

Secondary H/D Isotope Effects and Transition State Looseness in Nonidentity Methyl Transfer Reactions. Implications for the Concept of Enzymatic Catalysis via Transition State Compression

Russell J. Boyd,[†] Chan-Kyung Kim,[‡] Zheng Shi,[†] Noham Weinberg,[‡] and Saul Wolfe^{*†§}

Contribution from the Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3, and the Department of Chemistry, Simon Fraser University, Burnaby, BC, Canada V5A 1S6

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Abstract: The kinetic and thermodynamic CH₃/CD₃ isotope effects (k_H/k_D and K_H/K_D) in the forward and reverse directions of ten nonidentity methyl transfer reactions, $X^- + CH_3Y \rightarrow XCH_3 + Y^-$, and the kinetic isotope effects of five identity methyl transfer reactions have been computed ab initio using a 6-31++G(d,p) basis set. The kinetic isotope effect is smaller in the exoergic direction in five of the nonidentity reactions and larger in the exoergic direction in the other five. Over the entire data set there is no correlation between $(k_H/k_D)_{XY}$ and either ΔG° or ΔG . Instead, as in the Marcus treatment of rate–equilibrium relationships, $(k_H/k_D)_{XY}$ is determined by the kinetic isotope effects of the identity (X,X) and (Y,Y) reactions, by the thermodynamic isotope effect, and by the thermodynamic driving force $\Delta G/4\Delta G^\circ_0$, where ΔG°_0 is $0.5(\Delta G^\circ_{XX} + \Delta G^\circ_{YY})$. In a variant of the Marcus treatment, $(k_H/k_D)_{XY}$ has also been related to the looseness of the transition structure: with all other effects constant, an inverse $(k_H/k_D)_{XY}$ becomes more inverse as the transition structure loosens. The same trend is seen with identity reactions: a decrease in $(k_H/k_D)_{XX}$ is associated with loosening of the transition structure, and an increase in the barrier. Taken together, the observations on identity and nonidentity reactions suggest that when an S_N2 transition structure is altered by variation of the nature of the entering and leaving groups, a decrease in k_H/k_D reflects a looser geometry, which leads to inhibition, not catalysis. This raises the possibility that the decrease in k_H/k_D which accompanies enzymic catalysis of methyl transfer may be caused by factors other than changes in transition state geometry. The arguments in support of the idea that k_H/k_D decreases in such reactions because of specific compression of the transition state have, therefore, been reexamined. Some problems have been identified.

Introduction

Exoergic methyl transfer reactions (eq 1) normally proceed



with inverse secondary kinetic isotope effects ($k_H/k_D < 1$), both in the gas phase¹ and in solution.² According to the theory of isotope effects,³ this means that force constants involving the light and heavy atoms increase along the reaction coordinate. Until recently it was believed⁴ that changes in the HCY (HCX) bending force constants make the dominant contribution to the isotope effect, which should, therefore, become more inverse (k_H/k_D decreases) with increased tightening of the transition structure. Following the observation that k_H/k_D decreases in enzyme-catalyzed methyl transfer, this rationale led to the proposal that the transition state of the enzymatic reaction exhibits greater compression than that of a related non-enzymatic process.⁵ On the basis of a two-parabola model of methyl transfer,⁶ it is readily seen that, for a constant ΔG , increased tightening of the transition structure will lead to a decrease in the reaction barrier. Therefore,

if transition state compression has the same meaning as geometric tightening, this effect could contribute significantly to the enzymatic catalysis.⁵

However, several recent computational studies have found⁷ that the origin of the inverse secondary kinetic isotope effects in identity methyl transfer reactions does not reside in an increase in HCY (HCX) bending force constants but, rather, in the increase in the C–H stretching force constants that accompanies the tetrahedral to trigonal change in geometry along the reaction coordinate. The barriers of these reactions decrease with increased tightening of the transition structures,^{7c} as expected,⁶ but k_H/k_D increases.

Although these results seemed to be inconsistent with Schowen's ideas regarding the origin of the catalysis in enzymatic methyl transfer,⁵ our previous computations were concerned with identity reactions, but the enzymatic process is a *nonidentity* reaction. In such a reaction, e.g., eq 1, the looseness of the transition structure is given by $L^* = \%CY^* + \%CX^*$, the percent lengthening of the C–Y and C–X bonds in the forward (exoergic) and reverse (endoergic) directions, respectively.^{7c,8,9} In the exoergic direction, the transition state is reactant-like, and the bond to the leaving

[†] Dalhousie University.

[‡] Simon Fraser University.

[§] Holder of a Canada Council Killam Research Fellowship, 1990–1992.

