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Method for Estimating the Magnitude of Equilibrium Constants for Covalent Addition of Nucleophilic Reagents to Heteroaromatic Molecules[1]

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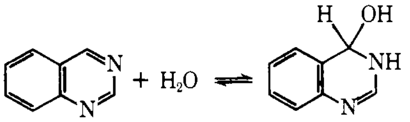
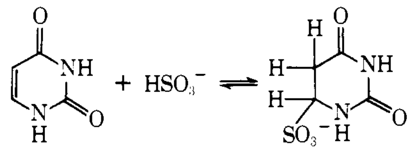
Abstract: A linear correlation is shown to exist between the first half-wave potentials for reduction at a dropping mercury electrode in 1 M HCl of quinazoline, purine, acridine, pyrimidine, 2-aminopyrimidine, and 2-amino-4-methylpyrimidine, and the logarithms of the equilibrium constants for covalent addition of HSO_3^- or SO_3^{2-} to a $>C{=}N^+<$ group of their conjugate acids. This correlation is used as the basis for a method of estimating the magnitude of the equilibrium constants for a wide variety of covalent additions to heteroaromatic molecules.

Scheme I

Covalent Addition of Water to Quinazoline[11]



Covalent Addition of HSO_3^- to Uracil[3]



The covalent addition of nucleophilic reagents such as water,[2] bisulfite ion (HSO_3^-),[3-7] cysteine,[8] and electron-rich functionalities in enzymes[9,10] across a double bond in heteroaromatic molecules has been implicated as the initial step in a variety of chemical and biochemical processes. Typical covalent addition reactions are illustrated in Scheme I. Arriving at decisions about the operational probability of these reactions would be facilitated if ways could be found for predicting the value of the equilibrium constants for specific covalent addition reactions.

This paper discusses a correlation which is shown to exist between the first half-wave potentials for reduction at a dropping mercury electrode in 1 M HCl of a variety of heteroaromatic molecules which contain a $>C{=}N-$ group and

Table I. First Half-Wave Potentials in 1 M HCl and Equilibrium Constants for Covalent Additions at 25 °C

Compd	Addend	$-E_{1/2}$,[a] V	log K_{add}[c] Exptl	log K_{add}[c] Calcd[d]
Quinazolinium ion	HSO_3^-	0.40	8.55[e]	8.31
Acridinium ion	SO_3^{2-}	0.53	6.04	6.20
Pyrimidinium ion	HSO_3^-	0.62	4.49	4.74
2-Aminopyrimidinium ion	HSO_3^-	0.71	3.26[f]	3.28
2-Amino-4-methylpyrimidinium ion	HSO_3^-	0.82	1.69[f]	1.50
Purine cation[b]	HSO_3^-	0.83	1.34	1.33
2-Amino-4,6-dimethylpyrimidine	HSO_3^-	0.91	Very small[f]	0.06
Adenine[b]	HSO_3^-	1.12	Very small[g]	−3.34

[a] Except for the case of acridine, the $E_{1/2}$ values did not vary more than ±0.01 V when concentrations were changed from 10^{-2}-5×10^{-5} M. The polarogram of acridine solutions is very complex when the concentration is in excess of 10^{-4} M. This is discussed by B. Breyer, G. S. Buchanan, and H. Duetvell, *J. Chem. Soc.*, 360 (1944). The reported $E_{1/2}$ value was measured in solutions that were 5×10^{-5}-10^{-4} M. [b] Solution contained 0.01% gelatin to supress maxima. [c] The K_{add} values are the equilibrium constants for the reactions in Scheme II. Values for purine and acridine were at $I = 1.0$ M and all others were at $I = 0.1$ M. [d] Calculated from the $E_{1/2}$ value by using eq 1. [e] Reference 12. [f] Reference 15. [g] Observed in this study.

the magnitude of the equilibrium constant for the covalent addition of a model nucleophilic reagent HSO_3^- (or SO_3^{2-}) to the same molecules. Bisulfite ion was chosen as the model nucleophilic reagent because it adds strongly (i.e., the magnitude of the equilibrium constant for the reaction is large) to a wide variety of >C=N- groups and it is relatively easy to determine values of the equilibrium constants for these reactions.[3,5] However, it is believed that the above correlation has much wider applicability because it has been previously shown[12] that the logarithms of the equilibrium constants for the covalent addition of a wide variety of nucleophilic reagents, including water, urea, HSO_3^-, hydroxylamine, and β-mercaptoethanol are related to the γ[13] values of the nucleophilic reagents. The γ value was originally defined[13] as the tendency of the reagent to covalently add across the >C=O bond of pyridine-4-carboxaldehyde and the γ values of many nucleophilic reagents have now been determined.[13]

Hence, from the estimates of the equilibrium constants for bisulfite addition to particular heteroaromatic molecules that can be obtained from the linear free-energy relationship that is discussed in this paper, it is possible to estimate the equilibrium constants for the covalent addition of a wide variety of nucleophilic reagents to the same molecules.

