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Using Incoming Nucleophile Primary Hydrogen−Deuterium Kinetic Isotope Effects To Model the S_N2 Transition State

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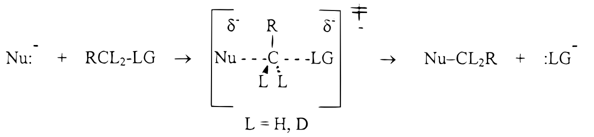
Abstract: The primary hydrogen−deuterium incoming nucleophile KIEs for the S_N2 reactions between para-substituted benzyl chlorides and borohydride ion in DMSO at 30.000 ± 0.002 °C are small ($\leq$1.14) and insensitive to a change in substituent at the α-carbon. The small Hammett ρ (0.51) and ρ^r (−0.52) values found when the para substituent on the benzene ring of the substrate is altered indicate there is very little charge on the α-carbon in the transition state. The large, constant secondary α-deuterium KIEs of 1.089 ± 0.002 and the large chlorine leaving group KIEs of 1.0076, 1.0074, and 1.0078 found for the *p*-methyl-, the *p*-hydrogen-, and the *p*-chlorobenzyl chloride reactions suggest that the transition states for these reactions are unsymmetric with short $H-C_\alpha$ and long $B-H$ and $C_\alpha-Cl$ bonds. The decrease in the chlorine leaving group KIE from 1.0076 ± 0.0003 for the *p*-methylbenzyl chloride reaction to 1.0036 ± 0.0003 for the *p*-nitrobenzyl chloride reaction indicates the $C_\alpha-Cl$ bond shortens markedly when a strongly electron-withdrawing substituent is on the α-carbon. Unfortunately, the bond strength hypothesis is the only theory that predicts the changes observed in transition-state structure and it only indicates the bond that changes but not how the transition-state structure is altered.

Introduction

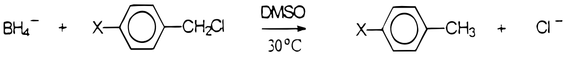
Despite a large volume of research, substituent effects on the structure of the S_N2 transition state, eq 1, are not understood.[1−4]



[1]

The problem is that most of the studies[5,6] have only demonstrated how the $C_\alpha-LG$ bond changes and since one needs to know how substituents affect both the reacting bonds (the total transition-state structure), more methods for estimating the length of the $Nu-C_\alpha$ transition-state bond are needed. The best method of determining how the $Nu-C_\alpha$ transition-state bond is changed by substituents is by measuring an incoming nucleophile KIE, and in fact, nitrogen incoming nucleophile KIEs have been measured for a variety of S_N2 reactions.[7−10] Ando and co-workers[8] and Kurz and co-workers,[9,10] measured the nitrogen incoming nucleophile KIEs for the S_N2 reactions between anilines and pyridines with methyl and ethyl halides and arenesulfonates. Unfortunately, these KIEs were too small to show how changes in the structure of the substrate, the leaving group, or the nucleophile affected the $Nu-C_\alpha$ bond in the S_N2 transition state. Matsson et al.[11] overcame this problem by measuring the $^{11}C/^{14}C$ incoming nucleophile KIEs (the mass difference of 3 between the isotopes increased the magnitude of the KIE) for the S_N2 reactions between labeled cyanide ion and para-substituted benzyl chlorides. Their $^{11}C/^{14}C$ KIEs, which were large (the smallest KIE was 1.0070 ± 0.0008) compared to the error in the KIE, showed that the $NC-C_\alpha$ transition-state bond was slightly shorter when a more electron-withdrawing substituent was at the α-carbon.

Because isotopes of hydrogen have the largest percentage change in mass possible, they produce the largest KIEs. This led us to measure the primary hydrogen−deuterium incoming nucleophile KIEs for the S_N2 reactions between sodium borohydride and several para-substituted benzyl chlorides in DMSO at 30.000 °C, eq 2, to determine whether these KIEs would be



[2]

useful for monitoring the changes in the $Nu-C_\alpha$ bond in an S_N2 reaction. Finally, a combination of (i) primary hydrogen−deuterium incoming nucleophile KIEs, (ii) chlorine leaving group KIEs, (iii) secondary α-deuterium KIEs, and (iv) Hammett ρ values have been used to learn how the transition state changes when the substituent at the α-carbon is changed in these S_N2 reactions.

Results and Discussion

The objectives of this study were to determine whether (i) primary hydrogen−deuterium incoming nucleophile KIEs could

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be used to monitor the changes in the Nu−C_α bond in S_N2 reactions and (ii) to learn how a change in substituent at the α-carbon affected the total structure of the transition state in the borohydride ion−para-substituted benzyl chloride reactions.

Mechanism of the Reaction. Although the reaction in eq 2 occurs,[12,13] it was necessary to prove these reactions occur by an S_N2 mechanism. Early investigators[13−16] found that the $NaBH_4$ reductions of alkyl halides were second order and concluded they were S_N2 processes. Bell and co-workers, on the basis of rate−structure profiles, also concluded that these reactions occurred by an S_N2 mechanism.[15,17] Although Ashby and co-workers concluded that the reduction of primary alkyl bromides and iodides by several metal hydrides occurs by a single-electron-transfer (SET) mechanism, they were unable to find any evidence suggesting that alkyl chlorides react by the SET mechanism and concluded that primary and secondary alkyl chlorides react by an S_N2 pathway.[18,19]

The results from this study confirm that all the para-substituted benzyl chloride−borohydride ion reactions occur by an S_N2 mechanism. All the reactions are second order, first order in substrate and first order in the nucleophile so both the nucleophile and the substrate are involved in the rate-determining step of the reaction. More importantly, the primary incoming nucleophile hydrogen−deuterium and chlorine leaving group KIEs found for these reactions (vide infra) indicate both Nu−C_α bond formation and C_α−LG bond rupture occur in the transition state of the rate-determining step of the reaction; i.e., that they are all S_N2 processes.

Primary Hydrogen−Deuterium KIEs. The primary hydrogen−deuterium KIEs for the S_N2 reactions between sodium borohydride and para-substituted benzyl chlorides were determined by reacting sodium borohydride or sodium borodeuteride with the para-substituted benzyl chloride in DMSO at 30.000 ± 0.002 °C. The average primary hydrogen−deuterium KIEs, Table 1, are surprising for two reasons. They are (i) all small and (ii) insensitive to a change in substituent at the α-carbon; i.e., the average KIE is 1.246 ± 0.010. Small primary hydrogen−deuterium KIEs have been attributed to a bent[20] and/or an unsymmetric transition state.[21,22] To determine which factor is responsible for the small KIE, the maximum primary hydrogen−deuterium isotope effect for the S_N2 reaction between borohydride ion and benzyl chloride was estimated using eq 3,

$$k_H/k_D = e^{-hc/2kT\,(\nu_{B-H} - \nu_{B-D})} \qquad (3)$$

which assumes the complete disappearance of the asymmetric B−H(D) stretching vibration in the transition state. Substituting the frequencies of the asymmetric stretching vibrations for the B−H and B−D bonds in the reactant ($\nu_{B-H} = 2272\ cm^{-1}$ and $\nu_{B-D} = 1721\ cm^{-1}$, respectively)[23] into eq 3 suggests the maximum primary hydrogen−deuterium KIE will be ∼3.7 at 30 °C. The observed $k_H/k_D = 1.25$ is only 34% of the maximum KIE of 3.7. Moreover, the observed hydrogen−deuterium KIE is the product of a primary hydrogen−deuterium KIE and a secondary hydrogen−deuterium KIE, eq 4, The $(k_H/k_D)_{Prim}$ is

