Competitive and Regiospecific Bridgehead Substitution in Electrophilic Oxidation Reactions of Homoadamantane

Robert J. Israel and Roger K. Murray, Jr.*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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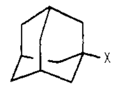
Oxidation of homoadamantane with chromic acid, lead tetraacetate, *p*-nitroperbenzoic acid, or bromine occurs by competitive attack at the C-3 (major) and C-1 (minor) bridgehead positions. In striking contrast, dry ozonation of homoadamantane adsorbed on silica gel leads to regiospecific substitution at the chemically equivalent C-3 and C-6 bridgehead positions. A consequence of this observation is that some 1,3- and 3,6-disubstituted homoadamantanes can be prepared by dry ozonation of suitably substituted homoadamantane derivatives.

A seemingly straightforward method for the synthesis of bridgehead substituted polycyclic alkanes is direct functionalization of the parent hydrocarbon. The utilization of reactions that proceed by electrophilic intermediates for such transformations helps to ensure that attack at bridgehead positions will be significantly favored over substitution at alternative secondary or primary sites. This approach has proved to be particularly useful in the preparation of derivatives of adamantane and compounds related to it. For example, ionic bromination of adamantane[1] (1), protoadamantane[2] (2), and diamantane[3] (3) gives 4, 5, and 6, respectively, in high yield. It is particularly intriguing that the brominations of 2 and 3 occur regiospecifically. However, it should be noted that the chemistry of diamantane has been sufficiently well investigated to show that nearly all other reactions of this hydrocarbon with electrophiles lead to competitive attack at the alternative bridgehead positions.[3,4]



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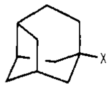
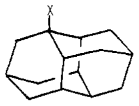
4, X = Br

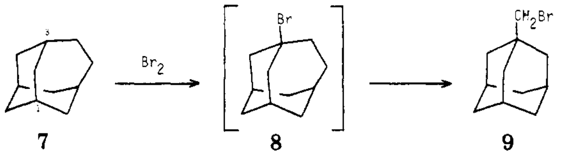


2, X = H
5, X = Br



3, X = H
6, X = Br

In view of these results, it is striking that electrophilic substitution reactions have been almost entirely ignored for the synthesis of derivatives of homoadamantane (7).

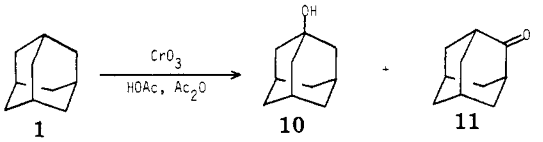


This may be the result of a passing observation by Liggero and Schleyer that treatment of 7 with bromine gives 1-(bromomethyl)adamantane (9).[5] Since ionic bromination seems to occur under thermodynamically controlled conditions,[6] the formation of 9 from 7 can be explained by the initial generation of 3-bromohomoadamantane (8), which then rearranges to 9 in the presence of the Lewis acid, bromine. The isomerization of 3-homoadamantyl to 1-adamantylcarbinyl derivatives under thermodynamically controlled solvolytic conditions is well-known.[7] Consequently, we became interested in examining the behavior of homoadamantane in other electrophilic reactions.

Results and Discussion

We have investigated the oxidation of homoadamantane with chromic acid, lead tetraacetate, *p*-nitroperbenzoic acid, and by dry ozonation of the substrate adsorbed on silica gel.

It is well established that the chromic acid oxidation of relatively unstrained bicyclic and polycyclic hydrocarbons shows a significant preference for substitution at bridgehead positions.[8–10] For example, treatment of 1 with chromium trioxide in a mixture of acetic acid and acetic anhydride gives 1-adamantanol (10) and 2-adamantanone (11) in yields of 71% and 9%, respectively.[9] Such reactions are believed to proceed by way of a species that is best represented as the resonance hybrid shown below.



$$\left[-\overset{|}{\underset{|}{C}}\cdot \quad \overset{H}{\overset{|}{O}}-\overset{V}{Cr}O_3H_2X \longleftrightarrow -\overset{|}{\underset{|}{C}}+ \quad \overset{H}{\overset{|}{O}}-\overset{IV}{Cr}O_3H_2X \right]$$

This intermediate may result from either hydrogen atom or hydride anion transfer from the hydrocarbon to the chromium(VI) complex.[11] We have found that oxidation of homoadamantane under these conditions provides a mixture of 3-homoadamantanol (12), 3,6-homoadamantanediol (13), 1-homoadamantanol (14), 4-homoadamantanone (15), and an unidentified component[12] in yields of 26%, 4%, 1%, 3%, and 3%, respectively. Thus, attack at C-3 in 7 is favored over that at C-1 by ca. 30:1.[13]

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[1] (a) Landa, S.; Kreibel, S.; Knobloch, E. *Chem. Listy* **1954**, *48*, 61. (b) Landa, S.; Hāla, S. *Collect. Czech. Chem. Commun.* **1959**, *24*, 93–98. (c) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Chem. Ber.* **1959**, *92*, 1629–1635.