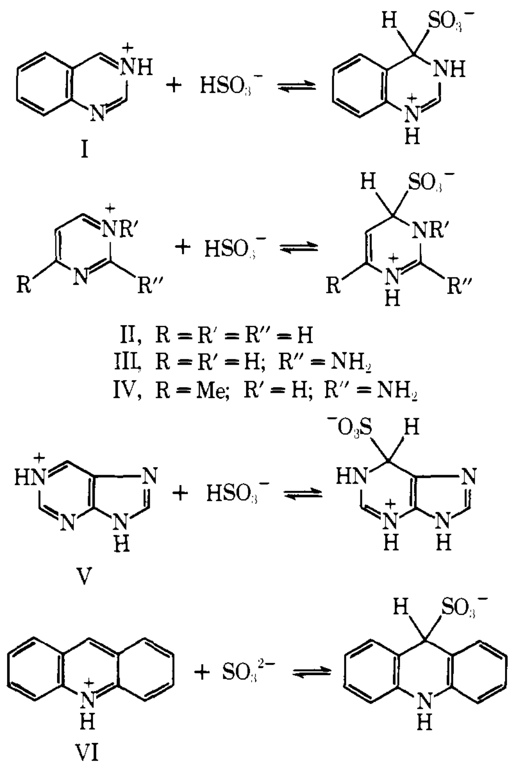
The linear free-energy relationship that is discussed in this paper cannot be used to predict the magnitude of equilibrium constants for covalent additions across the C(5)=C(6) bond of uracils because these compounds do not undergo polarographic reduction under similar conditions to molecules that contain >C=N- groups.[14]

Results and Discussion

Equilibrium Constants for Covalent Additions. The equilibrium constants, K_{add} values, for covalent addition of HSO_3^- at 25 °C to quinazolinium ion (I), 2-aminopyrimidinium ion (III), and 2-amino-4-methylpyrimidinium ion (IV) in accordance with the reactions shown in Scheme II have been reported previously[12,15] and are presented in Table I. The K_{add} value at 20 °C for addition of HSO_3^- to pyrimidine (II) in accordance with the reaction in Scheme II has been reported[2] to be 2.4×10^4 M^{-1} (this value was calculated from a pH-dependent equilibrium constant). The value of this equilibrium constant at 25 °C has now been determined and is included in Table I.

The covalent addition of HSO_3^- to purine (V) and acridine (VI) has not been previously reported. However, the changes in uv absorbance that followed the addition of sodium bisulfite to buffered solutions of these compounds were consistent with what would be expected if covalent addition was occurring. In each case one or more isosbestic points was maintained in the spectra of equilibrated solutions which contained different amounts of sodium bisulfite, the spectral changes were readily reversed upon dilution of equilibrated solutions with buffer, and plots of $(A_0 - A)/[S]_T$ against A (where A_0 and A are the absorbances of equilibrated solutions of the heteroaromatic molecule in a buffer and of similar solutions that contained a concentration of sodium bisulfite $[S]_T$, respectively) were linear. These features have been observed during covalent additions to other pyrimidines,[2,15] uracils,[3,5] and quinazolines.[11] Equilibrium constants, K_{obsd} values, were calculated from the slopes of plots of $(A_0 - A)/[S]_T$ against A at particular pH values and are listed in Table II.

