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

Carbon-14 Kinetic Isotope Effects. III.[1,2] The Hydrolysis of 2-Chloro-2-methylpropane-2-C^{14}

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2-Chloro-2-methylpropane-2-C^{14} has been prepared from sodium acetate-1-C^{14}. The kinetics of hydrolysis of the unlabeled compound in 60% dioxane–40% water have been determined. The kinetic isotope effect in the hydrolysis of 2-chloro-2-methylpropane-2-C^{14} has been determined by radioassay of the hydrolysis product, 2-methyl-2-propanol-2-C^{14} (in the form of its *p*-nitrobenzoate derivative) at various fractions of reaction. The kinetic isotope effect (k_{12}/k_{14}) was found to be 1.027 ± 0.015. This kinetic isotope effect in an SN1 (two-center reaction) is less than the kinetic isotope effects found in a number of SN2 (three-center reactions) involving methyl iodide-C^{14} and various nucleophiles. The differences in these kinetic isotope effects probably reflect differences in the leaving groups as well as differences in the mechanisms of the processes.

Carbon-14 kinetic isotope effects recently have been reported for several reactions of methyl iodide-C^{14} which fall into the SN2 category, those with triethylamine, pyridine and hydroxide ion.[2] The kinetic isotope effects (k_{12}/k_{14}) found in these experiments of 1.10, 1.14 and 1.09, respectively, were of the same magnitude as many effects noted in reactions proceeding only with bond rupture. It therefore appeared that the magnitude of the kinetic isotope effect could be used only with difficulty to differentiate between two-center and three-center reactions in nucleophilic substitution (SN1 and SN2 reactions). In order to determine the kinetic isotope effect in an SN1 reaction, the hydrolysis of 2-chloro-2-methylpropane-2-C^{14} in 60% dioxane–40% water has been investigated.

The hydrolysis of *t*-butyl chloride is a classical reaction that has been shown to conform to the mechanistic scheme described by Hughes and Ingold[3] as SN1. *t*-Butyl chloride is the molecule of lowest molecular weight and greatest simplicity whose hydrolysis has been shown to conform to the SN1 mechanism. The solvolysis of *t*-butyl chloride has been shown recently to be a limiting case (insensitive to nucleophilic character of the solvent) in the usual solvents.[4] For these reasons, the hydrolysis of *t*-butyl chloride was selected as a model reaction for the determination of the kinetic isotope effect in a heterolytic rate-determining process producing a carbonium ion. The *t*-butylcarbonium ion formed in the initial rate-determining step of the hydrolysis reacts by either or both of two subsequent fast steps to give products, by reaction with water to produce *t*-butyl alcohol or by loss of a proton to form isobutylene. In an aqueous solvent such as 60% dioxane–40% water, the main product is *t*-butyl alcohol (about 86%) and therefore the determination of the kinetic isotope effect of the reaction was carried out by the determination of the specific activity of *t*-butyl alcohol at various fractions of reaction.

Experimental

2-Chloro-2-methylpropane-2-C^{14}.—Anhydrous sodium acetate (47 g.) was mixed with 300 microcuries of sodium acetate-1-C^{14} (Nuclear Instrument and Chemical Co.) and heated to the fusion point to expel any water present. The sodium acetate was allowed to cool and then powdered. It was treated with 28 ml. of phosphorus oxychloride according to the procedure of Vogel.[5] The yield of acetyl chloride was 29 g., 56%. Methylmagnesium chloride was prepared from 22 g. of magnesium in 400 ml. of anhydrous ether. The acetyl chloride, diluted with its own volume of ether, was added to the vigorously stirred Grignard reagent. The mixture was stirred overnight, poured into 400 g. of crushed ice and 120 ml. of 5 *N* sulfuric acid. The reaction mixture was extracted with ether continuously for 12 hr. The ether extract was dried and distilled through an 8-inch fractionating column packed with glass helices. The yield of C^{14}-labeled *t*-butyl alcohol was 16 g., 59%.[6] The alcohol (15.4 g.) was then converted to the chloride by treatment with concentrated hydrochloric acid and calcium chloride.[5] The *t*-butyl chloride was distilled through an 8-inch fractionating column; b.p. 49.8 (749 mm.), $n^{24}D$ 1.3830–1.3832, yield 74%.

