

A Critical Examination of the Assumptions Inherent in the Treatment of Experimental Data from Dissociative Base-catalyzed H—D Exchange

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The assumptions inherent in the equations used to treat experimental data from studies of dissociative base-catalyzed *H—D* exchange are examined in detail. Observed rate constants evaluated from the slopes of log-time plots of primary data depend on the magnitudes of isotope effects and initial concentrations in a manner that may lead to discrepancies between independent studies. Obvious sources of curvature in such plots, including secondary isotope effects, are treated quantitatively.

The study of the rate at which a substrate incorporates deuterium or protium from its surroundings has become a common method of attempting to assess the effect of structural changes on the shape of the potential energy surface for the reaction in the neighbourhood of the transition state.¹⁻¹⁶ This development is in part due to the ease that NMR- and mass-spectroscopy afford in the determination of the degree of isotopic exchange at any point in time. However, this appears to have led to a certain indiscriminateness for lack of appreciation of the underlying kinetic theory of isotopic exchange reactions.

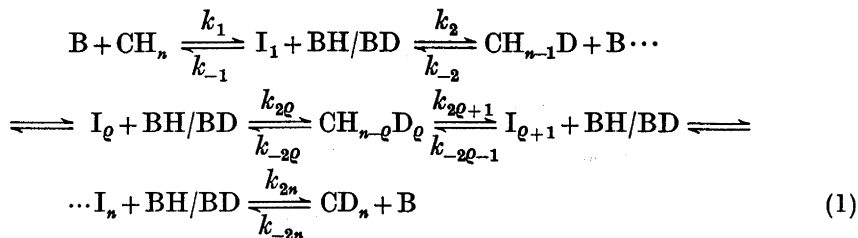
The purpose of this paper is to examine in detail the aspects of the underlying kinetic theory of dissociative H—D exchange which may have some relevance to discrepancies between independent investigations and curvature in the kinetic plots used to evaluate the rate constants for proton removal. It is addressed primarily to the NMR technique,²⁻¹² but applies equally well to studies employing mass-spectroscopy.¹³⁻¹⁶

RATE EQUATIONS

A mechanistic assumption concerning dissociative exchange is necessary. If one neglects any eventual problems arising from mixed-solvent isotope

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effects, ion-pairs, solvent separated ion-pairs, *etc.*, the following sequence may be assumed to adequately describe the exchange reaction for the general case,



where the I_ϱ are free, short-lived, reactive intermediates to which the steady-state approximation is applied, BH/BD the solvent, and B the active base-catalyst. No structure other than the complete equivalence of the n protons in CH_n is implied.

In an excellent treatise, Bunton, Craig, and Halevi have treated deviation from first-order kinetics for a general isotopic exchange reaction¹⁷ of which the sequence in (1) is a specific example. The general case could be handled conveniently *only* in the absence of secondary isotope effects. For the sequence in (1), this implies that

$$\left. \begin{aligned}
 k_{2\varrho-1} &= (n-\varrho+1)k_{2n-1} \\
 k_{-2\varrho} &= \varrho k_{-2} \\
 k_{2\varrho} &= k_2 \\
 k_{-2\varrho+1} &= k_{-1}
 \end{aligned} \right\} \varrho = 1, n \quad (2)$$

With the aid of the following definitions and abbreviations,

$$A = \sum_{\beta=0}^n \beta [\text{CH}_\beta \text{D}_{n-\beta}] = \text{protium content of } \text{CH}_n$$

$$D_0 = \sum_{\beta=0}^n \beta [\text{CH}_{n-\beta} \text{D}_\beta]_0 = \text{deuterium content of } \text{CH}_n \text{ at } t=0.$$

$$d_0 = [\text{BD}]_0$$

$$h_0 = [\text{BH}]_0$$

$$k_A = k_{2n-1}[\text{B}]; \quad i_A = k_{2n-1}/k_{-2} = \text{isotope effect for proton abstraction from } \text{CH}_n \text{ by B;}$$

