Using Incoming Group $^{11}C/^{14}C$ Kinetic Isotope Effects To Model the Transition States for the S_N2 Reactions between *Para*-Substituted Benzyl Chlorides and Labeled Cyanide Ion

O. Matsson,*,[†] J. Persson,[†] B. S. Axelsson,[†] B. Långström,[†] Y. Fang,[‡] and K. C. Westaway*,[‡]

Contribution from the Department of Organic Chemistry, Institute of Chemistry, Uppsala University, P.O. Box 531, S-751 21, Uppsala, Sweden, and the Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Ontario, Canada P3E 2C6

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Abstract: A large incoming group $^{11}C/^{14}C$ kinetic isotope effect of 1.0104 ± 0.0023 has been measured for the S_N2 reaction between benzyl chloride and labeled cyanide ion in 20% aqueous DMSO at 30.00 °C. These large incoming group kinetic isotope effects have also been measured for the S_N2 reactions of other *para*-substituted benzyl chlorides with cyanide ion. A combination of the incoming group $^{11}C/^{14}C$ and chlorine (Hill J. W.; Fry, A., *J. Am. Chem. Soc.* **1962**, *84*, 2763) leaving group kinetic isotope effects have been used to model the S_N2 transition states for these reactions. Adding a more electron-withdrawing *para* substituent to the substrate does not affect the stronger $N{\equiv}C\text{- - -}C_\alpha$ reacting bond significantly but shortens the weaker $C_\alpha\text{- - -}Cl$ reacting bond markedly.

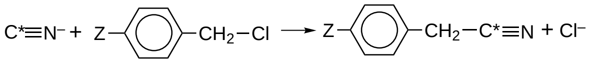
Introduction

Several workers have attempted to use incoming group kinetic isotope effects to determine the amount of nucleophile−α-carbon bond formation in the S_N2 transition state. These attempts have been largely unsuccessful, however, because these kinetic isotope effects (KIEs) were invariably very small. For example, Bourns and Hayes[1] found nitrogen incoming group kinetic isotope effects of between 0.9991 and 1.0020 ± 0.0006 in the S_N2 reactions between tertiary amines and several alkyl halides. In another study, Ando et al.[2] reported nitrogen incoming group kinetic isotope effects of 1.002−1.004 with an error in the individual isotope effects of 0.0004 in the S_N2 reactions between various substituted benzyl arenesulfonates and several *para*-substituted *N,N*-dimethylanilines in acetone at 35 °C. Kurz and co-workers also found very small nitrogen incoming group kinetic isotope effects in an extensive study of 25 S_N2 reactions between methyl and ethyl substrates and various amine nucleophiles. In spite of a wide variation in the leaving group, the nucleophile, and the solvent, the isotope effects are all very small, i.e., they were all between 1.0028 and 0.9937 with experimental errors ranging from 0.002 to 0.0002.[3] Finally, a small, but real, nitrogen kinetic isotope effect of 1.0019 ± 0.0001 in the Menshutkin reaction between methyl iodide and *N,N*-dimethyl-*p*-toluidine in methanol at 25 °C was reported by Paneth and O'Leary.[4] Two important observations are that (i) it is difficult to demonstrate that these very small incoming group isotope effects are real and (ii) the isotope effects are too small to indicate how changes in the structure of the nucleophile, the substrate, or the leaving group affect the isotope effect and transition state structure.

The results obtained by the above workers suggested that it would not be possible to use incoming group (nucleophile) kinetic isotope effects to model S_N2 transition states. However, Matsson and co-workers[5,6] recently began to use the accelerator-produced carbon-11 isotope to measure carbon-11−carbon −14 (k^{11}/k^{14}) kinetic isotope effects in organic reactions. This is an important advance because these are the largest heavy-atom isotope effects that have been measured. In fact, a $^{11}C/^{14}C$ isotope effect of 20% was found when the label was at the central carbon in the S_N2 reaction between methyl iodide and *N,N*-dimethylaniline.[6] In contrast, the largest $^{14}N/^{15}N$ nitrogen kinetic isotope effect that has been reported for an S_N2 reaction is 1.0202[7] and the maximum nitrogen isotope effect has been estimated to be only 4.4%.[8,9] As a result, it seemed possible that carbon $^{11}C/^{14}C$ incoming group kinetic isotope effects might be large enough to provide chemists with a new tool for modeling the S_N2 transition state. This paper demonstrates that carbon incoming group $^{11}C/^{14}C$ kinetic isotope effects can be measured for S_N2 reactions and that they are large enough to be useful for modeling the S_N2 transition state.

