

## Isotope Effects in Proton-transfer Reactions

## II.\* A Note on the Infinitely Unsymmetric Transition State

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An extremely exothermic hydrogen-transfer reaction could be expected to have a very reactant-like transition state and for isotopic hydrogen a specific-rate ratio approaching the square root of the inverse ratio between the reduced masses of the reactants. An extremely endothermic hydrogen transfer reaction could be expected to have a very product-like transition state and for isotopic hydrogen a specific-rate ratio approaching the square root of the inverse ratio between the reduced masses of the products multiplied by the ratio of the equilibrium constants of the corresponding isotopic reaction equilibria. The latter case could afford inverse primary kinetic hydrogen isotope effects. Such effects may have been observed.

Considerable interest is at present attached to very weak primary kinetic hydrogen isotope effects, particularly to the questions of how weak they may actually be and of the possibility of reconciling them with reasonable transition-state models. Some worry seems to have been caused by the problem of designing a three-center model which will comply with the weakest effects observed.<sup>1</sup> This together with results like the derivation from experimental data by Hibbert and Long<sup>2</sup> of a rate ratio of  $k_{\text{H}}/k_{\text{D}} = 1.02$  for the protonation/deuteration of the carbanions of malononitrile and *tert*-butylmalononitrile by  $\text{H}_3\text{O}^+/\text{DH}_2\text{O}^+$  makes the problem intriguing.

As explained below, in general only very reactant-like transition states can be expected to afford isotopic rate ratios very close to unity. Extremely product-like transition states may do it incidentally but only when the isotope effect on the equilibrium is of the same small strength. Because of these facts, conclusions about extensive unsymmetry of the transition state based on the weakness of the kinetic hydrogen isotope effect must always imply knowledge of whether the former resembles the reactants or the products. This question is generally one of strong exothermicity *versus* strong endothermicity of the

\* For Part I of this series, see Melander L. and Bergman, N.-Å. *Acta Chem. Scand.* 25 (1971) 2264.

reaction<sup>3</sup> and is not too hard to answer. In the case of a product-like transition state the equilibrium isotope effect must be known in some way for comparison, and such a figure may be difficult to obtain.

A very product-like transition state would in principle be able to give rise to an inverse primary kinetic hydrogen isotope effect provided that the equilibrium isotope effect is in the same direction, because an extreme model would make these effects approach one another fairly closely.

The above-mentioned facts seem to call for increased care in the mechanistic interpretation of experimental kinetic isotope effects.

#### TRANSITION-STATE SYMMETRY AND ITS IMPLICATIONS FOR THE ISOTOPE EFFECT AT THE LIMIT OF UNSYMMETRY

If the transition state in a (heterolytic or homolytic) hydrogen-transfer reaction is extremely unsymmetric it is either reactant-like or product-like. In the former case the isotopic rate ratio for deuterium/protium transfer will approach the *square root of the inverse ratio between the two isotopic reduced masses of the reactant molecules*, a ratio which will differ only slightly from unity for average-sized organic molecules. In the latter case the ratio will approach the *square root of the inverse ratio between the two isotopic reduced masses of the product molecules multiplied by the ratio of the equilibrium constants of the corresponding isotopic reaction equilibria*. In this case the kinetic isotope effect will differ only slightly from the equilibrium isotope effect, the difference corresponding to the first-mentioned factor.

The validity of the statements of the foregoing paragraph could be realized almost without any proof, but, nevertheless, it may be of interest to derive the specific-rate ratio for two isotopic reactions, the transition state of which consists of two very loosely interacting molecular units, corresponding to the two reactant molecules or the two product ones.

The reaction coordinate in an energetically highly unsymmetric hydrogen transfer could be expected to be almost identical with the distance between the hydrogen and the one of the two competing hydrogen acceptors which has the largest affinity for it (the strongest base in the case of an acid-base reaction). This is well illustrated by a comparison of the potential-energy surfaces for the hydrogen atom abstraction from methane by chlorine, bromine and iodine atoms.<sup>4</sup> The first of the three reactions is rather symmetric energetically, the second is considerably endothermic and the third is very much so. In the transition state of the hydrogen abstraction by an iodine atom the methyl-hydrogen distance has increased to more than twice the corresponding distance in methane while the hydrogen-iodine distance is only about one hundredth of an Ångström unit longer than in an unperturbed hydrogen iodide molecule. The reaction coordinate runs almost exactly parallel to the direction corresponding to constant hydrogen-iodine distance and is thus almost identical with the methyl-hydrogen distance. The carbon-hydrogen-iodine stretching mode which is truly periodic has a frequency only slightly lower than that of unperturbed hydrogen iodide. This is obviously a real unsymmetric system of the same kind as the model one for which the isotope effect was discussed by

Melander,<sup>5a</sup> and it illustrates how weak the interaction can be between the two fragments constituting the transition state.

