Radical Clorination and Bromination of (Halomethyl)cyclohexanes. Evidence for Halogen-Bridged Radicals[1]

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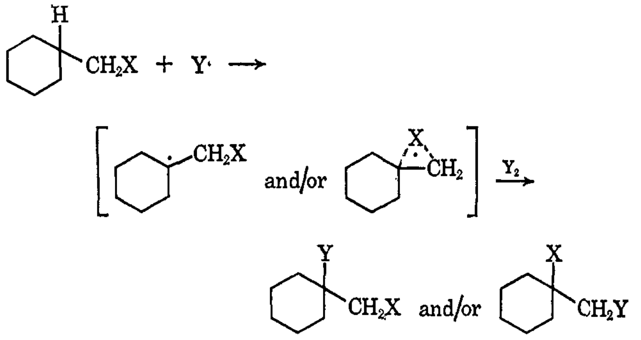
Abstract: To provide evidence about the importance of bridged radical intermediates in halogenation reactions, brominations and chlorinations of several (halomethyl)cyclohexanes have been carried out. Bromination is far more selective than chlorination, but in both processes substitution at the tertiary position vicinal to the halogen already present is much more extensive than is to be expected without assistance from neighboring halogen. Even chlorine, in 1-(chloromethyl)-4-methylcyclohexane, exerts a favorable neighboring group effect during bromination. Chlorination of (bromomethyl)cyclohexane gave an appreciable amount of rearranged product, 1-bromo-1-(chloromethyl)cyclohexane, but little or no rearrangement of neighboring chlorine occurred.

Enhancement of ionic substitution reactions by various neighboring groups has been extensively documented,[3] and evidence for similar effects of neighboring bromine on radical reactions has been obtained recently. High selectivity in brominations of alkyl bromides,[4] epr spectra of radicals generated by photoinitiated addition of hydrogen bromide to olefins,[5] and 1,2 rearrangements of a bromo substituent during chlorinations of selected alkyl bromides[6] have been rationalized in terms of bromine-bridged radicals. Strong evidence that some of the 1,2 rearrangements occur through an elimination–addition mechanism, however, rather than a bridged radical, has been presented.[7] The extent to which one can depend on bromine-bridged radical formation and the point along a reaction coordinate at which bridging becomes important are uncertain, however. Bromination of (+)-1-bromo-2-methylbutane gave optically active dibromide, but chlorination of the same bromide gave only optically inactive chloro bromide.[8] Solvent effects on the extents of rearrangement are apparently substantial.[6a,7]

While we are also unable to clarify the complete picture of neighboring bromine in radical reactions, we describe here some new halogenation data which strongly favor participation by a vicinal bromo substituent, leading to both enhanced selectivity in radical attack and to substantial (but incomplete) rearrangement of the bromo substituent from a primary to a tertiary position.

Earlier investigations had indicated that bridging by cationic bromine is apparently much more favored in additions of hypobromous acid to methylenecyclohexane than to isobutylene.[9] We therefore chose 1-(halomethyl)cyclohexanes for studies of radical halogenations, expecting the structural features that so strongly favored bromine bridging in the cationic reaction to be at least partially effective in the radical one.



X and Y = halogens (Cl and Br)

Since bromination is much more selective than chlorination,[4,10] we expected the more decisive probe of bridged radical participation in the reaction to be chlorination. Such participation would be revealed by substantial enhancement of selectivity for the vicinal (tertiary) position over that expected,[4] and by rearrangement of the bromo substituent from the primary to the tertiary carbon. When (bromomethyl)cyclohexane was chlorinated with molecular chlorine, and when (chloromethyl)cyclohexane was brominated with molecular bromine, analysis of the product mixtures by gas chromatography and nuclear magnetic

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[1] (a) Presented in part at the Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 1967, paper 169. (b) Based on the Ph.D. Dissertation of W. G. H., Louisiana State University, Jan 1968. The financial assistance from the Charles E. Coates Memorial fund, donated by George H. Coates, for preparation of the Ph.D. dissertation of W. G. H. is gratefully acknowledged.

[2] National Science Foundation Science Faculty Fellow, 1966–1967.

[3] See, for examples, (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 141–151; (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, Inc., New York, N. Y., 1959, pp 561-599.

[4] W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963). This paper includes a thorough discussion of the importance of selectivity (and the relative unimportance of rearrangement) to the issue of anchimeric participation by neighboring bromine in radical substitution reactions.

[5] P. I. Abell and L. H. Piette, *ibid.*, **84**, 916 (1962); see, however, M. C. R. Symons, *J. Phys. Chem.*, **67**, 1566 (1963).