Results and Discussion

The S_N2 reactions between a series of *para*-substituted benzyl chlorides and carbon-11 and carbon-14 labeled cyanide ion, eq 1, were chosen to determine (i) whether one could measure a significant (larger than the experimental error) incoming group kinetic isotope effect and (ii) whether these isotope effects could



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* Authors to whom correspondence should be addressed.

[†] Uppsala University.

[‡] Laurentian University.

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be used to model the S_N2 transition state. These reactions were chosen because the S_N2 reaction between benzyl chloride and cyanide ion occurred at a suitable rate, i.e., where a significant percent of reaction occurred at a reasonable temperature before the radioactive carbon-11 labeled cyanide ion decayed. This is of concern because carbon-11 has a half-life of only 20.34 min.[5] These reactions were also chosen because the *para* substituent could be altered and the substituent effect on these new isotope effects could be determined.

The carbon-11 generated in a N(p,α)^{11}C reaction in the cyclotron at the PET Centre (Uppsala University, Uppsala, Sweden) was rapidly converted into hydrogen [^{11}C]cyanide in three steps. First, the carbon-11 was converted into $^{11}CO_2$ by reaction with oxygen in the cyclotron. Then, the $^{11}CO_2$ was mixed with hydrogen gas and passed through a nickel oven at 400 °C. The $^{11}CH_4$ formed in this reaction was mixed with ammonia and passed through a platinum oven at 1450 °C giving hydrogen [^{11}C]cyanide.[10,11]

Several problems were encountered when using labeled cyanide as the nucleophilic reactant: (i) the carbon-11 labeled hydrogen cyanide occasionally contained an HCN oligomer (1,3,5-triazine which formed in the aqueous hydrogen [^{11}C]cyanide solution obtained at the PET Centre and/or in the acidic solution used to purify the labeled hydrogen cyanides) and (ii) the carbon-14 labeled potassium cyanide decomposed into potassium formate on storage even in the cold in a frozen solution. These problems were overcome by purifying the labeled hydrogen cyanides. This was accomplished by adding the solution containing the labeled cyanides (potassium [^{14}C]cyanide and hydrogen [^{11}C]cyanide) to concentrated sulfuric acid at room temperature and distilling the pure carbon-11 and carbon-14 labeled hydrogen cyanide into a 20% aqueous DMSO solution containing tetraethylammonium cyanide. This procedure also ensured that the isotopically labeled cyanides entered the reaction in the same form. The reaction was done in 20% aqueous DMSO where the carbon-11 and carbon-14 labeled HCN dissociated into cyanide ions that can react with benzyl chloride.[12] (Initially, the solvent was 5% aqueous DMF. The solvent was changed however, because side products formed in an irreproducible manner and the ionization to free cyanide ion was incomplete.) The reactions were second order. The kinetic method is a one-pot technique based on LC separation of the product and reactant and subsequent radioactivity measurements using liquid scintillation counting. The reported KIE is the mean of the KIE found for each point in the kinetic run. The kinetic method including the procedure for calculating the KIE has been described earlier.[6]

The $^{11}C/^{14}C$ kinetic isotope effect for the S_N2 reaction between benzyl chloride and cyanide ion was measured in 20% aqueous DMSO at 30.00 °C (Table 1). It is important to note that the $^{11}C/^{14}C$ incoming group kinetic isotope effects obtained from an experiment where an excess of hydroxide ion had been added was identical to the isotope effect for experiments where no hydroxide was added (Table 1). This indicates that all of the hydrogen cyanide was present as cyanide ion in 20% aqueous DMSO. A second observation is that the isotope effect in Table 1 is significantly greater than the error in the isotope effect. This clearly demonstrates that one can measure real $^{11}C/^{14}C$ incoming group kinetic isotope effects in an S_N2 reaction.

