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Akitami Ichihara, Kunio Shiraishi
Hiroji Sato, Sadao Sakamura*
Department of Agricultural Chemistry
Faculty of Agriculture, Hokkaido University
Sapporo 060,Japan

Koji Nishiyama, Ryutaro Sakai
National Institute of Agricultural Science
Tokyo 114, Japan

Akio Furusaki, Takeshi Matsumoto
Department of Chemistry, Faculty of Science
Hokkaido University
Sapporo 060, Japan

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The Determination of the Rate-Limiting Step in a Proton Transfer Reaction from the Breakdown of the Swain-Schaad Relation

Sir:

Streitwieser et al. showed[1] that for the base-catalyzed exchange of C–L bonds (where L = H, D, or T), the amount of internal return could be measured from the breakdown of the Swain-Schaad relation[2] which connects the deuterium isotope effect (k_D/k_H) and the tritium isotope effect (k_T/k_H):

$$(k_T/k_H) = (k_D/k_H)^{1.44} \tag{1}$$

When two or more transition states are partially rate limiting, eq 1 does not hold exactly and Northrop has recently suggested[3] that this breakdown could be used to investigate the details of enzyme catalyzed reactions. We show here that although the treatment can be applied to any sequence of catalytic steps, the breakdown is generally small. Before trying to use this approach one must therefore ask whether the experimental data will be sufficiently precise to enable useful information to be obtained.

Consider the simple two-step processes shown in Scheme I, where the second step is a proton transfer. The observed second-order rate constant, $k_{1,2}$, is given by

Scheme I

$$\mathrm{E + S} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_2} \mathrm{E + P}$$

	E + S		ES	E + P
Fractionation factors for D	ϕ_S	ϕ_1		ϕ_2
Fractionation factors for T	Φ_S	Φ_1		Φ_2

$$k_{1,2} = k_1/(1 + \kappa) \tag{2}$$

where

$$\kappa = k_{-1}/k_2 \tag{3}$$

The quantity κ describes the free energy difference between transition states 1 and 2 and it is the value of κ that we wish to obtain from the breakdown of the Swain-Schaad relation.

The effects of isotopic substitution are best described by fractionation factors[4] because a fractionation factor relates to a particular species. We are mainly interested in transition states 1 and 2 and so we define the mixed fractionation factors $\phi_{1,2}$ and $\Phi_{1,2}$ where

$$\frac{(k_{1,2})_D}{(k_{1,2})_H} = \frac{\phi_{1,2}}{\phi_S} \tag{4}$$

$$\phi_{1,2} = \frac{1 + \kappa}{\phi_1{}^{-1} + \kappa\phi_2{}^{-1}} \tag{5}$$

$$\Phi_{1,2} = \frac{1 + \kappa}{\Phi_1{}^{-1} + \kappa\Phi_2{}^{-1}} \tag{6}$$

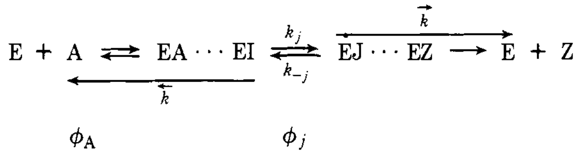
and

$$\Phi_n = \phi_n{}^{1.44} \text{ where } n = 1 \text{ or } 2$$

If the first step is rate limiting, $\kappa \ll 1$ and $\phi_{1,2} \rightarrow \phi_1$; if the second step is rate limiting, $\kappa \gg 1$ and $\phi_{1,2} \rightarrow \phi_2$. For isotopic substitution with deuterium, $\phi_{1,2}$ can be determined from eq 4 since the other quantities can all be measured experimentally. For isotopic substitution with tritium, $\Phi_{1,2}$ is determined by measuring the isotopic content of the reactant or product as a function of the extent of reaction.[5]

This treatment can be extended to the general case shown in Scheme II. The proton transfer occurs at the *j*th step (EI ⇄ EJ) and the only irreversible step is the loss of product Z. We can show that $\phi_{1,2....z}$, the observed fractionation factor (= $\phi_A(k_{\mathrm{obsd}})_D/(k_{\mathrm{obsd}})_H$), is given by