[2] (a) Karim, A.; McKervey, M. A.; Engler, E. M.; Schleyer, P. v. R. *Tetrahedron Lett.* **1971**, 3987–3990. (b) Karim, A.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2475–2479.

[3] Gund, T. M. Schleyer, P. v. R.; Unruh, G. D.; Gleicher, G. J. *J. Org. Chem.* **1974**, *39*, 2995–3003.

[4] (a) Courtney, T.; Johnston, D. E.; McKervey, M. A.; Rooney, J. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2691–2696. (b) Jones, S. R.; Mellor, J. M. *Ibid.* **1976**, 2576–2581. (c) Jones, S. R.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 511–517. (d) Leddy, B. P.; McKervey, M. A.; McSweeney, P. *Tetrahedron Lett.* **1980**, *21*, 2261–2264.

[5] "Unpublished observations" of S. H. Liggero and P. v. R. Schleyer reported in Bingham, R. C.; Schleyer, P. v. R. *J. Org. Chem.* **1971**, *36*, 1198–1201.

[6] Ōsawa, E.; Engler, E. M.; Godleski, S. A.; Inamoto, Y.; Kent, G. J.; Kausch, M.; Schleyer, P. v. R. *J. Org. Chem.* **1980**, *45*, 984–991.

[7] (a) Nordlander, J. E.; Jindal, S. P.; Schleyer, P. v. R.; Fort, R. C., Jr.; Harper, J. J., Nicholas, R. D. *J. Am. Chem. Soc.* **1966**, *88*, 4475–4484. (b) Liggero, S. H.; Sustmann, R.; Schleyer, P. v. R. *Ibid.* **1969**, *91*, 4571–4573.

[8] Wiberg, K. B. In "Oxidation in Organic Chemistry: Part A"; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Chapter 2.

[9] Bingham, R. C.; Schleyer, P. v. R. *J. Org. Chem.* **1971**, *36*, 1198–1201.

[10] Paquette, L. A.; Meehan, G. V.; Marshall, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 6779–6784.

[11] Roček, J. *Tetrahedron Lett.* **1962**, 135–138.

[12] This compound is not 2- or 9-homoadamantanone.

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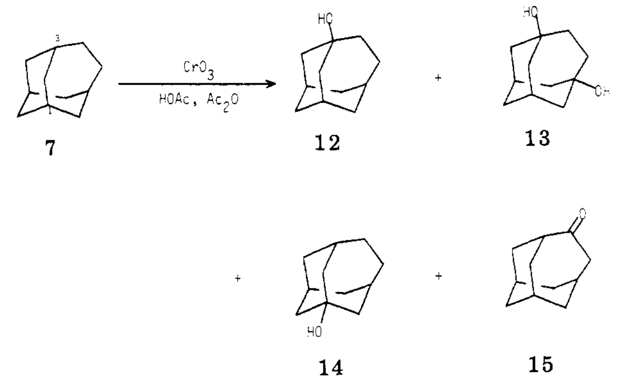
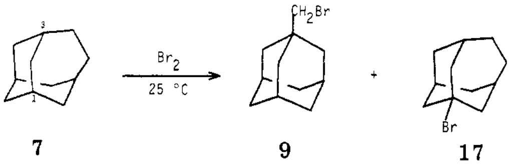


With respect to product assignments, all of these compounds, except **13**, are known and their structures were readily established by comparison of their spectroscopic characteristics with those of authentic samples. The structure of diol **13** principally follows from its proton-decoupled ^{13}C NMR spectrum which contains only five signals.

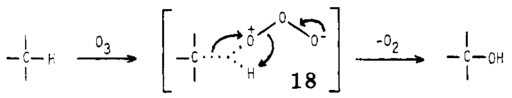
Jones and Mellor have reported that bridgehead functionalization of bicyclic and polycyclic hydrocarbons can be achieved by oxidation of these substrates with lead tetraacetate and chloride ion in a solution of trifluoroacetic acid and methylene chloride.[15] Subsequent hydrolysis of the resulting trifluoroacetates gives the corresponding alcohols. For example, treatment of **1** by this two-step process affords **10** in 94% yield.[15] The identity of the oxidizing agent in this reaction has not been established. However, it is clear that oxidation does not take place via a radical cation intermediate.[16] At present, a mechanism proceeding by electrophilic attack at a carbon–hydrogen bond is favored.[16] Oxidation of homoadamantane with lead tetraacetate under these conditions gives **12**, **13**, **14**, and 1-adamantanemethanol (**16**) in yields of 27%, 1%, 17%, and 9%, respectively. Since both **13** and **16** are expected to result from initial attack at C-3 of **7**, then LTA/TFA oxidation of **7** shows a preference for attack at C-3 over C-1 of ca. 2:1.

