

lyte systems, and the extension of the transient electric birefringence technique to smaller macromolecules, such as polypeptides of molecular

weight *ca.* 10^4 – 10^5 , are currently receiving attention in this Laboratory.

BERKELEY, CAL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Carbon-14 Kinetic Isotope Effects in Nucleophilic Substitution Reactions¹

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RECEIVED MARCH 21, 1957

The carbon-14 kinetic isotope effects in the nucleophilic substitution reactions of methyl iodide-C¹⁴ with triethylamine, pyridine, hydroxide ion and silver ion have been investigated. The kinetic isotope effects (k_{12}/k_{14}) found in these reactions were 1.10, 1.14, 1.09 and 1.09, respectively. The surprisingly large kinetic isotope effects in these S_N2 reactions are of the same magnitude as many effects noted in reactions proceeding only with bond rupture. A comparison has been made between the observed kinetic isotope effects and those calculated using an equation of Bigeleisen and Wolfsberg for three-center reactions. It appears that the magnitude of the kinetic isotope effect is of only limited use in differentiating between two-center and three-center reactions in nucleophilic substitution (S_N1 and S_N2 reactions).

Introduction

It has long been recognized³ and amply demonstrated by experiment^{4–6} that substitution of one isotope of an element for another in a bond undergoing rupture or formation in the rate-controlling step of a reaction influences the rate of the reaction. This kinetic isotope effect is particularly striking in the case of the substitution of deuterium for hydrogen and has been utilized to good advantage in the elucidation of the mechanism of many organic reactions.^{4,6} Although the kinetic isotope effect produced by the substitution of carbon-14 for carbon-12 is relatively small in magnitude, a large number of cases have been observed where such kinetic isotope effects occur.^{7–9}

Recently theoretical equations have been presented for the prediction of the magnitude of the kinetic isotope effects¹⁰ in two-center and three-center¹¹ reactions. These descriptions fit the type of covalency changes that are associated with the dual mechanisms of nucleophilic substitution reactions, S_N1 and S_N2.¹² It was therefore decided to investigate the carbon-14 kinetic isotope effects in S_N1 and S_N2 reactions, which Hammett has described as the most important in organic chemistry,¹³ in order to test the validity of the theoretical equations, in order to determine whether such

kinetic isotope effects could serve as a criterion of mechanism and whether the kinetic isotope effects would provide information for a more detailed understanding of the transition states of the S_N1 and S_N2 reactions. Carbon-14 kinetic isotope effects are reported here for three reactions of methyl iodide-C¹⁴ which fall into the S_N2 category, those with triethylamine, pyridine and hydroxide ion and for one reaction which falls into a borderline category, that with silver nitrate in aqueous ethanol.

Experimental

Materials.—Matheson, Coleman and Bell reagent grade methyl iodide was fractionally distilled at atmospheric pressure in a 14 in. column of glass helices, b.p. 42.5°, n_D^{20} 1.5295 (lit.¹⁴ b.p. 42.4°, n_D^{20} 1.5293). Methyl iodide-C¹⁴, purchased from Nuclear Instrument and Chemical Corp., was diluted with unlabeled methyl iodide. The methyl iodide-C¹⁴ was stored in an amber-colored glass-stoppered bottle at 0° in the dark. The refractive index of the methyl iodide-C¹⁴ remained unchanged for seven months, indicating negligible decomposition due to self-radiolysis.¹⁵ Eastman Kodak Co. white label triethylamine was fractionally distilled, b.p. 87.5°, n_D^{20} 1.4003 (lit.¹⁶ b.p. 89.4°, n_D^{20} 1.4003). Fisher reagent grade pyridine was distilled from sodium hydroxide pellets, b.p. 113–113.5° (lit.¹⁷ b.p. 115°). Benzene was purified by fractional distillation, b.p. 80°. Commercial dioxane was purified according to the method of Fieser.¹⁸ The purified anhydrous dioxane was freed of peroxides by passage over a column of activated alumina under a nitrogen atmosphere and used immediately in the kinetic studies. β -Naphthol was recrystallized twice from water; m.p. 121–122°.

