Radical Brominations of Alkyl Bromides and the Nature of β-Bromoalkyl Radicals

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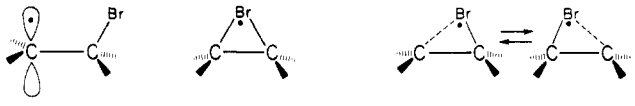
In 1962, Thaler reported[1] the unexpected preponderance of 1,2-dibromobutane in the product mixture from the radical bromination of 1-bromobutane and attributed that result to a rate-enhancing effect of the bromo substituent on the vicinal position.[2] Since that report, a variety of kinetic and stereochemical data illuminating the effect of a bromo substituent in similar radical substitution reactions has accumulated.[3-5] This Account summarizes these data that, taken all together, seem to us to make a compelling case for influential interaction between a developing radical center and a vicinal bromo substituent that can be periplanar with the incipient p orbital of the radical. This interaction has been designated bridging, and its manifestation is in unusual properties of the radical.

In a bridged radical, the bridging atom (group) need not be symmetrically placed between the two carbons. The significant distinction between an unsymmetrically bridged radical and a classical radical lies in reaction outcomes: Reactions creating bridged radicals (symmetrical or unsymmetrical) afford experimental evidence for a significant anchimeric effect of the substituent and for restricted rotation about the C–C bond and control of configuration at *both* carbon centers.



The proper structural description of a reaction intermediate is an important focus in a reaction mechanism study, and spectral data often provide the basis for such description.[6] Few useful spectral data have been reported for β-bromoalkyl radicals, however, and they do not reveal the precise structure of the radicals. Some groups have used ESR spectroscopy of matrices at low temperature,[7] but only one report has not been challenged, even rejected, by subsequent investigations. The one unchallenged ESR spectrum published for a β-bromoalkyl radical, $\cdot C(CH_3)_2CH_2Br$, was interpreted in terms of an unsymmetrical bridge, with stronger bonding of Br to the primary C than to the tertiary C.[7a] One CIDNP experiment involving a β-bromoalkyl radical, 2-bromoethyl radical, has been reported, and it indicates that the radical has an unsymmetrical structure.[8] This conclusion does not distinguish between no bridging and unsymmetrical bridging.

ESR spectroscopic studies of analogous chloroalkyl radicals have provided more spectra and more information. For β-chloroalkyl radicals with an unsymmetrical carbon skeleton, only one chloroalkyl radical, the one with chloro more strongly bonded to the less substituted of the vicinal carbons, is present.[6b] If necessary, chloro rearranges to give that structure, and there is an unexpected barrier to rotation about the C–C bond. These conclusions are consistent with those reached

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James G. Traynham, a native of Georgia, did undergraduate work at the University of North Carolina, Chapel Hill, and in 1950 took his Ph.D. at Northwestern University as Robert L. Letsinger's first doctoral student. After 3 years as a professor at Denison University, he joined the faculty of Louisiana State University, where he is Professor of Chemistry. Despite the demands of major administrative positions (Chairman of the Chemistry Department, 1968–1973; Vice Chancellor of Advanced Studies and Research and Dean of the Graduate School, 1973–1981) and a major commitment to undergraduate teaching (currently), he has maintained a consistent program of research on organic reaction mechanisms. His research interest has focused on carbocation processes, radical halogenations, and ipso intermediates in radical aromatic substitution reactions.

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(1) Thaler, W. *J. Am. Chem. Soc.* **1963**, *85*, 2607–13.

(2) Some less common terms used in this Account are defined, at the Editor's request: *Vicinal* refers to adjacent positions within a chemical species (e.g., in 1,2-dibromobutane, the bromo substituents are vicinal). *Classical radical* refers to a radical center without interaction with an intramolecular, nonconjugated group to be delocalize the unpaired electron density; *bridged radical* refers to a radical species with that kind of interaction (e.g., $BrCH_2CH_2\cdot$ represents a classical radical, and

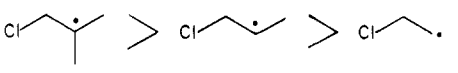
represents a bridged radical without implication of symmetry in bridging). *Anchimeric* refers to a rate-enhancing, direct intramolecular interaction between a reaction center and a nonconjugated neighboring group.

(3) (a) Tanner, D. D.; Darwish, D.; Mosher, M. W.; Bunce, N. J. *J. Am. Chem. Soc.* **1969**, *91*, 7398–401. (b) Tanner, D. D.; Mosher, M. W.; Das, N. C.; Blackburn, E. V. *Ibid.* **1971**, *93*, 5846–50. (c) Tanner, D. D.; Yabuuchi, H.; Blackburn, E. V. *Ibid.* **1971**, *93*, 4802–8. (d) Tanner, D. D.; Rowe, J. E.; Pace, T.; Kosugi, Y. *Ibid.* **1973**, *95*, 4705–11.

(4) (a) Skell, P. S.; Shea, K. J. *J. Am. Chem. Soc.* **1972**, *94*, 6550–2. (b) Skell, P. S.; Shea, K. J. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol 2, Chapter 26. (c) Skell, P. S.; Shea, K. J. *Isr. J. Chem.* **1972**, *10*, 493–516. (d) Skell, P. S. *Spec. Publ.–Chem. Soc.* **1964**, 131–145. (e) Skell, P. S.; Pavlis, R. R.; Lewis, D. C.; Shea, K. J. *J. Am. Chem. Soc.* **1973**, *95*, 6735–45.

(5) (a) Traynham, J. G.; Green, E. E.; Lee, Y.-S.; Schweinsberg, F.; Low, C.-E. *J. Am. Chem. Soc.* **1972**, *94*, 6552–3. (b) Traynham, J. G.; Lee, Y.-S. Ibid. **1974**, *96*, 3590–4.

(6) (a) For a review of ESR data and radical structure, see Kochi, J. K. *Adv. Free-Radical Chem.* **1975**, *5*, 189–317. (b) ESR data for β-chloroalkyl radicals have been interpreted to indicate unsymmetrical bridging by chloro; the closeness of the chloro substituent to the vicinal carbon decreases in the series



(7) (a) Symons, M. C. R.; Smith, I. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1362–70 and references therein. (b) Wood, D. E.; Lloyd, R. V. *Tetrahedron Lett.* **1976**, 345–8. R.V.L. now reports uncertainty about the identity of the radical for which they reported data; private communication with P.S.S., Feb 1982.