$$i_A' = k_{-1}/k_2 = \text{isotope effect for proton abstraction from BH by I;}$$

$$K_A = i_A/i_A' = \text{equilibrium isotope effect.}$$

and

$$a_1 = K_A^{-1} - 1$$

$$a_2 = \{(d_0 - A_0) + K_A^{-1}(h_0 + 2A_0 + D_0)\}$$

$$a_3 = K_A^{-1}\{A_0(h_0 + A_0 + D_0) + h_0 D_0\}$$

$$a_4 = d_0 + i_A' h_0$$

$$a_5 = i_A' - 1$$

$$*a_6 = K_A^{-1}(A_0 + D_0)$$

$$*a_7 = K_A^{-1}\{A_0(h_0 + A_0 + C_0 + D_0) + D_0(h_0 + C_0)\}$$

* These constants appear in connection with competitive H-D exchange. C_0 is defined as the protium content of a second group CH_m at $t=0$.

the rate equations derived¹⁷ by Bunton and co-workers can be shown to reduce to

$$\frac{1}{k_A} \frac{dA}{dt} = \frac{a_1 A^2 - a_2 A + a_3}{a_4 + a_5(A_0 - A)} \quad (3)$$

The subscript "0" refers to concentrations at $t=0$.

One may conveniently introduce two further sets of abbreviations which depend on the values assumed by i_A and i_A' . The set of constants $\{a_i', i=1,7\}$ is defined for the case when $i_A = i_A' \neq 1$ (no equilibrium isotope effect) from the set $\{a_i, i=1,7\}$ by substituting $K_A = 1$. The set $\{a_i'', i=1,7\}$ is similarly defined for the case when $i_A = i_A' = 1$ (no isotope effect whatever). As illustration, $a_1' = a_1'' = a_5'' = 0$.

Thus the equilibrium condition $dA/dt = 0$ for eqn. (3) gives for A_∞

$$A_\infty = \frac{a_2}{2a_1} \pm \left\{ \left[\frac{a_2}{2a_1} \right]^2 - \frac{a_3}{a_1} \right\}^{\frac{1}{2}} \quad (4)$$

whereas, in the case of no equilibrium isotope effect ($K_A = 1$),

$$A_\infty = a_3'/a_2' \quad (5)$$

In the event that there is a second group CH_m in the substrate which is nonequivalent to CH_n , but also undergoes H-D exchange, a second and competitive sequence of the type shown in (1) may be defined with

$$C = \sum_{\beta=0}^m \beta [\text{CH}_\beta \text{D}_{m-\beta}] = \text{protium content of } \text{CH}_m;$$

$$E_0 = \sum_{\beta=0}^m \beta [\text{CH}_{m-\beta} \text{D}_\beta]_0 = \text{deuterium content of } \text{CH}_n \text{ at } t=0;$$

$$k_C = k_{2m-1}'[\text{B}]; i_C = k_{2m-1}'/k_{-2}' = \text{isotope effect for proton abstraction from } \text{CH}_m \text{ by B};$$

$$i_C' = k_{-1}'/k_{-2}' = \text{isotope effect for proton abstraction from BH by I}';$$

$$K_C = i_C/i_C' = \text{equilibrium isotope effect for } \text{CH}_m.$$

The set of constants $\{c_i; c_i'; c_i'', i=1,7\}$ are formed from the set $\{a_i; a_i'; a_i'', i=1,7\}$ by systematically replacing A_0 by C_0 , K_A by K_C , i_A' by i_C' , C_0 by A_0 , and D_0 by E_0 in the latter. The resulting rate equations are now

$$\begin{aligned} \frac{1}{k_A} \frac{dA}{dt} &= \frac{a_1 A^2 - a_2 A - a_1(C_0 - C)A - a_6 C + a_7}{a_4 + a_5\{(A_0 - A) + (C_0 - C)\}} \\ \frac{1}{k_C} \frac{dC}{dt} &= \frac{c_1 C^2 - c_2 C - c_1(A_0 - A)C - c_6 A + c_7}{c_4 + c_5\{(C_0 - C) + (A_0 - A)\}} \end{aligned} \quad (6)$$