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Table I. Energy Changes,^a Kinetic and Thermodynamic Isotope Effects, and Looseness Indices of Methyl Transfer Reactions $X^- + \text{CH}_3\text{Y} \rightarrow \text{XCH}_3 + \text{Y}^-$

X,Y	Y,X	ΔG	ΔG^*	ΔG_0^{*b}	k_H/k_D^c	K_H/K_D^d	%CY	%CX	L^*
HCC,Cl		-58.95	10.03	37.15	0.92	1.27	19.3 ^e		
	Cl,CCH	58.95	68.98	37.15	0.73	0.79		63.6 ^f	82.9 ^g
HO,Cl		-53.83	5.49		0.92	0.96	13.2 ^e		
	Cl,OH	53.83	59.32		0.96	1.05		59.6 ^f	72.8 ^g
NC,Cl		-38.74	14.96	33.50	0.91	1.25	23.2 ^e		
	Cl,CN	38.74	53.70	33.50	0.73	0.80		57.3 ^f	80.5 ^g
F,Cl		-37.62	4.20	18.35	0.91	0.69	14.5 ^e		
	Cl,F	37.62	41.82	18.35	1.32	1.46		52.0 ^f	66.5 ^g
F,NC		-19.35	18.83	27.22	0.76	0.87	30.8 ^e		
	CN,F	19.35	38.18	27.22	0.87	1.14		39.4 ^f	70.2 ^g
F,SH		-18.72	19.00		0.77	0.75	26.6 ^e		
	HS,F	18.72	37.72		1.03	1.34		41.5 ^f	68.1 ^g
CN,Cl		-18.09	16.76	25.75	0.89	0.99	26.9 ^e		
	Cl,NC	18.09	34.85	25.75	0.90	1.01		47.2 ^f	74.1 ^g
NC,SH		-17.70	32.61		0.80	1.06	32.2 ^e		
	HS,CN	17.70	50.31		0.75	0.94		49.3 ^f	81.5 ^g
HO,F		-14.78	20.75		0.88	1.09	26.9 ^e		
	F,OH	14.78	35.53		0.80	0.92		39.1 ^f	66.0 ^g
NC,F		-2.50	34.26	34.97	0.92	1.49	34.7 ^e		
	F,CN	2.50	36.76	34.97	0.62	0.67		40.3 ^f	75.0 ^g
Cl,Cl		0.00	16.88		0.97		31.2		62.4
F,F		0.00	19.82		0.86		30.4		60.8
CN,NC		0.00	34.61		0.79		40.7		81.4
NC,CN		0.00	50.12		0.67		44.9		89.8
HCC,CCH		0.00	57.42		0.66		45.6		91.2

^a Energies are in kcal/mol, at 298 K. ^b Intrinsic barrier: $0.5(\Delta G^*_{\text{XX}} + \Delta G^*_{\text{YY}})$. ^c Kinetic isotope effect. ^d Thermodynamic isotope effect. ^e Percent lengthening of the C–Y bond of 1. ^f Percent lengthening of the C–X bond of 2. ^g Refers to the sum of %CY + %CX. In an identity reaction, $L^* = 2\% \text{CY}$.

group is "tight"; in the endoergic direction, the transition state is product-like, and the bond to the leaving group is "loose". Reference 7c contains one example of such a reaction (eq 1, X, Y = F, Cl). In the exoergic direction (X = F, Y = Cl, $\Delta G^* = 4.2$ kcal/mol, %CY* = 14.5), $k_H/k_D = 0.91$; in the endoergic direction ($\Delta G^* = 41.8$ kcal/mol, %CX* = 52.2), $k_H/k_D = 1.03$ (6-31+G* calculations).

Thus, for this single example, the kinetic isotope effect is more inverse in the direction having the lower barrier and the more reactant-like ("tighter") transition state.⁸ If this were to be a general result, the conclusions of Schowen and co-workers⁵ might still be valid, although not for the same reason.

The present work was, therefore, undertaken to explore in more detail the relationships among the secondary isotope effects, barriers, reaction energies, and transition state looseness in nonidentity methyl transfer reactions.

Computational Methods

The $X^- \cdots \text{CH}_3\text{Y}$ (1) and $\text{XCH}_3 \cdots \text{Y}^-$ (2) ion–molecule complexes⁹ and transition structures of an extended series of nonidentity methyl transfer reactions have been computed recently¹⁰ using GAUSSIAN 80¹¹ and GAUSSIAN 86,¹² the 6-31++G(d,p) basis set¹³ for C, X, and Y, and 6-31G¹⁴ for the methyl hydrogens. These structures and basis sets were employed in the present work, using GAUSSIAN 90,^{15a} to calculate the frequencies of all species. These frequencies were then subjected to a standard¹⁶ scaling of 0.917 for the computation of the isotope effects associated with the unimolecular process in which 1 and 2 interconvert via the $\text{S}_\text{N}2$ transition structure.^{7c,9} The calculations of looseness and the

individual contributions of %CX and %CY were also based on 1, 2, and the transition structures.

For isotope effect calculations on any (X,Y) combination to be valid, 1 and 2 must have zero and the transition structure must have only one imaginary frequency. The same criteria apply to the (X,X) and (Y,Y) identity reactions; as will be seen, the isotope effects of nonidentity reactions are determined, in part, by the isotope effects of the identity reactions. In ref 7c, only one genuine ion–molecule complex, corresponding to O-deprotonation of methanol, was found in the reaction $\text{HO}^- + \text{CH}_3\text{OH}$, using the 6-31+G* basis set. The isotope effect associated with methyl transfer could not be calculated in this case. In the present work, many of the ion–molecule complexes of ref 10, which had been optimized subject to C_{3v} or C_s symmetry constraints, were found to exhibit one or more imaginary frequencies. This was seen with all nonidentity structures in which one of (X, Y) was H, and with some nonidentity structures in which one of (X,Y) was NH_2 ; evidently in these reactions the preferred process involves attack of H^- upon a C–H bond or attack of certain nucleophiles upon an N–H bond. Methyl transfer isotope effects cannot be calculated in such cases. When these examples were eliminated from the study, eight (X, Y) combinations remained, corresponding in the exoergic directions to the following: F,Cl; NC,F; F,NC; NC,Cl; HO,F; F,SH; HO,Cl; NC,SH. However, in four of these, X or Y is OH or SH and, as with the 6-31+G* basis set, no genuine identity methyl transfer reaction exists. To increase the overall data base, two additional nonidentity reactions (CN,Cl and HCC,Cl) were calculated, using GAUSSIAN 92.^{15b}

All isotope effects refer to 298 K.

