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Kinetic Hydrogen/Deuterium Isotope Effects in Multiple Proton Transfer Reactions

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Dedicated to Prof. Dr. Herbert Zimmermann on the occasion of his 75th birthday

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Multiple Proton Transfer / Kinetic Isotope Effects

In this paper, a description of multiple kinetic isotope effects (MKIE) of degenerate double, triple and quadruple proton transfer reactions in terms of formal kinetics is developped. Both single and multiple barrier processes are considered, corresponding to so-called "concerted" and "stepwise" reaction pathways. Each step is characterized by a rate constant and the transfer of a given H isotopes or ensemble of H isotopes. The MKIE are expanded in terms of kinetic H/D isotope effects P contributed by single sites in which a proton is transferred in the rate limiting steps. By combination with a modified Bell tunneling model the formalism developed can be used in order to take into account tunneling effects of both concerted and stepwise multiple proton transfers at low temperatures.

1. Introduction

Proton transfer constitutes a very complex process, consisting not only of the transfer of a proton but also of diffusion, transport of electrical charges, reorientation and reorganisation of the solvent molecules, hydrogen bond breaking and forming processes. One way to obtain information about these elementary steps is the measurement and interpretation of kinetic H/D isotope effects. The first theories of these effects were developed by Bigeleisen [1] by a combination of transition state theory and the theory of isotopic fractionation, and by Bell [2], who included tunneling phenomena at low temperatures. Later

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theories were developed by Kusnetzov and Ulstrup [3], which has been applied recently by Klinman *et al.* to describe H-abstraction from carbon in enzymes [4]. In contrast to Marcus theory of electron transfer [5], there is, however, no accepted general theory of proton transfer up to date. For recent reviews see the papers of Steiner and of Vener *et al.* [6].

Most previous experimental and theoretical studies refer to single proton or hydrogen transfer reactions. However, in real systems, very often more than one proton is transferred. Therefore, in our laboratory, we have been involved for many years in the study of double proton transfer reactions, and in the elucidation of multiple kinetic isotope effects MKIE, here the HH/HD/DD isotope effects. These effects have been studied for several intra- [7] and intermolecular [8, 9] double proton transfer systems by NMR in the liquid and solid state. Solid state reactions are especially useful as they provide models in which most liquid state complications such as diffusion, molecular reorientation, hydrogen bond breaking and bond formation processes are suppressed. The data obtained have been used as input for testing dynamic MKIE theories [10].

Model systems where more than two protons transferred are, however, very rare. Horsewill *et al.* have reported an intramolecular quadruple proton tunneling process between the OH-groups of solid calixarene [11]. Several years ago, Elguero et al. have reported a series of pyrazole derivatives in the solid state which can form a surprising variety of cyclic hydrogen bonded dimers, trimers, tetramers, and chains in which often multiple proton transfers take place as detected by solid state NMR [12]. Especially interesting was the following series of pyrazole molecules [13]: in the crystalline state 3,5-diphenyl-4-bromopyrazole (DPBrP) forms cyclic dimers, 3,5-dimethylpyrazole (DMP) cyclic trimers, [12a] and 3,5-diphenylpyrazole (DPP) cyclic tetramers which exhibit degenerate double, triple and quadruple proton transfers. *Ab initio* calculations performed on pyrazole clusters reproduced these findings [14] and indicated a switch from concerted double and triple proton transfers to a stepwise mechanism for the quadruple transfer process, exhibiting two consecutive concerted double proton transfers. Up to date, only in the case of the cyclic trimer of DMP the full MKIE of the degenerate triple proton transfer [15] could be measured by dynamic high-resolution solid state ^{15}N NMR spectroscopy. To our knowledge, this study is up to date the only one reporting MKIE of a reaction with more than two protons transferred. The temperature – dependent kinetic HHH/HHD/HDD/DDD-isotope effects could be indeed rationalized in terms of a concerted triple proton transfer which takes place at low temperatures by tunneling. Moreover, by comparison with some additional pyrazole molecules which also form cyclic trimers in the solid a reduction of the barrier was observed when the size of the 3(5) substituents was reduced, an effect which could be explained in terms of a hydrogen compression mechanism assisting the triple proton transfer at higher temperatures [16]. Thus, it is clear that the knowledge of the full

MKIE is desirable. However, the difficulty to measure these effects increases with the number of protons transferred and only partial MKIE can be measured.

In order to motivate research in this at first sight very difficult research field we, therefore, explore in this paper the kinetic isotope effects of degenerate multiple H transfer reactions for various reaction mechanisms, using the simplest methods of formal kinetics. We assume that the transfer processes can be described in terms of rate constants, and that in each reaction step either a single hydrogen isotope or an ensemble of hydrogen isotopes is transferred, where an ensemble can be formally described in terms of a single particle transfer. The multiple isotope effects are related to the isotope effects P_i contributed by a given proton to the overall isotope effect. In a later step, these single particle isotope effects can be coupled with tunneling models referring to single barrier reaction steps, where one or more protons are transferred.

We will treat in a systematic way the cases of degenerate single up to quadruple proton transfer as indicated in Figs. 1 to 5 of the subsequent section. The first case of single barrier processes is depicted Fig. 1. When more than one proton is transferred this case has been also called "concerted" or "synchronous" transfer, but these terms may be misleading as they refer to the individual motions of the protons, whereas Fig. 1 refers only to the potential energy surface which does not contain an intermediate along the reaction pathway. Fig. 1 indicates the nomenclature we will use: each hydrogen bond site containing a mobile proton can adopt two states 0 or 1. Thus, each tautomeric state of a n-H transfer reaction can be characterized by a binary number with n digits. In Fig. 1 the corresponding hexadecimal number is included in round brackets. The index of the proton transferred in a given step is indicated in square brackets. In Figs. 2 and 3 are depicted the double and triple barrier or "stepwise" double and triple proton transfer cases. A four-protons transfer can either involve two or four barriers, with either one or three intermediates (Figs. 4 and 5). Note that there can be cases with a transition from a stepwise to a concerted transfer, caused by hydrogen bond compression [8b]. Such a case will be summarized here as a single barrier or concerted process.

In the following, we will treat the various cases in subsequent sections which are finally discussed and conclusions of how experiments could be carried out proposed.

2. Theoretical section

In this section we will provide a treatment of degenerate multiple proton transfer reactions using formal kinetics in order to derive values of the multiple kinetic isotope effects. Generally, the differential equations which govern a re-

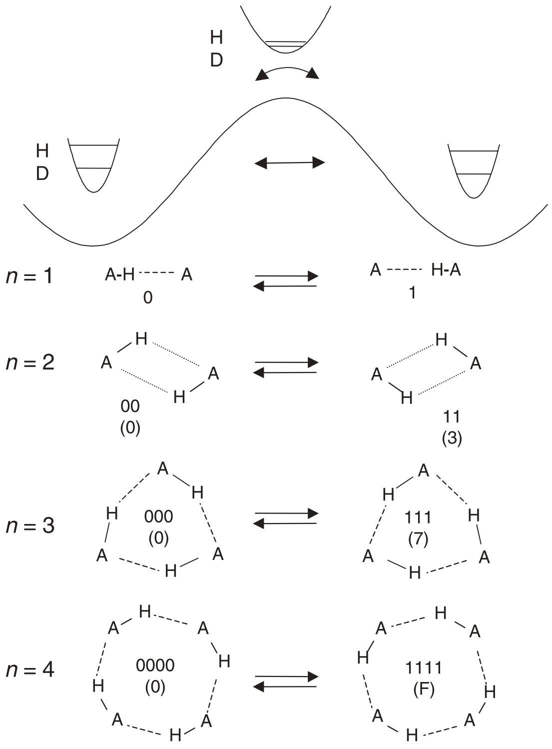


Fig. 1. Schematic one-dimensional energy profile of degenerate single-barrier hydron (H, D, T) transfer in coupled networks of $n = 1$ to 4 cyclic hydrogen bonds. Each hydron can occupy two positions labeled as 0 and 1. Each tautomeric state can then be labeled by n digits. In brackets is indicated the corresponding hexadecimal number. The hydron transfer can be an over-barrier process or a tunneling process as indicated by the double arrows in the energy profile. The over-barrier process leads to kinetic isotope effects P because of the loss of zero-point energy at the top of the barrier for each proton transferred as indicated schematically. The tunneling process leads to kinetic isotope effects because of different tunneling masses for the hydrogen isotopes.

action network are given by

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = -\sum_{j \neq i} \left(-k_{ij} c_i + k_{ji} c_j \right) , \tag{1}$$

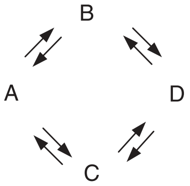
where c_i represents the concentration of state i and k_{ij} the first order rate constant of the interconversion between i and j. For the intermediate states the steady state condition holds, *i.e.*

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = 0 . \tag{2}$$

The interconversion between the reactant state r and the product state p is then given by

$$\frac{dc_r}{dt} = -k_{rp}c_r + k_{pr}c_p\ . \tag{3}$$

By combination of Eqs. (1) to (3) it is possible to obtain expressions of the observed rate constant k_{rp} as a function of the rate constants k_{ij} of the individual steps. As an example, we treat the simple reaction network of Scheme 1,



Scheme 1

with $r = A$ and $p = D$, and the intermediate states B and D. For this case it is straightforward to show that

$$k_{AD} = \frac{k_{AB}k_{BD}}{k_{BA} + k_{BD}} + \frac{k_{AC}k_{CD}}{k_{CA} + k_{CD}}\ . \tag{4}$$

An individual reaction step ij can give rise to the single proton kinetic isotope effect

$$P_{ij} = k_{ij}^{H}\big/k_{ij}^{D}\ . \tag{5}$$

The ratio of the kinetic isotope effects of the forward and the backward reaction

$$\phi_{ij} = \frac{P_{ij}^{-1}}{P_{ji}^{-1}} = \frac{k_{ij}^{D}k_{ji}^{H}}{k_{ij}^{H}k_{ji}^{D}} = \frac{K_{ij}^{D}}{K_{ij}^{H}} \tag{6}$$

corresponds to the equilibrium constant of the reaction

$$i(D) + j(H) \rightleftharpoons i(H) + j(D) \tag{7}$$

and is called the H/D fractionation factor between states i and j. We will include isotopic fractionation of individual reaction steps, but not isotopic fractionation between the reactant and product states as we are interested here in degenerate reactions.

One can distinguish two types of kinetic H/D isotope effects, *i.e.* “primary” effects referring to mobile protons “in flight” and secondary effects referring to bound protons. The above equations are valid for both types of isotope effects.

However, in order to keep the notation simple we will use the symbol P_{ij} for primary and S_{ij} for secondary isotope effects. Note that we will consider the latter only in the case of double proton transfer reactions, in the higher order reactions we will set these quantities to unity.

2.1 Degenerate one-step single and multiple proton transfer

In this section we treat the case of degenerate one-step single to quadruple proton transfer reactions illustrated in Fig. 1. In this case all protons of the system are in flight, *i.e.* all sites contribute only primary kinetic isotope effects. However, the isotopic rate constants can depend on the site in which H is replaced by D, and on which other sites contain already D. Here, we assume that all protons are chemically equivalent *i.e.* that all proton sites contribute the same kinetic isotope effect. We can then write for a double proton transfer

$$k^{\mathrm{HH}} = P_1 k^{\mathrm{DH}} = P_1 k^{\mathrm{HD}}, \quad k^{\mathrm{HD}} = k^{\mathrm{HD}} = P_2 k^{\mathrm{DD}}, \quad k^{\mathrm{HH}} = P_1 P_2 k^{\mathrm{DD}} . \tag{8}$$

The subscript i inP_i refers now to the number of H atoms replaced by D in the reaction with the larger number of D. For the triple and quadruple proton transfer cases it follows that

$$\begin{aligned} &k^{\mathrm{HHD}} = k^{\mathrm{HDH}} = k^{\mathrm{DHH}} = P_1 k^{\mathrm{HHH}} , \\ &k^{\mathrm{HDD}} = k^{\mathrm{DHD}} = k^{\mathrm{DDH}} = P_1 P_2 k^{\mathrm{HHH}} , \\ &k^{\mathrm{DDD}} = P_1 P_2 P_3 k^{\mathrm{HHH}} , \end{aligned} \tag{9}$$

and

$$\begin{aligned} &k^{\mathrm{HHHD}} = k^{\mathrm{HHDH}} = k^{\mathrm{HDHH}} = k^{\mathrm{DHHH}} = P_1 k^{\mathrm{HHHH}} , \\ &k^{\mathrm{HHDD}} = k^{\mathrm{HDHD}} = k^{\mathrm{DHHD}} = k^{\mathrm{DHDH}} = k^{\mathrm{DDHH}} = P_1 P_2 k^{\mathrm{HHHH}} , \\ &k^{\mathrm{HDDD}} = k^{\mathrm{DHDD}} = k^{\mathrm{DDHD}} = k^{\mathrm{DDDH}} = P_1 P_2 P_3 k^{\mathrm{HHHH}} , \\ &k^{\mathrm{DDDD}} = P_1 P_2 P_3 P_4 k^{\mathrm{HHHH}} . \end{aligned} \tag{10}$$

A further simplification is achieved if the so called rule of the geometric means is valid, *i.e.* if all isotope effects are identical, *i.e.*

$$P_i = P_j = P . \tag{11}$$

This rule is often fulfilled for over-barrier reactions, *i.e.* at high temperatures, whereas at low temperatures tunneling leads to a break-down of this rule in the sense that the replacement of subsequent H by D leads to a smaller isotope effects [15].

