm{TS} + \mathrm{XD} \rightleftharpoons \mathrm{TS}' + \mathrm{XH} \quad . \quad . \quad . \quad . \quad (24)$$

and it may be developed in the same way as equation (4) to give an expression analogous to (9), the only difference being a change of subscripts. The vibration frequency ν_{L} (of the transition state) which leads to decomposition is an imaginary number. Alternatively, the ratio of partition functions in equation (23) may be expressed in the form of equation (7).

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[50] S. Glasstone, K. J. Laidler, and H. Eyring, " The Theory of Rate Processes ", McGraw-Hill Book Co. Inc., New York, 1941, p. 187.

[51] J. Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675.

The latter form of presentation again separates the factor exp $(-\,\Delta E^0_\ddagger/\boldsymbol{k}T)$, where $\Delta E^0_\ddagger$ is the net difference in zero-point energy between the two sides of equation (24). The same conclusions hold, regarding the relative importance of the various factors involved in these expressions, as were reached regarding the analogous ones on p. 55 *et seq.* The importance of the difference in zero-point energies on the isotopic rate ratio was first pointed out by Polanyi.[52]

The effective mass m^* appearing in equations (22) is the reduced mass for the mode of vibration leading to decomposition.[53] For most reactions involving the detachment of hydrogen or the transfer of hydrogen from one heavy molecule to another, the value of the ratio $m^*/m^{*\prime}$ is expected to be very close to the ratio of the masses of the isotopic atoms.

Equation (23), which expresses the isotope effect on reaction velocity, must be modified to allow for the possible occurrence of quantum-mechanical tunnelling through the potential barrier. In the first approximation this can be formally achieved [54] by multiplying the right-hand side by the factor,

$$\left[1-\frac{(\boldsymbol{h}\nu_{\mathrm{L}})^2}{24(\boldsymbol{k}T)^2}\right]\Big/\left[1-\frac{(\boldsymbol{h}\nu_{\mathrm{L}})^2}{(24\boldsymbol{k}T)^2}\right]$$

Calculations based on hypothetical energy barriers have been held to indicate that appreciable tunnelling should occur for protium, particularly at temperatures below 0°.[55] A number of investigations [56] have attempted to discover its experimental manifestations, so far without success.

Assuming the tunnel effect to be negligible at the temperatures considered, and remembering that $[1-\exp(-\,u)]/\exp(-\,u/2) = -\,2\sinh u/2$, we may combine equations (9) and (23) to obtain

$$\frac{k'}{k}=\left(\frac{m^*}{m^{*\prime}}\right)^{1/2}\cdot\frac{\sigma'_1\,.\,\sigma_\ddagger}{\sigma_1\,.\,\sigma'_\ddagger}\cdot\frac{\prod\limits_i u_{i1}\,u'_{i\ddagger}\sinh(\tfrac{1}{2}u'_{i1})\sinh(\tfrac{1}{2}u_{i\ddagger})}{\prod\limits_i u'_{i1}\,u_{i\ddagger}\sinh(\tfrac{1}{2}u_{i1})\sinh(\tfrac{1}{2}u'_{i\ddagger})}\quad . \qquad . \quad (25)$$

This expression relates to the gas phase and should be multiplied by the factor $p^{0\prime}_1 p^0_\ddagger/p^0_1 p^{0\prime}_\ddagger$ [cf. equation (12)] for reactions in solution. This correction is probably unimportant and certainly impossible to apply in practice.

As a theoretical expression, equation (25) is much less useful than equation (9), since the former involves the vibration frequencies of the transition state which are not experimentally accessible and therefore must be obtained from calculations based on an assumed model for the transition state.[57, 58] (In the case of the heavy elements the term involving the

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[52] M. Polanyi, *Nature*, 1934, **133,** 26.

[53] N. B. Slater, *Proc. Roy. Soc.*, 1948, *A*, **194,** 113.

[54] E. P. Wigner, *Z. physikal. Chem.*, 1932, *B*, **19,** 203.

[55] R. P. Bell, " Acid–Base Catalysis ", Oxford, 1941.

[56] *E.g.*, E. F. Caldin and J. C. Trickett, *Trans. Faraday Soc.*, 1953, **49,** 772.

[57] J. Bigeleisen, *J. Phys. Chem.*, 1952, **56,** 823.

[58] H. Eyring and F. Wm. Cagle, *ibid.*, p. 889.

frequencies is less important than the ratio of the reduced masses,[57] but this is not the case for hydrogen-transfer reactions.)

