column. The yield and boiling point are given in Table I. An infrared spectrum of the xanthates showed the absence of –OH bands.

The ester was then pyrolyzed in a 50-ml. flask attached to an 18-in. Vigreux column at approximately 200°. The olefin was collected in a cooled receptacle and the mercaptan was trapped in a saturated solution of barium hydroxide. A free flame was found to offer the best control of foaming in the decomposition of the xanthate. The resulting olefins were analyzed by gas chromatography.

Preparation and Pyrolysis of Acetates.—The acetates were prepared by the action of 300 ml. of pure acetic anhydride and 10 ml. of dry pyridine on 0.75 mole of the corresponding alcohol. The mixture was heated on a steam-bath for two hours and then poured into ice-water. The oily layer which formed was separated and then washed with water and extracted with ether. The ether was evaporated under vacuum and the acetate was fractionally distilled; see Table I for physical constants.

The acetates were pyrolyzed in conventional fashion according to the method of Bailey.[18] The results are listed in Table II.

Isomerization Experiments.—Approximately 10 g. of 5,5-dimethyl-2-hexene, 2,2-dimethyl-3-hexene and the olefin mixture obtained from the pyrolysis of 5,5-dimethyl-3-acetoxyhexane, were passed independently through an alumina (Alcoa F-20) column, 1″ in diameter and 12″ long at 350°. Each olefin was passed through the column from 6 to 10 times under a slight nitrogen pressure. The olefins were collected in a trap at −78° and were analyzed after each run by gas chromatography. A Fisher–Gulf partitioner was employed with a flow rate of helium from 10 to 20 ml./min.; chart speed, $^1/_4$ in./min.; pressure, 20 p.s.i.; temperature, 67°; sensitivity, 40 to 50%; column packing, 50% β,β'-oxydipropionitrile on Fisher Columpak 30–60 mesh; column length, 14 ft; sample volume, 0.001 to 0.005 ml. The results of these isomerizations are listed in Table IV.

Acknowledgments.—The authors are grateful to the du Pont Company and the Purdue Research Foundation for fellowship grants. The authors also wish to express their thanks to Dr. James H. Brewster of the Purdue Chemistry Department for his suggestions and advice.

LAFAYETTE, IND.

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[18] W. J. Bailey and C. King, *J. Org. Chem.*, **21**, 858 (1956).

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

The Isotope Effect and its Relation to the Validity of Isotopic Tracer Experiments[1]

BY CLAIR J. COLLINS AND M. H. LIETZKE

RECEIVED MARCH 3, 1959

The ORACLE[11] has been employed to determine, for first-order irreversible reactions, the relation between fraction of reaction ($f = 1 - e^{-kt}$) and the accumulated product ratio $R\left(R = \frac{1 - e^{-k^*t}}{1 - e^{-kt}}\right)$ over a range of values for the isotope effect (k^*/k) of 0.05 to 0.99. Similar calculations have been made for f as a function of the ratio (x) of the differentials of the fractions of labeled to unlabeled molecules formed. All results are presented graphically, and are discussed with respect to their possible effect upon the validity of certain experiments with isotopic elements.

The isotopes of carbon have been widely used as tracers in the study of organic and biochemical reactions.[2] Deuterium and tritium also have been employed in mechanism studies,[2b] the tritium being nearly always in trace concentrations.[3] The difference in reaction rate between labeled and unlabeled compounds—that is, the isotope effect—pertains to tracer chemistry in at least three ways: (1) in determinations of the slow or so-called "rate-determining steps" of many reactions,[3,4] (2) in the study of hyperconjugation,[5,6] and (3) because of the possible doubt which might be cast upon the validity of tracer experiments when the manner of operation of the isotope effect is not clearly understood.