The extension to systems with a larger number of protons transferred is straightforward.

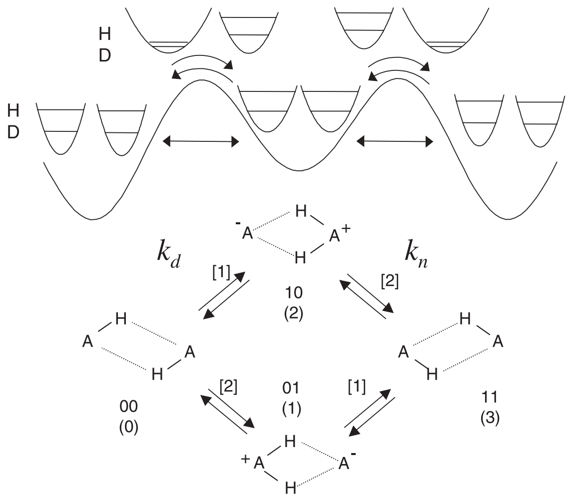


Fig. 2. Degenerate two-barrier double hydron transfer involving an intermediate and corresponding schematic energy reaction profile. In each reaction step only a single hydron is transferred as indicated by square brackets. The formation of the intermediate is called here "dissociation" and the backward reaction "neutralization", characterized by the rate constants k_d and k_n. The zero-point energy of the transferred proton is decreased at the configuration corresponding to the top of the barrier. If the zero-point energy of the other proton is affected also a secondary kinetic isotope effect S arises. Zero-point energy changes between the reactant and the intermediate states give rise to isotopic fractionation characterized by the fractionation factor ϕ_d corresponding to the ratio of the isotopic equilibrium constants for the dissociation.

2.2 Degenerate double barrier double proton transfer

The case of two-step degenerate double proton transfer illustrated in Fig. 2 has been treated previously in several papers [7a, 7b, 17]. We recall this case here because it will help us to simplify the treatment of the quadruple proton transfer case. Formally, the reaction network of Fig. 2 can be condensed into the general reaction network of Scheme 1 treated above. We will call the formation of the intermediates "dissociation" and the backward process "neutralization" according to the nomenclature used in protic solvents. We label now the rate constants with a two-hydron superscript where the first indicates the transferred and the second the non-transferred hydron. Thus, we rewrite Eq. (4) in the form

$$k_\mathrm{AD}^\mathrm{HH} = \frac{k_\mathrm{AB}^\mathrm{HH} k_\mathrm{BD}^\mathrm{HH}}{k_\mathrm{BA}^\mathrm{HH} + k_\mathrm{BD}^\mathrm{HH}} + \frac{k_\mathrm{AC}^\mathrm{HH} k_\mathrm{CD}^\mathrm{HH}}{k_\mathrm{CA}^\mathrm{HH} + k_\mathrm{CD}^\mathrm{HH}}, \quad k_\mathrm{AD}^\mathrm{HD} = \frac{k_\mathrm{AB}^\mathrm{HD} k_\mathrm{BD}^\mathrm{DH}}{k_\mathrm{BA}^\mathrm{HD} + k_\mathrm{BD}^\mathrm{DH}} + \frac{k_\mathrm{AC}^\mathrm{DH} k_\mathrm{CD}^\mathrm{HD}}{k_\mathrm{CA}^\mathrm{DH} + k_\mathrm{CD}^\mathrm{HD}}, \tag{12}$$

$$k_\mathrm{AD}^\mathrm{DH} = \frac{k_\mathrm{AB}^\mathrm{DH} k_\mathrm{BD}^\mathrm{HD}}{k_\mathrm{BA}^\mathrm{DH} + k_\mathrm{BD}^\mathrm{HD}} + \frac{k_\mathrm{AC}^\mathrm{HD} k_\mathrm{CD}^\mathrm{DH}}{k_\mathrm{CA}^\mathrm{HD} + k_\mathrm{CD}^\mathrm{DH}}, \quad k_\mathrm{AD}^\mathrm{DD} = \frac{k_\mathrm{AB}^\mathrm{DD} k_\mathrm{BD}^\mathrm{DD}}{k_\mathrm{BA}^\mathrm{DD} + k_\mathrm{BD}^\mathrm{DD}} + \frac{k_\mathrm{AC}^\mathrm{DD} k_\mathrm{CD}^\mathrm{DD}}{k_\mathrm{CA}^\mathrm{DD} + k_\mathrm{CD}^\mathrm{DD}}.$$

Taking into account primary and secondary isotope effects it follows that

$$\begin{aligned}
k_{\mathrm{AD}}^{\mathrm{HH}} &= \frac{k_{\mathrm{AB}}^{\mathrm{HH}} k_{\mathrm{BD}}^{\mathrm{HH}}}{k_{\mathrm{BA}}^{\mathrm{HH}} + k_{\mathrm{BD}}^{\mathrm{HH}}} + \frac{k_{\mathrm{AC}}^{\mathrm{HH}} k_{\mathrm{CD}}^{\mathrm{HH}}}{k_{\mathrm{CA}}^{\mathrm{HH}} + k_{\mathrm{CD}}^{\mathrm{HH}}}\,, \qquad (13)\\
k_{\mathrm{AD}}^{\mathrm{HD}} &= \frac{P_{\mathrm{AB}}^{-1} S_{\mathrm{BD}}^{-1} k_{\mathrm{AB}}^{\mathrm{HH}} k_{\mathrm{BD}}^{\mathrm{HH}}}{P_{\mathrm{BA}}^{-1} k_{\mathrm{BA}}^{\mathrm{HH}} + S_{\mathrm{BD}}^{-1} k_{\mathrm{BD}}^{\mathrm{HH}}} + \frac{S_{\mathrm{AC}}^{-1} P_{\mathrm{CD}}^{-1} k_{\mathrm{AC}}^{\mathrm{HH}} k_{\mathrm{CD}}^{\mathrm{HH}}}{S_{\mathrm{CA}}^{-1} k_{\mathrm{CA}}^{\mathrm{HH}} + P_{\mathrm{CD}}^{-1} k_{\mathrm{CD}}^{\mathrm{HH}}}\,,\\
k_{\mathrm{AD}}^{\mathrm{DH}} &= \frac{P_{\mathrm{AB}}^{-1} S_{\mathrm{BD}}^{-1} k_{\mathrm{AB}}^{\mathrm{HH}} k_{\mathrm{BD}}^{\mathrm{HH}}}{P_{\mathrm{BA}}^{-1} k_{\mathrm{BA}}^{\mathrm{HH}} + S_{\mathrm{BD}}^{-1} k_{\mathrm{BD}}^{\mathrm{HD}}} + \frac{P_{\mathrm{CD}}^{-1} S_{\mathrm{AC}}^{-1} k_{\mathrm{AC}}^{\mathrm{HH}} k_{\mathrm{CD}}^{\mathrm{HH}}}{S_{\mathrm{AB}}^{-1} k_{\mathrm{CA}}^{\mathrm{HD}} + P_{\mathrm{CD}}^{-1} k_{\mathrm{CD}}^{\mathrm{HH}}}\,,\\
k_{\mathrm{AD}}^{\mathrm{DD}} &= \frac{P_{\mathrm{AB}}^{-1} S_{\mathrm{AB}}^{-1} P_{\mathrm{BD}}^{-1} S_{\mathrm{BD}}^{-1} k_{\mathrm{AB}}^{\mathrm{HH}} k_{\mathrm{BD}}^{\mathrm{HH}}}{P_{\mathrm{BA}}^{-1} S_{\mathrm{BA}}^{-1} k_{\mathrm{BA}}^{\mathrm{HH}} + P_{\mathrm{BD}}^{-1} S_{\mathrm{BD}}^{-1} k_{\mathrm{BD}}^{\mathrm{HH}}} + \frac{P_{\mathrm{AC}}^{-1} S_{\mathrm{AC}}^{-1} k_{\mathrm{AC}}^{\mathrm{HH}} P_{\mathrm{CD}}^{-1} S_{\mathrm{CD}}^{-1} k_{\mathrm{CD}}^{\mathrm{HH}}}{P_{\mathrm{CA}}^{-1} S_{\mathrm{CA}}^{-1} k_{\mathrm{CA}}^{\mathrm{HH}} + P_{\mathrm{CD}}^{-1} S_{\mathrm{CD}}^{-1} k_{\mathrm{CD}}^{\mathrm{HH}}}\,.
\end{aligned}$$

In view of the degeneracy of A and D, and of B and C, it follows that

$$k_{\mathrm{d}}^{\mathrm{HH}} = k_{\mathrm{AB}}^{\mathrm{HH}} = k_{\mathrm{AC}}^{\mathrm{HH}} = k_{\mathrm{DB}}^{\mathrm{HH}} = k_{\mathrm{DC}}^{\mathrm{HH}}, \quad k_{\mathrm{n}}^{\mathrm{HH}} = k_{\mathrm{BA}}^{\mathrm{HH}} = k_{\mathrm{CA}}^{\mathrm{HH}} = k_{\mathrm{BD}}^{\mathrm{HH}} = k_{\mathrm{CD}}^{\mathrm{HH}}\,, \qquad (14)$$

$$k_{\mathrm{AD}}^{\mathrm{HH}} = k_{\mathrm{DA}}^{\mathrm{HH}} = k^{\mathrm{HH}}\,, \qquad (15)$$

$$P_{\mathrm{AB}} = P_{\mathrm{AC}} = P_{\mathrm{DB}} = P_{\mathrm{DC}} = P_{\mathrm{d}}, \quad P_{\mathrm{BA}} = P_{\mathrm{CA}} = P_{\mathrm{BD}} = P_{\mathrm{b}}, \quad \phi_{\mathrm{d}} = P_{\mathrm{n}}/P_{\mathrm{d}} \qquad (16)$$

where we have used the subscript “d” for the dissociation and “n” for the backward neutralization process. ϕ_{d} is the fractionation factor of the dissociation. This factor can be small if in the intermediate a stronger H-bonds are formed as compared to the initial state. We finally obtain

$$\begin{aligned}
k^{\mathrm{HH}} &= k_{\mathrm{d}}^{\mathrm{HH}}\,, \qquad (17)\\
k^{\mathrm{HD}} = k^{\mathrm{DH}} &= k_{\mathrm{d}}^{\mathrm{HH}} P_{\mathrm{d}}^{-1} \left[\frac{\phi_{\mathrm{d}} S_{\mathrm{n}}^{-1} + S_{\mathrm{d}}^{-1}}{\phi_{\mathrm{d}} S_{\mathrm{n}}^{-1} + P_{\mathrm{d}}^{-1}}\right]\\
k^{\mathrm{DD}} &= k_{\mathrm{d}}^{\mathrm{HH}} P_{\mathrm{d}}^{-1} S_{\mathrm{d}}^{-1}\,.
\end{aligned}$$

2.3 Degenerate triple barrier triple proton transfer

The details of the stepwise triple proton transfer are illustrated in Fig. 3. The stepwise process between the initial state 000 and the final state 111 can take place along different pathways via at least two metastable intermediates. For example, if hydrons 1, 2 and 3 are transferred one after the other the reaction pathway is 000 → 100 → 110 → 111. As we consider a degenerate reaction the reaction energy profile must be symmetric, leaving only two cases: in the first case the central reaction step is rate limiting and in the second case the first and the third steps as indicated schematically at the top of Fig. 3.