Kinetics of Hydrolysis of *t*-Butyl Chloride.—The kinetics of this hydrolysis usually have been studied in ethanol-water mixture.[7] However, since it was desirable to eliminate the reaction of ethanol with the carbonium ion, a 60% dioxane–40% water solvent was chosen for this work. The hydrolysis was carried out at 24.80 ± 0.05° in the presence of a slight excess of alkali to neutralize the acid formed in the reaction, avoiding the acid-catalyzed hydration of isobutene to *t*-butyl alcohol. Aliquots of the reaction mixture were quenched in absolute ethanol, cooled to −80° and then titrated with hydrochloric acid using lacmoid indicator. A linear first-order plot was obtained leading to a value of 0.44×10^{-4} sec.$^{-1}$ for the first-order coefficient. Experiments on the proportion of olefin formation were carried out according to those devised by Hughes, Ingold and co-workers[8] by titration with bromine. The results of these experiments indicated 14% olefin formation in this solvent system.

Kinetic Isotope Effect.—For the determination of the kinetic isotope effect, the product, *t*-butyl alcohol, was separated from the reaction mixture at various times and a solid derivative of the *t*-butyl alcohol was prepared for the determination of the specific activity of the product. A suitable derivative of the alcohol, *t*-butyl *p*-nitrobenzoate, was prepared by refluxing the alcohol in an inert solvent with *p*-nitrobenzoyl chloride in the presence of pyridine.[9] Since water reacts much more readily with this reagent than *t*-butyl alcohol does, it was necessary to dry the *t*-butyl alcohol extract rigorously. Though the yields were variable

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(1) This research was supported by Contract At(11-1)295 of the U. S. Atomic Energy Commission.

(2) Previous paper, M. L. Bender and D. F. Hoeg, THIS JOURNAL, **79**, 5649 (1957).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1954, Chap. VII; E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941); *cf.* N. C. Deno, T. Edwards and C. Perizzolo, THIS JOURNAL, **79**, 2108 (1957).

(4) S. Winstein, A. H. Fainberg and E. Grunwald, *ibid.*, **79**, 4152 (1957).

(5) A. I. Vogel, "Practical Organic Chemistry," Longmans-Green and Co., London, 1948.

(6) J. D. Roberts, R. E. McMahon and J. Hine, THIS JOURNAL, **72**, 4237 (1950).

(7) L. C. Bateman, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 881 (1938).

(8) E. D. Hughes, C. K. Ingold, S. Masterman and B. J. McNulty, *ibid.*, 910 (1940).

(9) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 164.

and the maximum yield obtained was 40%, the following procedure for derivatization was found satisfactory as seen in Table I showing the comparison of activities of the alcohol when measured directly and when measured *via* the *p*-nitrobenzoate. It should be pointed out that since the C^{14}–O bond is not broken in the derivatization step it is unlikely that there could be any kinetic isotope effect in the derivatization.

TABLE I

DERIVATIZATION OF 2-METHYL-2-PROPANOL-2-C^{14}

Sample	Specific activity, amp./mole × 10^{14}
t-Butyl alcohol	101.8
t-Butyl alcohol	101.4
t-Butyl alcohol	103.7
t-Butyl *p*-nitrobenzoate[a]	
5 recrystallizations	100.0
7 recrystallizations	102.0
9 recrystallizations	100.6
t-Butyl *p*-nitrobenzoate[b]	
5 recrystallizations	97.9
7 recrystallizations	98.6

[a] No added *t*-butyl chloride. [b] 0.11 *M* added *t*-butyl chloride.