The general theory of homocompetitive reactions is well known,[7,8] and has been applied to the field of isotopic chemistry by Bigeleisen[9] and by Melander,[10] who have drawn attention to some of the errors which can arise in tracer experiments because of the "lagging" of the heavy isotope.[10]

In the present paper we wish to enlarge upon the discussions of Bigeleisen[9] and Melander[10] by presenting the results of calculations carried out with the assistance of the ORACLE,[10a] which will show how the ratio of product from labeled reactant to product from unlabeled reactant varies over a wide range of isotope effect values. These calculations will illustrate several types of error which can be introduced into tracer experiments;

[1] This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corporation.

[2] (a) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert and P. Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949; (b) J. G. Burr, Jr., "Tracer Applications for the Study of Organic Reactions," Interscience Publishers, Inc., New York, N. Y., 1957; (c) A. Murray, III, and D. L. Williams, "Organic Syntheses with Isotopes," Parts I and II, Interscience Publishers, Inc., New York, N. Y., 1958; (d) S. Aronoff, "Techniques of Radiobiochemistry," Iowa State College Press, Ames, Iowa, 1956; (e) C. L. Comar, "Radioisotopes in Biology and Agriculture," McGraw-Hill Book Co., Inc., New York, N. Y., 1955.

[3] L. Melander, *Arkiv Kemi*, **2**, 211 (1950).

[4] (a) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955); (b) G. A. Ropp, *Nucleonics*, **10**, 22 (1952); (c) P. E. Yankwich, *Ann. Rev. Nuclear Sci.*, **3**, 235 (1953); (d) V. Gold and D. P. N. Satchell, *Quart. Revs.*, **9**, 51 (1955).

[5] V. J. Shiner, THIS JOURNAL, **74**, 5285 (1952); **75**, 2925 (1953); **76**, 1603 (1954); **78**, 2653 (1956); V. J. Shiner and S. Cross, *ibid.*, **79**, 3599 (1957).

[6] E. S. Lewis and C. E. Boozer, *ibid.*, **74**, 6307 (1952); **76**, 791 (1954); C. E. Boozer and E. S. Lewis, *ibid.*, **76**, 794 (1954); E. S. Lewis and G. M. Coppinger, *ibid.*, **76**, 4495 (1954).

[7] (a) A. W. Francis, A. J. Hill and J. Johnston, *ibid.*, **47**, 2211 (1925); (b) C. K. Ingold, A. Lapworth, E. Rothstein and P. Ward, *J. Chem. Soc.*, 1959 (1931); (c) M. L. Bird and C. K. Ingold, *ibid.*, 918 (1938); (d) C. K. Ingold and M. S. Smith, *ibid.*, 705 (1938); (e) G. A. Benford and C. K. Ingold, *ibid.*, 929 (1938); (f) E. D. Hughes, C. K. Ingold and N. Taher, *ibid.*, 949 (1940); (g) E. J. DeWitt, C. T. Lester and G. A. Ropp, THIS JOURNAL, **78**, 2101 (1956).

[8] T. S. Lee, "Rates and Mechanism of Reactions," Interscience Publishers, Inc., New York, N. Y., 1953, pp. 100–130.

[9] (a) J. Bigeleisen, *Science*, **110**, 14, 149 (1949); (b) J. Bigeleisen and M. Wolfsberg in "Advances in Chemical Physics," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1958, pp. 35–53.

[10] Reference 3, pp. 248–257.

[10a] Oak Ridge Automatic Computer and Logical Engine.

moreover they will be useful in assisting the investigator to estimate graphically the value of the isotope effect for a given reaction knowing (a) the isotopic ratio of initial reactant, (b) the isotopic ratio of the product accumulated at any time t, and (c) the fraction f of unlabeled material which has undergone reaction at any time t.[11]

