and 6 positions as expected, the limiting case of phenol itself giving no detectable intermediate under the optimum conditions for this solvent system. UV/visible spectral measurements give only a small shoulder for the intermediate species on the high wavelength side of the large absorption due to the solvent acid, and cannot be considered diagnostic for systems where no intermediate has been identified by NMR. The relative magnitudes of the two peaks will in any case limit the accuracy of such measurements.

However, neither the sensitivity of UV-visible measurements nor the diagnostic capabilities of NMR have been fully utilized to date (the latter by the low temperature limits imposed by the solvent system) and further work to find an alternate solvent system which is transparent in the region of the UV-visible and NMR absorptions of the intermediates and which can be taken to low temperatures would be worthwhile.

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Calculation of Carbon-14, Chlorine-37, and Deuterium Kinetic Isotope Effects in the Solvolysis of *tert*-Butyl Chloride

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Abstract: In the solvolysis of *tert*-butyl chloride, satisfactory α-carbon-14, β-deuterium, and chlorine kinetic isotope effects (KIE) may be calculated for a productlike transition state characterized by bond orders $n_{\mathrm{C-Cl}} = 0.2$, $n_{\mathrm{C-C}} = 1.18$, and $n_{\mathrm{C-H}} = 0.94$, employing a diagonal valence force field, provided that allowance is made for hydrogen-bonded solvation of the developing chloride ion with $n_{\mathrm{Cl-H}} \sim 0.05$ ($\sim$7 kcal/mol hydrogen bonds). The effect of the three solvating molecules appears to be to increase the "effective" mass of the incipient chloride ion and to decrease the loss of zero-point energy in going to the transition state. Reaction coordinates more complicated than a simple heterolysis of the carbon–chlorine bond appear to be unnecessary and there is no advantage in employing force fields more complex than a simple valence force field containing only diagonal elements for both the reactant and the transition state model. The structural and bonding features of the proposed transition state are in accord with earlier more qualitative conclusions concerning the polar nature and productlike character of the transition state, and provide a reasonable explanation of the kinetic and equilibrium isotope effects (EIE) for the reaction. An alternative transition state model involving weak solvent nucleophilic assistance provides reasonable calculated values for the KIE, but the EIE strongly suggest the importance of solvation of the leaving group which, together with the hyperconjugation of the β hydrogens, provides a preferred explanation of the *tert*-butyl solvolysis results.

The solvolysis of *tert*-butyl chloride is the prototypical example of both the S_N1 and E1 mechanisms.[2,3] It is generally agreed that the rate-determining process consists of heterolysis of the carbon–chlorine bond, involving a highly polar transition state.[4,5] Several estimates[6] have been made of the degree of charge separation in the transition state; for a simple electrostatic model, the charge separation in polar solvents has been estimated to be 0.8e,[7] corresponding to a nearly broken carbon–chlorine bond in a productlike transition state.

α-Carbon-14,[8] chlorine-37,[9,10] and total β-deuterium[11-13] (D_9) kinetic isotope effects (KIE) have been measured in a series of independent investigations for this reaction. Selected results from Table I are as follows: $^{12}k/^{14}k = 1.027$ (25 °C); $^{35}k/^{37}k = 1.01087$–1.00953 (10–60 °C); $^{H_9}k/^{D_9}k = 2.387$ (25 °C). Although these KIE were determined under comparable, but not strictly identical, conditions, the small effect of the solvent changes on KIE usually observed (except perhaps the chlorine KIE, vide infra) suggests that a reasonably reliable set of data is available for this reaction against which detailed calculations can be tested.

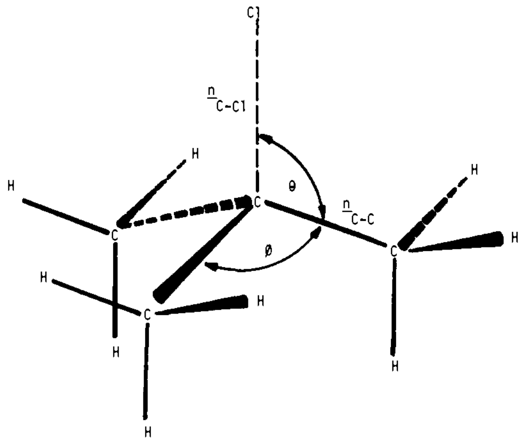

Figure 1. C_{3v} model for reactant and transition state.

The low α-carbon-14 and large β-deuterium KIE provide strong support for a hyperconjugative mechanism of stabilization of the incipient *tert*-butyl cation. Deuterium KIE for other reacting systems[14] strongly suggests that an inductive mechanism of stabilization cannot account for the large β-deuterium KIE observed for the *tert*-butyl chloride reaction; Shiner[15] has shown that (with the possible exception of the CF_3CH_2OH solvent system) the deuterium isotope effect cannot be accounted for by a contribution of an elimination component to the mechanism. Further support for a hyperconjugative release of the $^{\beta}$C–H electron density comes from the reported lowering of the C–H stretching frequencies in the *tert*-butyl cation;[16] the stretching force constants for C–H and C–C bonds in the Urey–Bradley force field applied[17] were significantly smaller and larger, respectively, than their values for the *tert*-butyl chloride reactant. The total β-deuterium *equilibrium* isotope effects (EIE) calculated on the basis of this force field[17] were remarkably close to the experimental *kinetic* isotope effects measured[12] at 25 °C and at 5.7 °C, which was interpreted as indicating that the transition state for the solvolysis reaction had a high degree of cationic character. However, in an independent study, Rapp[18] has calculated significantly higher EIE using the same force field;[16,17] Shiner[15] has suggested that the discrepancy may be due to the use by Olah, Evans, and co-workers[16,17] of experimental frequencies which were incorrectly assigned, whereas Rapp[18] used only calculated frequencies.

Chlorine isotope effects should, in principle, reflect directly the extent of C–Cl bond breaking in the transition state.[19] However, in the solvolysis of a series of para-substituted benzyl chlorides,[20,21] as well as for other systems,[9,10,21,22] surprisingly little variation in the chlorine KIE is observed as the leaving ability of the chlorine is varied. It has been suggested[21,23] that differential solvation may compensate for the loss of bonding to the chlorine at the transition state, and that in poorer solvating media, chlorine KIE might be significantly higher. Indeed, chlorine KIE measured in methanol by Turnquist, Taylor, Grimsrud, and Williams[10] for the methanolysis of *tert*-butyl chloride, and chlorine KIE measured in dimethylformamide for the solvolysis of benzyl chlorides by Fry and Reppond[24] are significantly higher than the corresponding KIE measured in aqueous solvents.