(8) Hargis, J. H.; Shevlin, P. B. *J. Chem. Soc., Chem. Commun.* **1973**, 179–80.

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earlier on the basis of product studies[4b,d,e] that showed vicinal migration of chloro.

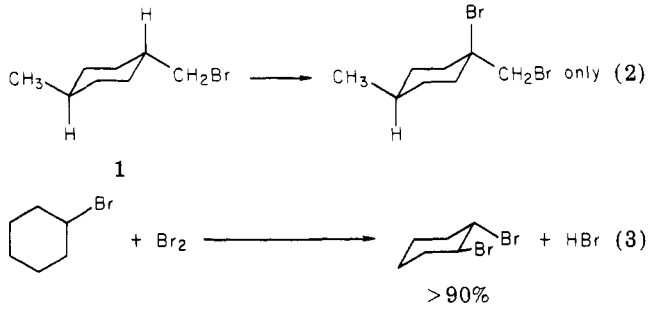
In contrast to the absence of definitive spectral data for β-bromoalkyl radicals, a substantial body of product data is available to reveal the effect of a β-bromo substituent on the course of radical bromination reactions. These data on chemical behavior differing substantially from that of alkyl radicals without a β-bromo substituent are the principal focus of this Account.

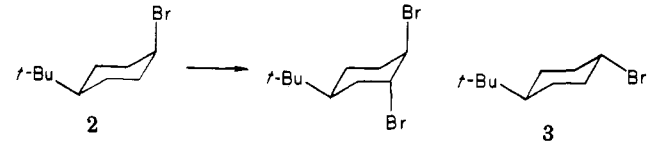
Enhancement of Rates of Bromination of Bromoalkanes

There are numerous reports, now without contradiction, that in radical brominations the position vicinal to a bromo substituent undergoes substitution more readily than does a similar position in the corresponding hydrocarbon or elsewhere in the bromo-substituted substrate. These results are contrary to the finding that the vicinal position is deactivated by other electronegative substituents.[9a,b] In both gas and liquid phase, brominations of 1-bromobutane (eq 1) occur mainly at C-2: At −23 °C, the rate of substitution at this position is 7.2 times that at the C-2 position of propane and 22.5 times that at the C-3 position of 1-bromobutane.[10a]

$$\begin{aligned} CH_3CH_2CH_2CH_2Br + Br_2 &\rightarrow CH_3CH_2CHBrCH_2Br \text{ (major)} \\ &\rightarrow CH_3CHBrCH_2CH_2Br \text{ (minor)} \end{aligned} \quad (1)$$

Intramolecular competition between the tertiary positions in *trans*-1-(bromomethyl)-4-methylcyclohexane (1) is revealing because of the remoteness of C-4 from the bromo substituent and the absence of any conformational effects on the competition (eq 2).[9b] Over 90% of the bromination product obtained from bromocyclopentane or from bromocyclohexane is *trans*-1,2-dibromocycloalkane (eq 3).[10b] Although the exposition in some instances may obscure the picture, the unusually high reactivity at C-2 of *cis*-1-bromo-4-*tert*-butylcyclohexane (2) and the normal behavior of the trans isomer (3, which reacts, at several positions, at much lower rates than does 2) indicate a maximum magnitude of this activation effect and the steric requirements for maximum activation.[10b] When compared with cyclohexane on a per hydrogen basis, 2 is 115 times more reactive. A reasonable estimate of the deactivation that normally would be attributable to a position β to an electronegative substituent (reactivity = 0.14 times the alkane rate of reaction) indicates that 2 is approximately 10^3 times as reactive at C-2 as would have been expected. A change of rate of this magnitude corresponds to 3.4 kcal/mol stabilization of the β-bromo radical. (The absence of such an effect with 3 is strong evidence against the classical radical being formed from 2.)



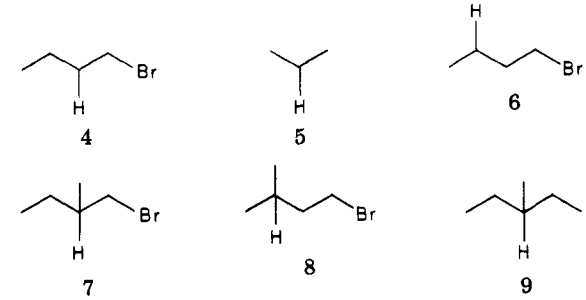


Chloroalkanes usually show a much smaller deviation from expected behavior, the deviation being small enough to leave one in doubt,[1,9] except for alkyl chlorides with a tertiary vincinal position, which are more reactive than are the corresponding alkanes.[9b] The fluoroalkanes show the anticipated deactivation at the β-position.[4b]

Analogous observations have been reported for radical-chain autoxidations of alkyl bromides that involve H abstraction by $RO_2\cdot$ and trapping of the bromoalkyl radicals by O_2.[11,12] These reactions also show substantial enhancements of rates at the β-positions.

Comparative Activation Parameters

Sets of competitive kinetic data for hydrogen abstractions from bromoalkanes have occasionally been obtained at different temperatures.[10a,12] These data show that the bromo substituent has a favorable effect on the activation energy and an unfavorable effect on the activation entropy for radical attack at a secondary[10a] or tertiary[12] position vicinal (β) to a bromo substituent compared to attack at a similar position γ to the bromo substituent or at one in an unsubstituted alkane. For secondary positions, the differences in activation energy (ΔE_a = −3 kcal/mol) and entropy ($\Delta\Delta S^\ddagger$ = −7 eu) for bromine atom attack are about the same for 4 vs. 5 and 4 vs. 6.[10a] For tertiary positions, the differences for *tert*-butylperoxyl radical (t-$BuO_2\cdot$) attack are ΔE_a = −3 kcal/mol, $\Delta\Delta S^\ddagger$ = −4 eu for 7 vs. 8 and E_a = −0.9 kcal/mol, $\Delta\Delta S^\ddagger$ = −2 eu for 7 vs. 9.[12]