Results and Discussion

Kinetic H/D Isotope Effects of Nonidentity Methyl Transfer Reactions Do Not Correlate with ΔG^* or with ΔG . Table I summarizes the isotope effects, free energies of activation, intrinsic

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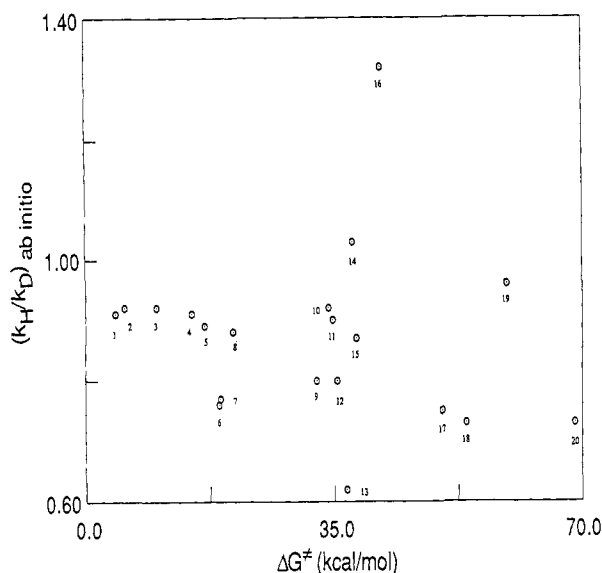


Figure 1. Secondary kinetic H/D isotope effects of nonidentity methyl transfer reactions as a function of ΔG^\ddagger . Data points 1–20 refer to the following: 1, F,Cl; 2, HO,Cl; 3, HCC,Cl; 4, NC,Cl; 5, CN,Cl; 6, F,NC; 7, F,SH; 8, F,OH; 9, NC,SH; 10, NC,F; 11, Cl,NC; 12, F,OH; 13, F,CN; 14, HS,F; 15, CN,F; 16, Cl,F; 17, HS,CN; 18, Cl,CN; 19, Cl,OH; 20, Cl,CCH.

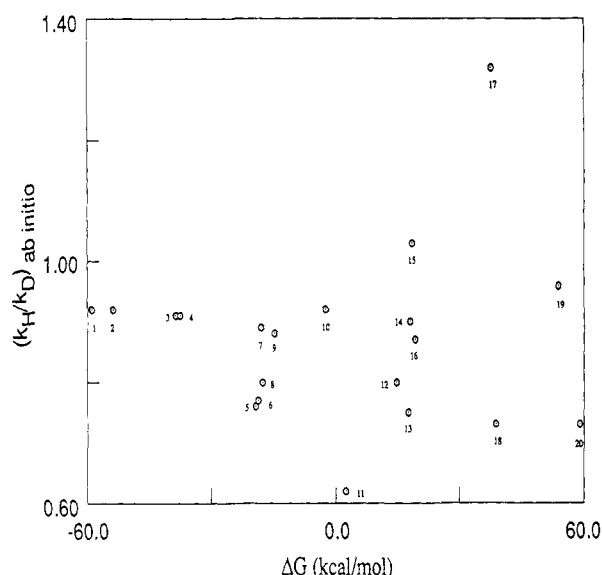


Figure 2. Secondary kinetic H/D isotope effects of nonidentity methyl transfer reactions as a function of ΔG . Data points 1–20 refer to the following: 1, HCC,Cl; 2, HO,Cl; 3, NC,Cl; 4, F,Cl; 5, F,NC; 6, F,SH; 7, CN,Cl; 8, NC,SH; 9, HO,F; 10, NC,F; 11, F,CN; 12, F,OH; 13, HS,CN; 14, Cl,NC; 15, HS,F; 16, CN,F; 17, Cl,F; 18, Cl,CN; 19, Cl,OH; 20, Cl,CCH.

barriers, and looseness indices in the exoergic and endoergic directions for ten nonidentity and five identity methyl transfer reactions. The kinetic isotope effect is smaller in the exoergic direction in five of these reactions and larger in the exoergic direction in the other five. When the entire set of kinetic isotope effects is examined as a function of ΔG^\ddagger (Figure 1) or ΔG (Figure 2), it is evident that there is no straightforward correlation between k_H/k_D and either of these quantities.