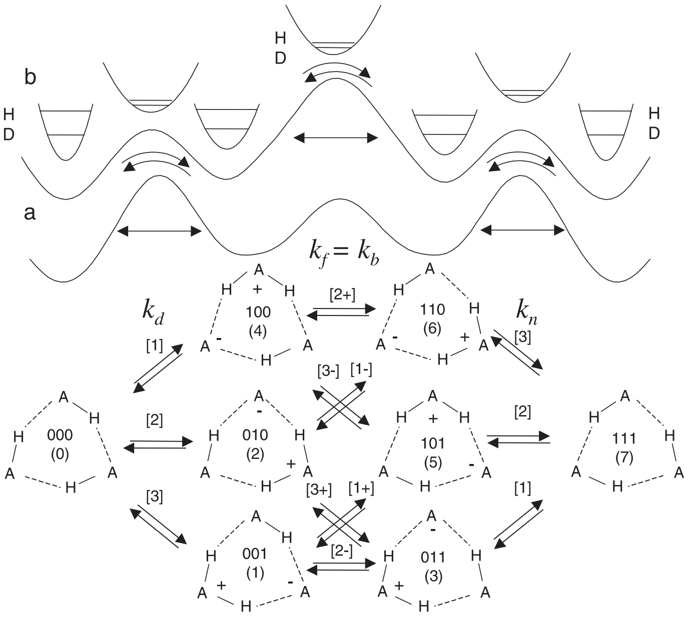


Fig. 3. Degenerate triple-barrier triple hydron transfer involving two zwitterionic intermediates. A complete transfer consists of a dissociation step, one or more cation or anion “propagation” steps, characterized by the forward and backward rate constants $k_\mathrm{f} = k_\mathrm{b}$, and a neutralization step. The isotope dependent rate constants $k_\mathrm{f} = k_\mathrm{b}$ depend on whether a cation or an anion is propagated. Cation and anion propagation are included in the square brackets indicating the hydron number transferred as plus- or minus sign in the square brackets. The rate limiting step may correspond to the propagation (a) or the dissociation (b). In each step only a single hydron looses zero-point energy at the configuration at the top of the barrier. Isotopic fractionation.

2.3.1 *Dissociation and neutralization as rate limiting steps*

For the reaction profile of Fig. 3a where the dissociation and the neutralization are the rate limiting steps, *i.e.* $k_\mathrm{n} \ll k_\mathrm{f}$ we obtain

$$k^{\mathrm{LLL}} = k^{[1][2][3]} \tag{18}$$

$$= \frac{\left(k_\mathrm{d}^{[1]} + k_\mathrm{d}^{[2]} + k_\mathrm{d}^{[3]}\right)\left(k_\mathrm{n}^{[1]} + k_\mathrm{n}^{[2]} + k_\mathrm{n}^{[3]}\right)}{\left(k_\mathrm{n}^{[1]} + k_\mathrm{n}^{[2]} + k_\mathrm{n}^{[3]}\right) + \left(k_\mathrm{n}^{[1]} + k_\mathrm{n}^{[2]} + k_\mathrm{n}^{[3]}\right)} = \frac{1}{2}\left[k_\mathrm{d}^{[1]} + k_\mathrm{d}^{[2]} + k_\mathrm{d}^{[3]}\right] .$$

With the single primary isotope effects $P_\mathrm{d} = k_\mathrm{d}^\mathrm{H}/k_\mathrm{d}^\mathrm{D}$ we obtain

$$k^{\mathrm{HHH}} = \frac{3}{2} k_\mathrm{d}^\mathrm{H} , \tag{19}$$

$$k^{\mathrm{HHD}} = \frac{1}{2} k_\mathrm{d}^\mathrm{H}\left[2 + P_\mathrm{d}^{-1}\right] , \tag{20}$$

$$k^{\mathrm{HDD}} = \frac{1}{2} k_{\mathrm{d}}^{\mathrm{H}} \left[1 + 2P_{\mathrm{d}}^{-1}\right] , \tag{21}$$

$$k^{\mathrm{DDD}} = \frac{3}{2} P_{\mathrm{d}}^{-1} k_{\mathrm{d}}^{\mathrm{H}} . \tag{22}$$

2.3.2 Proton propagation as rate limiting steps

For the reaction profile of Fig. 3b where the propagation transfer step is rate limiting we obtain

$$k = K_{\mathrm{d}}^{[1]} \left(k_{\mathrm{f}}^{[2+]} + k_{\mathrm{f}}^{[3-]}\right) + K_{\mathrm{d}}^{[2]} \left(k_{\mathrm{f}}^{[1-]} + k_{\mathrm{f}}^{[3+]}\right) + K_{\mathrm{d}}^{[3]} \left(k_{\mathrm{f}}^{[1+]} + k_{\mathrm{f}}^{[2-]}\right) . \tag{23}$$

Here, we have introduced a plus or minus superscript in order to indicate a cation or an anion transfer. We define now a “commitment” factor

$$\alpha = k_{\mathrm{f}}^{i-} / k_{\mathrm{f}}^{i+} \tag{24}$$

as the ratio between the rate constants of corresponding anion and cation transfers. We assume that α is the same for the isotopic reactions, *i.e.* that P_{f} is the same for the cation and the anion propagation. Thus, we can now drop the plus superscript, *i.e.* k_{f}^{i} refers now only to the cation transfer rate constants. It follows that

$$k = K_{\mathrm{d}}^{[1]} \left(k_{\mathrm{f}}^{[2]} + \alpha k_{\mathrm{f}}^{[3]}\right) + K_{\mathrm{d}}^{[2]} \left(\alpha k_{\mathrm{f}}^{[1]} + k_{\mathrm{f}}^{[3]}\right) + K_{\mathrm{d}}^{[3]} \left(k_{\mathrm{f}}^{[1]} + \alpha k_{\mathrm{f}}^{[2]}\right) . \tag{25}$$

In order to obtain the isotopic rate constants we write

$$\begin{aligned} k_{\mathrm{f}}^{[i]} &= k_{\mathrm{f}}^{\mathrm{H}} \quad \text{for} \quad i = \mathrm{H} \quad \text{and} \quad k_{\mathrm{f}}^{[i]} = P_{\mathrm{f}}^{-1} k_{\mathrm{f}}^{\mathrm{H}} \quad \text{for} \quad i = \mathrm{D} \\ K_{\mathrm{d}}^{[i]} &= K_{\mathrm{d}}^{\mathrm{H}} \quad \text{for} \quad i = \mathrm{H} \quad \text{and} \quad K_{\mathrm{d}}^{[i]} = \phi_{\mathrm{d}} K_{\mathrm{d}}^{\mathrm{H}} \quad \text{for} \quad i = \mathrm{D} . \end{aligned} \tag{26}$$

We find that

$$k^{\mathrm{HHH}} = 3 k_{\mathrm{f}}^{\mathrm{H}} K_{\mathrm{d}}^{\mathrm{H}} (1 + \alpha) , \tag{27}$$

$$k^{\mathrm{HHD}} = k_{\mathrm{f}}^{\mathrm{H}} K_{\mathrm{d}}^{\mathrm{H}} (1 + \alpha) \left[1 + P_{\mathrm{f}}^{-1} + \phi_{\mathrm{d}}\right] , \tag{28}$$

$$k^{\mathrm{HDD}} = k_{\mathrm{f}}^{\mathrm{H}} K_{\mathrm{d}}^{\mathrm{H}} (1 + \alpha) \left[P_{\mathrm{f}}^{-1} + \phi_{\mathrm{d}} + \phi_{\mathrm{d}} P_{\mathrm{f}}^{-1}\right] , \tag{29}$$

$$k^{\mathrm{DDD}} = 3 k_{\mathrm{f}}^{\mathrm{H}} K_{\mathrm{d}}^{\mathrm{H}} (1 + \alpha) \phi_{\mathrm{d}} P_{\mathrm{f}}^{-1} . \tag{30}$$

2.4 Degenerate two-step quadruple proton transfer

In this section we treat the case of a degenerate two-step quadruple proton transfer reaction according to Fig. 4. In each step two hydrons are transferred.

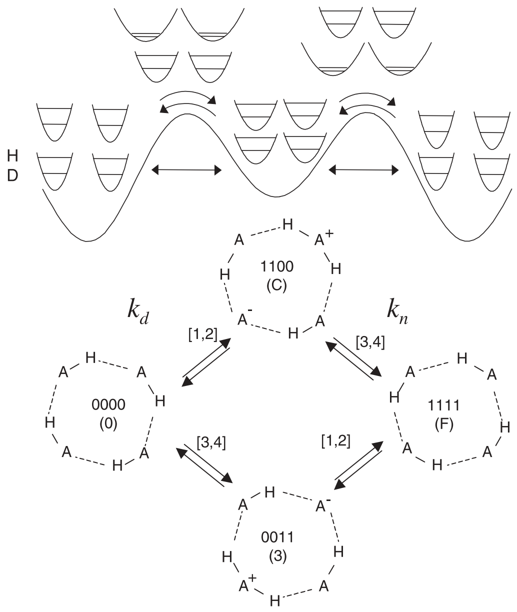


Fig. 4. Degenerate two-barrier quadruple hydron transfer involving a single zwitterionic intermediate. Two hydrons loose zero-point energy in the configuration corresponding to the top of the barrier. Isotopic fractionation ϕ_d can occur for the dissociation.

The reaction diagram corresponds to the network of Scheme 1. As in each step two hydrons are transferred we label the rate constants correspondingly. Because of the symmetry of the system it follows that

$$\begin{aligned}
&k_\mathrm{AB}^\mathrm{HH} = k_\mathrm{AC}^\mathrm{HH} = k_\mathrm{DB}^\mathrm{HH} = k_\mathrm{DC}^\mathrm{HH} = k_\mathrm{d}^\mathrm{HH}, \quad k_\mathrm{BA}^\mathrm{HH} = k_\mathrm{CA}^\mathrm{HH} = k_\mathrm{BD}^\mathrm{HH} = k_\mathrm{CD}^\mathrm{HH} = k_\mathrm{n}^\mathrm{HH}, \qquad (31)\\
&k_\mathrm{d}^\mathrm{HD} = P_\mathrm{d1}^{-1} k_\mathrm{d}^\mathrm{HH}, \quad k_\mathrm{n}^\mathrm{HD} = P_\mathrm{n1}^{-1} k_\mathrm{d}^\mathrm{HH},\\
&k_\mathrm{d}^\mathrm{DD} = P_\mathrm{d1}^{-1} P_\mathrm{d2}^{-1} k_\mathrm{d}^\mathrm{HH}, \quad k_\mathrm{n}^\mathrm{HD} = P_\mathrm{n1}^{-1} P_\mathrm{n2}^{-1} k_\mathrm{d}^\mathrm{HH}\\
&\phi_\mathrm{d} = P_\mathrm{n1}/P_\mathrm{d1} = P_\mathrm{n2}/P_\mathrm{d2} = P_\mathrm{n}/P_\mathrm{d}\,.
\end{aligned}$$