[6] (a) P. S. Skell, R. G. Allen, and N. D. Gilmour, *ibid.*, **83**, 504 (1961); (b) P. S. Juneja and E. M. Hodnett, *ibid.*, **89**, 5685 (1967).

[7] W. O. Haag and E. I. Heiba, *Tetrahedron Lett.*, 3683 (1965). These authors describe rearrangement of bromine from a tertiary to a primary carbon.

[8] (a) P. S. Skell, D. L. Tuleen, and P. D. Readio, *J. Amer. Chem. Soc.*, **85**, 2849 (1963). (b) A referee has suggested that "the probable main difference between stereochemistry of chlorinations and brominations [is] the lifetime of the radical." This suggestion, which may be correct, is tantamount to proposing that hydrogen abstraction from RBr proceeds without participation by neighboring bromine. Initial formation of a conventional (unbridged) radical which may or may not change to a bridged one has been proposed elsewhere.[6b]

[9] J. G. Traynham and O. S. Pascual, *Tetrahedron*, **7**, 165 (1959).

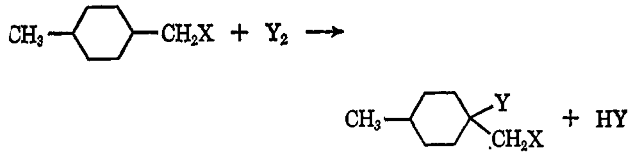
[10] P. C. Anson, P. S. Fredricks, and J. M. Tedder, *J. Chem. Soc.*, 918 (1959).

resonance spectroscopy revealed that attack did occur largely at the tertiary position and some migration (12–15%) of the bromo substituent did occur.

Although early suggestions of bromine-bridged radicals were associated specifically with 1,2 rearrangements of a bromo substituent,[5,6a] the significance of the amount of rearrangement in our experiments is blurred by the evidence for an elimination–addition mechanism for related rearrangements.[7] Elimination of bromine atom from the 1-(bromomethyl)cyclohexyl radical followed by recombination of the olefin–atom pair[7] (unexpectedly) at the tertiary carbon, as well as a bromine-bridged radical which suffers predominant but not exclusive attack at the tertiary carbon, would account for the rearrangement. When a carbon tetrachloride solution of BrCl (generated from Cl_2 and Br_2)[11] was added to a chilled solution of methylenecyclohexane, the mixture of addition products consisted of 1-bromo-1-(chloromethyl)cyclohexane and 1-chloro-1-(bromomethyl)cyclohexane, as well as some 1-bromo-1-(bromomethyl)cyclohexane (product ratio about 1:4:1, respectively). While the 1-bromo-1-(chloromethyl) product is consistent with a bromine-bridged intermediate (cationic or radical, depending on the nature of the BrCl addition), we cannot now exclude more direct addition of Br to the more substituted carbon of the olefin.

The intimate details of the path for 1,2 rearrangement, however, are only secondarily related to neighboring group participation by bromine in the crucial radical attack on hydrogen in the alkyl bromide.[4] The central issue is the effect of the substituent on the relative rates of competing hydrogen abstraction steps.[4] In the liquid phase chlorination of alkanes (branched, but otherwise unsubstituted), the selectivity of a chlorine atom for hydrogens bound to primary (p), secondary (s), and tertiary (t) carbons has been shown to be p:s:t = 1:2.5:4.2.[12a] These relative rates of attack lead us to expect that chlorination of (bromomethyl)cyclohexane, which has ten hydrogens bound to secondary positions[12b] and one to a tertiary position in each molecule, would produce a yield ratio of secondary alkyl chlorides (several isomers) to tertiary alkyl chloride of about s:t = 6:1, in the absence of any effect of the bromo substituent. A bromo substituent retards attack at a vicinal position by chlorine, however;[4] chlorinations of 1-bromobutane and 1-chlorobutane produce very similar isomer distributions, and substitution at position 2 compared to substitution at position 3 is retarded by factors of 0.43 and 0.49, respectively.[4,13] Such a retarding effect would favor secondary alkyl chlorides over the tertiary one from (bromomethyl)cyclohexane even more than the ratio s:t = 6:1. The actual ratio of yields, however, was about s:t = 1:3. The selectivity for attack of chlorine at a tertiary position over a secondary position in (bromomethyl)cyclohexane has been enhanced by a factor of 18 over estimates which ignore the effect of neighboring bromine and by as much as 42 if the rate-retarding effect of vicinal bromine is considered.[4,14] The magnitude of this effect is the largest reported for neighboring bromine in chlorination reactions, although larger effects are manifested in the more selective brominations of cycloalkyl bromides.[4] Such enhancement of selectivity is persuasive evidence of anchimeric assistance by bromine in the radical reaction.