However, certain deductions from equation (25) are straightforward. For instance, it would seem to be reasonable to assume that the hydrogen atom which is being detached or transferred in a reaction will be less tightly bound in the transition state than in the reactant molecule, and therefore the vibrations involving its movement will have lower force constants in the transition state than in the reactant molecule. If this is the case it can readily be shown [51] that k'/k will be less than unity, *i.e.*, that the reaction velocity involving the breaking of a bond to hydrogen will be smaller the heavier the isotope concerned. This result is familiar and has been used to decide whether or not the detachment of hydrogen enters into the rate-determining step of a reaction.[59–64] On the other hand it has been suggested [65] that in certain circumstances the transferred hydrogen atom or ion may become more tightly bound in the transition state. There do not appear to be any undisputed examples of this phenomenon on record,[66] except for reactions involving the attachment of a free hydrogen atom which will become more strongly bound in the transition state.[67]

Equation (25) also leads to a minimum value for the ratio k'/k for particular reactions for the different pairs of hydrogen isotopes, provided the tunnel effect is absent. This value is obtained by calculating k'/k for the model of the transition state in which the hydrogen atom (or ion) is completely free. There will therefore be no isotope effect on any of the frequencies of the transition state and k'/k involves, in addition to the ratio of the effective masses $m^*/m^{*\prime}$, only the frequencies of the normal molecules. Minimum values for k'/k (for deuterium/protium) calculated on this basis lie in the approximate range 0·05—0·1, depending on the molecule concerned. The reported experimental values for k'/k are in the range 0·1—0·5 for deuteron- compared to proton-transfer reactions, and therefore compatible with the calculated minimum value. The difference indicates that the chosen model is very imperfect and that there is appreciable bonding of hydrogen in the transition state. An exact value of the ratio k'/k may therefore be expected to depend not only on the nature of XH but also on the nature of B. These factors have never been satisfactorily analysed.[16b] [It will be appreciated that reactions (21) and (21*a*) are not

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[59] F. H. Westheimer and N. Nicolaides, *J. Amer. Chem. Soc.*, 1949, **71**, 25 ; M. Cohen and F. H. Westheimer, *ibid.*, 1952, **74**, 4387.

[60] V. J. Shiner, *ibid.*, p. 5285 ; 1953, **75**, 2925.

[61] L. Melander, *Arkiv Kemi*, 1950, **2**, 211 ; T. G. Bonner, F. Bowyer, and G. Williams, *J.*, 1953, 2650 ; W. M. Lauer and W. E. Noland, *J. Amer. Chem. Soc.*, 1953, **75**, 3689.

[62] U. Berglund-Larsson and L. Melander, *Arkiv Kemi*, 1953, **6**, 219.

[63] D. Bryce-Smith, V. Gold, and D. P. N. Satchell, *J.*, 1954, 2743.

[64] H. Zollinger, *Experientia*, 1954, **10**, 481.

[65] P. D. Bartlett and F. A. Tate, *J. Amer. Chem. Soc.*, 1953, **75**, 91.

[66] L. Kaplan and K. E. Wilzbach, *ibid.*, 1952, **74**, 6152 ; cf. H. Gilman, G. E. Dunn, and G. S. Hammond, *ibid.*, 1951, **73**, 4499.

[67] H. I. Schiff and E. W. R. Steacie, *Canadian J. Chem.*, 1951, **29**, 1.

by themselves exchange reactions, but can play a part in the establishment of an exchange equilibrium.]

For reactions in solution other factors sometimes have an influence on the isotope rate ratio.

First, isotopically different molecules may possess different solvent properties. The velocity of a given reaction may therefore change as the isotopic composition of the medium is altered. For instance, the change of solvent from H_2O to D_2O reduces the catalytic rate constant for the bromination of nitromethane by one-fifth.[68] Consequently, if an exchange reaction involves the solvent species and produces an appreciable change in its isotopic composition, the kinetics may be complicated. Secondly, isotopic solvent molecules may have appreciably different strengths as acids or bases,[69] and therefore if a reaction contains as one of its steps an equilibrium between one reactant and a solvent molecule, there will be present another type of isotopic medium effect. The combined operation of these effects has been found to cause the rate constant to *increase* by 30—40%.[70]

Even when the relative concentrations of solute and solvent are such that there is no appreciable change in the isotopic solvent composition, it is still true that the velocity measurements are valid only for a particular composition. Consequently, some of the earlier work on exchange kinetics using D_2O–H_2O mixtures does not readily lend itself to quantitative interpretation, and all attempts to measure isotopic rate ratios are liable to meet with complicating factors of this kind.

