Solvent and Complexation Effects upon Yield and Stereoselectivity in Brominolysis of Tri-*exo*-2-norbornylborane with Chloramine T

Donna J. Nelson* and Raman Soundararajan

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019

Received August 23, 1988

The effect upon the title reaction caused by switching from a nonpolar solvent (CCl_4) to THF is to increase the yield of 2-bromonorbornane marginally due to a typical favorable effect of THF on the ionic brominolysis pathway combined with a competing radical reaction in CCl_4 leading to alternate products. A yield increase upon galvinoxyl addition gives evidence for the latter phenomenon. The above switch in solvent also decreases the stereoselectivity for the exo isomer from 95–99% to 76–77%, probably due to involvement of the different mechanistic pathways. In THF, yields and stereoselectivities are greater for reaction with bromine generated in situ than with bromine chloride generated in situ, but are comparable in CCl_4. A brief study of the effects of complexing agents reveals that stronger complexes give more of the endo product.

Introduction

Halogenolysis of organometals is a convenient route to organohalides,[1] many of which have important uses, such as synthetic intermediates or radiopharmaceuticals.[2] When coupled with hydrometalation, anti-Markovnikov alkyl halides are easily obtained from alkenes via organoboron,[3] organoaluminum,[4] and organozirconium[5] compounds. Yields and stereoselectivities of several methods of iodinolysis,[6] brominolysis,[7a,8] and chlorinolysis[8,9] of trialkylboranes have been reported. Polar base-induced halogenolysis[6,7b] of tri-*exo*-2-norbornylborane proceeds predominantly via an S_E2 (back) mechanism which results in inversion of stereochemistry to yield the endo product. On the other hand, halogenolysis via radical reactions[7a,8,9a,h] favors the exo product by approximately 7:1 to 9:1, depending on the coreactant, but presumably not on the stereochemistry of trinorbornylborane.

Kabalka developed a mild brominolysis of trialkylboranes,[6] which uses bromine chloride generated in situ from chloramine T and sodium bromide, and this has provided a remarkably simple route to many biologically important radiobrominated (*) compounds.[2] While the

$$R_3B \xrightarrow[NaBr^*,\ HCl]{\text{chloramine T}} RBr^* \qquad (1)$$

reaction is postulated to proceed by an ionic S_E2 mechanism, neither the stereoselectivity nor a mechanistic investigation of this synthetically useful reaction has been reported. Therefore, we have undertaken and report the results of such studies.

Table I. Yields[a] and Exo:Endo Stereoselectivities[b] of Brominolysis of Tri-*exo*-2-norbornylborane at 0 °C with Acidified Aqueous Solutions of Chloramine T (ClT) and Sodium Bromide and with Bromine

no.	reagent	NaBr: ClT:R_3B (equiv)	acid	solvent: THF	solvent: CCl_4
1	ClT	1:2:1	10% HCl	23.2 74.7:25.3	21.3 85.5:14.5
2				26.8[c] 74.2:25.8	
3	ClT	2:2:1	10% HCl	25.8 73.1:26.9	23.2 95.2:4.8
4					35.6[d] (62.8) 98.2:1.8 (97.4:2.6)
5	ClT	2:2:1	10% HCl[e]	66.2 65.5:34.5	
6	ClT	2:2:1	concd HBr	53.1 79.6:20.4	23.9 85.4:14.6
7				53.8[c] 79.6:20.4	35.0[d] 89.1:10.9
8	Br_2[f]			30–40 >99:<1	88[g] >99:<1
9	Br_2, $TsNH_2$ (1 equiv)			11.24 87.5:12.5	
10	Br_2, NaOMe[f]			>99 25:75	

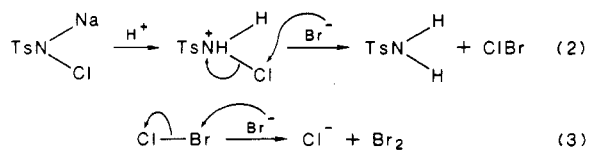
[a] Yields (in percent) are based on trinorbornylborane. [b] Exo:endo ratios are below the corresponding yields. [c] Trinorbonylborane was added to the bromination reagent mixture (inverse addition). [d] Galvinoxyl added, 0.01 equiv (0.1 equiv). [e] 6 equiv of acid is used. [f] References 7a,b. [g] Yield is based on alkene.