Bromination of (chloromethyl)cyclohexane gave exclusively 1-bromo-1-(chloromethyl)cyclohexane, but the selectivity of bromine for a tertiary position over a secondary one is already so high[10] that no indication of chlorine participation is implied by that result. Strong evidence for chlorine participation[8] in the hydrogen abstraction step was obtained in experiments with *trans*-4-methyl-1-(chloromethyl)cyclohexane. The expected retardation[4] by chlorine vicinal to one tertiary position should lead to preferential attack at the more remote tertiary position by bromine. However, bromination of *trans*-4-methyl-1-(chloromethyl)cyclohexane produced only 1-bromo-1-(chloromethyl)-4-methylcyclohexane. To our knowledge, this is the first report of apparent rate enhancement of bromination by neighboring chlorine. As would be expected for the highly selective bromination of an alkyl bromide,[4] bromination of *trans*-1-(bromomethyl)-4-methylcyclohexane also proceeded by exclusive attack at the tertiary position vicinal to the bromo substituent.[15] Either the retardation effects reported[4] for vicinal secondary positions are completely inapplicable to vicinal tertiary ones, or both bromo and chloro substituents exhibit (to different degrees) considerable anchimeric assistance in the hydrogen abstraction step of these reactions with halomethylcyclohexanes.



The 1-halo-1-(halomethyl)cyclohexanes are distinguishable from each other by gas chromatographic (gc) and nuclear magnetic resonance (nmr) data. The chemical shift of the exocyclic methylene protons responds to changes in halogen attached to the same and adjacent carbons in the usual way.[16] Deshielding

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(11) A. I. Popov and J. J. Mannion [*J. Amer. Chem. Soc.*, **74**, 222 (1952)] report that BrCl in CCl_4 is 43.2% dissociated into Br_2 and Cl_2. See also S. Barratt and C. P. Stein, *Proc. Roy. Soc.* (London), **A122**, 582 (1929).

(12) (a) G. A. Russell, *J. Amer. Chem. Soc.*, **80**, 4987, 4997 (1958); W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., New York, N. Y., 1966, p 154. The relative reactivity for hydrogen bound to secondary carbon is for cyclohexane hydrogens and is based upon twelve hydrogens per molecule. (b) We should perhaps limit the consideration of hydrogens on secondary carbons in cyclohexane rings to the axial ones. Radical additions of HBr to cyclohexenes apparently proceed by axial addition of both Br and H [B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962)]. Although other data on the preferred direction for hydrogen abstraction from cyclohexanes do not appear to be available, these addition reaction results may indicate a preference for axial hydrogen abstraction by Br·. If we do exclude equatorial hydrogens on secondary positions from our calculations, however, the relative rate of hydrogen abstraction from cyclohexane should be doubled and the estimates of selectivity enhancement by neighboring bromine are unchanged from those in the text.

(13) Bromine attack on the 2 position of 1-bromobutane is strongly enhanced, but bromine attack on the 2 position of 1-chlorobutane is retarded.[4]

(14) Data reported[6b] for chlorination of isobutyl bromide permit a similar estimate of selectivity enhancement (tertiary over primary) by a factor of about 6 in that reaction. This small enhancement was also considered[6b] to be evidence for anchimeric assistance by bromine.

(15) Chlorinations of *trans*-1-(bromomethyl)-4-methylcyclohexane produced complex mixtures of monochlorides for which useful separations and analyses were not achieved.

(16) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, England, 1965, p 672.

by halogen attached to the same carbon is more effective with chlorine, but deshielding by vicinal halogen is more effective with bromine. Thus the exocyclic methylene protons of the major product from chlorination of (bromomethyl)cyclohexane absorb as a sharp singlet at −3.65 ppm and those of the major product from bromination of (chloromethyl)cyclohexane and of (bromomethyl)cyclohexane at −3.88 ppm.[17]

Experimental Section

Nmr data[17] were obtained with a Varian Associates A-60A spectrometer with the assistance of Mr. W. Wegner. Infrared spectra were recorded on Perkin-Elmer Model 137 and Beckman IR-10 spectrophotometers. Gc data were obtained with a Beckman GC-5 gas chromatograph equipped with a hydrogen flame detector and $^1/_8$-in. packed columns (either 6-ft silicone SE-30 or 10-ft Carbowax 20M). Element analyses were performed by Mr. R. Seab in these laboratories.

