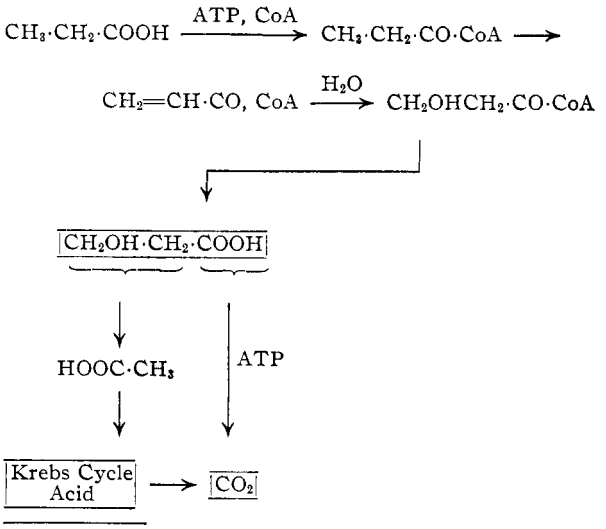
with time. This spot, identified as βHP, was characterized by (a) two dimensional co-chromatography with authentic βHP, (b) dichromate oxidation[7] of βHP derived from propionate-2-C^{14}, to a dicarboxylic acid which co-chromatographed with malonic acid. The dicarboxylic acid was degraded by pyrolysis[8] to radioactive acetate and CO_2 and (c) esterification of the acid with diazomethane and conversion to a hydroxamic acid (with hydroxylamine) which co-chromatographed with authentic βHP hydroxamate.

Both propionate-1-C^{14} and βHP-1-C^{14}[9] rapidly release the carboxyl-C^{14} as $C^{14}O_2$. No radioactive Krebs cycle acids are produced. The cofactor required for the oxidation of βHP-1-C^{14} to $C^{14}O_2$ is ATP.

Under the same conditions, propionate-2-C^{14} and βHP-2-C^{14}[9] slowly release C^{14} as $C^{14}O_2$, only after the appearance of radioactive citric, succinic, malic and fumaric acids. With propionate-3-C^{14} a rate of $C^{14}O_2$ release between that of propionate-1-C^{14} and of -2-C^{14} is observed with the formation of labeled Krebs cycle acids. Succinate derived from propionate-1-C^{14} is not labeled. Succinate derived from propionate-2-C^{14} is labeled exclusively in the methylene groups and succinate derived from propionate-3-C^{14} is labeled exclusively in the carboxyl groups.

The conversion of propionate-C^{14} to βHP-C^{14} is dependent on oxygen, ATP and CoA. Other cofactors were not tested.

The pathway may be formulated as[10]



(7) By the method used for lactate oxidation in S. Aronoff, "Techniques of Radiobiochemistry," The Iowa State College Press, Ames, Iowa, 1956, p. 141.

(8) S. Aronoff, ref. 7, p. 140.

(9) Radioactive βHP, presumably labeled as shown, was isolated by paper chromatography of the reaction product of propionate-1-C^{14} or -2-C^{14} oxidation.

(10) Compounds in blocks were isolated and characterized.

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THE STEREOSPECIFIC RADICAL ADDITION OF HYDROGEN BROMIDE TO *cis*- AND *trans*-2-BROMO-2-BUTENE[1]

Sir:

In previous work it was found that a high degree of stereospecificity is observed in the radical addition of hydrogen bromide to cyclohexene[2,3] and cyclopentene[4] derivatives. From this and other considerations it appeared possible that under favorable conditions stereospecificity might be observed with this addendum in acyclic systems. We wish to report that the radical addition of hydrogen bromide to the isomeric 2-bromo-2-butenes in liquid hydrogen bromide at −80° is indeed stereospecific and results in almost complete *trans* addition. Other radical additions which have been investigated have been found to be non-stereospecific[5] and apparently this is the first report of a stereospecific radical addition in an acyclic system.

