Medium Effects on Heavy-Atom Kinetic Isotope Effects. I. Cell Model without Internal–External Coordinate Interaction

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Abstract: The method of Stern, Van Hook, and Wolfsberg for the calculation of vapor pressure isotope effects was applied to model calculations of medium effects on ^{13}C kinetic isotope fractionation in the decompositions (*via* several reaction coordinates) of a hypothetical triatomic molecule, formic acid, and oxalic acid. Molecular parameters were given values characteristic of organic compounds, while the necessary external force constants were adjusted to yield associated frequencies typical of moderate H bonding (30–90 cm^{-1}). No interactions between external and internal coordinates were introduced, nor was any external coordinate included in a reaction coordinate. When the same external force field is applied to the reactant and transition states (chemically inactive medium), isotope fractionation due to the medium is small in comparison with the ordinary imprecision in kinetic isotope effect measurements. Differences in external force fields between reactant and transition states yield increments to the kinetic isotope effects proportional to the differences, but still of the size of experimental errors, in the absence of internal coordinate force constant shifts and internal–external coordinate couplings. The cell model predicts that medium-induced isotope fractionation effects will be negligible unless medium-reactant interactions are so strong that corresponding gross rate effects would be observable.

Corrections for possible phase and medium effects in the theoretical calculation of heavy-atom kinetic isotope effects have been neglected in the past, either because they were assumed small or because they were difficult to calculate. It is the purpose of this paper to demonstrate some of the limits of the former assumption. Two extreme types of models for medium effects seem obvious: in one, the medium is considered to have a generalized effect on the reacting molecule, but to be without specific structure, mass, or defined attachment (cell model); in the other, the medium is treated as a system of specific mass points each capable of having some weak but established link with the reacting molecule (structured medium model). This paper will explore the properties of the former model in relationship to the calculated ^{13}C kinetic isotope effect (KIE) in three different molecules undergoing simple decompositions: a hypothetical three-atom nonlinear molecule (TAM), formic acid, and oxalic acid.

The Cell Model

Stern, Van Hook, and Wolfsberg[1] have demonstrated the use of a cell-type model for the study of vapor pressure isotope effects (VPIE). The translational and rotational coordinates of a molecule in a continuous condensed phase are represented (within the Wilson **GF** matrix method[2]) as having small harmonic force constants and associated nonzero vibrational frequencies. These external coordinates are employed in addition to the internal coordinates in defining a **G** matrix for the molecule in the condensed phase and have the form[1]

$$T_x = (M)^{-1}\sum_{i=1}^{N} m_i \Delta x_i$$

$$T_y = (M)^{-1}\sum m_i \Delta y_i$$

$$T_z = (M)^{-1}\sum m_i \Delta z_i$$

$$R_x = (I_{xx})^{-1}\sum m_i(b_i\Delta z_i - c_i\Delta y_i)$$

$$R_y = (I_{yy})^{-1}\sum m_i(c_i\Delta x_i - a_i\Delta z_i)$$

$$R_z = (I_{zz})^{-1}\sum m_i(a_i\Delta y_i - b_i\Delta x_i)$$

Here Δx_i, Δy_i, and Δz_i are the Cartesian displacement coordinates for atom i (axes chosen parallel to the principle axes); a_i, b_i, and c_i are the equilibrium principal Cartesian coordinates for atom i; m_i is the atomic mass of atom i; M is the molecular mass; and I_{xx}, I_{yy}, and I_{zz} are the principal moments of inertia. T_x, T_y, and T_z represent the three translational coordinates and R_x, R_y, and R_z are the three possible rotational coordinates.

The additional six coordinates are not mass independent as are all internal coordinates.[1,3,4] To maintain an isotope-independent potential energy surface, the six external coordinates corresponding to one of the isotopic molecules (α) is used as a basis in forming the external coordinates of all other isotopically related molecules (β_1, β_2, etc.). In general, the matrix $\mathbf{G}_\alpha$ will have only diagonal external elements and no external–internal cross terms. The same is not true for $\mathbf{G}_\beta$, but its elements are easily computed by first determining the basis B matrix[2] for all $3N$ coordinates; then $\mathbf{G}_\alpha = \mathbf{B}\mathbf{M}_\alpha^{-1}\mathbf{B}^T$ and $\mathbf{G}_\beta = \mathbf{B}\mathbf{M}_\beta^{-1}\mathbf{B}^T$. Internal coordinate **B** matrix elements are readily available from geometrical considerations, and the external elements may be determined from the definitions of the external coordinates.