For the heavy elements which show no isotopic rate or medium effects the establishment of the exchange equilibrium must be a first-order process irrespective of the mechanism involved.[71] For hydrogen exchange a complete treatment would be complicated. It has, however, been shown [72] that the reaction will still be of first order provided that there is no isotopic medium effect and that one isotope is in great excess. These conditions will, in fact, always be satisfied in the case of exchange reactions involving tritium because of the micro-chemical occurrence of this isotope. They can also be made to apply for deuterium exchanges if a small concentration of isotopically different solute is dissolved in an isotopically pure solvent or if a solvent containing only a small proportion of deuterium is used with a light solute.[31b] The most economical method and, at the same time, that yielding data most useful for comparative purposes, is to dissolve a partially deuterated solute in an excess of light solvent. The first-order law may be given in the form

$$\ln (F_0/F) = \lambda t \quad . \quad . \quad . \quad . \quad . \quad (26)$$

where λ is the rate constant for the exchange and F_0 and F are the fractional

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[68] O. Reitz, *Z. physikal. Chem.*, 1936, *A*, **176**, 363.

[69] R. P. Bell, *op. cit.*, p. 145.

[70] S. H. Maron and V. K. La Mer, *J. Amer. Chem. Soc.*, 1938, **60**, 2588.

[71] H. A. C. McKay, *Nature*, 1938, **142**, 997.

[72] G. M. Harris, *Trans. Faraday Soc.*, 1951, **47**, 716; L. Melander, *Arkiv Kemi*, 1954, **7**, 287.

abundances {*i.e.*, $[XD]/([XH] + [XD])$} initially, and after a time t, respectively, of distinguishable isotope in one of the reactants (the solute).

Classification of Reaction Mechanisms

The replacement of one isotope by another is the simplest substitution process, and thus the three familiar mechanisms (electrophilic, nucleophilic, and homolytic) are conceivable. They correspond respectively to the cases when the expelled hydrogen atom leaves the molecule without electrons, with two, or with one. The electrophilic mechanism is expected to be by far the most common mode of reaction in hydroxylic solvents.

Exchange reactions which take place through the transfer of larger molecular fragments (such as methyl or hydroxyl groups) from one molecule to another are not included in the following discussion. These exchanges do not involve hydrogen substitution reactions and their occurrence can be established through isotopic labelling of another atom of the migrating group.

Substitution processes can, in general, be imagined to proceed in one or two steps. These alternatives are set out in the simplest terms below (electric charges being omitted):

(i) One-step (synchronous mechanism):

$$R' + SR \longrightarrow \overset{\text{transition state}}{R'\cdots S\cdots R} \longrightarrow R'S + R$$

(ii) Two-step (additive mechanism):

$$R' + SR \rightleftharpoons R'SR \longrightarrow R'S + R$$

(iii) Two-step (dissociative mechanism):

$$R' + SR \rightleftharpoons R' + S + R \longrightarrow R'S + R$$

Each of these alternatives is, in theory, possible for electrophilic, nucleophilic, and homolytic replacements.

Electrophilic Mechanisms

In these mechanisms exchange is initiated by the separation from or addition to the substrate of hydrogen in the form of a positive ion. These steps are also those involved in acid–base catalysis and, for this reason, the two subjects are intimately connected. Isotope studies have, therefore, frequently been used to elucidate the mechanisms of this catalysis.[55]

Dissociative Mechanism.—When the exchange of a solute XD is effected under the influence of a single acid–base pair A,B which is itself in rapid isotopic equilibrium with the solvent, the reaction can be represented by the equations

$$\left.\begin{array}{lll} XD + B \underset{k'_-}{\overset{k'_+}{\rightleftharpoons}} X^- + A' & & \text{(i)} \\ X^- + A \underset{k_+}{\overset{k_-}{\rightleftharpoons}} XH + B & & \text{(ii)} \end{array}\right\} \quad . \quad . \quad . \quad (27)$$

where the isotopically different acids A and A′ are related to the base B by the Brönsted definition $B + H^+ = A$ and $B + D^+ = A'$. We shall, throughout this section, formulate the exchange as loss of deuterium from the solute XD to a light solvent which is isotopically pure, since, as previously mentioned, the kinetic laws assume a simple form under these conditions. For the case of slight dissociation into X^-, it can readily be shown that, for the example considered, λ (as defined by equation 26) is given by

$$\lambda = k'_+[\mathrm{B}] \quad . \quad . \quad . \quad . \quad . \quad (28)$$

i.e., by the rate constant for deuteron loss in a light solvent. This mechanism of exchange is possible for all potentially acidic substrates.