Kinetics of the Substitution Reactions.—The kinetics of the alkylation of triethylamine with methyl iodide were measured in benzene solution at 25.05 \pm 0.02°. After appropriate times of reaction, the contents of the reaction flasks were washed into excess hydrochloric acid with ethanol, which was used to disperse the benzene–water interface. The excess hydrochloric acid was then titrated with standard sodium hydroxide using lacmoid as indicator. No difference was observed in measurements made with ordinary methyl iodide and methyl iodide-C¹⁴.

The kinetics of the displacement reaction of hydroxide ion with methyl iodide-C¹⁴ were measured in 50% dioxane–

(1) This research was supported by Contract At(11-1)295 of the U. S. Atomic Energy Commission. A preliminary account was reported in *Chemistry & Industry*, 463 (1957).

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water (by volume) at $25.05 \pm 0.02^\circ$ in double-cell reaction flasks. After thermal equilibration the contents of the cells were mixed, and after suitable time intervals the contents washed into excess standard hydrochloric acid and titrated with standard sodium hydroxide using brom thymol blue as indicator.

Although the kinetics of the reaction of pyridine with methyl iodide in benzene have been studied by Hinshelwood and Laidler¹⁹ by means of acid-base titration, our attempts to use this method gave unsatisfactory end-points. Consequently, the kinetics of the reaction of pyridine with methyl iodide-C¹⁴ in benzene at $25.05 \pm 0.02^\circ$ were determined by observation of the increase in the ultraviolet absorption of N-methyl-C¹⁴-pyridinium iodide at $226 \mu\mu$, using a Cary recording spectrophotometer. Aliquots of the reaction mixture, after suitable time intervals, were diluted 167 times in ethanol before spectroscopic analysis. In this way, analyses were carried out in that dilute region in which Beer's law is obeyed.²⁰

The kinetics of the reaction of methyl iodide-C¹⁴ with silver ion in 70% ethanol (7 volumes of ethanol and 3 volumes of water) were determined at $24.88 \pm 0.02^\circ$ by the method of Dostrovsky and Hughes.²¹

Isolation of Samples for the Measurement of the Carbon-14 Kinetic Isotope Effect.—In the determination of the carbon-14 kinetic isotope effect, the specific activity of either the reactant or the product as a function of the fraction of reaction may be measured. Usually it was more convenient to isolate the reactant, methyl iodide-C¹⁴, from the reaction mixture and measure its specific activity in the form of a solid derivative, β -methoxy-C¹⁴-naphthalene. In the reaction of triethylamine with methyl iodide-C¹⁴, the reaction mixture, after suitable time intervals, was treated with excess 0.1 *N* hydrochloric acid and the unreacted methyl iodide-C¹⁴ was extracted from the aqueous suspension with multiple ether extractions. The ether extract was added to an ethanol solution containing β -naphthol and sodium hydroxide (a small molar excess of β -naphthol was used so that no free sodium hydroxide was present) and the derivatization was allowed to proceed for not less than one week at room temperature. The derivatization mixture was extracted with sodium hydroxide to remove excess β -naphthol and then washed twice with water. The derivative, β -methoxy-C¹⁴-naphthalene, was recrystallized to constant melting point (72.5 – 73°) usually requiring 3–6 recrystallizations, and then to constant activity, usually requiring 1–2 further recrystallizations.

In the reaction of hydroxide ion with methyl iodide-C¹⁴ the same procedure of acidification, extraction and derivatization was used for the preparation of the β -methoxy-C¹⁴-naphthalene. In the reaction of silver ion with methyl iodide-C¹⁴, the reaction was stopped with excess sodium iodide, following which the methyl iodide-C¹⁴ was extracted and derivatized as above.

In the reaction of pyridine with methyl iodide-C¹⁴, the product of the reaction, N-methyl-C¹⁴-pyridinium iodide was isolated. After suitable time intervals, the reaction mixture was washed into an ether-water mixture. Three ether extractions of the aqueous layer were made. The aqueous layer was then evaporated and the residue crystallized from ethanol-ether three times and dried in a vacuum desiccator over phosphorus pentoxide.

