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Relative Strength of CH Acids

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The problem of the differentiating action of solvents on the relative strength of acids is examined from the point of view of the modern theory of acid-base equilibrium, according to which hydrocarbons and their derivatives behave under appropriate conditions as acids. Methods are described for determining the strength of such CH acids. The factors on which the differentiating effect of solvents depends are discussed. The most detailed consideration is given to the question—newly posed in the literature—of the possible causes of the change in the relative kinetic acidity of CH acids produced by solvents, which has been established by measuring the rate of the protophilic isotopic exchange of the hydrogen in them with bases. The bibliography contains 110 references.

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I. INTRODUCTION

The essential nature of acid–base reactions and acid–base catalysis was explained by Brønsted's theory[1-5], which not only summarised many phenomena occurring in aqueous and non-aqueous solutions and gave a quantitative description of these phenomena but was also able to make predictions. In the course of time, however, facts accumulated which indicated that the theory was limited and imprecise[6,7]. Thus the discovery of the differentiating action of solvents on the relative strengths of acids and bases contradicted the theory. The mechanism of protolytic processes was found to be more complicated than was postulated by the theory, and substances which according to it were aprotic, i.e. incapable of acting as either acids or bases, could take part in such processes. It became obvious that the theory of acids and bases must be reexamined and refined, by changing the actual definitions of concepts. According to the new definitions[3,8] a *base* is an electron-donor reagent, which possesses affinity for a proton; an *acid* is an electron-acceptor reagent, whose hydrogen takes part in an equilibrium reaction with a base. An

acid combines with a base by means of a hydrogen bond or donates a proton to it. All substances containing hydrogen can under appropriate conditions react as acids. These include all organic compounds, among which are hydrocarbons[8,9]. They are termed carbo-acids or *CH acids*, since the hydrogen is combined with a carbon atom. Our knowledge of hydrocarbons, as of acids and their conjugate bases (carbanions), has greatly increased during recent years[6,10,11], while proof of the acidic function of hydrocarbons has now very greatly extended the acidity scale, which now covers about fifty pK_a units.

New methods were required for the quantitative assessment of the acidity of hydrocarbons, and it was proposed[6,9,14] to supplement methods of determining the equilibrium ionisation constants of the hydrocarbons, i.e. their thermodynamic acidity[12,13], by determining the kinetic acidity of hydrocarbons and their derivatives by measuring the rate constants for the isotopic exchange of hydrogen with strong bases. This method was intended for establishing the strength of very weak CH acids, right down to saturated hydrocarbons, and had the advantage of enabling a quantitative estimate to be made of the acidity of individual carbon–hydrogen bonds in organic molecules[15,16].

A prerequisite for use of the kinetic method to measure the acidities of organic substances is correlation between the rate constants and the ionisation constants of the acids. Correlation of this type was first expressed in the form of Brønsted's relation[17] (in logarithmic form $\lg k = \alpha \lg K + G$, where k is the rate constant, K is the equilibrium constant, and α and G are constants). The Brønsted relation is the prototype of the Hammett equation and its modifications. The physical meaning of all these equations reduces to a statement of the principle of the linearity of free energies[18-21].

An important conclusion of Brønsted's quantitative theory of acid–base equilibrium is that the relative strength of equally charged acids is independent of the solvent (S or M): i.e. $\lg (K_i/K_0)_S - \lg (K_i/K_0)_M$ is constant (where K_i is the ionisation constant of any acid and K_0 that of the standard acid). If values of $\Delta pK = pK_0 - pK_i$ in any two solvents are plotted along the coordinate axes, the points should lie on a common straight line passing through the origin at an angle of 45° to the horizontal axis. Actually, however, if the solvents differ in physical and chemical properties, the points for acids differing in structure lie on more than one straight line. This shows the differentiating effect of solvents on the relative strengths of acids as expressed by the value of ΔpK.

The present paper is concerned mainly with the differentiating action of solvents on the kinetic acidity of CH acids determined from the isotopic exchange of hydrogen. This question has been posed recently, and little work has yet been done on it. First it is necessary to consider briefly the factors on which depends the differentiating effect of solvents with respect to the strength of acids, and to indicate the methods which are available for determining the strengths of CH acids.

II. FACTORS DETERMINING THE DIFFERENTIATING EFFECTS OF SOLVENTS

1. Correlation of Thermodynamic and Kinetic Acidities

Arndt and Eistert[22] were the first to emphasise the necessity of introducing the concept of the proton lability of compounds, and to note that the dissociation constant K of an acid is by no means a simple function of the lability of the hydrogen it contains. In their opinion a parallelism between the dissociation constants of acids and the proton labilities of hydrogen in them, i.e. kinetic parameters, is possible only with compounds of similar structure. This was confirmed by Pearson and Dillon[23], who measured, from the rate of bromination, rates of ionisation in aqueous solution for a large number of CH acids containing one or more strongly polar groups (carbonyl, ethoxycarbonyl, nitrile, nitro, and sulpho). They compared the values of $\lg k$ and pK_a for the acids, the latter parameters being determined either by them or by other workers, e.g. potentiometrically or by some other method.

While a general correlation was observed between $\lg k$ and pK_a for a series of acids, large departures from it were found. The reasons for deviations from the Brønsted relation have been discussed in detail by Bell[5,24,25], Leffler, Grunwald[19,26,27], etc. The deviations are determined by the structure and the conditions of solvation of the initial substances, the transition states, and the reaction products. If the structure of the transition state on ionisation of the acid is close to the structure of its anion, the parameters tending to enhance the stability of the latter will stabilise also the transition state, and this should favour an increase both in the equilibrium constant and in the rate constant of ionisation; in this case correlation can be expected between $\lg k$ and pK_a.

Let us write the equation for the ionisation of CH acids by a base B in the form

$$\equiv C{-}H + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \equiv C^- + BH^+ \qquad (1)$$

where k_1 is the ionisation rate constant, k_{-1} is the rate constant of the reverse reaction (addition of the acid proton to the carbanion $\equiv C^-$), and $k_1/k_{-1} = K_a$ is the ionisation equilibrium constant.

Cram[10] notes that a linear correlation between rate constants and equilibrium constants of ionisation requires constancy of the rates of recombination of various carbanions with a proton having the same donor: in fact, if k_1 is constant, it follows that $k_1 = \text{const} \times K_a$.

