

APPLICATION OF THE SUCCESSIVE LABELLING TECHNIQUE TO SOME CARBON, NITROGEN AND CHLORINE ISOTOPE EFFECT STUDIES OF ORGANIC REACTION MECHANISMS

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INTRODUCTION

The use of kinetic isotope effects in interpretation of organic reaction mechanisms has undergone a remarkable development in the past few years. The exploitation of deuterium and tritium primary¹ and secondary² isotope effects has been particularly fruitful in this regard. Although a considerable amount of research has been reported in which studies on kinetic isotope effects of elements other than hydrogen have been interpreted in terms of reaction mechanisms, a great deal of the work on these "heavy element" isotope effects has been directed primarily towards the basic physical chemical interpretations of the effects themselves in terms of fundamental theory. Of course, it is necessary to have some understanding of this fundamental theory in order to make proper interpretations of kinetic isotope effects in terms of reaction mechanisms, but the basic theory has been available for many years^{3, 4}, and is easy to apply in qualitative and semi-quantitative form to reaction mechanism studies.

Fundamentally, the theory is an outgrowth of absolute reaction rate theory where the rate of the reaction is proportional to the equilibrium constant relating the concentrations of reactants and activated complex. These equilibrium concentrations of reactants and activated complex are expressed in terms of their respective partition functions. The partition functions are then evaluated in terms of molecular weights, moments of inertia and vibrational frequencies for the reactants and activated complex⁴; or, by application of the Teller and Redlich product rule, in terms of vibrational frequencies for the reactants and activated complex³. These vibrational frequencies are dependent on the masses of the atoms involved in the vibration, and, in general, if substitution of an isotopic atom is made, the vibrational frequency will change[†]. If there are differences in number or magnitude of the isotope-dependent frequencies between reactants and activated complex, the rates of reaction for the labelled and unlabelled molecules will be different.

For the present purpose, it is convenient to discuss this matter further in terms of Bigeleisen's formulation³, omitting the symmetry numbers (thinking

† For instance, for pseudo diatomic ¹²C-¹²C and ¹²C-¹⁴C molecules, the ratio of vibrational frequencies, ν_{12}/ν_{14} , as given for a harmonic oscillator, $\nu = \frac{1}{2}\pi\sqrt{k/\mu}$, (assuming the force constant is invariant upon isotopic substitution) is $\nu_{12}/\nu_{14} = \sqrt{(\mu_{14}/\mu_{12})} = 1.038$.

of effects "per position") and assuming the transmission coefficients to be the same for labelled and unlabelled molecules:

$$k_1/k_2 = (\nu_{1L}^\ddagger/\nu_{2L}^\ddagger) [1 + \sum_i^{3n-6} G(u_i) \Delta u_i - \sum_i^{3n'-7} G(u_i^\ddagger) \Delta u_i^\ddagger]$$

The symbols are as defined by Bigeleisen³. The function $G(u)$ has been tabulated by Bigeleisen and Mayer⁵. The isotopic rate constants k_1 and k_2 refer to the molecules containing the light and heavy isotopes, respectively. The $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ term represents the light-to-heavy isotope ratio for the imaginary frequency (decomposition mode) of the vibration along the reaction coordinate in the activated complex. The term is always greater than unity whether bond rupture[†] or bond formation⁶ is involved. Various methods have been used for evaluation of this term^{3, 4}, and, in particular, an expression has been derived for it for three-centre reactions⁷. The expression in the square brackets arises from the evaluation of the partition functions (mainly zero point energy terms) for the reactants (first summation term) and activated complex (second summation term) in terms of the vibrational frequencies, u_i and u_i^\ddagger and the frequency shifts upon isotopic substitution, Δu_i and Δu_i^\ddagger . The Δu 's are taken so as to be always positive (except for intramolecular isotope effects). Thus, for every isotope-dependent frequency in the reactants, a positive term from the first summation will be added to unity, and for every isotope-dependent frequency in the activated complex a positive term from the second summation will be subtracted[§].