The additions were promoted by irradiation with a quartz-jacketed Hanovia type SC-2537 lamp which fit into the reaction vessel so that the reaction mixture occupied the annular space between the walls of the lamp and reaction vessel. During the reaction the vessel was immersed in a Dry Ice–acetone bath. Mixtures of approximately 20 ml. of anhydrous liquid hydrogen bromide and 5 g. of *cis*- or *trans*-2-bromo-2-butene (shown to be homogeneous by gas chromatographic analysis[6] and physical properties) were irradiated after which the hydrogen bromide was allowed to evaporate and the composition of the residual reaction mixture determined by gas chromatographic[6] and infrared analysis.

In a typical experiment pure *cis*-2-bromo-2-butene in liquid hydrogen bromide was irradiated for 7.5 minutes. The composition of the product (gas chromatographic analysis[6]) was found to be < 0.5% 2-bromo-2-butene (largely isomerized to the *trans* isomer), 3% 2,2-dibromobutane (presumably formed by ionic addition), 92% *meso*-2,3-dibromobutane, 5% *dl*-2,3-dibromobutane and < 0.5% 1,2-dibromobutane.

Irradiation of *trans*-2-bromo-2-butene for 15 minutes under similar conditions gave a mixture consisting of 5% of unreacted *trans*-2-bromo-2-butene, 83% *dl*-2,3-dibromobutane, 8.5% *meso*-2,3-dibromobutane and 3.5% 1,2-dibromobutane. The analytical method was calibrated and confirmed using pure authentic samples of all of the components and synthetic mixtures of these. Infrared spectroscopic examination of the reaction products also showed that the *cis*-bromobutene is converted primarily to *meso*-dibromide and the

(1) This work was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF 18(600)1037.

(2) H. L. Goering, P. I. Abell and B. F. Aycock, Jr., THIS JOURNAL, **74**, 3588 (1952).

(3) H. L. Goering and L. L. Sims, *ibid.*, **77**, 3465 (1955).

(4) K. L. Howe, unpublished work.

(5) P. S. Skell and R. C. Woodworth, THIS JOURNAL, **77**, 4638 (1955); P. S. Skell, R. C. Woodworth and J. H. McNamara, *ibid.*, **79**, 1253 (1957).

(6) Excellent separation was obtained with a 10 ft. column packed with the commercial detergent, Tide. An operating temperature of 70° and flow rate of 40 ml. helium per minute were used to check for intercontamination of the isomeric 2-bromo-2-butenes. An operating temperature 120° was used for analysis of the reaction mixtures.

trans-bromobutene gives primarily *dl*-dibromide. These experiments were repeated several times and found to be reproducible. Increasing the reaction (irradiation) time to one hour did not result in any significant changes.

That the above additions are radical rather than ionic is clear from the orientation. When a mixture of *cis*-2-bromo-2-butene and liquid hydrogen bromide was allowed to stand in the dark at −80° for one hour the reaction mixture was found to contain 8.5% of bromobutene (mostly *trans* isomer) and 91.5% 2,2-dibromobutane. Under similar conditions using *trans*-2-bromo-2-butene the reaction mixture consisted of 10% of unreacted bromobutene, 87% 2,2-dibromobutane and 3% *dl*-2,3-dibromobutane (presumably formed by radical addition). These experiments also were found to be reproducible.

The present work demonstrates clearly that under the present conditions the radical addition involves a stereospecific *trans* addition. Assuming that the chain process involves two steps, (1) addition of a bromine atom to form an intermediate radical followed by (2) transfer with the addendum,[3,7] it is clear that different intermediate radicals are formed from the isomeric bromobutenes which undergo the transfer step faster than they are interconverted. Clearly the time interval between the two steps must be very short. A concerted process involving attack of a bromine atom on a substrate molecule complexed with hydrogen bromide has been suggested previously[3] and may be involved in the present case.

(7) M. S. Kharasch, J. V. Mansfield and F. R. Mayo, THIS JOURNAL, **59**, 1155 (1937).

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ISOPROPOXYFLUOROMETHYLENE[1]

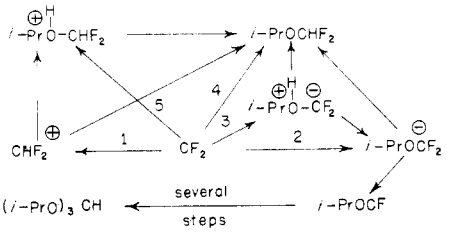
Sir:

Methylene is formed in such homolytic reactions as the decomposition of diazomethane and the photolysis of ketene,[2] and some of its derivatives apparently are formed in analogous reactions. Many of the polar reactions claimed to involve methylenes have been shown not to,[3] but the basic hydrolysis of chloroform, the reaction for which such a mechanism was first suggested,[4] does proceed through dichloromethylene.[5] The *dihalo*methylenes[6] appear to be the only ones that have been established as intermediates in polar reactions, since it is not clear just how concerted the observed α-eliminations with rearrangement are.[7] We now present evidence for the intermediate, isopropoxyfluoromethylene.