2. Differentiating Action of Solvents on Thermodynamic Acidity

The reasons for the differentiating action of solvents on thermodynamic acidity have been discussed by Izmailov[7]. He shows that the dissociation of protolytes involves a series of equilibria—solvation of molecules and ions of the acids, ionic association—and deduces an equation for the dependence of the difference ΔpK_a between the dissociation constants of the acid in two solvents M and S on their properties, in particular their activities (a_M and a_S, the standard state being a vacuum), and on the energy of solvation of the molecules (A'_{mol}, A_{mol}) and the ions (A'_{ion}, A_{ion}) of the acid:

$$\Delta pK_a = \lg \frac{a_M}{a_S} + \lg \frac{K_{a(MH^+)}}{K_{a(SH^+)}} + \frac{\Sigma A'_{ion} - \Sigma A_{ion}}{2.3RT} - \frac{A'_{mol} - A_{mol}}{2.3RT} \qquad (2)$$

$K_{a(MH^+)}$ and $K_{a(SH^+)}$ being the thermodynamic acidities of the lyonium ions MH^+ and SH^+ respectively in M and S.

The first two terms in Eqn. (2) are the same independently of the structure of the acid. Hence the differentiating effect of solvents on the dissociation constants of acids depends on the relative solvation energies of the ions and molecules of the acid in the solvents. If the acids are similar in structure, the last two terms in Eqn. (2) differ

little in magnitude. This is not observed when acids differing in structure are compared in solvents of different types, and then a differentiating effect is observed.

Izmailov has also suggested that values of ΔpK_a should be measured by a method of single null activity coefficients γ_0, which represent the change in energy of a substance on passing from an infinitely dilute solution in any non-aqueous solvent to an infinitely dilute aqueous solution:

$$\Delta pK_a = 2 \lg \gamma_{0(ion)} - \lg \gamma_{0(mol)}. \quad (3)$$

The same equation has been deduced subsequently by Grunwald[28].

Differences in the energy of interaction of acid molecules differing in structure with solvents of different chemical types result from the formation of solvates differing in composition, stability, and polarity. According to Izmailov the solvates—not molecules of the acid itself—undergo ionisation. The differentiating action of solvents on the relative strengths of acids is due to differences in the solvation energy of ions and molecules by the solvent, differences in the solvation energy of the anions being especially important. This point was subsequently stressed also by Parker[29-31].

Equations (2) and (3) are thermodynamic in character, and do not reveal the nature of the forces responsible for solvation of the acid molecules and ions. Account must be taken[29] of the following parameters—proton affinity of the solvent molecule, its ability to form a hydrogen bond or other type of donor–acceptor interaction with the acid or with the anion, forces of electrostatic dipole–dipole and ion–dipole interaction, and also dispersion interaction between solvent molecules and acid anion—the last depending on the polarisability and the ionisation potentials of the solvent molecule and the anion, and on the radius of the latter. The electrostatic component of the solvation energy is a function of the dipole moments of acid and solvent molecules, the dielectric constant of the latter, and the ionic charge and radius (for further details see Refs. 7, 19, and 32–34).

3. Relative Rates of Steps and Transition-state Structures in Protophilic Isotopic Exchange of Hydrogen

Arndt and Eistert[22] pointed out that measurement of the rate of deuterium exchange could suitably be used for determining lability of hydrogen in organic compounds. They considered that signs of proton lability were absent with fluorene and triphenylmethane, for example, since these compounds exhibited no isotopic exchange of hydrogen with deuterioalcohol.

A kinetic method for the quantitative determination of the acid and basic properties of hydrocarbons follows from the concept of the protolytic nature of heterolytic isotopic exchange, in which hydrocarbons take part as acids or bases[35]. This idea arose and was justified during investigation of the isotopic exchange of hydrogen in hydrocarbons with non-aqueous solvents which are strong bases or acids[6].

In 1950 Shatenshtein and Vyrskii[14] proposed the use of liquid ammonia for determining the kinetic acidity of hydrocarbons. Because of the protophilic nature of ammonia and the high proton affinity of the amide ion, which catalyses exchange reactions in liquid ammonia, hydrogen can be exchanged for its isotopes even in saturated hydrocarbons, which are then reacting as very weak CH acids. This placed the kinetic method for determining the acidity of hydrocarbons on a practical course, and led to many analogous investigations in the USSR and abroad (see e.g. Tupitsyn and Zatsepina[36-38], Streitwieser[11,39-43], Schriesheim[44], Ebel[45], etc.).

It follows from subsection 1 that a condition for the kinetic method of determining the strength of CH acids to be applicable is a linear relation between their ionisation rate and equilibrium constants. And this in turn presupposes a direct relation between the measured rate constant of isotopic exchange and the ionisation rate constant of the CH acid involved in the exchange reaction.

The problem of the relation between the experimental rate constant of hydrogen exchange and the rate constants of its individual stages is closely linked with that of the structure of the transition state in the rate-determining stage of the isotopic exchange of hydrogen. Information on these questions is obtained by measuring the deuterium–tritium kinetic isotope effect (k.i.e.), i.e. the ratio of the rate constants for the exchange of deuterium and tritium respectively present in the same bonds with a carbon atom (k_D/k_T). The k.i.e. of reactions involving the protophilic exchange of hydrogen isotopes were first determined by Yakushin[46-49] in a series of studies in the Isotopic Reactions Laboratory of the Karpov Institute.

In exchange reactions with liquid ammonia (in absence of a catalyst and catalysed by potassamide) and also with aliphatic amines (methylamine and ethylamine) the ratio $(k_D/k_T)_{0-25\,^\circ C}$ varied from 1.9 to 2.7 for different systems. Within these limits the ratio has a tendency to increase if the base becomes more protophilic or the reactivity of the CH acid increases.