If these isotope-dependent vibrations primarily involve parts of the molecule where the bonding is unaltered between reactants and activated complex, the terms from the two summations will cancel ($\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ will also be unity), and there will be no isotope effect. However, if there is an alteration of the bonding at the isotopically labelled position upon going from reactants to activated complex, the terms will not cancel, and there will be an isotope effect. By a simple reversal of the argument in these last two sentences, it is clear that one can tell whether or not the bonding at a particular atomic position is altered in going from reactants to activated complex by measuring *whether or not* there is a kinetic isotope effect for the molecule labelled at that atomic position. *As an extension of this concept, by measuring whether or not kinetic isotope effects are observed for the molecule successively labelled at different atomic positions, all of the atomic positions at which bonding changes take place in going from reactants to activated complex can be identified.* This is the most basic information needed in describing the activated

† For simple bond rupture of the pseudo-diatomic $^{12}\text{C}-^{12}\text{C}$ and $^{12}\text{C}-^{14}\text{C}$ molecules, this ratio is usually taken as 1.038, the square root of the inverse ratio of reduced masses.

§ For simple bond rupture of the pseudo-diatomic $^{12}\text{C}-^{12}\text{C}$ and $^{12}\text{C}-^{14}\text{C}$ molecules, one vibration is involved in the reactants, for which $G(u)\Delta u = 0.0532$ (at 300°K, assuming $\nu_{12} = 1000 \text{ cm}^{-1}$ and $\nu_{12}/\nu_{14} = 1.038$ so that $\Delta\nu = 37 \text{ cm}^{-1}$). No vibration is involved in the activated complex. Thus, $k_1/k_2 = 1.038 (1 + 0.0532 - 0) = 1.0932$. As an alternate approach, involving additional approximations, one could assume that the only difference in energy required to break the bonds in the pseudo-diatomic $^{12}\text{C}-^{12}\text{C}$ and $^{12}\text{C}-^{14}\text{C}$ molecules is the difference in zero point energy, $\Delta(\frac{1}{2}h\nu)$. Assuming $\nu_{12} = 1000 \text{ cm}^{-1}$ and $\nu_{12}/\nu_{14} = 1.038$, the difference in zero point energy (at 300°K) is 52.8 cal/mole. This corresponds to a rate constant ratio of $k_{12}/k_{14} = 1.0926$.

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complex and in elucidating the mechanism of the reaction. Note that the *qualitative information*, "whether or not" an isotope effect is observed, *is all that is essential* (however, care must be exercised because of the possibility of accidental cancelling of opposing factors—see the next paragraph). Additional, extremely valuable mechanistic information can be gained by relating the magnitudes of the measured isotope effects to theory, and ideally, an exact description of the vibrational frequencies (and hence, bonding) of the reactants and activated complex will lead to exact agreement between theory and experiment. Unfortunately, detailed experimental (or calculated) vibrational frequencies and frequency shifts are lacking in most cases for the reactants and in all cases for the activated complexes in most systems of interest to organic chemists. Resort to various model systems permits considerable advance toward the ideal, but for isotope effects of all elements but hydrogen, many of the subtle differences in bonding between related models give predicted isotope effect differences which are within the experimental error limits. This makes the successive labelling qualitative approach mentioned above all the more significant.

Amplifying and extending the above discussion, further consideration of the Bigeleisen equation makes it clear that if there is less bonding (fewer vibrations or lower frequency vibrations) in the activated complex than in the reactants, the second summation will be smaller than the first, and the term in square brackets will be greater than one ("bond rupture case"). Correspondingly, if there is more bonding (more vibrations or higher frequency vibrations) in the activated complex than in the reactants, the terms in square brackets will be less than one ("bond formation case"). In both cases, the $\nu_{1L}^{\ddagger}/\nu_{2L}^{\ddagger}$ term will be greater than one⁶, and it is seen that the product of the two terms for "bond rupture cases" will always be greater than unity. This product for "bond rupture cases" generally will be greater than for "bond formation cases" (involving the same isotopes), for which the product could be greater than one (the usual case), exactly one (accidental cancelling of opposing effects) or less than one, depending on the particular values involved. It is to be noted that the bonding changes from which secondary isotope effects arise are specifically included in the above considerations, but again, except for the isotopes of hydrogen, most secondary isotope effects fall within the experimental error range.