Radioassay.—The variables which must be determined in order to evaluate the kinetic isotope effect are the fraction of reaction and the specific activity of the product or the reactant at that fraction of reaction. Equation 1 gives the ratio of rate constants of the unlabeled and labeled reactions, k/k^* , as a function of f , the fraction of reaction and r , the ratio of the specific activity of the total accumulated product to the specific activity of the initial labeled reactant.²² This equation may be applied to any competitive

$$k/k^* = \ln(1-f)/\ln(1-rf) \quad (1)$$

process, such as $xA + B$ (or B^*) \rightarrow Products, where the order in A may be any value but the reaction must be first

order in B.²³ Equation 2, which is valid irrespective of reaction order, relates the ratio of rate constants to functions of f , the fraction of reaction and to S_t , the specific activity of the reactant, at time t and time 0.²⁴

$$k^*/k = 1 + \ln(S_t/S_0)/\ln(1-f) \quad (2)$$

For the determination of the fraction of reaction, the kinetics previously described were utilized. The radioassay of the various samples was accomplished by the oxidation of the samples to carbon dioxide in a sealed tube at 640° .²⁵ The activity of the carbon dioxide samples was measured in an ionization chamber (atmospheric pressure of carbon dioxide) using a vibrating reed electrometer to measure the ionization current under a collecting potential of 540 volts.²⁶ The rate of charge method was used in this investigation.

The amount of material used for radioassay was measured in two ways. The first method, which involved weighing of the sample on a semi-micro balance, necessitated sealing the weighed sample in a small piece of Pyrex tubing before placing it in the combustion tube because of the volatility of the β -methoxynaphthalene. The second method involved the measurement of the carbon dioxide resulting from the oxidation process in a constant volume manometer, using a cathetometer. The latter process was utilized for the radioassay of the pyridine and silver ion reactions while the former process was used for the triethylamine and hydroxide ion reactions. The precision of the latter process seems preferable to that of the former.

Results

Kinetics.—The kinetics of the reactions of methyl iodide-C¹⁴ with the various reagents are summarized in Table I.

In the determination of the specific activity of the reactants or products at various fractions of reaction, reaction conditions identical to those used in the kinetic determinations were used. In some cases, the same reaction mixture was utilized for both kinetic and radioassay determinations. In Table II are given the results of the determinations of the kinetic isotope effects in the reactions of triethylamine, hydroxide ion, pyridine and silver ion with methyl iodide-C¹⁴. It is to be noted that direct determination of the activity of methyl iodide-C¹⁴ and extraction and fractionation were performed to ascertain that no fractionation occurred in the extraction or derivatization of the methyl iodide-C¹⁴.

In the reaction of pyridine with methyl iodide-C¹⁴, the kinetics could not be determined simultaneously with the isotope effect. In view of the larger uncertainty in the velocity coefficient in this case, measurements of the change in the specific activity of the product were made at 10% reaction where an error in the fraction of reaction has least effect on the kinetic isotope effect, calculated according to equation 1.²⁷ In Fig. 1, the data of Table II (except for the pyridine reaction) have been plotted according to equation 2 and the best lines drawn by the method of least squares. The intercepts of the triethylamine and hydroxide ion lines yield values of 7.806 and 7.817×10^{-15} amp./mg., respectively, as the initial specific activity of the methyl iodide-C¹⁴, which agrees well with the values obtained from direct measurement.

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TABLE I
KINETICS OF SOME SUBSTITUTION REACTIONS^a OF METHYL IODIDE-C¹⁴

Methyl iodide-C ¹⁴ , <i>M</i>	Reagent	Solvent	<i>k</i> × 10 ⁴ , l./mole sec.
0.0998	Triethylamine, 0.0998 <i>M</i>	Benzene	1.45 ± 0.012 ^b
.1170	Hydroxide Ion, 0.1822 <i>M</i>	50% Dioxane	0.238 ± .006
.1000	Pyridine, 0.1000 <i>M</i>	Benzene	0.0175 ± .001 ^c
.0498	Silver Ion, 0.0700 <i>M</i>	70% Ethanol	13.0 ^d