We have also found that direct hydroxylation of homoadamantane can be affected by heating it with *p*-nitroperbenzoic acid in refluxing chloroform. The reaction took place with 78% conversion of **7** to provide **12** and **14** in yields of 44% and 16%, respectively. Thus, the relative reactivity of C-3 to C-1 under these conditions is ca. 3:1. This method for the oxidation of hydrocarbons has recently been reported by Müller and Schneider.[17] They have provided some evidence that the reaction mechanism involves the development of electrophilic character.[17,18]

In summary, both the C-3 and C-1 bridgehead C–H bonds in homoadamantane are reactive in the oxidation of **7** with chromic acid, lead tetraacetate, and *p*-nitroperbenzoic acid. The extent to which reaction occurs at each of these sites depends on the particular conditions employed. The preference for attack at C-3 vs. C-1 in all of these cases is consistent with earlier reports that the 3-homoadamantyl cation is more stable than the 1-homoadamantyl cation.[14,19] These observations prompted us to reexamine the ionic bromination of homoadamantane. Stirring **7** with neat bromine for 2 h at room temperature provided **9** and 1-bromohomoadamantane (**17**) in yields of 62% and 15%, respectively. Thus, contrary to the earlier report of Liggero and Schleyer,[5] ionic bromination of **7** also occurs by competitive attack at C-3 *and* C-1.



In contrast to all of these reactions, we have found that the alternative bridgehead positions in homoadamantane show strikingly different reactivities in the dry ozonation of **7** adsorbed on silica gel. Under these conditions, we have not detected any products resulting from attack at C-1 of **7**. This method for the introduction of oxygen into unactivated tertiary carbon–hydrogen bonds in cyclic hydrocarbons has been developed by Mazur and his coworkers.[20,21] It involves initial adsorption of the hydrocarbon on silica gel by impregnation with a volatile solvent. A stream of ozone is then passed through this material at −78 °C until the silica gel is apparently saturated with ozone. The silica gel is then allowed to slowly warm to room temperature. Workup simply involves elution of the products from the silica gel with an organic solvent. Mazur has proposed that this reaction proceeds by the formation of an ozone-alkane complex which decomposes electrophilically via transition state **18** with insertion of an oxygen atom into the C–H bond.[22]



When ozone was passed for 2.5 h through silica gel bearing 1% by weight of homoadamantane, we obtained 3-homoadamantanol (**12**), 3,6-homoadamantanediol (**13**), and 4-homoadamantanone (**15**) in yields of 4%, 36%, and 6%, respectively. We attribute the high regiospecificity of this reaction to the ordered packing of the hydrocarbon on the surface of the silica gel. Beckwith has already demonstrated that ordering molecules in a close-packed array hinders reaction at proximate sites and directs attack towards exposed terminal areas.[23]

It might be supposed that the formation of diol **13** occurs by subsequent oxidation of alcohol **12** rather than by simultaneous attack at both the C-3 and C-6 C–H bonds in **7**. However, it does not appear that **13** is generated by **7** → **12** → **13** since dry ozonation of **12** adsorbed on silica gel only leads to the recovery of starting material. Moreover, if the local partial pressure of ozone available for reaction during the warm-up period is reduced, then less of the diol and more of the monoalcohol are obtained.

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(13) In a more cursory examination of this reaction,[14] it has been reported that chromic acid oxidation of **7** favors attack at C-3 over C-1 by 20:1.

(14) Godleski, S. A.; Graham, W. D.; Bentley, T. W.; Schleyer, P. v. R.; Liang, G. *Chem. Ber.* **1974**, *107*, 1257–1264.

(15) Jones, S. R.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2576–2581.

(16) Jones, S. R.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 511–517.

(17) Müller, W.; Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 407–408.

(18) Schneider, H.-J.; Müller, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 146–147.

(19) (a) Olah, G. A.; Liang, G. *J. Am. Chem. Soc.* **1973**, *95*, 194–197. (b) Langhals, H.; Rüchardt, C. *Chem. Ber.* **1974**, *107*, 1245–1256. (c) Langhals, H.; Mergelsberg, I.; Rüchardt, C.; Burger, U. *Ibid.* **1982**, *115*, 1509–1524.

(20) (a) Cohen, Z.; Keinan, E.; Mazur, Y.; Varbony, T. H. *J. Org. Chem.* **1975**, *40*, 2141–2142. (b) Cohen, Z.; Varkony, H.; Keinan, E.; Mazur, Y. *Org. Synth.* **1980**, *59*, 176–182.

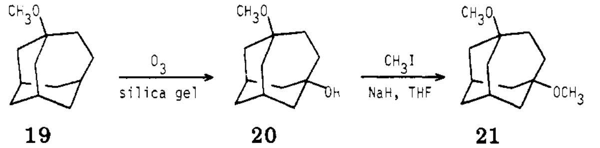
(21) For a review see: Bailey, P. S. "Ozonation in Organic Chemistry"; Academic Press: New York, 1982; Vol. 2, pp 312–319.

(22) Tal, D.; Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1978**, *100*, 502–503.

(23) Beckwith, A. L. J.; Bodkin, C. L.; Duong, T. *Aust. J. Chem.* **1977**, *30*, 2177–2188.