Kinetic Isotope Effects of Nonidentity Methyl Transfer Reactions and the Marcus Relationship. There is some resemblance between Figures 1 and 2 and the rate–equilibrium plot shown as Figure 2 of ref 18. In that work,¹⁸ an excellent correlation between rates and equilibria was achieved when the intrinsic barriers were

Table II. The Calculated Isotope Effects of Nonidentity Methyl Transfer Reactions and the Isotope Effects Predicted by Equations 4 and 5

X,Y	k_H/k_D	eq 4	eq 5	X,Y	k_H/k_D	eq 4	eq 5
HCC,Cl	0.92	0.90	0.89	F,NC	0.76	0.77	0.78
Cl,CCH	0.73	0.71	0.71	CN,F	0.87	0.88	0.90
NC,Cl	0.91	0.90	0.89	CN,Cl	0.89	0.86	0.88
Cl,CN	0.73	0.72	0.71	Cl,NC	0.90	0.88	0.89
F,Cl	0.91	0.76	0.87	NC,F	0.92	0.93	0.92
Cl,F	1.32	1.10	1.26	F,CN	0.62	0.62	0.62

taken into account, as predicted by Marcus theory (eq 2, where

$$\Delta G^\ddagger_{XY} = \Delta G^\ddagger_0(1 + \Delta G/4\Delta G^\ddagger_0)^2 \quad (2a)$$

$$= \Delta G^\ddagger_0 + \Delta G/2 + \Delta G^2/16\Delta G^\ddagger_0 \quad (2b)$$

ΔG^\ddagger_0 , the intrinsic barrier, is $(\Delta G^\ddagger_{XX} + \Delta G^\ddagger_{YY})/2$.^{6a} This suggested that the kinetic isotope effects exhibited by (X,Y) combinations may also depend upon “intrinsic” (X,X) and (Y,Y) isotope effects. Isotopic substitution in eq 2b gives

$$\Delta G^\ddagger_{XY}(H) - \Delta G^\ddagger_{XY}(D) = [\Delta G^\ddagger_0(H) - \Delta G^\ddagger_0(D)] + \frac{[\Delta G(H) - \Delta G(D)]}{2} + \frac{1}{16} \left[\frac{\Delta G(H)^2}{\Delta G^\ddagger_0(H)} - \frac{\Delta G(D)^2}{\Delta G^\ddagger_0(D)} \right] \quad (3)$$

The left-hand side of eq 3 is $-RT \ln (k_H/k_D)_{XY}$. The first term on the right-hand side is $-0.5RT \ln (k_H/k_D)_{XX} (k_H/k_D)_{YY}$. The second term is $-0.5RT \ln (K_H/K_D)_{XY}$, where $(K_H/K_D)_{XY}$ is the equilibrium isotope effect. With the assumptions $\Delta G(H) + \Delta G(D) \approx 2\Delta G^\ddagger_0$ and $\Delta G^\ddagger_0(H) \cdot \Delta G^\ddagger_0(D) \approx \Delta G^\ddagger_0(H)^2$, the bracketed part of the third term in eq 3 becomes $[-2RT(\Delta G/\Delta G^\ddagger_0) \ln(K_H/K_D)_{XY} + 0.5RT(\Delta G^2/\Delta G^\ddagger_0)^2 \ln(k_H/k_D)_{XX}(k_H/k_D)_{YY}]$. When the thermodynamic driving force $\gamma = \Delta G/4\Delta G^\ddagger_0$ is small, the final expression for $(k_H/k_D)_{XY}$, based on the Marcus equation, is^{6a}

$$(k_H/k_D)_{XY} \approx \sqrt{(k_H/k_D)_{XX} (k_H/k_D)_{YY} (K_H/K_D)_{XY}} \quad (4)$$

When γ is taken into account, the relationship is

$$(k_H/k_D)_{XY} \approx \sqrt{(k_H/k_D)_{XX}^{1-\gamma^2} (k_H/k_D)_{YY}^{1-\gamma^2} (K_H/K_D)_{XY}^{1+\gamma}} \quad (5)$$

As seen in Table II, eq 4 provides satisfactory results, except for the largest values of $|\gamma|$. Equation 5 improves the situation, as can also be seen in Figure 3. It is clear that the secondary kinetic H/D isotope effects in nonidentity methyl transfer reactions, like the barriers of these reactions, have a complicated origin, but are well described by the Marcus treatment.

Kinetic Isotope Effects of Nonidentity Methyl Transfer Reactions and Transition State Looseness. Because of its derivation from the Marcus equation, which is not concerned with the geometry of the transition state, eq 5 provides no information regarding the relationship between the kinetic isotope effect and transition state looseness. This information can be obtained by consideration of Figure 4, which depicts the free energy difference $\Delta\Delta G (= [\Delta G(H) - \Delta G(D)])$ between protonated and deuterated species along the reaction coordinate. The dashed lines in Figure 4 refer to the identity reactions (X,X) and (Y,Y), which are shifted relative to one another by the equilibrium free energy difference, $\Delta\Delta G^\circ_{XY}$. The solid line represents the nonidentity reaction, eq 1, as an interpolation between the two identity processes.

The identity transition states, TS_{XX} and TS_{YY} , have D_{3h} symmetry. If we suppose that a nonidentity transition structure, TS_{XY} , also contains a planar methyl group and C–X and C–Y bond lengths close to their identity values (Figure 5), we can estimate the free energy difference $\Delta\Delta G^\circ_0$ using eq 6.

