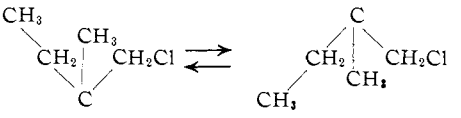
COMMUNICATIONS TO THE EDITOR

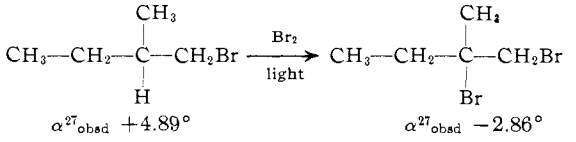
Stereochemical Evidence of Bridged Radicals

Sir:

There have been a number of observations that free radical intermediates from optically active starting materials yield racemic products when the center of asymmetry is located at the radical site. The forerunner of these experiments was reported in 1940 by Brown, Kharasch, and Chao.[1] They observed that radical chain chlorination of optically active (+)-1-chloro-2-methylbutane produced inactive 1,2-dichloro-2-methylbutane. The intermediate radical is racemized before it is converted to the dichloride.



We have found that radical chain bromination of (+)-1-bromo-2-methylbutane yields (−)-1,2-dibromo-2-methylbutane of high optical purity. This observation requires a modification of the accepted halogenation mechanism.



We are indebted to Dr. Warren Thaler for the information[2] that photobromination of alkyl bromides is a radical chain process which proceeds in a selective manner to yield a preponderance of vicinal dibromoalkanes. This directive influence of a bromine substituent in radical-chain bromination is in marked contrast to the effects generally observed in the halogenation of alkanes bearing an electron-withdrawing substituent. Substitution usually occurs preferentially at positions removed from the substituent; such behavior is consistent with the higher electron density at the more remote sites.

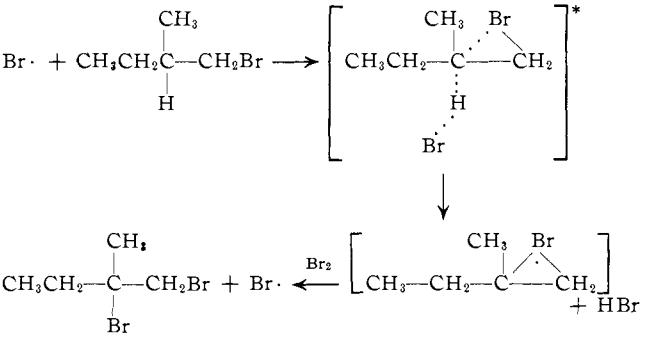
Liquid phase photobromination of (+)-1-bromo-2-methylbutane, α^{27}_{obsd} +4.89° at 0°, yielded (−)-1,2-dibromo-2-methylbutane, α^{27}_{obsd} −2.86°. Vapor phase chromatography (Carbowax on firebrick, 110°) of the crude reaction mixture indicated the presence of only two components: unreacted monobromide and 1,2-dibromo-2-methylbutane. The observed rotation of the dibromide was −2.86° in reactions carried out between −40 and +40°. One run, made at 72–80°, produced 1,2-dibromo-2-methylbutane, α^{27}_{obsd} −2.33°. A similar effect is observed with variations of bromine concentration. Low concentrations of bromine yield a slightly levorotatory product; as the bromine concentration is increased the rotation of the dibromide levels off at −2.86°.

Bromination of 1-bromo-2-methylbutane differs from chlorination of the corresponding chloride in two important respects. First, bromination is selective and yields only 1,2-dibromo-2-methylbutane, whereas chlorination is a reaction of low discrimination and all possible dichlorides are produced.[1] Second, bromination yields an optically active product, whereas chlorination affords inactive 1,2-dichloro-2-methylbutane.

(1) H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Am. Chem. Soc.*, **62**, 3435 (1940).

(2) W. Thaler, *ibid.*, **85**, 2607 (1963).

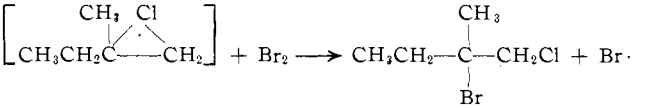
These differences require explanation in terms of a mechanistic scheme wherein the bromine substituent assists the departure of the tertiary hydrogen atom. This assistance manifests itself in the formation of a bridged radical, which is capable of maintaining its stereochemical configuration until reaction with molecular bromine occurs.[3,4] The effects of temperature and bromine concentration suggest that the bridged radical can isomerize to an open-chain form which racemizes.



