

consistent with compression of reacting groups across a hydrogen bond.

(3) The solvent kinetic isotope effects in the range $k_p^{BH}/k_p^{BD} = 0.8-2.5$ for proton transfer to the leaving group oxygen in the breakdown of acetaldehyde hemiacetals anions are consistent with similar relative contributions of proton transfer and heavy-atom motion along the reaction coordinate that increases the effective mass of the transferred proton and decreases the isotope effect.¹³ This effect can be modeled by using vibrational analysis calculations as described in detail in the following paper.

The results show that the small magnitude of solvent kinetic isotope effects in multibond reactions cannot, in and of themselves, be used as a criteria for solvation catalysis via hydrogen-bonded transition states. We suggest that the solvent isotope effects $k_{H_2O}/k_{D_2O} = 1.6-4$ for ester and amide hydrolysis catalyzed by hydrolytic enzymes¹⁷ can be interpreted within the framework of

a fully coupled, concerted mechanism without the requirement for compression of hydrogen-bonded groups on the enzyme.

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Registry No. H₃CCH(OH)OEt, 7518-70-9; H₃CCH(OH)OCH₂C₂H₅, 108743-22-2; H₃CCH(OH)OCH₂C≡CH, 2187-89-5; D₂, 7782-39-0.

Supplementary Material Available: Tables S1-S3 summarizing second-order rate constants k_B and k_{LB} for general-base and general-acid catalysis and rate constants k_0 for breakdown of acetaldehyde and acetaldehyde-*d*₄ hemiacetals in water and deuterium oxide (5 pages). Ordering information is given on any current masthead page.

Characterization of Transition States by Isotopic Mapping and Structure-Reactivity Coefficients: Vibrational Analysis Calculations for the General-Base-Catalyzed Addition of Alcohols to Acetaldehyde

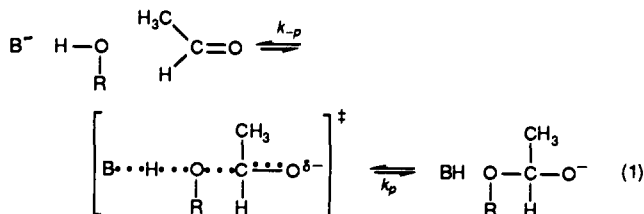
Christopher J. Murray* and Timothy Webb

Contribution from the Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas 72701. Received May 7, 1990

Abstract: General-base catalysis of the breakdown of acetaldehyde hemiacetals represents equilibrium ionization of the hemiacetal CH₃CH(OH)OR to form the hemiacetal anion, CH₃CH(O⁻)OR, followed by rate-determining general-acid catalysis of the cleavage of the hemiacetal anion to form acetaldehyde and ROH as described in the previous paper. Solvent deuterium isotope effects for the kinetically equivalent reverse reaction, general-base-catalyzed addition of alcohols ROH to acetaldehyde, have been modeled by using vibrational analysis calculations. Two independent weighting parameters that describe the bond orders for the catalyst O-H bond (W_{OH}) and the C-O bond between the central carbon and oxygen atoms (W_{CO}) were allowed to vary independently between 0 and 1 to generate isotopic maps as a function of transition-state structure. The effect of coupling of proton transfer to heavy-atom motion on the magnitude of the solvent kinetic isotope effect k_{H_2O}/k_{D_2O} was investigated by varying the relative ratios of several interaction force constants f_{ij} that couple two internal stretching coordinates. This process generates models of the reaction-coordinate motion for decomposition of the transition state to reactants and products. It is concluded that a reaction coordinate with essentially equal contributions of proton and heavy-atom motion is most consistent with the experimental isotope effects $(k_p^B)_{H_2O}/(k_p^B)_{D_2O} = 1.7 \pm 0.5$ for general-base catalysis of the addition of alcohols to acetaldehyde.

Introduction

The preceding paper¹ describes experimental evidence using kinetic isotope effects that confirms and extends evidence based on changes in structure-reactivity coefficients for a fully coupled, concerted reaction mechanism for the breakdown of acetaldehyde hemiacetals anions. In the reverse direction, this reaction corresponds to a class n reaction involving the general-base-catalyzed attack of alcohols on acetaldehyde.



(1) Coleman, C. A.; Murray, C. J. *J. Am. Chem. Soc.* 1991, previous paper in this issue.

In this paper we describe a method of characterizing the transition-state structure in eq 1 using model vibrational analysis calculations of the solvent isotope effects.^{2,3} An important streamlining of the modeling process has been developed by Schowen and his co-workers,⁴⁻⁶ who suggested that the properties

(2) For details on vibrational analysis calculations of isotope effects see: (a) Van Hook, W. A. In *Isotope Effects in Chemical Reactions*; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand-Reinhold: Princeton, NJ, 1970; pp 1-89. (b) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. (c) Sims, L. B.; Lewis, D. E. In *Isotopes in Organic Chemistry*; Buncl, E., Lee, C. C., Eds.; Elsevier: New York, 1980; pp 161-259. (d) McClellan, D. J. In *Isotopes in Organic Chemistry*; Buncl, E., Lee, C. C., Eds.; Elsevier: New York, 1987; pp 393-480.

(3) Buddenbaum, W. E.; Shiner, V. J., Jr. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: Baltimore, MD, 1977; pp 1-36.

(4) Hogg, J. L.; Rodgers, J.; Kovach, I.; Schowen, R. L. *J. Am. Chem. Soc.* 1980, 102, 79.

(5) Rodgers, J.; Femac, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* 1982, 104, 3263.

(6) Huskey, W. P. Ph.D. Thesis, University of Kansas, 1985.