Analysis of k.i.e. measurements combined with other data on protophilic substitutions of hydrogen (in particular on metallation reactions) has led to a two-stage mechanism[48,49]. The first stage consists in attack by the base B^- on the hydrogen atom combined with the carbon atom, the bond being stretched or in the limit ruptured with formation of the carbanion $\equiv C^-$:

$$\equiv C - D(T) + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \equiv C^- + D(T)B. \quad (4)\dagger$$

In the second stage a proton of the solvent molecule HB adds to the intermediate carbanion, to give a compound differing in isotopic composition:

$$\equiv C^- + HB \xrightarrow{k_2} \equiv CH + B^-. \quad (5)$$

The scheme does not include the gegenion (the metal cation), which is incorrect, since the gegenion can in principle be involved in the transition state.

If the bond with the hydrogen isotope is completely ruptured in the transition state, the k.i.e. value is calculated by means of the equation[50]

$$k_D/k_T = e^{N_0(h\nu_{C-D} - h\nu_{C-T})/2RT} \quad (6)$$

where k_D and k_T are the rate constants for exchange of protium by deuterium and by tritium, ν_{C-D} and ν_{C-T} are the C–D and C–T stretching frequencies, and $(k_D/k_T)_{25\,^\circ C} = 2.6$. If deformation vibrations are also perturbed, $(k_D/k_T)_{25^\circ C} = 3.2$.

It follows from theory[50-52] that maximum values of k.i.e. correspond to the case in which the reaction velocity is limited by the first stage (4), while its transition state has a linear three-centre structure $[C^{\delta-} \ldots D^{\delta+}(T) \ldots B^{\delta-}]^-$, the hydrogen isotope being located at the centre of symmetry

† The right-hand side of Eqn.(4) can also be written $\equiv C^- \ldots D(T)B$, to show that the carbanion is solvated, and then

$$\equiv C^- \ldots D(T)B \xrightarrow[HB]{k_2} \equiv CH + B^-$$

and the force constants of the C–D(T) and B–D(T) bonds being equivalent one to the other. According to Westheimer[51] disturbance of the symmetry of the linear three-centre transition state produces a decrease in k.i.e.

Bell[53] has shown that the degree of equivalence of the force constants of the bonds with the hydrogen atom in the transition state is measured by the difference in pK_a between the reactant CH acid and the conjugate acid of the reactant base. A symmetrical transition-state structure corresponds to $\Delta pK_a \simeq 0$; conversely, if ΔpK_a is large, the transition state is very unsymmetrical, and the ratio k_D/k_T differs little from unity.

The above experimental values of k_D/k_T, obtained from a study of exchange reactions with liquid ammonia and amines, are close to the theoretical maximum value. This enabled a two-stage mechanism to be considered, and the first stage of the reaction to be accepted as the limiting stage, while the transition state was almost symmetrical[46–49]. The results and the principal conclusions of this work[46–49] have been confirmed by Streitwieser[11,39–42], Tupitsyn[36–38], and Ebel and his coworkers[45].

For reactions occurring under steady-state conditions the concentration of the intermediate carbanion is constant, and the equation[10,36,54,55]

$$k = \frac{k_1 k_2}{k_{-1} + k_2} \qquad (7)$$

links the experimental rate constant of the exchange reaction k with the rate constants of the stages k_1, k_{-1}, and k_2.

Let us suppose that the rate of the exchange reaction is limited by ionisation of the C–D(T) bond, while the intermediate carbanion is relatively stable. If $k_2 \gg k_{-1}$, we can neglect k_{-1} in the denominator of Eqn. (7). Hence $k = k_1$: i.e. the observed rate constant of the exchange reaction is equal to the rate constant for ionisation of the C–D(T) bond. In such case measurement of the kinetics of hydrogen exchange (in particular with liquid ammonia or with amines) adequately characterises the acidity associated with the given bond.

Kinetic studies of the protophilic isotopic exchange of hydrogen in C–H bonds with dimethyl sulphoxide catalysed by an alkali-metal t-butoxide has shown[56] substantial differences in the relative kinetic acidities of certain CH acids compared with those found from measurements in solutions in ammonia. A similar phenomenon was noted by Streitwieser[57] on comparing his kinetic measurements on exchange reactions in cyclohexylamine with Schriesheim's measurements[44] in dimethyl sulphoxide (for fuller details see below). Deuterium–tritium exchange with dimethyl sulphoxide gave[56,58–60] a value of k_D/k_T close to unity.

For deuterium–tritium exchange involving the methyl group of toluene in the dimethyl sulphoxide–potassium t-butoxide system Jones[61] has explained the low k.i.e. on the basis of Bell's conclusions[53], considering that, since the difference in pK_a between toluene and t-butyl alcohol is large ($\Delta pK_a \simeq 20$), the ionisation stage corresponds to an extremely unsymmetrical transition state. In this state the proton is far closer to the base (B^-) than to the benzyl anion (A^-): i.e. $[A^{\delta-} \ldots H^{\delta+} B^{\delta-}]^-$.

Cram[10,54,62] had earlier observed a low value of k.i.e. for racemisation catalysed by a t-butoxide in dimethyl sulphoxide. In his opinion, supported by Streitwieser[57,63] and by Schriesheim[60], the reason for the low k.i.e. is that the rate of the exchange reaction is limited by a stage—the second one (Eqn. 5)—which is insensitive to isotopic replacement of hydrogen in the CH acid. Its low rate may be due to the fact that t-butyl alcohol formed in the first stage (Eqn. 4) slowly diffuses away from the carbanion, which is again able to capture a heavy isotope of hydrogen: i.e. $k_2 \ll k_{-1}$‡. In such case the term k_2 in the denominator of Eqn. (7) can be neglected, so that $k = k_1 k_2 / k_{-1} = K k_2$. Thus there is no direct relation between the rate constants of the exchange reaction and of ionisation. If Cram's treatment is correct, the low value of k.i.e. is an indication that measurements of the rate of the exchange reaction in the given medium do not give a correct idea of the strength of the CH acid. We shall return to the discussion of this question again.