$$(k_H/k_D)_{Obs} = (k_H/k_D)_{Prim}(k_H/k_D)_{Sec} \qquad (4)$$

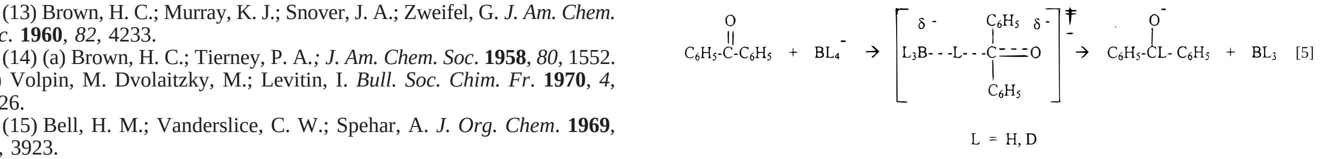
primarily determined by the change in the asymmetric stretching vibration of the transferring hydron, and the $(k_H/k_D)_{Sec}$ is determined by the changes in the B−H(D) vibrations of the nontransferring hydrons as the reactant is converted into the transition state. The latter KIE arises because the boron changes from sp^3 to sp^2 hybridization as the hydride ion is transferred to the α-carbon. Because the observed KIE is the product of a secondary and a primary hydrogen−deuterium KIE, $(k_H/k_D)_{Prim}$ must be smaller than the observed KIE of 1.25.

Table 1. Rate Constants and Primary Hydrogen−Deuterium KIEs for the S_N2 Reactions between Borohydride Ion or Borodeuteride Ion and Para-Substituted Benzyl Chlorides in DMSO at 30.000 °C

para substituent	$k_H \times 10^3$	$k_D \times 10^3$	$(k_H/k_D)_\alpha$
CH_3	1.468 ± 0.032	1.195 ± 0.019[a]	1.228 ± 0.033[b]
CH_3[c]	1.360 ± 0.002	1.094 ± 0.008	1.243 ± 0.009
av			1.236 ± 0.01[d]
H	1.317 ± 0.013	1.052 ± 0.017	1.252 ± 0.020
H[c]	1.239 ± 0.031	0.988 ± 0.093	1.254 ± 0.020
H[c]	1.290 ± 0.017	1.032 ± 0.032	1.250 ± 0.017
av			1.252 ± 0.002
Cl	1.808 ± 0.012	1.465 ± 0.015	1.234 ± 0.015
Cl[c]	1.780 ± 0.015	1.437 ± 0.029	1.239 ± 0.027
Cl[c]	1.889 ± 0.014	1.517 ± 0.012	1.245 ± 0.014
av			1.239 ± 0.006
NO_2	3.318 ± 0.010	2.644 ± 0.067	1.255 ± 0.032
NO_2[c]	3.049 ± 0.049	2.422 ± 0.042	1.259 ± 0.029
av			1.257 ± 0.003

[a] Standard deviation for the average rate constant. [b] The error is $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta\ k_D)^2]^{1/2}$,where Δk_H and Δk_D are the standard deviations for the average rate constants for the reactions of the undeuterated and deuterated nucleophiles, respectively.[3] [c] Measured in a different batch of DMSO. [d] Standard deviation of the average KIE.

Yamataka and Hanafusa[24] measured $^{12}C/^{14}C$ α-carbon and hydrogen−deuterium KIEs for the reaction between benzophenone and $NaBH_4$, eq 5, and used a BEBOVIB-IV calculation



to match the transition-state structure with the observed KIEs. Their calculations suggested that the secondary hydrogen−deuterium KIE increases dramatically from 1.1 to 1.7 as the C_α−H transition-state bond order increases from 0.10 to 0.90. This presumably occurs because as the C_α−H bond order in the transition state increases, the hybridization at boron changes from sp^3 to sp^2, and there is less steric hindrance to the nontransferring B−H(D) out-of-plane bending vibrations. As a

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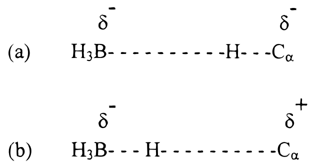

$$\text{(a)}\quad \overset{\delta^-}{H_3B}\text{---------}H\text{---}\overset{\delta^-}{C_\alpha}$$

$$\text{(b)}\quad \overset{\delta^-}{H_3B}\text{---}H\text{---------}\overset{\delta^+}{C_\alpha}$$

Figure 1. A productlike (a) and reactant-like (b) unsymmetric form for the hydride-transfer portion of the transition state.

result, the zero-point energy difference in the transition state is small relative to that in the initial state and a large secondary KIE is observed. The results reported by Yamataka and Hanafusa can be used to estimate the magnitude of the maximum primary hydrogen−deuterium KIE in the borohydride ion−benzyl chloride reactions because (i) the vibrations involved in the reduction of benzophenone to benzhydrol are similar to those involved in the reduction of benzyl chloride to toluene. The only differences will be at the α-carbon because the B−H(D) vibrations in $NaBH_4$ and $NaBD_4$ are the same in both reactions. The symmetric and asymmetric C_α−H stretching vibrations formed in these reactions are found at 2930 and 2890 cm^{-1}, respectively, for benzhydrol[25] while they are at 2960 and 2930 cm^{-1}, respectively, for toluene.[25] (ii) Changing the solvent to DMSO from 2-propanol will not affect this comparison because Yamataka and Hanafusa concluded that the solvent does not contribute significantly to the KIE either through hydrogen bonding to the hydride ion or through nucleophilic assistance in the hydride transfer. Since the dipolar aprotic solvent, DMSO, cannot form hydrogen bonds, it should not affect the reaction or the KIE. (iii) The calculations performed by Yamataka and Hanafusa and the calculation to determine the maximum KIE in this study both assumed that the hydride-transfer transition state is linear.

If the range of secondary deuterium KIEs in the benzophenone reduction (between 1.1 and 1.7) is applied to the benzyl chloride reactions, the observed hydrogen−deuterium KIE of 1.25 corresponds to a primary deuterium KIE of between 1.25/1.1 = 1.14 and 1.25/1.7 = 0.74. The actual value will, of course, depend on the amount of hydron transfer from B to C_α in the transition state. The Westheimer−Melander theory[21,22] states that the maximum primary hydrogen−deuterium KIE (3.7) is observed when the hydrogen is symmetrically located (50% transferred) between the two heavier atoms in the transition state and that a smaller KIE is found when the hydron-transfer transition state is unsymmetric. Therefore, if the transition state is linear, the small primary hydrogen−deuterium KIE of ≤ 1.14 suggests the hydride is unsymmetrically located, i.e., either very near the boron or the α-carbon in the transition state, Figure 1.