If we now consider the ionisation equilibrium between XD and X^- in a medium in which the concentrations of A′ and B are such that they are not appreciably altered by the introduction of the solute, then the first-order rate of attainment of the equilibrium is governed by the rate constant $(k'_+[\mathrm{B}] + k'_-[\mathrm{A}'])$ or $k'_+([\mathrm{B}] + [\mathrm{A}']/K)$, where K is the equilibrium constant k'_+/k'_-. Considering the case when K is small, $k'_+([\mathrm{B}] + [\mathrm{A}]/K) \simeq k'_+[\mathrm{A}']/K$. In these expressions the value of k'_+ will probably be different from its value in equation (27) (i), since in that case we considered a pure light solvent. This solvent change would not, however, be expected to cause the two values to differ by more than an order of magnitude (cf. p. 64). Therefore the rate of establishment of the ionisation equilibrium will be faster than the exchange rate by a factor of about $[\mathrm{A}]'/[\mathrm{B}]K$. It is possible that all ionisation equilibria of this type involving O–H bonds are attained extremely rapidly [73] (half-life $\leqslant 10^{-4}$ sec.), so that it will only be possible to measure the rate of exchange if $[\mathrm{A}']/[\mathrm{B}]K$ is very large indeed. This circumstance, together with the possibility of a rapid exchange by an additive mechanism when $[\mathrm{A}']/[\mathrm{B}]$ is made very large, as in acid solution, may explain why O–H bonds have, up till now, always yielded virtually instantaneous reactions. However, in the absence of kinetic measurements such conclusions are only speculative and it is likely that such reactions proceed largely by a rapid synchronous process (see p. 68).

On the other hand, measurable exchange rates have been found for C–H bonds and for hydrogen attached to a nitrogen atom which has no free lone-pair of electrons, as in the ammonium ion and the metal ammines. The rates of these $\overset{+}{\mathrm{N}}$–H bond exchanges have been found to decrease with acidity as the proposed mechanism requires. (There being no available position for the direct attachment of a positive hydrogen ion the occurrence of the associative mechanism under the influence of an acidic species is not possible.)

The occurrence of the dissociative mechanism for certain (" active ") C–H bonds has been demonstrated by the identity of the rates of exchange and racemisation (*i.e.*, formation of the flat anion in which optical activity is lost) for the ketone Ph·CO·CHMeEt in an excess of alkaline dioxan–D_2O mixture as solvent.[38, 74] It has further been shown in a number of cases

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[73] R. P. Bell and R. G. Pearson, *J.*, 1953, 3443.

[74] S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J.*, 1938, 78; see also C. K. Ingold, E. de Salas, and C. L. Wilson, *J.*, 1936, 1328; D. J. G. Ives and G. C. Wilks, *J.*, 1938, 1455.

that the rates of bromination and racemisation of these compounds are identical and also equal to the rate of ionisation. A detailed investigation of the exchange kinetics of these compounds, including the influence of structural changes on the velocity, has therefore never been carried out, as the same information can be derived [75, 76] from studies of the kinetics of other reactions, such as halogenation. Besides the C–H bonds adjacent to carbonyl groups (as in carboxylic acids, ketones, esters, etc.) the α-hydrogen atoms in nitroparaffins,[77] nitriles,[74] azoethane,[78] and the hydrogen atoms of *s*-trinitrobenzene,[79] trichloroethylene,[80] acetylene,[81] etc., undergo exchange in alkaline hydroxylic media by what are thought to be dissociative mechanisms. The exchange reactions of hydrogen [12b, 32] and of aromatic and olefinic ring compounds in liquid ammonia in the presence of potassium amide [12a] are further possible instances of this mechanism.