These differences reflect the expected effect of a bridged transition state in vicinal hydrogen abstraction, namely, lowered E_a (more resonance stabilization) and

(9) (a) Electronegative groups usually deactivate the vicinal position, relative to other position(s) of the same classification, in halogenation reactions, thereby favoring substitution at the more remote positions; Thaler, W. A. In "Methods in Free Radical Chemistry"; Huyser, E. S., Ed.; Marcel Dekker: New York, 1969; Vol. 2, pp 180–1; Tedder, J. M. *Tetrahedron* **1982**, 313–29. (b) Alkyl chlorides undergo bromination at vicinal tertiary positions more rapidly than do the corresponding alkanes: Everly, C. R.; Schweinsberg, F.; Traynham, J. G. *J. Am. Chem. Soc.* **1978**, *100*, 1200–5. (c) Traynham, J. G.; Hines, W. G. *Ibid.* **1968**, *90*, 5208–10.

(10) (a) Shea, K. J.; Lewis, D. C.; Skell, P. S. *J. Am. Chem. Soc.* **1973**, *95*, 7768–76. (b) Skell, P. S.; Readio, P. D. *Ibid.* **1964**, *86*, 3334–7.

(11) (a) Miyajima, S.; Ichihara, S.; Simamura, O. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 531–2. (b) Miyajima, S.; Simamura, O. *Ibid.* **1975**, *48*, 533–5.

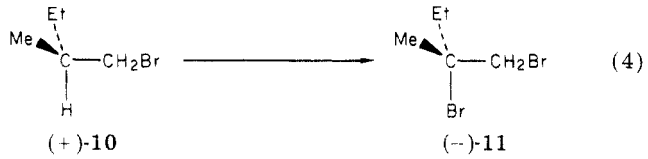
(12) (a) Howard, J. A.; Chenier, J. H. B. *Can. J. Chem.* **1979**, *57*, 2484–90. (b) In private communications to each of us in Oct 1983, Professor Tanner reported results of liquid-phase brominations of 2-bromobutane at different temperatures; the product distributions reported permit the calculation of ΔE_a and $\Delta\Delta S^\ddagger$ values for attack at the 3-position (major product) vs. that at the 2-position substantially the same as those cited for secondary positions.[12a]

more negative $\Delta S^{\ddagger}$ (loss of rotational freedom).[10a,12]

Control of Configuration at a Dissymmetric Substitution Center

For all cases reported, dissymmetry is lost at a dissymmetric center that becomes a radical center during a substitution reaction, unless a β-bromo (or β-chloro) substituent is present. With a β-bromo (or β-chloro) substituent in the substrate, dissymmetry is substantially retained in the intermediate.

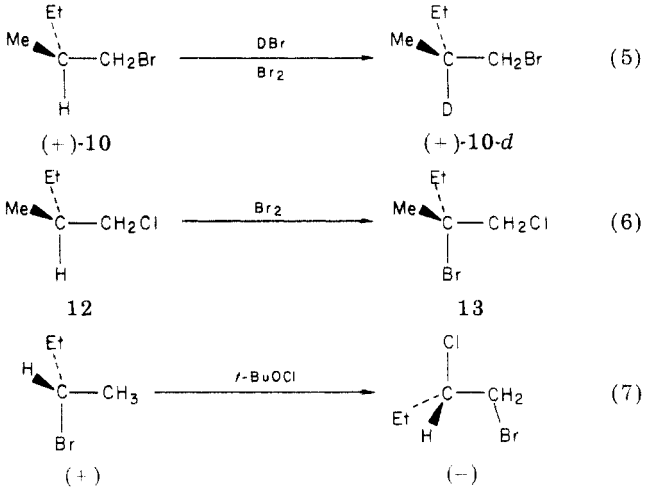
Radical-chain bromination of (+)-(*S*)-1-bromo-2-methylbutane (**10**) leads to (−)-(*R*)-1,2-dibromo-2-methylbutane (**11**) (eq 4).[4b,d] The product is ~95%



(4)

one enantiomer, with the same relative configuration as the starting material. The optical purity depends on the Br_2 concentration, being maximum at >0.05 M Br_2 and falling to 50% at 0.007 M Br_2. Hydrohaloelimination with base from the dibromide **11**, made from unlabeled Br_2 and **10** labeled with radioactive ^{82}Br, produced EtMeC=CHBr which had retained 95% of the ^{82}Br at C-1.[4b] Similar results have been reported with $^{81}Br_2$ and unlabeled **10**.[3c] These results are not compatible with mechanism proposals that place major emphasis on an alkene intermediate in the bromination reaction, but they are requisites of substantial influential involvement of vicinal bromo.

Other examples of extensive retention of enantiomeric purity at a center undergoing radical substitution have been reported (eq 5–7).[4b] The conversion of **10**



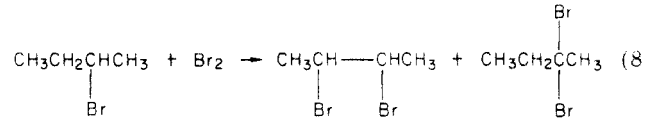
to **10**-*d* without loss of optical activity is without ambiguity and is inconsistent with a classical radical intermediate.