From Eq. (4) it follows that

$$k^\mathrm{HHHH} = \frac{k_\mathrm{BD}^\mathrm{HH} k_\mathrm{AB}^\mathrm{HH}}{k_\mathrm{BA}^\mathrm{HH} + k_\mathrm{BD}^\mathrm{HH}} + \frac{k_\mathrm{CD}^\mathrm{HH} k_\mathrm{AC}^\mathrm{HH}}{k_\mathrm{CA}^\mathrm{HH} + k_\mathrm{CD}^\mathrm{HH}} = k_\mathrm{d}^\mathrm{HH} \qquad (32)$$

$$k^\mathrm{HDHH} = \frac{k_\mathrm{AB}^\mathrm{HD} k_\mathrm{BD}^\mathrm{HH}}{k_\mathrm{BA}^\mathrm{HD} + k_\mathrm{BD}^\mathrm{HH}} + \frac{k_\mathrm{AC}^\mathrm{HH} k_\mathrm{CD}^\mathrm{HD}}{k_\mathrm{CA}^\mathrm{HH} + k_\mathrm{CD}^\mathrm{HD}} = k_\mathrm{d}^\mathrm{HH} P_\mathrm{d1}^{-1} \frac{1+\phi_\mathrm{d}}{1+P_\mathrm{d1}^{-1}\phi_\mathrm{d}} \qquad (33)$$

$$k^{\mathrm{DDHH}} = \frac{k_{\mathrm{BD}}^{\mathrm{HH}} k_{\mathrm{AB}}^{\mathrm{DD}}}{k_{\mathrm{BA}}^{\mathrm{DD}} + k_{\mathrm{BD}}^{\mathrm{HH}}} + \frac{k_{\mathrm{CD}}^{\mathrm{DD}} k_{\mathrm{AC}}^{\mathrm{HH}}}{k_{\mathrm{CA}}^{\mathrm{HH}} + k_{\mathrm{CD}}^{\mathrm{DD}}} = k_{\mathrm{d}}^{\mathrm{HH}} P_{\mathrm{d1}}^{-1} P_{\mathrm{d2}}^{-1} \frac{1+\phi_{\mathrm{d}}^{2}}{1+\phi_{\mathrm{d}}^{2} P_{\mathrm{d1}}^{-1} P_{\mathrm{d2}}^{-1}} = k^{\mathrm{HHDD}} \tag{34}$$

$$k^{\mathrm{HDHD}} = \frac{k_{\mathrm{BD}}^{\mathrm{HD}} k_{\mathrm{AB}}^{\mathrm{HD}}}{k_{\mathrm{BA}}^{\mathrm{HD}} + k_{\mathrm{BD}}^{\mathrm{HD}}} + \frac{k_{\mathrm{CD}}^{\mathrm{HD}} k_{\mathrm{AC}}^{\mathrm{HD}}}{k_{\mathrm{CA}}^{\mathrm{HD}} + k_{\mathrm{CD}}^{\mathrm{HD}}} = k_{\mathrm{d}}^{\mathrm{HH}} P_{\mathrm{d1}}^{-1} \tag{35}$$

$$k^{\mathrm{HDDD}} = \frac{k_{\mathrm{BD}}^{\mathrm{DD}} k_{\mathrm{AB}}^{\mathrm{HD}}}{k_{\mathrm{BA}}^{\mathrm{HD}} + k_{\mathrm{BD}}^{\mathrm{DD}}} + \frac{k_{\mathrm{CD}}^{\mathrm{HD}} k_{\mathrm{AC}}^{\mathrm{DD}}}{k_{\mathrm{CA}}^{\mathrm{DD}} + k_{\mathrm{CD}}^{\mathrm{HD}}} = k_{\mathrm{d}}^{\mathrm{HH}} P_{\mathrm{d1}}^{-1} P_{\mathrm{d2}}^{-1} \frac{1+\phi_{\mathrm{d}}}{1+\phi_{\mathrm{d}} P_{\mathrm{d2}}^{-1}} \tag{36}$$

$$k^{\mathrm{DDDD}} = \frac{k_{\mathrm{BD}}^{\mathrm{DD}} k_{\mathrm{AB}}^{\mathrm{DD}}}{k_{\mathrm{BA}}^{\mathrm{DD}} + k_{\mathrm{BD}}^{\mathrm{DD}}} + \frac{k_{\mathrm{CD}}^{\mathrm{DD}} k_{\mathrm{AC}}^{\mathrm{DD}}}{k_{\mathrm{CA}}^{\mathrm{DD}} + k_{\mathrm{CD}}^{\mathrm{DD}}} = k_{\mathrm{d}}^{\mathrm{HH}} P_{\mathrm{d1}}^{-1} P_{\mathrm{d2}}^{-1} \, . \tag{37}$$

2.5 Degenerate four barrier quadruple proton transfer

In this section we treat the case of a degenerate four-step quadruple proton transfer reaction with a single proton transfer in each step as indicated in Fig. 2. We need to take into account 16 tautomeric states which we label as 0000 to 1111 as indicated in Fig. 5. We exclude however the states 0101 and 1010 which exhibit two cations and two anions as unphysical.

The treatment of this reaction scheme in terms of Eq. (1) is very tedious. The problem is the large number of rate constants of all individual reaction steps. Therefore, we will focus here only on partial solutions representing two limiting cases, *i.e.* dissociation – recombination and propagation as rate limiting steps, in a similar way as in the case of the triple proton transfer.

2.5.1 Dissociation and neutralization as rate limiting steps

The first case is illustrated in Fig. 6 in more detail. It strongly resembles the corresponding triple proton transfer case. All the inner states 2 to D are rapidly interconverting and their ensemble can then be treated as a single intermediate state I. This state is reached by the dissociation of one of the four protons, and annihilated by neutralization. By analogy to Eq. (18) we obtain

$$k^{\mathrm{LLLL}} = \frac{1}{2} \left[k_{\mathrm{d}}^{[1]} + k_{\mathrm{d}}^{[2]} + k_{\mathrm{d}}^{[3]} + k_{\mathrm{d}}^{[4]} \right] . \tag{38}$$

We obtain

$$k^{\mathrm{HHHH}} = 2k_{\mathrm{d}}^{\mathrm{H}} \, , \tag{39}$$

$$k^{\mathrm{HHHD}} = \frac{1}{2} k_{\mathrm{d}}^{\mathrm{H}} \left[3 + P_{\mathrm{d}}^{-1} \right] , \tag{40}$$

$$k^{\mathrm{HHDD}} = k^{\mathrm{HDHD}} = k_{\mathrm{d}}^{\mathrm{H}} \left[1 + P_{\mathrm{d}}^{-1} \right] , \tag{41}$$

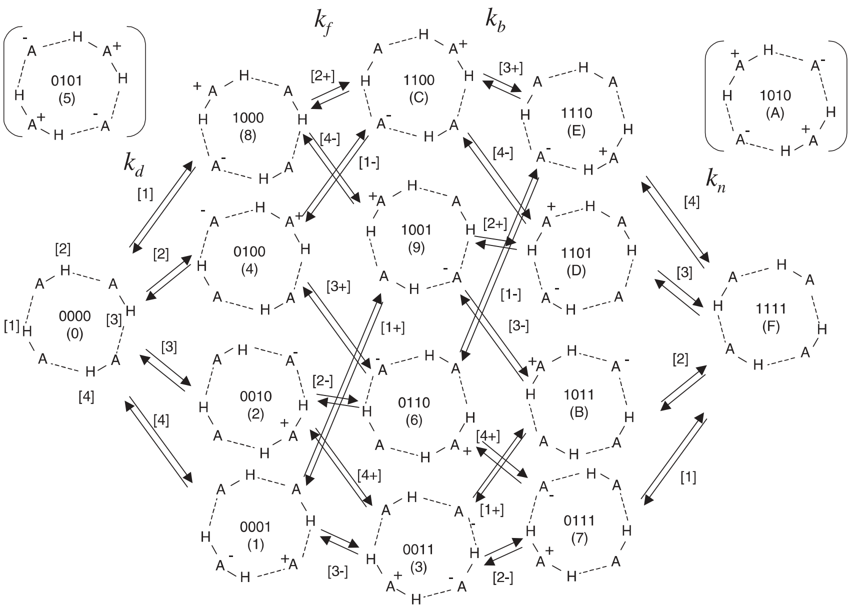


Fig. 5. Degenerate quadruple barrier quadruple hydron transfer. A complete transfer consists of a dissociation step, two or more propagation steps or more steps and a neutralization step. The double-cation-double-anion intermediates 0101 and 1010 are not further considered as they are considered as very high in energy.

$$k^{\mathrm{HDDD}} = \frac{1}{2} k_{\mathrm{d}}^{\mathrm{H}} \left[1 + 3P_{\mathrm{d}}^{-1}\right] , \tag{42}$$

$$k^{\mathrm{DDDD}} = 2 k_{\mathrm{d}}^{\mathrm{H}} P_{\mathrm{d}}^{-1} . \tag{43}$$

2.5.2 Proton propagation as rate limiting step

In the second case we assume that the propagation steps are rate limiting. However, even in this case it is not easy to find simple expressions for the kinetic isotope effects. As we deal here only with single proton transfers the intermediate states C, 9, 6, and 3 in Fig. 5 cannot interconvert directly and the complex reaction network factorizes into four subsystems as illustrated in Fig. 7. The total rate constant corresponds then to the sum of the rate constants of each subsystems. We introduce according to Fig. 7 the forward $k_{\mathrm{f}}^{[i\pm]}$and backward $k_{\mathrm{b}}^{[i\pm]}$ rate constants of the propagation steps transfer of hydron i, where we have added a plus or minus sign in order to indicate a cation or anion transfer. By application of Eq. (4) to the first subsystem involving C as intermediate it follows that

$$k_{0\mathrm{F}} = \frac{k_{0\mathrm{C}} k_{\mathrm{CF}}}{k_{\mathrm{C}0} + k_{\mathrm{CF}}} . \tag{44}$$

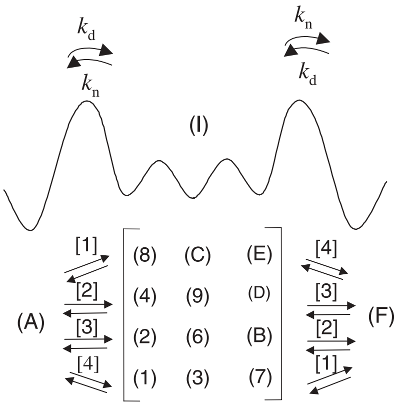


Fig. 6. Dissociation as rate limiting step in the degenerate quadruple barrier quadruple hydron transfer. The 12 zwitterionic intermediates interconvert rapidly and can be considered one single intermediate I which can be reached by dissociation of each of the four hydrons.

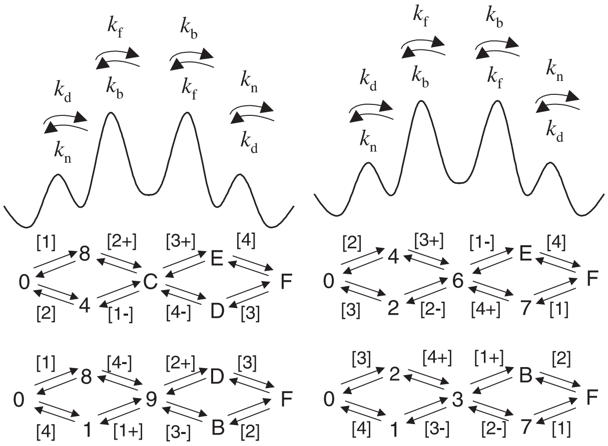


Fig. 7. Cation and anion propagation as rate limiting step in the degenerate quadruple barrier quadruple hydron transfer. The reaction network factorizes in four parts which can be treated separately as indicated in the text.