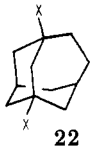
Thus, passing ozone for 0.5 h through silica gel bearing 1% by weight of **7** gives **12**, **13**, and **15** in yields of 18%, 12%, and 5%, respectively. The same net result can be achieved by increasing the loading of the substrate on the silica gel and so affording less available surface area on the support for the adsorption of ozone. Passing a stream of ozone for 2.5 h through silica gel bearing 5% by weight of **7** provides **12**, **13**, and **15** in yields of 18%, 14%, and 3%, respectively.

The synthesis of diol **13** permits the preparation of a variety of 3,6-disubstituted homoadamantanes. Entry to these compounds can also be obtained by the oxidation of 3-substituted homoadamantanes. Thus, dry ozonation of 3-methoxyhomoadamantane (**19**) adsorbed on silica gel gives 6-methoxyhomoadamantan-3-ol (**20**) as the only isolated product. The identity of **20** was firmly established by its conversion to 3,6-dimethoxyhomoadamantane (**21**). Consistent with the assigned structure, the proton-decoupled ^{13}C NMR spectrum of **21** contains only six signals.



19 **20** **21**

Of course, there are three possible arrangements for homoadamantane to be substituted at two bridgehead positons: 1,3 (**22**), 1,8 (**23**), and 3,6 (**24**). The high reactivity of the C-3 and C-6 bridgehead positions in the oxidations of **7** and **19** by the dry ozonation method suggested that 1,3-disubstituted homoadamantane derivatives could be prepared by oxidation of suitable 1-substituted homoadamantanes under comparable conditions. Although 1-homoadamantanol proved to be unreactive, dry ozonation of 1-methoxyhomoadamantane (**25**) adsorbed on silica gel provided **26** in 89% yield. While this reaction does not lead to 1,8-disubstituted homoadamantanes, it should be noted that symmetrically substituted derivatives of **23** are already available by an alternative synthetic approach.[24]



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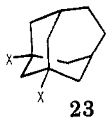

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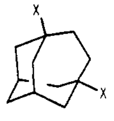

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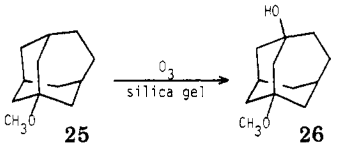
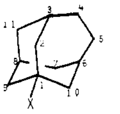


25 **26**

Experimental Section

Melting points were obtained in sealed capillary tubes by using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Unicam SP1100 spectrophotometer. Proton magnetic resonance spectra were obtained with Perkin-Elmer R-12B 60-MHz or Brüker Spectrospin 250-MHz spectrometers and are referenced to an internal standard of tetramethylsilane. Apparent splittings are reported in all cases. Carbon magnetic resonance spectra were recorded with the Brüker instrument at 62.9 MHz and are referenced to an internal standard of tetramethylsilane. Electron impact mass spectra were obtained with a DuPont 21-492B mass spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

The numbering schemes employed for the assignment of ^{1}H and ^{13}C NMR signals in 1-homoadamantyl (**27**), 3-homoadamantyl (**28**), and 1-adamantylcarbinyl (**29**) derivatives are as follows:



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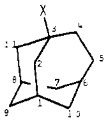

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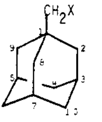

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Homoadamantane (7). A solution of 4-homoadamantanone[25] (4.0 g, 29.5 mmol) and hydrazine (25 mL; 98–100%) in triethylene glycol (200 mL) containing glacial acetic acid (14.5 mL) was heated at 85 °C under nitrogen for 24 h. The reaction flask was then fitted with a fractionating column and a water-cooled condenser. Potassium hydroxide (43.0 g) was added to the reaction mixture and it was heated at 200 °C for 16 h. During this time, a sublimate collected in the condenser. At the conclusion of the reaction, this material was dissolved in ether. Distillation of the solvent at atmospheric pressure provided 2.65 g (76% yield) of **7** as a white solid. The identity of **7** was confirmed by its ^{13}C NMR spectrum δ ($CDCl_3$) 38.3 (C-2, C-7, C-10, and C-11), 36.3 (C-9), 33.8 (C-4 and C-5), 31.8 (C-3 and C-6), and 27.5 (C-1 and C-8).

Identification of the Reaction Products from Oxidations of Homoadamantane. Oxidation of homoadamantane at its bridgehead positions could lead to 3-homoadamantanol (**12**), 1-homoadamantanol (**14**), and by rearrangement to 1-adamantanemethanol (**16**). Since all of these alcohols had the same retention times under a variety of GLC conditions, the crude reaction residues were analyzed by ^{13}C NMR. Consequently, **12**, **14**, and **16** were each independently synthesized and their ^{13}C NMR spectra were obtained with $CDCl_3$ as solvent. **12**:[7a,26] δ 73.3 (C-3), 47.1 (C-2 and C-11), 41.8 (C-4), 37.5 (C-7 and C-10), 35.6 (C-5), 31.2 (C-6), 29.8 (C-9), 27.7 (C-1 and C-8). **14**:[14] δ 69.0 (C-1), 46.1 (C-2 and C-10), 44.7 (C-9), 36.9 (C-7 and C-11), 32.9 (C-4 and C-5), 31.8 (C-3, C-6, and C-8). **16**: δ 73.9 (CH_2OH), 39.1 (C-2, C-8, and C-9), 37.2 (C-4, C-6, and C-10), 34.5 (C-1), 28.2 (C-3, C-5, and C-7).