Applying the equilibrium conditions ($dA/dt = dC/dt = 0$) when $K_A = K_C = 1$ gives for A_∞ and C_∞

$$\begin{aligned} A_\infty &= \frac{a_6' c_7' - a_7' c_2'}{a_6' c_6' - a_2' c_2'} \\ C_\infty &= \frac{a_7' c_6' - a_2' c_7'}{a_6' c_6' - a_2' c_2'} \end{aligned} \quad (7)$$

Eqns. (3) and (6) are the most complete description of simple and competitive $H-D$ exchange, respectively, for the mechanism in (1) and the subsequently specified conditions. For many studies of $H-D$ exchange, however, the rate equations

$$\begin{aligned} \frac{1}{k_A} \frac{dA}{dt} &= -A & \frac{1}{k_A'} \frac{dA}{dt} &= -A + D_0 \\ & & \text{or} & \\ \frac{1}{k_C} \frac{dC}{dt} &= -C & \frac{1}{k_C'} \frac{dC}{dt} &= -C + E_0 \end{aligned} \quad (8)$$

are employed for both simple and competitive reaction sequences;^{2-6,8,9,11,12,14-16} a result of assuming that exchange is irreversible- ($[BH]/[BD]$ or $[BD]/[BH] = 0$ at all times, respectively). These first-order equations neglect equilibrium concentrations of protonated or deuterated substrate together with primary equilibrium and kinetic isotope effects.

Experimentally, these rate equations have been simplified by adjusting the initial conditions in one of two ways:

Method 1. $h_0 = D_0 = E_0 = 0$ (corresponds to deuteration of substrate)

$$A_0 = n[\text{CH}_n]_0; \quad [\text{CH}_\beta\text{D}_{n-\beta}]_0 = 0 \text{ for } \beta = 0, n-1$$

$$C_0 = m[\text{CH}_m]_0; \quad [\text{CH}_\beta\text{D}_{m-\beta}]_0 = 0 \text{ for } \beta = 0, m-1$$

Method 2. $d_0 = A_0 = C_0 = 0$ (corresponds to protonation of substrate)

$$D_0 = n(\text{CD}_n)_0; \quad [\text{CH}_{n-\beta}\text{D}_\beta]_0 = 0 \text{ for } \beta = 0, n-1$$

$$E_0 = m(\text{CD}_m)_0; \quad [\text{CH}_{m-\beta}\text{D}_\beta]_0 = 0 \text{ for } \beta = 0, m-1$$

Method (1) appears to be the most frequently used, but use of Method (2) occurs also.^{11,12} Only Method (1) with provision for nonzero values of h_0 will be considered in detail in the analysis that follows. Some observations regarding the use of Method (2) will be made without proof, however.

A and C are not measured directly. However, the relationship between these quantities and the observables is usually straightforward. Thus the integrated intensity, H , of a proton signal in the NMR is related to the reaction variable A or C by an expression

$$\begin{aligned} H_{\text{CH}_n} &= \alpha_A^{-1} A \\ H_{\text{CH}_m} &= \alpha_C^{-1} C \end{aligned} \quad (9)$$

where α_A and α_C are proportionality constants dependent on a given set of instrumental constants. Data from IR and mass-spectroscopic measurements may similarly be defined in terms of A and C .

INTEGRATED SOLUTIONS FOR $D_0 = E_0 = 0$

The rate equations just enumerated represent varying degrees of sophistication and approximation. Their integrated forms are those generally used in some manner to extract an observed rate constant from primary data. This

most often takes the form of some type of log-time plot whose slope is the observed rate constant.^{2-5,7-9,11-16} The Guggenheim procedure¹⁸ has also been used,¹⁰ as well as nonlinear analysis of the exponential form of a logarithmic expression.^{6,19} (It is presumed that k_A and k_C are the information of interest, since these are the quantities on which any eventual conclusions concerning the effect of structural changes on the rates of proton removal must be based.)