To obtain 50% of the maximum optical purity of **13** in brominations of **12**, a Br_2 concentration equal to 0.45 M is required, indicating that racemization of the intermediate chloroalkyl radical is 70 times faster than racemization of the corresponding bromoalkyl radical.[4d]

Racemic 2-halo products result from (a) bromination of 1-fluoro-2-methylbutane,[4b] presumably because there is no fluoro bridge, and (b) chlorinations of **10** and **12** because trapping of the bridged intermediate is too slow.[4d]

Stereoselectivity at Diastereotopic Sites β to a Bromo Substituent

Radical-chain bromination of 2-bromobutane leads mainly to a mixture of (*R**,*S**)- and (*R**,*R**)-2,3-dibromobutanes[13] (along with a small amount of 2,2-dibromobutane) (eq 8).[1,4e,14a] The distribution among the

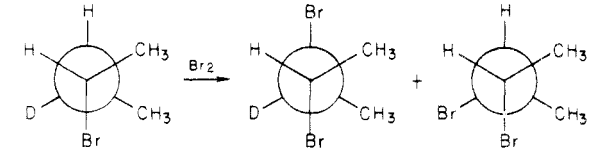


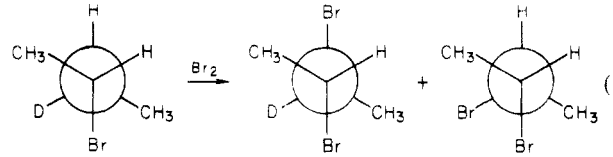
(8)

(*R**,*R**) + (*R**,*S**)[13]

conformations of 2-bromobutane and of the diastereomeric 2-bromo-3-deuteriobutanes must be closely the same. Consequently it is striking that brominations of these isotopically different 2-bromobutanes lead to such different (*R**,*S**):(*R**,*R**) ratios.[4e] (Classical radical intermediates would presumably give identical (*R**,*S**):(*R**,*R**) ratios.) Further, analysis of the dibromide mixtures showed that the following scheme (eq 9, 10) describes the course of the reaction, with less than 6% crossover in these labeled products.[4e,15a] Whichever hydrogen is abstracted, the second bromo is introduced in the stereochemical position identical with that previously occupied by that hydrogen.

	2,3-dibromobutanes (*R**,*S**):(*R**,*R**)
2-bromobutane	2.5
(2*R**,3*S**)-2-bromo-3-deuteriobutane	0.6
(2*R**,3*R**)-2-bromo-3-deuteriobutane	6.5



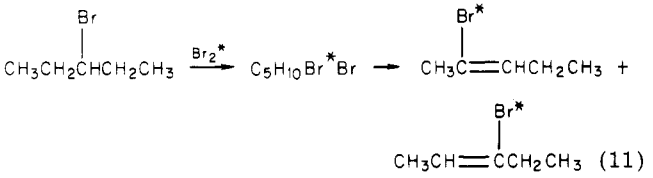


(13) *R**,*S** and *R**,*R** express *relative* configuratons of two chiral centers within the same molecule (Fletcher, J. H.; Dermer, O. C.; Fox, R. B. "Nomenclature of Organic Compounds"; American Chemical Society: Washington, D.C., 1974; *Adv. Chem. Ser.* No. 126, p 108). For example, with 2,3-dibromobutane, (*R**,*S**) = meso, and (*R**,*R**) = enantiomeric.

(14) (a) Tanner, D. D.; Blackburn, E. V.; Kosugi, Y.; Ruo, T. C. S. *J. Am. Chem. Soc.* **1977**, *99*, 2714–23. For other reports of gas-phase brominations, see: (b) Fredericks, P. S.; Tedder, J. M. *J. Chem. Soc.* **1960**, 144–50. (c) Fredericks, P. S.; Tedder, J. M. *Ibid.* 1961, 3520–5. However, compare these gas-phase results (p 3523) with liquid phase ones (ref 1, 3e, 5e). (d) Ashton, D. S.; Tedder, J. M.; Walton, J. C. *J. Chem. Soc. D* **1971**, 1487–9. (e) Ashton, D. S.; Tedder, J. M.; Walker, M. D.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1346–50.

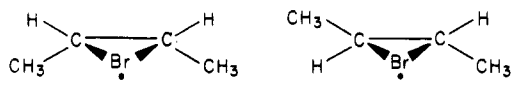
(15) (a) Skell, P. S.; May, D. D.; Peyerimhoff, S. D.; Shea, K. J.; Marslett, E., Jr., unpublished research. (b) Much slower rates (10^4–10^6 s^{-1}) for rearrangement of chloro in some β-chloroalkyl radicals have been reported [Gasanov, R. G.; Ivansra, L. V.; Freidlina, R. Kh. *Bull. Acad. Sci. USSR (Engl. Transl.)* **1979**, *28*, 2618–20; *Izv. Akad. Nauk SSSR Ser. Khim.* **1979**, 2810–2. Gasanov, R. G. *Bull. Acad. Sci. USSR (Engl. Transl.)* **1980**, *29*, 1583–6; *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1980**, 2264–8], but the more recent work by Skell and co-workers[15a] indicates the faster rate (10^8–10^9 s^{-1}) for rearrangement of chloro.

In the 2,3-dibromopentane formed by bromination of ^{82}Br-labeled 3-bromopentane, the original bromo substituent is equally distributed between C-2 and C-3.[4e] Base hydrohaloelimination from the 2,3-dibromopentane leads to 2-bromo-2-pentene and 3-bromo-2-pentene, both of which have the same label concentrations (eq 11). Minor amounts of label appeared in the inorganic pool during the bromination.



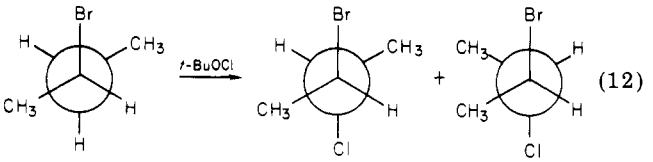
(11)

The explanation of the results of this set of experiments must account for the stereospecificity that the bromo at C-2 produces at C-3 and for the equal probability of the original bromo substituent being at C-2 or C-3 in the final product. The simple explanation depends on two symmetrically bridged intermediates (**14** and **15**) or, if unsymmetrical bridging is a better



14 (meso) 15 (2*S*,3*S*)

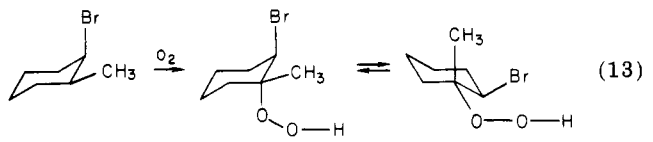
description, on the bromo substituent shuttling between C-2 and C-3 faster than the β-bromoalkyl radical is trapped.[16] This rationalization is consistent with the observations that (a) (+)-(*S*)-2-bromobutane is brominated to a mixture of meso and largely racemic dibromide [only 5% of the dissymmetric product is excess (−)-(2*S*,3*S*) dibromide][4e,14a] and (b) chlorination of (+)-(*S*)-2-bromobutane (**16**) leads to virtually racemic (2*R**,3*R**)-2-bromo-3-chlorobutane and (+)-(2*S*,3*R*)-2-bromo-3-chlorobutane in high enantiomeric purity.[4e] Since intermediate **15** does not have a plane of symmetry, chlorination of it leads to enantiomerically pure 2*S*,3*R* dihalide, while bromination of it produces meso 2*R*,3*S* dibromide.