Another explanation for the small primary hydrogen−deuterium KIE is that the hydride-transfer transition state is not linear. In a linear transition state, the ZPE difference in the transition state is zero and the KIE is a maximum when the hydride is symmetrically located.[21,22] In a nonlinear, symmetric transition state, the hydride will not be motionless and the vibrational energy will be dependent on isotopic substitution. Hence, the ZPE difference will be larger in a bent transition state and the KIE will be smaller. Calculations by More O'Ferrall[26] suggest that small deviations of 5° from linearity have little effect on the KIE. However, deviations greater than 5° cause the magnitude of the KIE to decrease significantly and the curve relating the position of the hydron in the transition state to the magnitude of the primary hydrogen−deuterium KIE to become broader, Figure 2. This means the position of the hydride in the transition state can vary markedly without changing the primary hydrogen−deuterium KIE. Therefore, if the hydron-transfer portion of the transition state is sufficiently bent, the primary hydrogen−deuterium KIEs would be insensitive to a change in substituent at the α-carbon, even if the change in substituent causes a relatively large change in transition-state structure. Ab initio calculations[27] on the methyl chloride−borohydride ion reaction at the 6-31+G* level indicate that the transfer of hydride between boron and carbon is nonlinear with a B−H−C_α bond angle of 144°. It is worth noting that calculations at a higher level are expected to yield a larger B−H−C_α bond angle[27] and that a looser transition state is expected for the benzyl chloride reaction. However, a B−H−C_α bond angle of 144° suggests that the maximum primary hydrogen−deuterium KIE would be reduced from 3.7 to ~2.7. Even if the maximum KIE is 2.7, the small primary hydrogen−deuterium KIE of ≤ 1.14 is still very small with respect to the maximum value. Therefore, it is clear that the hydron-transfer portion of the S_N2 transition state must be very unsymmetric, even if it is bent.

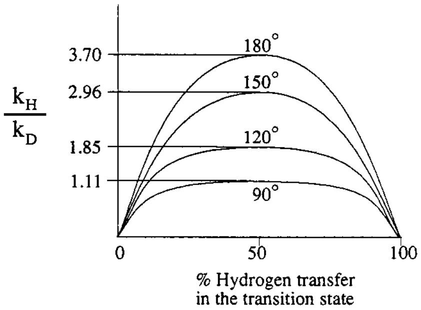

Figure 2. Westheimer−Melander curve for the hydron transfer showing the maximum primary hydrogen−deuterium KIEs for linear and bent hydride transfer transition states.

The second problem is to explain why the primary hydrogen−deuterium KIEs (the B−H−C_α portion of the transition state) do not change with the substituent. Westaway[28] proposed a bond strength hypothesis for S_N2 reactions which suggests there will be a significant change in the weaker reacting bond but little or no change in the stronger reacting bond in an S_N2 transition state when a substituent at the α-carbon is changed. For the borohydride ion−para-substituted benzyl chloride S_N2 reactions, the C_α−H bond stretching vibration for the product (toluene) is at 2960 cm^{-1} while the C_α−Cl stretching vibration for the reactant (benzyl chloride) occurs at 650 cm^{-1}.[25] Because the stronger C_α−H reacting bond in the S_N2 transition state should not change significantly with substituent, the identical primary hydrogen−deuterium KIEs that are found in these reactions are expected.

Although it seems certain that the hydron-transfer portion of the transition state is unsymmetric, it is not known whether the hydride ion is more or less than 50% transferred to C_α in the transition state. However, a productlike transition state with a short H−C_α bond is favored because in all the S_N2 reactions where the transition state is unsymmetric, the strongest reacting bond is short and the weaker reacting bond is long.[29] Therefore, one would expect that the stronger H−C_α bond would be short and the weaker C_α−Cl bond would be long in the hydride ion S_N2 portion of the transition state. Another reason for *favoring*

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a productlike hydron-transfer portion of the transition state is that if the bond strength hypothesis can be applied to the hydride ion-transfer portion of the transition state (a nucleophile is being transferred between two electrophiles, B and C_α, whereas in an S_N2 transition state, an electrophile is being transferred between two nucleophiles), one would expect the B−H−C_α transition state to be productlike. The stretching vibration for the B−H bond in sodium borohydride[23] and the C_α−H bond in toluene[25] are at 2294 and 2960 cm^{-1}, respectively. If the bond strength hypothesis is applied to this hydride-transfer transition state, one would expect the stronger C_α−H reacting bond to be shorter than the B−H reacting bond (a productlike transition state). Although this is only speculation, it is worth noting that Yamataka and Hanafusa proposed a productlike transition state with B−H and H−C_α bond orders of 0.25 and 0.75, respectively, for the hydride-transfer reaction between borohydride ion and benzophenone.[24]

Hammett ρ Value. Because the rate constants for all the para-substituted benzyl chlorides are greater than the rate constant for benzyl chloride (see the k_H rate constants in Table 1), a U-shaped Hammett plot is observed for the S_N2 reactions between sodium borohydride and para-substituted benzyl chlorides. Three explanations have been suggested for the curved Hammett ρ plots found for the S_N2 reactions between benzylic substrates and anionic nucleophiles. One is a change from an S_N2 to a carbocation mechanism when a more electron-donating substituent is on the substrate.[30−32] The second is a change in the relative importance of bond breaking and bond making in the transition state,[33−35] and the third is that the curvature is due to a greater resonance effect of the +M (methyl and chloro) substituents.[3,36] The curvature in the Hammett plot is not due to a change in mechanism because all of the substrates react by an S_N2 mechanism (vide supra). Nor is it due to a change from a productlike to a reactant-like transition state because the primary hydrogen−deuterium KIEs are identical for all the para-substituted benzyl chloride reactions. Therefore, it must be due to a greater resonance effect by the +M substitutents.

The variable resonance effect can be demonstrated by applying the modified Yukawa−Tsuno expression,[36] eq 6, to

$$\log k/k_o = \rho\sigma^n + \rho^r(\sigma^+ - \sigma^n) \qquad (6)$$

the data. The ρ and ρ^r terms represent the sensitivity of the reaction to the polar and resonance effects of the substituent, respectively. The σ^+ terms are substituent constants representing the interaction of a substituent with a carbocation while the σ^n terms represent the substituent's polar (no resonance) effect on the reaction site. If resonance between the α-carbon and the benzene ring ($\rho^r(\sigma^+ - \sigma^n)$) is important in a reaction series where the substituent on the substrate is varied, ρ^r is large. Also, if conjugation is important in the transition state, ρ^r will be larger than ρ.[3] A plot of $\log(k_X/k_H)$ vs σ^n for the reactions of the p-hydrogen- and p-nitro-substituted benzyl chlorides (the p-hydrogen and p-nitro substituents have little or no resonance interaction with the benzene ring and their ($\sigma^+ - \sigma^n$) values are 0.000 and 0.012, respectively) gives a line with slope ρ of 0.51. When the other substituents were placed on this Hammett plot, the points corresponding to the p-methyl and p-chloro substituents show positive deviations from the $\rho = 0.51$ line. Plotting these deviations ($\Delta\log k_X/k_H$) vs ($\sigma^+ - \sigma^n$) for the p-methyl and p-chloro substituents gives a line with a slope $\rho^r = -0.55$. When the values of ρ and ρ^r are used, the Yukawa−Tsuno plot, Figure 3, has a high correlation coefficient of 0.994. This confirms that the curvature in the Hammett plot is caused by a variable resonance effect.