Eqn. (3) is a nonlinear first-order differential equation which is easily integrated for all combinations of i_A and i_A' . It reduces to first-order kinetics only when $i_A = i_A' = 1$, yielding the integrated expression

$$\ln \left[\frac{A_0 - A_\infty}{A - A_\infty} \right] = \frac{a_2''}{a_4''} k_A t = \frac{d_0 + h_0 + A_0}{d_0 + h_0} k_A t \quad (10)$$

A_∞ may be determined experimentally or evaluated directly from the initial conditions with (5). The slope of the usual logarithmic plot reduces to k_A only in the event that $d_0 \gg h_0$ and A_0 .

Solutions to (3) may also be obtained for $i_A = i_A' \neq 1$ and for $i_A \neq i_A' \neq 1$. The former case, which implies the absence of an equilibrium isotope effect, yields

$$\ln \left[\frac{A_0 - A_\infty}{A - A_\infty} \right] = \frac{a_2' k_A t + a_5' (A_0 - A)}{a_4' + a_5' (A_0 - A_\infty)} \quad (11)$$

and the latter case yields an equation of the form

$$\ln \left\{ \left[\frac{A_0 - A_\infty}{A - A_\infty} \right] \left[\frac{A_0 - A_\infty + \alpha}{A - A_\infty + \alpha} \right]^{(\alpha - \beta)/\beta} \right\} = \gamma k_A t \quad (12)$$

where α , β , and γ are constants containing d_0 , h_0 , A_0 , i_A , and i_A' . A_∞ is as in (4). Plots of $\ln \{(A_0 - A_\infty)/(A - A_\infty)\}$ vs. t will clearly be nonlinear if isotope effects are present.

Eqns. (6), which represent the experimentally common case of competitive $H-D$ exchange at two nonequivalent groups (e.g. in 2-butanone), reduce to first-order kinetics when $K_A = K_C = 1$ and $i_A' = i_C' = 1$; i.e. in the complete absence of primary equilibrium and kinetic isotope effects. If such is the case, they may be written in the form

$$\begin{aligned} -\frac{1}{k_A} \frac{d(A - A_\infty)}{dt} &= \frac{a_2''(A - A_\infty) + a_6''(C - C_\infty)}{a_4''} \\ -\frac{1}{k_C} \frac{d(C - C_\infty)}{dt} &= \frac{c_6''(A - A_\infty) + c_2''(C - C_\infty)}{c_4''} \end{aligned} \quad (13)$$

which may be integrated by standard techniques to give

$$\begin{aligned} A - A_\infty &= \frac{(A_0 - A_\infty)\{\lambda_1 + k_C p\} - (C_0 - C_\infty)k_A q}{(\lambda_1 - \lambda_2)} \exp(\lambda_1 t) - \\ &\quad \frac{(A_0 - A_\infty)\{\lambda_2 + k_C p\} - (C_0 - C_\infty)k_A q}{(\lambda_1 - \lambda_2)} \exp(\lambda_2 t) \end{aligned} \quad (14)$$

$$C - C_\infty = \frac{(C_0 - C_\infty)\{\lambda_1 + k_A u\} - (A_0 - A_\infty)k_C v}{(\lambda_1 - \lambda_2)} \exp(\lambda_1 t) - \frac{(C_0 - C_\infty)\{\lambda_2 + k_A u\} - (A_0 - A_\infty)k_C v}{(\lambda_1 - \lambda_2)} \exp(\lambda_2 t) \quad (15)$$

where

$$p = c_2''/c_4''; \quad q = a_6''/a_4''; \quad u = a_2''/a_4''; \quad v = c_6''/c_4'';$$

and

$$\lambda_1 = - \left[\frac{r + \sqrt{(r^2 - 4s)}}{2} \right] \quad \lambda_2 = - \left[\frac{r - \sqrt{(r^2 - 4s)}}{2} \right]$$