(Bromomethyl)cyclohexane[18] was prepared by stirring an initially chilled mixture of cyclohexanemethanol[19] and phosphorus tribromide overnight at room temperature: nmr −3.24 ppm (d, J = 5.4 Hz, CH_2Br). **(Chloromethyl)cyclohexane** was prepared in 73% yield from the alcohol[19] and thionyl chloride: bp 75–80° (33–38 mm); n^{24}D 1.4670; nmr −3.31 ppm (d, J = 5.6 Hz, CH_2Cl). *Anal.* Calcd for $C_7H_{13}Cl$: C, 63.4; H, 9.9. Found: C, 62.5; H, 9.9.

trans-**1-(Chloromethyl)-** and *trans*-**1-(bromomethyl)-4-methylcyclohexanes** were prepared from the corresponding alcohol[20] and thionyl chloride or phosphorus tribromide, respectively. The chloride was obtained in 83% yield: bp 46–52° (3 mm); n^{24}D 1.4586; nmr −3.33 ppm (d, J = 5.4 Hz, CH_2Cl). *Anal.* Calcd for $C_8H_{15}Cl$: C, 65.5; H, 10.3. Found: C, 65.1; H, 10.4. The bromide was obtained in 50% yield: bp 61–62° (0.3 mm); n^{25}D 1.4830; nmr −3.24 ppm (d, J = 5.4 Hz, CH_2Br). *Anal.* Calcd for $C_8H_{15}Br$: C, 50.3; H, 7.9. Found: C, 50.1; H, 8.0.

A small sample of **1-bromo-1-(bromomethyl)cyclohexane** was prepared in carbon tetrachloride solution by passing a nitrogen stream of bromine into an ice-chilled solution of methylenecyclohexane until the color of bromine persisted in the solution. Excess bromine was removed by a nitrogen stream, and the nmr spectrum of the solution was recorded. The spectrum included a sharp singlet at −3.88 ppm ($CBrCH_2Br$).

Halogenations of (Halomethyl)cyclohexanes. Several halogenation procedures were investigated, including bulk addition of halogen at the beginning of the experiment and slow addition of halogen in a nitrogen stream, irradiation by a Sylvania RS sunlamp and by 2537-Å lamps in a Rayonet photochemical reactor, use of Pyrex and of quartz reaction vessels, and use of sulfuryl chloride and benzoyl peroxide. Although the products obtained were dependent but little on the procedure employed, the yields of monohalogenation product obtained were consistently highest when the halogen was introduced slowly in a nitrogen stream and 2537-Å irradiation into quartz vessels was used. The reaction times selected led to partial consumption of the (halomethyl)cyclohexane and to little polyhalogenation. A typical procedure is described.

A solution of (chloromethyl)cyclohexane (0.1 mol) in carbon tetrachloride (40 ml) was placed in a quartz tube equipped with a reflux condenser and a gas inlet tube. The quartz tube was suspended in a Rayonet photochemical reactor equipped with lamps for 2537-Å radiation, and, while the lamps were turned on, a stream of nitrogen was directed through liquid bromine (0.1 mol) and then into the (chloromethyl)cyclohexane solution until all the bromine had been added (5–6 hr). After irradiation had been continued for a total of 24 hr, gc and nmr data obtained on the entire product mixture indicated that monobromo product had been formed in 63% yield and that 85–90% of that product was 1-bromo-1-(chloromethyl)cyclohexane: nmr −3.88 ppm (s, $CBrCH_2Cl$). No more than a trace (or none at all) of 1-chloro-1-(bromomethyl)cyclohexane [nmr −3.63 ppm (s, $CClCH_2Br$)] appeared to be present in the mixture.

In a similar fashion, chlorination of (bromomethyl)cyclohexane produced a mixture of monochlorination products (30–40% yield) consisting of 1-bromo-1-(chloromethyl)cyclohexane, 1-chloro-1-(bromomethyl)cyclohexane, and other chloro(bromomethyl)cyclohexanes[21] in the approximate relative amounts 1:6:2, respectively.