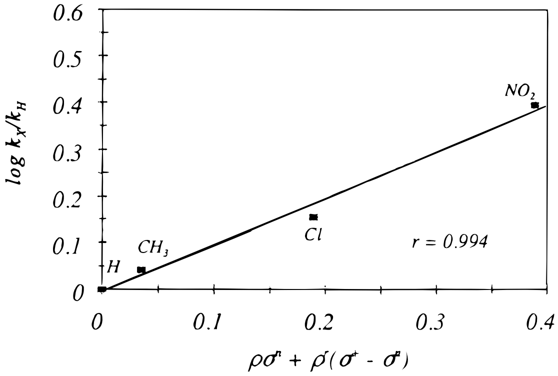

Figure 3. Yukawa−Tsuno plot for the S_N2 reactions between borohydride ion and para-substituted benzyl chlorides in DMSO at 30.000 ± 0.002 °C.

Table 2. ρ^r and ρ Values Found for S_N2 Reactions between Various Anionic Nucleophiles and Para-Substituted Benzyl Chlorides

nucleophile	solvent	temp (°C)	ρ^r	ρ	ref
borohydride ion	DMSO	30	−0.55	0.51	*a*
thiophenoxide ion	$LiOCH_3/CH_3OH$	20	−1.67	0.94	3
thiosulfate ion	60% aq acetone	30	−3.99	0.52	37
thiosulfate ion	60% aq acetone[b]	30	−0.96	0.67	37
cyanide ion	80% aq dioxane	30	−6.39	1.44	38
n-butyl sulfide ion	$LiOCH_3/CH_3OH$	20	−4.08	0.89	39

[a] This study. [b] The substrates in these reactions were para-substituted *m*-chlorobenzyl chlorides.

Although the ρ and ρ^r values are only approximate, a comparison of the ρ and ρ^r values found for these reactions with those found for other S_N2 reactions between para-substituted benzyl chlorides and anionic nucleophiles, Table 2, allows the structure of the transition state for the borohydride ion reactions to be elucidated in more detail. The small $\rho^r = -0.55$ is between 0.5 ($\rho^r = -0.96$ for the reactions with thiosulfate ion) and 0.08 times ($\rho^r = -6.39$ for the cyanide ion reactions) the ρ^r values found for the other S_N2 reactions. This suggests there is little conjugation between the benzene ring and the α-carbon in the transition state and that there is very little charge on the α-carbon in the transition state. If this is correct, the ρ value, which is primarily due to charge development on the α-carbon in going to the transition state, should also be small. In fact, the ρ value of 0.51 found in this study is the smallest value; i.e., it is equal to the ρ value of 0.52 found for the reactions with thiosulfate ion and is only 0.33 of the largest ρ value ($\rho = 1.44$ for the cyanide ion reaction) found for S_N2 reactions between benzyl chlorides and anionic nucleophiles, Table 2. This also suggests there is only a small charge on the α-carbon in the transition states of these reactions and supports the conclusion based on the ρ^r value.

Although the use of Hammett ρ values to suggest transition-

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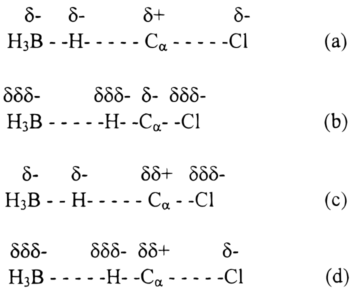

Figure 4. Possible unsymmetric S_N2 transition states for the reaction between borohydride ion and para-substituted benzyl chlorides.

state structure has been criticized,[41,42] the Hammett ρ value appears to be a valuable tool for determining the relative charge density on atoms in the transition state in a series of similar reactions because the substituent effects suggested by KIE data and the Hammett ρ values are identical.[3,4,43,44]

The primary hydrogen−deuterium KIEs indicated that the hydride is unsymmetrically placed between the boron and the α-carbon in the transition state. There are four possible linear, unsymmetric, hydride ion-transfer transition states, Figure 4. Transition state a with bond rupture ahead of bond formation would have significant positive charge on the α-carbon and a large negative Hammett ρ value would be found. Transition state b has short and strong $H-C_\alpha$ and $C_\alpha-Cl$ bonds, there would be significant negative charge on the α-carbon, and the ρ value would be large and positive. The small ρ and ρ^r values found in this study are obviously not consistent with either of these transition states. However, small ρ and ρ^r values are consistent with transition states c and d, where the α-carbon is unsymmetrically located between the hydride and the chloride ions and there is only a small charge on the α-carbon. Although the small Hammett ρ and ρ^r values cannot distinguish between unsymmetric reactant-like c and productlike d S_N2 transition states, a productlike transition state is more likely for two reasons. First, the primary hydrogen−deuterium KIEs *suggest* that the B−H−C portion of the S_N2 transition states for these reactions are productlike. Second, the small positive ρ value suggests there is more bond formation than bond rupture in the transition states.[45]

Secondary α-Deuterium KIEs

The secondary α-deuterium KIEs for the reactions between sodium borohydride and the para-substituted benzyl chlorides were determined by reacting sodium borohydride with the unlabeled or the labeled para-substituted benzyl-1,1-d_2 chloride in DMSO at 30.000 ± 0.002 °C. All the average secondary α-deuterium KIEs, Table 3, are large, i.e., ∼1.044 per α-D, and do not change with substituent. The $(k_H/k_D)_\alpha$ per α-deuterium for a carbenium ion S_N reaction of an alkyl chloride, where the first step is fully rate-determining, is 1.11.[46−48] If dissociation of the intimate ion pair or formation of the free carbocation is rate-determining, the $(k_H/k_D)_\alpha$ would be ∼1.15 per α-deuterium.[48] Recent work has shown that a $(k_H/k_D)_\alpha \leq 1.06$ per α-deuterium is indicative of an S_N2 mechanism[3,49−52] so the secondary α-deuterium KIEs of between 1.042 and $1.045/_{\alpha-D}$ found in this study confirm that these reactions are S_N2 processes.

Table 3. Average Rate Constants and Secondary α-Deuterium KIEs for the Sodium Borohydride S_N2 Reactions with Para-Substituted Benzyl Chlorides in DMSO at 30.000 ± 0.002 °C

para substituent	$k_H \times 10^3$	$k_D \times 10^3$	$(k_H/k_D)_\alpha$	$(k_H/k_D)/_{\alpha-D}$
CH_3	1.735 ± 0.015[a]	1.595 ± 0.004[a]	1.088 ± 0.010[b]	1.043
CH_3[c]	1.698 ± 0.003	1.553 ± 0.017	1.093 ± 0.012	1.045
av			1.091 ± 0.004[d]	1.044
H	1.102 ± 0.005	1.005 ± 0.018	1.096 ± 0.020	1.047
H[c]	1.121 ± 0.011	1.035 ± 0.003	1.082 ± 0.01	1.040
av			1.089 ± 0.010	1.044
Cl	1.806 ± 0.012	1.655 ± 0.009	1.091 ± 0.009	1.045
Cl[c]	1.640 ± 0.009	1.502 ± 0.002	1.092 ± 0.006	1.045
av			1.092 ± 0.0007	1.045
NO_2	3.420 ± 0.093	3.160 ± 0.004	1.082 ± 0.029	1.040
NO_2[c]	3.471 ± 0.044	3.161 ± 0.049	1.088 ± 0.022	1.043
av			1.085 ± 0.004	1.042

[a] Standard deviation. [b] The error is $1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2(\Delta k_D)^2]^{1/2}$,where Δk_H and Δk_D are the standard deviations for the average rate constants for the reactions of the undeuterated and deuterated nucleophiles, respectively.[3] [c] Measured in a different batch of DMSO. [d] Standard deviation of the average KIE.