$$r = (k_A + k_C) + \frac{k_A A_0 + k_C C_0}{d_0 + h_0}$$

$$s = \frac{(d_0 + h_0 + A_0 + C_0)}{d_0 + h_0} k_A k_C$$

If, and only if $d_0 \gg A_0, C_0,$ and h_0 may these solutions be reduced to the simple form

$$\ln \left[\frac{A_0 - A_\infty}{A - A_\infty} \right] = -\lambda_1 t \quad (16)$$

$$\ln \left[\frac{C_0 - C_\infty}{C - C_\infty} \right] = -\lambda_2 t$$

where λ_1 and λ_2 may be approximated as

$$\lambda_1 \simeq - \frac{d_0 + h_0 + A_0}{d_0 + h_0} k_A \sim -k_A$$

$$\lambda_2 \simeq - \frac{d_0 + h_0 + C_0}{d_0 + h_0} k_C \sim -k_C$$

The slope of a log-time plot will give $-\lambda_1$ or $-\lambda_2$.

There is one additional case for eqns. (6) which should be dealt with. This occurs in the event that one group, let us say CH_m , exchanges to completion before measurable exchange has occurred at the other group, CH_n . If such is the case, a pseudo-equilibrium may be defined for both A and C , where $A = A_0$ in dC/dt , and $C \equiv \tilde{C}_\infty$ in dA/dt . This results in

$$\tilde{A}_\infty = \frac{a_7' - a_6' \tilde{C}_\infty}{a_2'} \quad \text{and} \quad \tilde{C}_\infty = \frac{c_7' - c_6' A_0}{c_2'} \quad (17)$$

for $K_A = K_C = 1$, and the integrated expressions when $i_C' = i_A' = 1$ are

$$\ln \left[\frac{A_0 - \tilde{A}_\infty}{A - \tilde{A}_\infty} \right] = \frac{a_2''}{a_4''} k_A t = \frac{d_0 + h_0 + A_0}{d_0 + h_0} k_A t \quad (18)$$

$$\ln \left[\frac{C_0 - \tilde{C}_\infty}{C - \tilde{C}_\infty} \right] = \frac{c_2''}{c_4''} k_A t = \frac{d_0 + h_0 + C_0}{d_0 + h_0} k_C t$$

The rate equations under the conditions implied in (17) also integrate for $i_A' \neq i_C' \neq 1$ and yield two equations similar to (11), one for A and one for C .

THE LOG-TIME PLOT

A log-time plot is usually the method used to abstract observed rate constants from data for simple first-order reactions. From a statistical point of view, however, this procedure is often unsatisfactory.¹⁹ Instead, the exponential form of the integrated rate equation should be analyzed for k^{obs} , e.g. with nonlinear least-squares routines.

The following discussion will be limited to log-time plots, since this has been the most common method of analyzing data. Curvature in these plots is equivalent to significant trends in the algebraic magnitudes of the residuals from a nonlinear least-squares analysis. In this way, the discussion of the merits of a particular equation is quite general.

Let us assume for the sake of simplicity that the substrate contains only one group of equivalent protons, CH_n . In the absence of any isotope effect, then, (10) is the *correct* equation to apply to primary data. Neglect of equilibrium concentrations of protonated species *vis-a-vis* the assumption of irreversibility and application of (8) to the primary data is an approximation: a singularly poor approximation which may be a major source of curvature in log-time plots for conditions common in the NMR method. An additional source of error introduced by neglect of A_∞ is reflected in the initial slopes of (8) and (10). A correct plot would have as its initial slope,

$$\left[\frac{d \ln \left[\frac{A_0 - A_\infty}{A - A_\infty} \right]}{dt} \right]_{A=A_0} = - \frac{1}{A_0 - A_\infty} \left[\frac{dA}{dt} \right]_{A=A_0} = \frac{a_2''}{a_4''} k_A = \frac{d_0 + h_0 + A_0}{d_0 + h_0} k_A \equiv S_0 \quad (19)$$

whereas the initial slope obtained by neglecting A_∞ is

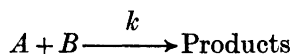
$$\left[\frac{d \ln \left[\frac{A_0}{A} \right]}{dt} \right]_{A=A_0} = - \frac{1}{A_0} \left[\frac{dA}{dt} \right]_{A=A_0} = \frac{d_0}{d_0 + h_0} k_A \quad (20)$$

where the expression for dA/dt is (3). For nonzero values of h_0 , the assumption of irreversibility is without validity, and the initial slope does not correspond to k_A as it should.