We shall limit our discussion to irreversible, first-order reactions of the type in which A and A*

$$\mathrm{A} \xrightarrow{k} \mathrm{B}$$

$$\mathrm{A}^* \xrightarrow{k^*} \mathrm{B}^*$$

are the unlabeled and labeled reactants, B and B* are the products arising from the unlabeled and labeled reactants, respectively, and k and k^* are the appropriate specific reaction rate constants. If n and n^* refer to the number of molecules or concentrations of A and A* in a given reaction at time t, and n_0 and n_0^* represent these same molecules at time zero, then

$$-\mathrm{d}n(t)/\mathrm{d}t = kn$$

hence

$n/n_0 = e^{-kt}$ = fract. of unlabeled molecules remaining at time t

Then

$f = 1 - e^{-kt}$ = fract. of unlabeled molecules which have undergone reaction at time t

Similarly,

$* = 1 - e^{-k^*t}$ = fract. of labeled molecules which have undergone reaction at time t

Thus the ratio of product fraction of the labeled to unlabeled molecules at any time becomes

$$R = \frac{1 - e^{-k^*t}}{1 - e^{-kt}}$$

Clearly, for very low concentrations of the labeled material, R in the case of radioactive isotopes becomes equal to the ratio of the molar radioactivity of the accumulated product at any time, to the molar radioactivity of reactant at time zero, providing the radioactive atoms go with the product molecules. Although calculation of the points necessary to provide plots of R *versus* f over a wide range of values for k^*/k would be very time consuming if done by hand, we have been able to perform the calculations very rapidly through the use of the ORACLE.[11] Given in Fig. 1 are plots of R *versus* f in which k^*/k has been varied from 0.05 to 0.80 in increments of 0.05 (the deuterium, tritium isotope effect range) for values of f from zero to unity. In Fig. 2 are presented plots of R *versus* f in which k^*/k has been varied from 0.81 to 0.99 in increments of 0.01 (the carbon-14, carbon-13 isotope effect range). In Fig. 3 are the corresponding plots for k^*/k from 0.950 to 0.998 in increments of 0.002, for values of f from zero to 0.5 (the range useful for stable isotopes of carbon, oxygen nitrogen and sulfur). In the plots shown in Figs. 1, 2 and 3 the intercept of each curve on the R axis at $f = 0$ corresponds to the value of k^*/k for that particular curve. Given in Fig. 4 are curves representing plots of R *versus* f for values of k^*/k between 0.05 and 0.80 in increments of 0.05 for values of f between 0.90 and 0.99, and in Fig. 5 similar plots for values of f from 0.990 to 0.999.

Finally it is of interest to consider, in addition to the *cumulative* ratio R, the ratio[2] of the differentials of the fractions of labeled to unlabeled molecules formed. At any time t the infinitesimal increment of the fraction of unlabeled product formed in the time interval dt for a first-order reaction is

$$\mathrm{d}f = \frac{-\mathrm{d}n}{n_0} = ke^{-kt}\,\mathrm{d}t$$

The corresponding expression for the labeled product is

$$\mathrm{d}f^* = \frac{-\mathrm{d}n^*}{n_0^*} = k^*e^{-k^*t}\,\mathrm{d}t$$

Then

$$x \equiv \frac{\mathrm{d}f^*}{\mathrm{d}f} = \frac{k^*}{k} \cdot \frac{e^{-k^*t}}{e^{-kt}} = \frac{k^*}{k} \cdot e^{k(1-\frac{k^*}{k})t}$$

and

$$\ln x = \ln \frac{k^*}{k} - kt\left(\frac{k^*}{k} - 1\right)$$

Now the fraction of unlabeled molecules remaining at time t is

$$(1 - f) = \frac{n}{n_0} = e^{-kt}$$

or

$$\ln(1 - f) = \ln \frac{n}{n_0} = -kt$$

Hence

$$\ln x = \left(\frac{k^*}{k} - 1\right)\ln(1 - f) + \ln \frac{k^*}{k}$$

By use of the foregoing equation, and with the assistance of the ORACLE,[11] we now have made plots of x *versus* f (fraction of reaction) for values of k^*/k of 0.05, 0.10 and 0.30 (Fig. 5); and for values of k^*/k of 0.7 ,0.8 0.9 and 0.93 (Fig. 6).[12a,b,c]