A sample was removed from the reaction mixture at a given time and cooled to 0°. An equal volume of trichloroethylene was added and immediately enough solid potassium carbonate was added to saturate all the water. The flask was shaken for 30 seconds, keeping the flask immersed in ice to minimize the effect of the exothermicity of the hydration reaction. The organic layer was separated and dried successively over potassium carbonate (four days) and calcium sulfate (four days) and then poured into a reaction flask containing some calcium hydride. Pyridine (six times the calculated amount of alcohol) was added and left for two hours. *p*-Nitrobenzoyl chloride (two- to threefold excess) was added and refluxed for two to three days (without removal of the calcium hydride). After the derivatization reaction, 0.5 ml. of water was added to hydrolyze the excess *p*-nitrobenzoyl chloride and most of the solvent was evaporated. Dioxane (15 ml.) was added and the solution was evaporated again to remove the trichloroethylene. Cold water was then added with stirring and the mixture was treated with excess sodium bicarbonate solution to remove *p*-nitrobenzoic acid. The mixture was cooled in ice, the solid was filtered and recrystallized repeatedly from ethanol-water.

Experiments were carried out to determine whether the hydrolysis of *t*-butyl chloride was stopped during the procedure described above for the extraction and derivatization of the *t*-butyl alcohol. A solution of 2-methyl-2-propanol-2-C^{14} in 60% dioxane–40% water was prepared and the derivative prepared according to the above procedure, with and without the prior addition of *t*-butyl chloride (non-radioactive). The amounts of chloride and alcohol used simulated 20% reaction in the hydrolysis of 0.14 *M* *t*-butyl chloride, (*t*-butyl chloride, 0.11 *M*; *t*-butyl alcohol, 0.028 *M*). The results of these experiments are shown in Table I.

The results show that some dilution of the alcohol (2.6%) has occurred in the derivatizations with added *t*-butyl chloride. Calculation showed that about 0.67% of the *t*-butyl chloride had hydrolyzed, which would lead to negligible error in the worst cases in determining the kinetic isotope effect; this is primarily due to the small difference between the specific activities of the chloride and alcohol at any time. For example, an assumed kinetic isotope effect of 1.030 would lead to an experimental value of 1.027 at 10% reaction (the worst case) and 1.029 at 25% and 50% reaction, using the data in Table I.

Specific activity determinations were carried out as described previously[2] by combustion of the sample with copper-copper oxide to carbon dioxide. The carbon dioxide was introduced into an ionization chamber and the ionization current measured with a vibrating reed electrometer. One modification was the measurement of the amount of carbon dioxide in a constant volume manometer. The constant volume readings were corrected for the small amount of carbon dioxide produced in a blank experiment with the copper and copper oxide alone. This correction was ordinarily 2% of a sample of normal size.

Results and Discussion

The results of the determination of the kinetic isotope effect in the hydrolysis of 2-chloro-2-methylpropane-2-C^{14} are presented in Table II.

TABLE II

KINETIC ISOTOPE EFFECT IN THE HYDROLYSIS OF 2-CHLORO-2-METHYLPROPANE-2-C^{14}[e]

Fraction of reaction	Recrystns.	Specific activity,[a] amp./mole × 10^{14}	k/k^*
1.000	6	83.2	
1.000	8	84.7	
0.000	. .	84.1[b]	
.125	5[c]	82.7	1.018
.200	9[c]	83.6	1.007
.269	6[c]	80.3	1.055
.312	4[c]	83.0	1.016
.370	8	83.0	1.016
.486	6,8	83.4	1.042
.546	4[c]	83.3	1.015
		Av.	1.027 ± 0.015[d]

[a] These are mean values of from one to five determinations. [b] This value was used as a basis for calculating k/k^*. The initial specific activity of the *t*-butyl chloride was determined directly, not *via* a derivative. [c] In these determinations, it was not possible to ascertain whether the number of recrystallizations had been sufficient to reach constant activity. [d] The mean was calculated using weights for the individual points according to the number of individual determinations taken for each point. The standard deviation was calculated in the usual way.[10] [e] 60% dioxane–40% water at 24.80°.

The results indicate a value of k_{12}/k_{14} somewhat different in magnitude from those found in the nucleophilic substitution reactions of methyl iodide.[2] The specific activity of *t*-butyl alcohol from the infinity sample is seen to agree well with the initial specific activity of the *t*-butyl chloride. This confirms that there is no isotopic discrimination in the fast steps of the reaction where the carbonium ion is partitioned to produce 14% isobutylene and 86% *t*-butyl alcohol. It should be noted that the precision of the results is not as great in these determinations as in the determination of the kinetic isotope effects with methyl iodide,[2] probably because of the difficulties inherent in the isolation and derivatization of *t*-butyl alcohol.