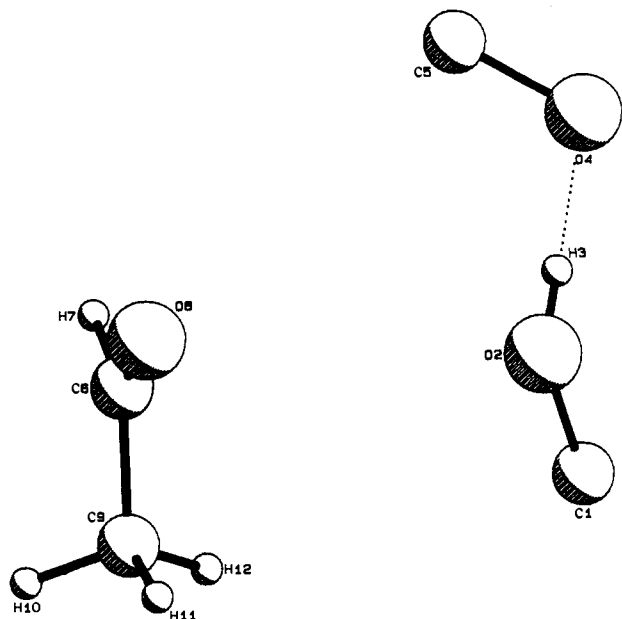


Figure 1. PLUTO drawing of the reactant model according to the reaction shown in eq 1. The numbers refer to the numbering system used to designate the internal coordinates. The dotted line corresponds to the hydrogen bond between the oxygen of the catalyst and the nucleophilic oxygen of the alcohol ROH.

of the transition state (P_{TS}) can be described by weighted averages (W) of the properties of the reactant (P_R) and product (P_P) according to

$$P_{TS} = WP_P + (1 - W)P_R \quad (2)$$

Properties such as bond orders, bond angles, and force constants are allowed to vary according to eq 2, and a reaction-coordinate model is generated by using off-diagonal ("interaction") force constants that describe the strength of coupling between the motion of two internal coordinates.

For a particular reaction-coordinate construction, the calculated isotope effects vary with the weighting parameters that describe the extent of bond breaking and bond making at the transition state. In the case of the addition of alcohols to acetaldehyde shown in eq 1, two independent variables W_{CO} and W_{OH} describe the weighting parameters for heavy-atom reorganization and proton transfer, respectively. This approach has the advantage of modeling any lag in the extent to which the various properties have occurred in the transition state. From three-dimensional plots of the isotope effect versus the weighting parameters, one can compare the observed isotope effect as well as changes in the isotope effect with reactant structure with the calculated isotope effect and thus "map" the experimental isotope effects.

There is an analogy in this approach to the empirical approach of mapping the "electronic structure" of reactions by using structure-reactivity coefficients and changes in these coefficients with reactant structure.^{7,8} In that case, the properties of ground states refer to acidities and basicities and the weighting parameters can be described by structure-reactivity parameters such as β and ρ_n . Changes in these parameters can also be described by interaction or cross coefficients. An empirical description of the curvatures and reaction-coordinate direction at the saddle point that represent the relative contributions of bond-making and bond-breaking processes can be calculated from these interaction coefficients.⁷

Our present lack of knowledge of energy surfaces in solution limits our approach to a semiquantitative description of observed experimental parameters such as kinetic isotope effects, Brønsted coefficients, and interaction coefficients. Nevertheless, descriptions of transition-state structure using either vibrational analysis

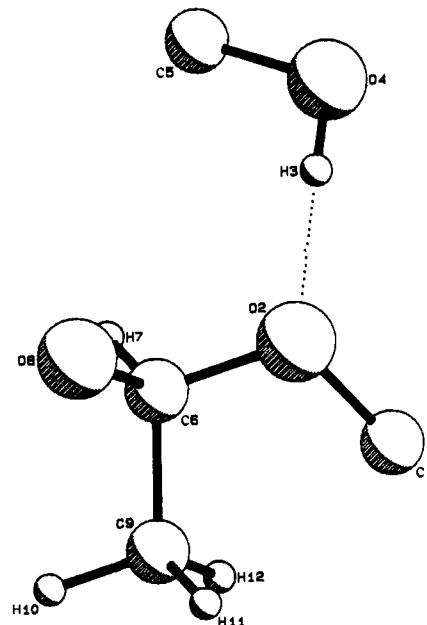


Figure 2. PLUTO drawing of the product model that corresponds to the hemiacetal anion, $\text{CH}_3\text{CH}(\text{O}^-)\text{OR}$.

Table 1. Standard Bond Lengths and Stretching Force Constants

bond	r^0 ^a	F^0 ^b
C-C	1.525 ^c	4.49 ^c
C-H	1.112 ^c	4.74 ^c
C-O	1.419 ^d	5.4 ^e
O-H	0.977 ^d	7.8 ^e

^aÅ. ^bmdyn/Å. ^cReference 11. ^dReference 13. ^eAverage stretching force constants from ab initio (ref 20) and spectroscopically (Mallinson, P. D.; McKean, D. C. *Spectrochim. Acta A*, 1974, 30A, 1133. Mallinson, P. D. *J. Mol. Spectrosc.* 1975, 58, 194) derived force constants for methanol.

calculations of isotope effects or structure-reactivity relationships provide self-consistent pictures in each case. Furthermore, when both approaches are applied to the same series of reactions, the different assumptions inherent in each model will tend to limit the transition-state structures that are consistent with each other. The aim of this work is not to find a transition state that gives an exact fit to the experimental solvent isotope effects but rather to examine the extent to which these two empirical approaches can give fully consistent descriptions of transition-state structure.

Experimental Section

The BEBOVIB-IV program of Sims and his co-workers^{9,10} was modified to run on an IBM PC-AT compatible microcomputer with a 80287 math coprocessor. The program was used to perform a normal mode analysis of reactant, product, and transition-state structures at 298 K. Isotope effects were calculated from the resulting vibrational frequencies of isotopic species and were not corrected for tunneling effects. The force fields were the redundant simple valence type for reactant and product models and were developed in analogy with force fields^{5,11,12} and geometries^{13,14} of molecules similar in structure to the reactants and products.

(9) The program is described in more detail in ref 2c.

(10) Burton, G. W.; Sims, L. B.; Wilson, J. C.; Fry, A. *J. Am. Chem. Soc.* 1977, 99, 3371.

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(14) (a) Harmony, M. D.; Laurie, V. W.; Kuczowski, R. L.; Schwendeman, R. H.; Ramsey, D. A.; Lovas, F. J.; Lafferty, W. J.; Maki, A. G. *J. Phys. Chem. Ref. Data* 1979, 8, 619. (b) Iijima, T.; Kimura, M. *Bull. Chem. Soc. Jpn.* 1969, 42, 2159.

(7) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* 1977, 99, 7948.

(8) Jencks, W. P. *Chem. Rev.* 1985, 84, 511, and references cited therein.

Table 11. Standard Bending Force Constants

atoms	F_{ϕ}^{0a}	atoms	F_{ϕ}^{0a}
C-C-H	0.59 ^b	O-C-O	0.35 ^c
H-C-H	0.55 ^b	O-H-O	0.35 ^c
C-O-H	0.64 ^c	O-C-H	0.9 ^d
C-O-C	1.3 ^d	O-C-C	1.2 ^d

^a mdyne·Å/rad². ^b Reference 11. ^c Reference 20. ^d Reference 17. ^e Engdahl et al. *J. Am. Chem. Soc.* **1983**, *105*, 4767.