Methods of Calculation

All calculations were carried out within the transition state theory and the theory of small vibrations using a modification of the Schachtschneider program[5]

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(1) M. J. Stern, W. A. Van Hook, and M. Wolfsberg, *J. Chem. Phys.*, **39**, 3179 (1963).

(2) E. B. Wilson, Jr., J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill, New York, N. Y., 1955.

(3) A. Babloyantz, *Mol. Phys.*, **2**, 39 (1959).

(4) M. Wolfsberg, *J. Chim. Phys.*, **60**, 15 (1963).

(5) J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, **19**, 177 (1965).

for solution of the Wilson **GF** matrix problem. Calculations were made in double precision. Input parameters for each model molecule are shown in Table I along with the corresponding internal force constants, while the principal external force constant sets are given in Table II.

Table I. Values of Input Parameters[a]

Internal Coordinate	No. *i*	$F_{i,i}$[d]
	TAM[b,c]	
B—C	1	4.4
A—B	2	4.4
A—B—C[e]	3	1.63
	Formic Acid[f]	
C—H	1	4.7
C—O	2	6.5
C=O	3	11.8
O—H	4	7.1
C—O—H	5	0.6
H—C—O	6	0.6
O=C—O	7	1.1
H—C(=O)—O	8	0.4
H—C—O—H	9	0.1
	Oxalic Acid[g]	
C_1—C_2	1	4.5
C_2=O	2	12.0
C_1=O	3	12.0
C_2—O_2	4	5.0
C_1—O_1	5	5.0
O_2—H	6	7.0
O_1—H	7	7.0
O=C—C	8, 9	0.71
O—C—C	10, 11	0.77
C—O—H	12, 13	0.70
C—C(=O)—C	14, 15	0.60
H—O—C—C	16, 17	0.30
O=C—C=O	18	0.30

[a] Masses are in atomic mass units. [b] Atomic masses: A, 12.0; B, 12.0; C, 12.0/13.0. [c] Bond distances (angstroms): A–B, B–C, 1.54; the bond angle is tetrahedral. [d] Stretching force constants are in mdyn/Å; bond, wag, and torsion force constants (tabulated in that order) are in mdyn Å. [e] C is ^{13}C in the heavy species. [f] Bond distances (angstroms): C—O, 1.34; C—H, 1.10; O—H, 0.97, C=O, 1.20. Bond angles (degrees): C—O—H, 106; O=C—O, 125; H—C—O, 111. [g] Bond distances (angstroms): C—C, 1.54; C—O, 1.37; C=O, 1.22; O—H, 0.96. Bond angles (degrees): O=C—O, 125; O=C—C, 122; C—O—H, 108.

Table II. External Force Constants[a,b]

	φ_1	φ_2	φ_3	φ_4
F_{T_x}	0.04	0.08	0.16	0.16
F_{T_y}	0.04	0.08	0.16	0.16
F_{T_z}	0.04	0.08	0.16	0.08
F_{R_x}	0.0049	0.0098	0.0196	0.0098
F_{R_y}	0.0047	0.0094	0.0188	0.0094
F_{R_z}	0.0050	0.010	0.02	0.02

[a] Translational force constants are in mdyn/Å; rotational force constants are in mdyn Å. [b] These external force constant sets are representative; combinations between these sets were also used.

The TAM bond lengths and bond angles were chosen to be representative of the skeleton of a hydrocarbon chain. Formic acid was assumed planar with hydrogens cis; bond lengths and bond angles were based on the results of Trambarulo and Moser.[6] The bond lengths and bond angles for oxalic acid were obtained from a variety of sources;[7] the molecule was assumed planar with carbonyl groups trans and hydroxyl hydrogens interior. All molecules were defined in the *x–y* plane, and in all cases the isotopically light species for a particular molecule was used as the basis in forming the $\mathbf{G}_\beta$ matrices for all heavy species.