Chromic Acid Oxidation of Homoadamantane. Chromium trioxide (800 mg, 8.0 mmol) was added in small portions to a stirred solution of **7** (500 mg, 3.33 mmol) in acetic acid (7.5 mL) and acetic anhydride (7.5 mL) at room temperature. After the addition was complete, the reaction mixture was stirred for 6 h at room temperature. At this point the reaction mixture was diluted with ice water (50 mL) and it was then extracted with ether (4 × 25 mL). The combined ether extracts were washed with 10% aqueous sodium carbonate (3 × 50 mL) and water (2 × 50 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided an oil which was hydrolyzed by refluxing this material with a mixture of water (25 mL), methanol (25 mL), and potassium hydroxide (1.0 g) for 16 h. During this time, a white solid sublimed onto the condenser coils. This material was dissolved in ether. The crude reaction mixture was also extracted with ether (3 × 30 mL). The various ether extracts were combined and dried over anhydrous magnesium sulfate. Distillation of the solvent at atmospheric pressure provided a white solid residue. Analysis of this material by a combination of quantitative GLC (5 ft × 0.25 in. QF-1 column, 150 °C) and quantitative ^{13}C NMR showed that **12**, **13**, **14**, 4-homoadamantanone (**15**), and an unidentified ketone were obtained in yields of 26%, 4%, 1%, 3%, and 3%, respectively. Diol **13**, ketone **15**, and the unidentified product were separated from alcohols **12** and **14** by GLC (above conditions). The compounds were identified by comparison of their spectral parameters with those of authentic samples.

Oxidation of Homoadamantane with Lead Tetraacetate. Homoadamantane (500 mg, 3.33 mmol) and lead tetraacetate (1.65 g, 3.75 mmol, partially dried by suction filtration under dry nitrogen and then further dried over potassium hydroxide under

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[24] Henry, R. S.; Moodie, W. T.; Parker, W.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 803–805.

[25] (a) Schleyer, P. v. R.; Funke, E.; Liggero, S. H. *J. Am. Chem. Soc.* **1969**, *91*, 3965–3967. (b) Black, R. M.; Gill, G. B. *J. Chem. Soc. C* **1970**, 671–676.

[26] In an earlier report on the ^{13}C NMR spectrum of **12**,[14] the signals at δ 29.8 and 31.2 were incorrectly assigned to C-6 and C-9, respectively.

vacuum and stored in a dessicator over phosphorus pentoxide) were stirred with trifluoroacetic acid (25 mL) that was 0.1 M in lithium chloride and methylene chloride (25 mL) for 24 h in the dark. The reaction mixture was then partitioned between ether (50 mL) and aqueous sodium hydroxide (2.0 g in 50 mL of water). The aqueous layer was extracted with ether (3 × 50 mL). The organic extracts were combined and then washed with saturated aqueous sodium bicarbonate (3 × 50 mL) and water (3 × 50 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a mixture of trifluoroacetates which were hydrolyzed by refluxing this material with 10% aqueous sodium hydroxide for 16 h. During this time, a considerable amount of white solid sublimed onto the condenser coils. This material was dissolved in ether. The crude reaction mixture was also extracted with ether (3 × 25 mL). The various ether extracts were combined and dried over anhydrous magnesium sulfate. Distillation of the solvent at atmospheric pressure provided a white solid residue. Analysis of this material by a combination of quantitative GLC (5 ft × 0.25 in. QF-1 column, 150 °C) and quantitative ^{13}C NMR showed that **12**, **13**, **14**, and **16** were obtained in yields of 27%, 1%, 17%, and 9%, respectively.

Oxidation of Homoadamantane with *p*-Nitroperbenzoic Acid. A mixture of **7** (200 mg, 1.33 mmol) and *p*-nitroperbenzoic acid (400 mg, 2.2 mmol) in methylene chloride (20 mL) was refluxed for 16 h. At this point another 400 mg of *p*-nitroperbenzoic acid was added and the mixture was refluxed for an additional 16 h. The reaction mixture was then cooled and filtered and the filter-cake was washed with ether (3 × 20 mL). The filtrate and ether extracts were combined and washed with 1 N sodium hydroxide (3 × 25 mL) and water (3 × 25 mL) and then dried over anhydrous magnesium sulfate. Distillation of the solvent at atmospheric pressure provided 171 mg of a solid residue. Analysis of this material by a combination of quantitative GLC (5 ft × 0.25 in. QF-1 column, 150 °C) and quantitative ^{13}C NMR showed that the oxidation occurred with 78% conversion of **7** to give **12** and **14** in yields of 44% and 16%, respectively.