Results and Discussion

The nature of the brominolysis agent in reactions with chloramine T depends upon the stoichiometry of the reaction. Thus, if the ratio of bromide to chloramine T is ≤ 1, then bromine chloride is generated in situ.[2a] A possible ionic mechanism for this is similar to the nucleophilic attack at halogen reported in several other *N*-halo systems.[10] If the ratio of bromide to chloramine T is ≥ 2,

(1) Negishi, E. *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Vol. 1.
(2) (a) Kabalka, G. W.; Sastry, J. A. R.; Hsu, H. C.; Hylarides, M. D. *J. Org. Chem.* **1981**, *46*, 3113-5. (b) Kabalka, G. W.; Sastry, K. A. R.; Pagni, P. *J. Radioanal. Chem.* **1982**, *74*, 315. (c) Kabalka, G. W.; Sastry, K. A. R.; Knapp, F. F.; Srivastava, P. C. *Synth. Commun.* **1983**, *13*, 1027.
(3) (a) Brown, H. C.; Rathke, M. W.; Rogic, M. M. *J. Am. Chem. Soc.* **1968**, *90*, 5038. (b) Brown, H. C.; Lane, C. F. *Ibid.* **1970**, *92*, 6660. (c) Lane, C. F.; Brown, H. C. *Ibid.* **1970**, *92*, 7212. (d) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1978. (e) Kabalka, G. W.; Gooch, E. E., III. *J. Org. Chem.* **1980**, *45*, 3578.
(4) (a) Isagawa, K.; Tatsumi, K.; Otsuji, Y. *Chem. Lett.* **1976**, 1145. (b) Sato, F.; Sato, S.; Sato, M. *J. Organomet. Chem.* **1976**, *122*, C25. (c) Sato, F.; Sato, S.; Sato, M. *Ibid.* **1977**, *131*, C26. (d) Sato, F.; Sato, S.; Kodama, H.; Sato, M. *Ibid.* **1977**, *142*, 71.
(5) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. (b) Schwartz, J. In *New Applications of Organometallic Reagents in Organic Synthesis*; Seyferth, D., Ed.; Elsevier: Amsterdam, 1976; p 461. (c) Schwartz, J. *Angew. Chem.* **1976**, *88*, 402.
(6) (a) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1981**, *46*, 2582-4, and references cited therein. (b) Brown, H. C.; De Lue, N. R.; Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 1270-1.
(7) (a) Lane, C. F.; Brown, H. C. *J. Am. Chem. Soc.* **1970**, *92*, 7212-3. (b) Brown, H. C.; Lane, C. F. *J. Chem. Soc., Chem. Commun.* **1971**, 521-2. (c) Brown, H. C.; Lane, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 6660-1. (d) Hall, L. D.; Neeser, J.-R. *Can. J. Chem.* **1982**, *60*, 2082. (e) Lane, C. F.; Brown, H. C. *J. Organomet. Chem.* **1971**, *26*, C51. (f) Bergbreiter, D. E.; Rainville, D. P. *J. Organomet. Chem.* **1976**, *121*, 19.
(8) Lane, C. F. *J. Organomet. Chem.* **1971**, *31*, 421-31.
(9) (a) Brown, H. C.; De Lue, N. R. *J. Organomet. Chem.* **1977**, *135*, C57-9. (b) Davies, A. G.; Hook, S. C. W.; Roberts, B. P. *J. Organomet. Chem.* **1970**, *23*, C11-2. (c) Johnson, J. R.; Snyder, H. R.; Campen, M. G. V., Jr. *J. Am. Chem. Soc.* **1938**, *60*, 115-21. (d) Jigajinni, V. B.; Paget, W. E.; Smith, K. *J. Chem. Res., Synop.* **1981**, 376-7. (e) Arase, A.; Masuda, Y.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2511-4. (f) Davies, A. G.; Maki, T.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. II* **1972**, 744. (q) Davies, A. G.; Griller, D.; Roberts, B. P.; Tudor, R. *J. Chem. Soc., Chem. Commun.* **1970**, 640. (h) Nelson, D. J.; Soundararajan, R. *J. Org. Chem.*, in press.