^a 25.05 ± 0.02° except for the silver ion reactions at 24.88 ± 0.02°. ^b This value agrees with the values obtained using unlabeled methyl iodide and also with one obtained by Hinshelwood and Laidler.¹⁹ ^c This value agrees with one extrapolated from data obtained at higher temperatures.¹⁹ ^d This is an average value. As has been found typical of the reactions of silver ion with alkyl halides, this reaction follows an approximate second-order rate expression over only a small portion of the reaction, the velocity coefficient decreasing monotonically as the reaction proceeds.²¹

Discussion

As mentioned earlier, theoretical equations have been derived for the calculation of kinetic isotope effects in two-center and in three-center reactions, of which the nucleophilic substitution reactions are prime examples. The present results will be discussed in terms of an equation of Bigeleisen and Wolfsberg (3).^{11,23}

$$k_1/k_2 = \left[\frac{\alpha^2 \left(\frac{1}{m_{B_1}} + \frac{1}{m_{C_1}} \right) + \beta^2 \left(\frac{1}{m_{B_1}} - \frac{1}{m_{A_1}} \right) - 2\alpha\beta \frac{1}{m_{B_1}} \cos ABC}{\alpha^2 \left(\frac{1}{m_{B_2}} + \frac{1}{m_{C_2}} \right) + \beta^2 \left(\frac{1}{m_{B_2}} - \frac{1}{m_{A_2}} \right) - 2\alpha\beta \frac{1}{m_{B_2}} \cos ABC} \right]^{1/2} \left[1 + \sum_i^{3n-6} G(u_i) \Delta u_i - \sum_i^{3n'-6} G(u_i') \Delta u_i' \right] \quad (3)$$

where the path of decomposition is

$$X_L = \alpha |r_B - r_C| - \beta |r_B - r_A|$$

A, B and C refer to the three molecular (not necessarily atomic) fragments in the reaction complex ABC; m_A , m_B and m_C refer to the masses of these fragments and ABC is the angle made by the lines joining the three centers of mass at the center of mass of B. $r_B - r_C$ is the distance from the center of mass of fragment B to that of fragment C; α and β are parameters which indicate the relative magnitudes of the two types of motions, bond-formation and bond-rupture, at the activated complex. It is seen that the difference in chemical reactivity of bonds of varying isotopic composition is due to two factors. One is the difference in the loss of vibrational energies of the bonds in the activation process for the labeled and unlabeled reactions. The other factor is the difference in the "effective mass" of the critical complex for the labeled and unlabeled reactions.

Equation 3 is similar to an earlier equation of Bigeleisen and Wolfsberg¹¹ but differs with respect to the temperature independent factor, in particular by the replacement of atomic masses by molecular fragment masses. This modification was taken after a critical examination²⁸ of the earlier hypothesis of Slater.²⁹

Theoretical Calculation of the Kinetic Isotope Effect in the Substitution Reactions of Methyl Iodide-C¹⁴.—Although spectroscopic information concerning the frequency shifts accompanying substitution of carbon-14 for carbon of normal

isotopic composition in methyl iodide is not available, data are on record for methyl iodide-C¹³.³⁰ Therefore, in principle it is possible to make a reasonable approximation of $\sum G(u_i) \Delta u_i$ for methyl iodide-C¹⁴ by calculating that for methyl iodide-C¹³ and doubling the result.

The maximum kinetic isotope effect would occur in a reaction in which the molecule dissociated

completely in the transition state, so that the G function for the activated complex would be reduced to zero. A closer approximation to the actual transition state may be made by assuming that only the bond undergoing fission changes in the activation process, the force constant for the