Scheme II



The pH dependence of the K_{obsd} value for addition to purine suggested that the reaction involved HSO_3^- and the cation of purine. Hence, the term $K_{obsd}/f_{HSO_3^-}f_{Het^+}$ (where $f_{HSO_3^-}$ and f_{Het^+} are the fractions of total sulfite that existed as HSO_3^- and of V that was protonated) was pH independent. The value of this pH-independent constant, which describes the equilibrium shown in Scheme II, was designated K_{add} and is given

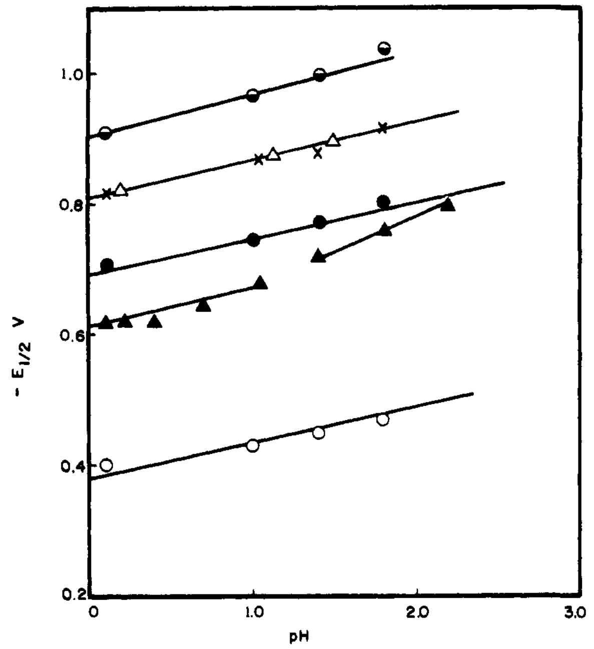


Figure 1. A plot of $E_{1/2}$ values for the first reduction wave of compounds I (○), II (▲), III (●), IV (×), V (△), and VII (◓) against pH.

Table II. pH-Dependent Equilibrium Constants for Covalent Additions to Purine and Acridine in Aqueous Sodium Bisulfite at 25 °C, I = 1.0 M

Compd	pH	Analytical λ, mm	K_{obsd}
V	2.00	260	11
	3.00	260	4.2
VI	2.10	354	32
	3.08	354	456

in Table I. The pH dependence of the K_{obsd} value for addition to acridine (VI) was consistent with the postulate that the reaction involved the cation of acridine and SO_3^{2-} because the term $K_{obsd}/f_{SO_3^{2-}}f_{Het^+}$ (i.e., the fractions of total sulfite and VI that existed as SO_3^{2-} and the cation, respectively) was essentially pH independent. The value of this term is the K_{add} value in Table I.

The reactions of V and VI that have been described above are believed to yield the products that are shown in Scheme II, although the structures of these adducts were not elucidated. The double bond in each heteroaromatic molecule to which covalent nucleophilic addition has been proposed is the same moiety that has been previously[16] postulated to be the most easily reduced electrochemically. In cases where the structures of covalent adducts have been determined it has always been found that addition occurs most readily to the bond that is most easily reduced.[17]

Half-Wave Potentials. The first half-wave potentials (i.e., the least negative $E_{1/2}$ values relative to a standard calomel electrode) for reduction at a dropping mercury electrode of solutions of compounds I-VI and 2-amino-4,6-dimethylpyrimidine (VII) and adenine (VIII) are presented in Table I and values for compounds I-VI are shown plotted against pH in Figure 1.

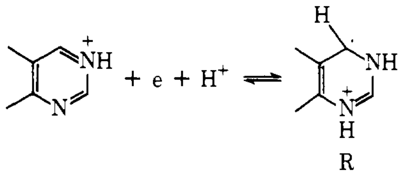
The reactions which give rise to the first polarographic wave in solutions of each compound at pH 0.1 (i.e., in 1 M HCl) appear to be essentially one-electron reversible processes, as values of the term $0.059/(E_{3/4} - E_{1/4})$ were 1.0 ± 0.1[18] and $E_{1/2}$ values did not vary when the drop rate was changed from one drop in 0.5 s to one drop in 2.0 s. This interpretation of the experimental observations is somewhat different from conclusions that have been reached by others. Hence, whereas it has been reported that the first wave in the polarogram of pyrimidine relates to a reversible reduction in aprotic solvents such as DMF,[19] it has been suggested that this wave is not completely reversible in aqueous buffers with pH values between 0.5 and 5.[20] It has also been reported[21] that the first reduction wave in the polarogram of purine in aqueous solutions with pH values between 1.78 and 4.72 was caused by a two-electron process and not by a one-electron process. However the results of the present study do support the conclusion that all the reactions involve only one electron and are largely reversible at pH 0.1.

The slopes of the linear plots of $E_{1/2}$ against pH, which are shown in Figure 1 for compounds I-V and compound VII, had values very close to 0.059. The lines in this figure are, in fact, drawn so that they do have slopes of 0.059 and the experimental points sit very close to them. This pH dependence of $E_{1/2}$ values is consistent with the proposal that the reactions involve the addition of one electron and one proton to a substrate.