Reactant and Product Models. Figures 1 and 2 show PLUTO drawings of the 12-atom models for reactant and product models for the reaction illustrated in eq 1 that retain all atoms within at least two bonds of the isotopically substituted hydrogen H3 on the nucleophilic alcohol.¹⁵ Bond orders for reactants and products were calculated from literature bond lengths for related stable molecules such as acetaldehyde,¹⁴ methanol,¹⁶ and dimethoxy ether¹⁷ by using Sims' modification¹⁰ of the Pauling relation:

$$r_i = r^0 - 0.3 \ln(n_i) \quad (3)$$

In eq 3, n_i is the Pauling bond order¹⁸ and r^0 is a standard bond length of unit bond order. Values for standard bond lengths were taken from various compilations and are summarized in Table I. The bond orders for the hydrogen bond between the base catalyst (O4) and the nucleophilic oxygen (O2) were arbitrarily set at 0.05 in the reactant model. Bond angles about all sp^3 -hybridized atoms were 109.5°. The bond angles about the sp^2 -hybridized carbon and the transferred hydrogen (H3) were 120° and 180°, respectively. The proton transfer was assumed to be linear.

Stretching and bending force constants were constrained to obey eqs 4 and 5, respectively.⁹

$$F_{ii} = F^0 n_i \quad (4)$$

$$F_{\phi} = F_{\phi}^0 (n_i n_j)^{1/2} g_{\phi} \quad (5)$$

In eq 4, F^0 is the standard stretching force constant for a bond i of unit bond order. In eq 5, F_{ϕ}^0 is the standard angle bending force constant for the angle ϕ defined by the bonds i and j and g_{ϕ} is an empirically derived geometry factor⁹ given by

$$g_{\phi} = 1.39 + 1.17 \cos \phi \quad (6)$$

that has values of $g = 1.0$ for $\phi = 109.5^\circ$ and $g = 0.6$ for $\phi = 120^\circ$. Standard stretching and bending force constants are summarized in Tables I and II, respectively.

Torsional force constants, F_{τ} , were assigned to all possible four-atom chains through a given bond.⁶ As discussed by Williams et al.,¹⁹ this is not the best procedure to follow; however, making use of all four-atom torsional coordinates at least ensures that all of the atoms expected to move in a single torsional motion are associated with a quasi-torsional coordinate and force constants. Torsional force constants were interpolated from a plot of force constants against bond order as proposed by Husky.⁶ Points for propane ($n = 1$; $F_{\tau} = 0.011$ mdyne·Å/rad²; one-ninth the torsional force constant), benzene ($n = 1.67$; $F_{\tau} = 0.05$ mdyne·Å/rad²), and ethene ($n = 2$; $F_{\tau} = 0.125$ mdyne·Å/rad²) define the limits of interpolation.

The force constant for the out-of-plane bend in acetaldehyde was set at $F_{OOP} = 0.35$ mdyne·Å. The inclusion of torsional and out-of-plane bending force constants usually has little effect on the calculated kinetic isotope effect.²

Transition-State Models. Two independent variables, W_{OH} and W_{CO} , describe the weighting parameters that were allowed to vary from zero (reactant model) to unity (product model) as shown in the reaction-coordinate energy diagram of Figure 3. The x axis is defined by the weighting parameter W_{OH} that can be described by the change in the Pauling bond order n_{O4-H3} for the O-H bond of the catalyst. The y axis is defined by W_{CO} and represents the change in the bond order n_{C6-O2} between the carbonyl carbon and the central oxygen atom. A concerted reaction corresponds to a transition state that is located at some value of the transition-state coordinates W_{OH}, W_{CO} within the center of the

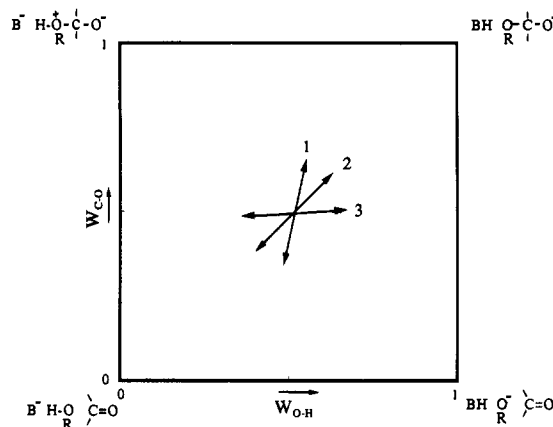


Figure 3. Reaction-coordinate energy diagram for the class n reaction of alcohols with acetaldehyde. The x and y axes are defined in terms of the weighting parameters W_{OH} and W_{CO} that represent proton transfer and C-O bond formation/breaking, respectively. The z axis corresponds to free energy, and energy contour lines are omitted. For the addition reaction shown in eq 1, the reaction proceeds from the lower left hand corner to form the hemiacetal anion in the upper right hand corner. The solid lines illustrate the relative contributions of changes in proton transfer and heavy-atom reorganization to the reaction coordinate that corresponds to the decomposition mode of the transition state. The relative orientations of the reaction coordinates for models 1-3 are shown qualitatively.

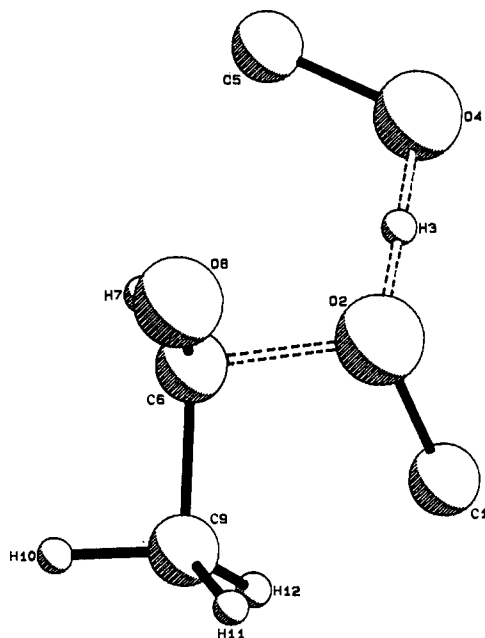


Figure 4. PLUTO drawing for the transition state shown in eq 1. The structure is drawn for a transition state in which partial bonds between the central oxygen and the transferred proton (W_{OH}) and between the central carbon and oxygen (W_{CO}) have Pauling bond orders equal to 0.5.

diagram. In the limit of a fully stepwise mechanism, the reaction would proceed through the intermediates along the edge of the diagram corresponding to formation of the protonated ether T^{\ddagger} in the upper left hand corner ($W_{OH} = 0, W_{CO} = 1$) or the alkoxide ion in the lower right hand corner of the diagram ($W_{OH} = 1, W_{CO} = 0$). If there is a linear relationship between bond order and structure-reactivity coefficients, the x and y axes of Figure 3 should be related to the experimentally determined coefficients β and ρ_n , respectively, described in the previous paper.