0022-3263/89/1954-0340$01.50/0 © 1989 American Chemical Society



(2)

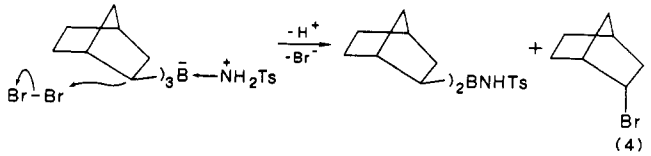
(3)

then molecular bromine is generated as shown in eq 3.[11a] The generation of bromine chloride or bromine is apparent from the red or purple color of the organic layer, which can be removed and used to convert alkenes to bromochloroalkanes[11b] or dibromoalkanes,[11a] respectively. Although radicals are involved in some reactions of *N*-haloammonium compounds,[12] this is ruled out here, since galvinoxyl has no effect on the color of the organic layer.

While the red or purple color is observed in each reaction involving chloramine T, this does not necessarily mean that bromine chloride or bromine is the brominolysis agent. It is conceivable that a different source of electropositive bromine might also be generated and effect brominolysis. An excellent differentiating test is to compare the yields and stereoselectivities of two sets of reactions that are identical except that in one, trinorbornylborane is added to the reaction flask first, before the generation of BrCl or Br_2, while in the other, it is added after the generation of the compound. If the values are identical within experimental error, assuming that the formation of bromine chloride (and that of bromine) is irreversible, then the same compound must be the brominolysis agent in both reactions.

Yields and stereoselectivities for brominolysis of tri-*exo*-2-norbornylborane with chloramine T under various conditions are presented in Table I. Comparing results in THF of entry 1 (23%; 75:25) versus 2 (27%; 74:26) and those of entry 6 (53%; 80:20) versus 7 (54%; 80:20) reveals that these reactions do indeed give quite similar yields and stereoselectivities. Therefore, the likely brominolysis agent in entries 1–5 is BrCl, while bromine is likely in entries 6–10.

If the brominolysis agent in entries 7 and 8 in THF is the same, the reactions should differ only in that byproducts are present in 7. Therefore, comparing these should give the effects of the byproducts upon the reaction. One reason for the reduction in yield and stereoselectivity would be formation of a complex with *p*-toluenesulfonamide (NH_2Ts), which is stronger and less reactive than that with THF. Thus, the amount of the endo isomer



(4)

formed would be increased in entry 7 relative to 8. To test this theory, we carried out a reaction identical with entry 8 in the presence of 1 equiv of *p*-toluenesulfonamide. The yield was reduced from 30–40% to ~11%, and the stereoselectivity was decreased from >99:<1 (entry 8) to 87.5:12.5 (entry 9). The results of this reaction (entry 9) are not similar to those involving in situ generation of bromine (entry 7), and they are not expected to be since the reactions differ in pH, in salt concentration, and in overall concentration of *p*-toluenesulfonamide. The effect of methoxide, which forms a stronger complex, is to increase endo isomer formation to 75% (Table I, entry 10). Thus, THF, *p*-toluenesulfonamide, or methoxide increases the reactivity toward the S_E2 (back) mechanism and increases the amount of endo isomer formed, probably due to complexation at boron. These effects are difficult to compare because of differences in concentration of the complexing agent. However, it appears that generally the stronger complex gives more of the endo isomer. This also agrees with earlier reports that complexation with THF can retard the rate,[13b] reduce the selectivity,[9e,13c] or change the course[13a] of some reactions of organoboranes.

Based upon this, one might expect a reduction in stereoselectivity of reactions involving chloramine T upon switching from CCl_4 to THF. The reactions in THF solvent give higher yields (23–54%) and lower stereoselectivities (~73:27 to ~80:20) than those in CCl_4 (21–35%; ~86:14 to ~95:5), with the effects being more pronounced when concentrated HBr is used than with 10% HCl. Thus, while the reduction in stereoselectivity is observed, the yield increases. The main reason for the yield increase is probably a typical favorable effect of THF upon an ionic reaction. However, in CCl_4 there also could occur a competing radical reaction that leads to alternate products and lower yields of 2-bromonorbornane.