Table 1. The Incoming Group $^{11}C/^{14}C$ Kinetic Isotope Effect Found for the S_N2 Reaction between Benzyl Chloride and Carbon-11 and Carbon-14 Labeled Cyanide Ions in 20% Aqueous DMSO at 30.00 °C[a]

experiment	k^{11}/k^{14} [b]
1	1.0115 ± 0.0082
2	1.0079 ± 0.0041
3	1.0142 ± 0.0042
4	1.0104 ± 0.0019
5	1.0093 ± 0.0082
6	1.0093 ± 0.0034[c]
av	1.0104 ± 0.0023

[a] The concentrations of the cyanide ion and the benzyl chloride were 0.032 and 0.10 M, respectively. [b] The error is the standard deviation for the 7 to 10 individual isotope effects obtained at various extents of reaction in a single experiment. [c] This reaction was done with an excess of hydroxide ion to ensure that all the carbon-14 and carbon-11 hydrogen cyanide in the reaction mixture existed as labeled cyanide ion.

This incoming group $^{11}C/^{14}C$ isotope effect can be examined in the light of two other carbon incoming group kinetic isotope effects that have been measured for cyanide ion S_N2 reactions. Fry[13] reported a k^{12}/k^{14} incoming group isotope effect of 1.005 ± 0.005 for the S_N2 reaction between benzyl chloride and cyanide ion in 80% aqueous ethanol at 50 °C and Lynn and Yankwich[14] found an even larger k^{12}/k^{13} incoming group isotope effect of 1.0091 ± 0.007 for the S_N2 reaction between cyanide ion and methyl iodide in water at 31.0 °C. A crude calculation based on the change in the reduced mass suggests that the $^{11}C/^{14}C$ isotope effect should be approximately 1.6 times the magnitude of a $^{12}C/^{14}C$ isotope effect[15] assuming the same reaction and transition state structure (*vide infra*). Thus, Fry's $^{12}C/^{14}C$ isotope effect found for the benzyl chloride reaction seems reasonable. However, the observed k^{11}/k^{14} of 1.0104 for the benzyl chloride−cyanide ion reaction in Table 1 is clearly not consistent with the k^{12}/k^{13} isotope effect of 1.0091 reported by Lynn and Yankwich for the methyl iodide reaction.[14] A simple calculation based on the isotope effects observed by Fry and in this study suggests the k^{12}/k^{13} isotope effect for the methyl iodide reaction should be approximately 1.003.[16] In fact, the k^{12}/k^{13} isotope effect for the methyl iodide reaction should be even smaller than 1.003 because it is expected that the methyl iodide transition state would be tighter with a shorter nucleophile-α-carbon (cyanide ion−α-carbon) bond than the benzyl chloride transition state (*vide infra*).

Another important observation is that the $^{11}C/^{14}C$ isotope effect found in the benzyl chloride−cyanide ion S_N2 reaction is large enough to suggest that these isotope effects can be used to learn how substituents on the benzene ring of the substrate affect the length of the nucleophile−α-carbon bond in the S_N2 transition state. The $^{11}C/^{14}C$ kinetic isotope effects for the S_N2 reactions between some *para*-substituted benzyl chlorides and cyanide ion in 20% aqueous DMSO at 30.00 °C (Table 2) were measured to test this hypothesis.

The magnitude of an incoming group kinetic isotope effect is determined by two factors, a temperature-independent factor ($\nu_{11}^{\ddagger}/\nu_{14}^{\ddagger}$) and a temperature-dependent factor $[1 + \sum G(u_i)\Delta u_i - \sum G(u_i^{\ddagger})\Delta u_i^{\ddagger}]$, eq 2.

$$k^{11}/k^{14} = (\nu_{11}^{\ddagger}/\nu_{14}^{\ddagger})\,[1 + \sum G(u_i)\Delta u_i - \sum G(u_i^{\ddagger})\Delta u_i^{\ddagger}] \quad (2)$$

where $G(u_i) = [1/2 - 1/u_i + 1/e^{u_i} - 1]$, $\Delta u_i = hc/kT(\Delta\nu_i)$, and $\Delta\nu_i$ is the change in the frequency of a vibration upon isotopic