Table I. Experimental Kinetic Isotope Effects for the Solvolysis of *tert*-Butyl Chloride under Various Conditions

Isotope	$k/{}^*k$	Conditions	Ref
α-^{14}C	1.027 ± 0.015	25 °C; water–dioxane (40:60)	8
D_9	2.387 ± 0.008[b]	25 °C; water–ethanol (50:50)	11
	2.45[c]	20 °C; water	11
	2.274	56 °C; methanol	11
	2.327[d]	25 °C; 60% aqueous ethanol	12
	2.30–2.46[e]	25 °C; various [e]	13
^{37}Cl[a]	1.01087 ± 0.00015	10 °C; 0.25 M $LiOCH_3$–CH_3OH	10
	1.01058 ± 0.00015	20 °C; 0.25 M $LiOCH_3$–CH_3OH	10
	1.00953 ± 0.00015	60 °C; 0.25 M $LiOCH_3$–CH_3OH	10
	1.008 ± 0.002	20 °C; 0.1 M NaOH/water–EtOH (50:50)	9
	1.008 ± 0.001	20 °C; 0.1 M $AgNO_3$/water–EtOH (2:98)	9

[a] $\Delta_{60}{}^{10}$ = KIE(10 °C) – KIE(60 °C) = 13.4×10^{-4} [b] Data are also given for other temperatures from 5.7 to 30 °C. [c] Data are also given at other temperatures from 2.1 to 20 °C. [d] Data are also given for the D_1, D_2, D_3, and D_6 compounds. [e] Six solvent systems with the same "ionizing power" but widely different electrophilic and nucleophilic properties were used; the point is made that the values are nearly the same despite these differences.

Williams and Taylor,[25] on the other hand, have reported calculated chlorine KIE in excellent agreement with the experimental results from 10 to 60 °C for the methanolysis of *tert*-butyl chloride.[10] These calculations are based on a five-atom model for both reactant and transition state with no consideration of solvation; the model is not appropriate for calculation of the carbon-14 or β-deuterium KIE, but their resulting best model involves a very reactant-like transition state with little apparent charge separation, which is qualitatively different from the results inferred from the carbon-14 and β-deuterium KIE. Williams and Taylor[25] employed a symmetrized valence force field which was optimized so as to reproduce spectroscopically measured isotopically dependent frequencies for the reactant. The force field contained significant off-diagonal (interaction) terms which couple the C–Cl stretch to other stretching and deformation modes; these interaction terms were assumed to be transferrable to the transition state with little or no change. The reaction coordinate was generated by setting the symmetrized force constant to zero which corresponded *mainly* to C–Cl stretch, but the actual reaction coordinate motion is complicated and involves several other important stretching and deformation motions. The calculated chlorine KIE from this model was very sensitive to geometry, in marked contrast to the general lack of geometric sensitivity for KIE calculated for other model systems, such as those of Stern and Wolfsberg[26] involving a simpler diagonal valence force field.

It, therefore, seemed feasible and of considerable interest to attempt a calculation of the KIE for the solvolysis reactions of *tert*-butyl chloride utilizing a full 14-atom model for the reactant and transition state, and to investigate the validity of a diagonal valence force field for these reactions.

Calculations

Initially, a 14-atom model with C_{3v} symmetry (Figure 1) was used for the calculation of both reactant and transition state frequencies, molecular weights, and principal moments of inertia. Subsequently, transition state models were modified to contain additional atoms when solvation was explicitly considered; this aspect will be discussed more fully in the Discussion section.

For the reactant model, bond distances were assigned by analogy to other stable molecules[27] (all bond angles were assumed to be 109.5°, and only diagonal valence force constants obtained from other relevant molecules[28] were included in the force field). Since structural parameters and force constants are not known for the transition state, it is necessary to calculate isotope effects for a range of transition state structures, employing sufficient variation of the relevant force constants so as to encompass the likely force constants for the actual transition state. This was done systematically by relating the force constant *changes* between reactant and transition state to the appropriate structural changes through several empirical relationships. Bond distances, r_i, were adjusted by means of a revision[29] of Pauling's rule

$$r_i = r_i^0 - 0.30 \ln (n_i) \qquad (1)$$

where r_i^0 is the reactant bond distance for a single bond i, for which the bond order, n_i, is defined to be unity. The bond angle θ at the α carbon (Figure 1) was directly related to the value of the carbon-chlorine bond order, n_{C-Cl}, according to

$$\theta = 90.0 + 19.5 n_{C-Cl} \qquad (2)$$

which simulates a progressive change toward trigonal geometry as n_{C-Cl} decreases ($109.5° > \theta > 90.0°$) toward a limiting value of $n_{C-Cl} = 0.0$ for the *tert*-butyl cation. The bond angles at the β-carbon atoms were maintained at 109.5°.

Stretching force constants, F_{ii}, are related to bond distances through Badger's rule[30]

$$-\ln (F_{ii}) = (r_i - a)/b \qquad (3)$$

where a and b are constants. Combination of this expression with the revised Pauling expression (eq 1) yields

$$F_{ii} = F_{ii}^0 n_i^{0.30/b} \qquad (4)$$

Johnston[31] has shown that for bonds containing hydrogen, eq 4 may be approximated by the simple expression

$$F_{ii} = F_{ii}^0 n_i \qquad (5)$$

where F_{ii}^0 as before is the reactant force constant. Herschbach and Laurie[32] have shown that for hydrogen and elements in the first three rows of the periodic table, $0.24 \leq b \leq 0.32$, so that eq 5 is approximately valid for all bonds involving these atoms, and this equation has, therefore, been applied to our transition state models.

Force constants F_θ associated with bending motions of the valence bond angle θ were varied according to

$$F_\theta = g_\theta (n_i n_j)^{1/2} F_\theta^0 \qquad (6)$$

where F_θ^0 is the reactant value of the bond angle bending force constant for the angle θ defined by bonds i and j, and g_θ is a geometry factor given by

$$g_\theta = 1.39 + 1.17 \cos \theta \qquad (7)$$

which gives $g_\theta = 1.0$ for $\theta = 109.5°$. Equations 6 and 7 are to be regarded simply as postulates predicting the overall effects of changes in hybridization and nonbonded interactions on the valence force constant.[33] Equation 6 is an elaboration of a relation proposed earlier by Johnston.[31] Experience with other model systems indicates that only secondary deuterium isotope effects are seriously affected by these assumptions[34] (however, see Results and Discussion section).

Torsional force constants were assumed to be unchanged from their reactant values. Calculated isotope effects were found to be insensitive to modest variations of these force constants in the transition state.