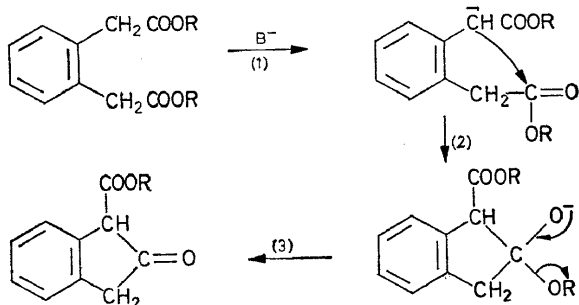
A number of our applications of this successive labelling technique to isotope effect studies of reaction mechanisms are discussed below.

THE DIECKMANN CONDENSATION⁸

The Dieckmann Condensation involves the base-catalysed internal cyclization of a dicarboxylic acid ester to a β -ketoester. The generally accepted mechanism for the reaction as applied to diethyl phenylenediacetate, the compound used in this study, is as shown at the top of page 412. Any one of the three steps might be rate determining.

Isotope effects were measured with the compound successively labelled with carbon-14, first at the methylene carbon, and second, at the carbonyl carbon. If step (1) were rate controlling, the activated complex would involve bonding changes at the methylene carbon, but not (to any large

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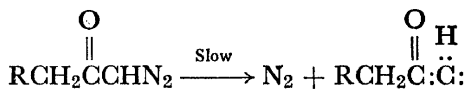


extent, at least) at the carbonyl carbon, so an isotope effect would be expected with the methylene labelled compound, but not with the carbonyl labelled compound. If step (2) were rate controlling, the activated complex clearly involves bonding changes at both the methylene and carbonyl carbons, so isotope effects would be expected for both labelled compounds. If step (3) were rate controlling, the activated complex does not involve bonding changes at the methylene carbon, but does involve them at the carbonyl carbon, so an isotope effect would be expected for the latter compound, but not with the former.

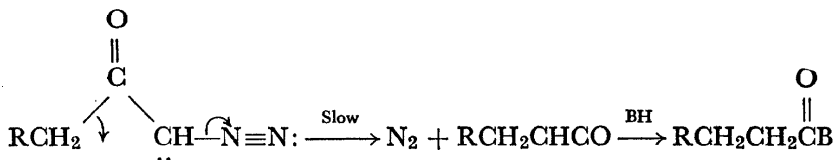
Experimentally, k_{12}/k_{14} for the methylene-labelled compound is 1.089 ± 0.014 , and for the carbonyl-labelled compound, 1.084 ± 0.004 (intermolecular isotope effects). Clearly, step (2), the formation of the new carbon-carbon bond is rate determining.

THE WOLFF REARRANGEMENT⁹

In the Wolff rearrangement, a diazomethyl ketone loses nitrogen and rearranges to a ketene, which reacts with an active hydrogen compound to give an acid derivative. It has been proposed that loss of nitrogen leads to an "open sextet" reactive intermediate, which rearranges in a subsequent fast step. Alternatively, the loss of nitrogen and the rearrangement might be concerted.



Reactive intermediate mechanism



Concerted mechanism

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In the fast reaction of a reactive intermediate, isotope effects are bound to occur. However, these effects will ordinarily not be experimentally observable. By its very nature a reactive intermediate cannot be isolated after it has only partially reacted, and so before any measurements can be made, the reaction (destruction of the intermediate) will have gone to completion, and the isotopic composition of the product measured will be the same as that of the reactive intermediate. Thus, no isotope effect will be observed in the decomposition of the intermediate.

Clearly, then, for the reactive intermediate mechanism, bonding changes in going to the activated complex are involved at the nitrogen, the CH carbon, and possibly at the carbonyl carbon (considering resonance structures) but not at the methylene carbon. Thus, isotope effects would be expected for the compound labelled at nitrogen, at the CH carbon, possibly at the carbonyl carbon, but not at the methylene carbon. For the concerted mechanism, bonding changes at all of the above positions are involved in going to the activated complex, so isotope effects would be expected for the compound labelled at each of the above positions.