Figure 4 shows a transition-state structure with $W_{CO} = W_{OH} = 0.5$ that corresponds to a centrally located transition state on the diagram of Figure 3. The reaction trajectory to reach this transition-state structure was chosen so that the nucleophilic electron pair on the O2 oxygen is aligned along the axis of the forming C-O bond. Force constants, bond angles, and bond orders were allowed to vary smoothly from reactant to product models according to eq 2 for 81 different combinations of the weighting parameters. This process generates an "isotopic

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map" of the calculated isotope effect as a function of the transition-state coordinates W_{OH}, W_{CO} .⁵

It was necessary to reduce the number of adjustable parameters for the models by assuming that the sum of the bond orders about all atoms except the nucleophilic O2 oxygen was constant. For the reactant and product models, the sum of the bond orders, n_{tot} , about the nucleophilic oxygen was calculated from

$$n_{tot} = n_{C1-O2} + n_{O2-H3} + n_{C6-O2} \quad (7)$$

with $n_{tot} = 2$. For the transition-state models, the sum of the bond orders about the nucleophilic oxygen varied from $n_{tot} = 1.1$, corresponding to the hydrogen-bonded alkoxide ion in the lower right hand corner of Figure 3, to $n_{tot} = 2.9$, corresponding to the protonated ether T* that is hydrogen bonded to the catalyst in the upper left hand corner of Figure 3.

The force constants for the C-O and C-H stretches of methanol vary with the extent of protonation or deprotonation on oxygen.^{20,21} This effect represents negative hyperconjugation of the lone pairs on oxygen with the adjacent C-H bonds that weakens the C-H bonds and strengthens the C-O bond of methanol and methoxide ion. This effect was first suggested by Hine²² and is consistent with infrared data for methanol and methoxide ion.²³ To model this effect, the force constant for the C-O stretch of the nucleophilic alcohol, F'_{CO} , was allowed to vary with the weighting parameters W_{OH} and W_{CO} according to

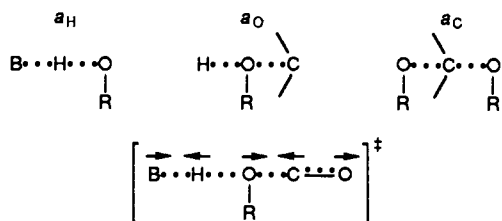
$$F'_{CO} = F_{CO}(1 - (W_{CO} - W_{OH})/4) \quad (8)$$

where F_{CO} refers to the C-O force constant calculated from eqs 2 and 4. The term $(W_{CO} - W_{OH})/4$ in eq 7 is analogous to the disparity of progress variable proposed by Grunwald²⁴ for these reactions.

Reaction-Coordinate Generation. The decomposition mode along the reaction coordinate for each given transition-state coordinate W_{OH}, W_{CO} was examined by using off-diagonal (interaction) force constants to generate an imaginary reaction-coordinate frequency. Bond stretches were allowed to interact according to²⁵

$$f_{ij} = a_{ij}(F_{ii}F_{jj})^{1/2} \quad (9)$$

The interaction constants a_{ij} represent asymmetric (for $a_{ij} > 0$) stretching motions of adjacent bonds i and j . Interaction force constants f_{ij} were assigned so as to represent realistic reaction-coordinate motions as follows. The interaction constants a_{ij} are denoted a_H (O-H-O coupling), a_O (H-O-C coupling), and a_C (O-C-O coupling).



For a_H , a_O , and a_C all positive values, the reaction-coordinate motion corresponds to the overall asymmetric stretching motion shown. The requirement for an imaginary frequency for the reaction coordinate is that the determinant of the force constant matrix F for the transition state be negative. $|F^*| < 0$. When expanded, this leads to

$$1 - a_H^2 - a_O^2 - a_C^2 + a_H^2 a_C^2 = D \quad (10)$$

where D represents the barrier curvature parameter that is negative.² A systematic exploration of reaction-coordinate models involves variations of the curvature parameter D and/or the interaction constants a_{ij} . The curvature parameter D was maintained constant at -0.2 in this work. This generated values of the imaginary reaction-coordinate frequency of less than a few hundred cm^{-1} . Using larger values of the curvature parameter generated solvent kinetic isotope effects that were substantially larger than the experimentally observed isotope effects.

Table III. Experimental Solvent Isotope Effects and Transition-State Coordinates for the Addition of ROH to Acetaldehyde

catalyst	$(k_p^B)_{H_2O}/(k_p^B)_{D_2O}^{a,b}$	β^b	ρ_n^c
ROH = CH ₃ CH ₂ OH			
CH ₃ OCH ₂ COO ⁻	0.9	0.48	0.61
ClCH ₂ CH ₂ COO ⁻	1.5	0.48	0.57
CH ₃ COO ⁻	2.2	0.48	0.52
(CH ₃) ₂ AsO ₂ ⁻	1.8	0.48	0.42
ROH = ClCH ₂ CH ₂ OH			
CH ₃ OCH ₂ COO ⁻	1.2	0.57	0.34
ClCH ₂ CH ₂ COO ⁻	1.3	0.57	0.31
CH ₃ COO ⁻	1.7	0.57	0.26
(CH ₃) ₂ AsO ₂ ⁻	1.7	0.57	0.15
ROH = HC≡CCH ₂ OH			
CH ₃ OCH ₂ COO ⁻	0.9	0.72	0.37
ClCH ₂ CH ₂ COO ⁻	1.7	0.72	0.33
CH ₃ COO ⁻	1.9	0.72	0.28
(CH ₃) ₂ AsO ₂ ⁻	2.7	0.72	0.18

^a Solvent isotope effect for the reaction shown in eq 1. ^b Calculated from the data for the microscopic reverse breakdown of hemiacetal anions described in ref 29. ^c Fractional amount of C-O bond formation/cleavage calculated from the transformation of coordinates: $\rho_n = \beta + \beta_{ig}$ as described in ref 32.