In order to mimic the effect of the hyperconjugative release of electron density from the β-carbon-hydrogen bonds to the electron-deficient α carbon, the decrease in the carbon-hydrogen bond order, $(1 - n_{C-H})$, and the increase in the carbon-carbon bond order, $(n_{C-C} - 1)$, were assumed to be in direct proportion to the decrease in the carbon-chlorine bond order, $(1 - n_{C-Cl})$, via

$$(n_{C-C} - 1) = (1 - n_{C-Cl})P/3 \qquad (8)$$

$$(1 - n_{C-H}) = (n_{C-C} - 1)/3 \qquad (9)$$

The proportionality constant, $P/3$, in eq 8 was initially chosen to be $\frac{1}{6}$, which represents the fractional part of the loss of C-Cl bonding which is compensated for by strengthening *each* C-C bond due to hyperconjugative interaction. It was envisaged that adjustment of this parameter would significantly affect the deuterium and carbon-14 isotope effects (see Results and Discussion section).

Through eq 1, 2, and 5-9, it was possible to vary systematically transition state structural parameters and force constants simply by varying the carbon-chlorine bond order, n_{C-Cl}. Even though some of these equations may be only approximately valid, it is important to realize that KIE are primarily manifestations of *changes* in force constants between reactant and transition state rather than structural changes per se.[26,34] Thus, the most important function of the procedure outlined above is to vary force constants in a systematic fashion and in a manner which attempts to be consistent with the presumed structural changes.

As in the case of the reactant, no off-diagonal (interaction) force constants were used in the transition state force field. For the most part, a simple reaction coordinate was used by assigning the carbon-chlorine stretching force constant a zero (flat barrier) or a small negative (e.g., −0.1, curved barrier) value, unless stated otherwise. More complex reaction coordinates (involving coupling of the carbon-chlorine stretch to other coordinates of the same symmetry) were briefly investigated, which necessarily introduced some off-diagonal terms into the symmetrized force constant matrix. Reactant and transition state parameters are summarized in Table II.

Frequencies, molecular weights, and principal moments of inertia were calculated sequentially and stored for the normal and various isotopically substituted reactant and transition state models, using an appropriately modified version of the normal coordinate and vibrational analysis program of Gwinn.[36] The KIE were calculated directly using the expression of Bigeleisen and Mayer,[37] expressed in the notation of Wolfsberg and Stern[26b]

$$k/{}^*k = (\text{MMI})(\text{EXC})(\text{ZPE}) \qquad (10)$$

where the asterisk denotes the heavier isotope. The factors represent ratios of transition state to reactant contributions of molecular masses and moments of inertia (MMI), excited vibrational levels (EXC), and zero-point energy (ground vibrational levels, ZPE) to the isotope effect. The ratio of isotopic imaginary frequencies for motion along the reaction coordinate, $(\nu_L/{}^*\nu_L)^\ddagger$, was obtained either directly or by means of the Teller-Redlich product rule,[38] through

$$(\nu_L/{}^*\nu_L)^\ddagger = \text{MMI}/\text{VP} \qquad (11)$$

where VP represents the vibrational frequency product ratio.[26b]

Results and Discussion

The trends in the calculated α-carbon-14, β-deuterium, and chlorine-37 KIE as a function of shifts in the transition state character from reactant-like ($n_{C-Cl} = 0.9$) to productlike ($n_{C-Cl} = 0.1$) are illustrated in Figure 2 for a model in which 50% of the loss of formal bonding between the chlorine and the α carbon is compensated for by increased bonding to the β carbon atoms ($P/3 = 0.1667$ or $P = 0.50$ in eq 8; this corresponds to a decrease in C-H bond order from 1.0 to 0.955 (or an increase in C-H bond length of 0.0135 Å) and an increase in C-C bond order from 1.0 to 1.133 (a decrease in C-C bond length of 0.0375 Å) only). The deuterium KIE shows the greatest degree of sensitivity to the amount of carbon-chlorine

Table II. Structural Parameters[a] and Force Constants[b] for Reactant and Transition State Models

Coordinate	Reactant values		Transition state values	
Bond stretch	r_i^0	F_{ii}^0	$(r_i - r_i^0)/0.30$[c]	F_{ii}[d]
C-Cl	1.760	3.2	$\ln (n_{C-Cl})$	$3.2n_{C-Cl}$
C-C	1.537	4.5	$\ln (n_{C-C})$	$5.0n_{C-C}$[g]
C-H	1.094	5.0	$\ln (n_{C-H})$	$5.0n_{C-H}$
Angle bend	Angle	F_{bend}^0	Angle[e]	F_{bend}
C-C-Cl	109.5	1.00	$\theta = 90 + 19.5n_{C-Cl}$	$1.0(n_{C-Cl}n_{C-C})^{1/2}g_\theta$
C-C-C	109.5	1.00	$\cos \phi = (1 - 1.5 \sin^2 \theta)$	$1.0n_{C-C}g_\phi$
C-C-H	109.5	0.65	109.5	$0.65(n_{C-C}n_{C-H})^{1/2}$
H-C-H	109.5	0.55	109.5	$0.55n_{C-H}$
Torsion[f]	Angle	F_{tors}^0	Angle	F_{tors}
H-C-C-Cl	180	0.024	180	0.024
H-C-C-C	180	0.024	<180	0.024

[a] Reference 27. Bond distances are given in angstroms, bond angles in degrees. [b] Reference 28. Stretching force constants are given in mdyn/Å, bending and torsional force constants in mdyn Å/rad^2. [c] See eq 1 of text. [d] See eq 5-9 of text. [e] Relationship between θ and ϕ assumes C_{3v} symmetry about the C-Cl bond at all times. See Figure 1. [f] Three torsional coordinates used to describe torsion of each CH_3 group; torsional force constant = 3 × 0.024 = 0.072 mdyn Å/rad^2 corresponds to the value for ethane quoted in ref 28c. [g] The value 5.0 is taken from the *tert*-butyl cation. A value of $4.5n_{C-C}$ with a value of $n_{C-Cl} = 0.35$ and other parameters as in footnote *a* of Table III yields almost identical calculated KIE.

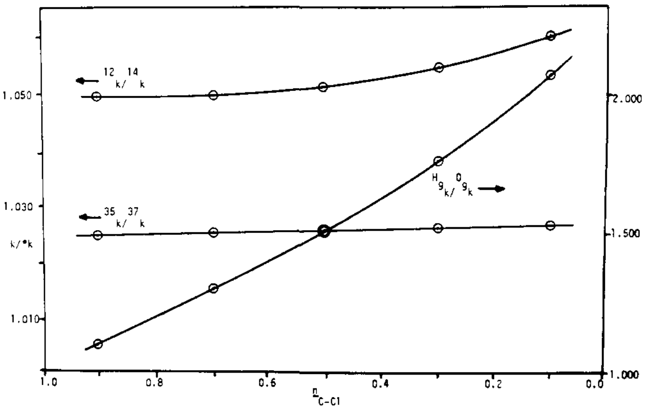

Figure 2. Calculated α-carbon-14, chlorine-37, and total deuterium kinetic isotope effects at 10 °C for several *tert*-butyl chloride transition state models with $P/3 = 0.1667$ (see text).