Following Bigeleisen's derivation of an equation for the kinetic isotope effect in a reaction having a two-centered transition state,[11] Bigeleisen and Wolfsberg have proposed an equation for the effect in a three-centered transition state reaction[12]

$$k/k^* = \left[\frac{\dfrac{1}{m_b} + \dfrac{1}{m_c} + p\left(\dfrac{1}{m_b} + \dfrac{1}{m_a}\right) + \dfrac{2p^{1/2}}{m_b}}{\dfrac{1}{m_b{}^*} + \dfrac{1}{m_c{}^*} + p\left(\dfrac{1}{m_b{}^*} + \dfrac{1}{m_a{}^*}\right) + \dfrac{2p^{1/2}}{m_b{}^*}}\right]^{1/2} \left[1 + \sum_i^{3n-6} G(u_i)\Delta\mu_i - \sum_i^{3n'-6} G(u_i{}^{\ddagger})\Delta\mu_i{}^{\ddagger}\right] \quad (1)$$

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(10) A. G. Worthing and J. Geffner, "Treatment of Experimental Data," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 170.

(11) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).

(12) J. Bigeleisen and M. Wolfsberg, *ibid.*, **21**, 1972 (1953); **22**, 1264 (1954).

k/k^* is the ratio of rate constants for the reactions involving the molecular fragments[13] A, B and C and their respective isotopes at the reaction center

$$\mathrm{A} + \text{-B-C} \longrightarrow \mathrm{A}\ldots\mathrm{B}\ldots\mathrm{C} \longrightarrow \text{A-B-} + \mathrm{C}$$

The m's are the masses of the respective molecular fragments. p is the ratio of the formation of the A–B bond to the extension of the B–C bond in the transition state. The sums in (1) are functions $G(u_i)$, of vibrational frequencies only, multiplied by differences of vibrational frequencies upon isotopic substitution.

The first term in square brackets, the temperature-independent factor, is the ratio of the effective masses of the normal and isotopically substituted molecules in the transition state along the coördinate which leads to the products of reaction. Once a value of p has been chosen, the temperature-independent factor may be calculated readily. The choice of p will be discussed later, although it should be noted that the temperature-independent factor is not sensitive to this parameter.

In most cases simplifying assumptions have to be made in order to permit calculation of the temperature dependent factor, since the relevant vibrational frequencies in the transition state usually are not known. The usual simplification made is that the vibrational frequency of the bond undergoing rupture is zero in the transition state and that the frequencies of the other bonds are unaltered.[14] This corresponds to a model of the transition state in which the B–C bond is completely broken and the others unaltered. Notwithstanding these rather drastic simplifications, fair agreement between theory and experiment had been found with a number of reactions. But when one considers the limited range of values of k/k^* found experimentally for carbon-14 kinetic isotope effects (this range is 1.00 to about 1.15) it is evident that this agreement is of limited significance in these systems.

In the present work interest centers on the kinetic isotope effect in nucleophilic aliphatic substitution reactions, in particular the relation of the kinetic isotope effect to the mechanisms of these reactions. The two most important mechanisms concerned are the unimolecular and bimolecular mechanisms, designated S_N1 and S_N2, respectively.[3] In the S_N1 reaction the incoming group does not participate in the rate-determining step and the transition state may be represented as the partial ionization of the carbon–x bond. Interactions with the solvent, though important in facilitating the reaction, have been omitted from consideration as they are usually thought to be electrostatic in nature.[14a] In the S_N2 mechanism the incoming group does participate in the rate-determining step and therefore the transition state will consist of the entering group, the alkyl group and the leaving group. Degrees of participation of the entering group are, of course, to be expected; if a series of reactions is imagined in which the entering group is made progressively weaker in nucleophilic power, then the reaction will approach the S_N1 mechanism and there will be a region in which it will not be possible, in practice, to determine whether the reaction is still S_N2 or has changed completely to S_N1.