Discussion

The plots of Figs. 1, 2 and 3 extend those given by Melander[10] over a wide range of possible isotope effects, and allow an estimation of k^*/k for any first-order reaction, when the quantities f and R are given. It is only necessary to find that curve which most nearly fits the experimental values of f and R, then extrapolate to zero f, where R becomes equal to k^*/k. The plots of Figs 4 and 5 offer rather dramatic evidence of the dependence of R upon f. For example, Fig. 5 illustrates that after 99.9% of the unlabeled molecules have reacted ($f = 0.999$), for $k^*/k = 0.20$, only 75% of the labeled molecules have been converted to product; or for $k^*/k = 0.05$, only 29% of the labeled molecules have undergone reaction! An interesting example of the extent to which the operation of an isotope effect can lead different investigators to

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[11] For the derivation of exact equations which allow a calculation of the experimental isotope effect knowing the foregoing quantities, see J. Y. Tong and P. E. Yankwich, *J. Phys. Chem.*, **61**, 540 (1957).

[12] (a) The data represented by the plots of Figs. 1–5 are published in "Tables of Isotope Effect Functions for Homocompetitive First-Order Reactions," and in the supplement thereto, by M. H. Lietzke and C. J. Collins, Oak Ridge National Laboratory Report No. 2678. Large scale plots of Figs. 1–7 are also reproduced. (b) It can be demonstrated for any of the curves of Figs. 6 and 7, that the area bounded by the curve and the horizontal line $x = 1$ to the left of the point where the curve intersects the line $x = 1$ must equal the area bounded by the curve and the horizontal line $x = 1$ to the right of the intersection point (see ref. 12a); the theorem is also a consequence of the law of conservation of mass. (c) See also A. M. Downes, *Austr. J. Sci. Res.*, **5A**, 521 (1952); ref. 9b, p. 43, and W. A. Bonner and C. J. Collins, THIS JOURNAL, **75**, 3693 (1953).

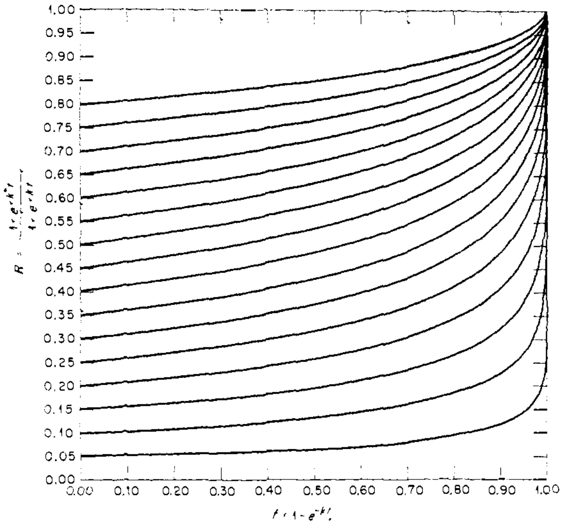

Fig. 1.

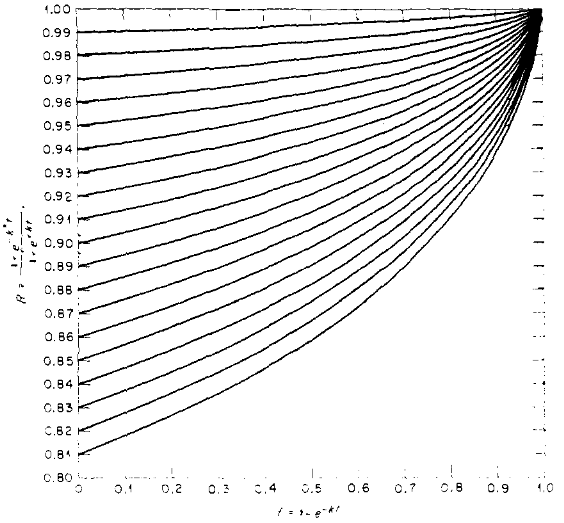

Fig. 2.