With

$$\begin{aligned} k_{0C} &= \frac{k_{08}k_{8C}}{k_{80}+k_{8C}} + \frac{k_{04}k_{4C}}{k_{40}+k_{4C}} \approx \frac{k_{08}k_{8C}}{k_{80}} + \frac{k_{04}k_{4C}}{k_{40}} \\ &= K_d^{[1]}k_{8C} + K_d^{[2]}k_{4C} = K_d^{[1]}k_f^{[2+]} + K_d^{[2]}k_f^{[1-]}\,, \end{aligned} \tag{45}$$

$$k_{\mathrm{C0}} = \frac{k_{\mathrm{C8}} k_{80}}{k_{\mathrm{8C}} + k_{80}} + \frac{k_{\mathrm{C4}} k_{40}}{k_{\mathrm{4C}} + k_{40}} \approx k_{\mathrm{C8}} + k_{\mathrm{C4}} = k_{\mathrm{b}}^{[2+]} + k_{\mathrm{b}}^{[1-]} ,$$

$$k_{\mathrm{CF}} = k_{\mathrm{C8}} + k_{\mathrm{C4}} = k_{\mathrm{b}}^{[3+]} + k_{\mathrm{b}}^{[4-]}$$

we obtain

$$k_{\mathrm{0F}} = \frac{k_{\mathrm{0C}} k_{\mathrm{CF}}}{k_{\mathrm{C0}} + k_{\mathrm{CF}}} = \frac{\left(K_{\mathrm{d}}^{[1]} k_{\mathrm{f}}^{[2+]} + K_{\mathrm{d}}^{[2]} k_{\mathrm{f}}^{[1-]}\right)\left(k_{\mathrm{b}}^{[3+]} + k_{\mathrm{b}}^{[4-]}\right)}{k_{\mathrm{b}}^{[2+]} + k_{\mathrm{b}}^{[1-]} + k_{\mathrm{b}}^{[3+]} + k_{\mathrm{b}}^{[4-]}} \tag{46}$$

where $K_{\mathrm{d}}^{[i]}$ is the equilibrium constant of dissociation of the proton in site i. The total rate constant is then given by the sum of the four terms indicated in Fig. 7, *i.e.*

$$\begin{aligned} k = \Bigg[& \frac{\left(K_1^{[1]} k_{\mathrm{f}}^{[2+]} + K_1^{[2]} k_{\mathrm{f}}^{[1-]}\right)\left(k_{\mathrm{b}}^{[3+]} + k_{\mathrm{b}}^{[4-]}\right)}{\left(k_{\mathrm{b}}^{[2+]} + k_{\mathrm{b}}^{[1-]} + k_{\mathrm{b}}^{[3+]} + k_{\mathrm{b}}^{[4-]}\right)} \\ & + \frac{\left(K_1^{[4]} k_{\mathrm{f}}^{[1+]} + K_1^{[1]} k_{\mathrm{f}}^{[4-]}\right)\left(k_{\mathrm{b}}^{[2+]} + k_{\mathrm{b}}^{[3-]}\right)}{\left(k_{\mathrm{b}}^{[1+]} + k_{\mathrm{b}}^{[4-]} + k_{\mathrm{b}}^{[2+]} + k_{\mathrm{b}}^{[3-]}\right)} \\ & + \frac{\left(K_1^{[2]} k_{\mathrm{f}}^{[3+]} + K_1^{[3]} k_{\mathrm{f}}^{[2-]}\right)\left(k_{\mathrm{b}}^{[4+]} + k_{\mathrm{b}}^{[1-]}\right)}{\left(k_{\mathrm{b}}^{[3+]} + k_{\mathrm{b}}^{[2-]} + k_{\mathrm{b}}^{[4+]} + k_{\mathrm{b}}^{[1-]}\right)} \\ & + \frac{\left(K_1^{[3]} k_{\mathrm{f}}^{[4+]} + K_1^{[4]} k_{\mathrm{f}}^{[3-]}\right)\left(k_{\mathrm{b}}^{[1+]} + k_{\mathrm{b}}^{[2-]}\right)}{\left(k_{\mathrm{b}}^{[4+]} + k_{\mathrm{b}}^{[3-]} + k_{\mathrm{b}}^{[1+]} + k_{\mathrm{b}}^{[2-]}\right)} \Bigg] . \end{aligned} \tag{47}$$

Defining again the “commitment” factor α

$$k_{\mathrm{f}}^{i-} = \alpha k_{\mathrm{f}}^{i+} = \alpha k_{\mathrm{f}}^{i} \text{ and } k_{\mathrm{b}}^{i-} = \alpha k_{\mathrm{b}}^{i+} = \alpha k_{\mathrm{b}}^{i} \tag{48}$$

as the ratio between the rate constants of corresponding anion and cation transfers, we drop again the plus superscript for cation transfer and write

$$\begin{aligned} k = \Bigg[& \frac{\left(K_1^{[1]} k_{\mathrm{f}}^{[2]} + \alpha K_1^{[2]} k_{\mathrm{f}}^{[1]}\right)\left(k_{\mathrm{b}}^{[3]} + \alpha k_{\mathrm{b}}^{[4]}\right)}{\left(k_{\mathrm{b}}^{[2]} + \alpha k_{\mathrm{b}}^{[1]} + k_{\mathrm{b}}^{[3]} + \alpha k_{\mathrm{b}}^{[4]}\right)} + \frac{\left(K_1^{[4]} k_{\mathrm{f}}^{[1]} + \alpha K_1^{[1]} k_{\mathrm{f}}^{[4]}\right)\left(k_{\mathrm{b}}^{[2]} + \alpha k_{\mathrm{b}}^{[3]}\right)}{\left(k_{\mathrm{b}}^{[1]} + \alpha k_{\mathrm{b}}^{[4]} + k_{\mathrm{b}}^{[2]} + \alpha k_{\mathrm{b}}^{[3]}\right)} \\ & + \frac{\left(K_1^{[2]} k_{\mathrm{f}}^{[3]} + \alpha K_1^{[3]} k_{\mathrm{f}}^{[2]}\right)\left(k_{\mathrm{b}}^{[4]} + \alpha k_{\mathrm{b}}^{[1]}\right)}{\left(k_{\mathrm{b}}^{[3]} + \alpha k_{\mathrm{b}}^{[2]} + k_{\mathrm{b}}^{[4]} + \alpha k_{\mathrm{b}}^{[1]}\right)} + \frac{\left(K_1^{[3]} k_{\mathrm{f}}^{[4]} + \alpha K_1^{[4]} k_{\mathrm{f}}^{[3]}\right)\left(k_{\mathrm{b}}^{[1]} + \alpha k_{\mathrm{b}}^{[2]}\right)}{\left(k_{\mathrm{b}}^{[4]} + \alpha k_{\mathrm{b}}^{[3]} + k_{\mathrm{b}}^{[1]} + \alpha k_{\mathrm{b}}^{[2]}\right)} \Bigg] . \end{aligned} \tag{49}$$

With the kinetic isotope effects P_{f} and P_{b} and the fractionation factor

$$\phi_{\mathrm{f}} = P_{\mathrm{b}}^{-1} \,/\, P_{\mathrm{f}}^{-1} \tag{50}$$

of the propagation step we finally obtain

$$k^{\mathrm{HHHH}} = 2k_{\mathrm{f}}^{\mathrm{H}}(1+\alpha)K_1^{\mathrm{H}}\,, \tag{51}$$

$$k^{\mathrm{HHHD}} = \frac{k^{\mathrm{HHHH}}}{2}\left[\frac{1+\phi_{\mathrm{d}}+\alpha P_{\mathrm{f}}^{-1}(1+\phi_{\mathrm{f}})}{\left(2+\alpha+\alpha\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)} + \frac{\alpha(1+\phi_{\mathrm{d}})+P_{\mathrm{f}}^{-1}(1+\phi_{\mathrm{f}})}{\left(1+2\alpha+\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)}\right], \tag{52}$$

$$k^{\mathrm{HHDD}} = k^{\mathrm{HHHH}}\left[\frac{P_{\mathrm{f}}^{-1}(\phi_{\mathrm{f}}+\phi_{\mathrm{d}})}{2\left(1+\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)} + \frac{\phi_{\mathrm{d}}+P_{\mathrm{f}}^{-1}}{4}\right], \tag{53}$$

$$k^{\mathrm{HDHD}} = k^{\mathrm{HHHH}}\left[\frac{\left(P_{\mathrm{f}}^{-1}+\alpha\phi_{\mathrm{d}}\right)\left(1+\alpha\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)+\left(\phi_{\mathrm{d}}+\alpha P_{\mathrm{f}}^{-1}\right)\left(\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}+\alpha\right)}{(1+\alpha)^2\left(1+\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)}\right], \tag{54}$$

$$\begin{aligned} k^{\mathrm{HDDD}} = \frac{k^{\mathrm{HHHH}}}{2}P_{\mathrm{f}}^{-1}\Bigg[&\frac{\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}(1+\phi_{\mathrm{d}})+\alpha\phi_{\mathrm{d}}(\phi_{\mathrm{f}}+1)}{\left(2\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}+\alpha+\alpha\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)} \\ &+\frac{\alpha\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}(1+\phi_{\mathrm{d}})+\phi_{\mathrm{d}}(1+\phi_{\mathrm{f}})}{\left(1+2\alpha\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}+\phi_{\mathrm{f}}P_{\mathrm{f}}^{-1}\right)}\Bigg], \end{aligned} \tag{55}$$

$$k^{\mathrm{DDDD}} = P_{\mathrm{f}}^{-1}\phi_{\mathrm{d}}k^{\mathrm{HHHH}}\,. \tag{56}$$

2.6 Summary of kinetic isotope effects

In order to discuss later the kinetic expressions derived we have summarized them in Tables 1 to 3 for some special cases.

Table 1. Kinetic Isotope Effects of degenerate double proton transfer.

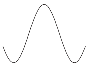
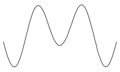
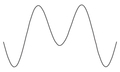
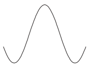
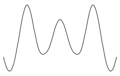
			
case	$P_1 = P_2 = P$		$P^{-1} = S_{\mathrm{d}}^{-1} =$ $P_{\mathrm{d}}^{-1} = S_{\mathrm{n}}^{-1} = P_{\mathrm{n}}^{-1}$
$\frac{k^{\mathrm{HD}}}{k^{\mathrm{HH}}}$	P^{-1}	$P_{\mathrm{d}}^{-1}\left[\frac{\phi_{\mathrm{d}}S_{\mathrm{n}}^{-1}+S_{\mathrm{d}}^{-1}}{\phi_{\mathrm{d}}S_{\mathrm{n}}^{-1}+P_{\mathrm{d}}^{-1}}\right]$	P^{-1}
$\frac{k^{\mathrm{DD}}}{k^{\mathrm{HH}}}$	P^{-2}	$P_{\mathrm{d}}^{-1}S_{\mathrm{d}}^{-1}$	P^{-2}

Table 2. Kinetic isotope effects of degenerate triple proton transfer.

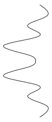
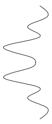
			
KIE	$P_1 = P_2 = P_3 = P$	–	$\phi_d < 1,\ P_f^{-1} \ll 1$
$\frac{k^{HHD}}{k^{HHH}}$	P^{-1}	$\frac{1}{3}\left[2 + P_d^{-1}\right]$	$\frac{1}{3}\left[1 + \phi_d\right]$
$\frac{k^{HDD}}{k^{HHH}}$	P^{-2}	$\frac{1}{3}\left[1 + 2P_d^{-1}\right]$	$\frac{\phi_d}{3}$
$\frac{k^{DDD}}{k^{HHH}}$	P^{-3}	P_d^{-1}	$P_f^{-1}\phi_d$

2.7 A modified bell tunneling model for multiple H transfer reactions

In the above treatment we did not yet describe the temperature dependence of the rate constants. For this purpose, we describe in this section a modified Bell tunnel model, although we are aware that more rigorous quantum-mechanical treatments are possible. The modified Bell treatment has the advantage of the simplest possible model. The experimentalist can then check whether his data provide enough information to go beyond this simple model.

The Bell tunneling model [2] is a very crude one-dimensional model which does not take into account the variation of the barrier for proton transfer with changes of the hydrogen bond geometries caused by vibrational excitation, as has been discussed by Gerritzen and Limbach [8a]. According to Fig. 8 we define the coordinates $q_1 = \frac{1}{2}(r_1 - r_2)$ and $q_2 = r_1 + r_2$, where r_1 and r_2 correspond to the two heavy atom-H bond lengths. In the case of linear hydrogen bonds q_1 represents the distance of H from the H-bond center and q_2 the distance between the two heavy atoms. As depicted schematically in Fig. 8a, the barrier of the double well describing the proton motion decreases when q_2 is decreased, and eventually a single well configuration can be reached. Quantization of the AH vibrational states is indicated by the horizontal lines in each well. Only few states are available, here only the vibrational ground states are indicated. Within the Bell model it is assumed, that coherent tunneling is destroyed by inter- and intramolecular interactions which can give rise to tunnel splittings. The two-dimensional model can then be reduced to a one-dimensional Bell model by setting $E_d = \text{constant}$ as indicated in Fig. 8b and by assuming a continuous distribution of configurations with different values of q_2. Such as situation can

Table 3. Kinetic isotope effects of degenerate quadruple proton transfer.