III. DETERMINATION OF STRENGTH OF CH ACIDS

The acidity of hydrocarbons was first measured by Conant and Wheland[12], and the acidity scale was improved and extended by McEwen[13]. In these studies a colorimetric method was used to examine metallation equilibria in benzene or ethereal solution

$$RH + R'M \rightleftarrows R'H + RM \qquad (8)$$

where RH and R'H are hydrocarbons, while RM and R'M are their metal derivatives. With pK_a for one substance taken as standard (on McEwen's scale methanol has $pK_a = 16$), the difference in pK_a is determined. Thus the scale depends on the standard adopted. This work, undertaken in the 1930s, has been continued only recently by Streitwieser and his coworkers[64,65], who have measured the equilibrium constants between lithium or caesium cyclohexylamide and hydrocarbons (mainly fluorene derivatives) in cyclohexylamine, with phenylfluorene having $pK_a = 18.49$ taken as standard

Several papers, mainly by American workers[62,66–72], have reported the use of an indicator method of determining Hammett's acidity function[73] for measuring the pK_a of CH acids. The function H_- represents the ability of a base to detach a proton from an electrically neutral acid HA. By definition

$$H_- = \lg \frac{a_{H^+} f_{A^-}}{f_{HA}} = pK_a + \lg \frac{A^-}{HA} \qquad (9)$$

where a_{H^+} is the proton activity, f_{HA} and f_A are the activity coefficients of the acid and its anion, and HA and A^- are their concentrations. In dilute aqueous solution the H_- scale is identical with the usual pH scale, which is its virtue (papers on the acidity function H_- have been reviewed[74]).

The function H_- has been determined for many systems containing bases (e.g. mixtures of dimethyl sulphoxide with water or alcohol, in which tetra-alkylammonium hydroxides, caustic alkalis, or alkoxides are dissolved—for reviews of several systems see Refs. 74–76).

Kuhn and his coworkers[77–80] have successfully used spectrophotometric measurements combined with H_- data to determine the pK_a of strongly acidic polycyclic ethylenic and other hydrocarbons containing a large number of fused rings (e.g. trisbiphenylenylvinylmethane, $pK_a = 6.2$).

Ritchie[32,33] has recently been able to develop a technique for the potentiometric determination of pK_a for CH acids using a glass electrode in non-aqueous solvents, in particular in dimethyl sulphoxide, this method being suitable for the determination of high values of pK_a (~ 30).

Apart from the above, other methods have been suggested for assessing the equilibrium acidities of hydrocarbons, e.g. by estimating the relative stability of carbanions,

‡ It is assumed[63] that the return stage (k_{-1}) is especially rapid if conversion of the carbanion into the hydrocarbon involves only slight changes in structure.

including those of saturated hydrocarbons, by measuring equilibria in which organometallic compounds are involved. Thus Applequist[81] recommended study of an equilibrium of type

$$RX + R'M \rightleftarrows RM + R'X \qquad (10)$$

(where X = I and M = Li) coupled with equilibrium (8). Dessy[82,83] has shown that a similar stability sequence of the carbanions is obtained by studying a series of exchange equilibria between organomercury and organomagnesium compounds

$$RMg + R'Hg \rightleftarrows RHg + R'Mg\,. \qquad (11)$$

In this paper we are unable to give results obtained by different workers or discuss the reasons for differences in the values of pK_a for the same hydrocarbons obtained by different methods and especially in different solvents, where the differentiating effect of the medium is exhibited[11,18,32,33,65,68]. Discrepancies between the values of pK_a depend both on the method of determination and the standard adopted and on the properties of the solvent, especially on the structure of the CH acids, and even on the nature of the gegenion. Work done before 1965 has been surveyed comprehensively in Cram's book[55], which has been translated into Russian[10].

The suitability of the kinetic method for determining the acidity of hydrocarbons from the rate of isotopic exchange of hydrogen first received a theoretical basis[14] from the existence of a correlation between the logarithm of the rate constant of deuterium exchange with liquid ammonia (the first numeral in the parentheses is the rate constant) and the pK_a value for the same hydrocarbon determined by McEwen[13] (the second numeral in parentheses)—indene (0.4, 21), fluorene (0.02, 25), triphenylmethane (2×10^{-7}, 33), diphenylmethane (7×10^{-9}, 35)—and similar papers have appeared since then.

Dessy[84] has compared McEwen's results[13] with the exchange rate constants (in a dimethylformamide–deuterium oxide–triethylamine mixture) of cyclopentadiene (0.011, 14–15), acetophenone (2.2×10^{-4}, 19), phenylacetylene (6.6×10^{-5}, 21), and fluorene (2.2×10^{-6}, 25). Streitwieser[11,85] has shown a linear relation between the relative rate constant measured in methanol with sodium methoxide as catalyst and the pK_a value which he determined in cyclohexylamine: 9-phenylfluorene (47, 18.5), benzo[*c*]fluorene (26.3, 19.4), benzo[*a*]fluorene (7.6, 20), 4,5-methylenefluorene (1.93, 22.6), fluorene (1, 22.9), and benzo[*b*]fluorene (0.60, 23.2).

A rather more indirect comparison establishes[86] a linear relation between the kinetic acidities of 9-substituted fluorenes determined in methanolic solution (45°C) and the dissociation constants of acetic acids having the same substituents (CH_3, CH_3CH_2, $C_6H_5CH_2$, CH_3OCH_2, CF_3).

The good correlation between the thermodynamic and the kinetic acidities of hydrocarbons induced Cram (Ref. 10, p. 28) to try to set up a single acidity scale for hydrocarbons, based both on equilibrium and on kinetic measurements made by McEwen[13], Streitwieser[11], Applequist[81], and Dessy[84] (including Wooding and Higginson's data[87] for acetylene). This scale is named after the authors as the MSAD scale. Cram[10] stresses that "subsequent work will undoubtedly lead to modification of this scale".

Mention may be made also of comparisons between the results of polarographic measurements and data on the stability of carbanions obtained by an independent method. Streitwieser[88] notes that only limited application can be made of the polarographic reduction of benzyl chlorides and polycyclic arenemethyl chlorides for determining the stability of carbanions.

Dessy[83] used the polarographic reduction of organomercury compounds for this purpose. Reutov, Beletskaya, and their coworkers[89,90] proposed a polarographic scale of CH acidity based on the correlation

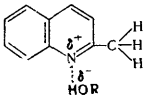
$$\alpha E_{1/2} = f(pK_a) \qquad (12)$$

where $E_{1/2}$ is the half-wave potential in the polarographic reduction of symmetrical organomercury compounds R_2Hg, α the electron transfer coefficient, and pK_a the ionisation equilibrium constant of the acid RH on the MSAD scale. Hence a correlation is observed between electrochemical kinetic data and the strengths of CH acids.