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Table 2. The Carbon Incoming Group and the Chlorine Leaving Group Kinetic Isotope Effects for the S_N2 Reactions between Cyanide Ion and a Series of *Para*-Substituted Benzyl Chlorides

para substituent	$k^{11}/k^{14\ a}$	$k^{35}/k^{37\ b}$
CH_3	1.0104 ± 0.001	1.0079 ± 0.0004
H	1.0105 ± 0.002	1.0072 ± 0.0003
Cl	1.0070 ± 0.001	1.0060 ± 0.0002
NO_2		1.0057 ± 0.0002

[a] Measured at 30.00 °C in 20% (v/v) aqueous DMSO. The concentrations of the cyanide ion and the *para*-substituted benzyl chloride were 0.032 and 0.10 M, respectively. [b] Measured at 30.00 °C in 20% (v/v) aqueous dioxane.

Table 3. The Frequency of the Vibrations Used in Calculating[a] the Magnitude of the Temperature-Dependent Factor for the Carbon and Chlorine Kinetic Isotope Effects

	frequency (cm^{-1})		
bond	reactant	product	ref
$^{12}C-^{12}C_\alpha$		938^b	19
$^{12}C\equiv^{14}N^-$	2054		12
$^{12}C\equiv^{14}N$		2250	12
$^{12}C-^{35}Cl$		673	20

[a] The wavenumber for each isotopically labeled bond was calculated from the above wavenumber and the square root of the reduced masses of the labeled and unlabeled bonds. The reduced masses were calculated from the masses of the atoms in the bond. [b] The absorbance for the $^{12}C-^{12}C_\alpha$ bond in acetonitrile is at 920 cm^{-1}.[21] The absorbance chosen for the $^{12}C-^{12}C_\alpha$ bond in benzyl cyanide was 938 cm^{-1}.[19]

substitution. The temperature-independent factor is always greater than unity since the imaginary frequency is always larger for the reaction with the lighter isotope. The value of the temperature-independent factor cannot be determined. However, Melander and Saunders[17] have suggested equations that allow one to estimate this factor. Based on their equations, the temperature-independent factor for an incoming group $^{11}C/^{14}C$ isotope effect should be approximately 1.02.

The temperature-dependent factor, on the other hand, is determined by the changes that occur in the vibrational energy of the isotopically labeled atom as the reactants are converted into the S_N2 transition state. The bonding to the labeled carbon atom of the cyanide ion will be greater in the transition state than in the reactants because the cyanide carbon (nucleophile−α-carbon) bond is forming in the S_N2 transition state. As a result, the vibrational energy of the labeled carbon will be greater in the transition state and the temperature-dependent factor, eq 2, will be less than one. The magnitude of the temperature-dependent factor also depends on transition state structure. Since the vibrational energy of the labeled carbon increases with increasing nucleophile−α-carbon bond formation in the S_N2 transition state, the magnitude of the temperature-dependent factor decreases as the nucleophile−α-carbon bond formation becomes more complete in the S_N2 transition state. This means the kinetic isotope effect, which is the product of the temperature-independent and the temperature-dependent factor, will be less than the magnitude of the temperature-independent factor, i.e., <1.02. (The magnitude of the temperature-independent factor varies with the structure of the transition state. However, preliminary BEBOVIB-IV calculations (*vide infra*) suggest that the change in the magnitude of the temperature-independent factor is small with respect to the change in transition state structure (the temperature-dependent factor), e.g., the calculations suggest that the maximum change in the temperature-independent factor is only 2.6% when the $N\equiv C$- - -C_α bond order is changed from 0.1 to 0.99. The temperature-dependent factor changes by 16% for the same change in bond order.) In fact, a simple calculation using the observed vibrational frequencies, Table 3, for the reactant (the cyanide ion)[12] and the product (benzyl cyanide)[12] and assuming complete cyanide ion−α-carbon bond formation in the transition state shows that the minimum value for the temperature-dependent factor is 0.85. This implies that the observed kinetic isotope effect should be between 1.02 and 0.87. The actual value will, of course, be determined by the amount of nucleophile−α-carbon bonding in the S_N2 transition state.