					
KIE	$P_1 = P_2 =$ $P_3 = P$	$P_{d1}^{-1} = P_{d2}^{-1}$ $= P_d^{-1} \ll 1$	$P_d^{-1} \ll 1$	$\phi_d < 1, \phi_f < 1,$ $P_f^{-1} \ll 1, \alpha = 1$	$\phi_d < 1, \phi_f < 1,$ $P_f^{-1} \ll 1, \alpha = 0$
$\frac{k^{\mathrm{HHHD}}}{k^{\mathrm{HHHH}}}$	P^{-1}	$P_d^{-1}(1+\phi_d^{-1})$	$\frac{3}{4}$	$\frac{1+\phi_d}{3}$	$\frac{1+\phi_d}{4}$
$\frac{k^{\mathrm{HHDD}}}{k^{\mathrm{HHHH}}}$	P^{-2}	$P_d^{-2}(1+\phi_d^{-2})$	$\frac{1}{2}$	$\frac{\phi_d}{4}$	$\frac{\phi_d}{4}$
$\frac{k^{\mathrm{HDHD}}}{k^{\mathrm{HHHH}}}$	P^{-2}	P_d^{-1}	$\frac{1}{2}$	$\frac{\phi_d}{2}$	$P_f^{-1}(1+\phi_d\phi_f)$
$\frac{k^{\mathrm{HDDD}}}{k^{\mathrm{HHHH}}}$	P^{-3}	$P_d^{-2}(1+\phi_d^{-1})$	$\frac{1}{4}$	$P_f^{-1}\phi_d(1+\phi_f)$	$\frac{P_f^{-1}(1+3\phi_d+2\phi_d\phi_f)}{4}$
$\frac{k^{\mathrm{DDDD}}}{k^{\mathrm{HHHH}}}$	P^{-4}	P_d^{-2}	P_d^{-1}	$P_f^{-1}\phi_d$	$P_f^{-1}\phi_d$

be practically reached by excitation of low-frequency H-bond vibrations or phonons. The situation of Fig. 8b can be practically be replaced by an inverted parabola as a barrier, with a continuous distribution of vibrational levels on both sides of the barrier, which leads to the one-dimensional modified Bell model indicated in Fig. 9. This model will now be explained in more detail.

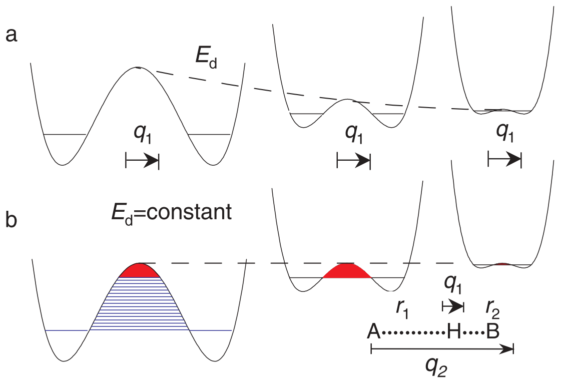


Fig. 8. Reduction of a two-dimensional double-well potential problem to a one-dimensional Bell model. Adapted from Ref. [8a]. For further description see text.

According to Bell, the probablility of a particle passing through or crossing a barrier is given by [2]

$$G(W) = \frac{1}{1 + D(W)}\,, \tag{57}$$

where W represents the energy of the particle and $D(W)$ the transmission coefficient, given according to Wenzels–Kramers–Brioullin approximation [18] by

$$D = \exp\left(-\frac{2}{\hbar}\int\limits_{-a}^{a} p_i \mathrm{d}x\right) = \exp\left(-\frac{2}{\hbar}\int\limits_{-a'}^{a'} \sqrt{2m\,(V(x) - W)}\mathrm{d}x\right)\,. \tag{58}$$

p_i represents the momentum and m the mass of the particle moving in x-direction, and $V(x)$ the potential energy experienced by the particle. a' represents the position of the particle when it enters or leaves the barrier region. Classically $G(W) = 0$ for $W < E_\mathrm{d}$ and $G(W) = 1$ for $W > E_\mathrm{d}$, but quantum mechanically $G(W) > 0$ for $W \leqq E_\mathrm{d}$ and $G(W) < 1$ for $W \geqq E_\mathrm{d}$. We note here that D is related to the energy splitting of a symmetric double oscillator by [18]

$$\Delta E = \frac{h\nu}{\pi} D^{1/2}\,. \tag{59}$$

Assuming that the barrier region can be approximated by an inverted barrier, *i.e.*

$$V(x) = E_\mathrm{d}\left(1 - \frac{x^2}{a^2}\right), \quad W = E_\mathrm{d}\left(1 - \frac{a'^2}{a^2}\right)\,. \tag{60}$$

Here, $2a$ represents the barrier width (Å), E_d the barrier energy.

One can easily show that

$$D(W) = \exp\left(-\frac{E_\mathrm{d} - W}{h\omega_t}\right), \quad \omega_t = 2\pi\nu_t = \frac{1}{\pi a}\sqrt{\frac{E_\mathrm{d}}{2m}}, \tag{61}$$

where ν_t represents a "tunnel frequency".

The fraction of particles in the energy interval dW is given by the Boltzmann law

$$\frac{\mathrm{d}N}{N} = \frac{\exp\left(-W/kT\right)\mathrm{d}W}{\int\limits_0^\infty \exp\left(-W/kT\right)\mathrm{d}W} = \frac{1}{kT}\exp\left(-W/kT\right)\mathrm{d}W\,. \tag{62}$$

The classical integrated reaction probability is then given by

$$\left(\frac{\Delta N}{N}\right)_\mathrm{class} = \frac{1}{kT}\int\limits_{E_\mathrm{d}}^\infty \exp\left(-W/kT\right)\mathrm{d}W = \exp\left(-E_\mathrm{d}/kT\right)\,, \tag{63}$$

the quantum mechanical integrated reaction probability by

$$\left(\frac{\Delta N}{N}\right)_\mathrm{QM} = \frac{1}{kT}\int\limits_0^\infty G(W)\exp\left(-W/kT\right)\mathrm{d}W\,, \tag{64}$$

and the ratio both quantities by

$$\begin{aligned} Q_t = \frac{\left(\frac{\Delta N}{N}\right)_\mathrm{QM}}{\left(\frac{\Delta N}{N}\right)_\mathrm{class}} &= \frac{\frac{1}{kT}\int_0^\infty G(W)\exp\left(-W/kT\right)\mathrm{d}W}{\exp\left(-E_\mathrm{d}/kT\right)} \\ &= \int\limits_0^\infty \frac{G(W)}{kT}\exp\left(\left(E_\mathrm{d} - W\right)/kT\right)\mathrm{d}W\,. \end{aligned} \tag{65}$$

Using an Arrhenius type law for the classical temperature dependence it follows that

$$k = k_\mathrm{class}Q_t = A\exp(-E_\mathrm{d}/kT)\int\limits_0^\infty \frac{G(W)}{kT}\exp\left(\left(E_\mathrm{d} - W\right)/kT\right)\mathrm{d}W\,. \tag{66}$$

Replacing the Boltzmann constant by the gas constant, and introducing a superscript as label for the isotope L = H, D it follows that

$$k^\mathrm{L} = A^\mathrm{L}\exp\left(-E_\mathrm{d}^\mathrm{L}/RT\right)\int\limits_0^\infty \frac{G^\mathrm{L}(W)}{RT}\exp\left(\left(E_\mathrm{d}^\mathrm{L} - W\right)/RT\right)\mathrm{d}W, \mathrm{L} = \mathrm{H}, \mathrm{D}\,. \tag{67}$$

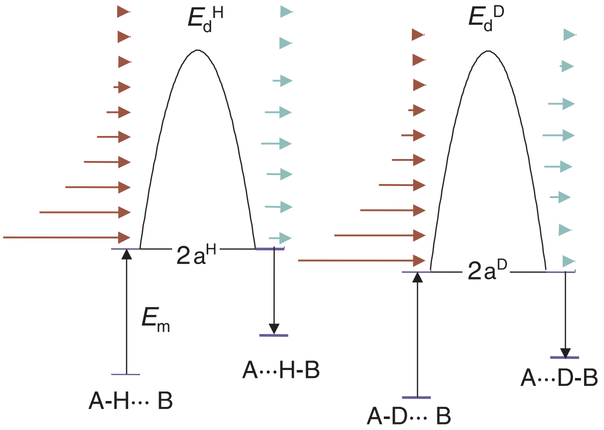


Fig. 9. Modified Bell tunneling model for H and D transfer according to Ref. [8]. For further description see text.

This equation is visualized in Fig. 9. A Boltzman distribution of particles, where the populations are symbolized by arrows of different length hits the barrier from the left side. The arrows on the right side represent the particles who came through the barrier by tunneling. As the tunneling mass of H is smaller than of D, at a given temperature, the energy for the maximum number of H tunneling through the barrier is smaller than for D.

From Eq. (67) one obtains the following expression for the kinetic isotope effect

$$P = \frac{k^{\mathrm{H}}}{k^{\mathrm{D}}} = \frac{A^{\mathrm{H}} Q^{\mathrm{H}} \exp(-E_{\mathrm{d}}^{\mathrm{H}}/RT)}{A^{\mathrm{D}} Q^{\mathrm{D}} \exp(-E_{\mathrm{d}}^{\mathrm{D}}/RT)} \tag{68}$$

as a function of temperature. This equation has been introduced by R. P. Bell [2].

As Limbach *et al.* have proposed in different papers, Eq. (67) needs to be modified in a minor way for application in multiple proton transfer reactions [7, 8, 15]. The most important change is to replace the lower integration limit in Eq. (66) by a minimum energy E_{m} for tunneling to occur as indicated in Fig. 9, *i.e.*

$$k^{\mathrm{L}} = A^{\mathrm{L}} \exp\left(-E_{\mathrm{d}}^{\mathrm{L}}/RT\right) \int_{E_{\mathrm{m}}}^{\infty} \frac{G^{\mathrm{L}}(W)}{RT} \exp\left(\left(E_{\mathrm{d}}^{\mathrm{L}} - W\right)/RT\right) \mathrm{d}W, \mathrm{L} = \mathrm{H}, \mathrm{D}\,. \tag{69}$$

This modification is necessary for example, when the reaction pathway involves an intermediate as illustrated in the previous sections. Tunneling can then take place only at an energy which corresponds to the energy of the intermediate. Then, one can identify E_m with the energy E_i of this intermediate. However, E_m may also represent an energy E_r necessary for a heavy atom rearrangement preceding the tunneling process. In this interpretation, it represents also the “work term” in Marcus theory of electron transfer [5].

The use of Eq. (69) for multiple proton transfer reactions is now straightforward as shown in the following. It depends on the following parameters:

(i) $E_\mathrm{m} = E_\mathrm{r} + E_\mathrm{i}$ represents the minimum energy for tunneling to occur as described above and is assumed to be isotope independent. For a concerted multiple H transfer step E_i is zero.

(ii) E_d^H and E_d^D are the barrier heights for the reaction step of interest where a single H is replaced by D. E_m is not included which means that $E_\mathrm{m} + E_\mathrm{d}^\mathrm{H}$ represents the total barrier height for the H transfer. In principle, E_d^D can be expanded in terms of zero-point energy losses between the reactant and the transition state. However, we find it more convenient to leave E_d^D as adaptable parameter. However, it is possible to use the RGM in the sense that

$$E_\mathrm{d}^\mathrm{D} = E_\mathrm{d}^\mathrm{H} + \Delta\varepsilon, \quad E_\mathrm{d}^\mathrm{HD} = E_\mathrm{d}^\mathrm{HH} + \Delta\varepsilon, \quad E_\mathrm{d}^\mathrm{DD} = E_\mathrm{d}^\mathrm{HH} + 2\Delta\varepsilon\,, \qquad (70)$$
$$\ldots E_\mathrm{d}^\mathrm{DDDD} = E_\mathrm{d}^\mathrm{HHHH} + 4\Delta\varepsilon$$

for a concerted transfer of several H in a given step, leaving the increase of the barrier height by replacement of a single H by D as parameter.

(iii) $2a^\mathrm{H}$ is the barrier width of the H transfer in Å at the energy E_m. $2a^\mathrm{D}$ can be calculated using Eq. (60).

(iv) In good approximation, also a single frequency or pre-exponential factor A in s^{-1} is used for all isotopic reactions, *i.e.* a possible mass dependence is neglected within the margin of error. A may include a term arising from an entropy change between the initial configuration and the configuration where tunneling can occur.

(vi) The tunneling masses are given by $m_\mathrm{eff} = \sum m^\mathrm{L} + \Delta m$, where the first term corresponds to the sum of the masses of all particles transferred in the step considered and where Δm takes into account the possibility of small heavy atom displacements during the tunnel process. For example, in a concerted quadruple transfer $m_\mathrm{eff}^\mathrm{HHDD} = 6 + \Delta m$.