However, correlation is not always found between kinetic and thermodynamic values. The principal question in which we are interested in this paper is the differentiating effect on the relative kinetic acidity of CH acids determined by measuring the rates of isotopic exchange of hydrogen. Section II contains a general discussion of the factors which may govern the appearance of a differentiating effect.

We shall now show with actual examples that the change in the relative kinetic acidity can be caused both by specific solvation of the acids themselves, as a consequence of which the lability of the hydrogen varies, and by phenomena occurring during the reaction whose rate is used to measure the kinetic acidity.

For example, a comparison of the rates of isotopic exchange of hydrogen in certain hydrocarbons and nitrogen heterocycles with liquid ammonia and with alcohols showed[91] that the rate of exchange of hydrogen in a methyl group of the heterocycle is abnormally high in alcoholic solutions. Whereas the rate constant for the exchange of hydrogen in a methylene group in the hydrocarbon (indene, fluorene) with ammonia exceeds that with ethanol by factors of 10^7–10^8, hydrogen in the methyl group of quinaldine exchanges more rapidly with ethanol than with ammonia by a factor of 25. This is explained by specific solvation of the quinaldine molecule in alcoholic solution by formation of a hydrogen bond between the alcoholic hydroxyl and the nitrogen atom, which thus acquires a positive charge



Displacement of the electrons forming the methyl CH bonds towards the nitrogen facilitates protonation of these hydrogen atoms. The effect is stronger the more acidic the alcohol, and hence the higher the energy of the hydrogen bond: ethylene glycol (90, 547) > methanol (30, 50) > ethanol (20, 12) > propan-2-ol (7, 1) (the parentheses indicate the rate constants of the exchange reaction $10^7 k_{120°C}$ s^{-1} and the relative ionisation constants of the alcohol[92]).

An analogous differentiating effect is observed[93] on comparing the rates of deuterium exchange in the methyl group of quinaldine and in the methine group of triphenylmethane with ethylenediamine and aminoethanol. Owing to the more protophilic character of the former solvent, the hydrogen in triphenylmethane is exchanged five times as rapidly as in quinaldine, whereas with the latter solvent the hydrogen in quinaldine exchanges eight times as rapidly as in the hydrocarbon, because of the formation of a hydrogen bond between the alcoholic hydroxyl and the heterocyclic nitrogen atom.

In the above examples the differentiating action of the solvent on the kinetic acidity was due to the specific solvation in the ground state of molecules of CH acids distinguished from the others by their structure. Let us now

turn to examples which reveal the effect of catalytic systems in different solvents on kinetic acidities also determined by hydrogen exchange, where the differentiating effect depends on phenomena associated with the course of the reaction itself.

Mention has already been made (Section II, 3) of the very large differences in relative kinetic acidities which we have found[56] on comparing the kinetics of deuterium exchange with dimethyl sulphoxide (catalysed by potassium or lithium t-butoxide) and with liquid ammonia (catalysed by potassamide). Thus the rate constants for exchange with dimethyl sulphoxide of C–D bonds in the methyl group and in the ring of toluene were found to differ by factors of 10^6 instead of the 10^2 on exchange with ammonia[56].

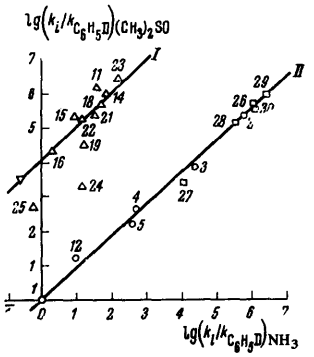
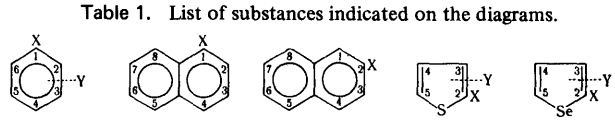


Figure 1. Comparison of kinetic acidities, determined in liquid ammonia with potassamide as catalyst, and in dimethyl sulphoxide with potassium t-butoxide as catalyst, for the exchange of deuterium in:
I) alkyl groups; II) the benzene ring and alkylthio-groups.

In Fig. 1[94] values of $\lg(k_i/k_{C_6H_5D})_{(CH_3)_2SO}$ are plotted against $\lg(k_i/k_{C_6H_5D})_{NH_3}$ for a series of CH acids (a key to the numbering of the compounds in Fig. 1 and the following diagrams will be found in Table 1). The points for the methyl groups in toluene, the xylene isomers, and the tolyl ethers (other than the *para*-isomers) and for the alkyl groups in alkylbenzenes lie on the straight line *I*, while those for benzene derivatives containing an *ortho*-deuterium atom are grouped about the straight line *II*. Points for alkylthio-groups attached to a benzene ring lie on the same line. The postulate that one reason for such a differentiating effect may be unequal conditions of solvation by the two solvents of transition states differing in structure is supported by the fact that the position of the deuterium atom in the toluene molecule, for example, does not affect the heat of solvation of the latter. Yet replacement of the solvent may have unequal effects on the heats of solvation of the transition states in the exchange of deuterium in the alkyl group and in the aromatic ring. Since the contribution of the heat of solvation of the transition state lowers the activation energy of the reaction *E*,[95] the unequal differences in the heats of solvation of the transition states by the two solvents will result in a differentiating action on the relative kinetic acidity of CH acids differing in structure. Tentative values of the activation parameters calculated from kinetic measurements (Ref. 6, p. 135) agree[96,97] in general with the above hypothesis.

The activation energies for exchange with ammonia catalysed by potassamide of hydrogen in the side-chain of alkylbenzenes (*14–16*)§ and in the ring of substituted benzene (*6–8*, *10*) have similar values of about 14.5–16.0 kcal mole^{-1}, and variations in the rates of the exchange reactions are associated with differences in the pre-exponential term. The activation energies for deuterium exchange in the dimethyl sulphoxide–potassium t-butoxide system are about 5–6 kcal mole^{-1} smaller for the substituents in alkylbenzenes than for the aromatic ring[94] (17.5–18.2 kcal mole^{-1} for compounds *14* and *15* compared with 23.0–24.5 kcal mole^{-1} for *3–5*)¶. Heats of solvation of benzene and toluene in dimethyl sulphoxide are the same within 0.25 kcal mole^{-1}.[99] On considering the origin of the differences in solvation energy of the transition states of deuterium exchange occurring in dimethyl sulphoxide and in ammonia, one is struck by the differing polarity of these solvents (Table 2, in which μ is the dipole moment and ϵ the dielectric constant). They differ also in their proton-donor properties, which are weakly developed in the CH bonds of dimethyl sulphoxide.