An examination of the incoming group $^{11}C/^{14}C$ kinetic isotope effects in Table 2 suggests that there is no change in the length of the nucleophile−α-carbon bond in the S_N2 transition state when the *para* substituent is methyl or hydrogen but that the nucleophile−α-carbon bond formation is more complete (the C- - -C_α bond is shorter) when the *para* substituent on the benzene ring is chlorine. However, the very small change in the magnitude of these incoming group $^{11}C/^{14}C$ kinetic isotope effects relative to the maximum possible change in the temperature-dependent factor of the KIE equation, i.e., the isotope effect only changes by 0.0035 in a possible range of 0.15, suggests that there is little or no change in the nucleophile−α-carbon bond in these S_N2 transition states when the *para* substituent on the benzene ring is altered.

While the $^{11}C/^{14}C$ kinetic isotope effects suggest there is little or no change in the nucleophile−α-carbon bond when the *para* substituent on the benzene ring is altered, it would be desirable to be able to model the changes in these S_N2 transition states more completely. This is possible because Hill and Fry[18] have measured the chlorine leaving group ($^{35}Cl/^{37}Cl$) kinetic isotope effects for the same S_N2 reactions in 20% aqueous dioxane at 30.00 °C. Although the $^{35}Cl/^{37}Cl$ and the $^{11}C/^{14}C$ kinetic isotope effects have been measured in slightly different solvents, 20% aqueous dioxane and 20% aqueous DMSO, respectively, it is reasonable to assume that the changes (trend) in the chlorine kinetic isotope effects with substituent in 20% aqueous DMSO would be similar to those found in 20% aqueous dioxane. This is because the two solvents have a similar amount of water, i.e., they are both 11.11 M in water, and have almost identical mole fractions of water, i.e., the mole fraction of water in the 20% aqueous dioxane is 0.50 whereas that in 20% aqueous DMSO is 0.49. If this assumption is valid, the $^{35}Cl/^{37}Cl$ isotope effects in Table 2 can be used to indicate how the α-carbon−leaving group (the C_α- - -Cl) transition state bond varies when the *para* substituent is altered in these S_N2 reactions.

The chlorine leaving group kinetic isotope effects (Table 2) decrease when a more electron-withdrawing substituent is added to the benzene ring of the substrate. This clearly demonstrates that the α-carbon−leaving group transition state bond becomes shorter as a more electron-withdrawing substituent is added to the benzene ring of the substrate.

The transition states for these reactions can be modeled in even more detail. The relative change in the length of the $N\equiv C$- - -C_α and the C_α- - -Cl bonds with substituent can be estimated in two ways. One approach is to compare the observed change in the isotope effect with the maximum change expected in the temperature-dependent factor. This comparison assumes that the change in the temperature-independent factor is small with respect to the change in the vibrational energy (the temperature-dependent factor). This method of estimating the relative change in the $N\equiv C$- - -C_α and the C_α- - -Cl transition state bonds is attractive because the magnitude of the temperature-dependent factors can be estimated from published

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frequencies for the bonds involved in determining the isotope effect (Table 3).

The change in the chlorine isotope effects with *para* substituent is large. In fact, the change in the isotope effect from the *p*-methyl to the *p*-chlorobenzyl chloride is 0.0019. However, when this change in isotope effect is compared to the estimated maximum change in the temperature-dependent factor for the chlorine isotope effect of 0.0111, the change in the chlorine isotope effect (the length of the α-carbon−chlorine transition state bond) is significant, i.e., it is 17.1% of the estimated maximum value. In comparison, the change in the incoming group carbon isotope effects is only 0.0035 or only 2.36% of the estimated maximum change of 0.148. Thus, the change in the chlorine isotope effect is 7.2 times greater than the change in the carbon isotope effect when the *para* substituent is changed from methyl to chloro in the cyanide ion−*para*-substituted benzyl chloride reactions. This approach suggests that adding an electron-withdrawing substituent to the *para* position of the benzene ring of the substrate causes little or no change in the nucleophile−α-carbon transition state bond but a significant shortening of the α-carbon−leaving group bond.