3. Discussion

We have derived expressions for the multiple kinetic H/D isotope effects of multiple degenerate proton transfer reactions involving single and multiple barriers along the reaction pathways. These expressions relate the isotope effects of the individual steps to the overall isotope effects which can be measured experimentally. The expressions useful for the experimental chemist which may arrive at conclusions about a given reaction mechanism of a multiple H-transfer reaction even if not all multiple isotope effects can be measured, and for planning appropriate experiments. The expressions are also useful if one wants to estimate overall rate constants from computational results. Note that we did not derive any expression for the kinetic isotope effects P of the individual steps which may be affected both by losses of zero-point energies in the transition states and by incoherent tunneling. The HH has been discussed in several previous papers [7, 8, 17], and the HHH case in one paper [15]. However, we did not explicitly treat the possibility of isotopic fractionation between the reactant and intermediate states, included here. A treatment of the HHHH case has not been presented before and constitutes the main novel result of this paper. In the following, we will first discuss the HH and HHH cases as this will facilitate the discussion of the HHHH case.

For the graphical representation of the results in Figs. 10–13 we used the following Arrhenius equation for the reaction of the protons, *i.e.*

$$k^{\mathrm{HH}} = k^{\mathrm{HHH}} = k^{\mathrm{HHHH}} = 10^{13} \exp(-27.6\,\mathrm{kJ\,mol^{-1}}/RT)\,, \tag{71}$$

for the kinetic isotope effects

$$P = P_{\mathrm{d}} = P_{\mathrm{f}} = \exp(-7\,\mathrm{kJ\,mol^{-1}}/RT)\,, \tag{72}$$

and for the fractionation factors

$$\phi_{\mathrm{d}} = \phi_{\mathrm{f}} = \exp(-0.92\,\mathrm{kJ\,mol^{-1}}/RT) \tag{73}$$

unless the latter values were set to 1.

3.1 HH transfer

The kinetic isotope effects are illustrated in Fig. 10 and summarized in Table 1. Let us firstly assume that the secondary isotope effects are equal to the primary ones. This case means that both protons are in flight in the rate limiting step which means that now the double barrier case reduces to the single barrier case. Then, we obtain the rule of the geometric mean (RGM) with $k^{\mathrm{HH}}/k^{\mathrm{HD}} = k^{\mathrm{HD}}/k^{\mathrm{DD}} = P$, and the overall isotope effect is $k^{\mathrm{HH}}/k^{\mathrm{DD}} = P^2$. This result represents in fact a derivation of the RGM for the single barrier case. In the Arrhenius plot of Fig. 10a we have assumed this rule. However, this rule is valid only in the absence of tunneling and if both proton sites are equivalent. In the presence of tunneling $k^{\mathrm{HH}}/k^{\mathrm{HD}} > k^{\mathrm{HD}}/k^{\mathrm{DD}}$ as has been verified previously [7, 8].

In Fig. 10b we plot the two-barrier or stepwise transfer Arrhenius diagram, assuming that the secondary isotope effects of dissociation and neutralization are small, *i.e.* equal to 1. In addition, we assume absence of isotopic fractionation, *i.e.* $\phi_{\mathrm{d}} = 1$. In this case, $k^{\mathrm{DD}}/k^{\mathrm{HH}}$ is equal to the kinetic isotope effects

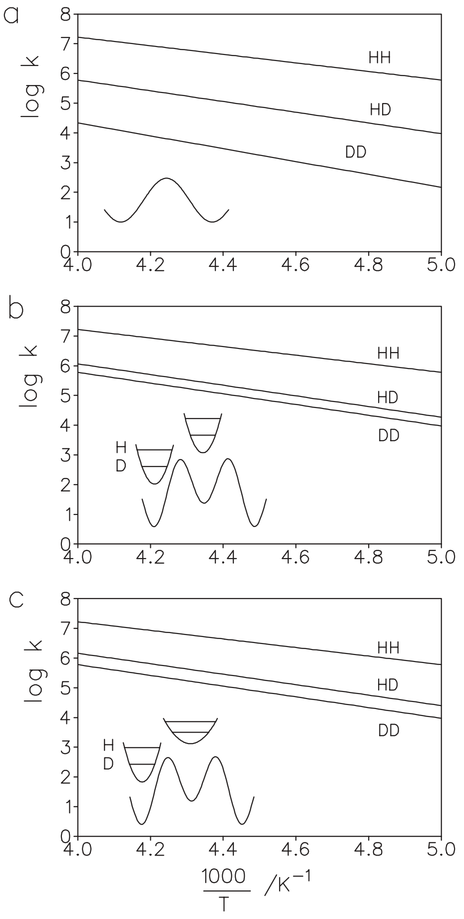


Fig. 10. Arrhenius diagrams of a degenerate double hydron transfer. Arrhenius laws are assumed for the HH transfer using the arbitrary parameters indicated in Eqs. (71) to (73). (a) Single barrier case. (b) Double barrier case with the H/D fractionation factor of dissociation $\phi_d = 1$. (c) as (b) but with an arbitrary value of $\phi_d = \exp(-0.92\ \mathrm{kJ\,mol^{-1}}/RT)$.

$P_d = P_n$, *i.e.* of the dissociation and neutralization step. When these isotope effects are large, which is the case at low temperatures, k^{HD}/k^{DD} is equal to 2. The statistical factor arises from the fact that in the DD reaction D is transferred in both steps. Therefore, when the intermediate is reached, return to the reactant as well as reaction to the product occur with equal probability. By contrast, there is no internal return in the HD reaction which exhibits only one rate limiting step, *i.e.* the one in which D is transferred.

When isotopic fractionation takes place, for example through a strenghtening of the H-bond in the intermediate leading to reduced zero-point ener-

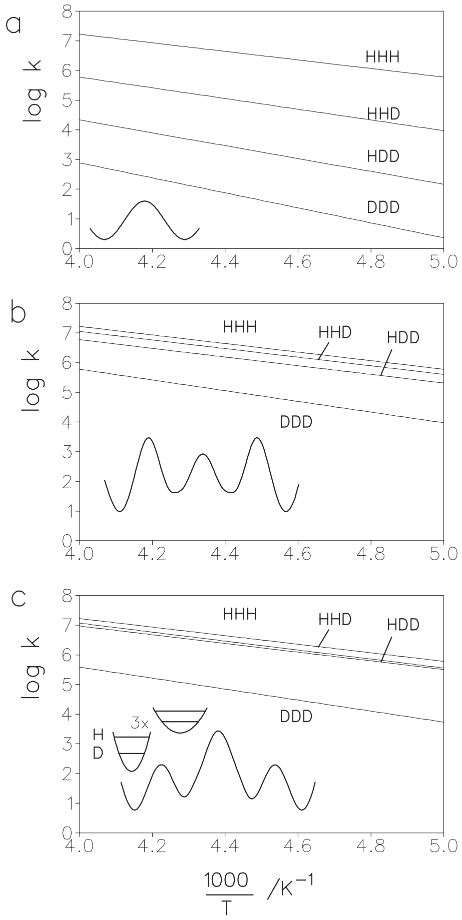


Fig. 11. Arrhenius diagrams of a degenerate triple hydron transfer. Arrhenius laws are assumed for the HHH transfer using the arbitrary parameters indicated in Eqs. (71) to (73). (a) Single barrier case. (b) Triple barrier case with the dissociation as rate limiting step. The rate constants are independent of ϕ_{d}. (c) Triple barrier case with $\phi_{\mathrm{d}} = \exp(-0.92\,\mathrm{kJmol}^{-1}/RT)$ and equal rate constants $k_{\mathrm{f}} = k_{\mathrm{b}}$ for the cation and anion propagation, *i.e.* $\alpha = 1$.

gies [19], the factor will be larger than 2, leading to an increase of $k^{\mathrm{HD}}/k^{\mathrm{DD}}$ as illustrated in Fig. 10c.

3.2 HHH transfer

The single barrier case and is illustrated in Fig. 11a, where again the rule of the geometric mean is assumed to be valid. Now, the overall isotope effect is larger than in the HH case, *i.e.* $k^{\mathrm{HHH}}/k^{\mathrm{DDD}} = P^3$, however the individual isotope effects are the same if P is kept constant.

By contrast to the HH case, in the stepwise triple barrier case with the dissociation and the neutralization as rate limiting steps the overall isotope effect is only given by $k^{\mathrm{HHH}}/k^{\mathrm{DDD}} = P_{\mathrm{d}}$. However, it is very astonishing that the individual isotope effects $k^{\mathrm{HHH}}/k^{\mathrm{HHD}} = 2/3$ and $k^{\mathrm{HHD}}/k^{\mathrm{HDD}} = 1/3$ when P_{d} is large (Table 2) and the Arrhenius curves of the HHH, HHD and HDD reaction are grouped closely together as illustrated in Fig. 11b. This result can be explained as follows. When the central step is rate limiting either a H is transferred in this step with the probability $1/3$ or a D with the probability $2/3$. The latter D transfer does not contribute substantially to the overall rate constant, as the reaction where H is transferred in the central step is as fast as a single HHH reaction sequence. Therefore, the HHH/HHD and the HHD/HDD isotope effects are constant and given only by statistical factors.

When the propagation is the rate limiting step (Fig. 11c) a similar phenomenon occurs, as in the HDD reaction there are sequences where the remaining H is transferred both in the first and the final rate limiting steps, *e.g.* the sequence 000 → 100 → 101 → 001 → 011 → 111. Therefore, also in this case only replacement of the last proton by a deuteron exhibits a non-statistical kinetic isotope effect. However, the HDD process will experience isotopic fractionation of the dissociation process. Moreover, the DDD process is additionally affected by isotopic fractionation.

3.3 HHHH transfer

Finally, let us discuss the HHHH case (Table 3). The single and double barrier cases are illustrated in Fig. 12. Whereas the single barrier case is simply an extension of the corresponding situations for the HH and the HHH cases, with an overall isotope effect of $k^{\mathrm{HHHH}}/k^{\mathrm{DDDD}} = P^4$, the two-barrier case is very interesting: essentially it resembles the concerted HH case. We observe three groups of Arrhenius curve, *i.e.* the HHHH curve, the group of the HHHD and the HDHD curves and the groups of the HHDD, HDDD and DDDD curves which are closely related to the three Arrhenius curves of the two-barrier HH-transfer. Introduction of isotope fractionation between the reactant and the intermediate state does not really affect the results in a very significant way. The overall kinetic isotope effect is given by $k^{\mathrm{HHHH}}/k^{\mathrm{DDDD}} = P_{\mathrm{d}}^2$, typical for a concerted double proton transfer in the rate limiting step. We note that already replacement of the first H by D leads to a substantial isotope effect of $k^{\mathrm{HHHH}}/k^{\mathrm{HHHD}} = 2P_{\mathrm{d}}$.

In Fig. 13a is illustrated the case of dissociation and neutralization as rate limiting step. We note that a similar phenomenon occurs as in the corresponding case of the HHH reaction: only the DDD reaction really experiences the kinetic isotope effect of the dissociation process, P_{d} (Table 3), whereas all other

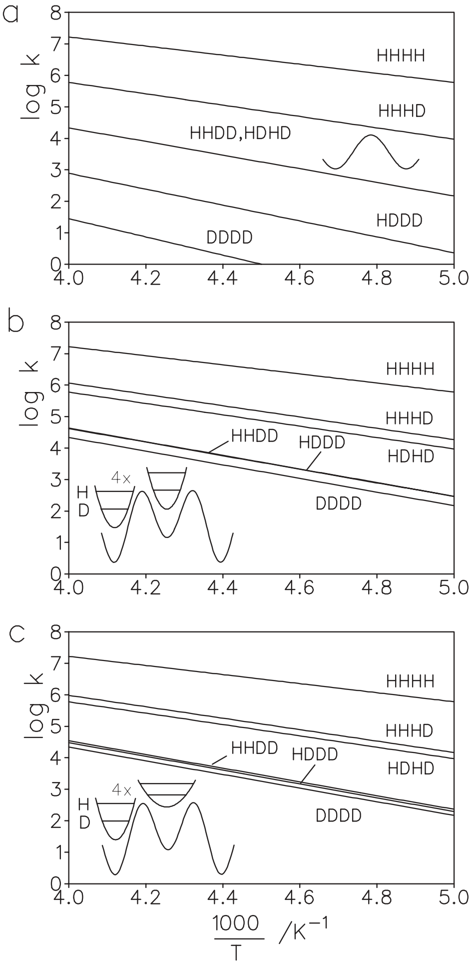


Fig. 12. Arrhenius diagrams of a degenerate quadruple hydron transfer. Arrhenius laws are assumed for the HHH transfer using the arbitrary parameters indicated in Eqs. (71) to (73). (a) Single barrier case. (b) Double barrier case with $\phi_d = 1$. (d) Double barrier case with $\phi_d = \exp(-0.92\,\mathrm{kJ\,mol^{-1}}/RT)$.

curves are grouped together. As long as one assumes that cation and anion propagation (see Fig. 5) exhibit the same kinetic isotope effect, *i.e.* $P_d = P_n$, the resulting overall isotope effects are independent on α, the ratio of the rate constants of both processes.