Halogenation of (+)-1-bromo-2-methylbutane was effected by *t*-butyl hypochlorite[5] and *t*-butyl hypobromite[6] at 25°. Hydrogen abstraction by the *t*-butoxy radical occurred with low discrimination. Chlorination with *t*-butyl hypochlorite or chlorine in carbon disulfide solution yielded inactive 1-bromo-2-chloro-2-methylbutane. Bromination with *t*-butyl hypobromite afforded (−)-1,2-dibromo-2-methylbutane, α^{27}_{obsd} −1.8 to −2.0°.

The low selectivities observed in the hypohalite halogenations preclude appreciable assistance of bromine in the abstraction step. The preservation of optical activity in the product of active amyl bromide with *t*-butyl hypobromite is consistent with a mechanism in which some bridging occurs after the abstraction process, but before a rotation about the C-1–C-2 bond can occur. This bridge radical is trapped by the more reactive *t*-butyl hypobromite, but opens to allow rotation before reaction with either *t*-butyl hypochlorite or chlorine occurs.

The photobromination of (+)-1-chloro-2-methylbutane, α^{29}_{obsd} +1.38°, proceeds in a selective manner to yield (−)-2-bromo-1-chloro-2-methylbutane, α^{29}_{obsd} −1.45°, as the sole dihalide (~97%). The structure of this dihalide was established by dehydrohalogenation with sodium ethoxide in ethanol to 1-chloro-2-methyl-1-butene, indicating that the opening of the bridged intermediate by bromine proceeds entirely *via* attack at the tertiary position.



The conclusion that chlorine also is incorporated into an intermediate bridged radical is consistent with 1,2 migrations of chlorine atoms in free radicals.[7]

(3) Bridging by bromine is consistent with the facile 1,2 migrations of bromine observed: P. S. Skell, R. G. Allen, and N. D. Gilmour, *ibid.*, **83**, 504 (1961).

(4) The current status of bridged radical theory is summarized by P. I. Abell and L. H. Piette, *ibid.*, **84**, 916 (1962).

(5) H. M. Teeter and E. W. Bell, *Org. Syn.*, **32**, 20 (1952).

(6) C. Walling and A. Padwa, *J. Org. Chem.*, **27**, 2976 (1962).

(7) Such migrations are not nearly as facile as those of bromine. Unpublished results of P. S. Skell, D. L. Tuleen, and E. J. Goldstein.

Further applications of radical bridging to the control of the stereochemistry of substitution reactions are under active investigation. For example, *cis*-4-*t*-butyl cyclohexyl bromide (axial bromine) is considerably more reactive than is *trans*-4-*t*-butyl cyclohexyl bromide (equatorial bromine).

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The Mechanism of Aliphatic Bromination by N-Bromosuccinimide

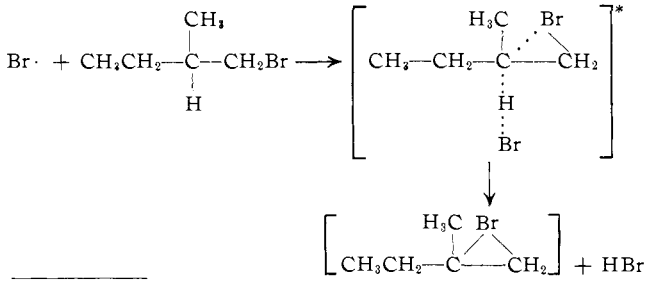
Sir:

The following results demonstrate that in radical-chain bromination with N-bromosuccinimide (NBS), the intermediate alkyl radical does not react with NBS to complete the bromination.

Recent investigations of the H abstraction step of radical-chain benzylic bromination by NBS raised serious doubt about the validity of the previously accepted[1] mechanism, which assumed hydrogen abstraction by the N-succinimidyl radical. The $\sigma^+\rho$ correlation for the reaction of substituted toluenes with bromine, NBS, N-bromotetrafluorosuccinimide, and N-bromotetramethylsuccinimide exhibit identical values of ρ.[2] Hydrocarbons exhibit the same relative reactivities toward benzylic substitution by molecular bromine or NBS.[3] Primary deuterium isotope effects in photobromination and bromination with NBS are nearly identical.[4] These data suggest that the abstracting specie in benzylic bromination by NBS is the bromine atom. NBS merely furnishes a low concentration of molecular bromine, presumably *via* its rapid ionic reaction with HBr.