(12)

(+)-16 (+)-(2*S*,3*R*) (±)-(2*R**,3*R**)

Other examples of this type of control are seen in the brominations of cyclopentyl, cyclohexyl, and *cis*-4-*tert*-butylcyclohexyl bromides, each of which is converted to the trans vicinal dibromide.[4b] The autoxidations of bromocyclohexane and of *cis*-1-bromo-2-methylcyclohexane result in introduction of an oxygen substituent at C-2, also trans to the bromo substitutent (eq 13).[11]



(13)

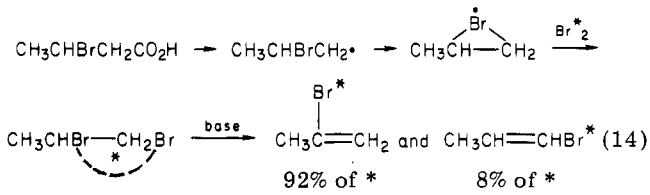
(16) The analogous chloro-bridged species are demonstrably unsymmetrical, a facet recognizable because shuttling of chloro occurs at rates only 10^{-2} times that of bromo, making possible the trapping of the chloro-bridged species before shuttling.[15]

1,2-Rearrangements

Rearrangements in most radicals are slow, and product formation by this route is usually observed only at elevated temperatures. Rearrangements of bromo and chloro substituents vicinal to a radical site, however, occur with rates $>10^8$ s^{-1} for chloro[15] and $>10^{10}$ s^{-1} for bromo.[4]

Chlorinations proceeding by hydrogen abstraction at C-1 of 2-bromo-2-methylpropane, 2-bromopropane, and 2-bromobutane result in 100% rearrangement of the bromo substituent to C-1.[17] The latter case is particularly instructive if (+)-(*S*)-2-bromobutane is chlorinated; the product is (−)-(*S*)-1-bromo-2-chlorobutane, with inverted configuration at C-2, and possibly enantiomerically pure[4e] (eq 7).

The bromodecarboxylation of 3-bromobutyric acid with HgO and $^{82}Br_2$ leads to radioactive 1,2-dibromopropane (activity equivalent to one ^{82}Br per molecule), and base-promoted hydrohaloelimination from this product produces 1-bromo-1-propene with 8% of the radioactivity and 2-bromo-1-propene with 92% of the radioactivity (eq 14).[4b] Thus formation of the major bromodecarboxylation product involves a 1,2-rearrangement of the original bromo substituent.

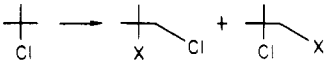


(14)

92% of * 8% of *

There are numerous examples of halo (especially chloro) rearrangements in β-halo radicals.[18]

Chlorination of ^{36}Cl *tert*-butyl chloride with *tert*-butyl hypochlorite produces largely rearranged dichloride.[3d] Similarly, bromination of *tert*-butyl chloride with *tert*-butyl hypobromite (*t*-BuOBr) at low concentration gives the fully rearranged bromo chloride, but increasing the *t*-BuOBr concentration decreases the amount of rearrangement (eq 15).[4d,19] Brominations of 2,2-dichloropropane with NBS and Br_2 yield increasing amounts of 2-bromo-1,2-dichloropropane at the expense of 1-bromo-2,2-dichloropropane as the stationary concentration of bromine is decreased.[19]



(15)

X = Cl or Br from the reagent

There are no reported examples of 1,2-rearrangements of fluoro substituents.

While these rearrangements provide no direct information about the key hydrogen-abstraction step in radical halogenations, they do share a common feature: intermediacy of radicals with a β-bromo or β-chloro substituent and significant interaction between the substituent and the radical center.

(17) (a) Skell, P. S.; Allen, R. G.; Gilmour, N. D. *J. Am. Chem. Soc.* **1961**, *83*, 504–5. (b) Juneja, P. S.; Hodnett, E. M *Ibid.* **1967**, *89*, 5685–7.

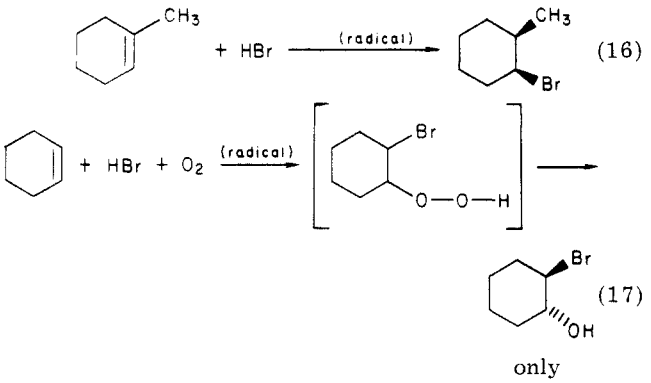
(18) (a) For earlier references, see: Wilt, J. W. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 8. (b) Lee, F. S. C.; Rowland, F. S. *J. Phys. Chem.* **1977**, *81*, 1222–9. (c) Starnes, W. H., Jr.; Schilling, F. C.; Abbas, K. B.; Cais, R. E.; Bovey, F. A. *Macromolecules* **1979**, *12*, 556–62. (d) Freidlina, R. Kh *Adv. Free-Radical Chem.* **1965**, *1*, 211–78.

(19) Skell, P. S.; Tlumak, R. L.; Seshadri, S. *J. Am. Chem. Soc.* **1983**, *105*, 5125–9.