Results

The effect of coupling the nuclear motions of heavy atoms to proton transfer on the magnitude of the solvent deuterium kinetic isotope effect for the general-base-catalyzed addition of alcohols to acetaldehyde illustrated in eq 1 was investigated for several combinations of the interaction constants a_H , a_O , and a_C that are defined under Experimental Section. It is important to note that for any given transition-state coordinate there exists several reasonable reaction-coordinate motions for decomposition of the transition state. This is illustrated qualitatively by the solid lines in Figure 3 for the transition-state coordinate $W_{OH} = W_{CO} = 0.5$. The *direction* of the reaction coordinate describes the relative motions of the atoms along the reaction coordinate and reflects the relative ratios of the interaction constants a_H , a_O , and a_C .²⁶

Three separate reaction-coordinate constructions illustrate the general trends observed.²⁷ Model 1 ($a_H = a_O = 0.347$, $a_C = 1.044$) involves predominantly heavy-atom motion with a smaller contribution of proton transfer along the reaction coordinate. Model 2 ($a_H = a_O = a_C = 0.689$) represents equal contributions of heavy-atom motion and proton transfer along the reaction. Finally, model 3 ($a_H = 1.044$, $a_O = a_C = 0.347$) represents predominant proton transfer with a smaller contribution of heavy-atom motion along the reaction coordinate.

Parts A-C of Figure 5 show isotopic maps for these three reaction-coordinate constructions. Each map was generated from 81 transition-state coordinates W_{OH}, W_{CO} that reflect the extent of proton transfer and carbon-oxygen bond cleavage/formation at the saddle point. The x and y axes represent proton transfer and C-O bond formation/breaking as defined by the weighting parameters W_{OH} and W_{CO} , respectively. The z axis corresponds to the calculated solvent kinetic isotope effect k_{H_2O}/k_{D_2O} . Calculated isotope effects as a function of the weighting parameters for models 1-3 are summarized in Tables S1-S3.²⁸

(26) More correctly, the direction of reaction-coordinate motion corresponds to the direction of the eigenvector derived from diagonalization of the FG matrix, where G is the transformation matrix which relates the 3N-6 internal coordinates to Cartesian coordinates; see ref 1b and: Maggiora, G. M.; Christoffersen, R. E. In *Transition States of Biochemical Processes*; Gaudour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 119-159.

(27) In a limited attempt to model a reaction-coordinate resembling "solvation catalysis" (Swain, C. G.; Kuhn, D. A.; Schowen, R. L. *J. Am. Chem. Soc.* 1965, 87, 1553) ratios of the interaction constants a_O/a_H and $a_C/a_H \geq 10$ were used while the curvature parameter D in eq 9 was varied. To generate solvent isotope effects $k_{H_2O}/k_{D_2O} \geq 1.2$, rather unrealistic values for the interaction constants $a_O = a_C \geq 3$ and absolute values of the imaginary reaction-coordinate frequencies $> 2200 \text{ cm}^{-1}$ were required. This is not a test of solvation catalysis because the modeling scheme requires that proton motion be part of the reaction coordinate.

(20) Williams, I. H. *J. Mol. Struct.* 1983, 105, 105.

(21) Defrees, D. J.; Hassner, D. Z.; Hehre, W. J.; Peter, E. A.; Wolfsberg, M. *J. Am. Chem. Soc.* 1978, 100, 641.

(22) Hine, J.; Hine, M. *J. Am. Chem. Soc.* 1952, 74, 5266.

(23) Seubold, F. H. *J. Org. Chem.* 1956, 21, 156.

(24) Grunwald, E. *J. Am. Chem. Soc.* 1985, 107, 4710.

(25) Coupling only stretches ensure that only one imaginary reaction-coordinate frequency is generated because the bond stretches are not part of a redundant coordinate set. See refs 2c and 6 for a discussion of this point.