Table III. Kinetic and Equilibrium Isotope Effects for *tert*-Butyl Chloride Solvolysis Calculated at 25 °C

	$^{12}k/^{14}k$	$^{H_9}k/^{D_9}k$	$^{35}k/^{37}k$	$10^4\Delta_{60}^{10}$ $(^{35}k/^{37}k)$
KIE[a]	1.02963	2.29247	1.02564	23.4
EIE	1.02668[b]	2.24162[b]	1.00933[c]	25.6[c]

[a] Transition state model with $n_{C-Cl} = 0.2$, $n_{C-C} = 1.18$, $n_{C-H} = 0.94$, $\theta = 94°$, and reaction coordinate force constant, $F_{C-Cl}{}^{\ddagger} = 0.0$. [b] Calculated for equilibrium 12 of text. Trigonal planar cation with $n_{C-C} = 1.18$, $n_{C-H} = 0.94$, $\phi = 120°$. [c] Calculated for equilibrium 13 of text.

bond breaking. The α-carbon-14 and deuterium KIE were brought into better agreement with the experimental values (Table I) by adjustment of the value of $P/3$ to 0.225, for a productlike transition state with $n_{C-Cl} = 0.2$; these results are shown in the top row of Table III. It is possible that solvation of the developing *tert*-butyl cationic center may also be important; this would tend to *lower* the α-carbon-14 KIE from that shown in Figure 2 and bring it into better agreement with experiment (see Table I); however, this would also lower the deuterium KIE, whereas the value in Figure 2 is already smaller than the measured value (Table I), so that hyperconjugation (which tends to *raise* the deuterium isotope effect) remains an important feature of the system. The calculation of a large β-deuterium KIE and a small α-carbon-14 KIE, in agreement with the experimental values, supports the hyperconjugative mechanism of stabilization in the transition state. It is noteworthy that conjugative release of electrons from phenyl substituents has been invoked to explain the inverse α-carbon-13 EIE for the ionization of triphenylmethyl chloride[39] and the inverse α-carbon-13 KIE for the methanolysis of 1-(4-methylphenyl)-1-bromoethane.[40]

Perhaps the most noteworthy feature of these calculations, however, is the large discrepancy between the calculated and experimental chlorine-37 KIE, and its temperature dependence, defined as the difference of the KIE at 10 and 60 °C, Δ_{60}^{10} (see Table I); the use of a small negative carbon-chlorine transition state stretching force constant ($F_{C-Cl}{}^{\ddagger} = -0.1$) did not affect these results significantly. In this same regard, it is of interest to compare the KIE and the EIE calculated for ionization of *tert*-butyl chloride. This may be done by calculating the individual equilibrium constants for the isotopic exchange reactions (eq 12) for either α-carbon-14 or β-deuterium (D_9), and reaction 13 for chlorine-37.

$$(CH_3)_3CCl + (CH_3)_3{}^*C^+ \rightleftarrows (CH_3)_3{}^*CCl + (CH_3)_3C^+ \qquad (12)$$

$$(CH_3)_3C^{35}Cl + {}^{37}Cl^- \rightleftarrows (CH_3)_3C^{37}Cl + {}^{35}Cl^- \qquad (13)$$

The results are given in the bottom row of Table III. The α-carbon-14 and β-deuterium EIE, which were calculated for exchange with a trigonal planar cation, using carbon-carbon and carbon-hydrogen bond orders identical with those used to obtain the KIE reported in the same table, are only slightly smaller than the respective KIE. The chlorine EIE, however, is considerably smaller than the KIE, but the value of the temperature dependence has increased slightly. The EIE represents (VP·EXC·ZPE), the maximum contribution that may be made by the reactant to the overall KIE;[37] this may be compared with the corresponding term in the KIE expression

$$k/{}^*k = (\nu_L/{}^*\nu_L)^{\ddagger}(VP \cdot EXC \cdot ZPE) \qquad (14)$$

This term is at near maximum for the chlorine KIE, as can be seen by inspection of Table IV, in which the individual contributions to the KIE and EIE are listed. It is immediately apparent from Table IV that the reaction coordinate contribution $(^{35}\nu_L/^{37}\nu_L)^{\ddagger}$ is responsible for the calculated KIE being considerably larger than both the experimental KIE and the calculated EIE. The large zero-point energy term, ZPE, ac-

Table IV. Components of Chlorine Kinetic Isotope Effect and Chlorine Equilibrium Isotope Effect Calculated at 25 °C

	MMI	EXC	ZPE	VP	VP·EXC·ZPE	$(^{35}\nu_L/^{37}\nu_L)^{\ddagger}$	Isotope effect
KIE[a]	0.99937	1.00402	1.02219	0.98250	1.00832	1.01718	1.02564
EIE[b]	0.97077	1.01107	1.02835	0.97077	1.00933	1.00000	1.00933

[a] Refers to model described in footnote *a* of Table III. [b] Refers to model described in footnote *c* of Table III.

Table V. Kinetic Isotope Effects Calculated at 25 °C for a Concerted Reaction Coordinate[a,b,c]

n_{C-Cl}[d]	θ[d]	$\nu_L^{\ddagger}$[e]	$^{12}k/^{14}k$	$^{H_9}k/^{D_9}k$	$^{35}k/^{37}k$	$10^4\Delta_{60}^{10}$ $(^{35}k/^{37}k)$
0.9	108	143.4*i*	1.07590	1.73171	1.01184	3.6
0.5	100	109.5*i*	1.06421	2.28874	1.01761	12.0
0.1	92	50.7*i*	1.07388	3.05107	1.02417	21.8

[a] Reaction coordinate obtained by coupling C–Cl stretching coordinate with symmetric $C-CH_3$ stretching coordinates. See Figure 1. [b] Reaction coordinate force constant $F_L^{\ddagger} = 1.05(F_{C-Cl}^{\ddagger}F_{C-C}^{\ddagger})^{1/2}$. [c] An increased value of *P* would be expected to give better agreement with the experimental α-carbon-14 and β-deuterium KIE but would not be expected to provide sufficient reduction in the chlorine KIE for productlike transition states. [d] Structural parameters and force constants are the same as those used for models shown in Figure 2; $P/3 = 0.1667$; angles in degrees. [e] Imaginary reaction coordinate frequency in wavenumbers for normal molecule.