Additions and Eliminations of Alkenes

Radical additions to alkenes that proceed through β-bromoalkyl radical intermediates provide further examples of the stereoselective constraint of the β-bromo substituent in product formation from the intermediate radical. These examples of radical-chain addition reactions clearly supplement those of radical substitution reactions with bromoalkanes, summarized above.

Radical-chain additions of hydrogen bromide and/or deuterium bromide to 1-bromocyclohexene, 1-methylcyclohexene, 1-deuterio-1-butenes, 2-butenes, 2-bromo-2-butenes, and propyne are stereospecific anti (eq 16).[4b] Anti addition is preferred but not exclusive with 1-bromocyclobutene, 1-bromocyclopentene, and 1-bromocycloheptene.[20] The radical-chain reactions of cyclohexene and of 1-methylcyclohexene with HBr and O_2 produce 2-bromocyclohexyl hydroperoxides that are reduced exclusively to *trans*-2-bromocyclohexanols (eq 17).



only

Photoinitiated additions of iodine to *cis*- and *trans*-2-butenes at low temperature are also cleanly anti, as are the photoinitiated deiodinations of the addition products at room temperature.[21]

Reduction of the diastereomeric 2,3-dibromobutanes with tributyltin hydride shows anti stereoselectively, the degree of stereoselectively increasing with increasing concentration of the hydride and with decreasing temperature.[22] This result strongly implies a first-formed intermediate radical with preservation of configuration which can change to a radical that loses configurational identity, that is, a bromo bridged radical that can open to an unbridged species at higher temperature or when trapping reactant is in low concentration.

Other Proposals for Effect of β-Bromo Substituent

Few, if any, of the experimental results summarized above are now disputed. Interpretations of these results in terms of mechanistic details are not free of dispute, however. The apparent high reactivity of a position vicinal to a bromo substituent and the stereochemistry of substitution at that position have been attributed to factors other than anchimeric assistance by the β-bromo substituent. To provide evidence for the operation of these factors, Tanner and co-workers have, in a series of papers,[3,14a,23,24] described experiments in the gas phase and in solution, usually with large initial amounts of HBr and often with excesses of Br_2 over the substrate. Though these conditions are quite unlike those used in most of the bromination studies summarized above, the experiments have documented significantly elimination and exchange reaction pathways that had not been studied extensively.

By the assessment of H/D kinetic isotope effects and exchange,[23] of ^{79}Br:^{81}Br isotopic composition of product bromides and dibromides,[24] and of enantiomeric purity in products obtained from optically active substrates,[14a] Tanner and co-workers have provided persuasive evidence, especially when HBr is a major component of the reaction mixture, for selective HBr reversal of the initial radical-forming reactions,[23] for elimination to alkene intermediate from a β-bromoalkyl radical,[24] for partial racemization of optically active products by their bromination reaction and product isolation conditions (when a symmetrically bridged β-bromoalkyl radical would yield racemic product),[14a] and for cage processes involving alkyl radical intermediates.[23]

While these several processes apparently can occur during radical bromination reactions, especially under the atypical reaction conditions chosen to favor those occurrences, Tanner's conclusion is that they do not, even taken together, account for all of the effect of vicinal bromo substituent favorable for product formation. For example, an ingenious dissection of mass spectral data to show the isotopic composition of each Br in the 1,2-dibromobutane product formed from 1-bromobutane and $^{81}Br_2$ implicated some elimination–addition,[24] but the extent of that process was "not sufficient to rationalize the high yield of 1,2-dibromobutane formed",[24a] and HBr reversal of the radical-forming reactions from 1-bromobutane was "not extensive enough to explain the product distributions found".[24b] (The original treatment[24a] of the data appears to have overestimated the extent of elimination–addition pathway.[25]) Further, the most optimistic estimate of the racemization by reaction and isolation conditions implied by the data for bromination of (*R*)-2-bromobutane[14a] accounts for less than half of the racemization in the (*R**,*R**)-2,3-dibromobutane product. A classical radical intermediate formed from (*R*)-2-bromobutane would yield a mixture of *meso*- and *enantiomerically pure* (*R*,*R*)-2,3-dibromobutane (eq 18), contrary to the experimental reports.

Cage reversals may occur in most of these brominations, but a modest change in Br_2 concentration is reported to affect the extent of cage reversal of cyclohexyl radicals (from cyclohexane) dramatically: 0.54 mole

(20) Abell, P. I.; Chiao, C. *J. Am. Chem. Soc.* **1960**, *82*, 3610–3. See also: LeBel, N. A. *Ibid.* **1960**, *82*, 623–7.

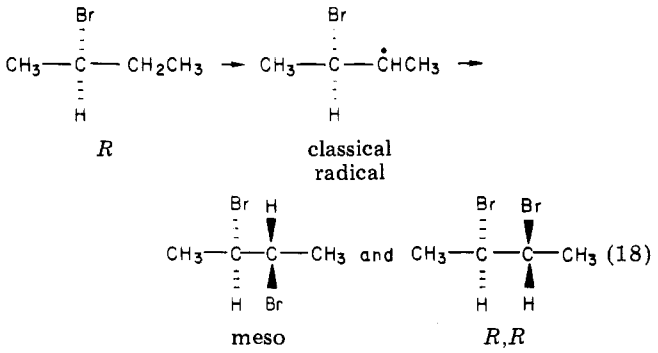
(21) Skell, P. S.; Pavlis, R. R. *J. Am. Chem. Soc.* **1964**, *86*, 2956.

(22) (a) Castro, C. E.; Kray, W., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 2768–73; **1964**, *86*, 4603–8. (b) Singleton, D.; Kochi, J. K. *Ibid.* **1967**, *89*, 6547–55; **1968**, *90*, 1582–9.

(23) (a) Tanner, D. D.; Ochiai, T.; Pace, T. *J. Am. Chem. Soc.* **1975**, *97*, 6162–5. (b) Tanner, D. D.; Pace, T.; Ochiai, T. *Ibid.* **1975**, *97*, 4304–7. (c) Tanner, D. D.; Ochiai, T.; Rowe, J.; Pace, T.; Takiguchi, H.; Samal, P. W. *Can. J. Chem.* **1977**, *55*, 3536–43. (d) Tanner, D. D.; Pace, T.; Ochiai, *Ibid.*, **1975**, *53*, 2202–9.