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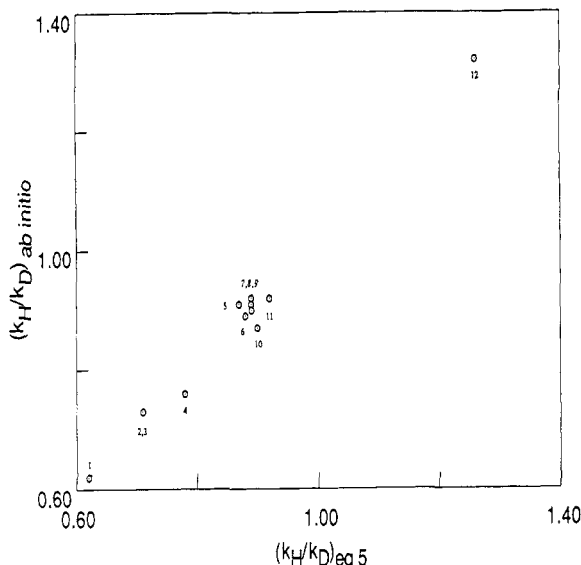


Figure 3. Calculated secondary kinetic isotope effects of nonidentity methyl transfer reactions and those predicted by eq 5. Data points 1–12 refer to the following: 1, F,CN; 2, Cl,CCH; 3, Cl,CN; 4, F,NC; 5, F,Cl; 6, CN,Cl; 7, Cl,NC; 8, NC,Cl; 9, HCC,Cl; 10, CN,F; 11, NC,F; 12, Cl,F.

$$\begin{aligned}\Delta\Delta G^*_0 &= 0.5 [\Delta\Delta G^*_{YY} + (\Delta\Delta G^*_{XX} + \Delta\Delta G^{\circ}_{XY})] \\ &= 0.5 [\Delta\Delta G^*_{XX} + \Delta\Delta G^*_{YY} + \Delta\Delta G^{\circ}_{XY}] \quad (6)\end{aligned}$$

We now note that the isotope effect, k_H/k_D , is related to $\Delta\Delta G^*$ as

$$k_H/k_D = \exp(-\Delta\Delta G^*/RT) \quad (7)$$

so that approximation of $\Delta\Delta G^*_{XY}$ as $\Delta\Delta G^*_0$ (eq 6) leads directly to eq 4. However, nonidentity transition structures, TS_{XY} , do not have planar methyl groups, and their C–Y and C–X bond lengths are determined by the Bell–Evans–Polanyi–Leffler–Hammond principle (Figure 5).¹⁹

Accordingly, the position of TS_{XY} in Figure 4, unlike that of $'TS'_{XY}$, must reflect the asymmetry of the transition structure. For the example shown in the figure the transition structure is reactant-like, i.e., $\%CY < 0.5L^*_{YY}$, and we may estimate $\Delta\Delta G^*_{XY}$ as a fraction, $\%CY/0.5L^*_{YY}$, of $\Delta\Delta G^*_0$, eq 8. Substitution into

$$\begin{aligned}\Delta\Delta G^* &= (2\cdot\%CY/L^*_{YY}) \Delta\Delta G^*_0 \\ &= (2\cdot\%CY/L^*_{YY}) (\Delta\Delta G^*_{XX} + \Delta\Delta G^*_{YY} + \Delta\Delta G^{\circ}_{XY}) \quad (8)\end{aligned}$$

eq 7 then leads to eq 9 for an exoergic methyl transfer reaction.

$$\begin{aligned}(k_H/k_D)_{XY} &= \\ (k_H/k_D)_{XX}^{\%CY/L^*_{YY}} \cdot (k_H/k_D)_{YY}^{\%CY/L^*_{YY}} \cdot (K_H/K_D)_{XY}^{\%CY/L^*_{YY}} \quad (9)\end{aligned}$$

For an endoergic reaction, $Y^- + CH_3X \rightarrow YCH_3 + X^-$,

$$\begin{aligned}(k_H/k_D)_{YX} &= (k_H/k_D)_{XY} (K_H/K_D)_{YX} \\ &= (k_H/k_D)_{XX}^{\%CY/L^*_{YY}} \cdot (k_H/k_D)_{XX}^{1-\%CY/L^*_{YY}} \cdot (K_H/K_D)_{YX}^{1-\%CY/L^*_{YY}} \quad (10)\end{aligned}$$

As seen in Table III and Figure 6, eqs 9 and 10 appear to capture the complex relationship between the isotope effect and the looseness of the transition structure.

When the Transition Structure Is Varied by Variation of the Entering and Leaving Groups, a Decrease in k_H/k_D Implies Increased Looseness and Is Accompanied by an Increase, Not a

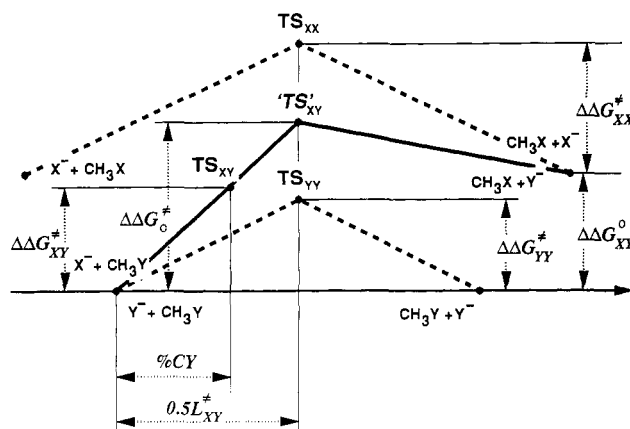


Figure 4. Schematic treatment of the free energy difference between protonated and deuterated species along the reaction coordinates of identity and nonidentity methyl transfer reactions.