In the formulation of this mechanism (equation 27) only a single acid–base pair was considered. As in the analogous case of general base catalysis we must, even for the simplest solutions, consider the possibility that the velocity of deuteron abstraction is made up of a sum of terms corresponding to reactions between XD and all the basic species in the solvent. Equation (28) must, therefore, be generalised, to give

$$\lambda = \sum k'^{\mathrm{B}}_{+}[\mathrm{B}] \quad . \quad . \quad . \quad . \quad . \quad (29)$$

the individual terms of which may, in principle, be found by suitable experiments with buffer mixtures, as in the study of general base catalysis. An example of this is the recent study of the exchange of $CDCl_3$ with H_2O.[82]

Additive Mechanism.—When hydrogen is attached to a basic atom there is the possibility of exchange in the presence of any species capable of acting as an acid. The definitions of equation (27) being used, the reactions are

$$\left.\begin{array}{lcll} \mathrm{XD} + \mathrm{A} & \underset{k_{-}}{\overset{k_{+}}{\rightleftharpoons}} & \mathrm{XDH}^{+} + \mathrm{B} & \text{(i)} \\ \mathrm{XDH}^{+} + \mathrm{B} & \underset{k'_{+}}{\overset{k'_{-}}{\rightleftharpoons}} & \mathrm{XH} + \mathrm{A}' & \text{(ii)} \end{array}\right\} \quad . \quad . \quad . \quad (30)$$

This provides a route for the exchange of amines and hydroxyl compounds in the presence of Brönsted acids but, as mentioned earlier, these reactions are always too rapid for a kinetic study of reaction mechanism. The expected rate equation, derived on the same assumptions as equation (28), is

$$\lambda = k_{+}[\mathrm{A}].k'_{-}/(k_{-} + k'_{-}) = \phi k_{+}[\mathrm{A}] \quad . \quad . \quad . \quad (31)$$

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[75] R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176,** 88 ; R. P. Bell, *Trans. Faraday Soc.*, 1943, **39,** 253.

[76] K. F. Bonhoeffer, K. H. Geib, and O. Reitz, *J. Chem. Phys.*, 1939, **7,** 664.

[77] O. Reitz, *Z. Elektrochem.*, 1936, **42,** 582.

[78] G. L. Curran and D. Rittenberg, *J. Biol. Chem.*, 1951, **190,** 17.

[79] M. S. Kharasch, W. G. Brown, and J. McNab, *J. Org. Chem.*, 1937, **2,** 36.

[80] L. C. Leitch and H. J. Bernstein, *Canadian J. Res.*, 1950, **28,** *B*, 35.

[81] L. H. Reyerson, *J. Amer. Chem. Soc.*, 1935, **57,** 779 ; L. H. Reyerson and B. Gillespie, *ibid.*, p. 2250.

[82] J. Hine, R. C. Peek, and B. D. Oakes, *ibid.*, 1954, **76,** 827.

In view of the discussion on p. 63, ϕ will be expected to have a value in the range 0·09—0·33. If more than one acid–base pair is considered, equation (31) becomes

$$\lambda = \sum k_{+}[\mathrm{A}]\cdot\frac{\sum k'^{\mathrm{B}}_{-}[\mathrm{B}]}{\sum k^{\mathrm{B}}_{-}[\mathrm{B}] + \sum k'^{\mathrm{B}}_{-}[\mathrm{B}]} \quad . \quad . \quad . \quad (32)$$

which reduces to

$$\lambda = \phi \sum k_{+}[\mathrm{A}] \quad . \quad . \quad . \quad . \quad (33)$$

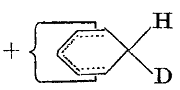
on making the assumption that

$$\frac{\sum k'^{\mathrm{B}}_{-}[\mathrm{B}]}{\sum k^{\mathrm{B}}_{-}[\mathrm{B}] + \sum k'^{\mathrm{B}}_{-}[\mathrm{B}]} = \frac{k'^{\mathrm{B}_1}_{-}[\mathrm{B}_1]}{k^{\mathrm{B}_1}_{-}[\mathrm{B}_1] + k'^{\mathrm{B}_1}_{-}[\mathrm{B}_1]} = \frac{k'^{\mathrm{B}_2}_{-}[\mathrm{B}_2]}{k^{\mathrm{B}_2}_{-}[\mathrm{B}_2] + k'^{\mathrm{B}_2}_{-}[\mathrm{B}_2]} = \ldots = \phi$$

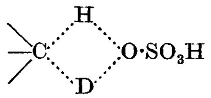
General acid catalysis has been found for the exchange of phosphine with water.[31b]

The slow exchange of the hydrogen atom at the 9-position in anthracene [83] has been interpreted as being an example of the additive mechanism, in line with the suggestion that anthracene exhibits feeble basicity at that position.[84] Thus, it appears that the rate constant for the addition of a proton to a conjugated hydrocarbon system is sufficiently small for the reaction to be measurable.