1-(1-Naphthyl)-3-diazo-2-propanone, successively labelled with carbon-14 as indicated above (natural abundance material was used for the nitrogen isotope effect measurements) was decomposed in hot aniline to form 3-(1-naphthyl)-propionanilide, and the isotope effects were measured. The results are summarized as follows:

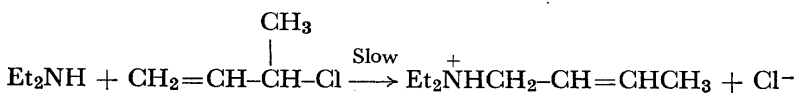
$$\alpha\text{-C}_{10}\text{H}_7\text{-CH}_2\text{-}\overset{\text{O}}{\parallel}\text{C}\text{-}\overset{\text{H}}{\text{C}} = \overset{+}{\text{N}} = \overset{-}{\text{N}}$$

Isotope	¹⁴ C	¹⁴ C	¹⁴ C	¹⁵ N
% Isotope effect	1.5	0.3	8.0	3.8
Estimated error	0.5	0.5	0.5	0.1

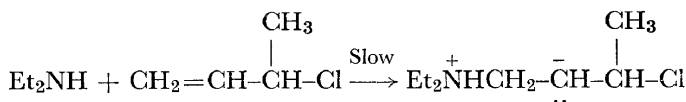
The results are consistent with the predictions for the concerted mechanism, but not with those for the reactive intermediate mechanism, particularly in that an isotope effect was found for the methylene carbon-14 labelled compound. It appears that a reactive intermediate is not involved in the Wolff rearrangement of this compound, but rather that the reaction is concerted. Similar studies are currently being made on the Curtius, Hofmann and Lossen reactions.

THE S_N2' REACTION¹⁰

The S_N2' reaction between diethyl amine and 3-chloro-1-butene offers a particularly good opportunity to test the principles involved in the successive labelling isotope effect technique of establishing which atomic positions undergo bonding changes in going from reactants to activated complex, because bonding changes at so many positions are involved:



According to the proposed mechanism for the reaction¹¹, the nitrogen-carbon bond formation, the double bond shift and the elimination of the chloride ion are all concerted. If this is so, isotope effects should be obtained for nitrogen labelling, for successive carbon labelling at the 1, 2 and 3 positions, and for chlorine labelling. A carbanion (reactive intermediate) mechanism would lead to the prediction of no isotope effects for the carbon-14 3-labelled compound or for chlorine labelling.



The nitrogen isotope effect has not been measured (almost certainly there would be one). For carbon-14 labelling at the 1, 2 and 3 positions, the isotope effects were measured as $k_{12}/k_{14} = 1.057 \pm 0.007$, 1.074 ± 0.003 and 1.079 ± 0.003 , respectively. The chlorine isotope effect (natural abundance), was $k_{35}/k_{37} = 1.0112 \pm 0.0006$ (a large effect for chlorine). Bonding changes at all positions in going to the activated complex are clearly involved. Thus, the proposed concerted mechanism is confirmed, as is the principle of using the successive labelling technique to reach such conclusions.

DISPLACEMENT REACTIONS IN THE BENZYL SYSTEM

Nucleophilic displacement reactions generally have been discussed in terms of two step (ionization) mechanisms, (S_N1), and one step (concerted) mechanisms (S_N2), together with various combinations of the two, or mechanisms of intermediate nature between the two extremes¹². The bonding changes in going from reactants to activated complex are clearly different for the different mechanisms, so isotope effect measurements, especially successive labelling isotope effect experiments, would be expected to furnish valuable insight into the mechanistic problem. In addition to our work mentioned below, a number of other "heavy element" isotope effect studies involving nucleophilic displacement reactions[†] have been carried out¹³. The emphasis in much of this work was not on the mechanisms of the reactions, and in other work, the systems used for reactions by different mechanisms differ so greatly that meaningful comparisons are difficult to achieve.