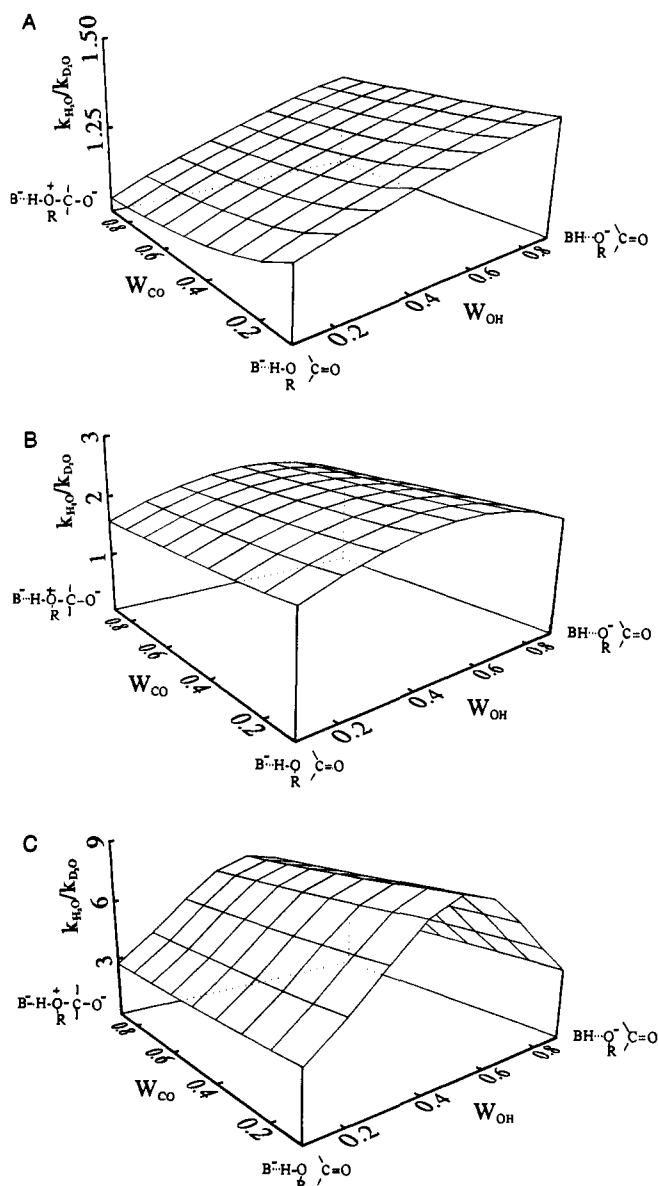


Figure 5. Isotopic maps calculated for the class n mechanism shown in eq 1. The x and y axes represent proton transfer and C–O bond formation/breaking as defined by the weighting parameters W_{OH} and W_{CO} , respectively. The z axis corresponds to the calculated kinetic isotope effect k_{H_2O}/k_{D_2O} as described under Experimental Section. The reaction-coordinate motion illustrated qualitatively by the solid lines 1–3 in Figure 3 were modeled by using off-diagonal interaction force constants as described in the text. (A) Model 1. $a_H = a_O = 0.347$ and $a_C = 1.044$; this model corresponds to a reaction coordinate dominated by heavy-atom reorganization. (B) Model 2. $a_H = a_O = a_C = 0.697$; the reaction coordinate corresponds to fully coupled proton and heavy-atom motion. (C) Model 3. $a_H = 1.044$, $a_O = a_C = 0.347$; this model corresponds to predominantly proton motion along the reaction coordinate.

Table III summarizes the experimental solvent isotope effects²⁹ (k_{-p}^B)_{H₂O}/(k_{-p}^B)_{D₂O} along with experimental measures of the transition-state coordinates β and ρ_n determined from observed structure–reactivity correlations³² for a series of alcohols ROH

(28) See paragraph concerning supplementary material at the end of this paper.

(29) The isotope effects in Table III were calculated from the solvent isotope effects for the reverse reaction corresponding to eq 1 that involves the general-acid-catalyzed cleavage of acetaldehyde hemiacetal anions (k_p^{BH}) described in the previous paper.¹ The equilibrium isotope effect for eq 1 was assumed to be $(K_p)_{H_2O}/(K_p)_{D_2O} = \phi_{ROH}/\phi_{BH} = 1.06/0.96 = 1.10$, where ϕ_{ROH} is the fractional factor for methanol³⁰ and ϕ_{BH} is the fractionation factor for acetic acid.³¹

(30) Jarrei, R. M.; Saunders, M. *J. Am. Chem. Soc.* **1985**, *107*, 2648.

(31) Gold, V.; Lowe, B. M. *J. Chem. Soc. A* **1968**, 1923.

Table IV. Comparison of Stretching Force Constants for Acetaldehyde and Methanol Derivatives^a

coordinate	F^0 ^a		
	spectroscopic	ab initio	this work
C=O	11.01 ^b	12.27 ^d	11.30
C–C	4.63 ^b	4.29 ^d	4.67
C–H _{ald}	4.14 ^b	4.25 ^d	4.29
C–H _{ecf}	4.95 ^b	4.99 ^d	4.99
C–OH	5.28 ^c	4.8 ^e	5.4
O–H	8.14 ^c	7.3 ^e	7.8
C–O ⁻	–	4.9 ^e	6.8
C–OH ₂ ⁺	–	2.7 ^e	4.1 ^f

^a mdyn/Å. ^b Hollenstein, H.; Gunthard, H. Hs. *Spectrochim. Acta A* **1971**, *27A*, 2027. ^c Mallinson, P. D.; McKean, D. C. *Spectrochim. Acta A* **1974**, *30A*, 1133. Mallinson, P. D. *J. Mol. Spectrosc.* **1975**, *58*, 194. ^d Scaled force constants calculated at the 6-31G* level of SCF-MO theory in ref 12. ^e Scaled force constants calculated at the 4-31G level of SCF-MO theory in ref 20. ^f Force constant for the C–O stretch of the protonated ether in the intermediate T[‡] shown in the upper left hand corner of Figure 3, calculated according to eq 8 in the text.

Table V. Comparison of Calculated and Experimental Equilibrium Isotope Effects^a

isotopic site	equilibrium isotope effect	
	exptl	SVFF models
β -D ₃	0.82–0.88 ^b	0.83
α -D	0.72–0.73 ^c	0.72
H3	1.10 ^d	1.03

^a In water at 25 °C; the equilibrium constant is defined according to eq 1 as $K_{-p} = k_{-p}/k_p$. ^b Cook, P. F.; Blanchard, J. S.; Cleland, W. W. *Biochemistry* **1980**, *19*, 4853. ^c Based on the hydration and methanolysis of aldehydes: Lewis, C. A., Jr.; Wolfenden, R. *Biochemistry* **1977**, *16*, 4886. Hill, E. A.; Milosevich, S. A. *Tetrahedron Lett.* **1976**, 4553. ^d Based on the measured fractionation factors for methanol (ref 30) and acetic acid (ref 31).

and catalysts B⁻ in eq 1. The transition-state coordinates β, ρ_n should be related to the transition state-coordinates W_{OH}, W_{CO} if observed structure–reactivity coefficients describe transition-state bond orders.³³

Discussion

Comparison with Experimental and Theoretical Data. The simple valence force field (SVFF) used in these calculations is unrefined relative to ab initio or spectroscopically derived force fields. This raises the question as to whether reasonable estimates of transition-state structure can be obtained from the procedure outlined under Experimental Section. Table IV shows that stretching force constants for reactant and product models calculated by using eqs 3 and 4 are in good agreement with force constants calculated by using ab initio and spectroscopic methods for acetaldehyde, methanol, and methoxide ion. The limiting force constants F_{CO}^0 for the C–O stretch of methoxide ion and the protonated ether T[‡] shown in the upper left hand corner of the diagram in Figure 3 that were calculated from eq 7 show reasonable agreement with the trends in C–O stretching force constants for methoxide ion and methoxonium ion, CH₃OH₂⁺, calculated by using SCF-MO methods.