We are now going to discuss the partition-function ratio for two isotopic composite bodies, each consisting of two loosely coupled molecular aggregates. The isotopic difference will be assumed to be limited to one of these aggregates, and the two bodies will be denoted  $D_{(1)}E$  and  $D_{(2)}E$ , the indices referring to an isotopic difference in the part D. The coupling between D and E will be assumed to involve a weak resistance toward bending, a weak attractive or repulsive force along the connecting "bond" and free rotation or a weak resistance against twisting around the same "bond". The situation is pictured in Fig. 1.

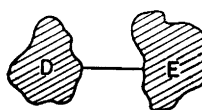


Fig. 1. General model illustrating two weakly interacting molecular aggregates.

According to well-known laws the isotopic partition-function ratio for identical conditions of volume and temperature will be

$$\frac{Q_{D(1)E}}{Q_{D(2)E}} = \left( \frac{M_{D(1)E}}{M_{D(2)E}} \right)^{\frac{3}{2}} \left( \frac{A_{D(1)E} B_{D(1)E} C_{D(1)E}}{A_{D(2)E} B_{D(2)E} C_{D(2)E}} \right)^{\frac{1}{2}} \prod_i^{DE} \left( \frac{e^{-\frac{1}{2}u_i(1)}}{e^{-\frac{1}{2}u_i(2)}} \times \frac{1 - e^{-u_i(2)}}{1 - e^{-u_i(1)}} \right)$$

where  $M$  refers to the mass and  $A, B, C$  to the principal moments of inertia of the combined DE molecule. The symbol  $u_i$  denotes  $h\nu_i/kT$ ,  $h$  being Planck's constant,  $\nu_i$  frequency,  $k$  Boltzmann's constant and  $T$  the absolute temperature. Contributions from differences in nuclear spin and symmetry number are trivial in the present context and are simply left out.

By means of the product theorem of Teller and Redlich<sup>6</sup> it is possible to replace the mass and moment-of-inertia factors by atomic-mass ratios and frequency ratios for the two isotopic molecules. The well-known result of this procedure is

$$\frac{Q_{D(1)E}}{Q_{D(2)E}} = \prod_j^{DE} \left( \frac{m_{j(1)}}{m_{j(2)}} \right)^{\frac{3}{2}} \prod_i^{DE} \left( \frac{\nu_{i(1)}}{\nu_{i(2)}} \times \frac{e^{-\frac{1}{2}u_i(1)}}{e^{-\frac{1}{2}u_i(2)}} \times \frac{1 - e^{-u_i(2)}}{1 - e^{-u_i(1)}} \right)$$

According to the assumptions the isotopic mass difference is limited to part D, and hence only  $m_{j(1)}/m_{j(2)}$  ratios belonging to this fragment will differ from unity. The assumption of a loose coupling allows a division of the frequencies into three groups. The two fragments D and E will keep their internal frequencies approximately independent of the coupling. The D frequencies will be isotopic, but the E frequencies will be non-isotopic and the corresponding ratios equal to unity. There remain six frequencies arising from the combination of D and E. One of these may appear as an internal rotation around the D-E bond, and one is imaginary if DE is a transition state, but this does not alter the following conclusions. A loose coupling can only give rise to low frequencies, and such frequencies will drop out at the limit by cancellation

within the corresponding three-membered factor of the last product even when they are isotopic. (The last fraction will approach  $u_{i(2)}/u_{i(1)} = \nu_{i(2)}/\nu_{i(1)}$  when the  $u$ 's become small.) The partition-function ratio can obviously be written

$$\frac{Q_{D(1)E}}{Q_{D(2)E}} = \prod_j^D \left( \frac{m_{j(1)}}{m_{j(2)}} \right)^{\frac{3}{2}} \prod_i^D \left( \frac{\nu_{i(1)}}{\nu_{i(2)}} \times \frac{e^{-\frac{1}{2}u_{i(1)}}}{e^{-\frac{1}{2}u_{i(2)}}} \times \frac{1 - e^{-u_{i(2)}}}{1 - e^{-u_{i(1)}}} \right)$$

where the two large products extend only over masses and frequencies belonging to D as a separate molecule. The same expression would have been obtained for the partition-function ratio of D alone. Hence it is obvious that under the assumption of an extremely loose coupling between D and E

$$\frac{Q_{D(1)E}}{Q_{D(2)E}} = \frac{Q_{D(1)}}{Q_{D(2)}}$$

This result is rather trivial and could have been foreseen also from the well-known principle that classical behavior will not give rise to equilibrium isotope effects.<sup>7</sup> The new frequencies introduced by the coupling of D to E are either non-isotopic (those within E) or very low (the six ones arising from the loss of three translational and three rotational degrees of freedom).