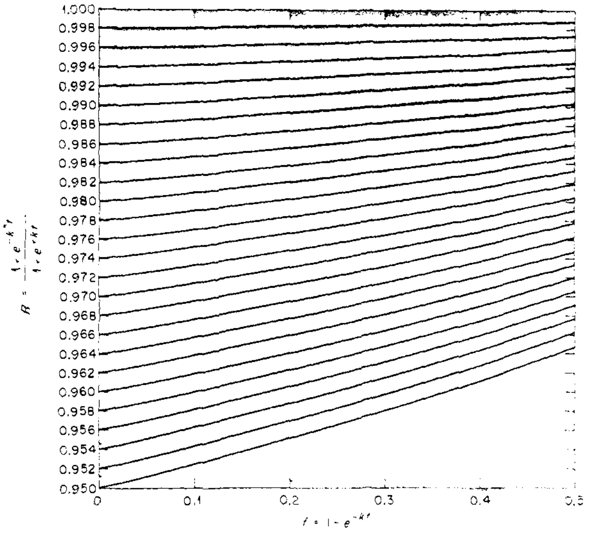

Fig. 3.

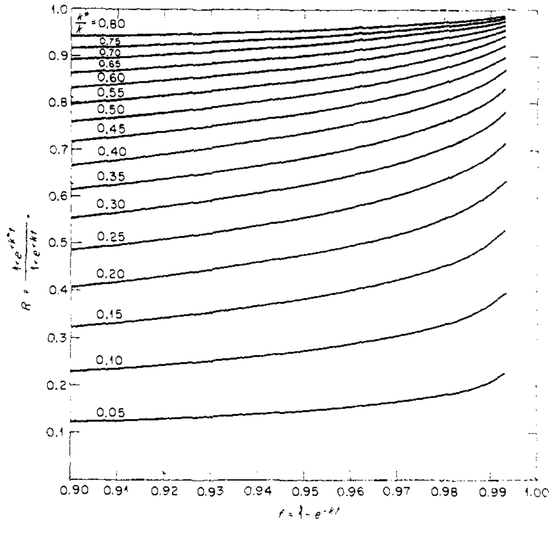

Fig. 4.

opposite conclusions is to be found in the work of Friedberg and Kaplan[13] and of Weygand, Simon and Klebe.[14] Friedberg and Kaplan,[13] on the basis of their observation that glycose-1-$^{3}H_1$ is converted to its phenylosazone without loss of tritium, concluded that the mechanism of Weygand,[15] involving an Amidori rearrangement, was invalidated. These investigators[13] also state that an isotope effect (k_H/k_T) of at least fifty would be necessary during the Amidori rearrangement to explain their results, and that it is, therefore, extremely unlikely that an isotope effect could account for the essentially quantitative retention of tritium during glucosazone formation. Weygand and his co-workers,[14] however, in a very convincing and exhaustive study, prepared glucose labeled in the 1-position *both with deuterium and with tritium.* The k_T/k_D isotope effect is considerably smaller than the k_T/k_H effect, the deuterium being present in the 1-position essentially "carrier free," whereas the tritium was in trace-label concentrations. The doubly labeled glucose was found to yield osazone in which 10% of the tritium had been lost when the reaction was carried out in D_2O. When the reaction was carried out in the presence of *p*-toluidine, 32% of the tritium was lost. The intimate mechanism of osazone formation has not yet been established. Since a total yield of crude osazone of 55% was reported,[14,16] however, it is clear from Figs. 1–5, as well as from Weygand's work,[14] that the observation[13] of Friedberg and Kaplan is not, of itself, sufficient evidence upon which to invalidate the operation of an Amidori rearrangement.[13–15]

Finally, the plots of Figs. 6 and 7 illustrate the dangers inherent in tracer experiments which proceed in low yields, and for which the reaction mechanisms are unknown. Consider, for example, a carbon-14 tracer first-order reaction in which no radioactivity is lost from the reactant or product

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[13] F. Friedberg and L. Kaplan, THIS JOURNAL, **79**, 2600 (1957).