The reaction coordinate eigenvector (RCEV) and the corresponding transition state force constants were generated for a flat barrier ($\nu_1^{\ddagger} = 0i$) by using one of two techniques: (1) only the *i*th element in the RCEV was nonzero and the transition state **F** matrix was the same as that for the reactant with the exception that $F_{i,i}$ was set to zero (corresponding to simple bond rupture and called type I); (2) only the *i* and *j* elements of RCEV were nonzero and the transition state **F** matrix was the same as that for the reactant with the exception that $F_{i,j} = -(F_{i,i} \cdot F_{j,j})^{1/2}$ or $F_{i,j} = +F_{i,i} \cdot F_{j,j})^{1/2}$ (the former corresponding to a symmetric stretch, the latter to an asymmetric, and both are called type II).

Vapor Pressure Isotope Effects

Vapor pressure isotope effects (VPIE's) were calculated as a procedural test and because it was likely that trends in such results would relate to those observed in the KIE studies. The VPIE for each molecule was computed by using one of the external force constant sets given in Table II. These force constants were chosen so as to produce external frequencies under 100 cm^{-1}. The basis field (φ_1) was patterned after that employed by Stern, Van Hook, and Wolfsberg in calculations on angular HXH.[1] Sets intermediate between those tabulated were also employed, so that the VPIE was determined over a wide and varied range of external force constants.

Plots of 100 ln (VPIE) = *L*(VPIE) = $L([X_{\text{gas phase}}]/[X_{\text{cond phase}}])$ *vs.* 1000/*T*°K are parabolic, demonstrating the T^2 dependence expected from the small external frequencies produced. As expected, the effects are themselves small, and there is a linear relationship between increments in any external force constant and the resulting shift in *L*(VPIE). Table IIIA contains *L*(VPIE) data at a number of temperatures to be em-

Table III. Calculated Vapor Pressure Isotope Effects

A. *L*(VPIE) Values

	TAM		Formic acid		Oxalic acid	
T, °C	φ_2	φ_3	φ_2	φ_3	φ_2	φ_3
12.55	0.03745	0.07482	0.02690	0.05389	0.00551	0.01058
25.00	0.03439	0.06870	0.02468	0.04946	0.00507	0.00972
60.17	0.02751	0.05497	0.01971	0.03951	0.00407	0.00779
99.20	0.02204	0.04404	0.01576	0.03162	0.00327	0.00625

B. Effects on *L*(VPIE) at 25° of Doubling Individual External Force Constants in Set φ_2

	ΔL(VPIE)		
Doubling	TAM	Formic acid	Oxalic acid
2 × F_{T_x}	+0.00943	+0.00582	+0.00153
2 × F_{T_y}	0.00939	0.00583	0.00154
2 × F_{T_z}	0.00935	0.00577	0.00152
2 × F_{R_x}	0.00326	0.00719	0.00000
2 × F_{R_y}	0.00157	0.00000	0.00004
2 × F_{R_z}	0.00130	0.00010	0.00002

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(6) R. Trambarulo and P. M. Moser, *J. Chem. Phys.*, 22, 1622 (1954).

(7) For a summary see T. T.-S. Huang, W. J. Kass, W. E. Buddenbaum, and P. E. Yankwich, *J. Phys. Chem.*, 72, 4431 (1968).