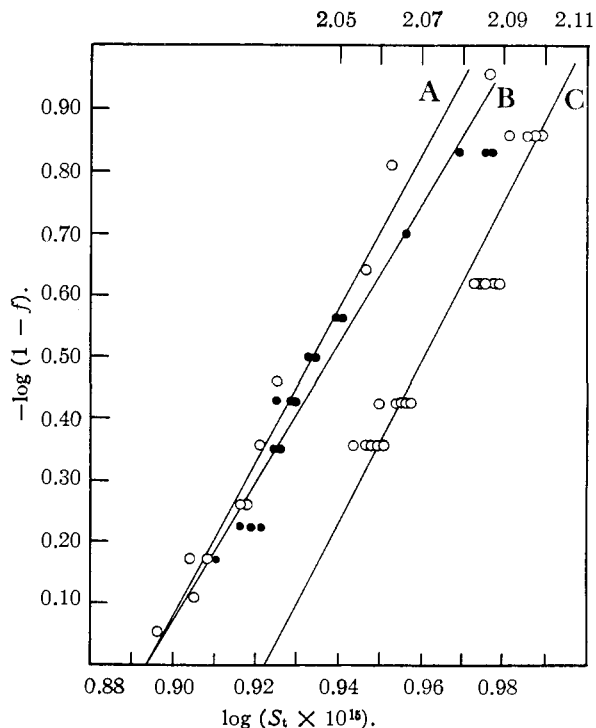


Fig. 1.—Kinetic isotope effects in the displacement reactions of methyl iodide-C¹⁴: A, hydroxide ion; B, triethylamine; C, silver ion (top scale).

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TABLE II
CARBON-14 KINETIC ISOTOPE EFFECTS IN THE REACTIONS
OF METHYL IODIDE-C¹⁴

Sample	Specific activity, amp./mg. × 10 ¹⁵	Fraction of reaction	k ₁₂ /k ₁₄
Triethylamine			
Initial ^a	7.93
Initial	7.81
1	8.15	0.337	1.116
2	8.24	.404	1.117
2	8.30	.404	1.134
2	8.35	.404	1.150
3	8.44	.557	1.106
3	8.40	.557	1.099
4	8.47	.633	1.089
4	8.51	.633	1.094
4	8.40	.633	1.079
5	8.57	.687	1.087
5	8.58	.687	1.088
6	8.75	.726	1.096
6	8.70	.726	1.092
8	9.48	.855	1.112
8	9.52	.855	1.115
8	9.32	.855	1.101
			Av. 1.102 ± 0.012
Hydroxide ion			
Initial ^b	7.85
1	8.10	0.333	1.082
1	8.02	.333	1.067
2	8.25	.453	1.098
2	8.27	.453	1.102
3 ^b	8.34	.560	1.085
4	8.42	.657	1.074
5 ^b	8.85	.774	1.091
6 ^b	8.97	.845	1.079
7 ^b	9.47	.890	1.095
			Av. 1.088 ± 0.010
Pyridine			
Initial	99.46 ^e
Initial	98.31
Initial	99.13
Initial ^c	99.90
Initial	99.11
1	87.83	0.10	1.134
1	87.57	.10	1.137
1	87.00	.10	1.145
2	88.63	.10	1.124
2	86.23	.10	1.156
3	86.65	.10	1.144
3	87.09	.10	1.154
			Av. 1.142 ± 0.009
Silver ion			
Initial ^d	106.4 ^e
Initial	109.4
Initial	109.4
1	114.0	0.562	1.077
1	114.0	.562	1.077
1	114.9	.562	1.088
1	113.3	.562	1.068
1	114.2	.562	1.079
1	114.7	.562	1.086
1	114.7	.562	1.086
2	116.5	.629	1.089

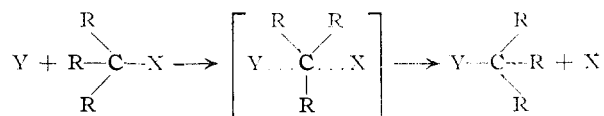
2	116.0	.629	1.083
2	116.4	.629	1.088
2	114.7	.629	1.070
2	117.0	.629	1.093
2	116.0	.629	1.083
3	122.1	.761	1.098
3	121.2	.761	1.092
3	121.6	.761	1.094
3	121.2	.761	1.092
3	122.3	.761	1.099
3	122.5	.761	1.101
4	125.0	.862	1.083
4	123.4	.862	1.075
4	124.5	.862	1.080
4	125.2	.862	1.084