Compounds I, II, III, IV, V, and VII have pK_a values[23] of 1.5 (at 20 °C), 1.23 (at 25 °C), 3.45 (at 25 °C), 4.11 (at 25 °C), 2.30 (at 20 °C), and 4.82 (at 20 °C), respectively. Hence, the predominant form of these molecules at pH 0.1 would be the cation and it is believed that this form is also likely to be the substrate in the reduction reactions.

Further support for this conclusion comes from the previously noted observation that plots of $E_{1/2}$ against pH for compounds I,[24] III,[20] and IV[20] are discontinuous near the pK_a value and the magnitude of the slopes approach a value of 0.118. This suggests that the neutral molecules are the substrates in reductions above the pK_a values of the conjugate acids of the bases and that beyond this point reactions involve two protons. Hence, it is proposed that the reductions of compounds I-V, VII, and VIII proceed in accordance with the mechanism shown in Scheme III. The structure labeled R in Scheme III is taken to represent the radical cation that would be formed from the various heteroaromatic cations.

Scheme III



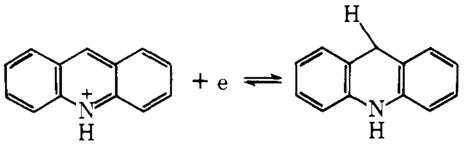
The $E_{1/2}$ values of acridine (VI) were essentially independent of pH over the range of 0.1-1.8. Because this compound exists predominantly as a cation throughout this pH range (pK_a of VI is 5.58 at 20 °C),[23] the most likely reaction involves addition of an electron to VI in a reaction such as that shown in Scheme IV. The structure of each of the radicals in Schemes III and IV is consistent with the reduction products of the various compounds.[16]

Correlation Between $E_{1/2}$ Values and K_{add} Values. Figure 2 is a plot of the logarithms of the equilibrium constants for the reactions in Scheme II against the first half-wave potentials for those compounds in 1 M HCl. The plot is essentially linear over a 10^8-fold difference in magnitude of K_{add} values and it can be described by

$$\log K_{add} = 16.2E_{1/2} + 14.8 \qquad (1)$$

This empirical equation has a very similar form to a theoretical equation that can be derived by making the postulate that the standard free-energy changes in isoprotonic covalent addition reactions ($\Delta G_c°$) and one-electron reduction ($\Delta G_R°$) processes

Scheme IV



VI R

are linearly related in such a way that

$$\Delta G_c^\circ = \alpha \Delta G_R^\circ + \beta \qquad (2)$$

where α and β are constants. The term isoprotonic is used to indicate that the difference between the number of protons in the products of both the covalent addition and electrochemical reduction reactions and in the common substrate are equal. The terms ΔG_c° and ΔG_R° are related to the K_{add} values for the reactions in Scheme II and the standard electrode potentials (E°) for the reactions in Scheme III by the identities

$$2.303RT \log K_{add} = -\Delta G_c^\circ \qquad (3)$$

$$nFE^\circ = -\Delta G_R^\circ \qquad (4)$$

In these identities n is the number of electrons and F is the Faraday constant. By combining eq 2, 3, and 4 it can be concluded that K_{add} values would be related to E° values by the equation

$$\log K_{add} = \frac{\alpha nFE^\circ}{2.303RT} - \frac{\beta}{2.303RT} \qquad (5)$$

This theoretical equation has a similar form to eq 1. The values of $E_{1/2}$ at pH 0 for the reactions in Scheme III would be close to the standard electrode potential because it has been established that the reactions are essentially reversible at pH values close to 0.[18] Because plots of $E_{1/2}$ pH values close to 0 against pH have a slope of 0.059 or less, it is reasonable to equate the $E_{1/2}$ value in 1.0 M HCl (i.e., at pH 0.1) with the E° value and use the $E_{1/2}$ value to plot against log K_{add} according to eq 5. The value of the slope of the plot in Figure 2 is 16.2 and is very close to 16.9, which is the value of $nF/2.303RT$ at 25 °C for a one-electron process. Hence, the theoretical model is consistent with the experimental results if the value of α in eq 2 and 5 is 1. The postulate that is expressed in eq 2 seems reasonable on the basis that a major common effect of adding either an electron or a nucleophilic reagent to a heteroaromatic molecule that contains one or more >C=N- groups is quite likely to be localization of the π electrons in the same double bond with concomitant loss of aromatic character.