Identification of the Reaction Products from the Bromination of Homoadamantane. It was anticipated that likely products that might result from this reaction would be 1-bromohomoadamantane (**17**), 3-bromohomoadamantane (**8**), and 1-(bromomethyl)adamantane (**9**). Since **8** is known to isomerize to **9** under typical GLC conditions,[27] the crude reaction residue was analyzed by ^{13}C NMR. To this end **8** and **9** were synthesized by literature methods and their ^{13}C NMR were obtained with $CDCl_3$ as solvent. **8**:[28] δ 74.1 (C-3), 50.9 (C-2 and C-11), 46.1 (C-4), 37.2 (C-7 and C-10), 35.2 (C-5), 33.0 (C-9), 31.2 (C-6), 30.2 (C-1 and C-8). **9**:[27] δ 48.5 (CH_2Br), 40.7 (C-2, C-8, and C-9), 36.7 (C-4, C-6, and C-10), 33.6 (C-1), 28.4 (C-3, C-5, and C-7).

1-Bromohomoadamantane[29] (**17**) was prepared by the dropwise addition of a solution of freshly distilled phosphorus tribromide (150 mg) in dry benzene (5 mL, distilled from sodium) to a stirred solution of **14** (172 mg, 1.036 mmol) in dry benzene (10 mL) that was maintained at 0 °C. The resulting solution was stirred for 0.5 h at 0 °C, then 1 h at 25 °C, and finally 2 h at 40 °C. The reaction mixture was then cooled and poured into ice water (25 mL). The layers were separated and the aqueous layer was extracted with benzene (3 × 15 mL). The organic layers were combined and washed with saturated aqueous sodium bicarbonate (3 × 50 mL) and water (3 × 50 mL). After drying over anhydrous magnesium sulfate, the solvent was distilled at atmospheric pressure to give a solid residue. Sublimation of this material provided **17**: ^{13}C NMR δ ($CDCl_3$) 69.8 (C-1), 50.1 (C-2 and C-10), 48.4 (C-9), 36.2 (C-7 and C-11), 34.2 (C-3 and C-6), 33.0 (C-8), 28.4 (C-4 and C-5).

Bromination of Homoadamantane. A mixture of **7** (150 mg, 1.0 mmol) and liquid bromine (3 mL) was stirred at room temperature for 2 h. The reaction mixture was then dissolved in carbon tetrachloride (10 mL) and poured into water (20 mL). The excess bromine present was destroyed by the addition with stirring of solid sodium bisulfite. The organic layer was then separated, washed with water (3 × 20 mL), and dried over anhydrous magnesium sulfate. Distillation of the solvent at atmospheric pressure provided a solid which was established by ^{13}C NMR spectroscopy to only consist of a mixture of **9** and **17**. Analysis of this material by quantitative GLC (5 ft × 0.25 in. QF-1 column, 150 °C) showed that **9** and **17** were obtained in yields of 62% and 15%, respectively. The reaction products were separated by GLC (above conditions) and identified by comparison of their spectral parameters with those of authentic samples of **9** and **17**.

Dry Ozonation of Homoadamantane Adsorbed on Silica Gel. A solution of **7** (500 mg, 3.33 mmol) in pentane (100 mL) was mixed with silica gel (50 g of Merck silica gel 60) and the solvent was evaporated at reduced pressure and room temperature with a rotary evaporator. The resulting dry powder was allowed to rotate for an additional 2 h. The homoadamantane–silica gel dispersion was then poured into a tightly closed gas washing bottle and immersed in a cooling bath that was maintained at −78 °C. A flow of oxygen was passed through the vessel for 2 h and then an ozone–oxygen mixture was passed through the vessel for 2.5 h. At this point the cooling bath was removed and the reaction vessel was allowed to slowly warm to room temperature. The silica gel was then transferred to a chromatography column and it was eluted sequentially with heptane (1 L) and ethyl acetate until no more material eluted from the column. Distillation of the solvent from the heptane eluent at atmospheric pressure provided no residue. Evaporation of the solvent from the ethyl acetate eluent gave a white solid. Analysis of this material by quantitative GLC (5 ft × 0.25 in. QF-1 column, 150 °C) and ^{13}C NMR showed that ozonation provided a mixture of 3-homoadamantanol (**12**), 3,6-homoadamantanediol (**13**), and 4-homoadamantanone (**15**) in yields of 4%, 36%, and 6%, respectively. The reaction products were separated and purified by GLC (above conditions). Alcohol **12** and ketone **15** were identified by comparison of their spectral parameters with those of authentic samples. Diol **13** was obtained as a white solid: mp 265–268 °C; ^{1}H NMR δ (CD_3OD) 2.17–2.03 (m, 2 H, bridgehead protons), 1.96–1.61 (m, 14 H), 1.51 (br t, 2 H, CH_2 at C-9); ^{13}C NMR δ (CD_3OD) 72.9 (C-3 and C-6), 47.0 (C-2, C-7, C-10, and C-11), 38.6 (C-4 and C-5), 36.2 (C-9), 30.9 (C-1 and C-8); IR ν ($CHCl_3$) 3595, 3460 (br), 3015, 2925, 2855, 1460, 1075, 1005 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.42; H, 9.94.