Table 1. List of substances indicated on the diagrams.



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

No.	Formula	X	Y	No.	Formula	X	Y
1	I	D	H	*24*	I	CD_3	4-CH_3O
2	I	D	2-F	*25*	I	CD_3	4-$N(CH_3)_2$
3	I	D	2-C_6H_5O	*26*	I	SCD_3	H
4	I	D	2-CH_3O	*27*	I	SCD_3CH_3	H
5	I	D	2-CH_3S	*28*	I	SCD_3	2-CH_3O
6	I	D	2-C_6H_5	*29*	I	SCD_3	3-CH_3O
7	I	D	3-C_6H_5	*30*	I	SCD_3	4-CH_3
8	I	D	4-C_6H_5	*31*	IV	D	H
9	I	D	2-CH_3	*32*	IV	D	3-CH_3
10	I	D	3-CH_3	*33*	IV	D	4-CH_3
11	I	D	4-CH_3	*34*	IV	D	5-CH_3
12	II	D	H	*35*	IV	D	4-CH_3S
13	III	D	H	*36*	V	D	H
14	I	CD_3	H	*37*	V	D	3-CH_3
15	I	CD_2CH_3	H	*38*	V	D	5-CH_3
16	I	$CD(CH_3)_2$	H	*39*	II	CD_3	H
17	I	CD_3	2-CH_3	*40*	II	CD_3	4-CH_3
18	I	CD_3	3-CH_3	*41*	II	CD_3	5-CH_3
19	I	CD_3	4-CH_3	*42*	II	CD_3	8-CH_3
20	I	CD_3	4-*i*-C_3H_7	*43*	III	CD_3	H
21	I	CD_3	3,5-$(CH_3)_2$	*44*	III	CD_3	3-CH_3
22	I	CD_3	2-CH_3O	*45*	III	CD_3	6-CH_3
23	I	CD_3	3-CH_3O	*46*	III	CD_3	7-CH_3

47—$(C_6H_5)_3CD_3$ *48*—$CH_3CH_2CH_2CH{=}CH_2$

The transition states for the ionisation of CH acids are similar in structure to the carbanions. The dipole moment of the solvent, the effective charge, and the polarisability of the ions have a substantial effect on the ion–dipole and dispersion interaction energies. Molecules of proton-donor solvents are capable of forming a hydrogen bond with

§ Here and subsequently italic numerals relate to the numbering of compounds in Table 1.

¶ Still, tentative data suggest that a decrease in activation energy by 3–4 kcal mole^{-1} for the exchange of hydrogen in the alkylthio-groups[98] of methyl phenyl sulphide and ethyl phenyl sulphide compared with data for the aromatic ring in benzene derivatives applies to exchange both with liquid ammonia and with dimethyl sulphoxide. Thus this phenomenon requires further investigation.

the carbanion. Dimethyl sulphoxide can interact with a carbanion, since its sulphur atom is positively charged. Consequently new possibilities of solvation of the transition state appear when the solvent is changed. Nevertheless, their realisation depends on the structural peculiarities of the carbanion, especially those producing a particular degree of localisation of the negative charge on the carbon atom[94] (cf. Ref. 30). On these principles it becomes understandable that a differentiating effect should be developed when the acidities of CH acids (carbanions) differing in structure are compared in solvents which differ markedly in polarity and in proton-donor and other properties.

Table 2. Kinetic isotope effects of hydrogen exchange and polar properties of solvents.

Solvent	Catalyst	Temp., °C	k_D/k_T	μ, D	$\epsilon_{25°C}$
NH_3	KNH_2	0	2.7*	1.46	16.9
$C_6H_{11}NH_2$	$C_6H_{11}NHLi$	50	2.7	1.32	4.5(22°)
$(CH_3)_3COH$	$(CH_3)_3COK$	50	1.9*	1.66	12.3**
$(CH_3)_2SO$	$(CH_3)_3COK$	25	1.2	4.3***	46***
$(CH_3OCH_2)_2P(O)CH_3$	$(CH_3)_3COK$	25	1.3	3.6***	24.2***

* Determined by F.S.Yakushin.
** Mixture of 70 vol.% of t-butyl alcohol and 30 vol.% of 2,5,8-trioxanonane (dielectric constant of mixture ~10).
*** Determined in Yu.Ya.Fialkov's laboratory.

Let us now compare the kinetic acidities of a series of CH acids determined in dimethyl sulphoxide and in a mixture of t-butyl alcohol and 2,5,8-trioxanonane (diglyme), with an alkali-metal t-butoxide as catalyst. When

$$\lg (k_i/k_{(C_6H_5)_2CD_2})_{(CH_3)_2SO}$$

is plotted against

$$\lg (k_i/k_{(C_6H_5)_2CD_2})_{t\text{-}C_4H_9OH}$$

(Fig. 2), the points for five-membered heterocycles—thiophen[58,100], selenophen[101], and some of their derivatives containing a 2-deuterium atom—lie on a straight line (*I*), whereas the points for mono- and di-methylnaphthalenes[102], in which alkyl groups take part in the exchange reaction, are located near the straight line *II*. (Differentiation between the positions of the points for α- and β-isomers begins to show.) A common feature of the graphs in Figs. 1 and 2 is that points representing the acidity of C–H bonds in aromatic or heteroaromatic rings lie on one straight line, whereas points obtained from deuterium-exchange kinetics for methyl groups attached to the aromatic ring are on a second straight line. Furthermore, t-butyl alcohol, like liquid ammonia, differs from dimethyl sulphoxide in polar and proton-donor properties. Ammonia and t-butyl alcohol belong to one group of solvents, while dimethyl sulphoxide belongs to another group among those listed in Table 2. Cyclohexylamine is akin to ammonia both in chemical properties and in its dipole moment.