One explanation for the large secondary α-deuterium KIEs observed for these hydride-transfer reactions is tunneling. Klinman and co-workers[53] measured primary and secondary hydrogen−tritium (k_H/k_T) and deuterium−tritium (k_D/k_T) KIEs for the oxidation of benzyl alcohol to benzaldehyde by yeast alcohol dehydrogenase. Significant deviations from Saunders[54] semiclassical relationship, eq 7, which neglects tunneling, were

$$k_H/k_T = (k_D/k_T)^{3.26} \tag{7}$$

observed for both the primary and the secondary KIEs. Substituting the observed secondary α (k_D/k_T) of 1.03 ± 0.01 into eq 7 gives an expected semiclassical secondary α (k_H/k_T) = 1.11 ± 0.02. However, the observed secondary α (k_H/k_T) = 1.35 ± 0.04 was significantly larger than the calculated value, and Klinman's group concluded it was the result of tunneling by the transferring hydride. This tunneling affected the secondary hydrogen KIE because the motion of the transferring and nonreacting hydrogens were coupled in the reaction coordinate. Although the large secondary α-deuterium and small primary hydrogen−deuterium KIEs observed in the borohydride ion−para-substituted benzyl chloride reactions could arise because the motion of the transferring hydride is coupled to the vibrations of the benzylic hydrogens and tunneling is present, this is unlikely for a several reasons. First, it is difficult to explain the constant secondary α-deuterium KIEs in the presence of tunneling. If the $H-C_\alpha$ bond is identical in all the transition states in the reaction series, as the primary hydrogen−deuterium KIEs suggest, the contribution of tunneling must also be constant throughout the series. This is unlikely because the probability

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of tunneling should be smaller for the faster reactions because more of the molecules will have the energy to cross over the barrier rather than tunnel through it. Second, eliminating $(k_H/k_T)_\alpha$ from the semiclassical relationship proposed by Saunders,[54] and the semiclassical relationship proposed by Swain and co-workers,[55]

$$k_H/k_T = (k_H/k_D)^{1.44} \tag{8}$$

leaves a semiclassical expression,

$$k_H/k_T = (k_D/k_T)^{3.26} = (k_H/k_D)^{1.44} \tag{9}$$

relating (k_H/k_D) with (k_D/k_T)

$$k_H/k_D = (k_D/k_T)^{2.26} \tag{10}$$

Because of the larger mass of deuterium and tritium, the tunneling contribution to (k_D/k_T) is small and hence this KIE is primarily due to the semiclassical ZPE differences between the reactant and transition state. Because the semiclassical KIEs are related by reduced-mass considerations and a carbon−hydrogen bond is being formed in both systems, to a first approximation, the systems can be compared. Substituting the average secondary k_D/k_T = 1.03/α-deuterium found by Klinman's group in eq 10 gives a $k_H/k_D = 1.069/_{\alpha-D}$. Since a $k_H/k_D > 1.069$ suggests tunneling is important, the smaller $(k_H/k_D)/_{\alpha-D}$ of 1.044 found in this study suggests there is no tunneling in the borohydride ion reactions. Two other factors suggest that tunneling is not the cause of the large secondary α-deuterium KIEs observed in this system. The probability of tunneling increases as the energy of reactants and products approach one another.[56] Because the energy of the reactants in the sodium borohydride−para-substituted benzyl chloride reactions is significantly greater than the energy of the products, the probability of tunneling is small. Tunneling is also unlikely because carbon motion probably contributes to the reaction coordinate motion in these unsymmetric transition states.[57]

A possible explanation for the large, and identical, secondary α-deuterium KIEs found in these reactions is provided by the work of Westaway and co-workers[29] who suggested that, in some transition states, the magnitude of the secondary α-deuterium KIE is not determined by the Nu···LG distance[58,59] but rather by only the shortest (strongest) reacting bond in an unsymmetric S_N2 transition state. This occurs because the weakest bond to the nucleophiles in the transition state is long and any changes in this bond occur too far away from the α-carbon to affect the C_α−H(D) out-of-plane bending vibrations and, hence, the KIE. In these cases, the secondary α-deuterium KIE does not change with substituent. Thus, the primary hydrogen−deuterium KIEs, the Hammett ρ and ρ^r values, and the secondary α-deuterium KIEs all indicate the transition states for these S_N2 reactions are unsymmetric.

Of the two possible unsymmetric S_N2 transition states, Figure 4c and d, the unsymmetric transition state with a long H−C_α and a short C_α−Cl bond, Figure 4c, is unlikely for several reasons. First, the bond strength hypothesis[28] suggests that the stronger H−C_α bond will not change significantly when a substituent is changed in the substrate. This suggestion is supported by the constant primary hydrogen−deuterium KIEs. If the structure of the transition state changes with substituent, as has been observed in every system that has been examined,[29] a change in substituent must cause a change in the C_α−Cl bond. If the C_α−Cl bond were short and the H−C_α bond long in the transition state, the change in the C_α−Cl bond with substituent would cause a significant change in the secondary α-deuterium KIE. Since the secondary α-deuterium KIEs do not change with substituent, the transition state cannot have a short C_α−Cl bond. The small positive Hammett ρ value of 0.51 is also not consistent with transition state c. When bond formation lags behind bond rupture, there would be a positive charge on the α-carbon in the transition state and a small negative ρ value would be found.

The productlike S_N2 transition state d is favored for several reasons. First, the small, positive Hammett ρ value of 0.51 is consistent with the productlike S_N2 transition state d where bond making exceeds bond breaking.[45] Second, in all the reactions where it has been possible to determine the relative lengths of the two reacting bonds in an unsymmetric S_N2 transition state, the shorter bond has been the stronger of the two reacting bonds whether the substituent change is in the nucleophile, the substrate, or the leaving group in an S_N2 reaction.[2,29] Because the H−C_α bond is much stronger than the C_α−Cl bond, one would predict that the H−C_α bond will be short and the C_α−Cl bond will be long in these transition states. Also, the bond strength hypothesis[28] predicts there will be little or no change in the stronger reacting bond but a significant change in the weaker reacting bond in an S_N2 transition state with a change in substituent at the α-carbon. Since there will be little change in the shorter, stronger H−C_α reacting bond in the S_N2 transition state, the secondary α-deuterium KIE, which is determined by the short, strong (C_α−H) reacting bond in the transition state, will not change with substituent as is observed. Transition state d is also preferred because the secondary α-deuterium KIEs are all very large for S_N2 reactions with unsymmetric transition states. The secondary α-deuterium KIEs for all the other S_N2 reactions with unsymmetric transition states[2,29] have small secondary α-deuterium KIEs, i.e., close to unity. This presumably occurs because the bond to one nucleophile is short and the energy of the C_α−H(D) out-of-plane bending vibrations is not significantly different from that in the tetrahedral reactant or product. As a result, the difference in the zero-point energy between the reactant and the transition state is small and the KIE is small. This makes the large secondary α-deuterium KIEs observed in this system difficult to understand for an unsymmetric transition state where either the H−C_α or the C_α−Cl bond is short. However, it seems that large secondary α-deuterium KIEs could be found for these unsymmetric S_N2 transition states because the hydride ion is very small. Even if the H−C_α transition state bond is short, the small incoming hydride ion will be too small to affect the C_α−H(D) out-of-plane bending vibrations in the transition state significantly, Figure 5. If this is the case, the energy of the C_α−H(D) out-of plane bending vibrations in the transition state will be small, the ZPE difference between the reactant and the transition state will be large and a large KIE will be found even though the bond to the nucleophile is short in the transition state. Finally, it is important to note that if the chloride ion were close to the α-carbon in the transition state, the large chlorine would affect

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[57] Theoretical calculations by Saunders and co-workers (Table 2, ref 45) have shown that the contribution of heavy atom motion to the reaction coordinate motion is more pronounced in unsymmetric transition states. Heavy atom motion increases the effective mass of the transferring hydride ion and reduces the probability of tunnelling.