Chlorodifluoromethane reacted rapidly ($k = 8 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$) with potassium isopropoxide in dry isopropyl alcohol at 0° to give isopropyl difluoromethyl ether (b.p. 44.2–44.5°, d^{25}_4 0.97604, n^{25}D 1.3204, molecular refraction calcd. 22.115, found 22.404), triisopropyl orthoformate and about 1% fluoroform as the only detected organic products (no carbon monoxide or propylene[8]). The yields of the two major products were calculated from the base and chloride concentrations by stoichiometric considerations. The fraction of isopropyl orthoformate produced increased from 0.15 with 0.02 *M* isopropoxide to 0.30 with 0.10 *M* isopropoxide. The isopropyl difluoromethyl ether was inert under the reaction conditions and reacted very slowly even at 50°.

The basic decomposition of chlorodifluoromethane in methanol must involve difluoromethylene since with sodium thiophenolate the formation of phenyl difluoromethyl sulfide is powerfully catalyzed by sodium methoxide.[9] Under the more strongly basic conditions of the present case the α-dehydrochlorination is even better facilitated. The competing initial removal of hydrogen fluoride must be a negligible side reaction. While fluorine atoms increase the reactivity of haloforms from which other halogens may be removed to give fluoromethylenes, the initial removal of fluoride ions is very difficult, fluoroform being inert even to potassium *t*-amyl oxide at 50°.[10] This rules out the possibility that the orthoester is produced from chlorofluoromethylene, a hypothesis that is also incompatible with the change in orthoester yield with changing isopropoxide concentration.

The only subsequent reactions of the difluoromethylene that seem plausible are



protonation (1), coördination with isopropoxide ion (2) or isopropyl alcohol (3), or simultaneous protonation and coördination with isopropoxide (4) or alcohol (5). Reactions 1, 4 and 5 can lead reasonably only to *i*-PrOCHF$_2$, as do 2 and 3 if the carbanions formed thereby are protonated. Hence the isopropyl orthoformate must be formed through reaction 2 and/or 3 followed (or accompanied) by loss of a fluoride ion.[11] Reaction through the *i*-PrOCF$_2^-$ anion seems more reason-

(1) This investigation was supported in part by the Office of Naval Research.

(2) F. O. Rice and A. L. Glasebrook, THIS JOURNAL, **56**, 2381 (1934); T. G. Pearson, R. H. Purcell and G. S. Saigh, *J. Chem. Soc.*, 409 (1938).

(3) F. Adickes, *Ber.*, **60**, 272 (1927); **63**, 3012 (1930); C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor and A. E. Brodhag, THIS JOURNAL, **78**, 1653 (1956).

(4) A. Geuther, *Ann.*, **123**, 121 (1862).

(5) J. Hine, THIS JOURNAL, **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *ibid.*, **76**, 2688 (1954).

(6) We use the term to include only species in which carbon is attached to two other atoms, neglecting isocyanides, for example.

(7) D. G. Hill, W. A. Judge, P. S. Skell, S. W. Kantor and C. R. Hauser, THIS JOURNAL, **74**, 5309 (1952).

(8) *Cf.* J. Hine, E. L. Pollitzer and H. Wagner, *ibid.*, **75**, 5607 (1953).

(9) J. J. Porter, unpublished experiments from this Laboratory. *Cf.* ref. 5.

(10) J. Hine, A. M. Dowell, Jr., and J. E. Singley, Jr., THIS JOURNAL, **78**, 479 (1956); and N. W. Burske, unpublished experiments from this Laboratory.

(11) Sn2 attack on the intermediate *i*-PrOCF$_2^-$ anion seems improbable for the same reason that applied in the case of the trichloromethyl anion.[8]