The magnitude of the curvature of a logarithmic plot of primary data according to the integrated form of (8) may be estimated for some arbitrary point in the reaction (say $A = 0.5A_0$) by evaluating the second derivative of the logarithmic term with respect to time for some assumed parameters. The curvature

$$\frac{d^2 \ln \left[\frac{A_0}{A} \right]}{dt^2} = k_A^2 \left[\frac{a_2'''}{a_4'''} \right]^2 \left(1 - \frac{A_\infty}{A} \right) \left(-\frac{A_\infty}{A} \right) \quad (21)$$

may be expressed as a fraction of k_A^2 and has units of sec^{-2} . The results are given in Table 1 for the specified parameter values. By way of comparison, it may be noted that an attempt to plot data in logarithmic form for a reaction obeying second-order kinetics.



will result in a curvature equal to $-0.25k^2B_0^2$ (sec^{-2}) at $A = 0.5A_0$ for $A_0 = B_0$.

The obvious way to avoid the error inherent in the use of (8) is to treat data according to eqn. (10). Inability to determine A_∞ experimentally is overcome by an estimate based on (5). Since values of A_∞/A_0 for many NMR studies are in the range 0.06–0.20, use of (5) is clearly better than assuming $A_\infty = 0$. Pronounced curvature has been observed, for example, in plots from a study of H–D exchange employing mass-spectroscopy when A_∞ was neglected.¹³

Even (10), however, is strictly valid only in the complete absence of any form of isotope effect. Because in work involving H–D exchange subject to a mechanism similar to (1), isotope effects are almost certainly present and large, treatment of primary data by (10) is an approximation as well, and is expected to result in nonlinear plots. Primary equilibrium and kinetic isotope effects are also expected to influence the rate constant for exchange as evaluated from initial rate data.

For $i_A = i_A' \neq 1$ (no equilibrium isotope effect), the initial slope of the log-time plot is

$$\left[\frac{d \ln \left[\frac{A_0 - A_\infty}{A - A_\infty} \right]}{dt} \right]_{A=A_0} = \frac{a_2'}{a_4'} k_A = \frac{d_0 + h_0 + A_0}{d_0 + i_A' h_0} k_A \equiv S_0' \quad (22)$$

By comparing (19) and (22), one observes that for $i_A' > 1$ and $h_0 \neq 0$, $S_0 > S_0'$; *i.e.* the isotope effect reduces the observed rate constant determined from the initial slope. This problem is particularly acute if there are two groups within a molecule, one of which exchanges much more rapidly than the other, because the more slowly exchanging group will experience an apparent h_0 that is significantly greater than zero (see eqns. (6), (17), and (18)). Only by ensuring that $d_0 \gg i_A' h_0$, can this effect be minimised.

The second derivative of the logarithmic term $\ln\{(A_0 - A_\infty)/(A - A_\infty)\}$ with respect to time may again be used to estimate the curvature of the log-

time plot; this time for the effect of an unrecognized primary kinetic isotope effect. For brevity, only the case where $i_A = i_A' \neq 1$ is considered, whence

$$\frac{d^2 \ln \left[\frac{A_0 - A_\infty}{A - A_\infty} \right]}{dt^2} = -k_A^2 \frac{a_2'^2 a_5'(A - A_\infty)}{\{a_4' + a_5'(A_0 - A)\}^3} \quad (23)$$

The curvatures are tabulated in Table 2 for the specified parameter values. It is apparent from the data that eqn. (10) will be a good approximation (*i.e.* curvature equals zero) only when $d_0 \gg A_0$. In the case of the NMR technique, this approximation may not always be a good one because of the relatively large values of A_0/d_0 required (used). Eqn. (10) or (18), however, are in all events preferable to (8).