counts for the large calculated temperature dependence. This is not surprising, since all bonding to chlorine is lost in the product in the equilibrium process, and the zero-point energy of the carbon–chlorine bond is lost in the transition state by virtue of the nature of the reaction coordinate, $F_{C-Cl}^{\ddagger} = 0.0$. (A nonzero value of n_{C-Cl} is used for adjustment of structural parameters, bond lengths, and bond angles, as well as for bending force constants in the transition state, and only the stretching force constant is set equal to zero.) In order to improve the calculated chlorine KIE and the temperature dependence of this KIE, it is therefore important that the contributions of the above two terms be reduced. One way of achieving this might be to choose a more complex reaction coordinate, by coupling of the carbon–chlorine stretch to other symmetric normal modes. Additional atoms will be involved necessarily more directly in the reaction coordinate motion in this case, which will lessen the effect of substitution of chlorine-37 on the reduced mass for this coordinate. Furthermore, such coupling will cause a greater isotopic dependence of other normal modes of the transition state, and the associated zero-point energy contributions will help to offset the total zero-point energy contributions of the reactant. Williams and Taylor[25] employed a complex reaction coordinate to calculate chlorine KIE with their five-atom model. However, α-carbon-14 KIE were not reported, and deuterium KIE cannot be calculated with their cutoff model.

We briefly explored the consequences of more complex reaction coordinates using our transition state model. Generation of a reaction coordinate by direct coupling of the carbon–chlorine stretching coordinate to the symmetric carbon–carbon stretching coordinate, so as to give concerted contraction of the carbon–carbon bonds with extension of the carbon–chlorine bond, produced chlorine KIE which now increase with the degree of carbon–chlorine bond breaking; but sufficiently low KIE are obtained only for very reactant-like transition states (see Table V). Use of a different reaction coordinate obtained by coupling of the carbon–chlorine stretch to the symmetric angular deformation, involving C–C–C and C–C–Cl bending, gave even less improvement in the chlorine KIE. Williams and Taylor[25] used reactant and transition state force fields with proportionately many more off-diagonal terms, including those associated with the reaction coordinate, than have been used in this work. Furthermore, it is important to note that in their model, the transition state force constant associated with C–C–Cl bending was maintained at its reactant value, and the force constant associated with the symmetric angular deformation was increased in relation to its reactant value. This is in direct contrast with our model, for which all force constants associated with the stretching and bending coordinates involving chlorine were reduced in the transition state, through eq 5 and 6, for reasons already given. The importance of the bending modes in Williams and Taylor's model[25] is illustrated by the fact that they were able to obtain a chlorine KIE in good agreement with the experimental value by varying the transition state force constant for the symmetric angular deformation, and similarly to adjust the temperature dependence of the KIE by varying the transition state force constant for the C–C–Cl bending coordinates. However, their model corresponds to a highly reactant-like transition state which is not in accord with a highly polar transition state deduced from kinetic data for the reaction.

Since we were able to obtain good carbon-14 and deuterium KIE using a far simpler force field than that of Williams and Taylor, we preferred to explore the consequences to the calculated chlorine KIE of introducing into our model provision for solvation of the incipient chloride ion. The potential importance of solvation in determining the chlorine KIE has already been briefly mentioned in the introduction. Very recently, Cromartie and Swain[41] have provided strong support for this idea through their measurements of the chlorine EIE in the cyclization of 2-chloroethanol in several solvents. It has been reported[42] that the solubility of *tert*-butyl chloride in D_2O is the same as in water, and therefore hydrogen bonding to a ^{35}Cl species and to a ^{37}Cl species were assumed to be the same. Furthermore, since only the differential effect of solvation of the transition state over that of the reactant is important in determining KIE, the reactant was treated as an unsolvated *tert*-butyl chloride. Thus, formation of new bonds by solvent to chlorine in the transition state introduces additional isotopically dependent frequencies, which will contribute to the transition state zero-point energy term, and also will decrease the effect of chlorine-37 substitution on the reduced mass of the reaction coordinate by increasing the "effective" mass of chlorine. It might also be expected that this modification of the model would not greatly affect the α-carbon-14 and β-deuterium KIE.

Calculations of chlorine EIE were explored first, through the isotopic exchange reaction

$$^{35}Cl^- + {}^{37}Cl(H_2O)_4^- \rightleftarrows {}^{37}Cl^- + {}^{35}Cl(H_2O)_4^- \qquad (15)$$

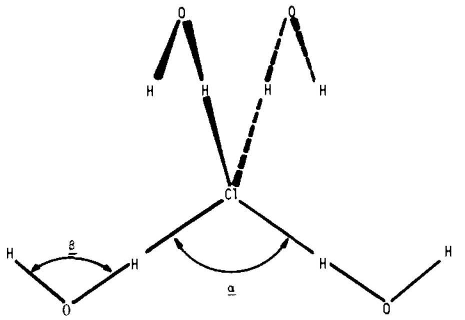

Figure 3. Model of chloride ion solvated with four water molecules arranged tetrahedrally about the chloride ion; overall symmetry is $D_{2d} = V_d$; $\alpha = 109.5°$; $\beta = 105°$.

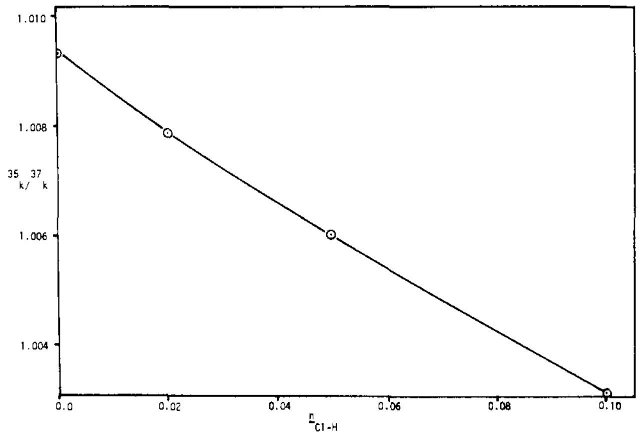

Figure 4. Chlorine equilibrium isotope effect for the ionization at 25 °C of *tert*-butyl chloride to give solvated chloride ion, for various hydrogen bond strengths (see eq 16 of text).

Table VI. Isotope Effect, $^{35}K/^{37}K$, for the Equilibrium between Gaseous Chloride Ion and Tetrahedrally Solvated Chloride Ion and Two of Its Cutoff Models Calculated at 25 °C, for Several Hydrogen Bond Strengths[a]

n_{Cl-H}	$Cl(H_2O)_4^-$	$Cl(HO)_4^-$	$Cl(H)_4^-$
0.02	0.99865	0.99886	0.99906
0.05	0.99681	0.99707	0.99761
0.10	0.99392	0.99422	0.99551

[a] The structural parameters and force constants are $r_{HCl}{}^0 = 1.274$ Å, $F_{Cl-H}{}^0 = 5.16$ mdyn/Å; $r_{OH}{}^0 = 0.957$ Å, $\theta_{HOH}{}^0 = 105°$, $F_{H-O}{}^0 = 7.7$ mdyn/Å, $F_{H-O-H}{}^0 = 0.76$ mdyn Å/rad^2, linear bending force constant F_{O-H-Cl} varied by eq 6 of text, with $g_{linear} = 1.0$ and $F_{O-H-Cl}{}^0 = 0.33$ mdyn Å/rad^2; torsional force constant about Cl–H–O subgroup assumed to be 0.072 mdyn Å/rad^2 (full model only). The Cl - - - H bond distance and the force constants involving the Cl atom were adjusted according to eq 1, 5, and 6 of text; bond distances and force constants of the water molecule were held constant at values listed above.