No differentiating effect is apparent when relative kinetic acidities are compared in solvents belonging to the same group in Table 2. In fact, if values of $\lg (k_i/k_{C_6H_5D})$ in ammonia[6,15] are plotted against those in cyclohexylamine[11,40–42], fifteen points for aromatic compounds lie on the straight line passing through the origin at an angle of 45° to the horizontal axis, independently of whether the exchangeable deuterium atom is present in the benzene ring or in an alkyl group (Fig. 3). Only the points for *o*-deuteriobiphenyl (*6*) and for cumene containing a deuterium atom in the methine group (*16*) lie away from the straight line. This is probably due to steric hindrance, for the cyclohexylamide ion and the cyclohexylamine molecule are larger than the amide ion and the ammonia molecule. It is noteworthy that the enthalpies of activation $\Delta H^{\neq}$ of the catalytic exchange reactions of benzene and of the methyl group in toluene with cyclohexylamine (13 and 15 kcal $mole^{-1}$),[42] as of the catalytic exchange with ammonia, are similar in magnitude and also differ little from that for the exchange of benzene with ammonia (15 kcal $mole^{-1}$).[103]

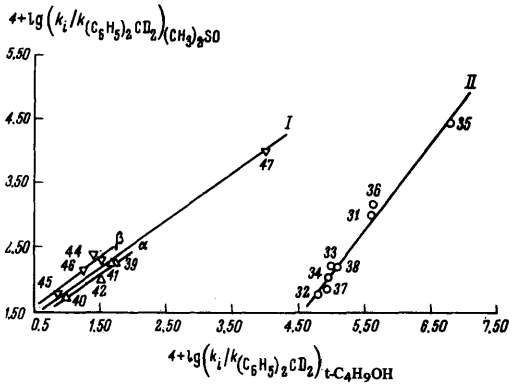


Figure 2. Comparison of kinetic acidities, determined in a mixture of t-butyl alcohol and 2,5,8-trioxanonane with potassium t-butoxide as catalyst, and in dimethyl sulphoxide with lithium butoxide as catalyst, for the exchange of deuterium in:
I) methyl groups; II) thiophen and selenophen rings.

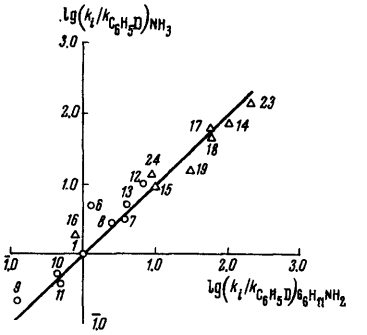


Figure 3. Comparison of kinetic acidities determined in cyclohexylamine with lithium cyclohexylamide as catlyst, and in liquid ammonia with potassamide as catalyst.

Fig. 4 compares the relative acidities $\lg (k_i/k_{C_6H_5CD_3})$ for a series of CH acids determined in catalytic systems with solvents—dimethyl sulphoxide[94] and methylbismethoxymethylphosphine oxide (medifos) $(CH_3OCH_2)_2PO.CH_3$ [104]—belonging to the second group in Table 2. In this case, too, the points for CH acids of different structural types, which in Fig. 1 are located on two straight lines, lie on one straight line. This also contains the point *24*, which in Fig. 1 occupied a position between the two straight lines.

The discussion and the facts lead to the conclusion that the differentiating action of the given solvents on the kinetic acidity of the CH acids listed in Table 1 depends on the structure and the solvation of the transition states formed during the protophilic isotopic exchange of hydrogen, at

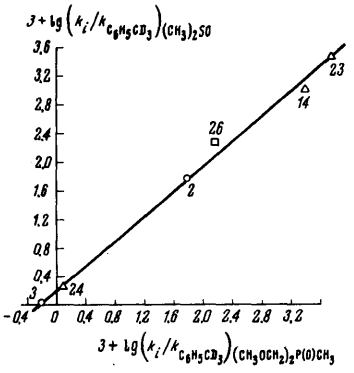


Figure 4. Comparison of kinetic acidities determined in methylbis-methoxymethylphosphine oxide and in dimethyl sulphoxide, with potassium t-butoxide as catalyst.

the ionisation stage of the CH acid. We shall not consider here the question of the structural features of the CH acids which predetermine the appearance of a differentiating effect in the catalytic systems assigned to different groups in Table 2.

Let us now consider the influence of solvents on the structure of the transition states and on the relative rates of the stages in the exchange reactions, which are shown in the k.i.e. value. Table 2 shows that the above division of solvents into two groups applies to a first approximation also to the ratios k_D/k_T, which have been determined[48,58,59] by measuring the rates of exchange of the heavy isotopes of hydrogen in the aliphatic bonds in toluene or diphenylmethane. Experiments with ammonia and cyclohexylamine have given k.i.e. values which are close to those calculated theoretically (Section II, 3). Hence it may be supposed that the stages of exchange reactions, the structure of the transition states, and their solvation are similar in these solvents, so that comparison of the relative kinetic acidities determined in them naturally reveals no differentiating effect, while measurements give a correct idea of the relative strength of the CH acids, since Brønsted's relation is observed. This is probably applicable also to the systems containing t-butyl alcohol which have been studied (Fig. 2), although this compound differs from ammonia and cyclohexylamine in its chemical properties, in that, being an OH acid, it is a stronger donor of protons. Differences in specific solvation are therefore possible, as we have seen, for example, in the solvation of heterocyclic molecules (p. 849). Alcohols readily solvate anions by hydrogen bonding.

Low k.i.e. values, close to unity, have been found[55,58-60] for exchange reactions in solvents belonging to the second group in Table 2 (dimethyl sulphoxide and methylbismethoxymethylphosphine oxide). As noted above (Section II, 3), there are two views (Jones[61] and Cram[10,54,62]) on the reason for the low k.i.e. in hydrogen exchange with dimethyl sulphoxide catalysed by an alkali-metal t-butoxide[59]. The former considers only the degree of symmetry of the transition state (within the framework of a linear three-centre model), whereas the latter view regards the second—not the first—stage in the exchange reaction as rate-determining.