[14] F. Weygand, H. Simon and J. F. Klebe, *Chem. Ber.*, **91**, 1567 (1958).

[15] F. Weygand, *Ber.*, **73**, 1284 (1940).

[16] See also E. Knecht and F. P. Thomson, *J. Chem. Soc.*, **125**, 222 (1924), for a study of the relation between yield of osazone and reaction conditions.

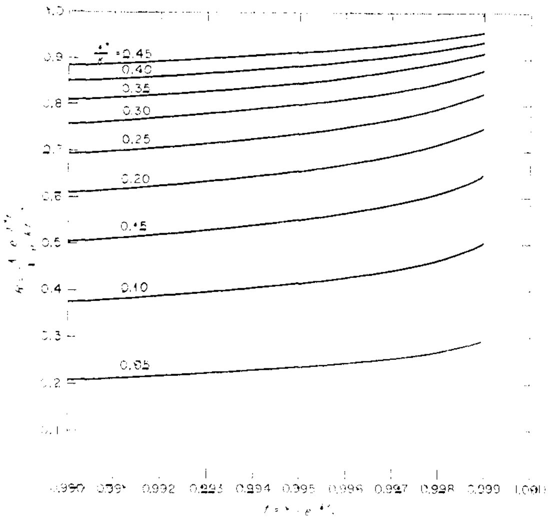


Fig. 5.

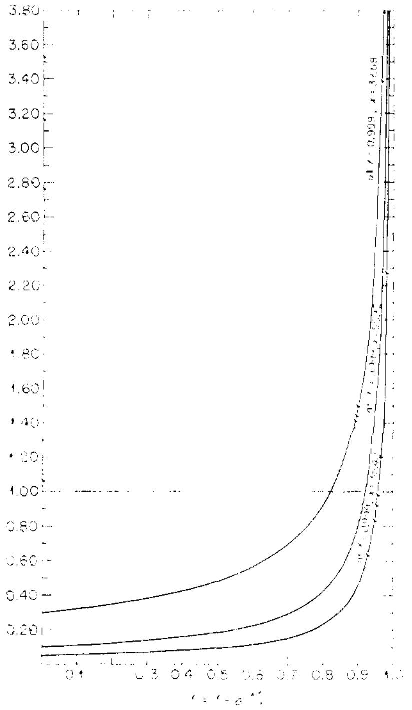


Fig. 6.

molecules, but in which the isotopic bond is involved in the slow step. We next assume an intermolecular isotope effect (k^*/k) of 0.90 and a total yield of 10% during this reaction. If the 10% of product accumulates during f = 0 to f = 0.10, then it will have a molar radioactivity of about 0.91 that of reactant. If, however, the 10% of product accumulates during f = 0.90 to f = 1.00, then it will possess a molar radioactivity about 1.2 that of reactant. For such reactions proceeding in smaller yields, the situation becomes correspondingly worse. Figures 6 and 7 may thus provide a clue for the peculiar results noticed during the iodoform reaction.[17,18] For example,