The result will now be applied to the problem of finding the kinetic isotope effect for a reaction in which the transition state is extremely unsymmetric and the movement along the reaction coordinate is the mere approach or separation of the two reactants or products, respectively. This implies that the mutual perturbation between the two parts of the transition state is infinitely small. The general expression for the specific-rate ratio is<sup>5b</sup>

$$\frac{k_1}{k_2} = \frac{Q_1^\ddagger}{Q_2^\ddagger} \times \frac{Q_2}{Q_1}$$

where  $k_i$  denotes the specific rate with the isotopic species  $i$ ,  $Q_i^\ddagger$  is the partition function of the corresponding transition state and  $Q_i$  that of the corresponding isotopic reactant. (Since we are dealing exclusively with ratios between partition functions for identical conditions of volume and temperature it is irrelevant whether they refer to unit volume or not.)

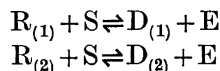
If the transition state is extremely reactant-like, D and E will be the reactants and DE the transition state. It should be kept in mind that the partition function corresponding to the movement along the reaction coordinate is to be excluded from  $Q_1^\ddagger$  and  $Q_2^\ddagger$ ;<sup>5b</sup> in all other respects the transition state can be treated as DE above. Thus  $Q_{D(1)E}/Q_{D(2)E}$  can be used together with a correction equal to the square root of the ratio of the reduced masses along the reaction coordinate.

$$\frac{k_1}{k_2} = \left( \frac{M_{D(2)}}{M_{D(1)}} \times \frac{M_{D(1)} + M_E}{M_{D(2)} + M_E} \right)^{\frac{1}{2}} \frac{Q_{D(1)E}}{Q_{D(2)E}} \times \frac{Q_{D(2)}}{Q_{D(1)}} = \left( \frac{M_{D(2)}}{M_{D(1)}} \times \frac{M_{D(1)} + M_E}{M_{D(2)} + M_E} \right)^{\frac{1}{2}}$$

For the case of an extremely product-like transition state DE, D and E will play the roles of the products. The reactants will be denoted by R and S, the former being isotopic.

$$\begin{aligned} \frac{k_1}{k_2} &= \left( \frac{M_{D(2)}}{M_{D(1)}} \times \frac{M_{D(1)} + M_E}{M_{D(2)} + M_E} \right)^{\frac{1}{2}} \frac{Q_{D(1)E}}{Q_{D(2)E}} \times \frac{Q_{R(2)}}{Q_{R(1)}} = \\ &= \left( \frac{M_{D(2)}}{M_{D(1)}} \times \frac{M_{D(1)} + M_E}{M_{D(2)} + M_E} \right)^{\frac{1}{2}} \frac{Q_{D(1)}}{Q_{D(2)}} \times \frac{Q_{R(2)}}{Q_{R(1)}} \end{aligned}$$

It is obvious that the product of the two last ratios \* is equal to the ratio of the equilibrium constants for the two isotopic reactions



Hence the statements made above concerning the isotopic rate ratios have been proved.

#### DISCUSSION

In principle, there seems to be nothing preventing the equilibrium isotope effect from being in either direction. Thus, indeed, a very product-like transition state could give rise to an inverse kinetic isotope effect provided that the equilibrium effect is sufficiently strong and in the proper direction. In general, this would require that a strongly endothermic reaction leads to a product in which the frequencies concerned with the atom transferred are higher than those of the reactant. Although the opposite is probably more common, no general principle seems to prevent the existence of such reactions.

Experimental results which may be of this kind have been discussed by Cram,<sup>8</sup> who interprets them in terms of a two-step reaction mechanism. The observed specific rate would then be a product of an equilibrium constant and a single-step rate constant. The former represents a full hydrogen-transfer equilibrium, the latter a reaction step for which no appreciable isotope effect is to be expected. According to the present writer's opinion there is no reason to invoke a multistep mechanism unless there is some argument for it which is independent of the isotope effect, such as stereochemical evidence not explicable otherwise. As shown above, a primary single-step kinetic isotope effect is able *per se* to reflect the isotope effect of the corresponding equilibrium provided that the reaction is sufficiently endothermic.

For more than twenty years kinetic hydrogen isotope effects have been used as an important tool in the exploration of reaction mechanisms. It has been taken for granted that a rate-determining hydrogen transfer would give rise to a measurable kinetic isotope effect. The fact that it may actually be weak has not been understood qualitatively until the last decade. In view of the above, considerable care should be exercised in the interpretation of vanishingly weak or even inverse isotope effects. While an appreciable observed kinetic isotope effect indicates that a hydrogen transfer is involved in the rate-determining step, the absence of such an effect does not prove the contrary. In the latter case the proof is conclusive only if it is probable that the possible hydrogen transfer would not be too endothermic or exothermic.

\* From the experimental point of view it is important that this product is also equal to the equilibrium constant for the exchange reaction  $R_{(1)} + D_{(2)} \rightleftharpoons R_{(2)} + D_{(1)}$ .

One might question how many misinterpretations have been made owing to unawareness of these facts. They are probably not very numerous, because the difference in affinity between the donor and the acceptor must be very high, as, for instance, in the chemistry of poorly stabilized carbanions.

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