Table VII. Kinetic Isotope Effects Calculated at 25 °C for a *tert*-Butyl Chloride Transition State Model with Varying Degrees of Solvation of the Incipient Chloride Ion[a,b]

n_{Cl-H}	$^{12}k/^{14}k$	$^{H_9}k/^{D_9}k$	$^{35}k/^{37}k$	$10^4\Delta_{60}{}^{10}$ ($^{35}k/^{37}k$)
0.02	1.03311	2.32941	1.01178	19.6
0.05	1.03297	2.32940	1.01036	15.4
0.10	1.03281	2.32938	1.00815	9.1

[a] Bond orders of the *tert*-butyl chloride section of the model are the same as those for the productlike transition state model given in footnote *a* of Table III. Structural parameters and force constants for the $Cl(HO)_3$ section of the model are $\theta_{HClC} = 109.5°$; $F_{H-Cl-C}{}^0 = 0.6$ mdyn Å/rad^2; others as given in footnote *a* of Table VI. [b] Reaction coordinate force constant, $F_{C-Cl}{}^{\ddagger} = 0.0$.

since the additional complication of the reaction coordinate does not occur here. The chloride ion was assumed to be tetrahedrally hydrogen bonded to four water molecules, resembling the librational (hindered rotation) model of Swain and Bader,[43] which in turn was based on the model of liquid water used by Bernal and Fowler[44] (Figure 3). The bond orders of the four hydrogen-chlorine bonds, n_{Cl-H}, were varied from 0.02 to 0.10, corresponding to an approximate hydrogen bond energy of 3-12 kcal/mol.[45] The results (column 1, Table VI: $^{35}K/^{37}K = 0.99865$ ($n_{Cl-H} = 0.02$), 0.99681 ($n_{Cl-H} = 0.05$), and 0.99392 ($n_{Cl-H} = 0.10$)) may be compared with the value of 0.9950 reported by Howald[46] for the isotope effect on the equilibrium between gaseous chloride ion and chloride ion dissolved in slightly aqueous acetic acid (temperature not reported). Reasonable agreement with Howald's result is obtained for a bond order n_{Cl-H} a little greater than 0.05. Table VI also shows that the cutoff model $Cl(HO)_4^-$ obtained by omitting the peripheral hydrogen atoms of the water molecules in Figure 3 yields results very similar to those obtained for the full model, whereas the second cutoff model $Cl(H)_4^-$, obtained by cutting off the OH groups of the water molecules, gives results which are seriously in error. Replacement of the peripheral hydrogen atoms by carbon atoms, so as to formally mimic an alcoholic solvent, also gave results in good agreement with a full model calculation, lending support to the cutoff model used for many of the calculations.

Using the chlorine EIE from the previous calculations, one may calculate the chlorine EIE for the dissociation of *tert*-butyl chloride to produce a solvated chloride ion, as in

$$(CH_3)_3C^{35}Cl + {}^{37}Cl(H_2O)_4^- \rightleftarrows (CH_3)_3C^{37}Cl + {}^{35}Cl(H_2O)_4^- \quad (16)$$

The results, shown graphically in Figure 4, include the EIE for an unsolvated chloride ion. The EIE and its temperature dependence, $\Delta_{60}{}^{10}$ (not shown), exhibit a smooth monotonic decrease as the chlorine-hydrogen bond order is increased. It is noteworthy that, again, for a value of $n_{Cl-H} \sim 0.05$, the calculated EIE compares favorably with the values measured by Cromartie and Swain[41] for the cyclization of 2-chloroethanol ($^{35}K/^{37}K = 1.0053$-1.0060), despite the fact that two different substrates are being compared. The above results suggest that the chlorine-hydrogen bond order in the transition state model should be no greater than ~0.05 (corresponding to a Cl - - - H distance of ~2.2 Å, about 1 Å longer than a normal Cl-H single bond).

Chlorine-37 KIE were calculated using a transition state model (Figure 5) in which one of the water molecules was replaced by the *tert*-butyl fragment with the same structural parameters and force constants which gave satisfactory α-carbon-14 and β-deuterium KIE (see Table I: $n_{C-Cl} = 0.2$, $n_{C-C} = 1.18$, $n_{Cl-H} = 0.94$, $\theta = 94°$). A staggered conformation about the carbon-chlorine bond was assumed. The results, obtained with the usual simple reaction coordinate ($F_{C-Cl}{}^{\ddagger} = 0.0$), are shown in Table VII. The chlorine KIE, and the temperature dependence $\Delta_{60}{}^{10}$, for $n_{Cl-H} = 0.05$, compare favorably with the results measured by Turnquist, Taylor, Grimsrud, and Williams[10] for the methanolysis of *tert*-butyl chloride. The α-carbon-14 KIE, though still slightly higher than the calculated results reported in Table III, is still well within the experimental error of the KIE measured by Bender and Buist.[8] The experimental value has a fairly high uncertainty ($2\sigma = \pm 0.03$ = 95% confidence limit), and the isotope effect may be somewhat smaller than 1.027 as some have suggested. A

Table VIII. Kinetic Isotope Effects at 25 °C for a Transition State Model with Weak S_N2-Like Solvent Participation[a-c]

$n_{O\text{-}C}$[d]	$\nu_L^{\ddagger}$[e]	$^{12}k/^{14}k$	$^{H_9}k/^{D_9}k$	$^{35}k/^{37}k$	$10^4\Delta_{60}^{10}$ $(^{35}k/^{37}k)$
0.02	$37.1i$	1.03377	2.28579	1.00803	18.1
0.05	$52.3i$	1.03374	2.29616	1.01156	18.1
0.08	$59.4i$	1.03209	2.29806	1.01417	18.1

[a] See Figure 6. [b] Transition state parameters: $n_{C\text{-}Cl} = 0.2$, $n_{C\text{-}C} = 1.18$, $n_{C\text{-}H} = 0.94$, $\theta = 90°$, $\phi = 120°$. [c] Reaction coordinate force constant $F_L^{\ddagger} = 1.05(F_{C\text{-}Cl}^{\ddagger}F_{C\text{-}O}^{\ddagger})^{1/2}$. A corresponding force constant using a proportionality constant of 1.00 (corresponding to a flat barrier) gave results which were little different from those reported. [d] Carbon-oxygen bond order. [e] Imaginary reaction coordinate frequency in cm^{-1} for the isotopically unsubstituted model.

smaller calculated value could be obtained by a slight increase in the hyperconjugative interaction with the methyl groups, but the calculated deuterium isotope effect would then be somewhat larger also. The β-deuterium KIE also remains in satisfactory agreement with the experimental results, with a calculated difference between 5.7 and 25° of −0.138, which compares favorably with the experimental difference of −0.155.[11] This calculated temperature effect is obtained irrespective of whether or not allowance is made for solvation of the chloride ion; it does, however, provide a measure of the accuracy of the force field describing the potential energy changes affecting the hydrogen atoms at the transition state.