With the exception of the basic mechanistic assumption embodied in (1), only the assumption concerning the absence of secondary isotope effects is universal to the equations already derived. The presence of a secondary isotope effect implies the failure of the conditions specified in (2). Albery and Davies have recently considered in some detail deviations from the "rule of the geometric mean" for isotopic exchange equilibria at XH_2 .²⁰ One such reason is the existence of a secondary isotope effect. For CH_2 , there are four possible secondary isotope effects according to sequence (1), but since treatment of the problem in this form is impractical, we are forced to assume that $[\text{BH}]/[\text{BD}] \simeq 0$ at all times, thus approximating to irreversible first-order kinetics. The reaction sequence resulting after the application of the steady-state condition is



where k_1 and k_3 are the real, physically measurable rate constants. A rate constant k_3' may be defined which represents the constant for the transformation $\text{CHD} \rightarrow \text{CD}_2$ in the absence of a secondary isotope effect. Thus $k_1 = 2k_3'$. A correction δ may also be defined such that $k_3 = k_3'(1 + \delta)$. In terms of the reaction variable A , the integrated expression for this sequence is²

$$A = A_0 \exp(-k_1[\text{B}]t) + 0.5A_0 \frac{k_1}{k_3 - k_1} \{ \exp(-k_1[\text{B}]t) - \exp(-k_2[\text{B}]t) \} \quad (24)$$

Substituting $k_1 = 2k_3/(1 + \delta)$, rearranging, and taking the logarithm of both sides results in an equation of the form

$$\ln \left[\frac{A_0}{A} \right] = k_3'[\text{B}](1 + \delta)t - \ln \left[1 + \frac{\delta \{ 1 - \exp(-k_3'[\text{B}](1 - \delta)t) \}}{(1 - \delta)} \right] \quad (25)$$

which may be approximated to

$$\ln \left[\frac{A_0}{A} \right] \simeq k_3'[\text{B}](1 + \delta)t - \frac{\delta \{ 1 - \exp(-k_3'[\text{B}](1 - \delta)t) \}}{(1 - \delta)} \quad (26)$$

For small values of t corresponding to the initial stages of exchange, $\exp(-k_3'[\text{B}](1 - \delta)t) \simeq 1 - k_3'[\text{B}](1 - \delta)t$, which gives

$$\ln \left[\frac{A_0}{A} \right] = k_3' [B] t$$

Hence the initial slope is equal to the rate constant containing no secondary isotope effect ($k_3' [B] = k_A$ for $n = 2$). To obtain the influence of the secondary isotope effect on curvature in the log-time plot, the exponential in (26) is approximated as

$$\simeq 1 - k_3' [B] (1 - \delta) t + \{k_3' [B] (1 - \delta) t\}^2 / 2$$

whence

$$\ln \left[\frac{A_0}{A} \right] = k_3' [B] t + \delta k_3'^2 [B]^2 t^2 (1 - \delta) / 2 \quad (27)$$

From this the curvature is obtained as

$$\frac{d^2 \ln \left[\frac{A_0}{A} \right]}{dt^2} = k_A^2 \delta / (1 - \delta) \quad (28)$$

where the secondary isotope effect k_H/k_D is $(1 + \delta)^{-1}$. Thus at least initially, the curvature is independent of A and is constant. The approximations inherent in (28) tend to cause overestimation of the curvature; by as much as a factor of 2 near $A = 0.5A_0$. Eqn. (28) holds best when both A_0/A and k_H/k_D are close to unity. Curvature values are found in Table 3. Note that in this case, curvature is not a result of deviation from first-order kinetics.