Indeed, addition of 0.01 equiv of galvinoxyl to the reactions in CCl_4 increased the yields by ~50% and the stereoselectivities (entries 3 (23%; 95:5) versus 4 (36%; 98:2) and 6 (24%; 85:15) versus 7 (35%; 89:11)). The use of additional galvinoxyl (0.1 equiv, entry 4) increases the yield further (63%; 97:3). Furthermore, GC/MS analysis of the products of entry 3 (in THF and in CCl_4) identifies one of the products as 2-norbornyl-2-norborneol, which would be the product expected from the radical reaction reported by Brown and Lane[7a,14] upon exposure to water.

The use of concentrated HBr gives higher yields (53%) and stereoselectivities (80:20) than 10% HCl (26%; 73:27) in THF (entries 6 and 3) and comparable yields in CCl_4 (23–24%). Doubling the amount of 10% HCl more than doubles the yield (from 26% to 66%; entries 3 and 5) and lowers the stereoselectivity (from 73:27 to ~66:34). Therefore, the pH of the reaction mixture must be important. Increasing the amount of sodium bromide from 1 equiv (entry 1) to 2 (entry 3) only increases the yields marginally (from 23% to 26%) with little effect on stereoselectivity (75:25 to 73:27). Thus, the yield increase with concentrated HBr (entry 6) versus 10% HCl (entry 3) is probably more related to acid concentration than to the change in halide.

The large difference in yield in entries 6 (24% conversion of 1 alkyl) and 8 (88% conversion of 3 alkyls) in CCl_4 solvent probably reflects the predominance of entirely different reaction mechanisms. Reaction 8 is a radical reaction involving an α-bromo organoborane species.[7a] The same intermediate cannot be responsible for norbornyl bromide in reaction 6, since it would react with the water present as discussed above.[7a,14]

Since the brominolysis agent in these systems is probably BrCl or Br_2 and since a radical mechanism does not

(10) (a) Underwood, G. R.; Dietze, P. E. *J. Org. Chem.* **1984**, *49*, 5225 and references therein. (b) Cho, B. R.; Yoon, J. C.; Bartsch, R. A. *J. Org. Chem.* **1985**, *50*, 4943. (c) White, W. N.; White, H. S. Third Chemical Congress of North America, Toronto, Canada, June 1988; American Chemical Society, Washington, D.C., 1988; ORGN 37.

(11) (a) Slayden, S. W.; Do, T. H.; Smiley, K. Y.; Nelson, D. J. *J. Chem. Ed.* **1987**, *64*, 368. (b) Heasley, G. E.; Bundy, J. M.; Heasley, V. L.; Arnold, S.; Gipe, A.; McKee, D.; Orr, R.; Rodgers, S. L.; Shellhamer, D. F. *J. Org. Chem.* **1978**, *43*, 2793.

(12) (a) Bock, H.; Kompa, K.-L. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 783; (b) *Chem. Ber.* **1966**, *99*, 1357, 1361. (c) Wawzonek, S.; Thelan, P. J. *J. Am. Chem. Soc.* **1950**, *72*, 2118.

(13) (a) Blue, C. D.; Nelson, D. J. *J. Org. Chem.* **1983**, *48*, 4538–42. (b) Nelson, D. J.; Blue, C. D.; Brown, H. C. 185th National Meeting of the American Chemical Society, Seattle, WA, March 1983; American Chemical Society: Washington, D.C., 1983; ORGN 133. (c) Midland, M. M.; Zolopa, A. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 248–9.

(14) Lane, C. F. *Intra-Sci. Chem. Rep.* **1973**, *7*, 133.

lead to norbornyl bromide, the reaction pathway which best accounts for the observed stereoselectivities is a combination of the S_E2 (back) mechanism, as proposed earlier,[7a] along with the S_E2 (front) and/or the S_Ei mechanism(s), all with BrCl or Br_2. On the basis of the stereoselectivities of the reactions with chloramine T, the S_E2 (back) contributes less in CCl_4 (≤11% with Br_2; ≤2% with BrCl) than in THF (~20% with Br_2; ≤27% with BrCl).

Experimental Section

Materials. Norbornene, *exo*-2-bromonorbornane, chloramine T, borane–THF complex, and galvinoxyl were purchased from Aldrich Chemical Co. *p*-Toluenesulfonamide and bromine were purchased from Eastman Kodak Co. and Fisher Scientific Co., respectively. Internal standards (*n*-alkanes, 99%) were used as received from Humphrey Chemical Co. The borane complex was standardized according to the published procedure.[15] Tetrahydrofuran and carbon tetrachloride solvents were distilled under N_2 over LAH and phosphorus pentoxide, respectively.