It has been shown [61] that certain electrophilic aromatic substitution reactions (*viz.*, halogenation and nitration) are initiated by the attachment of a cation to the aromatic ring, the loss of the replaced proton being a subsequent and kinetically insignificant process. Hydrogen-isotope exchange between aromatic C–H bonds and acids is known to be an electrophilic substitution reaction, both from the relative effectiveness of different substituting reagents and from the effect of substituent groups in the ring upon ease and position of substitution of the entering hydrogen isotope.[85] If the mechanism of this reaction is analogous to the mechanisms at present accepted for nitration and halogenation [86] and involves the primary formation of the intermediate (I), then aromatic hydrogen-isotope exchanges are in fact examples of the additive mechanism.[25]



(I)



(II)

Synchronous Mechanism.—This mechanism was originally proposed to explain the exchange reaction between sulphuric acid and both aromatic

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[83] V. Gold and F. A. Long, *J. Amer. Chem. Soc.*, 1953, **75**, 4543.

[84] V. Gold and F. L. Tye, *J.*, 1952, 2172.

[85] (*a*) C. K. Ingold, C. G. Raisin, and C. L. Wilson, *J.*, 1936, 915, 1637 ; (*b*) A. P. Best and C. L. Wilson, *J.*, 1938, 28 ; (*c*) S. Olsson and L. Melander, *Acta Chem. Scand.*, 1954, **8**, 523.

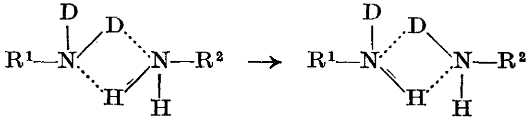
[86] C. K. Ingold, " Structure and Mechanism in Organic Chemistry ", Bell and Son, Ltd., London, 1953, p. 279.

and paraffinic hydrocarbons. The cyclic intermediate (II) was suggested [87] in accordance with the mechanism then accepted for substitution reactions of this type. The exchange reaction with paraffin has since been studied in greater detail and has received a somewhat different interpretation (see p. 71). For aromatic exchanges an alternative interpretation (p. 68) is at least a possibility.

Nevertheless, certain exchange reactions seem to be most easily explained in terms of this mechanism. In a recent investigation [18b] it was found that the exchange between deuterated ethylamine and *n*-heptylamine, which also acted as solvent, is immeasurably fast. In view of the very feeble acidity of aliphatic amines, it was expected that a two-step reaction

$$R^1ND_2 + R^2NH_2 \rightleftharpoons R^1NHD_2^+ + R^2NH^- \rightleftharpoons R^1NHD + R^2NHD$$

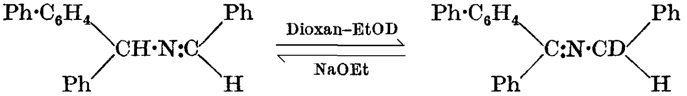
might be measurable. One possible interpretation of the result is that proton transfers over hydrogen bridges



are very rapid and provide an alternative one-step mechanism for the exchange. The same possibility exists for exchange between different hydroxyl compounds (see p. 66).

If this synchronous mechanism is the main path in the rapid exchange reactions between compounds capable of associating by hydrogen bridges, the behaviour of thiols—which are not associated like their hydroxyl analogues (cf. the relative volatility of water and hydrogen sulphide)—would not be expected to be comparable to that of hydroxyl compounds. A slow exchange between methanol and hydrogen sulphide [23] would therefore not be incompatible with the finding that methanol and water exchange rapidly and that hydrogen sulphide is a stronger acid than water, as it would be if a two-step mechanism involving hydrogen-ion transfer from hydrogen sulphide respectively, operated in each case.

Mechanisms for Prototropic Systems.—Prototropic isomerisations can occur by both associative and dissociative mechanisms involving intermediate mesomeric carbonium ions or carbanions which can respectively lose or add hydrogen ions at more than one position. Hence, exchange in these systems will occur at more than one site. A special type of synchronous mechanism is also possible. It involves simultaneous attachment and detachment of positive hydrogen ions at two different points of the conjugated chain. The occurrence of this mechanism (S_E2') for isotope exchange [38, 84] has been demonstrated [88] for the reaction



$$(Ph{\cdot}C_6H_4)(Ph)CH{\cdot}N{:}C(Ph)(H) \underset{NaOEt}{\overset{Dioxan-EtOD}{\rightleftharpoons}} (Ph{\cdot}C_6H_4)(Ph)C{:}N{\cdot}CD(Ph)(H)$$