(24) (a) Tanner, D. D.; Pace, T.; Kosugi, Y.; Blackburn, E. V.; Ruo, T. *Tetrahedron Lett.* **1976**, 2413–6. (b) Tanner, D. D.; Kosugi, Y.; Arhart, R.; Wada, N.; Pace, T.; Ruo, T. *J. Am. Chem. Soc.* **1976**, *98*, 6275–84.

(25) Soumillion, J. Ph.; Ronneau, C.; Dejaifve, P. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1907–13. Private communication of manuscript to P.S.S., Feb 1983. Using a statistical treatment of the results of bromination of 1-bromobutane by these authors (*Tetrahedron Lett.* **1972**, 317–8), Tanner and co-workers estimated[24a] that 37% of the 1,2-dibromobutane product was formed by an elimination–addition pathway; by a similar but improved statistical treatment of their data, these authors calculate that no more than 20% of that product was formed by an elimination–addition pathway.



fraction of Br_2 scavenges all radicals formed (no cage reversal detected), but 0.43 mole fraction of Br_2 is not sufficient to stop extensive cage reversal.[23a] At low HBr concentrations, the data indicate small extents[23c,d,24a] of and no significant position selectivity[23c] for reversal reactions of haloalkyl radicals, and it is not clear why position selectively should be much greater within the cage than external to it.

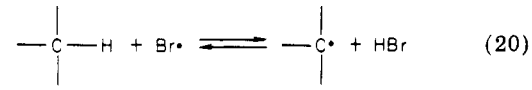
The relative rates of reaction of the isomeric bromoalkyl radicals with HBr and Br_2 and their effect on the fate of the initially generated radicals have been a major focus in the investigations of the Tanner group. By use of 1-bromobutane-d_9 and HBr concentrations 100–300 times those generated by the bromination reaction itself, those investigators determined that for competitive vapor-phase reactions, $k_{Br_2}/k_{HBr} = 52.8$ for C-2 ($CD_3\dot{C}D_2CDCD_2Br$) and 6.33 for C-3 ($CD_3\dot{C}DCD_2CD_2Br$).[24b,26] When substituted in the complex kinetic expression for competitive reactions at C-2 (β) and C-3 (γ) in 1-bromobutane (eq 19),[27] these

$$\frac{d[R^{\beta}Br]/dt}{d[R^{\gamma}Br]/dt} = \frac{k_3k_4k_{-5}}{k_5k_6k_{-3}} \frac{1 + (k_6/k_5)([Br_2]/[HBr])}{1 + (k_4/k_{-3})([Br_2]/[HBr])} \quad (19)$$

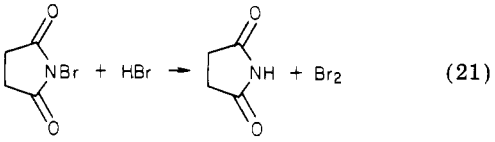
ratios along with data on reactant concentrations[22b] reproduce the product ratios for some, but not all, of the four experiments reported.[22b,28] More recently Zavitsas and co-workers have determined these relative rates for reactions in solution and report inverted ratios: k_{Br_2}/k_{HBr} for C-2 = 0.88 and for C-3 = 0.59.[28] When used in the above kinetic expression along with the reactant data of the Tanner group, these ratios reproduce the product distributions reported[22b] at least as well as do the other ratios.[28] Apparently the calculated isomer ratios are rather insensitive to this significant difference in k_{Br_2}/k_{HBr} values. Therefore reproduction of experimental product distributions may not be a good measure of the reliability of the relative rates for these competitive reactions of isomeric radicals derived from 1-bromobutane by hydrogen abstraction by Br.

Scavenging of HBr

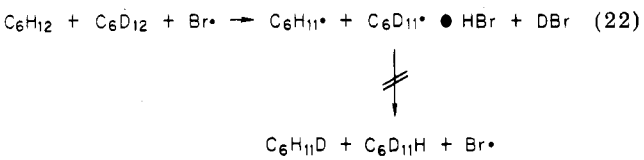
To eliminate the possible impact of the reversal of the alkyl radical generating step (eq 20) on product



distributions from radical bromination reactions, some investigations have included an HBr-scavenging reagent in the reactant mixture. *N*-Bromosuccinimide (NBS) or an epoxide has been used, and they are apparently completely effective as scavenging reagents. The reaction of NBS with HBr in solution (eq 21) is rapid and



complete, even at low temperature.[10a,29] Brominations of a mixture of cyclohexane and cyclohexane-d_{12} (eq 22)



or a mixture of neopentane and CD_2Cl_2, both in the presence of NBS, did not lead to any H/D exchange in the substrates; the product HBr (DBr) and the reversal reaction were completely eliminated.[30]

Many of the product data cited in early sections of this Account were obtained with NBS scavenging of HBr and were therefore free of any influence of the HBr-reversal reaction.

Especially under conditions of effective scavenging of HBr by NBS or epoxide, the favorable effect of vicinal bromo on the course of the free-radical bromination reaction is distinct, conspicuous, and unambiguous.

Summary

Controversies in chemistry develop from two kinds of disagreements: disagreement on the experimental data and disagreement on interpretation of the data. A controversy over radical-chain brominations of alkyl bromides emerged and has been nourished by both kinds of disagreements,[1,3,5] although the disagreement on experimental data has apparently withered.[3d]

Brominations of alkyl bromides form product mixtures dominated by vicinal substitutions. Experimental evidence from different groups of investigators shows that the substitution reaction can be made to follow more than one pathway. Various reactions that consume some of the initially generated radicals become substantial at high concentrations of HBr, and under those circumstances the complete description of the reacting system becomes complex. For some investigators, the choice of the dominant effect of a β-bromo substituent among the several competing "processes must be left to the discretion of the reader."[14a] For us,

(26) The difference in ratio supports the view, long advocated by Tanner and co-workers, that neighboring bromo will retard the reaction of the alkyl radical with polar HBr more than with Br_2. The data led to the conclusion: "Thus only 3.4% of the radicals formed reverse with hydrogen bromide when the concentrations of bromine and hydrogen bromide are equal".[24b]

(27) The kinetic expression given is included in ref 24b; see that reference for the identity of each rate constant in the expression. (k_{Br_2}/k_{HBr}) at C-2 = (k_4/k_{-3}) and at C-3 = (k_6/k_{-5}). An even more complex expression is used by Tanner et al.: Tanner, D. D.; Ruo, T. C-S.; Takiguchi, H.; Guillaume, A. *Can. J. Chem.* **1981**, *59*, 1368–74.