In applying the Bigeleisen–Wolfsberg equation to these reactions, it is necessary to choose a suitable value of p in the temperature-independent factor. In the S_N1 mechanism the choice of $p = 0$ is fairly straightforward. In the S_N2 mechanism when there is a symmetrical transition state (*i. e.*, the entering and leaving groups are both joined to carbon with half bonds) the value $p = 1$ would be used. Values of p greater than unity are not normally considered as they would imply a covalency greater than four for carbon. But values between 0 and 1 are possible, particularly for those reactions whose mechanism is intermediate between S_N1 and S_N2. It will, however, be shown that the temperature-independent factor is usually insensitive to the value chosen for p.

In the temperature independent-factor of equation 1, let $m_{\mathrm{a}} = am_{\mathrm{b}}$, $m_{\mathrm{c}} = cm_{\mathrm{b}}$ and $m_{\mathrm{b}*} = bm_{\mathrm{b}}$. Then

$$\text{TIF}\quad(\text{Temperature-independent factor}) = \left[\frac{1 + p + 2p^{1/2} + p/a + 1/c}{(1/b)(1 + p + 2p^{1/2}) + p/a + 1/c}\right]^{1/2}$$

When fragment B is $C^{12}H_3$ and B* is $C^{14}H_3$

$$\text{TIF} = \left[\frac{1 + 1/c}{0.882 + 1/c}\right]^{1/2} \text{ for } p = 0 \qquad (2)$$

$$\text{TIF} = \left[\frac{4 + 1/d}{3.528 + 1/d}\right]^{1/2} \text{ for } p = 1 \qquad (3)$$

where $1/d = 1/a + 1/c$. Using equations 2 and 3 the temperature-independent factor was calculated for various values of c and d. The results are plotted in Fig. 1. Some representative examples are given in the Table III.

TABLE III

THE EFFECT OF THE PARAMETER, p, ON THE TEMPERATURE-INDEPENDENT FACTOR OF THE REACTIONS OF CH_3X AND $C^{14}H_3X$

Leaving group C	Entering group A	c	a	d	Temperature-independent factor $p = 0$	$p = 1$
Cl	OH	2.37	1.13	0.77	1.045	1.048
I	OH	8.47	1.13	1.00	1.057	1.051
Cl	I	2.37	8.47	1.85	1.045	1.055
OH	I	1.13	8.47	1.00	1.033	1.051
I	NH_3	8.47	1.13	1.00	1.057	1.051
I	$N(C_2H_5)_3$	8.47	6.73	3.75	1.057	1.061

It is evident that the effect of changing p from 0 to 1 is generally small. It is further evident that in some cases the temperature-independent factor is greater for $p = 0$ than for $p = 1$, while in other cases the opposite occurs. To obtain the greatest differential between $p = 0$ and $p = 1$, the outgoing group should be as light as possible and the displacing group as heavy as possible. Of all the groups that participate in nucleophilic substitution, hydroxyl (outgoing) and iodine (incoming) are the best pair from this point of view and, even in this case, the change in the temperature-independent factor is only 1.8%. A difference of 2% between two and three center reactions should be measurable. However, to utilize a kinetic isotope effect

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[13] J. Bigeleisen and M. Wolfsberg, "Theoretical and Experimental Aspects of Isotope Effects in Chemical Kinetics," in "Advances in Chemical Physics," Interscience Publishers, Inc., New York, N. Y., 1957.

[14] J. Bigeleisen, *J. Phys. Chem.*, **56**, 823 (1952).

[14a] See, however, 3c and references cited therein.

TABLE IV

CARBON-14 KINETIC ISOTOPE EFFECTS IN NUCLEOPHILIC SUBSTITUTION REACTIONS

Reaction	Solvent	Temp., °C.	Mechanism	k_{12}/k_{14}	Reference
Methyl iodide-C^{14} + triethylamine	Benzene	25.05	SN2	1.10	2
Methyl iodide-C^{14} + pyridine	Benzene	25.05	SN2	1.14	2
Methyl iodide-C^{14} + hydroxide ion	50% Dioxane–water	25.05	SN2	1.09	2
Methyl iodide-C^{14} + N,N-dimethyl-*p*-toluidine	Methanol	48.5	SN2	1.12	15
Methyl iodide-C^{14} + N,N-diethylaniline	Methanol	62.7	SN2	1.12	15
Methyl iodide-C^{14} + N,N-dimethyl-*o*-toluidine	Methanol	62.7	SN2	1.13	15
Methyl iodide-C^{14} + silver ion	70% Ethanol–water	24.88	SN1 + SN2	1.09	2
2-Chloro-2-methylpropane-2-C^{14}	60% Dioxane–water	25.02	SN1	1.03	Present investigation