Table IV. Calculated Values of $L(k/k') = L(\mathrm{KIE})$[a]

T, °C	Reaction coordinate			
	1	2	1,2	1,-2
A. TAM				
Gas Phase: No External Force Field				
12.55	6.11698	0.38586	2.65555	1.32913
60.17	5.35883	0.37744	2.40037	1.18622
99.20	4.90008	0.37383	2.225625	1.10550
126.84	4.63799	0.37223	2.17857	1.06211
L(TIF)	2.54392	0.36818	1.80128	0.85684
Condensed Phase: External Force Field φ_2				
12.55	6.18746	0.39747	2.70458	1.35730
60.17	5.42925	0.38906	2.44939	1.21436
99.20	4.97047	0.38595	2.30528	1.13361
126.84	4.70838	0.38386	2.22760	1.09022
L(TIF)	2.61427	0.37980	1.85033	0.88490
Condensed Phase: External Force Field φ_3				
12.55	6.18758	0.39747	2.70462	1.35733
60.17	5.42933	0.38906	2.44942	1.21437
99.20	4.97053	0.38545	2.30529	1.13362
126.84	4.70842	0.38386	2.22761	1.09022
L(TIF)	2.61427	0.37980	1.85033	0.88490
B. Formic Acid				
Gas Phase				
12.55	1.55386	4.81065	1.09640	4.27837
25.00	1.48757	4.59492	1.04259	4.08217
60.17	1.32621	4.07177	0.91395	3.60528
99.20	1.18141	3.60763	0.77812	3.18098
126.84	1.09509	3.33522	0.74185	2.93159
L(TIF)	0.02443	0.80547	0.67465	0.75305
Condensed Phase, φ_2				
12.55	1.55421	4.82978	1.11249	4.29609
25.00	1.48792	4.61401	1.05867	4.09988
60.17	1.32658	4.09084	0.93002	3.62297
99.20	1.18180	3.62668	0.81979	3.19866
126.84	1.09548	3.35427	0.75791	2.94926
L(TIF)	0.02494	0.82449	0.69072	0.77069
Condensed Phase, φ_3				
12.55	1.55422	4.82981	1.11252	4.29616
25.00	1.48794	4.61407	1.05870	4.09994
60.17	1.32659	4.09088	0.93004	3.62301
99.20	1.18181	3.62671	0.81980	3.19869
126.84	1.09549	3.35429	0.75792	2.94928
L(TIF)	0.02494	0.82449	0.69072	0.77069

T, °C	Reaction coordinate			
	1	5	1,5	1,-5
C. Oxalic Acid (Intermolecular Isotope Effect)				
Gas Phase				
12.55	3.46407	3.19174	−1.22374	4.17670
60.17	2.91278	2.65409	−1.02866	3.45007
99.20	2.56902	2.31253	−0.89636	2.99903
126.84	2.36821	2.11057	−0.81383	2.73766
L(TIF)	0.55050	0.18715	0.26159	0.66729
Condensed Phase, φ_2				
12.55	3.47015	3.19426	−1.22071	4.18427
25.00	3.30870	3.03801	−1.16528	3.97143
60.17	2.91887	2.65662	−1.02562	3.45764
99.20	2.57510	2.31506	−0.89333	3.00660
126.84	2.37430	2.11309	−0.81080	2.74523
L(TIF)	0.55659	0.18969	0.26463	0.67487
Condensed phase, φ_3				
12.55	3.47017	3.19427	−1.22072	4.18429
25.00	3.30871	3.03802	−1.16528	3.97145
60.17	2.91888	2.65663	−1.02563	3.45765
99.20	2.57511	2.31605	−0.89333	3.00661
127.84	2.37430	2.11310	−0.81080	2.74524
L(TIF)	0.55659	0.18969	0.26463	0.67487
D. Oxalic Acid (Intramolecular Isotope Effect)				
Gas Phase				
12.55	0.0	−3.07442	+2.30714	−3.58589
25.00	0.0	−2.92193	+2.19879	−3.39291
60.17	0.0	−2.54858	+1.93395	−2.92495
99.20	0.0	−2.21274	+1.69563	−2.51155
126.84	0.0	−2.01350	+1.55386	−2.27080
L(TIF)	0.0	−0.09807	+0.15382	−0.31386
Condensed Phase, φ_2				
12.55	0.0	−3.07578	+2.30881	−3.58947
25.00	0.0	−2.92330	+2.20046	−3.39650
60.17	0.0	−2.54994	+1.93562	−2.92854
99.20	0.0	−2.21411	+1.69730	−2.51513
126.84	0.0	−2.01487	+1.55553	−2.27439
L(TIF)	0.0	−0.09944	+0.15549	−0.31745
Condensed Phase, φ_3				
12.55	0.0	−3.07580	+2.30882	−3.58949
25.00	0.0	−2.92331	+2.20047	−3.39651
60.17	0.0	−2.54995	+1.93563	−2.92855
99.20	0.0	−2.21411	+1.69730	−2.51514
126.84	0.0	−2.01487	+1.55553	−2.27440
L(TIF)	0.0	−0.09944	+0.15549	−0.31745