The reactions of benzyl halides fall into the borderline region in nucleophilic displacements, and the mechanism can be shifted toward S_N1 or S_N2 by introducing appropriate substituents into the benzene ring. The steric environment of the central atom in the displacement reaction is kept constant, while the electrical environment can be changed drastically by changing the substituent. Our displacement reaction isotope effect research involves this system.

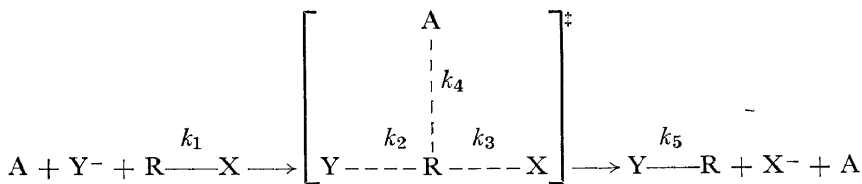
The symbolic model

For purposes of qualitative discussion, it is convenient to set up the

[†] Much deuterium secondary isotope effect work also bears on this problem².

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displacement reaction in general symbolic terms, utilizing a model adapted from that of Doering and Zeiss¹⁴. For the charge type $Y^- + RX \rightarrow RY + X^-$ (other charge types would have analogous developments) we have:



Motion of R from X to Y is motion along the reaction coordinate (assumed to be linear), and k_1 , k_2 , k_3 and k_5 are symbolic stretching force constants involving X, R and Y. The A---R interaction represents, in symbolic form, all other bonding changes at R in going from reactants to activated complex. Specifically included are changes in resonance stabilization and solvation. The force constant, k_4 , is meant to summarize these effects in one term for purposes of discussion[†]. To make the problem tractable, we discuss the A---R interactions independently of the YRX system, although this is obviously a great oversimplification. Specific consideration of bending motions is omitted in this first treatment, but the extension to include them is easily envisioned.

When k_2 and k_3 are large, the activated complex is of the S_N2 type; when k_2 and k_3 are very small, it is of the S_N1 type. Other combinations of values for k_2 and k_3 permit representation of all intermediate situations. For an S_N2 mechanism, k_4 is small (the A---R interactions are small); for an S_N1 mechanism, k_4 is large (ionization unassisted by increased bonding, as by solvation and resonance stabilization, would require more energy than reaction by the S_N2 path).

The R-X bond in the reactants goes over in the activated complex to an asymmetric stretching vibration for which there is no restoring force (the reaction coordinate, which is evaluated as $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$), and a normal, more or less symmetric, stretching vibration[‡]. This symmetric vibration represents bonding in the activated complex not present in the reactants[¶], and, if isotope dependent, would lead to a decreased isotope effect. If k_2 and k_3 are equal or nearly so, little or no motion of R is involved in the symmetric stretching vibration, and the frequency will be nearly independent of the isotopic mass of R, but not of the isotopic mass of Y and X. If $k_2 > k_3$ (product-like activated complex) or if $k_3 > k_2$ (reactant-like activated complex) R will move, and the frequency will depend on the isotopic mass of R, Y and X.

[†] The term could be broken down into individual vibrations for purposes of calculation if desired. A more detailed analysis would include interactions similar to A---R for Y- and X- and the changes in these at the activated complex.

[‡] The ensuing development concerning the symmetric stretching vibration follows closely that of Westheimer for the AHB system¹, and is implicit in the original theoretical development⁹.

[¶] This is a somewhat more formal way of stating the frequently heard comment that the energy required to form the S_N2 activated complex is less than that required to break the R-X bond, because there is some driving force supplied by R-Y bonding.