Thus, by making specific allowance for the effects of solvation of the incipient chloride ion at the transition state, the model has yielded results for all three KIE which are in satisfactory agreement with the available experimental results.

It is important to acknowledge the possibility of an alternative solvolysis mechanism, in the event that our transition state model may represent an oversimplification of the actual kinetically important steps. Indeed, the present understanding of solvolysis mechanisms involves considerably more elaborate pathways[15,47] than have been considered here. In fact, Albery and Robinson[42] have proposed, on the basis of the variation with temperature of the solvent deuterium isotope effect, that the solvolysis of *tert*-butyl chloride undergoes a change in rate-determining step, tentatively associated with release of one or more water molecules from the solvent water structures at the reaction site. This explanation was preferred to one involving changes in structures of ion pairs. Nevertheless, it is of some interest to consider the consequences of the existence of ion pairs on the calculated KIE, according to a general scheme of ion pair formation:

$$(CH_3)_3C\text{-}Cl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (CH_3)_3C^+Cl^- \xrightarrow{k_2} (CH_3)_3C^+ + Cl^- \tag{17}$$

Applying the steady-state treatment to the concentration of ion pairs gives

$$k_{\text{obsd}} = k_1/(1 + k_{-1}/k_2) \tag{18}$$

for the observed rate constant. If $k_{-1} \sim k_2$ the measured isotope effect will be a composite of the isotope effects on all three steps. Calculation of the KIE would then require explicit consideration of models for the reactant, ion pair, and transition states for each step. However, if $k_2 \gg k_{-1}$ the first step becomes rate determining ($k_{\text{obsd}} = k_1$), and the results of the present calculations may be applied to this case. If, on the other hand, $k_{-1} \gg k_2$, so that the second step becomes rate determining ($k_{\text{obsd}} = k_1k_2/k_{-1}$), the observed isotope effect will be a product of the isotope effect on the preequilibrium formation of the ion pair ($K/{}^*K = (k_1/k_{-1})/({}^*k_1/{}^*k_{-1})$) and the isotope effect for the second step ($k_2/{}^*k_2$). However, upon reflection, it is seen that calculation of a value for ($k_{\text{obsd}}/{}^*k_{\text{obsd}}$) requires the isotopic partition function ratios for only the reactant and the transition state associated with the second step, since the partition function ratio of the intermediate ion pair will cancel in the product $Kk_2/{}^*K{}^*k_2$. The results of the present calculations may be considered to apply to this case also, since, to a first approximation, the differences in the transition state structures associated with k_1 and k_2 should mainly be confined to differences in the relative carbon-chlorine bond distances, a wide range of which have been considered in the present models.

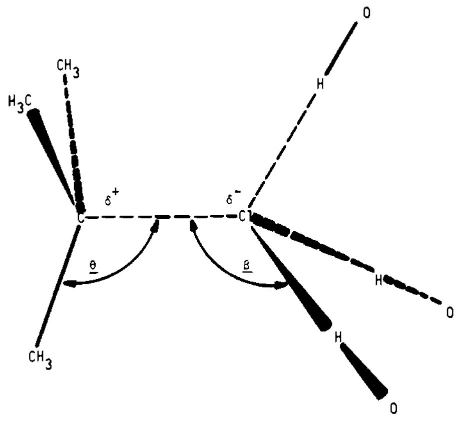

Figure 5. Staggered conformation of productlike transition state model with partial solvation of the chlorine. ($\theta = 94°$, $\beta = 109.5°$).

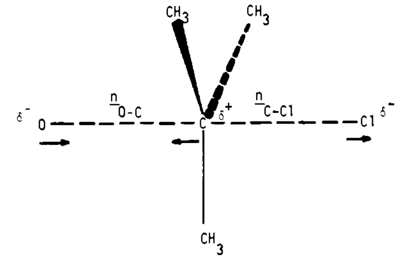

Figure 6. Trigonal bipyramidal model for loose, ion pair-like transition state associated with backside nucleophilic assistance by solvent. The arrows illustrate the atomic displacements in the reaction coordinate.

The role of solvent may be important, however, in ways other than that already considered. For example, Gold[48] has estimated that the *tert*-butyl cation intermediate is stabilized by solvation in dilute aqueous solution by at least 50 kcal/mol, so it is likely that solvation of the incipient cation in the transition state is very important. Although some stabilization might be attributable to nonspecific interaction which may not appreciably affect force constants involving isotopic atoms, it is possible that direct interaction may also need to be considered as suggested by Doering and Zeiss.[49] Thornton and Frisone[13] have proposed that solvolysis of *tert*-butyl chloride proceeds with weak backside nucleophilic assistance by solvent, through a loose ion pair-like transition state, to give the solvated cation intermediate. Such an interaction must be sufficiently weak that no second-order kinetic term associated with nucleophilic attack arises. Either step in the ion pair scheme (eq 17) could be susceptible to such assistance. It should be noted that Thornton's "merged mechanism"[13] approach to the S_N1-S_N2 problem is compatible with the ion pair scheme if either k_1 or k_2 is rate determining, since, for reasons already discussed, the isotopic partition function ratio of the reactant and the relevant transition state need only be considered. By appropriate coupling of the force constant of the weak solvent oxygen-carbon bond to the carbon-chlorine bond to generate

Table IX. Relative Contributions to the Chlorine-37 Reactant Reduced Partition Function Ratio at 25 °C for Two Force Fields[a]

ν, cm^{-1} [b]	$\Delta\nu$, cm^{-1} [c]	VP·EXC·ZPE	Relative contribution,[d] %	Net contribution[e]
		Williams and Taylor[23,f]		
560.04	2.60	1.00253	29.0	1.00695 (79.6%)
370.18	4.12	1.00281	32.1	
295.98	1.44	1.00080	9.2	
295.98	1.44	1.00080	9.2	
Total product for 9 frequencies[f]		1.00874		
		This Work[g]		
604.12	2.36	1.00244	26.5	1.00666 (72.4%)
330.62	3.85	1.00236	25.7	
309.92	1.59	1.00092	10.0	
309.92	1.59	1.00092	10.0	
Total product for 36 frequencies[g]		1.00921		