By contrast, if the propagation constitutes the rate limiting steps, even if $P_d = P_n$ the resulting isotope effects depend on the value of α as illustrated in Fig. 13b and c, where $\alpha = 1$ in the former and $\alpha = 0$ in the latter. When $\alpha = 1$ the Arrhenius curves of the HHHH, HHHD and the HHDD reaction are

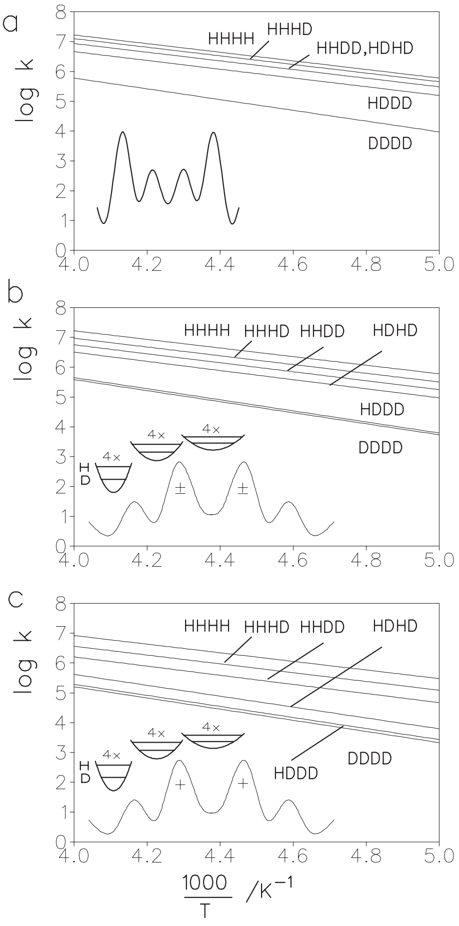


Fig. 13. Arrhenius diagrams of a degenerate quadruple hydron transfer. Arrhenius laws are assumed for the HHH transfer using the arbitrary parameters indicated in Eqs. (71) to (73). (a) Single barrier case with dissociation as rate limiting step. (b) Quadruple barrier case with propagation as rate limiting step, equal cation and anion propagation $\alpha = 1$ (as indicated by the ± signs), $\phi_\mathrm{d} = \phi_\mathrm{f} = \exp(-0.92\,\mathrm{kJ\,mol^{-1}}/RT)$. (c) Quadruple barrier case with propagation as rate limiting step, only cation propagation $\alpha = 0$ (as indicated by the + signs), $\phi_\mathrm{d} = \phi_\mathrm{f} = \exp(-0.92\,\mathrm{kJ\,mol^{-1}}/RT)$.

grouped together, as well as the curves of the HDDD and the DDDD reaction. Only the two latter experience the isotope effect P_f^{-1} of the propagation reaction. $k^{\mathrm{DDDD}}/k^{\mathrm{HHHH}}$ is given by the product $P_\mathrm{f}^{-1}\phi_\mathrm{d}$, where ϕ_d corresponds to the fractionation factor of the fast dissociation process preceding the rate-limiting propagation. We note that for the case where the cation propagation is much faster than the anion propagation, *i.e.* $\alpha = 0$, the rate constants of the HDHD reaction are decreased and become dependent on P_f^{-1} as indicated in Fig. 13c.

3.4 Inclusion of tunneling

In order to demonstrate how the above equations can be used with any given tunneling model let us discuss the effects of tunneling on the Arrhenius curves of the quadruple H-transfers. The results of some model calculations obtained are depicted in Fig. 14. All parameters are arbitrary, except the tunneling masses of H and D, which are 1 and 2. We assume some heavy atom tunneling during the H-tunneling, which is taken into account by an additional tunneling mass of $\Delta m = 2$. Tunneling at low temperatures leads to concave Arrhenius curves, a well-known Bell criterion of tunneling. In the single barrier case (Fig. 14a) the slope at low temperatures is given by E_m – which mainly could arise from a heavy atom reorganization energy – and the slope at high temperatures by the sum of $E_\mathrm{m} + E_\mathrm{d}$. The assumption that $\Delta\varepsilon$ is the same for each substitution of H by D in the single barrier case (Fig. 14a) leads to the fulfillment of the rule of the geometric mean (RGM) at high temperatures, where all primary isotope effects in Eq. (10) are equal. However, tunneling at low temperatures increases the light particle tunneling processes. Thus, the more H are replaced by D, the smaller are the isotope effects. In the case of the double and quadruple barrier cases (Fig. 14b and c) we have increased arbitrarily E_m, keeping $E_\mathrm{d} + E_\mathrm{m} = \mathrm{constant}$, because energy required to reach the intermediate states.

4. Conclusions

From the above discussion we conclude that it is possible to obtain information about the reaction pathways of degenerate multiple proton transfer reactions from experimental rate constants of the individual isotopic reactions. The situation is especially interesting if one can find a system where the number of protons transferred is varied. Then, estimates about the contribution of a single proton site to the total isotope effect can be made. These results encourage the experimentalist to try to measure kinetic isotope effects even of a HHHH reaction, where it is difficult to obtain all multiple kinetic isotope effects experimentally. In fact, only the knowledge of the overall isotope effect $k^\mathrm{HHHH}/k^\mathrm{DDDD}$ and the first isotope effect $k^\mathrm{HHHD}/k^\mathrm{HHHH}$ are needed in order to derive the reaction mechanism. From the first value the number of protons in flight in the rate limiting step can be obtained. The value should be unusually large for a concerted single barrier process, and unusually small for a quadruple barrier process. $k^\mathrm{HHHD}/k^\mathrm{HHHH}$ should correspond to the effect $k^\mathrm{HH}/k^\mathrm{DD}$ of a concerted double proton transfer in the two-barrier mechanism; interestingly, $k^\mathrm{HHHD}/k^\mathrm{HHHH}$ is large only in the single and double barrier cases, but small in the quadruple barrier cases.

The equations derived can be combined with any tunneling model refering to a single step proton transfer reaction. Here, we combined the equations with a modified Bell tunneling model in order to include the effect of tunnel-

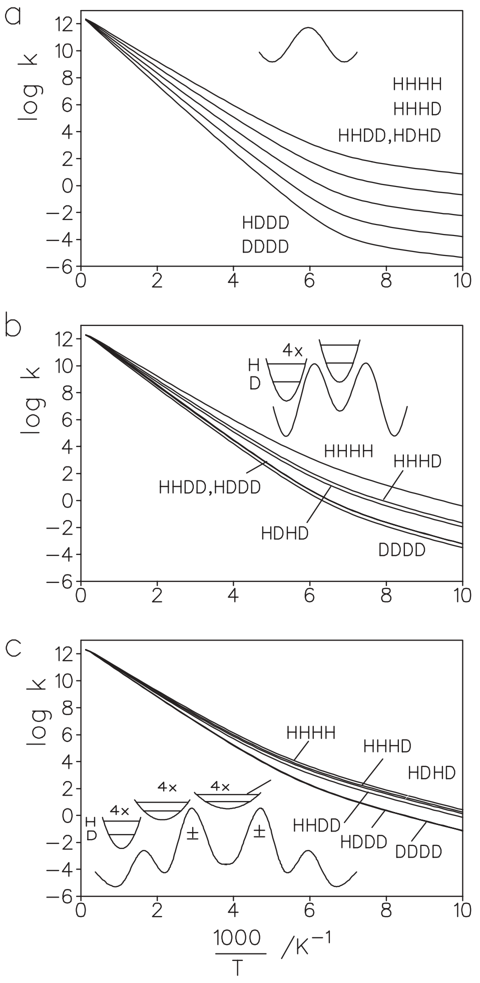


Fig. 14. Arrhenius diagrams of a degenerate quadruple hydron transfer including tunneling calculated according to a modified Bell tunneling model as described in the text. Arbitrary parameters were used. (a) Single barrier case. Tunneling parameters: $E_\mathrm{d}^\mathrm{HHHH} = 29.295\,\mathrm{kJ\,mol^{-1}}$; for each substitution of H by D $E_\mathrm{d}^\mathrm{LLLL}$ is increased by $\Delta\varepsilon = 4.185\,\mathrm{kJ\,mol^{-1}}$. $E_\mathrm{m} = 4.185\,\mathrm{kJ\,mol^{-1}}$, $2a = 0.5\,\mathrm{Å}$, $A = 10^{12.65}\,\mathrm{s^{-1}}$, $\Delta m = 2$, $m^\mathrm{HHHH} = 4$. For each substitution of H by D the m^LLLL is increased by 1. (b) Double barrier case with $\phi_\mathrm{d} = 1$. Tunneling parameters of the dissociation step: $E_\mathrm{d}^\mathrm{HH} = 20.925\,\mathrm{kJ\,mol^{-1}}$, $E_\mathrm{d}^\mathrm{HD} = E_\mathrm{d}^\mathrm{HH} + \Delta\varepsilon$ $E_\mathrm{d}^\mathrm{DD} = E_\mathrm{d}^\mathrm{HH} + 2\Delta\varepsilon$, $\Delta\varepsilon = 4.185\,\mathrm{kJ\,mol^{-1}}$. $E_\mathrm{m} = 12.555\,\mathrm{kJ\,mol^{-1}}$, $2a = 0.5\,\mathrm{Å}$, $A = 10^{12.65}\,\mathrm{s^{-1}}$, $m^\mathrm{HHHH} = 2$, $m^\mathrm{LLLD} = m^\mathrm{LLLH} + 1$, $\Delta m = 2$. (c) Quadruple barrier case with propagation as rate limiting step, equal cation and anion propagation $\alpha = 1$ (as indicated by the ± signs), $\phi_\mathrm{d} = \phi_\mathrm{f} = \exp(-0.92\,\mathrm{kJ\,mol^{-1}}/RT)$. Tunneling parameters of the dissociation step: $E_\mathrm{d}^\mathrm{H} = 20.925\,\mathrm{kJ\,mol^{-1}}$, $E_\mathrm{d}^\mathrm{HD} = E_\mathrm{d}^\mathrm{H} + \Delta\varepsilon$, $\Delta\varepsilon = 4.185\,\mathrm{kJ\,mol^{-1}}$. $E_\mathrm{m} = 12.555\,\mathrm{kJ\,mol^{-1}}$, $2a = 0.5\,\mathrm{Å}$, $A = 10^{12.65}\,\mathrm{s^{-1}}$, $m^\mathrm{H} = 1$, $m^\mathrm{D} = 2$, $\Delta m = 2$.

ing on rate constants and isotope effects at least in crude approximation. The case of more than two protons transferred in the rate limiting steps can be accounted for the over-barrier reaction by assuming that the rule of geometric means holds for the rate constants at high temperatures; in the tunneling motion multiple proton transfer is simply taken into account by adapting the tunneling masses. By the introduction of a minimum energy for tunneling the effects of intermediate formation is taken into account.

We note again that the Bell tunneling model is a crude one, and more sophisticated models such as the Dogonadze–Kusnetzov–Ulstrup model [3] or any other theory is, in principle, more desirable. However, we would like to make the following point. Most often, only few independent dynamic parameters can be obtained from experimental Arrhenius curves, *e.g.* two pre-exponential factors and two activation energies in the case of a H and D reaction. These parameters are not sufficient as evidence of a particular tunneling model. In this case, it seems us that either the simplest model with a minimum number of parameters should be applied, knowing that the model is too simple, or more sophisticated models, when additional parameters can be obtained from first principles by quantum-chemical calculations, as demonstrated in the case of double proton transfers betweeen acetic-acid and methanol in tetrahydrofuran and in porphyrin by Smedarchina *et al.* [10e, 10f] and in the case of the proton transfer in the porphyrin anion [20] by Brackhagen *et al.* [21].

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