Labelled R—For the case where the central carbon atom in the displacement reaction is labelled, $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ is almost the same (about 1.058 for a simple C–C–Cl system) for all mechanisms as calculated using the three-centre equation of Bigeleisen and Wolfsberg⁷. The R–X bond frequency present in the reactants will be absent in the activated complex for all mechanisms. Combination of these two terms gives a more or less standard bond rupture value, which is the value to be expected from the balanced ($k_2 = k_3$) S_N2 mechanism. There is no activated complex term from the symmetric stretching vibration, since the frequency is isotope independent, and little or no term from the A–---R interactions, since these interactions are small. For cases where $k_2 > k_3$ or $k_3 > k_2$, there will be an activated complex term from the symmetric stretching frequency, which will lead to a lower isotope effect. For the S_N1 case, there is no symmetric stretching frequency in the activated complex. But there are large A–---R interaction isotope dependent vibrational frequency terms in the activated complex, and these will combine with the standard bond rupture value to give a lower isotope effect. These A–---R interaction terms may be quite large, leading to quite low isotope effect values for S_N1 reactions. In summary, the central carbon isotope effect is expected to be greater for the S_N2 mechanism than for the S_N1 mechanism.

Labelled X—For the case where the displaced group is labelled, ^{35}Cl *v.* ^{37}Cl in our work, $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$, calculated using the Bigeleisen–Wolfsberg method⁷ on an O–C–Cl model, varies from 1.0069 for the S_N1 case down to 1.0018 for the S_N2 case. Again the R–Cl bond frequency present in the reactants will be absent in the activated complex, contributing the same greater than unity factor (~ 1.0060 for a simple C–Cl model) for both mechanisms. In addition, for the S_N2 case, there will be a symmetrical stretching vibrational frequency term in the activated complex, which will lead to a decreased isotope effect. There will be no such isotope effect lowering term for the S_N1 mechanism since k_2 and k_3 are very small. For both mechanisms there will be some increased solvation bonding in the activated complex relative to the reactants. This will lower the isotope effect for both mechanisms, but probably somewhat more for the S_N1 case. In summary, the chlorine isotope effect is expected to be greater for the S_N1 mechanism than for the S_N2 mechanism.

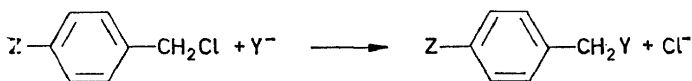
Labelled Y—For the case where the incoming nucleophile is labelled, $^{14}\text{CN}^-$ in our work, $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ is 1.014 (for the C–C–Cl model) for the balanced ($k_2 = k_3$) S_N2 mechanism. Any isotopic fractionation of the incoming nucleophile for the S_N1 mechanism must take place in the second step; by definition the nucleophile is not involved in the first step. In order that it be an activated process, this bond formation between the negative incoming ion and the carbonium ion must involve localization of the carbonium ion positive charge and disruption of the carbonium ion solvation bonding. This approximates the bonding situation in the S_N2 process. Thus $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ and the other bonding considerations are very similar for the two mechanisms. In all these cases there will be a symmetrical stretching frequency term in the activated complex not present in the reactants. This

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will lead to a lower, and perhaps even inverse isotope effect. However, there will undoubtedly be less solvation bonding to the incoming nucleophile in the activated complex (more diffuse charge) than in the reactants. If the vibrations involving this solvation bonding are isotope dependent, this factor will lead to a higher isotope effect. In summary, the incoming nucleophile isotope effects are expected to be small, not very sensitive to mechanism, and even of uncertain direction.

The experimental approach

Experimentally, work is in progress on an extensive successive labelling investigation of isotope effects in displacement reactions of benzyl and substituted benzyl chlorides with various nucleophiles¹⁵. In the reaction system:



chlorine, benzyl carbon and Y ($^{14}\text{CN}^-$) isotope effects are being measured for: Z = CH_3O , CH_3 , H, Cl and NO_2 , and for Y = H_2O , CN^- and $\text{S}_2\text{O}_3^{2-}$. Other nucleophiles, and leaving groups than Cl may also be investigated.