Scheme II



$$\phi_{1,2....z} = \frac{1 + \kappa'}{\overline{\phi}^{-1} + \kappa'\phi_j{}^{-1}}$$

where

$$\frac{1}{\kappa'} = \frac{k_j}{\overleftarrow{k}} + \frac{k_{-j}}{\overrightarrow{k}}$$

$$\overline{\phi} = \frac{1 + \kappa''}{\phi_{1,2...j-1}{}^{-1} + \kappa''\phi_{j+1,...z}{}^{-1}}$$

and

$$\kappa'' = \overleftarrow{k}k_{-j}/\overrightarrow{k}k_j$$

The rate constants $\overleftarrow{h}$ and $\overrightarrow{k}$ describe the rates of EI to E + A and of EJ to E + Z, respectively.[6] Since the equations for the general case have the same form as those for the simple two-step reaction, we continue our discussion using the simpler Scheme I.

Now, if *c* is the percentage breakdown of the Swain-Schaad relationship, as derived from the experimentally observed quantities $\phi_{1,2}$ and $\Phi_{1,2}$, we may write:

$$1 + \frac{c}{100} = \frac{\phi_{1,2}}{\Phi_{1,2}{}^{0.69}} = \frac{(k_{1,2})_D}{(k_{1,2})_H}\left(\frac{\Phi_S}{\Phi_{1,2}}\right)^{0.69} \tag{7}$$

where $0.69 = 1.44^{-1}$.

The quantity *c* is calculated from experimental values of the isotope effects and does *not* depend on any fractionation in reactants or intermediates. From eq 5, 6, and 7 we obtain:

$$\frac{c}{100} = \frac{(1 + \kappa)^{0.31}\,[1 + \kappa(\phi_1/\phi_2)^{1.44}]^{0.69}}{1 + \kappa\phi_1/\phi_2} - 1 \tag{8}$$

Since ϕ_2 describes a proton transfer and ϕ_1 does not, $\phi_1/\phi_2 > 1$. Most primary deuterium isotope effects[7] lie in the range 3

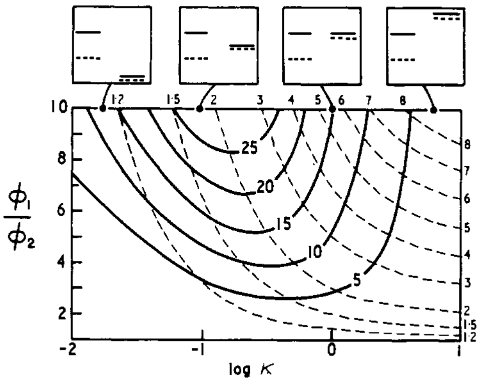


Figure 1. Contour diagram showing breakdown of the Swain-Schaad relation. The full lines are contours for different values of c (the percentage breakdown of the Swain-Schaad relation) as a function of ϕ_1/ϕ_2 (the ratio of fractionation factors for the two steps) and κ (which describes the extent to which one step is cleanly rate limiting). The dashed lines are contours for $\phi_1/\phi_{1,2}$ (which is approximately equal to the *observed* deuterium kinetic isotope effect) as a function of ϕ_1/ϕ_2 and κ. The square boxes show typical free energy levels (H, full lines; D, dashed lines) for the two transition states. Transition state 1 (on the left of the boxes) has a bound proton ($\phi_1 \simeq 1$) and there is a difference in the zero point energies; transition state 2 (on the right) has the proton in flight ($\phi_2 < 1$) and the H and D levels are much closer.

to 10. For the range $10 > \phi_1/\phi_2 > 1$, therefore, we construct Figure 1, which is a contour diagram for c calculated from eq 8. In addition, the broken lines show contours for $\phi_1/\phi_{1,2}$ (from eq 5). Since ϕ_1 does not involve a proton transfer, this ratio may be estimated from the experimental data:[8]

$$\frac{\phi_1}{\phi_{1,2}} = \frac{(k_{1,2})_\mathrm{H}}{(k_{1,2})_\mathrm{D}}\left(\frac{\phi_1}{\phi_\mathrm{S}}\right) \simeq \frac{(k_{1,2})_\mathrm{H}}{(k_{1,2})_\mathrm{D}} \tag{9}$$

That is, $\phi_1/\phi_{1,2}$ is approximately equal to the *observed* deuterium isotope effect.