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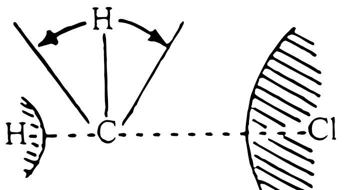

Figure 5. Transition state for the hydride ion S_N2 reactions showing that the hydride ion is too small to affect the $C_\alpha-H(D)$ out-of-plane bending vibrations significantly.

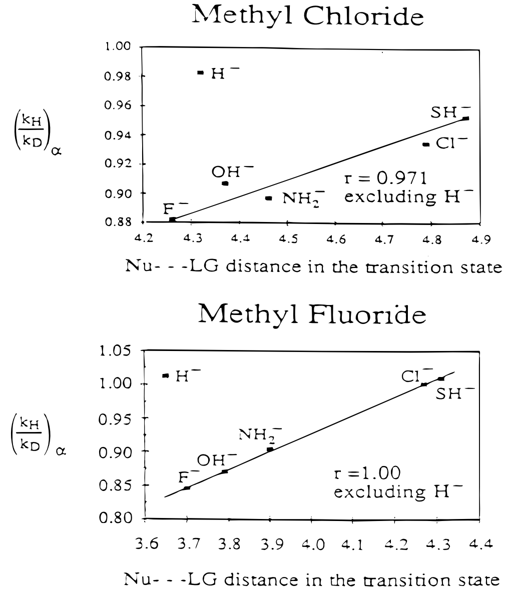

Figure 6. Secondary α-deuterium KIE as a function of nucleophile leaving group distance in the transition state for the S_N2 reactions between methyl chloride and fluoride and various nucleophiles.

the out-of-plane bending vibrations markedly and small secondary α-deuterium KIEs would be observed.

A theoretical study in which Poirier, Wang, and Westaway[58,60] calculated the transition-state structures and secondary α-deuterium KIEs for a series of S_N2 reactions between methyl chloride and fluoride and various nucleophiles at the ab initio 6-31+G* level showed that the hydride ion reactions have much larger than expected secondary α-deuterium KIEs given their Nu···LG distance in the transition state, Figure 6. For instance, the hydroxide ion and hydride ion reactions with methyl chloride have similar Nu···LG distances in the transition states, but the hydride ion reaction has a significantly larger KIE. This is because the bending contribution to the KIE (the portion of the KIE due to transition-state structure) is 15.9% larger for the hydride ion reaction than for the hydroxide ion reaction, Table 4. This presumably occurs because the hydride ion does not increase the energy of the transition-state $C_\alpha-H(D)$ out-of-plane bending vibrations as much as the larger hydroxide ion, Figure 5.[60] As a result, the total secondary α-deuterium KIE for the hydride ion reaction is much larger than expected given the Nu···LG distance in the transition state. This effect is even more dramatic in the methyl fluoride reactions. Here, the hydride ion and fluoride ion reactions have similar Nu···LG distances in the transition state. However, the bending contribution to the KIE in the hydride ion reaction is 42.0% larger than that observed for hydroxide ion reaction (the stretching components of the KIEs only differ by 3.5%). Because the small hydride ion does not affect the $C_\alpha-H(D)$ out-of-plane bending vibrations in the transition state as much as the larger fluoride ion, Figure 5, one finds a larger secondary α-deuterium KIE in hydride ion reaction even when the $H-C_\alpha$ transition-state bond is short. This means that transition state d, Figure 4, is possible whereas transition state c with a short $C_\alpha-Cl$ bond cannot display the large secondary α-deuterium KIEs that are observed.

Table 4. Comparison of the Bending and Stretching Contributions to the Secondary α-Deuterium KIE for Hydride Ion and Other Nucleophiles with a Similar Nucleophile Leaving Group Distance in the Transition State

	methyl chloride			methyl fluoride		
	OH^-	H^-	% diff	F^-	H^-	% diff
$(k_H/k_D)_{total}$	0.907	0.983	8.4	0.846	1.013	20.0
Nu···LG distance	4.37	4.32	1.1	3.69	3.65	1.1
$(k_H/k_D)_{bend}$	1.112	1.288	15.9	0.978	1.389	42.0
$(k_H/k_D)_{stretch}$	0.714	0.707	1.0	0.677	0.653	3.5

Table 5. Chlorine Leaving Group KIEs for the Sodium Borohydride S_N2 Reactions with Para-Substituted Benzyl Chlorides in DMSO at 30.000 ± 0.002 °C

para substituent	k^{35}/k^{37}		
	trial 1[a]	trial 2[a,b]	average
CH_3	1.0078 ± 0.00006[c]	1.0073 ± 0.0001[c]	1.0076 ± 0.0004[d]
H	1.0076 ± 0.0002	1.0072 ± 0.0003	1.0074 ± 0.0003
Cl	1.0082 ± 0.0014	1.0074± 0.0006	1.0078 ± 0.0006
NO_2	1.0039 ± 0.0005	1.0033 ± 0.0009	1.0036 ± 0.0004

[a] The KIE was calculated according to the formula $k^{35}/k^{37} = \ln(1 - f)/\ln(1 - (R_o/R_f)f)$, where f is the average fraction of reaction, R_o is the average $^{35}Cl/^{37}Cl$ ratio in five samples taken after the reaction reached 100% of completion, and R_f is the $^{35}Cl/^{37}Cl$ ratio in the chloride ion collected after different fractions of reaction ranging from 9 to 25% of completion.[75] [b] The isotope effects were measured by two different workers several months apart. [c] Standard deviation for the individual measurements of the KIE from five different reactions. [d] Standard deviation for the average KIE.

Chlorine Leaving Group KIEs. The best explanation of the small and constant primary hydrogen−deuterium KIEs, the small Hammett ρ and ρ^r values, and the large and constant secondary α-deuterium KIEs is that the transition states for the borohydride ion−para-substituted benzyl chloride reactions are unsymmetric with short $H-C_\alpha$ and long $C_\alpha-Cl$ bonds. In fact, the $C_\alpha-Cl$ bond must be long enough so that the changes that occur in the $C_\alpha-Cl$ bond when the substituent on the substrate is altered do not affect the $C_\alpha-H(D)$ out-of-plane bending vibrations (the magnitude of the secondary α hydrogen−deuterium KIE) significantly. Also, since the $H-C_\alpha$ bond changes very little with a change in substituent on the α-carbon, the changes in transition-state structure that occur when the substituent is changed on the α-carbon must be in the $C_\alpha-Cl$ bond. The chlorine leaving group KIEs were determined for these reactions in order to learn how the $C_\alpha-Cl$ bond changes with substituent.