Without some knowledge of the magnitudes of the various isotope effects, a discussion of the relative importance of the sources of curvature is not possible. Secondary isotope effects, however, are known to be small.²¹ Jones, for example, has found that the secondary isotope effect for detritiation of the two acetones shown below was 1.07 at 25°C.²²



By examining Tables 1 and 2 for values of A_0/d_0 common in the NMR technique (0.05–0.20), the secondary isotope effect is at once eliminated as a major source of curvature. It is not as easy to decide whether neglect of A_∞ or unrecognized primary kinetic isotope effects is the major cause of any observed

Table 1. Curvatures due to neglect of equilibrium concentrations of protonated substrate.

A_0/d_0	Curvatures (sec ⁻²) ^a
0.001	-0.002 k_A^2
0.01	-0.02 k_A^2
0.1	-0.18 k_A^2
0.2	-0.32 k_A^2

^a Evaluated at $A = 0.5A_0$, $h_0 = 0$.

Table 2. Curvatures due to the presence of a primary kinetic isotope effect.

A_0/d_0	Curvatures (sec^{-2}) ^a	
	$i_{A'}=3$	$i_{A'}=6$
0.001	-0.001 k_A^2	-0.0025 k_A^2
0.01	-0.01 k_A^2	-0.024 k_A^2
0.1	-0.07 k_A^2	-0.126 k_A^2

^a Evaluated at $A=0.5A_0$, $h_0=0$, $K_A=1$. Bunton and co-workers have reported that deviation from first-order kinetics is re-enforced or cancelled somewhat, depending on whether K_A is less than or greater than 1.¹⁷

deviation from linearity. For a given value of A_0/d_0 common for NMR studies, however, the absolute value of the curvature due to neglect of A_∞ is greater than for neglect of isotope effects.

Interestingly, it may be established that the absolute values of the curvature for neglect of A_∞ goes through a maximum at $A=2A_\infty$, whereas curvature for neglect of the primary isotope effect decreases continuously with A . Both approach zero as $A \rightarrow A_\infty$.

The sources of curvature just discussed apply to cases where only one group of equivalent protons is undergoing H-D exchange. Since many studies, however, have been concerned with the rate of exchange at two nonequivalent groups within the same molecule, it must be stressed that the competitive nature of the exchange for such a case constitutes in itself, even in the complete absence of any form of isotope effect, a possible source of curvature in log-time plots of primary data (see equations (14) and (15)) if d_0 is not present in large excess. Conclusions based on such exchange results must be regarded as containing an element of uncertainty to the extent that λ_1 and λ_2 do not approximate to their values in (16). How good this approximation is, and the values that λ_1 and λ_2 in fact assume are of course dependent on the initial conditions of the study. This, together with the influence of isotope effects on initial rates may lead to apparently conflicting results in independent studies where the initial conditions have not been the same.

Finally, a note about the experimental use of Method (2) in which one begins with completely deuterated substrate and measures the rate of protium

Table 3. Curvatures due to neglect of secondary kinetic isotope effects for irreversible H-D exchange at a methylene-like group.

k_H/k_D	Curvature (sec^{-2})
1.03	-0.029 k_A^2
1.07	-0.061 k_A^2
1.11	-0.11 k_A^2
1.25	-0.17 k_A^2
2.00	-0.33 k_A^2

incorporation: For this case, curvature due to neglect of equilibrium concentrations of deuterated substrate is negative, whereas primary and secondary kinetic isotope effects lead to positive curvature. The influence of the primary kinetic isotope effect on the initial slope and curvature of the plot are, however, less than the corresponding effect for Method (1) just analysed. In this respect, Method (2) is preferable to Method (1).

The only satisfactory way of avoiding all these pitfalls is to ensure that d_0 (or h_0) is at least two orders of magnitude greater than A_0 and C_0 (or D_0 and E_0) and that h_0 (or d_0) equals zero. It may be worth sacrificing some experimental precision in the determination of A and C in order to fulfill these conditions. And, of course, the correct equation should be used for analysing the exchange data.

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