Hence, for acridines, quinazolines, purines, and pyrimidines of the type studied, it appears possible to estimate the extent to which HSO_3^- would covalently add from a knowledge of the first $E_{1/2}$ value measured at pH 0.1. Table I lists the $E_{1/2}$ values, experimentally measured equilibrium constants, and the values that would be predicted by using eq 1.

The $E_{1/2}$ values of 2-amino-4,6-dimethylpyrimidine (VII) and adenine (VIII) were also measured and found to be −0.91 and −1.12 V in 1 M HCl. The use of eq 1 suggests that K_{add} values to these molecules would be 1.1 and 8×10^{-4} M^{-1}, respectively. This was consistent with the experimental observation that the extent of covalent addition of HSO_3^- to these molecules was too small to be detected by spectroscopic means.

Limitations of the Correlation between $E_{1/2}$ and K_{add} Values. Uracil and related compounds do covalently add HSO_3^- in aqueous solution,[3] but they do not give a polarographic reduction wave in 1 M HCl at a dropping mercury electrode.[14] The magnitude of the equilibrium constant for addition of HSO_3^- to uracil is 460 M^{-1} at 25 °C[25] and hence, according to the relationship developed in this paper, it was expected that uracil would have a reduction wave with an $E_{1/2}$ value close to −0.75 V. One difference between both the covalent addition of bisulfite ion to uracil (see Scheme I) and the anticipated electrochemical reduction (Scheme V) and equivalent reactions of quinazoline, pyrimidine, etc., is that the former reactions involve addition across a >C=C< double bond, whereas the latter involve addition across a >C=N⁺< double bond to a nitrogen.

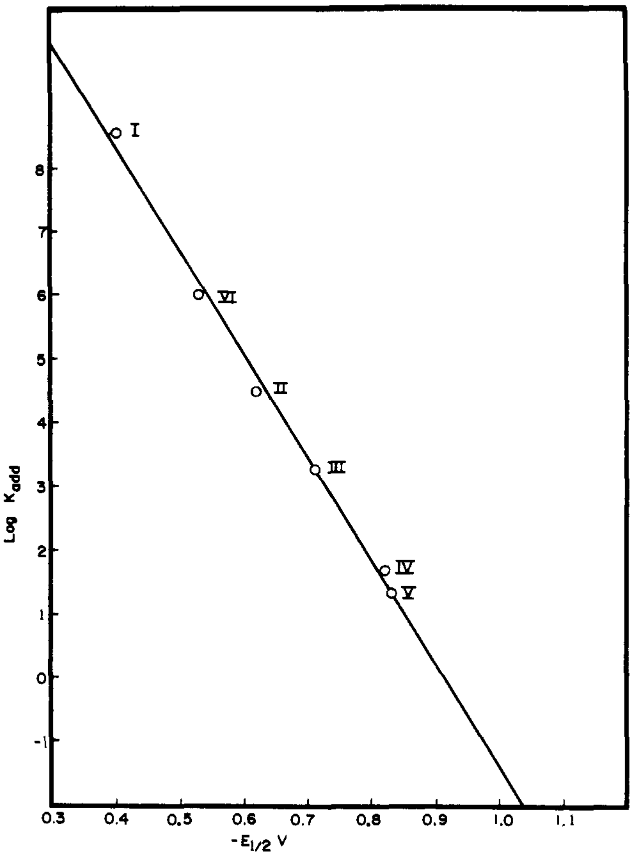
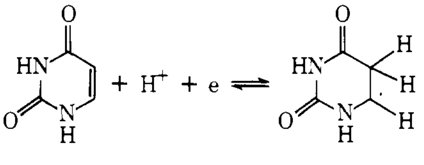


Figure 2. A plot of $E_{1/2}$ values at pH 0.1 for the first reduction wave of compounds I–VI against the logarithms of the equilibrium constants for covalent addition of HSO_3^-. The line was calculated using a least-squares fitting technique for the data.

Studies in our laboratories have demonstrated that the rate of addition of HSO_3^- across >C=C< double bonds is very much slower than the rate of addition across the >C=N⁺< double bond. For example, the pH independent second-order rate constants for the addition of HSO_3^- to quinazolinium ion and uracil neutral molecule are 1.69×10^7 M^{-1} s^{-1} [12] and 1.74×10^{-3} M^{-1} s^{-1},[25] respectively. In each of these cases the attack of SO_3^{2-} on the substrate is the rate-determining step. If a similar difference exists in the rate of the electrochemical reduction in Scheme V as compared to that of the reactions in Scheme IV, it is likely that the failure of uracil to reduce at a dropping mercury electrode is due to the high energy of activation of this process and not the fact that the electrode potential for the reaction is outside of the range that can be examined by this technique, i.e., 0 to −1.6 v in aqueous acid solutions.