Procedures. The standard procedures[15] for the manipulation of air-sensitive compounds were followed. The reactions were carried out according to the published procedure,[2a] substituting concentrated HBr for 10% HCl or increasing the amount of sodium bromide as indicated in Table I and increasing the reaction times to 30 min, the time required for the red or purple color of BrCl or Br_2 to disappear. Significantly shorter or longer reaction times lead to reduced yields, in agreement with results noted earlier.[2a] Products were identified by comparison with authentic samples, and yields were determined by GC and by GC/MS.

Radical quenching reactions were carried out as above and by adding the indicated amount 0.021 g (0.01 equiv) or 0.21 g (0.1 equiv) of galvinoxyl (Aldrich) immediately after the internal standard (entries 4 and 7).

The effect of *p*-toluenesulfonamide on the reaction of trinorbornylborane with bromine (entry 9) was determined by carrying out the reaction as described in entry 8,[7a,b] except 1 equiv (0.11 g) of $TsNH_2$ was added before the addition of bromine. After stirring for 24 h at 20 °C, the reaction was quenched by being washed with water and the organic layer was analyzed by GC.

Preparation of Tri-*exo*-2-norbornylborane (Nor_3B). Trinorbornylborane was prepared according to literature procedures.[15,16] In those reactions done in CCl_4, the trinorbornylborane was prepared as above in THF, the THF was removed under vacuum, and CCl_4 was added.

Preparation, Addition to 1-Hexene, and Attempted Quenching of Bromine Chloride. 1-Hexene was added to the BrCl generated in situ as described by Kabalka[6a] and let stand for 4 h. The organic layer was washed with water, dried, and analyzed by GC/MS.

In a separate experiment, BrCl was generated as before. To one sample was added galvinoxyl before addition of the acid, and to another, no galvinoxyl was added. Upon the addition of acid, both reaction mixtures showed a clear, intense red color, identical in appearance.

^{11}B NMR Spectra. Approximately 0.5 mL of the trinorbornylborane solution was transferred via a double-ended needle to a 5-mm NMR tube that had been heated overnight, fitted with a septum, and cooled under a flow of nitrogen. The ^{11}B NMR spectrum was scrutinized for oxidation of the trinorbornylborane, and only the signal for trinorbornylborane (80.3 ppm) was observed.

Mass Spectra. The mass spectral data of 2-norbornyl-2-norborneol show the following major peaks [*m/z* (rel intensity) 206 $[M]^+$ 24.7; 188 $[M - H_2O]^+$ 10.9; 95 $[Nor]^+$ 100] and those of 1-bromo-2-chlorohexane show [*m/z* (rel intensity) 165 $[M(^{81}Br) - Cl]^+$ 6.8; 163 $[M(^{79}Br) - Cl]^+$ 6.6; 123 $[M(^{37}Cl) - Br]^+$ 4.3%; 121 $[M(^{35}Cl) - Br]^+$ 5.6; 83 $[C_6H_{11}]^+$ 100].

Instruments. The ^{11}B spectra were obtained on an Varian XL-300 spectrometer equipped with a high frequency broad-band probe. The ^{11}B NMR shifts are reported relative to boron trifluoride–diethyl ether complex. Product identities and yields were determined on a Hewlett-Packard 5790A/3390A instrument equipped with a 3.2 mm × 6 m column with 15% Zonyl E-7 on 80–100-mesh Chromosorb WAW. Mass spectra were obtained on a Hewlett-Packard 5985 gas chromatograph/mass spectrometer/data system equipped with a 4 mm × 2 m column with 3% SE-30 on 100–120-mesh Chromosorb W.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. This material is based upon work supported by the National Science Foundation.

Registry No. ClT, 127-65-1; NaBr, 7647-15-6; tri-*exo*-2-norbornylborane, 22801-27-0.

(15) Brown, H. C. *Organic Syntheses via Boranes*; John Wiley and Sons, Inc.: New York, 1975.

(16) Nelson, D. J. *Org. Mass Spectrom.* **1986**, *21*, 811.