With the exception of the *p*-nitrobenzyl chloride reaction, all the average chlorine KIEs found in Table 5 are large; i.e., they are ~50% of the theoretical maximum chlorine isotope effect.[61] Since the magnitude of the chlorine KIE increases with the amount of $C_\alpha-Cl$ bond rupture in the transition state,[62,63] the $C_\alpha-Cl$ bonds are long in the transition states of the *p*-methyl-,

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the *p*-hydrogen-, and the *p*-chlorobenzyl chlorides. Also, the $C_\alpha-Cl$ bond in the *p*-methyl transition state is slightly longer than the $C_\alpha-Cl$ bond in the benzyl chloride transition state. The slightly larger chlorine KIE in the *p*-chlorobenzyl chloride reaction suggests the $C_\alpha-Cl$ bond is slightly longer in this transition state although this conclusion may be the result of the larger error in this KIE. Surprisingly, the slightly larger KIE in the *p*-chlorobenzyl chloride reaction has been observed in another study[39] but no explanation has been suggested and it is not apparent why it is found.

The chlorine KIEs found by Hill and Fry for the S_N2 reactions between cyanide ion and para-substituted benzyl chlorides[38] decrease from 1.0078 to 1.0060 while those found for the same substrates in the borohydride ion reaction with the *p*-methyl-, the *p*-hydrogen-, and the *p*-chlorobenzyl chlorides range from 1.0078 to 1.0074. The transition states in the cyanide ion−para-substituted benzyl chloride system are thought to be unsymmetric with a short $NC-C_\alpha$ and a long $C_\alpha-Cl$ bond.[11] In fact, the $C_\alpha-Cl$ bonds in the cyanide ion reactions are so long that the changes in the $C_\alpha-Cl$ bond with substituent do not affect the $C_\alpha-H(D)$ out-of-plane bending vibrations in the transition state (the magnitude of the secondary α-deuterium KIEs).[11] The equally large chlorine KIEs found in the borohydride ion reactions must mean the $C_\alpha-Cl$ bond in the *p*-methyl-, *p*-hydrogen-, and *p*-chlorobenzyl chloride transition states is also too long to affect the secondary α-deuterium KIEs.[64] Thus, the chlorine KIEs for these reactions are in agreement with the interpretation based on the other KIEs.

The chlorine KIE for the *p*-nitrobenzyl chloride is only 24% of the maximum KIE so there is less $C_\alpha-Cl$ bond rupture in this transition state. It is also interesting that the secondary α-deuterium KIE found for the *p*-nitrobenzyl chloride reaction (1.085) is slightly smaller than those for the other para-substituted benzyl chloride reactions. This smaller isotope effect in the *p*-nitrobenzyl chloride reaction may have been found because the $C_\alpha-Cl$ the transition-state bond is short enough to affect the $C_\alpha-H(D)$ out-of-plane bending vibrations and reduce the magnitude of the KIE.

The large decrease in the $C_\alpha-Cl$ bond when the para substituent is changed from methyl to nitro is consistent with what had been suggested by the primary and secondary KIEs and the Hammett ρ and ρ^r values, i.e., that the transition state is unsymmetric with a short $H-C_\alpha$ bond, which remains constant for the series of para substituents, and a long $C_\alpha-Cl$ bond, which varies with a change in substituent at the α-carbon. What is surprising is that the change in the $C_\alpha-Cl$ bond with substituent is very small when the substituent changes from *p*-methyl to *p*-chloro and that there is a big change in the $C_\alpha-Cl$ bond when the substituent changes from *p*-chloro to *p*-nitro. We are unable to provide an explanation for this observation. It is worth noting that the general change in transition-state structure with substituent is consistent with the bond strength hypothesis,[28] which predicts there will be little change in the stronger $H-C_\alpha$ reacting bond and a large change in the weaker $C_\alpha-Cl$ reacting bond in the transition state when the structure of the substrate is altered.

Table 6. Predicted Changes in Transition-State Structure When a More Electron-Donating Substituent Is Added to the α-Carbon in the S_N2 Reactions between Borohydride Ion and Para-Substituted Benzyl Chlorides

theory	change in transition-state bond on adding a more electron-donating substituent to C_α: $H-C_\alpha$	$C_\alpha-Cl$
experimental results	unchanged	longer
BEP principle (Hammond)	longer	shorter
Thornton reacting bond rule[a]	longer	longer
Harris and Kurz rule[b]	longer	shorter
More O'Ferrall−Jencks method[a]	longer	longer
More O'Ferrall−Jencks method[c]	shorter	longer
Pross-Shaik method	longer	longer
bond strength hypothesis[d]	little or no change	significant change

[a] The transition state is symmetrically placed in the energy surface. [b] H is lighter than Cl and in different rows of the periodic table. [c] Productlike transition state. [d] The $H-C_\alpha$ bond strength is greater than the $C_\alpha-Cl$ bond strength.

Theoretical Models. The experimental results indicate the transition states for the borohydride ion−para-substituted benzyl chloride reactions are productlike and that adding a more electron-donating substituent to the benzene ring of the substrate leads to a transition state with a longer $C_\alpha-Cl$ bond and little or no change in the $H-C_\alpha$ bond. These results can be compared, Table 6, to the predictions based on the theoretical models that indicate how substituents change transition-state structure.

Since the rate of the reaction increases when both electron-donating and electron-withdrawing substituents are added to the α-carbon, it is not possible to apply Hammond's thermal postulate (the Bell−Evans−Polyani principle) to this system. Thornton's reacting bond rule,[69] the More O'Ferrall−Jencks energy surface method,[70,71] and the Pross and Shaik model[72] all predict that adding a more electron-donating substituent to the α-carbon will lead to a transition state with longer $H-C_\alpha$ and $C_\alpha-Cl$ bonds. Therefore, none of these models predicts the experimental results. The More O'Ferrall−Jencks energy surface method reduces to a parallel effect if the transition state is productlike. Because a more electron-donating group on the α-carbon stabilizes the higher energy reactant more than the product, the parallel effect would lead to a transition state with a shorter $H-C_\alpha$ and a longer $C_\alpha-Cl$ bond. This also is not consistent with the experimental results. Harris and Kurz[73] extended Thornton's rule to include nucleophiles in different rows of the periodic table. Because hydride and chloride are in different rows, a more electron-donating substituent on the α-carbon should lengthen the bond to the lighter nucleophile and shorten the bond to the heavier nucleophile; i.e., the transition state should have a longer $H-C_\alpha$ bond and shorter $C_\alpha-Cl$ bond when a more electron-donating substituent is present. This prediction is also not consistent with the experi-

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(64) Hill and Fry's chlorine KIEs might be smaller than expected for the amount of $C_\alpha-Cl$ bond rupture in the transition state because they were measured in 20% aqueous dioxane rather than in DMSO and hydrogen bonding to the developing chloride ion in the transition state could add vibrational energy to the chlorine and reduce the KIE.[65] If hydrogen bonding has a significant effect on the KIE, the KIE versus percent $C_\alpha-Cl$ bond rupture in the transition-state curve would have a lower slope in 20% aqueous dioxane than in DMSO. Although theoretical calculations by Brubaker[66] showed that hydrogen bonding to a developing chloride ion decreased the magnitude of a chlorine KIE, several experimental studies on S_N2 reactions suggest the chlorine KIE changes very little with even drastic changes in solvent.[67,68] Although the effect of hydrogen bonding to the developing chloride ion on the chlorine KIE is not known, it seems likely that the $C_\alpha-Cl$ bonds are long in all the transition states, except perhaps the reaction with *p*-nitrobenzyl chloride (vide infra).