[a] Simple valence force field vs. symmetrized valence force field.[23] [b] Frequencies for the three isotopically dependent modes for the unsubstituted molecule. These are described approximately in ref 25 as (1) C–Cl stretch, (2) symmetric CH_3–C–Cl and CH_3–C–CH deformation, (3) doubly degenerate CH_3–C–Cl deformation. [c] $^{35}\nu - {}^{37}\nu$. [d] Calculated as the ratio of the difference from unity of the individual VP·EXC·ZPE terms to the corresponding difference for the total contribution from all $3N - 6$ frequencies. [e] Contribution from all four frequencies listed, calculated as in *d*. [f] 5-atom model. [g] 14-atom model.

a reaction coordinate corresponding to a large extension of the carbon–chlorine bond concurrent with a modest contraction in the carbon–oxygen distance, the $(^{35}\nu_L/^{37}\nu_L)^{\ddagger}$ and ZPE terms could be expected to decrease.

Kinetic isotope effects were calculated for the trigonal bipyramidal model shown in Figure 6, in which the oxygen atom represents a cutoff solvent molecule, and the bond orders n_{C-Cl}, n_{C-C}, and n_{C-H} have been maintained at their previous values. The results are given in Table VIII, for a range of carbon–oxygen bond orders corresponding to approximate bond energies of less than 7 kcal/mol. The effect of solvation of the developing chloride ion was not considered. The α-carbon-14 and β-deuterium KIE were little different from those reported in Table III, but the chlorine KIE, and the temperature dependence, $\Delta_{60}{}^{10}$, were significantly reduced. In fact, by increasing n_{C-Cl} to 0.3 for a carbon–oxygen bond order of 0.08, results for all three KIE and for $\Delta_{60}{}^{10}$ were at least as good as those obtained for the solvated chloride ion transition state model (Table VII). One then is presented with a choice of two transition state models. However, since the calculated chlorine EIE involving the solvated chloride ion model do encompass the experimental EIE measured by Howald[46] and by Cromartie and Swain,[41] it seems inescapable that the incipient chloride ion in the transition state must also be solvated. While weak solvent nucleophilic assistance of the type proposed by Thornton and Frisone[13] is possible, the KIE data presently available for this system do not make this feature an obligatory requirement for the transition state model. A successive labeling approach[50] utilizing calculated and measured incoming nucleophile KIE may enable a definitive choice between the two mechanisms to be made.

The results show also, for the *tert*-butyl chloride system at least, that simple (diagonal) valence force fields are adequate for calculation of isotope effects. The differences from the previous treatment of Williams and Taylor[25] arise primarily from the effect of applying the present simpler force fields to the transition state models. This is evident by comparing the frequencies and their isotopic shifts for the reactant predicted by the two force fields (Table IX). Although the symmetrized force field of Williams and Taylor produces frequencies which are in much better agreement with those measured for *tert*-butyl chloride in methanol,[25] the isotopic splitting caused by substitution of chlorine-37 is reproduced very accurately by our simpler valence force field; more importantly, the contribution of individual frequencies to the isotopic partition function ratio of the reactant are found to be very nearly the same for the two force fields. Thus, no advantage obtains from using an optimized force field to calculate the reactant contribution to the overall rate ratio. A further advantage to the simpler valence force field is that a more direct inference can be drawn between the parameters of the force field and bonding and structural changes which occur in going from the reactant to the transition state.

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Intramolecular General Base Catalysis of Schiff Base Hydrolysis by Carboxylate Ions

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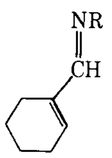
Abstract: The mechanism of the hydrolysis of a series of Schiff bases (**2**) derived from cyclohexene-1-carboxaldehyde (**1**) and various amines has been examined in aqueous solution. A correlation of the log of the rate of water attack ($k_1^{H_2O}$) with the Schiff base pK_a (slope = −0.98) shows large rate enhancements (60-fold) in $k_1^{H_2O}$ for Schiff bases derived from glycine (**2e**) and aspartic acid (**2g**), and a smaller acceleration (fivefold) for the β-alanine derivative (**2f**). The rate accelerations for **2e–g** are attributed to intramolecular general base catalysis of water attack by the internal carboxyl groups. Brønsted plots for the intermolecular general-base-catalyzed attack of water permitted the calculation of effective concentrations of the internal bases for **2e** (30 M) and **2f** (1 M). The pH-rate profiles for the hydrolysis at low pH, where carbinolamine breakdown is rate limiting, are incompatible with a simple two-step mechanism for Schiff base hydrolysis. Rather, these results, along with kinetic and structure-reactivity data, suggest that carbinolamine breakdown occurs via two concurrent pathways involving zwitterionic and protonated carbinolamine intermediates, respectively.

The intermediacy of a Schiff base in the catalytic action of several enzymes[1–10] has generated a great deal of interest in the mechanism of formation and hydrolysis of these compounds. Although these reactions have been investigated in great detail in model systems,[11] the mechanism by which enzymatic Schiff bases are formed and hydrolyzed is still incompletely understood. Even though the interconversion of many simple Schiff bases with the corresponding carbonyl compounds is very rapid,[12–14] it is often several orders of magnitude too slow to account for the corresponding enzymatic processes.[15] In a previous report[18] we demonstrated that general base catalysis of Schiff base hydrolysis by a carboxylate ion in a relatively nonpolar solvent mixture (dioxane–water) is exceedingly efficient, and we suggested that enzymatic Schiff base hydrolysis might be accelerated by a carboxylate ion acting as a general base at an apolar active site. In order to further evaluate this possibility, we wished to determine whether an internal carboxylate ion could efficiently catalyze Schiff base hydrolysis. Observation of intramolecular catalysis of this reaction would further demonstrate the feasibility of our proposal. In this report we describe the hydrolysis of a series of Schiff bases derived from cyclohexene-1-carboxaldehyde (**1**). Several of these Schiff bases (**2e–g**) have internal carboxylate ions, enabling us to assess the existence of intramolecular catalysis by these groups.



2a, R = $CH_2CH_2CH_3$
b, R = CH_2CH_2OH
c, R = CH_2CF_3
d, R = CH_2CONH_2
e, R = $CH_2COO^-K^+$
f, R = $CH_2CH_2COO^-K^+$
g, R = $CH(COO^-Na^+)CH_2COO^-Na^+$

Results

The series of cyclohexene-1-carboxaldehyde Schiff bases **2a–g** were synthesized by mixing the aldehyde (**1**) with the