As a first step, in the reaction of benzyl chloride with cyanide ion in eighty per cent ethanol, for carbon-14 label in the benzyl carbon, $k_{12}/k_{14} = 1.061 \pm 0.003$; for ^{35}Cl - ^{37}Cl fractionation (natural abundance material) $k_{35}/k_{37} = 1.0074 \pm 0.0005$; and for carbon-14 label in the cyanide ion, $k_{12}/k_{14} = \sim 1.01$. If the method of calculation of $\nu_{1L}^\ddagger/\nu_{2L}^\ddagger$ for the benzyl carbon indicated above is correct (which is by no means certain), the relatively low value of 1.061 indicates behaviour much closer to the S_N1 than the S_N2 mechanism. However, until results with substituted benzyl chlorides are available, no definitive statement can be made. The chlorine isotope effect value falls in the range where it might correspond to either mechanistic type, and no conclusion can be drawn from this result alone. However, in view of the results discussed below, the value is consistent with, and adds support to the hypothesis that this reaction has a borderline mechanism quite close to the S_N1 type. The value for the cyanide isotope effect is uncertain, but that it is small is consistent with the qualitative analysis given above, and with the small cyanide isotope effect observed by Yankwich and co-workers in the methyl halide system¹³.

The second phase of the benzyl system isotope effect programme, involving an extensive study of chlorine isotope effects, has been completed, and the results are presented in abbreviated form in *Table 1*.

For the reactions indicated in the table, both chlorine isotope effects and kinetic orders were determined. In all cases where first order kinetic behaviour was observed, the chlorine isotope effect was close to 1.0078, while for those reactions which exhibited second order kinetics, the isotope effect value was 1.0058. Reactions showing borderline kinetic behaviour had isotope effect values intermediate between those two extremes. Thus,

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it is seen that there is a clear relationship between chlorine isotope effect and kinetic behaviour. These results agree with the conclusions of the qualitative analysis given above. However, it is somewhat surprising that the isotope effect spread between the two mechanisms is no greater than it is.

Table 1. Chlorine isotope effects (k_{35}/k_{37}) and kinetic orders for the reactions of benzyl and substituted benzyl chlorides with various nucleophiles in 80 per cent aqueous dioxan at 30°

Para-substituent	Added nucleophile		
	None	CN ⁻	S ₂ O ₃ ²⁻
CH ₃ O	1.0078	1.0078 (1)	1.0081 (1)
CH ₃	1.0075	1.0079 (1)	1.0074 (B)
H	1.0078	1.0072 (B)	1.0064 (B)
Cl	1.0078	1.0062 (B)	1.0058 (2)
NO ₂	1.0076	1.0057 (2)	1.0058 (2)

(1) = First order, (2) = Second order, (B) = Borderline; Isotope effect precision, ± 0.0002 .

Nevertheless, the chlorine isotope effect and kinetic results dovetail quite well. For a given nucleophile (*i.e.*, cyanide ion or thiosulphate ion) the reaction is shifted from first-order kinetics and a maximum isotope effect to second-order kinetics and a minimum isotope effect as the *p*-substituent is changed from a powerful electron donor group to a powerful electron withdrawing group. For a particular one of the three compounds, *p*-methyl, *p*-chloro and unsubstituted benzyl chloride, the kinetics may be shifted toward second order by increasing the nucleophilicity of the displacing group, the isotope effect being decreased accordingly. It is therefore concluded that the relative magnitudes of these effects may be used as a mechanistic criterion, at least in a closely related group of compounds such as these.

From the above examples it is clear that the successive labelling isotope effect technique can provide much useful information about reaction mechanisms. With no more than qualitative and semi-quantitative consideration of isotope effect theory, reasonable qualitative agreement between theory and experiment can be attained. More quantitative consideration of theory, where practical, is bound to give even more meaningful results. When combined with kinetic and other experimental approaches, isotope effect research can go a long way in establishing the nature of the activated complex.

The author wishes to thank the United States Atomic Energy Commission for their support of this research through Contract AT-(40-1)-277. The experimental results mentioned here were obtained by his co-workers, Drs W. L. Carrick, D. B. Richardson, M. Ehrhardt, P. M. Nair, J. W. Hill and Messrs J. C. Wright and

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A. H. McKee; their assistance is gratefully acknowledged. Finally, the author wishes to thank Dr R. F. Kruh for his advice and counsel in many helpful discussions about isotope effects.

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