Table V shows that equilibrium α -deuterium, β -deuterium, and solvent deuterium isotope effects calculated from reactant and

(32) Sørensen, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4675. The value of ρ_n is calculated from the transformation of coordinates⁷ described in detail by Sørensen and Jencks: $\rho_n = \beta + \beta_{18}$; values of $\beta_{18} = \partial \log k_B / \partial p K_{18}$ were obtained by differentiation of $-\log k_B = 1/2 p_x p K_{BH}^2 + 1/2 p_y p K_{18}^2 + p_{xy} p K_{BH} p K_{18} - \beta_0 p K_{BH} - \beta_{18} p K_{18} + F$ with $p_x = 0$, $p_y = -0.2$, $p_{xy} = 0.07$, $\beta_0 = 1.53$, $\beta_{18}^0 = -2.83$, and $F = -12.92$. The values of ρ_n calculated from the transformation of coordinates are related to, but not identical with, values of ρ_n calculated from secondary α, β -deuterium isotope effects.¹

(33) It is important to note that changes in Bronsted coefficients may reflect reciprocal electrostatic interactions so there may be no unique relationship between values of β or ρ_n and bond order.^{7,8} Nevertheless, we shall assume for the purposes of discussion that $W_{OH} = \beta$ and $W_{CO} = \rho_n$.

product models are in good agreement with experimentally observed isotope effects for similar compounds. The equilibrium β -deuterium isotope effect $K^{\beta\text{H}}/K^{\beta\text{D}} = 0.83$ is slightly smaller than $K^{\beta\text{H}}/K^{\beta\text{D}} = 0.88$ reported by Schowen and co-workers on the basis of a similar force field.⁴ The calculated equilibrium α -deuterium isotope effect $K^{\alpha\text{H}}/K^{\alpha\text{D}} = 0.72$ can also be compared with an estimate of $K^{\alpha\text{H}}/K^{\alpha\text{D}} = 0.76$ that is based on isotopic fractionation factors derived from calculations employing more elaborate force fields than the ones used here.³⁴

The reaction trajectory used in these calculations (Figure 4) does not conform to the "curved trajectory" for nucleophilic additions to carbonyl centers proposed by Burgi, Dunitz, and their collaborators on the basis of crystallographic studies^{36,37} and SCF-MO calculations in the gas phase.³⁸ However, vibrational analysis calculations for the reaction of hydroxide ion with acetaldehyde⁴ suggest that isotope effects calculated for a curved trajectory do not differ significantly from the one proposed here. This conclusion is consistent with previous conclusions that isotope effects are largely governed by the isotopic sensitivity of vibrational frequencies and are not dependent upon exact geometries.¹⁹ Ab initio calculations at the 6-31+G* level and Monte Carlo simulations for nucleophilic addition of hydroxide ion to formaldehyde show no significant difference in reaction profiles for collinear or more orthogonal reaction trajectories when solvent water molecules are included in the calculations.³⁹

The agreement between experimental and theoretical data for stable molecules provides an internal check on the consistency of the force fields for reactant and product models. Furthermore, the reaction trajectory chosen conforms with results suggested by more sophisticated quantum-mechanical calculations. Because of its overall flexibility the model may not be expected to give an "exact" fit to experimental data. However, when changes in isotope effects are compared with changes in reactant structure, various uncertainties in the structure and force field for the transition state may tend to cancel out.⁵ We conclude that despite the simplifications used in the SVFF models they can provide reasonable estimates of transition-state force fields within the limitations imposed by the modeling process and can yield reliable insights into the factors controlling the experimental solvent isotope effects and their dependence on reactant structure.

Mapping the Solvent Isotope Effects. Table III shows the range of experimental solvent kinetic isotope effects²⁹ as a function of the observed structure-reactivity coefficients β and ρ_n that measure changes in charge distribution between the ground and transition states.^{32,33} The major conclusion to be drawn from comparison of the experimental data in Table III with the models summarized in Figure 5A-C is that a reaction coordinate with essentially equal contributions of heavy-atom motion and proton transfer (model 2) is most consistent with (a) the small magnitude of the solvent kinetic isotope effects for the catalytically active proton $(k_{-p}^{\text{B}})_{\text{H}_2\text{O}}/(k_{-p}^{\text{B}})_{\text{D}_2\text{O}} = 1.7 \pm 0.5$ and (b) the shallow dependence of the isotope effects upon the pK of base catalyst B⁻ and the alcohol as measured by β and ρ_n . Figure 6 shows the isotopic map for model 2 superimposed on the experimental data.

Examination of the models in Figure 5 reveals that for a given transition-state coordinate $W_{\text{OH}}, W_{\text{CO}}$ the magnitude of the kinetic isotope effect decreases as the ratio of the interaction constants

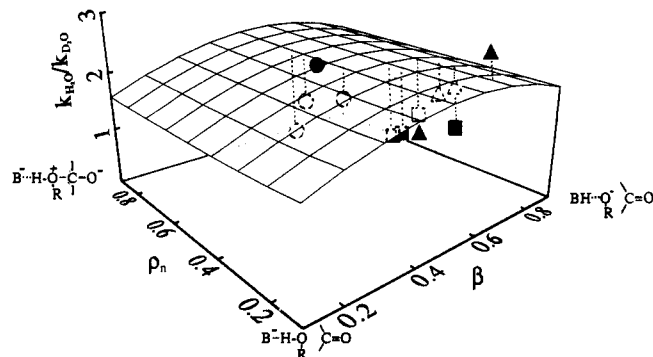


Figure 6. Experimental isotopic map of the solvent isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ for reactions of ethanol (●), chloroethanol (■), and propargyl alcohol (▲) with acetaldehyde as a function of the observed structure-reactivity coefficients β and ρ_n . The experimental isotope effects $(k_{-p}^{\text{B}})_{\text{H}_2\text{O}}/(k_{-p}^{\text{B}})_{\text{D}_2\text{O}}$ are summarized in Table III. The x and y axes represent proton transfer and C-O bond formation/breaking as defined by the observed structure-reactivity parameters β and ρ_n , respectively, that are derived from the structure-reactivity data. Superimposed is the isotopic map calculated for model 2 assuming $\beta = W_{\text{OH}}$ and $\rho_n = W_{\text{CO}}$. The dotted lines show the difference between the experimental kinetic isotope effect and the calculated kinetic isotope effect for a given transition-state coordinate.

$a_{\text{H}}/a_{\text{O}}$ and $a_{\text{H}}/a_{\text{C}}$ decreases, signifying a smaller contribution of proton motion, relative to heavy-atom motion, along the reaction coordinate. Participation of other modes besides proton motion in the reaction coordinate raises the effective mass for motion along the reaction coordinate and thus reduces the difference in effective mass between the hydron transfers in H₂O and D₂O. This change tends to reduce the isotope effect. This confirms the conclusion that heavy-atom motion in the reaction coordinate is a fundamental source of variation in $k_{\text{H}}/k_{\text{D}}$ in multibond reactions, as previously suggested by Saunders.⁴⁰

The relative ratios for the interaction constants $a_{\text{H}}/a_{\text{O}}$ and $a_{\text{H}}/a_{\text{C}} = 1$ for model 2 (Figure 5B) agree well with the semi-quantitative estimate of a diagonal reaction coordinate on the reaction-coordinate energy diagram analogous to Figure 3 that is defined by the experimental structure-reactivity parameters β and ρ_n .³² The reaction-coordinate direction at the saddle point can be determined from the experimental structure-reactivity data according to the procedure outlined by Jencks and Jencks.⁷ The slopes of the "level lines" of constant energy that bisect the saddle point can be obtained from the interaction coefficients that describe the second derivative of changes in rate constants with changes in substituents.⁷ The reaction-coordinate direction is rotated by only a few degrees from the diagonal, as described by Sørensen and Jencks,³² and is consistent with essentially equal contributions of heavy-atom motion and proton transfer at the transition state.