A second method of estimating the relative change in the length of the N≡C- - -C_α and the C_α- - -Cl bonds in the transition state when a more electron-withdrawing substituent is added to the benzene ring of the substrate is to compare the observed changes in the isotope effects with the maximum changes in the isotope effects suggested by BEBOVIB-IV calculations. The BEBOVIB-IV calculations were based on the model and parameters used by Sims and Brubaker[22,23] for the S_N2 reaction between benzyl chloride and cyanide ion and assumed conservation of the total bond order. The BEBOVIB-IV calculations predicted that the $^{11}C/^{14}C$ incoming group kinetic isotope effect changes from 1.0558 to 0.8476 when the N≡C- - -C_α bond order changes from 0.01 to 0.90. This means the change in the $^{11}C/^{14}C$ incoming group kinetic isotope effect is (0.0035/0.2082)·100% or 1.68% of the theoretical (BEBOVIB-IV) maximum isotope effect. The chlorine leaving group kinetic isotope effect, on the other hand, changes from 1.000 to 1.0226 when the C_α- - -Cl bond order changes from 0.99 to 0.10. Therefore, the change in the $^{35}Cl/^{37}Cl$ leaving group kinetic isotope effect is (0.0019/0.0226)·100% or 8.41% of the theoretical (BEBOVIB-IV) maximum isotope effect. Thus, this method predicts that the change in the chlorine isotope effect is 5.0 times greater than the change in the carbon isotope effect when the *para* substituent is changed from methyl to chloro in the cyanide ion *para*-substituted benzyl chloride reactions. (The model for the transition state in these calculations does not have any hydrogen bonds between water molecules in the solvent and the developing chloride ion. Hydrogen bonding to the developing chloride ion in the transition state reduces the magnitude of the chlorine isotope effect. Including hydrogen bonding to the developing chloride ion would mean the change of 0.0019 observed in the chlorine isotope effect would be a greater percent of the BEBOVIB-IV maximum isotope effect. This would increase the change in the C_α- - -Cl bond relative to that in the N≡C- - -C_α bond.) The agreement between the two methods (6 ± 1) is satisfactory given the approximations in each method, and it seems safe to conclude that adding an electron-withdrawing substituent to the *para* position of the benzene ring of the substrate causes little or no change in the nucleophile−α-carbon (the N≡C- - -C_α) transition state bond but a significant shortening of the α-carbon−leaving group (the C_α- - -Cl) bond.

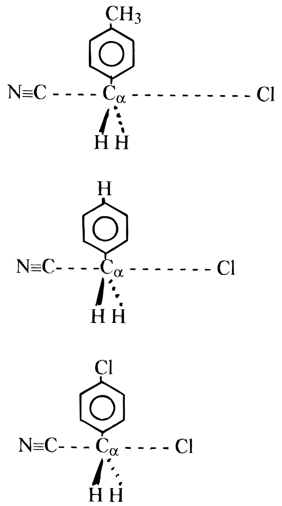

Figure 1. The relative structures for the S_N2 transition states for the reactions of *para*-substituted benzyl chlorides with cyanide ion.

Table 4. The α-Carbon k^{12}/k^{14} Kinetic Isotope Effects for the S_N2 Reactions between a Series of *Para*-Substituted Benzyl Chlorides and Cyanide Ion in 20% Aqueous Dioxane at 40 °C

para substituent	k^{12}/k^{14} [a]
CH_3	1.090
H	1.102
Cl	1.106

[a] No errors were given for these isotope effects.

This conclusion is interesting because it can be used to test the "Bond Strength Hypothesis"[24] which states that "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 substitutent in the nucleophile, the substrate, or the leaving group is altered in an S_N2 reaction". Since the carbon−chlorine bond is much weaker than the carbon−carbon bond in these S_N2 reactions, the Bond Strength Hypothesis would predict that adding an electron-withdrawing group to the substrate should not affect the nucleophile−α-carbon bond significantly, but should cause significant changes in the α-carbon−leaving group bond (Figure 1). It is interesting that these are the exact changes suggested on the basis of the isotope effects in Table 2.