Ozonation for 2.5 h of 500 mg of **7** adsorbed on 10 g of silica gel according to the procedure described above provided **12**, **13**, and **15** in yields of 18%, 14%, and 3%, respectively.

Ozonation for 0.5 h of 250 mg of **7** adsorbed on 25 g of silica gel according to the procedure described above afforded **12**, **13**, and **15** in yields of 18%, 12%, and 5%, respectively.

Ozonation for 9 h of 400 mg of **7** adsorbed on 40 g of silica gel according to the procedure described above gave **12**, **13**, and **15** in yields of 4%, 40%, and 3%, respectively.

3-Methoxyhomoadamantane[30] (19). A solution of **12** (550 mg, 3.31 mmol) in dry tetrahydrofuran (THF, 5 mL) was added dropwise to a stirred slurry of sodium hydride (485 mg, 20.2 mmol) in dry THF (10 mL) which was maintained at reflux under nitrogen. The reaction mixture was refluxed for 22 h and then methyl iodide (0.6 mL) was added via syringe and refluxing was continued for 18 h more. At this point the reaction mixture was cooled, water (50 mL) was added, and the resulting solution was extracted with ether (4 × 25 mL). The ether extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave an oil which was Kugelrohr distilled to provide 491 mg (82% yield) of **19**: ^{13}C NMR δ ($CDCl_3$) 76.8 (C-3), 48.3 (C-3), 43.1 (C-2 and C-11), 37.6 (C-7 and C-10), 35.9 (C-4 or C-5) 35.8 (C-4 or C-5), 31.1 (C-6), 29.7 (C-9), 27.5 (C-1 and C-8).

6-Methoxyhomoadamantan-3-ol (20). According to the general procedure described for **7** → **13**, a stream of ozone in oxygen was passed for 2.5 h through a mixture of **19** (298 mg, 1.65 mmol) adsorbed on silica gel (30 g) that was maintained at −78 °C. This material was then allowed to slowly warm to room temperature and the silica gel was eluted with ethyl acetate (1 L). Evaporation of the solvent at reduced pressure provided an

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oil which contained a single volatile product by GLC analysis (5 ft × 0.25 in. QF-1 column, 150 °C). Analysis of this residue by ^{1}H NMR indicated that **20** was obtained in ca. 85% yield. Kugelrohr distillation of this oil gave 212 mg (66% yield) of **20**: ^{1}H NMR δ ($CDCl_3$) 3.2 (s, 3 H, $-OCH_3$), 2.23–2.11 (m, 2 H, bridgehead protons), 1.84 (s, 4 H, CH_2CH_2), 1.86–1.70 (m, 8 H, methylene protons at C-2, C-7, C-10, and C-11), 1.60 (br s, 1 H, OH), 1.49 (br t, 2 H, CH_2 at C-9); ^{13}C NMR δ ($CDCl_3$) 75.8 (C-6), 72.4 (C-3), 48.2 (CH_3), 46.4 (C-2 and C-11), 42.3 (C-7 and C-10), 37.9 (C-4), 35.1 (C-5), 32.6 (C-9), 29.1 (C-1 and C-8); IR ν (CCl_4): 2925, 2860, 1520, 1040, 985 cm^{-1}; exact mass calcd for $C_{12}H_{20}O_2$, 196.146; found, 196.147.

3,6-Dimethoxyhomoadamantane (21). Methylation of **20** (212 mg, 1.08 mmol) with sodium hydride (450 mg, 18.8 mmol) and methyl iodide (0.6 mL) in dry THF by the procedure described for **12** → **19** provided an oil which was Kugelrohr distilled to afford 95 mg (42% yield) of **21** as a clear oil: ^{1}H NMR δ ($CDCl_3$) 3.20 (s, 6 H, OCH_3), 2.25–2.13 (br m, 2 H, bridgehead protons), 1.85 (s, 4 H, CH_2CH_2), 1.89–1.63 (m, 8 H, methylene protons at C-2, C-7, C-10, and C-11), 1.48 (br t, 2 H, CH_2 at C-9); ^{13}C NMR δ ($CDCl_3$) 76.0 (C-3 and C-6), 48.1 (CH_3), 42.3 (C-2, C-7, C-10, and C-11), 35.3 (C-9), 32.6 (C-4 and C-5), 28.8 (C-1 and C-8); IR ν (CCl_4) 2940, 2850, 2820, 1450, 1370, 1260, 1150, 1085 cm^{-1}; exact mass calcd for $C_{13}H_{22}O_2$, 210.162; found, 210.162.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.48; H, 10.77.