With regard to the explanation put forward by Jones (cf. Ref. 59), account must undoubtedly be taken of the degree of symmetry of the transition states in reactions in which the C–H bond is broken. Actually, the transfer of a proton (deuteron) from 9-methylfluorene to the 5-methylphenanthren-4-yl carbanion[105] and from triphenylmethane to the dimsyl anion [anion derived from dimethyl sulphoxide][106] has k_H/k_D ratios of 4.2 and 4.7 respectively (or on conversion by means of Swain's equation[107] the k_D/k_T ratio is 1.9 and 2.0). The high k.i.e. value is consistent with the conclusion on the symmetry of the transition state, since, in conformity with Bell's principle, the difference in pK_a is close to zero (for the first reaction $\Delta pK_a = 19.7 - 20 \simeq 0$, whereas for the second reaction $\Delta pK_a = 29 - 33 = -4$[67,68,106]). For isotopic exchange between diphenylmethane and dimethyl sulphoxide catalysed by lithium t-butoxide, however, $(k_D/k_T)_{25°C} = 1.3 \pm 0.1$, although $\Delta pK_a = 30 - 28 = 2$,[67,68,106] and if the view of Jones is accepted, the higher k.i.e. value can be expected. It may be noted also that, for all the substances, differing in acidity, investigated by us[59], almost identical values of the ratio $(k_D/k_T)_{25°C}$ have been obtained (values indicated in parentheses): $\alpha(d)t$-diphenylmethane (1.3 ± 0.1), $2(d)t$-thiophen (1.3 ± 0.1), $2(d)t$-furan (1.5 ± 0.1), $(d)t$-methyl phenyl sulphide (1.2 ± 0.1), $\alpha(d)t$-toluene (1.2 ± 0.1), and o-$(d)t$-diphenyl ether (1.1 ± 0.1 measured at 50°C).

Nevertheless, a considerable k.i.e. ($k_H/k_D = 4.4$ at 55°C) is observed for the isomerisation of pent-1-ene catalysed by potassium t-butoxide in dimethyl sulphoxide[108], although on the MSAD scale (Ref. 10, p. 28) the values of pK_a for pentene and toluene are similar. In Schriesheim's opinion[108] proton transfer to the carbanion takes place intramolecularly in the isomerisation of an alkene, i.e. by a different mechanism from that operative in isotopic exchange.

The small kinetic effect observed in isotopic exchanges with dimethyl sulphoxide catalysed by alkali-metal t-butoxides is apparently due to some specific features of exchange reactions in these systems, as a consequence of which the rates of the reactions are limited at a stage which is unaffected by labelling the substance with heavy isotopes.

In this connection we note[59] that for the exchange reaction between the methylene groups in indene and fluorene, one of which is labelled with deuterium and tritium, the k_D/k_T ratio lies in the range 1.0–1.3. The reaction has been conducted[109] in ethylene glycol ethers, tetrahydrofuran, and dioxan with lithium t-butoxide as catalyst. The role of the solvent in the reaction is merely to solvate the cation and to polarise its bond with the anion: the solvent does not take part in the exchange reaction. The concentration of hydrocarbons in the solution is low, and the rate of the exchange reaction is probably limited at the stage of proton transfer from the C–H bond of the hydrocarbon to the carbanion, so that the k.i.e. is close to unity. We recall that solvents belonging to different groups in Table 2 differ in their proton-donor power. The first group, having high k.i.e., contains OH and NH acids, whereas the second group contains CH acids (dimethyl sulphoxide and the phosphine oxide), and it is for the latter solvents that the k.i.e. is small.

It must also be noted[59] that alkali-metal t-butoxides are strongly associated in ethereal solutions (this applies also to solutions in dimethyl sulphoxide, where the degree of association is lower[110]). It is possible that a two-stage scheme for the exchange reaction and a linear three-centre model for the transition state are unrealistic in the given case.

It must be borne in mind, of course, that the k.i.e. value in a given catalytic system may vary in some cases depending on the substance studied. Moreover, examples are known of a considerable change in k.i.e. for different bonds in the same substance undergoing exchange reactions in the same system[63].

Intensive research is now being conducted both on the theory of the kinetic isotope effect and on its determination in hydrogen exchanges occurring in different systems.

In Streitwieser's view[11,57] the differentiating effect observed on passing from cyclohexylamine to dimethyl sulphoxide is determined by the fact that in the latter solvent, depending on the structure of the carbanion, the ratio changes between the rate of diffusion from the carbanion of a molecule of the heavy alcohol formed from the alkoxide and the rate of return of the heavy hydrogen isotope from the alcohol to the carbanion. But different k.i.e. values can be expected for exchange reactions with dimethyl sulphoxide of those CH acids whose relative kinetic acidity changes unequally on change in the solvent (from cyclohexylamine or ammonia to dimethyl sulphoxide). However, the facts are not consistent with this conclusion, since practically identical values of k_D/k_T have been obtained[59] in dimethyl sulphoxide for several substances whose points lie on different straight lines in Fig. 1.

The discussion has shown that, if systems for which the k.i.e. values differ little from those calculated theoretically are used in determining kinetic acidity by the isotopic exchange of hydrogen, the measurements will be highly likely to give correct ideas of the relative strengths of CH acids (effects of specific solvation in the ground state of their molecules are disregarded). The applicability, for measurements of kinetic acidity, of systems in which the exchange reaction is characterised by a low k.i.e. is not such an unambiguous question. However, it would be wrong to conclude that catalytic systems such as those comprising dimethyl sulphoxide and an alkali-metal t-butoxide are completely unsuitable for such measurements[11,57]. Figs. 1 and 2 show that, within a group of structurally similar substances, a correlation has been established empirically between the relative acidities in systems belonging to different groups in Table 2†. However, there are deviations due to structural causes, e.g. for substances which contain, together with a *para*-methyl group, an electron-donor substituent (methyl, methoxyl, dimethylamino).

The results reported in this paper indicate that, in the present state of our knowledge, the problem of determining not only kinetic but also thermodynamic acidity is quite complicated owing to the variety of types of interaction between substances and solvents, as well as catalysts, in ground and transition states. Therefore the appearance of differentiating effects can by no means always be foreseen. This applies especially to the least studied, CH acids. Further, intensive research is required in this important field of theoretical organic chemistry, especially as the generalisations made will be extremely useful also for synthetic organic chemistry.

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