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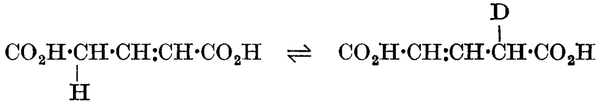
[87] C. K. Ingold, C. G. Raisin, and C. L. Wilson, *J.*, 1936, 1643.

in which it was found that the initial rates of deuterium uptake equalled the rates of racemisation and isomerisation. If an isomerisation of this kind regenerates the same molecule, as for the glutaconic acids,



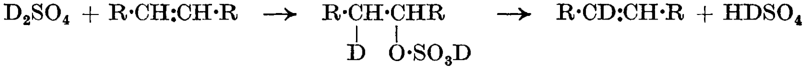
$$CO_2H\cdot\underset{H}{\underset{|}{C}}H\cdot CH{:}CH\cdot CO_2H \rightleftharpoons CO_2H\cdot CH{:}CH\cdot\overset{D}{\overset{|}{C}}H\cdot CO_2H$$

it provides a route for exchange without an accompanying chemical conversion.[89] The occurrence of isomerisation is demonstrated by the exchangeability of three hydrogen atoms besides those of the carboxyl groups.

Other Mechanisms

While most of the recorded examples of exchange reactions in the liquid phase without the intervention of heterogeneous catalysts are covered by the electrophilic mechanisms described above, a few special cases merit separate consideration.

Addition and Elimination across a Double Bond.—The exchange reaction between an unsaturated compound and an acid could conceivably occur by the steps [90]



$$D_2SO_4 + R\cdot CH{:}CH\cdot R \longrightarrow R\cdot\underset{D}{\underset{|}{C}}H\cdot\underset{O\cdot SO_3D}{\underset{|}{C}}HR \longrightarrow R\cdot CD{:}CH\cdot R + HDSO_4$$

This mechanism has been shown to be untenable for exchanges in aromatic systems. However, its occurrence for olefins cannot be entirely discounted,[16] although an additive electrophilic mechanism appears more attractive.

Homolytic Mechanisms.—Such mechanisms would be expected to be applicable to free-radical systems in which hydrogen-abstraction reactions occur in preference to dimerisation or substitution. A chain reaction of the type

$$\begin{array}{ll} \text{Initiation} & \quad XH \longrightarrow X\cdot \\ \text{Propagation} & \left\{\begin{array}{lcl} X\cdot + YD & \longrightarrow & XD + Y\cdot \\ Y\cdot + XH & \longrightarrow & YH + X\cdot \end{array}\right. \end{array}$$

would result in exchange between XH and YD. There are indications that such reactions occur between [*exocyclic*-$^2H_1$]-*p*-methylbenzyl radicals and [α-^2H]*p*-xylene, resulting in a random distribution of deuterium atoms.[91]

Enzyme Catalysis.—It has been shown that enzyme systems can influence the rate of exchange of a solute with water.[92] For instance, succinic

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[88] R. Perez Ossorio and E. D. Hughes, *J.*, 1952, 426; see also D. J. G. Ives and R. H. Kerlogue, *J.*, 1940, 1362.

[89] E. M. Evans, H. N. Rydon, and H. V. A. Briscoe, *J.*, 1939, 1673.

[90] M. Polanyi and J. Horiuchi, *Nature*, 1934, **134**, 847.

[91] J. I. G. Cadogan, V. Gold, and D. P. N. Satchell, *J.*, 1955, 561.

[92] (*a*) G. H. Bottomley, B. Cavanagh, and M. Polanyi, *Nature*, 1935, **136**, 103; (*b*) E. O. Weinmann, M. G. Morehouse, and R. J. Winzler, *J. Biol. Chem.*, 1947, **168**, 717.

dehydrogenase greatly accelerates the exchange of the aliphatic hydrogen atoms of succinic acid.[92b] This action is thought to be connected with the activity of the enzyme as a catalyst for the dehydrogenation.

Hydrogen Exchange of Saturated Hydrocarbons with Sulphuric Acid.—These exchange reactions [87, 93, 94, 95] have recently received considerable attention on account of the importance in the petroleum industry of the isomerisation reactions induced by acid catalysts. The main results of these two-phase experiments, as far as the exchange aspect is concerned, are : [95] (i) only paraffins possessing a tertiary carbon atom undergo exchange ; (ii) the minimum number of hydrogen atoms exchanged is equal to the number of hydrogen atoms attached to carbon atoms adjacent to the tertiary carbon ; (iii) exchange in other positions is the consequence of isomerisation reactions which result in the formation of a new tertiary carbon atom.