Av. 1.086 ± 0.005

^a Direct determination of the specific activity of methyl iodide-C¹⁴ samples gave values of 7.886 and 7.816 × 10⁻¹⁵ amp./mg. expressed in terms of an equivalent of β-methoxy-C¹⁴-naphthalene. In this set and the following set, results are given for those samples recrystallized eight or nine times. ^b Sample chromatographed on an alumina column during purification. Apparently this treatment had no effect on the specific activity of the samples. ^c This is a sample of β-methoxy-C¹⁴-naphthalene prepared from the stock solution of methyl iodide-C¹⁴. The specific activity is expressed as the equivalent of N-methyl-C¹⁴-pyridinium iodide. ^d All samples were recrystallized four or five times. ^e The specific activity in the pyridine and silver ion reactions is expressed in terms of I/(P/T) (millivolts/division per unit of pressure per unit of temperature) which is proportional to millivolts/division per millimole of carbon dioxide.

stretching vibration of that bond in the transition state being set equal to zero. This is a usual assumption that is made in such calculations in light of the fact that no suitable spectroscopic data are available for the complete evaluation of the G functions of the transition state.³¹ Following the assignments made for the fundamental frequencies in the methyl halide series as listed by Herzberg,³² the ν₃(a₁) frequency of methyl iodide (533.4 cm.⁻¹) was that chosen to be lost in the transition state. The results of such calculations are summarized in Table III together with the experimental results.

The first three reactions in Table III are representative of typical nucleophilic substitution reactions, which constitute the simplest examples of three-center reactions. The idealized mechanism of such reactions can be depicted as



Even though three of the four observed kinetic isotope effects listed in Table III agree well with the calculated values, the model of the transition state used in the calculation of the temperature dependent factor is clearly a crude representation of the transition state represented above. The agreement, therefore, is somewhat fortuitous. The model used in the calculations assumes that the difference between the ground state and the transition state involves only the loss of the carbon-X stretching vibration. The S_N2 reaction depicted above shows several differences between the ground

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TABLE III
CARBON-14 KINETIC ISOTOPE EFFECT IN SOME SUBSTITUTION REACTIONS OF METHYL IODIDE-C¹⁴

Reagent	k_{12}/k_{13} temp. independent factor	k_{12}/k_{13} temp. dependent factor	k_{12}/k_{13} calcd.	k_{12}/k_{14} calcd.	k_{12}/k_{14} exptl.
Triethylamine	1.031 ^a	1.015	1.046	1.092 ^d	1.102 ± 0.012
Pyridine	1.030 ^a	1.015	1.045	1.090	1.142 ± .009
Hydroxide ion	1.026 ^a	1.015	1.041	1.082	1.088 ± .010
Silver ion	1.031 ^b	1.015	1.046	1.092	1.086 ± .005
	1.030 ^c	1.015	1.045	1.090	

^a It is assumed that, β/α the ratio of bond formation to bond extension in the transition state, is equal to 1; that is, that these reactions are idealized bimolecular substitution reactions. ^b Calculated for $\alpha = 1, \beta = 0$. ^c Calculated for $\beta/\alpha = 1$. ^d By the use of eq. 3 involving molecular fragment masses, the calculated kinetic isotope effect is about 1% less than that calculated according to the earlier equation of Bigeleisen and Wolfsberg involving atomic masses.¹¹

state and the transition state, including partial bonding of the X and Y groups to the central carbon atom *via* $p_x/2$ orbitals and sp^2 hybridization of the central carbon to R bonds.³³ The increase in the s character of the carbon-R bonds should lead to higher vibrational frequencies and frequency shifts on isotopic substitution for those bonds, just as an increase in s character in the carbon-hydrogen bonds in ethane, ethylene and acetylene causes a corresponding increase in the carbon-hydrogen vibrational frequencies and frequency shifts.³⁴ The increase in these frequencies and frequency shifts increases the value of the G function of the transition state slightly and consequently tends to reduce the isotope effect. The addition of Y to the system increases the number of internal degrees of freedom by three, contributing further, although probably to a lesser degree, to the value for $\Sigma G(u_i^\ddagger)\Delta u_i^\ddagger$ (for the transition state), again tending to reduce the calculated kinetic isotope effect. Furthermore, the carbon-halogen bond is not completely ruptured in the transition state as is assumed in the model used for calculation. Consequently the sum $\Sigma G(u_i^\ddagger)\Delta u_i^\ddagger$ for the actual transition state is still larger than that calculated on the basis of the model chosen and the kinetic isotope effect is correspondingly smaller. Taken together, these considerations suggest that the kinetic isotope effect in the nucleophilic substitution reactions under consideration should be somewhat smaller than that calculated by the use of the simple model described above.³⁵