Scheme V



It is quite likely that other heterocyclic molecules will be found which do not behave in the same way as the molecules studied in this work with respect to covalent addition and electrochemical reduction reactions. In some further cases this different behavior may arise because of profound differences in the kinetics of the reactions as compared to those of the heterocyclic molecules that have been studied, but in other cases marked differences may exist between the structures of the most stable radicals and adducts, respectively. Studies are continuing in our laboratories to determine how widely applicable the correlation that has been discussed is to the prediction of covalent additions to heteroaromatic molecules.

Experimental Section

Quinazoline, acridine, purine, and pyrimidine were purchased from Aldrich Chemical Co. The other heterocyclic compounds were purchased from K & K Laboratories, Inc. These chemicals were used without further purification. All other chemicals were reagent or analytical grade.

Polarographic data were obtained with a Model 174 polarographic analyzer (Princeton Applied Research Corp., Princeton, N.J.) equipped with a model 174/70 drop timer. Polarographs were recorded on an Omnigraphic Model 2000 X-Y recorder (Houston Instrument Co., Austin, Texas). The dropping mercury electrode used had a flow rate $m = 3.2$ mg s^{-1} in deionized water at an uncorrected height of the mercury reservoir $h = 60$ cm and a natural drop time $t_\alpha = 2.1$ s in 0.1 M hydrogen chloride solution at −0.60 V vs. SCE. The cell was equipped with a saturated calomel reference electrode and graphite rod counter electrode. A purified nitrogen stream was used to deoxygenate the solutions. All measurements were carried out at room temperature. Measurements of pH were made with a Corning Model 112 expanded scale/digital pH meter. Buffer solutions in the range from pH 1.0 to 2.2 were prepared from 0.2 M HCl and 0.2 M KCl solutions. The compounds were dissolved in the desired buffer to give 5×10^{-5}–10^{-3} M solutions; the pH of each solution was measured. About 8 ml of test solution was transferred to the cell, purged with nitrogen for 10 min, and then polarographed. Gelatin (concentration 0.01%) was used in purine and adenine solutions to suppress maxima. A portion of the buffer solution was treated in identical fashion to obtain the background curve.

Equilibrium constants for bisulfite addition to purine and acridine were calculated from the results of similar experiments to those which have been described previously.[12] Ionic strength was maintained at 1.0 M with sodium chloride and the temperature was 25.0 ± 0.1 °C. Results are in Tables I and II.

References and Notes

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Evaluation of Possible SN2 Transition-State Models for Reaction of *n*-Butyl Chloride Using Chlorine Kinetic Isotope Effects[1]

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Abstract: A series of possible transition-state models for the reaction of *n*-butyl chloride with thiophenoxide anion in methanol is evaluated using chlorine kinetic isotope effects (KIE). Vibrational analysis of a skeletal ground-state model, assuming a point propyl group, reproduces the experimentally measured normal modes of both isotopically substituted molecules to an average error of ±0.030%. The central transition-state model results in KIE values of 1.00898 and 1.00791 at 20 and 60 °C, respectively, compared to observed values of 1.0089_8 and 1.0079_2. The correlation of KIE values with transition-state geometry shows that the C–Cl and C–H bond lengths correlate well with the difference in KIE values at 20 and 60°. The C–C bond length correlates to the temperature-dependent factor and the approach to planarity of the groups attached to the central carbon correlates with the temperature-independent factor. The most consistent model results in C–Cl = 1.186, C–C = 1.533, C–H = 1.110 Å, ∠Cl–C–C = 93.1, ∠Cl–C–H = 92.9, ∠C–C–H = 119.5, and ∠H–C–H = 116.2°. Calculated α-deuterium isotope effects for this model are in good agreement with those observed for a similar reaction.

Introduction

Experimental measurements of kinetic isotope effects (KIE) have shown great utility as a probe for reaction mechanisms.[2-4] The leaving group heavy-atom values have also been found to be very sensitive to the transition state structure[5-8] and are also useful in evaluating conflicting mechanistic explanations.[9] However, because theoretical KIE calculations require knowledge of all ground-state and transition-state frequencies as well as their isotopic shifts,[10] few rigorous model calculations