Finally, Pearson and Fry[25] measured the $^{12}C/^{14}C$ α-carbon kinetic isotope effects (Table 4) for the S_N2 reactions between cyanide ion and three *para*-substituted benzyl chlorides in 20% aqueous dioxane, the solvent that was used to measure the chlorine isotope effects for these reactions. If it is assumed that these isotope effects measured in 20% aqueous dioxane would be similar to those found in the 20% aqueous DMSO used in this study (*vide supra*), the $^{12}C/^{14}C$ isotope effects can be used to shed more light on the structure of the transition states for these reactions. The first observation is that the α-carbon C^{12}/C^{14} isotope effect increases as a more electron-withdrawing group is added to the benzene ring on the α-carbon. Since the maximum α-carbon kinetic isotope effect is observed when the S_N2 transition state is symmetrical, i.e., when the α-carbon is bonded with equal strength to the nucleophile and the leaving group in the transition state,[26,27] the transition state

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for the *p*-chlorobenzyl chloride reaction is the most symmetrical. Although the α-carbon kinetic isotope effect found for the *p*-chlorobenzyl chloride reaction is near the maximum expected for these isotope effects, one does not know that the *p*-chlorobenzyl chloride transition state is symmetrical but only that it is the most symmetrical of all the transition states and that the benzyl chloride and *p*-methylbenzyl chloride transition states are more unsymmetrical. The chlorine (leaving group) kinetic isotope effects indicate that the C_α- - -Cl transition state bond length decreases when a more electron-withdrawing substituent is present in the substrate. The incoming group carbon isotope effects, on the other hand, suggest there is only a very small decrease in the length of the N≡C- - -C_α bond when a more electron-withdrawing substituent is on the substrate. Since adding a more electron-withdrawing substituent does not change the nucleophile−α-carbon bond significantly but leads to a shorter α-carbon−leaving group transition state bond, adding a more electron-withdrawing substituent must lead to a more reactant-like transition state. Unfortunately, the only way a more symmetrical transition state can be achieved by adding a more electron-withdrawing substituent is if the transition states are product-like. If the transition states were product-like with short N≡C- - -C_α and long C_α- - -Cl bonds, shortening the C_α- - -Cl bond by adding a more electron-withdrawing substitutent would make the C_α- - -Cl bond more equal in strength to the short N≡C- - -C_α transition state bond (Figure 1). However, a product-like transition state is not consistent with the large incoming group carbon isotope effects found in this system. The answer to this dilemma clearly awaits further results.

Experimental Section

Reagents. The *para*-substituted benzyl chlorides (Aldrich) were purified by treatment with sodium bisulfite,[28] dried, and fractionally distilled under reduced pressure. The anhydrous dimethyl sulfoxide (DMSO) (99.8%, Aldrich, Sure/Seal) and tetraethylammonium cyanide (TEACN) (Aldrich) were used without further purification. Once opened, the TEACN was stored in a vacuum desiccator. Both ^{1}H- and ^{13}C-NMR spectrometry indicated all the reagents were pure.

The ^{11}C-labeled cyanide was produced at the Uppsala University PET Centre in the Scanditronix MC-17 cyclotron by the ^{14}N(p,α)^{11}C nuclear reaction. The ^{11}C-labeled carbon dioxide produced in the cyclotron target cell was converted into ^{11}C-labeled hydrogen cyanide in an on-line gas-processing synthesis.[10,11] The hydrogen [^{11}C]cyanide was trapped in 1 mL of water in a vial and transported in a lead container to the laboratory. The ^{11}C radioactivity of the hydrogen cyanide solution was usually between 1 and 3 GBq. All the operations with the ^{11}C-labeled hydrogen cyanide were done behind 5 cm thick lead shields in a fumehood. The potassium [^{14}C]cyanide, 37 MBq, 1.85−2.0 GBq/mmol (Amersham) was dissolved in 10 mL of distilled water and stored in a refrigerator. Both the labeled cyanides were purified prior to use (*vide infra*).

The LC-MS analyses were performed on a Fisons Instruments VG Platform which used negative electrospray ionization.