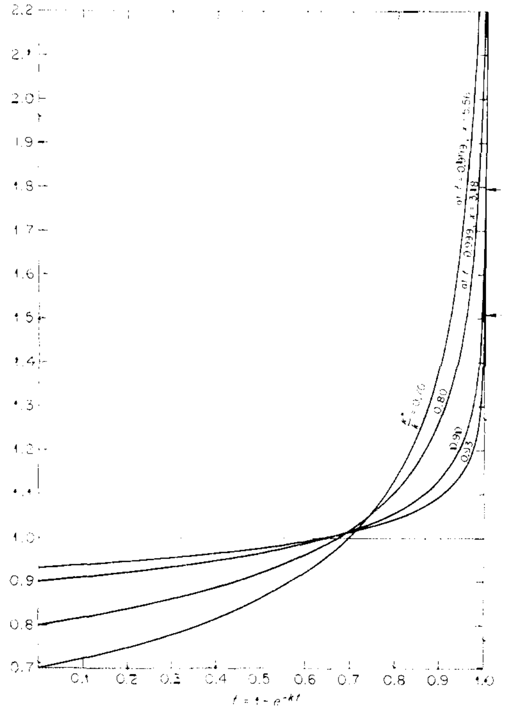
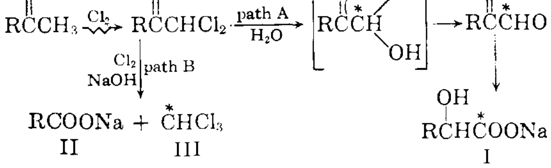


Fig. 7.

Roe[17] reported that the iodoform obtained from acetone-1-C^{14} had a higher molar radioactivity than the acetic-2-C^{14} acid derived therefrom. Later workers[19] observed no difference between the molar radioactivities of the iodoform-C^{14} and the acetic-2-C^{14} acid formed by the iodoform reaction of acetone-1-C^{14}. Bonner,[18] however, noticed that the iodoform-C^{14} obtained when 3-phenyl-2-butanol-1-C^{14} was subjected to this degradative procedure had an unaccountably high molar radioactivity in cases in which the yield was about 55% or less. It is significant that Kendrick, Benjamin and Collins[20] isolated chiefly *p*-methylmandelic acid, when chlorine was bubbled slowly through a methanol–sodium hydroxide solution of *p*-methylacetophenone, but when the chlorine addition was more rapid the chief product was *p*-toluic acid (equation 1, R = *p*-C_7H_7; for convenience the methyl group of the reactant is shown as labeled)

(1)


Equation 1 thus provides a possible explanation of the high molar radioactivities noticed[17,18] for the haloform (in equation 1 chloroform, but in the reported[17,18] cases, iodoform). Path A undoubtedly takes precedence over path B under conditions of slow chlorine addition, and high concentrations of

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[17] A. Roe and E. L. Albenesius, THIS JOURNAL, **74**, 2402 (1952).

[18] W. A. Bonner and D. D. Tanner, *ibid.*, **80**, 1448 (1958).

[19] G. A. Ropp, W. A. Bonner, M. T. Clark and V. F. Raaen, *ibid.*, **76**, 1711 (1954).

[20] L. W. Kendrick, B. M. Benjamin and C. J. Collins, *ibid.*, **80**, 4062 (1958).

alkali. As the reaction proceeds, however, the production of organic acid through path A uses up the available alkali, thus slowing down the production of I, and allowing path B to proceed. Path A thus could be considered to proceed from $f = 0$ to some intermediate fraction (Fig. 6) at which point path B becomes more important. If the slow step of the reaction occurs before the formation of the intermediate $R\overset{\overset{O}{\|}}{C}\overset{*}{C}HCl_2$, then from Fig. 6 it can be seen that Compound I should possess a smaller molar radioactivity than the reactant, whereas the molar radioactivity of the haloform III should be greater than that of the reactant.

Acknowledgment.—The authors wish to thank Dr. R. W. Stoughton for his assistance through several informative discussions of the contents of this paper.

Oak Ridge, Tenn.

[Contribution from the Department of Chemistry of The Pennsylvania State University]

Stereospecific *trans* Radical Addition of DBr to the 2-Butenes. Syntheses of *erythro*- and *threo*-3-Deuterio-2-bromobutanes[1,2]

By Philip S. Skell and Richard G. Allen

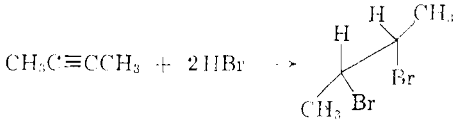
Received April 2, 1959

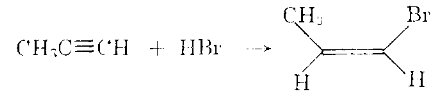
Pure *erythro*- and *threo*-3-deuterio-2-bromobutanes can be synthesized by radical chain additions of deuterium bromide to *trans*- and *cis*-2-butene, respectively. Structures and purity were determined by alkaline dehydrohalogenation, *erythro*-yielding *trans*-2-butene and 2-deuterio-*cis*-2-butene, *threo*- yielding *cis*-2-butene and 2-deuterio-*trans*-2-butene. The mechanistic implications are considered.