This mechanism, originally suggested by Goldfinger[5] in connection with studies of the analogous chlorination with N-chlorosuccinimide, is supported by the observation of McGrath and Tedder[6] that at low molecular bromine concentration, allylic substitution predominates over addition to a double bond.

Radical chain bromination of (+)-1-bromo-2-methylbutane, α^{27}_{obsd} +4.89°, with molecular bromine is a highly selective reaction leading to (−)-1,2-dibromo-2-methylbutane, α^{27}_{obsd} −2.86°, of high optical purity.[7] The high selectivity of hydrogen abstraction by the bromine atom is attributed to bridging in the intermediate complex, leading to the formation of a bridged radical.



This behavior is contrasted by the low selectivity demonstrated in hydrogen abstraction by a chlorine atom or *t*-butoxy radical, in which bridging is relatively unimportant. The high degree of optical purity of 1,2-dibromo-2-methylbutane obtained in bromination with molecular bromine suggests that the second step in photohalogenation, the reaction of the radical with bromine, is also very rapid. Low concentration of bromine, or a less reactive halogenation agent, such as *t*-butyl hypochlorite, will not trap the bridged radical before it has undergone racemization.

These considerations suggested that it might be possible to elucidate the details of the mechanism of NBS brominative substitution of aliphatic compounds.

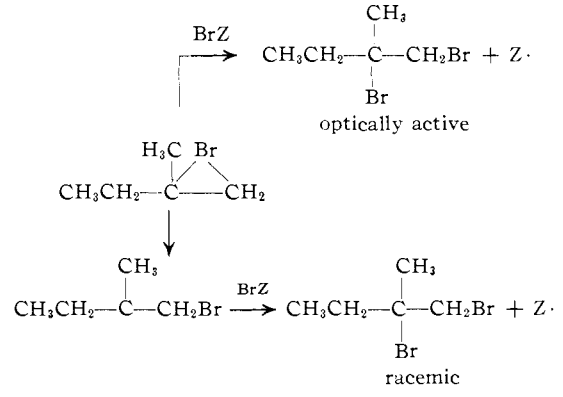
The photobromination of (+)-1-bromo-2-methylbutane (+4.89°) with NBS was studied under the conditions listed in Table I. In each case the selectivity was identical with that observed in reaction with molecular bromine; 1,2-dibromo-2-methylbutane was the only dibromide produced.

TABLE I

Solvent	Temp., °C.	Solubility of NBS (mole/l.)	α_{obsd} (temp., °C.)[a]
$CFCl_3$	25	0.0006	−0.25 (28)
CH_2Cl_2	40	0.29	−0.30 (25)
CCl_4[b]	76	0.006	−0.06 (35)

[a] Observed rotation of the 1,2-dibromo-2-methylbutane produced. [b] Photoinitiation and thermal initiation give identical results.

The preservation of optical activity in the 1,2-dibromo-2-methylbutane indicates that the reaction proceeds through a bridged radical.[7] Two major pathways are available to the bridged radical: reaction with a brominating agent, BrZ, to yield optically active dibromide; or ring opening and racemization, followed by reaction with the brominating agent.



Since a 500-fold change in the concentration of NBS produces only a small change in the rotation of the final product, *the reagent BrZ cannot be NBS.* Presumably, the radical reacts with molecular bromine at low concentration. Similar racemizations are observed when (+)-1-bromo-2-methylbutane is brominated with molecular bromine under high dilution conditions. The slow addition of bromine to an irradiated, refluxing solution of (+)-1-bromo-2-methylbutane in $CFCl_3$ produced (−)-1,2-dibromo-2-methylbutane, α^{29}_{obsd} −0.80°. The decreased concentration of bromine effectively increases the lifetime of the intermediate radical and allows partial racemization. The concentration of molecular bromine in the reaction of the active monobromide with NBS is less than that which may be mechanically maintained, and the observed rotation of the 1,2-dibromo-2-methylbutane produced is therefore quite small. We attribute the

(1) G. F. Bloomfield, *J. Chem. Soc.*, 114 (1944).
(2) R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.*, **85**, 354 (1963).
(3) G. A. Russell, C. DeBoer, and K. M. Desmond, *ibid.*, **85**, 365 (1963).
(4) K. B. Wiberg and L. H Slaugh, *ibid.*, **80**, 3033 (1958).
(5) P. Goldfinger, P. A. Gosselain, and R. H. Martin, *Nature*, **168**, 30 (1951).
(6) B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 80 (1961).
(7) P. S. Skell, D. L. Tuleen, and P. D. Readio, *J. Am. Chem. Soc.*, **85**, 2849 (1963).