for such a purpose, the experiments, through measurements of the temperature coefficient, would have to assign part of the effect to the zero point energy term and the remainder to the temperature-independent entropy term. In view of the uncertainty in the present measurements, it was not thought desirable to pursue this course.

The prediction derived from the Bigeleisen–Wolfsberg equation that the temperature-independent factor (and possibly the kinetic isotope effect itself) may be greater in some cases for an SN2 (three-center reaction) than for the corresponding SN1 (two-center reaction) is consistent with the results obtained in this investigation which are compared in Table IV with the kinetic isotope effects in other nucleophilic displacement reactions. However, the comparison between SN1 and SN2 reactions shown in Table IV must be seriously qualified by the presence of different leaving groups (Cl *vs.* I) and different reaction conditions, including solvent and temperature.

The temperature-independent factor of the kinetic isotope effect in a two-center reaction of 2-chloro-2-methylpropane-2-C^{14} (involving carbon–chlorine rupture) calculated from eq. 1 with $p = 0$ and $m_a = 0$ is equal to 1.013, which compares favorably with the experimental kinetic isotope effect of 1.027. The value of the temperature-independent factor for *t*-butyl chloride is considerably lower than those calculated for the reactions of methyl iodide-C^{14} and may account for a main part of the difference in the kinetic isotope effect noted between methyl iodide and *t*-butyl chloride.[16]

It appears that a more satisfactory approach to the use of kinetic isotope effects in differentiating between SN1 and SN2 reactions may be found in the determination of α-deuterium isotope effects in substitution reactions.[17] The isotope effects here apparently depend on differences in vibrational frequencies due to differences in hybridization in the transition states of the two processes and may be a more sensitive measure of SN1 and SN2 processes.

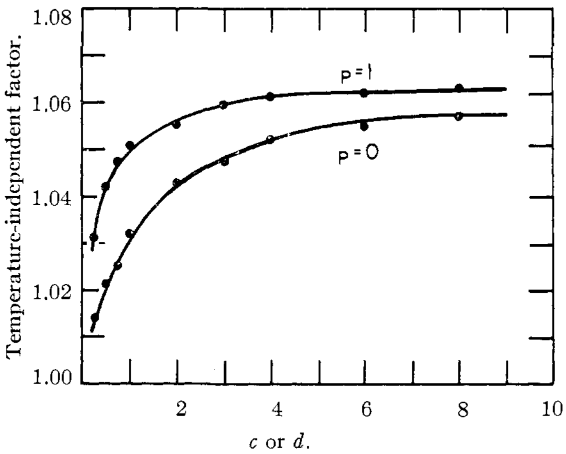

Fig. 1.—The effect of the masses of the entering and/or leaving molecular fragments on the temperature-independent factor of the kinetic isotope effect of reactions involving two-center or three-center transition states.

(15) G. J. Buist and M. L. Bender, THIS JOURNAL, **80**, 4308 (1958).

(16) A referee has pointed out that there is another possible reason for the lower isotope effect with 2-chloro-2-methylpropane-2-C^{14} as compared with methyl-C^{14} iodide, which has little to do with the SN1 or SN2 character of the reactions: the electron-releasing effect of the three methyl groups in the chloride may loosen the carbon–chlorine bond in the ground state resulting in a lower zero point energy (temperature dependent) effect with the chloride than with the methyl iodide.

(17) A. Streitwieser, Jr., and R. C. Fahey, *Chemistry & Industry*, 1417 (1957); W. H. Saunders, Jr., S. Asperger and D. H. Edison, *ibid.*, 1417 (1957); R. R. Johnson and E. S. Lewis, *Proc. Chem. Soc.*, 52 (1958).

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