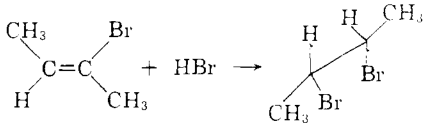
Introduction

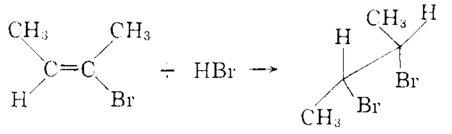
Optically active alkyl halides have been employed frequently in mechanism studies. Unfortunately there is no satisfactory criterion for establishing the optical purity of the alkyl halides prepared from optically pure alcohols. Since it has not been possible to prepare the pure enantiomers, in most instances the starting materials have been of uncertain purity, and the mechanistic conclusions may be ambiguous. There are often advantages in working with diastereoisomers employing, for example, infrared spectral analysis, since isomer purity can be determined without resorting to the tedium of exhaustive resolution. If these diastereomers are deuterium-labeled at one of the asymmetric centers removed from the reactive site, they should prove to be as valuable as the pure unlabeled enantiomorphs. Convenient synthetic routes to these substances have not been hitherto reported.

Radical chain addition reactions to acyclic olefins have been observed to be stereospecific only for hydrogen bromide,[3-8] which adds to olefins in *trans* processes.


(1)[4]


(2)[7]


(3)[5,6]


(4)[5,6]

Both Epstein[5] and Goering and Larsen[6] failed to obtain stereospecific *trans* additions to the isomeric 2-bromo-2-butenes, the products containing 5–10% of the 2,3-dibromobutane which would have resulted from *cis* addition. Although the isomer contamination may be attributed to isomerization of the starting olefin, it would also be reasonable to interpret the results in terms of a combination of stereospecific and non-stereospecific processes in approximately 4:1 ratio.

Results and Discussion

Since the 2-butenes are less readily isomerized than the 2-bromo-2-butenes, the addition of deuterium bromide to the 2-butenes promised to be a more favorable system to study.

At temperatures between −78 and −60°, illumination of a mixture of *cis*- or *trans*-2-butene and deuterium bromide initiates very rapid chain reactions to produce the 3-deuterio-2-bromo-

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[1] This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research & Development Command, under contract No. AF 49(638)-457.

[2] This paper was presented before the Organic Section of The American Chemical Society at the Chicago Meeting, September, 1958.

[3] P. S. Skell, R. C. Woodworth and J. H. McNamara, This Journal, **79**, 1253 (1957).

[4] C. Walling, M. S. Kharasch and F. R. Mayo, *ibid.*, **61**, 1711 (1939).

[5] M. Epstein, University of Syracuse, Thesis, 1951.

[6] H. L. Goering and D. W. Larsen, *ibid.*, **79**, 2653 (1957).

[7] P. S. Skell and R. G. Allen, *ibid.*, **80**, 5997 (1958).

[8] Similar additions have been observed with substituent cyclohexenes: (a) H. L. Goering, P. I. Abell and B. F. Aycock, *ibid.*, **74**, 3588 (1952); (b) H. L. Goering and L. L. Sims, *ibid.*, **77**, 3465 (1955); (c) H. L. Goering, D. I. Relyea and D. W. Larsen, *ibid.*, **78**, 348 (1956); (d) F. G. Bordwell and W. A. Hewett, *ibid.*, **79**, 3493 (1957).