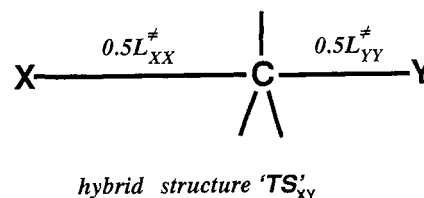
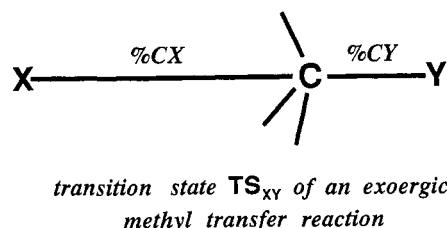


Figure 5. Hybrid transition structure $'TS'_{XY}$ and actual transition structure TS_{XY} of an exoergic nonidentity methyl transfer reaction.

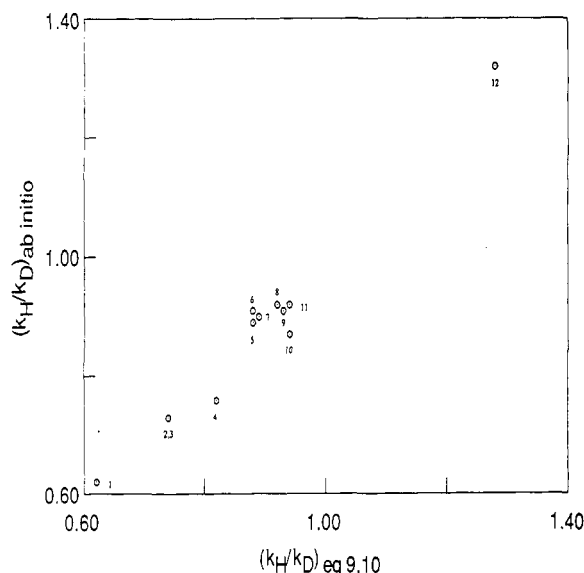


Figure 6. Calculated secondary kinetic isotope effects of nonidentity methyl transfer reactions and those predicted by eqs 9 and 10. Data points 1–12 refer to the following: 1, F,CN; 2, Cl,CCH; 3, Cl,CN; 4, F,NC; 5, CN,Cl; 6, F,Cl; 7, Cl,NC; 8, NC,F; 9, NC,Cl; 10, CN,F.

Decrease, in the Barrier. In the present work we have found that secondary H/D isotope effects in nonidentity methyl transfer reactions are determined, through the Marcus relationship, by the isotope effects of the corresponding identity reactions, by the

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Table III. The Calculated Isotope Effects of Exoergic and Endoergic Nonidentity Methyl Transfer Reactions and the Isotope Effects Predicted by Equations 9 and 10

X,Y	k_H/k_D	eq 9	eq 10	X,Y	k_H/k_D	eq 9	eq 10
HCC,Cl	0.92	0.94		F,NC	0.76	0.82	
Cl,CCH	0.73		0.74	CN,F	0.87		0.94
NC,Cl	0.91	0.93		CN,Cl	0.89	0.88	
Cl,CN	0.73		0.74	Cl,NC	0.90		0.89
F,Cl	0.91	0.88		NC,F	0.92	0.92	
Cl,F	1.32		1.28	F,CN	0.62		0.62

thermodynamic isotope effect, and by a thermodynamic driving force. We have also found a Marcus-type relationship in which the secondary isotope effect has been related to the looseness of the transition structure. Since all exoergic bimolecular methyl transfer reactions examined so far exhibit $k_H/k_D < 1$, it follows from eq 9 that, other factors being constant, these isotope effects will become more inverse with increasing looseness of the transition structure. Taken together with the results for identity reactions (ref 7c and Table I), all of our work suggests that when an S_N2 transition structure is altered by variation of the entering and leaving groups, a decrease in k_H/k_D reflects a looser geometry, and this is associated with an increase in the barrier.

Relationship to the Concept of Transition State Compression.

As mentioned in the Introduction, a two-parabola model of methyl transfer⁶ predicts that geometric tightening of the transition state will lower the barrier; an equivalent statement is that loosening of the transition structure will raise the barrier and inhibit the process, as we have found. However, these latter effects are accompanied by a decrease in k_H/k_D . This is not the result expected if the geometric tightness described in our work is equivalent to enzymic transition state compression as advocated by Schowen and co-workers.^{5,20}

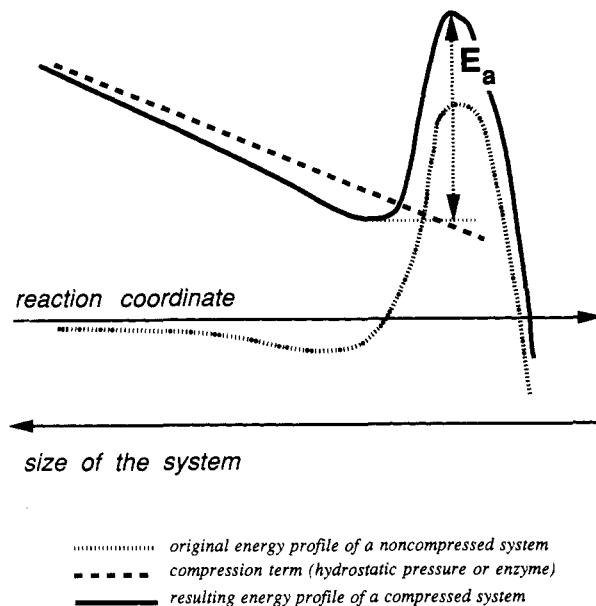
According to Schowen,^{20,21} the two phenomena are not the same: in our computations, transition structures are altered by variation of the entering and leaving groups, but the reaction conditions are invariant (gas phase, double well reaction coordinate, etc.). On the other hand, in the experiments of Schowen and co-workers, the entering and leaving groups remain the same, and the transition structure is altered by variation of the reaction conditions (uncatalyzed versus enzyme catalyzed). This changes k_H/k_D , from 0.97 ± 0.02 for methylation of methoxide ion by *S*-methylidibenzothiophenium ion at 25 °C in methanol to 0.83 ± 0.05 for methylation of 3,4-dihydroxyacetophenone by *S*-adenosylmethionine at 37 °C. To account for the decrease the concept of transition state (TS) compression is introduced as a property unique to the enzyme; although the compression destabilizes the TS, this has become structurally different from and specifically stabilized relative to the preceding and succeeding complexes, and the barrier is lowered.