(28) Professor A. A. Zavitsas (Long Island University, Brooklyn, NY) called our attention to these calculations through a poster presentation at the 1982 Gordon Research Conference on Radical Ions and through subsequent personal correspondence about that work. Co-workers with Professor Zavitsas were P. A. D. Legotte, G. Fogel, and K. Halwagi. We thank Professor Zavitsas for sharing his data with us before publication.

(29) Pearson, R. E.; Martin, J. C. *J. Am. Chem. Soc.* **1963**, *85*, 3142–6.

(30) Tanner, D. D.; private communication to J.G.T., July 1982. Tanner, D. D.; Ruo, T. C.-S.; Takiguchi, H.; Guillaume, A.; Reed, D. W.; Setiloane, B. P.; Tan, S. L.; Meintzer, C. P. *J. Org. Chem.* **1983**, *48*, 2743–7.

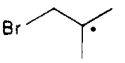
the accumulated experimental evidence is compelling: a β-bromo substituent provides, especially in solution reactions when HBr concentration is minimized, substantial neighboring group participation in radical brominations, facilitating hydrogen abstraction and constraining configuration at the vicinal site. Some product can be formed by other reaction pathways under certain conditions, but the direct, favorable effect of β-bromo accounts for most of the product.

We believe that the controversy over the interpretation of the experimental results should wither, just as has the controversy earlier over the results themselves.

Bromo Bridging: Single or Double Potential Energy Minimum Model?

To date, none of the product studies concerned with bromo bridging has provided evidence that could govern a choice between alternative descriptions of the bridged species: a single potential energy minimum or a double minimum with shuttling between them at rates over 10^{10} s^{-1}. Since data for chloro bridging required a double minimum description with rapid shuttling,[4e] the same model for bromo bridging seems reasonable for the present.

Although the ESR spectrum published for **17** was



17

interpreted in terms of an unsymmetrical bridge, with stronger bonding of Br to primary C than to tertiary C,[7a] it provided no evidence for $(CH_3)_2CBrCH_2\cdot$ and therefore no guide to the double vs. single minimum dilemna.

A CIDNP experiment indicated that $BrCH_2CH_2\cdot$ has an unsymmetrical structure.[8] Although there is no evidence for bridging from this experiment, it is reasonable to ascribe an unsymmetrical bridge, and thus a double-minimum model, to this species. This interpretation makes the description of 2-bromoethyl and 2-chloroethyl[31] systems consistent.

(31) Chen, K. S.; Elson, I. H.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 5341–9.

Electron-Rich Sulfur–Nitrogen Heterocycles

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The chemistry of inorganic heterocycles has a long history. The first representatives of the cyclothiazenes and cyclophosphazenes,[1a] S_4N_4[1b] and $(NPCl_2)_3$,[2] were discovered in the previous century and borazine ($B_3N_3H_6$) was isolated in 1926.[3] One aspect of the behavior of such heterocycles that has particularly intrigued chemists is the extent and consequences of delocalized π bonding in these ring systems. The concept of aromaticity has played a prominent role in these discussions. For example, borazine has been described as the inorganic analogue of benzene. However, the polarization of the π-electron density, which arises from the electronegativity difference between boron and nitrogen, results in much greater chemical reactivity than is observed for aromatic organic compounds. the possibility of aromatic behavior has also been a central issue in studies of cyclophosphazenes, $(NPX_2)_n$, for which an extensive homologous series is known (n = 3–17).[4]

Both borazine and the cyclophosphazenes are *π-electron-precise* molecules, i.e., the number of π electrons is equal to the number of atomic centers in the ring. By contrast, cyclothiazenes are *π electron rich*; i.e., the number of π electrons exceeds the number of atomic centers in the ring. In 1972 Banister proposed that planar sulfur–nitrogen heterocycles belong to a class of "electron-rich aromatics" which conform to the well know Hückel $(4n + 2)$ π-electron rule.[5] On the reasonable assumption that each sulfur contributes two electrons and each nitrogen one electron to the π system, S_2N_2 (6π), $S_4N_3^+$ (10π), and $S_5N_5^+$ (14π) were cited as examples in support of this contention.

Since then our knowledge of electron-rich heterocycles has been considerably enhanced by the discovery of numerous new sulfur–nitrogen rings and heterocyclothiazenes (Figure 1). The development of the subject has been accelerated by the application of physical techniques, particularly X-ray crystallography and, to a lesser extent, ^{15}N NMR and Raman spectroscopy, to structural determinations. Concomitantly, theoretical treatments have reached the stage where a good understanding of the thermodynamic stability, chemical reactivity, and intense colors of these electron-rich compounds has emerged and UV–visible and MCD spectroscopic measurements have provided corroborative evidence for the MO calculations.

Consistent with the philosophy of our research efforts, this Account illustrates the main features of the

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(1) (a) The terms cyclothiazene and cyclophosphazene refer to ring compounds formed by the oligomerization of the monomer units SN or R_2PN, respectively. (b) Gregory, W. *J. Pharm.* (*Antwerp*) **1835**, *21*, 315; *22* 301.

(2) Liebig, J.; Wöhler, F. *Liebigs Ann. Chem.* **1834**, *11*, 139. Rose H. *Ibid.* **1834**, *11*, 131.

(3) Stock, A.; Pohland, E. *Chem. Ber.* **1926**, *59*, 2215.

(4) Krishnamurthy, S. S.; Sau, A. C.; Woods, M. *Adv. Inorg. Chem. Radiochem.* **1978**, *21*, 41.

(5) Banister, A. J. *Nature* (*London*) **1972**, *237*, 92.

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