In the solvolysis of primary compounds, the collapse of the solvent shell is considered to occur almost immediately upon the formation of the highly unstable primary carbonium ion, resulting in 100% inversion of configuration.³⁶ The only significant difference in this mechanism from that of the S_N2 reaction appears to be in the degree of participation of the solvent in the transition state. In forming the transition state, the central carbon atom again changes its hybridization from sp^3 to

sp^2 . The consequences of the increase in s character in the carbon-R bonds are the same as previously considered. The extension of the carbon-X bond may be somewhat greater in this case, since it has been pointed out that considerable extension must occur prior to close approach by a solvent molecule.³⁵ The relative extension of the iodine bond in the above cases is probably of greater consequence in determining the magnitude of the kinetic isotope effect than the degree of proximity of the nucleophile because of the large frequency shifts upon isotopic substitution associated with this bond. However, it is not possible at this stage to state the quantitative significance of these contributing factors. It is seen that the solvolytic reaction of methyl iodide-C¹⁴ involving silver nitrate, which may be considered a borderline case between an S_N2 and S_N1 reaction, exhibits a kinetic isotope effect essentially no different from those involving pure S_N2 reactions.

In order to convert these qualitative considerations into a quantitative picture of the transition state, especially for the S_N2 reaction, it is necessary to obtain detailed spectroscopic information for all bonds in the transition state. Although Miller and Lee³⁷ have recently made such a calculation for a symmetrical system of iodide displacing iodide in methyl iodide, the unsymmetrical systems involved here are essentially insoluble at the present time.

The significance of the calculations made above with the three-center model is questionable since calculations with either two-center or three-center models yield good agreement with experimental values. Only one such comparison is shown, for the reaction of methyl iodide-C¹⁴ with silver nitrate. It is seen that the two-center model (corresponding to an S_N1 reaction ($\alpha = 1; \beta = 0$)) and the three-center model (corresponding to an S_N2 reaction ($\beta/\alpha = 1$)) yield almost identical calculated kinetic isotope effects. The same is true for comparable calculations with the other reactions. The apparent reason for the similarity of the results of the two sets of calculations is that in the systems under study, the values of the temperature independent factors for the two-center and three-center models lie very close to one another. In other words, the mass of the incoming group has little effect on the effective mass of the transition state.

(33) V. Gold, *J. Chem. Soc.*, 1430 (1951).

(34) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 13, 31 and 49.

(35) The referee has suggested that the contribution from the zero point energy of the C-Y bond will not necessarily mean that the estimate of the sum $\Sigma G(u_i^\ddagger)\Delta u_i^\ddagger$ would have to be raised because of the very approximate method used for evaluating this sum. A more reliable method for the calculation of the sum, the method of the "trace" is discussed briefly by J. Bigeleisen, *J. Chem. Phys.*, **23**, 2264 (1955).

(36) A. Streitwieser, Jr., *This Journal*, **77**, 1117 (1955).

(37) S. I. Miller and W. G. Lee, 130th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1956.

It has been found that no matter what the incoming or leaving groups, the difference in the temperature independent factors for two-center and three-center reactions involving carbon is never more than 3%.³³

From the examples studied here, it appears that a number of S_N2 processes possess a carbon-14 kinetic isotope effect approximately equal in magnitude to that of many reactions involving only bond rupture.⁷ It was thought at one time that the magnitude of the kinetic isotope effect could be used to differentiate two-center and three-center processes, such as S_N1 and S_N2 reactions. However, it now appears that only under favorable circumstances can this differentiation be achieved. In cases where the difference in the temperature independent factors for two-center and three-center reactions is of the order of 2 to 3%, it may be possible to utilize kinetic isotope effects to distinguish between S_N1 and S_N2 reactions. For this purpose, measurements of the temperature coefficient would

(38) Unpublished results of D. F. Hoeg and G. J. Buist.

have to be made in order to assign part of the effect to the zero point energy term and the remainder to the temperature independent entropy term.