For a reaction of the type $R_2S^+-CH_3 + ^-O-R' \rightarrow R_2S + CH_3-OR'$, taken as a model of the enzymic reaction,^{5d} a force field was constructed, with a number of assumptions. Isotope effect calculations based on this model force field were able to reproduce the reduction in k_H/k_D when the C-S and C-O bonds of the model reaction transition state were 0.15–0.29 Å longer than those in the enzymic transition state.

A significant factor leading to the compression proposal was the belief that the decrease in k_H/k_D observed in enzymic catalysis means that "the enzymic reaction has an unusually tight transition state,"^{5d} because "the α -deuterium isotope effect arises from changes in bending force constant and its magnitude and direction should depend on the 'tight-loose' character of the transition state."^{5c} This interpretation of the origin of the isotope effect is now known to be incorrect.⁷

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**Figure 7.** Effect of a constant external pressure on a reaction barrier.

There is extensive evidence, summarized on pp 188–191 of ref 9, that the S_N2 transition structure is a tightly bound, implastic, species, which is unaffected by solvation. This evidence includes the findings that C–X bond lengths of $[X-CH_3-X]^-$ are the same in the gas phase and in water solvent for $X = F, Cl$ and are identical to the C–X bond lengths of $[(H_2O)X-CH_3-X(H_2O)]^-$. It is difficult to accept that such environmental effects can be less passive than the transfer of the transition state from water to the active site of an enzyme, which supposedly decreases C–X (C–Y) bond lengths by 0.15–0.29 Å.

In a different attempt to model enzymic compression,^{7a} Williams carried out 4-31G calculations on the identity S_N2 reaction $H_3N + CH_3NH_3^+$. The barrier, taken as the energy difference between the ion–molecule complex and the transition structure, was 18.69 kcal/mol. The computed Cartesian force constants were then scaled by 0.82, and normal modes and vibrational frequencies were calculated. This led to $k_H/k_D = 0.913$. The 0.82 scaling of force constants corresponds to a 0.91 scaling of frequencies. We have repeated these calculations and obtained a barrier of 18.66 kcal/mol and, with a 0.91 scaling of the frequencies, an isotope effect of 0.914.

Williams then compressed the reacting system by placing the ion–molecule complex and the transition structure between two helium atoms located on the $N \cdots C \cdots N$ axes. The geometries of these species were reoptimized under the constraint that the helium atoms are a constant 8 Å apart. Each of the helium atoms was described with a single STO-2G basis function. This strategy changed the geometries and increased the energies of both the complex and the transition structure. From the data of Williams' Table I we calculate $L^* = 0.72$ and 0.56 for the uncompressed and compressed reactions, respectively, a substantial tightening. Since compression destabilizes the complex by 24.4 kcal/mol and the transition structure by 19.6 kcal/mol, the net effect is to decrease the barrier by 4.8 kcal/mol. We repeated these calculations and have reproduced the results.

When the size of a reaction complex is larger than that of a transition state, an external pressure will affect the complex more strongly and cause it to undergo a more extensive change in geometry.²² This effect is depicted in Figure 7, which shows that the application of a constant external pressure to a bimolecular reaction lowers the barrier via greater destabilization of the reactants.

(22) Basilevsky, M. V.; Weinberg, N. N.; Zhulin, V. M. *J. Chem. Soc., Faraday Trans. 1* 1985, 85, 875. Basilevsky, M. V.; Weinberg, N. N. *J. Mol. Liq.* 1986, 33, 1, 29. Stearn, A. E.; Eyring, H. *Chem. Rev.* 1941, 29, 509.

Table IV. "Catalysis" of the Reaction $\text{H}_3\text{N} + \text{CH}_3(\text{CD}_3)\text{NH}_3^+$ by Helium, Neon, Argon, Krypton, and Xenon Using the Strategy of Williams:^a Secondary Isotope Effects, C-H Bond Lengths, and TS Looseness

catalyst	ΔE^\ddagger ^b	$k_{\text{H}}/k_{\text{D}}$	C-H bond length (Å)		L^\ddagger
			reactant complex	TS	
none	18.66	0.916	1.073	1.063	0.72
He	13.89	0.864	1.069	1.063	0.56
Ne	17.87	0.858	1.068	1.062	0.61
Ar	7.64	1.003	1.068	1.073	0.38
Kr	4.62	1.115	1.071	1.081	0.32
Xe	0.70	1.204	1.086	1.096	0.19

^a 4-31G calculations. In the presence of the "catalysts", constrained at 8 Å separation on the N...C...N axis, there are two degenerate pairs of imaginary frequencies in the reactant complex and the TS, which are converted to real frequencies for the calculation of the isotope effects.