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mental results. Finally, the bond strength hypothesis[28] predicts that changing the substituent on the α-carbon in this reaction would not change the stronger $H-C_\alpha$ bond but would lead to a significant change in the weaker $C_\alpha-Cl$ bond. Thus, the place where the changes in transition-state structure occur is predicted by the bond atrength hypothesis. However, this theory does not predict how the transition-state bonds will change when an electron-donating substituent is added to the α-carbon. Although the bond strength hypothesis was able to predict which transition-state bonds changed when a substituent was altered at the α-carbon, in fact, none of the theoretical models were able to predict the changes that occurred.

Conclusion

This study has shown that primary incoming nucleophile hydrogen−deuterium KIEs can be measured, that they are large with respect to the experimental error, and that they can be used to determine the changes that occur in the $H-C_\alpha$ transition-state bond when a substituent is changed on the α-carbon.

The small, and identical, incoming nucleophile hydrogen−deuterium KIEs of 1.25 found for the borohydride ion−para-substituted benzyl chloride S_N2 reactions in DMSO at 30.000 °C indicate that the hydride is unsymmetrically located between the boron and the α-carbon in the transition state and that the $H-C_\alpha$ transition-state bond does not change with substituent on the benzene ring.[74] The small Hammett ρ^r value of −0.55 indicates there is little resonance between the α-carbon and the benzene ring in the transition state while the small Hammett ρ value of 0.51 suggests there is only a small negative charge on the α-carbon in the transition state. These data suggest that the transition states for these reactions are unsymmetric. Furthermore, the small positive Hammett ρ value indicates $H-C_\alpha$ bond formation is ahead of $C_\alpha-Cl$ bond rupture, i.e., that the unsymmetric S_N2 transition states have short $H-C_\alpha$ bonds that do not change with substituent, and long $C_\alpha-Cl$ bonds. The large, and identical, $(k_H/k_D)_\alpha = 1.09$ found for these reactions are consistent with transition states with short $H-C_\alpha$ and long $C_\alpha-Cl$ bonds. The change in the long $C_\alpha-Cl$ bonds caused by a change in substituent does not affect the $C_\alpha-H(D)$ out-of-plane bending vibrations so the magnitude of the secondary α-deuterium KIE is only determined by the length of the short $H-C_\alpha$ bond rather than the $H\cdots Cl$ transition-state distance. Finally, these larger than expected secondary α-deuterium KIEs suggest that the small hydride ion does not significantly affect the $C_\alpha-H(D)$ out-of-plane bending vibrations in the transition state even though the $H-C_\alpha$ bond is short. The reasonably large (∼50% of the theoretical maximum KIE) chlorine leaving group KIEs for the *p*-methyl-, *p*-hydrogen-, and *p*-chlorobenzyl chlorides indicate the $C_\alpha-Cl$ transition-state bond is long in these transition states. The chlorine KIEs decrease when a more electron-withdrawing substituent is on the α-carbon so the $C_\alpha-Cl$ bond changes significantly when the substituent on the benzene ring is changed. Therefore, adding a more electron-withdrawing substituent to the benzene ring on the α-carbon leads to a transition state with a shorter $C_\alpha-Cl$ bond and unchanged $H-C_\alpha$ and $B-H$ bonds.

Finally, neither the Thornton's reacting bond rule, the More O'Ferrall−Jencks energy surface method, the Pross−Shaik method, or the Harris−Kurz extension of Thornton's reacting bond rule predicts the observed change in transition-state structure. The bond strength hypothesis predicts the bond that changes with substituent but does not indicate how the transition-state structure is altered.

Experimental Section

Preparation of Reagents. The DMSO used in this study was a distilled in glass grade purchased from Caledon Laboratories Ltd. However, each isotope effect measurement was done with the same batch of solvent in order to reduce the effect small differences in the water content of the solvent had on the rate constant. The sodium borohydride and sodium borodeuteride were purchased from Aldrich Chemical Co. and used with no additional purification. However, they were stored in a vacuum desiccator once they had been opened. All the para-substituted benzyl chlorides were purchased from Aldrich Chemical Co. The benzyl chloride, *p*-methylbenzyl chloride, and *p*-chlorobenzyl chloride were purified by vacuum distillation. The *p*-nitrobenzyl chloride was recrystallized once from methanol and once from *n*-hexane. The ^1H NMR (200 MHz, $CDCl_3$) spectra of the purified substrates were as expected. A subsequent NMR analysis of the distilled and recrystallized substrates indicated they were stable throughout the study.

The preparation of the para-substituted benzyl-1,1-d_2 chlorides has been reported previously.[3] The ^1H NMR (200 MHz, $CDCl_3$) spectrum of benzyl-1,1-d_2 chloride had a single absorption at a δ of 7.42 ppm. Expansion of the region between 4.00 and 5.00 ppm, had a very small peak at a δ 4.64 ppm corresponding to the benzylic protons. Analysis of the peak areas suggested that the product was 98.5% deuterated at the benzylic position. A similar analysis of the purified *p*-nitrobenzyl-1,1-d_2 chloride, the *p*-chlorobenzyl-1,1-d_2 chloride, and the *p*-methylbenzyl-1,1-d_2 chloride suggested that these substrates were 99.4, 99.6, and 99.2%, respectively, deuterated at the benzylic carbon.

Kinetic Measurements. The detailed procedure used to measure the rate constants for the primary and secondary hydrogen−deuterium KIEs and the chlorine KIEs has been reported.[75]

The primary deuterium KIEs were measured as follows. Three borohydride ion and three borodeuteride ion rate constants were measured simultaneously, averaged, and divided to obtain the hydrogen−deuterium KIE. Each KIE was determined in at least two different batches of solvent. All the second-order plots were first order in both the substrate and the nucleophile and linear up to 90% reaction with correlation coefficients of ≥0.997. An NMR analysis of the products showed that no side reactions occurred.

The secondary α-deuterium KIEs were determined from three reactions of the labeled and three reactions of the unlabeled substrate that were done simultaneously. The three rate constants for the unlabeled (k_H) and labeled (k_D) substrates were averaged and divided to obtain the secondary α-deuterium KIE. Each KIE was determined twice and all the kinetic plots were linear to at least 90% of completion and had correlation coefficients ≥0.998.

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(74) A reviewer suggested the identical *observed* KIEs (eq 4) found when borodeuteride ion was the nucleophile in these reactions did not necessarily mean that the $B-H-C_\alpha$ portion of the transition states were identical. Although the exact magnitude of the *primary* hydride ion KIE in each reaction is not known, the only way the identical *observed* KIEs found in this system could not be related to transition-state structure is if a change in transition-state structure led to an equal and opposite change in the *primary* and *secondary deuterium* KIEs, i.e., if the *secondary deuterium* KIE increased by the same amount as the *primary deuterium* KIE decreased when the structure of the transition state changed. This is unlikely because the *secondary deuterium* KIEs are significantly larger than the *primary deuterium* KIEs in these reactions. In any case, the identical *secondary α-deuterium* KIEs found for these reactions indicate that the $H-C_\alpha$ bonds, and probably the $B-H-C_\alpha$ portion of all these transition states, are identical.

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