Limitations of the Model. An effort was made in these calculations to use the minimum number of assumptions possible to obtain a model consistent with the experimental data. This is a disadvantage of these vibrational analysis calculations, and there may be some possible inaccuracies in the results. Perhaps the most unrealistic assumption is that of conservation of total bond order about the carbonyl carbon (C6) and the transferred proton (H3). There is evidence for a nonadditivity of bond order changes or a net expansion of transition state about the central oxygen in eq 1 as the alcohol is made less basic based upon the absolute magnitude of the interaction coefficient $p_{xy} = \partial\beta/\partial\text{p}K_{\text{a}} = 0.09$ that is larger than $p_{yy} = \partial\rho_n/\partial\text{p}K_{\text{a}} = -0.069$.^{1,32} The p_{xy} coefficient describes changes in proton transfer (β) that are larger than changes in C-O bond order (ρ_n) about the central oxygen in eq 1. This conclusion is based on the effective charge "seen" by substituents and may not reflect nonconservation of bond order, however, because of an "imbalance" in the extent to which the various processes have occurred at the transition state. Calcu-

(34) This value is calculated from $K^{\alpha\text{H}}/K^{\alpha\text{D}} = 1.391/1.832$ by using estimates of the fractionation factors for $\text{CH}_3\text{Cl}=\text{O}$ and $\text{CH}_3\text{Cl}(\text{OH})_2$ relative to acetylene.^{3,35} These fractionation factors were estimated from tabulated fractionation factors by assuming the effect of a given change for a group attached at the α -carbon atom is independent of the other groups attached to the atom.

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lations employing more elaborate force fields are consistent with a net loosening of bond order about the central hydrogen atom in transfers between carbon-carbon and carbon-oxygen centers.⁴¹

Another possible limitation of these calculations may be the assumption, embodied in eq 2, that the effects of isotopic substitution on the properties of ground states and transition states may be treated in the same way because these states are related by a quasi-equilibrium. This assumption also forms the basis for characterizing transition states by using structure-reactivity relationships such as the extended Brønsted relationships described in the previous paper^{1,8,42} and has been criticized.⁴³⁻⁴⁵ For example, it has been suggested that the proton in eq 1 jumps from the central oxygen of the alcohol to the catalyst when the pK values of the catalyst and the partially bonded alcohol become equal in the transition state.⁴⁵ It has also been suggested⁴⁶ that the changes in Brønsted coefficients with changes in the pK of the alcohol ROH in eq 1 do not necessarily require that the motions of the proton be kinetically coupled with heavy-atom motion as required by the modeling process used here.⁴⁶ Indirect support for these views comes from the increase in C-OR bond lengths of acetals with more acidic leaving group alcohols ROH determined by X-ray crystallography⁴⁷ that suggest that changes in structure-reactivity coefficients may not reflect changes in transition-state bond orders but may simply reflect changes in ground-state bond orders, without any requirement for coupling between the motions of reacting atoms in the transition state.

Changes in ground-state C-O bond lengths with changing reactant structure cannot account fully for the observed changes in transition-state structure determined from structure-reactivity relationships, however. The correlation of the changes in C-O bond length r_{CO} in $\text{CH}_3\text{OCH}_2\text{-OR}$ acetals with changes in the pK of the alcohol ROH can be described by an apparent inter-action coefficient

$$p_y = \partial n_{CO} / -\partial \text{p}K_{\text{ROH}} \quad (11)$$

that is defined by the change in C-O bond order n_{CO} between the

CH_2 carbon and the oxygen of the leaving group alcohol ROH.⁴⁸ A value of $p_y = -0.013$ is calculated from eq 3 and $\partial r_{CO} / -\partial \text{p}K_{\text{ROH}} = 0.0037$ that describes the increase in C-OR bond length with more acidic leaving group alcohols.⁴⁷ The much larger coefficient $p_{yy'} = \partial \rho_n / -\partial \text{p}K_{\text{lg}} = -0.069$ that describes the change in the transition-state C-OR bond order with changes in leaving group pK for the breakdown of hemiacetals¹ shows that transition states can show much larger changes in bond order than ground states, if ρ_n is a measure of changes in C-O bond order.³³ This effect has been termed "transition-state plasticity"^{46,49} and is consistent with the view that transition-state force constants for breaking bonds are smaller than the corresponding force constants for ground-state molecules as required by eq 2.

Conclusion. The general agreement between the experimental data summarized in Table III and the semiempirical model (Figure 5B) described here provides evidence that proton transfer and heavy-atom motion are kinetically coupled in the general-base-catalyzed reactions of alcohols with carbonyl centers. The results provide additional support for the suggestion, based on structure-reactivity relationships, that the class n reactions of stable electrophiles with alcohols in water occur by a concerted, coupled mechanism.⁸ The ability to model the behavior of both structure-reactivity coefficients and kinetic isotope effects on the basis of eq 2 provides indirect support for the suggestion that substituent effects on the transition state are proportional to their effects on the ground state, and characterization of these effects provides a self-consistent description of transition-state structure in these reactions.^{8,42}

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Registry No. H_3CCHO , 75-07-0; EtOH, 64-17-5; $\text{Cl}(\text{CH}_2)_2\text{OH}$, 107-07-3; $\text{HC}\equiv\text{CCH}_2\text{OH}$, 107-19-7; D_2 , 7782-39-0.

Supplementary Material Available: Tables S1-S3 summarizing calculated kinetic isotope effects $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ as a function of the weighting parameters W_{OH} and W_{CO} for models 1-3 (4 pages). Ordering information is given on any current masthead page.

(48) The sign of the p_y coefficient in eq 11 is defined so that a negative value corresponds to a smaller C-O bond order (bond lengthening) with more acidic alcohols ROH. This is the same sign as the $p_{yy'}$ coefficient that describes the change to a smaller C-O bond order in the transition state for cleavage of hemiacetal anions with more acidic alcohols.¹

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