1-Methoxyhomoadamantane[29] (25). Methylation of 14 (90 mg, 0.54 mmol) with sodium hydride (100 mg, 4.20 mmol) and methyl iodide (0.6 mL) in dry THF by the procedure described for **12** → **19** provided an oil which was Kugelrohr distilled to give 87 mg (89% yield) of **25**: ^{13}C NMR δ ($CDCl_3$) 72.7 (C-1), 47.9 (CH_3), 41.2 (C-2 and C-10), 40.7 (C-9), 37.3 (C-7 and C-11), 33.0 (C-4 and C-5), 31.5 (C-3 and C-6), 31.4 (C-8).

1-Methoxyhomoadamantan-3-ol (26). According to the general procedure described for **7** → **13**, a stream of ozone in oxygen was passed for 2.5 h through a mixture of **25** (87 mg, 0.44 mmol) adsorbed on silica gel (10 g) that was maintained at −78 °C. This material was then allowed to slowly warm to room temperature and the silica gel was eluted with ethyl acetate (750 mL). Evaporation of the solvent at reduced pressure provided an oil which contained a single volatile product by GLC analysis (5 ft × 0.25 in. QF-1 column, 150 °C). Kugelrohr distillation of this oil provided 84 mg (89% yield) of **26**: ^{1}H NMR δ ($CDCl_3$) 3.24 (s, 3 H, OCH_3), 2.32–2.14 (m, 2 H, bridgehead protons), 2.07–1.43 (m, 15 H); ^{13}C NMR δ ($CDCl_3$) 73.4 (C-1), 72.6 (C-3), 50.1 (C-2), 48.2 (OCH_3), 46.4 (CH_2), 41.3 (CH_2, double intensity), 40.0 (CH_2), 36.6 (CH_2), 31.3 (CH), 29.8 (CH), 29.5 (CH_2); exact mass calcd for $C_{12}H_{20}O_2$, 196.146; found, 196.146.

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Registry No. **7**, 281-46-9; **8**, 14504-84-8; **9**, 14651-42-4; **12**, 14504-80-4; **13**, 87350-97-8; **14**, 31061-64-0; **15**, 24669-56-5; **16**, 770-71-8; 17, 21898-96-4; **19**, 21898-92-0; **20**, 87350-98-9; **21**, 87350-99-0; **25**, 21898-95-3; **26**, 87351-00-6; CrO_3, 1333-82-0; lead tetraacetate, 546-67-8; *p*-nitroperbenzoic acid, 943-39-5.

Stereochemistry of the Reactions of Lithium Di-*tert*-butylbiphenyl with Alkyl Halides

Peter K. Freeman* and Larry L. Hutchinson

Department of Chemistry, Oregon State University, Corvallis, Oregon 97330-4003

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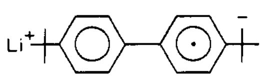
The stereochemistry of the reaction of lithium di-*tert*-butylbiphenyl with cyclopropyl halides, 7-chloronorcarane, 7-bromo-7-methylnorcarane, and *anti*-3-chloro-*exo*-tricyclo[3.2.1.0^{2,4}]octane generated syn/anti lithio reagent ratios of 1:10, 3:1, and 200:1, respectively. Similar treatment of noncyclopropyl secondary halides *syn*-7-bromonorbornene, *anti*-7-bromobenzonorbornadiene, *exo*-2-chloronorbornane, and 4-chloro-*tert*-butylcyclohexane resulted in lithio reagent ratios of 1:3.8 (syn/anti), 1:1.33 (syn/anti), 10:1 (exo/endo), and 1:14 (cis/trans), respectively. For the cyclopropyl radicals generated in the first group, the lithio reagent ratios describe the related radical equilibrium; the significance of the stereochemistry of the reaction of LiDBB with noncyclopropyl secondary halides is discussed in terms of both precursor radicals and carbanions.

A study of the stereochemistry of the reaction of the newly developed lithium *p*,*p*′-di-*tert*-butylbiphenyl (LiDBB,[1] 1) with alkyl halides is of interest for two reasons.



1 (LiDBB)

The mechanistic features revealed provide information about the reactions of a sterically hindered aromatic radical anion with alkyl halides and allow one to view the configurational equilibria of radicals and anions, the latter opportunity provided more easily and with fewer ambiguities than with other chemical methods. Second, the stereochemistry of the organolithium product is of considerable synthetic importance, and our study provides some useful guidelines.

Reactions with Cyclopropyl Halides

Cyclopropyl radicals are highly pyramidal and hold their configuration for on the order of 10^{-8}–10^{-10} s.[2-4] This is far longer than the time of a single collision between molecules in solution and is even longer than the time of an encounter. (An encounter is thought to consist of a number of collisions and lasts around 10^{-11} s.)[5] Thus, it is clear that any reaction which is diffusion controlled and reacts with retention of configuration to give stable products would be capable of accurately giving the equilibrium population of radicals. The expectation that LiDBB would react with cyclopropyl radicals at diffusion-controlled rates seems most reasonable. It is generally accepted that cyclopropyl radicals are highly unstable

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