Slow addition of bromine to 1-(chloromethyl)-4-methylcyclohexane and to 1-(bromomethyl)-4-methylcyclohexane produced 1-bromo-1-(chloromethyl)-4-methylcyclohexane (55% yield) and 1-bromo-1-(bromomethyl)-4-methylcyclohexane (22% yield), respectively, apparently the exclusive monobromination products.[22]

Addition of BrCl to Methylenecyclohexane. A solution was prepared by mixing 5 ml each of liquid chlorine and bromine in 100 ml of ice-chilled carbon tetrachloride. A portion of this solution of BrCl[11] was added dropwise to a stirred, ice-chilled solution of methylenecyclohexane (0.05 mol) in carbon tetrachloride (20 ml) until the color of the halogen solution persisted. The nmr spectrum of the solution included sharp singlets at −3.63 ($CClCH_2Br$, relative intensity about 4), −3.88 ($CBrCH_2Br$, relative intensity about 1), and −3.90 ppm ($CBrCH_2Cl$, relative intensity about 1).

Preparation of 1-Bromo-1-(chloromethyl)cyclohexane. A sample of 1-bromo-1-(chloromethyl)cyclohexane was prepared, apart from bromination of (chloromethyl)cyclohexane, by treating methylenecyclohexane bromohydrin[9,23] with thionyl chloride: nmr −3.87 ppm (s, $CBrCH_2Cl$). When a small sample of this bromo chloride was dehydrohalogenated in 1 molar equiv of refluxing 10% ethanolic potassium hydroxide, the product formed was characterized by its ir and nmr spectra as chloromethylenecyclohexane: ir absorption near 730 (C–Cl) but none near 630 cm^{-1} (C–Br); nmr −5.71 ppm (m, C=$CHCl$).

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[17] Nmr spectra were obtained for both neat samples and carbon tetrachloride solutions. All chemical shift data are relative to internal tetramethylsilane reference; a minus sign indicates downfield.

[18] D. Perlman, D. Davidson, and M. T. Bogert, *J. Org. Chem.*, **1**, 288 (1936).

[19] We gratefully acknowledge a generous gift of cyclohexanemethanol from The Dow Chemical Co., Midland, Mich.

[20] The *cis* and *trans* isomers of 4-methylcyclohexane-1-methanol, and their differentiation by solid derivatives, have been described by R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, 1245 (1939). We have observed that the nmr doublet (−3.29 ppm, J = 6 Hz) for CH_2OH in the *trans* isomer appears about 6 Hz upfield from the corresponding absorption by the *cis* isomer (J = 6 Hz).

[21] Identification of these chloro(bromomethyl)cyclohexanes was based on gc retention times and nmr spectra. Individual structures of these products of substitution at secondary positions have not yet been established.

[22] In one experiment, in which bromine was added all at once to 1-(chloromethyl)-4-methylcyclohexane, a gc analysis of the product mixture indicated that the low yield of monobromo derivative consisted of both 1-bromo-1-(chloromethyl)-4-methylcyclohexane (40%) and 1-bromo-1-methyl-4-(chloromethyl)cyclohexane (60%) [nmr −1.97 ppm (s, CH_3CBr)]. The influence of chlorine concentration on the selectivity of the chlorine atom during liquid phase chlorination of isobutane has been noted previously; see ref 12a (particularly footnote 28) and references cited there.

[23] The same bromohydrin is obtained by treating methylenecyclohexane with aqueous hypobromous acid, with an aqueous suspension of N-bromosuccinimide, or with a solution of N-bromosuccinimide in moist dimethyl sulfoxide (DMSO),[24] or by treating methylenecyclohexane oxide with aqueous or anhydrous HBr. The bromohydrin [mp 81–82.5°; nmr (DMSO-d_6) −3.42 (s, CH_2O, 2) and −3.63 ppm (s, OH, 1)] was characterized on the basis of chemical behavior as (1-bromocyclohexyl)methanol,[9] but the mutual influence of the vicinal substituents on each other makes the interpretation of both chemical and spectral data uncertain. The conversion of the bromohydrin into the same bromo chloride derivative which we obtain from bromination of (chloromethyl)cyclohexane [but different from the one obtained from chlorination of (bromomethyl)cyclohexane] strongly supports the tertiary bromide structure for the bromohydrin. The bis(bromohydrin) obtained by treatment of 1,4-dimethylenecyclohexane with aqueous N-bromoacetamide has been characterized as the bis(tertiary bromide, primary alcohol).[25]

[24] (a) D. R. Dalton, J. B. Hendrickson, and D. Jones, *Chem. Commun.*, 591 (1966); (b) D. R. Dalton and D. Jones, *Tetrahedron Lett.*, 2875 (1967). The mechanism proposed for this reaction involves attack of DMSO on a bromonium ion and would, we believe, favor primary alcohol rather than tertiary alcohol because of steric effects.

[25] G. O. Schulz, M. S. Thesis, The University of Akron, 1963.