[a] Same external force field in reactant and transition states.

ployed in the KIE calculations, while Table IIIB shows the effect on L(VPIE) at 25° of doubling each of the external force constants. The isotope effects shown in Table IIIA are but a few hundredths of a per cent, quite small in comparison with many ^{13}C kinetic isotope effects.

Additivity of the shifts in L(VPIE) is easily demonstrated. This property makes it possible to predict L(VPIE) for any arbitrary set of external force constants when given the sensitivity factor for each individual force constant. Interestingly enough, the resulting L(VPIE) appear to exhibit simple dependence on molecular mass; $L(\mathrm{VPIE}) = \mathrm{constant}(M)^{-2/3}$.

In the Table IIIB results for TAM, the average contribution of the rotational modes to the VPIE is smaller than that of the translational modes; this is due in part to the smaller size of the rotational force constants, which are on the order of a tenth of the translational. However, the formic acid and oxalic acid results indicate that the inverse dependence of $G_{i,j}$ on the principle moments of inertia drastically reduces the dependence of VPIE on the rotational in comparison with the translational frequencies to the point that choices of rotational force constants for molecules of quite modest molecular weight are of little importance.

Kinetic Isotope Effects

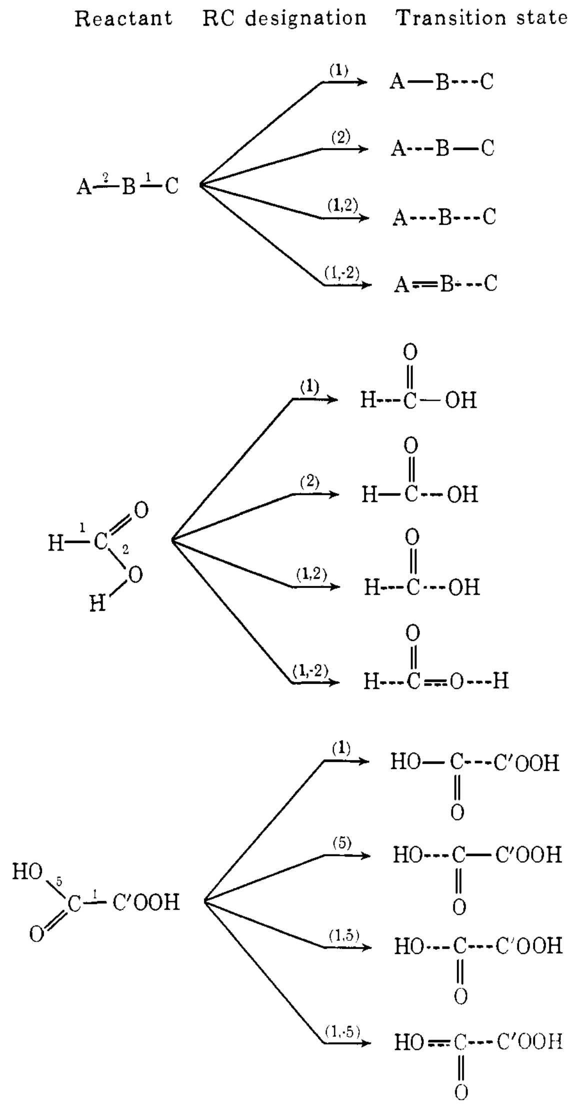
Two techniques were used in achieving a reaction coordinate, named type I and type II above. No external modes were involved in the reaction coordinates, which were representative of various simple decomposition pathways (Scheme I).