One factor that seems to have an effect on the magnitude of the kinetic isotope effect is the activation energy of the reaction. It is worthy of note that the largest kinetic isotope effect was observed for the reaction of methyl iodide-C¹⁴ with pyridine which has the largest activation energy of the reactions considered. It is considered possible that the kinetic isotope effect in the pyridine reaction is higher than the others listed and higher than the calculated value because of the higher activation energy of the pyridine reaction. It is hoped to treat this phenomenon in a quantitative fashion at a later date.

Acknowledgment.—The authors gratefully acknowledge valuable discussions with Drs. G. J. Buist, L. Kaplan, S. I. Miller, K. E. Wilzbach and M. Wolfsberg.

CHICAGO 16, ILLINOIS

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

Hexafluorobenzene from the Pyrolysis of Tribromofluoromethane^{1,2}

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RECEIVED APRIL 10, 1957

The pyrolysis of tribromofluoromethane was studied in graphite, Vycor and platinum tubes at temperatures ranging from 500 to 750°. In all cases hexafluorobenzene was formed. The lowest yields of hexafluorobenzene were obtained in Vycor tubes. Graphite performed nearly as well as platinum tubes under atmospheric pressures. At pressures of 4.5 atmospheres of nitrogen in platinum tubes an optimum net yield slightly over 55% was achieved at 540 to 550°. Side products of the reaction were chiefly bromofluoro derivatives of ethane, propane, benzene and toluene. A mechanism of the reaction is proposed.

Introduction

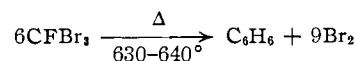
The synthesis of hexafluorobenzene was first reported by McBee, Lindgren and Ligett.³ Their method consisted of fluorinating hexachlorobenzene with bromine trifluoride, followed by treatment of the intermediate with antimony pentafluoride, and finally dehalogenation with zinc. This procedure led to the formation of small amounts of hexafluorobenzene together with a variety of other products, mainly perfluorocyclohexenes and cyclohexadienes as well as chlorofluoro compounds.

A more direct method, which also gave higher yields, was described by Desirant.⁴ It involved the pyrolysis of tribromofluoromethane in a platinum tube at 630 to 640°. The reported yield of hexafluorobenzene was 45% on the basis of reacted tribromofluoromethane.

Recently another synthesis of hexafluorobenzene

was described by Godsell, Stacey and Tatlow.⁵ Their paper dealt with the isolation of hexafluorobenzene from a mixture resulting from the treatment of a nonafluorocyclohexane with potassium hydroxide. The desired product was isolated by vapor phase chromatography.

In the light of currently increasing interest in hexafluorobenzene, and perfluoroaromatics in general, it was considered necessary to find a convenient method for synthesizing larger amounts of these compounds. Of the methods described above, the one by Desirant⁴ appeared to be the most promising, and consequently a study of this reaction was undertaken for the purpose of determining the effects of variation in tube materials, temperature and pressure on the course of the reaction. The pyrolysis reaction of interest can be represented by this stoichiometric equation



The tribromofluoromethane can be prepared from carbon tetrabromide and antimony trifluoride in the presence of a small amount of bromine.

In selecting the tubes for the pyrolysis three dif-

(1) This paper is based on work sponsored by the Bureau of Aeronautics, Department of the Navy, Washington, D. C.

(2) Presented as part of the Symposium on Fluorine Chemistry, Division of Industrial and Engineering Chemistry, at the 130th Meeting of the American Chemical Society in Atlantic City, N. J., September, 1956.

(3) E. T. McBee, V. V. Lindgren and W. B. Ligett, *Ind. Eng. Chem.*, **39**, 378 (1947).

(4) Y. Desirant, *Bull. Acad. Roy. Belg., Classe Sci.*, [5] **41**, 759 (1955).

(5) J. A. Godsell, M. Stacey and J. C. Tatlow, *Nature*, **178**, 199 (1956).