^b Energy difference between reactant complex and TS, in kcal/mol.

Since an external pressure, such as the model calculations of compression described above, destabilizes both the reactants and the transition state, it seems unreasonable to conclude that it is the transition state which is "specifically and strongly stabilize(d)".^{5d}

This was the approach taken in the force field calculations of isotope effects by Schowen and co-workers,^{5d} which do not take reactant state compression into account. This strategy was adopted, in part, because of evidence²¹ that the k_{cat} and $k_{\text{cat}}/K_{\text{m}}$ isotope effects of the enzymic reaction are about equal, indicating no reactant state compression. However, in view of the preceding paragraph, we suggest that, if there is evidence indicating no reactant state compression, this necessarily implies an absence of transition state compression.

Because the helium atoms are constrained to a separation of 8 Å in the Williams model, optimization of the complex and the transition state does not lead to proper stationary points, i.e., as described above under Computational Details, structures having respectively zero and one imaginary frequency. As we have argued earlier, only in such a case is a calculation of the isotope effect feasible. In fact, the complex has *four* imaginary frequencies, and the transition structure has *five*. The four imaginary frequencies of the complex are 244i, 244i, 200i, and 200i; the five imaginary frequencies of the transition structure are 613i, 220i, 220i, 209i, and 209i. As Williams noted, the offending vibrations correspond to lateral motion of the reactants and TS with respect to the helium atoms as the reacting system attempts to escape sideways from the cage.

A key feature of Williams' computational model is the finding that compression lowers $k_{\text{H}}/k_{\text{D}}$ from 0.913 to 0.872. To obtain this result, Williams converted all of the imaginary frequencies to real numbers, except for the imaginary frequency of the transition state that corresponds to the reaction coordinate. In addition, the masses of the helium atoms were increased from 4 to 4000. In our hands, using values of 244, 244, 200, and 200 cm^{-1} for the complex and 613i, 220, 220, 209, and 209 cm^{-1} , together with all other computed real frequencies, but retaining the masses of the helium atoms at 4, leads to $k_{\text{H}}/k_{\text{D}} = 0.864$, close to Williams' value of 0.872, and lower than the 0.914 obtained with full optimization in the absence of the helium atoms. Interestingly, the same isotope effect (0.864) is calculated when the offending frequencies are simply deleted, and the number of degrees of freedom of the system is reduced appropriately.

The conversion of imaginary frequencies to real frequencies to

allow calculation of the isotope effect is rationalized in Williams' work by the argument that it is equivalent to the inclusion of a restoring force for off-axis displacement. While this procedure has the advantage that it obeys the Teller-Redlich product rule for isotopic frequencies,²³ it is unreasonable to suppose that the real frequencies that would be computed for restricted translation and rotation after the inclusion of "walls" in the model would have the same numerical values as the imaginary frequencies that were calculated in their absence. The magnitude of a resulting $k_{\text{H}}/k_{\text{D}}$, and whether this isotope effect is normal or inverse, would then lose its meaning.

To take this point further, we extended the Williams compression model to the heavier group VIII atoms neon (mass 20), argon (mass 40), krypton (mass 84), and xenon (mass 131), with the results summarized in Table IV. This table also includes the looseness indices, L^\ddagger , and the C-H bond lengths of the reactant complexes and transition structures. We have already shown that the direction of the isotope effect is determined primarily by the changes in these C-H bond lengths along the reaction coordinate.^{7c}

Examination of Table IV indicates that increasing the Williams compression leads to a systematic tightening of the transition structure (L^\ddagger decreases), a systematic decrease in the barrier (neon is anomalous), and with the heaviest atoms Ar, Kr, and Xe, *normal* $k_{\text{H}}/k_{\text{D}}$. The reversal in the magnitude of the isotope effect is accompanied by a reversal in the C-H bond lengths on going from reactant to TS.

None of the foregoing considerations support the view that a decrease in $k_{\text{H}}/k_{\text{D}}$ is associated with the TS compression envisaged by Schowen and co-workers.

Desolvation Cannot be a Major Contributor to the Enzymic Catalysis. The transfer of an identity $\text{S}_{\text{N}}2$ reaction from water solvent to the gas phase leads to a decrease of at least 10 kcal/mol in the free energy of activation,⁹ and it has been suggested that enzymic catalysis results from the desolvation of a reacting system that exists at the active site of an enzyme.²⁴

For this effect to account for the origin of the enzymic catalysis in the process studied by Schowen and co-workers, $k_{\text{H}}/k_{\text{D}}$ for a methyl transfer reaction would have to be lower in the gas phase than in water solvent. This is not the case. For the chloride-methyl chloride reaction the $k_{\text{H}}/k_{\text{D}}$ values in the gas phase and in water solvent are 0.97 and 0.96, respectively.^{7b,c,25}

It thus appears that the decrease in $k_{\text{H}}/k_{\text{D}}$ that is associated with enzymic catalysis of methyl transfer is not the result of increased compression of the transition state or of desolvation of the reaction system. The origins of these isotope effects will have to be sought elsewhere.

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