In TAM and formic acid, C is the position of isotopy and the kinetic isotope effect is intermolecular. The bifunctionality of oxalic acid leads to two isotope effects: intermolecular when C is the position of isotopy, and intramolecular when the rate comparison is between transition states isotopic at C or C′.[8]

The KIE results calculated for each decomposition in the gaseous and two condensed phases are compared

[8] J. G. Lindsay, D. E. McElcheran, and H. G. Thode, *J. Chem. Phys.*, 17, 589 (1949).

Scheme I



in Table IV. The latter correspond to different chemically inactive solvent situations. $L(k/k')$ is the sum of two terms: $L(\text{TIF}) = L(\nu_1^{\ddagger}/\nu_1'^{\ddagger})$ is the ratio of the isotopic frequencies associated with the RC; L(TDF) arises in the isotopic shifts of genuine vibration frequencies between the reactant and transition states. In every case the KIE for reaction in the condensed phase is larger than for the corresponding reaction in the gas phase. These differences arise almost entirely in the temperature independent factor (TIF), are quite small, and lie within the limits of error of typical experimental data. The increase from gas phase results decreases as the total mass of the molecule increases, as one would expect from the general inverse mass dependence of external $G_{i,j}$. The contributions to ΔL(TIF) of the various external modes depend on their symmetry. External modes of the same symmetry class as the internal modes in the β molecule perturb the internal modes and increase L(TIF), while external modes not of the same symmetry class as any of the internal modes have no such effects.

Table V. Calculated Values of $L(k/k') = L(\text{KIE})$[a]

T, °C	Reaction coordinate 1	2	1,2	1,-2	$L(K_{eq})$[b]
		A. TAM			
		$R = \varphi_2, T = \varphi_3$			
12.55	6.15022	0.36011	2.66726	1.31997	−0.03736
60.17	5.40187	0.36161	2.42196	1.18691	−0.02746
99.20	4.94852	0.36345	2.28329	1.11162	−0.02201
126.84	4.68935	0.36479	2.20854	1.07115	−0.01907
		$R = \varphi_2, T = \varphi_1$			
12.55	6.20611	0.41619	2.72328	1.37601	0.01872
60.17	5.44297	0.40281	2.46313	1.22810	0.01375
99.20	4.98147	0.39647	2.31629	1.14463	0.01102
126.84	4.71791	0.39341	2.23714	1.09976	0.00955
		B. Formic Acid			
		$R = \varphi_2, T = \varphi_3$			
12.55	1.52723	4.80282	1.08553	4.26917	−0.02699
25.00	1.46316	4.58929	1.03393	4.07516	−0.02478
60.17	1.30679	4.07107	0.91023	3.60321	−0.01981
99.20	1.16595	3.61085	0.80394	3.18283	−0.01586
126.84	1.08176	3.34056	0.74419	2.93555	−0.01373
		$R = \varphi_2, T = \varphi_1$			
12.55	1.56772	4.84323	1.12599	4.30959	0.01352
25.00	1.50023	4.62638	1.07107	4.11225	0.01241
60.17	1.33649	4.10073	0.93993	3.63286	0.00992
99.20	1.18974	3.63460	0.82772	3.20658	0.00794
126.84	1.10235	3.36113	0.76478	2.95612	0.00687
		C. Oxalic Acid (Intermolecular Isotope Effect)			
	1	5	1,5	1,-5	
		$R = \varphi_2, T = \varphi_3$			
12.55	3.46510	3.18920	−1.22579	4.17921	−0.00507
25.00	3.30406	3.03336	−1.16994	3.96680	−0.00465
60.17	2.91516	2.65291	−1.02935	3.45394	−0.00372
99.20	2.57213	2.31209	−0.89630	3.00364	−0.00297
126.84	2.37173	2.11053	−0.81337	2.74266	−0.00257
		$R = \varphi_2, T = \varphi_1$			
12.55	3.47268	3.19679	−1.21817	4.18679	0.00254
25.00	3.31102	3.04033	−1.16295	3.97375	0.00233
60.17	2.92072	2.65847	−1.02377	3.45950	0.00186
99.20	2.57659	2.31654	−0.89184	3.00809	0.00159
126.84	2.37558	2.11438	−0.80951	2.74651	0.00129

[a] Different external force fields in reactant (R) and transition (T) states, but no medium-related shifts in internal force constants. [b] $K_{eq} = (R = \varphi_3)/(R = \varphi_2)$, an "equilibrium" constant.