Thus Figure 1 displays how the breakdown of the Swain–Schaad relation and the *observed* deuterium isotope effect depend on the properties of the transition states. The insets illustrate typical free energies associated with the transition states and the isotope effects. On the right of the diagram ($\kappa = k_{-1}/k_2 \gg 1$) the proton transfer transition state is cleanly rate limiting. Under these conditions c tends to zero, and the ratio $\phi_1/\phi_{1,2}$ tends toward the ratio of the single factors ϕ_1/ϕ_2. On the left of the diagram ($\kappa \ll 1$) the first transition state is cleanly rate limiting. Again c tends to zero, but now $\phi_1/\phi_{1,2}$ tends to unity ($\phi_{1,2} \simeq \phi_1$). Along the bottom of the diagram c tends to zero because there is very litle difference between the fractionation in the two transition states. Over most of the diagram c is small, but significant values do occur where (as shown in the inset) isotopic substitution actually changes the rate limiting step.

From the experimental values of the deuterium and tritium isotope effects, we can calculate c and $\phi_1/\phi_{1,2}$ from eq 7 and 9. The intersection of the appropriate contours for c (Figure 1, full lines) and for $\phi_1/\phi_{1,2}$ (Figure 1, broken lines) therefore allows us *in principle* to determine the values of κ and ϕ_1/ϕ_2. (In obtaining $\phi_1/\phi_{1,2}$ from eq 9 we must assume a value of ϕ_1, but this assumption is not serious, since we have a good knowledge of fractionation factors for bound sites[9] and the location of the intersection of contours is not very sensitive to the position of the $\phi_1/\phi_{1,2}$ contour. This latter point is not true for broken contours close to unity and means that the approach will not work if the observed $\phi_1/\phi_{1,2}$ is less than about 1.2.)

But the real problem with the method lies in the small values of c. We cannot be certain that the Swain-Schaad relation itself holds[10] to better than 10% and, for instance, when $\kappa = 2$ (i.e., the proton transfer step is certainly not yet cleanly rate limiting) c is always less than 10%. We must therefore conclude that this method is *not* a general one for determining the relative free energies of two transition states which are both partially rate limiting.

In certain cases, however, interesting information *may* be found and having measured one isotope effect, we may use Figure 1 to see whether it is worthwhile to measure the other isotope effect. Two factors are relevant: the size of the observed isotope effect and the precision of the data. If the deuterium isotope effect is about 2 then one has the best chance of obtaining extra information from the breakdown of the Swain–Schaad relation. This is because the (broken) contour for $\phi_1/\phi_{1,2} = 2$ climbs up the "spur" where the breakdown is largest. It is interesting that many enzymes do have deuterium isotope effects between 2 and 3.[11]

The error on c, E_c, is given by $E_c = 1.6E_k$, where E_k is the percentage error on the kinetic data. If E_k is 10%, the error in c (±16) will cover the whole diagram and nothing can be deduced from measuring the second isotope effect. *The experimental error on the kinetic data must therefore be less than 3%.* Even so it is probable that the intersection will not be precisely located. Figure 1 can then be used to show the pairs of values of κ and ϕ_1/ϕ_2 that are consistent with the data.

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References and Notes

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W. J. Albery*
Physical Chemistry Laboratory
Oxford, England

Jeremy R. Knowles
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

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Transmetalation: Preparation of Organometallic Reagents for Organic Synthesis by Transfer of Organic Groups from One Metal to Another. Transmetalation from Zirconium to Aluminum

Sir:

Organozirconium(IV) complexes (**1**), produced by hydrozirconation of olefins or acetylenes using $Cp_2Zr(H)Cl$ (Cp =