The observations are believed to be consistent with the following chain mechanism, *e.g.*, in the instance of *iso*butane :

$$\text{Initiation}\quad (CH_3)_3CH \xrightarrow{\text{Oxidation}} (CH_3)_3\overset{+}{C} \quad . \quad . \quad . \quad . \quad . \quad \text{(i)}$$

$$\text{Propagation}\begin{cases} (CH_3)_3\overset{+}{C} \xrightarrow{D_2SO_4} (CD_3)_3\overset{+}{C} \quad . \quad . \quad . \quad . & \text{(ii)} \\ (CD_3)_3\overset{+}{C} + (CH_3)_3CH \longrightarrow (CD_3)_3CH + (CH_3)_3\overset{+}{C} \quad . & \text{(iii)} \end{cases}$$

The reaction is thought to occur in solution in the sulphuric acid phase. It is found that the rate is increased by addition of *iso*butylene, which is converted into trimethylcarbonium ion by the uptake of a deuteron.

The detailed mechanism of step (ii) is puzzling. Otvos *et al.*[93] conclude, from the kinetic effect of added *iso*butylene, that deuteron uptake by this molecule is a relatively slow reaction and that the obvious mechanism for step (ii), *viz.*,

$$\begin{aligned} (CH_3)_3\overset{+}{C} + DSO_4^- &\longrightarrow (CH_3)_2C{:}CH_2 + HDSO_4 \\ (CH_3)_2C{:}CH_2 + D_2SO_4 &\longrightarrow (CH_3)_2\overset{+}{C}{\cdot}CH_2D + DSO_4^- \\ (CH_3)_2\overset{+}{C}{\cdot}CH_2D + DSO_4^- &\longrightarrow (CH_3)_2C{:}CHD + HDSO_4 \\ (CH_3)_2C{:}CHD + D_2SO_4 &\longrightarrow (CH_3)_2\overset{+}{C}{\cdot}CHD_2 + DSO_4^- \quad \text{etc.} \end{aligned}$$

is excluded for this reason, although it would provide an easy explanation of the restriction of exchange to the hydrogen atoms attached to carbon atoms adjacent to the tertiary carbon. Instead, they suggest that bimolecular synchronous electrophilic substitution by D^+ at a saturated carbon atom is exceptionally favourable under these conditions. This suggestion runs counter to the accepted principles regarding polar influences on substitution reactions, since the location of a positive pole on a carbon atom,

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[93] J. W. Otvos, D. P. Stevenson, C. D. Wagner, and O. Beeck, *J. Amer. Chem. Soc.*, 1951, **73,** 5741.

[94] T. D. Stewart and D. Harman, *ibid.*, 1946, **68,** 1135 ; R. L. Burwell and G. S. Gordon, *ibid.*, 1948, **70,** 3128 ; 1949, **71,** 2355.

[95] D. P. Stevenson, C. D. Wagner, O. Beeck, and J. W. Otvos, *ibid.*, 1952, **74,** 3269.

adjacent to the seat of electrophilic substitution would generally be expected to have a strong retarding influence on a bimolecular reaction. It seems that either the experimental or the theoretical aspect of this step requires reconsideration.

The step (iii) is a hydride-transfer reaction. In the present example it does not lead to exchange since under the particular experimental conditions all tertiary hydrogen atoms are light. If such a step occurs, it should be possible to observe hydrogen-isotope exchange (by virtue of hydride-ion transfer) between the tertiary hydrogen atoms of the two hydrocarbons $R^1{}_3CH$ and $R^2{}_3CD$ under the influence of concentrated sulphuric acid, *viz.*,

$$\begin{array}{lrcl}
\text{Initiation} & R^1{}_3CH & \longrightarrow & R^1{}_3\overset{+}{C} \\
\text{Propagation}\left\{\begin{array}{l} \\ \\ \end{array}\right. & \begin{array}{r} R^1{}_3\overset{+}{C} + R^2{}_3CD \\ R^2{}_3\overset{+}{C} + R^1{}_3CH \end{array} & \begin{array}{c} \longrightarrow \\ \longrightarrow \end{array} & \begin{array}{l} R^1{}_3CD + R^2{}_3\overset{+}{C} \\ R^2{}_3CH + R^1{}_3\overset{+}{C} \end{array}
\end{array}$$

but this has not yet been tested experimentally.