Changes in an external force constant set common to both reactant and transition state produce no changes in L(TIF), while changes in the temperature dependent factor (TDF) are observed but are very small. The increase in L(TDF) is confined to those external force constants which correspond to external modes in molecule β of the same symmetry class as the internal modes.[9] Again, perturbation of the internal modes is of central importance. The relative insensitivity of L(TIF) to external force constant changes is due to the absence of external modes from the reaction coordinate. The above results would be altered if there were in the F matrix any cross terms involving external modes.

Thus, the cell model predicts that wholly phase contributions to skeletal heavy-atom kinetic isotope effects are small and that between pairs of chemically inactive solvents the differences in such contributions are negligible in comparison with typical experimental errors.

Different Striction in the Transition State Than in the Reactant

We turn now to the situation in which the solvent is chemically active to a slight degree, *i.e.*, to situations in which the transition state is less tightly or more tightly bound by the medium than is the reactant. We

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[9] For TAM the β molecule belongs to the point group C_s and external force constant sets φ_2 and φ_4 will produce the same KIE.

assume, however, that the differences in striction are not so extreme as to introduce cross terms in F or to affect directly the *internal* force fields, the consequence of which would be a mixture of medium and reaction coordinate effects. Typical results of calculations subject to these limitations are collected in Table V.

The last column in Table V gives values of K_{eq} for the hypothetical equilibrium

$$X(\varphi^{\ddagger}) + X'(\varphi^{0}) = X(\varphi^{0}) + X'(\varphi^{\ddagger})$$

where superscript (0) refers to a reactant and $\ddagger$ to a transition state. Comparison of corresponding data in Tables IV and V shows that

$$L(k/k')_{\mathrm{V}} = L(k/k')_{\mathrm{IV}} + L(K_{\mathrm{eq}})$$

This result follows directly from the linear dependence of L(VPIE), and of the analogous quantity $L(K_{\mathrm{eq}})$, on the external force constants. The isotope effects arising in differences in striction between the reactant and transition states, as do those for VPIE, obey an additivity relationship. Results for the oxalic acid intramolecular isotope effect are not shown in Table V because all $L(K_{\mathrm{eq}})$ are zero; the referent species are identical except for orientation in the molecular plane. The general effects of differences in striction are predictable from the VPIE results in both sense and magnitude.

Conclusions

The Stern, Van Hook, and Wolfsberg cell model for medium effects is one of several under investigation. Because of its successes in accounting for VPIE it is an attractive approach. In accounting for KIE in reactions conducted in a chemically inactive solvent, this model predicts that no substantial isotope fractionation due to the presence of the medium itself need be assumed; the gas phase assumptions are adequate. Where a chemical reaction is accompanied by or achieved through solute–solvent interaction, isotope fractionation in the presence of the medium will be impressed upon the pure KIE. However, such effects will be small unless the differences of striction in the reactant and transition states result *per se* in changes in internal force constants or yield nonzero interaction force constants between internal and external coordinates.[10]

Before one can abandon all concern for the occurrence of appreciable medium effects on heavy-atom *kinetic* isotope effects, it is necessary to be certain of the validity of the assumptions of the cell model for *kinetic* as opposed to *equilibrium* isotope effects. The critical assumption here is that no internal force constant shifts or internal–external coordinate couplings result from medium interactions. We feel that this assumption is weak where medium-reactant interactions are sufficiently strong that gross rate effects would be observable. This is really the "chemically active solvent" situation and is commonplace. In such a situation calculation of the isotope fractionation due to the influence of the medium may be mixed with that accounting for the kinetic isotope effect, since shifts in the internal force field may be required.

Another concern must be for the applicability of the cell model as opposed to use of one nearer the other extreme, the structured medium model. An investigation of the latter is also underway in our laboratory.

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