Kinetic Procedure. One microliter of the K[^{14}C]N solution and 1 mL of concentrated sulfuric acid were added to the aqueous hydrogen [^{11}C]cyanide solution produced at the PET Centre and the ^{11}C- and ^{14}C-labeled hydrogen cyanide was distilled in a stream of nitrogen gas at room temperature through a Teflon tube to a vial containing 7 ± 0.5 mg (0.045 mmol) of TEACN in 1.8 mL of a 20/80 (v/v %) distilled water−DMSO mixture. The labeled TEACN solution was thermostated in a constant temperature bath maintained at 30.00 ± 0.05 °C with a HETO proportional regulating thermostat. A vial containing 10 ± 0.5 mg (60−80 mmol) of the appropriate benzyl chloride was dissolved in 100 μL of the solvent and thermostated. Then, 800 μL of the TEACN solution was added to the benzyl chloride solution with a thermostated syringe and the reaction clock was started. The vial was vigorously shaken for a couple of seconds and replaced in the thermostated bath. At various times the reaction vial was removed from the bath, 10 μL was injected onto the HPLC column (*vide infra*) by the HPLC injector, the vial was quickly returned to the bath, and the injection time was recorded.

The labeled unreacted cyanide ion and *para*-substituted benzyl cyanide were separated on a Hewlett Packard 1084 HPLC instrument with a β^+-flow detector in series with the variable-wavelength UV detector of the instrument and a Hewlett Packard 79825A fraction collector with the Teflon insert removed. The wavelength of the UV detector was set at 254 nm with 430 nm as the reference. A reversed phase end-capped C-18 column (Supelco ODS-1, 200 × 4.6 mm, 5 μm) was used with an isocratic flow of 2.00 mL/min. The mobile phase was 50 mM ammonium formate, pH 3.5, in 40/60 (v/v %) methanol−water. The HPLC-grade methanol was purchased from FSA. The time intervals for collecting the labeled reactant and product were programmed and controlled by the microprocessor of the instrument. Each fraction was collected for 2.00 min in a 20 mL plastic scintillation bottle containing 14 mL of Zinsser Quickscint 1 scintillation liquid. The radioactivity was measured by either a Beckman LS 6000LL or a LKB 1214 liquid scintillation counter with the energy windows set to 1−2000 keV.

The total radioactivity of each fraction was measured immediately. At least 10 h later, usually the next day, after all the ^{11}C had disintegrated, the ^{14}C radioactivity in each fraction was measured. The counting times for the ^{11}C and ^{14}C analyses were 1 min and between 10 and 60 min, respectively. The ^{11}C-radioactivity *Z* in counts per minute (CPM) was calculated by eq 3

$$Z = X - (Y_{\mathrm{corr}} + B) \tag{3}$$

where *X* is the total (^{11}C + ^{14}C) radioactivity in CPM, Y_{corr} is the corrected ^{14}C value in CPM, and *B* is the background value in CPM (measured for the position in the scintillation counter next to each fraction) when the total radioactivity was measured. The corrected ^{14}C value, eq 4, is

$$Y_{\mathrm{corr}} = Y - B_{14} \tag{4}$$

where *Y* is the observed ^{14}C value in CPM and B_{14} is the background value in CPM found in the ^{14}C measurement. The ^{11}C-radioactivity *Z* was corrected for the loss of ^{11}C that occurred during the ^{11}C measurement. The half-life corrections for the ^{11}C values were obtained from eq 5,

$$Z_{\mathrm{corr}} = Z/(0.5^{\{t/t_{1/2}\}}) \tag{5}$$

where $t_{1/2}$ is the half-life of ^{11}C (1220 s) and *t* is the elapsed time counted from the start of the radioactivity measurement of the first fraction. For each sample ("point") from the kinetic run, the fraction of reaction, *f*, was calculated for the ^{11}C and ^{14}C reactions, respectively, eq 6,

$$f = P/(P + R) \tag{6}$$

where *P* and *R* are the corrected CPM values (Z_{corr} or Y_{corr}) for the product and reactant fractions, respectively. Finally, the KIE for each point was calculated using

$$k^{11}/k^{14} = {}^{11}(Q_i - Q_0)/{}^{14}(Q_i - Q_0) \tag{7}$$

where $Q_i = \ln(1 - f)$ for the ^{11}C and ^{14}C reactions, respectively, and Q_0 is a correction for minor amounts of radioactive impurities in the "product fraction" at 0% conversion, *i.e.*, for a sample with no substrate added to the cyanide solution.

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