Effect of Remote Substitution on Face Selection in Addition Reactions of Nor- and Homoadamantan-9-ones and of Several Analogues

Mira Kaselj,[†] Elena M. Gonikberg,[‡] and William J. le Noble*

Department of Chemistry, State University of New York, Stony Brook, New York 11794-3400

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The effects of 3-halo substitution on face selection in borohydride reductions of both nor- and homoadamantan-9-ones **1-X** and **3-X**, respectively, have been compared with those of 5-halo substitution in the parent 5-haloadamantan-2-ones **2-X**. The differences between the product ratios in these three compounds are small, but the selectivity of **2-X** is somewhat larger than that of either of the homologues. This is also true of the corresponding aza- and diazaadamantanones, and of an electrophilic addition. It is concluded that the approach angle of the reagent is not a sensitive variable in addition reactions of cyclohexanone and its derivatives, and that well-aligned antiperiplanar bonds are preferred to achieve maximal remote substituent induced selectivities.

Introduction

The addition of many reagents to 4-*tert*-butylcyclohexanone[1] and to the corresponding olefin[2] takes place in contrasteric fashion: the principal product is often that stereoisomer which results from axial approach of the reagent to the trigonal carbon. This fact has stimulated much research and discussion. It is generally agreed that it has an electronic basis, but the exact nature of the effect has remained controversial. To remove the concurrent steric factor as well as conformational questions as much as possible, we have studied 5-substituted adamantan-2-ones **2-X** and their derivatives.[3] The results of many studies of addition and elimination processes of every description[4] have led us to the conclusion that the newly forming (or breaking) bond is electron-deficient in the transition states, and that the complex is stabilized by electron donation from antiperiplanar vicinal bonds.[5] The donation derives from the σ component of these bonds; the recipient orbital is the σ^* component of the bond in transition (Figure 1).

This picture is not universally accepted, however. The possibility of electrostatic interactions has been advanced by Adcock[6] and others.[7] Distortions of the trigonal site caused by substituents in the probe molecule have been proposed by Gung[8] as a possible cause of the observed selectivity. Ring flattening as part of the reaction pathway of nucleophilic addition to simple cyclohexanones has been a long-standing conjecture[9] in the Felkin−Anh account, and this leaves our results open to the objection that the rigid adamantanones cannot supply any insight in the stereochemistry of addition to the more flexible monocyclic species. In this paper, we address the latter of these arguments.

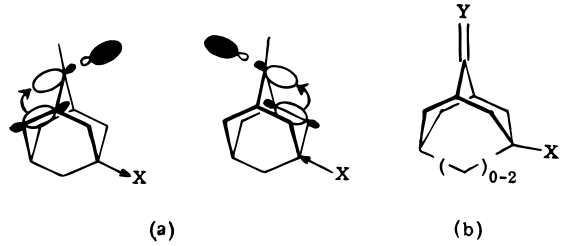

Figure 1. (a) The effect of remote substitution on face selection in additions to a trigonal site in adamantane derivatives according to the Cieplak model.[2,5] (b) General structure of the probes used in this study.

The net effect of ring flattening in simple cyclohexanones is that it reduces the hindrance offered by the axial hydrogen atoms at C-3 and C-5 to the reagent and thus allows a more favorable approach angle. This effect would be mimicked in noradamantan-9-ones **1-X**, not by flattening the ring but by pinning back the offending hydrogens. In contrast, the effect would be exacerbated in homoadamantan-9-ones **3-X**. To be sure, this is true for both the *en* and *zu* faces; however, if the approach angle is really the crucial factor envisioned for simple cyclohexanones, one might expect a systematic shift in *E*/*Z* product ratio toward unity or less for **1-X**, and an increase for **3-X**.

[†] Present address: Geo-Centers, Inc., 200 Valley Road, Suite 102, Mt. Arlington, NJ 07856.

[‡] Albany Molecular Research, 21 Corporate Circle, Albany, NY 12203.

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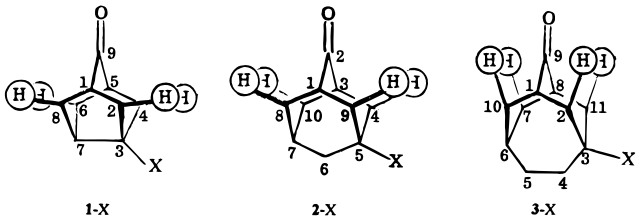
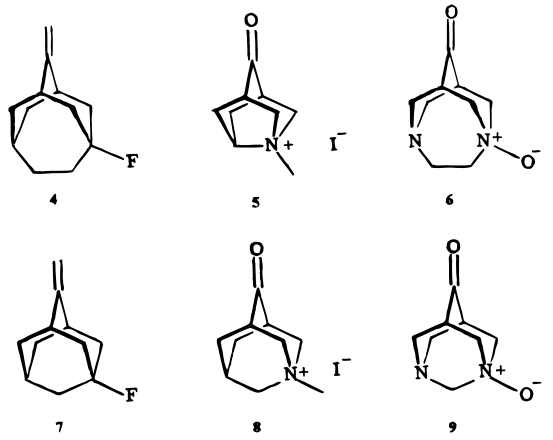
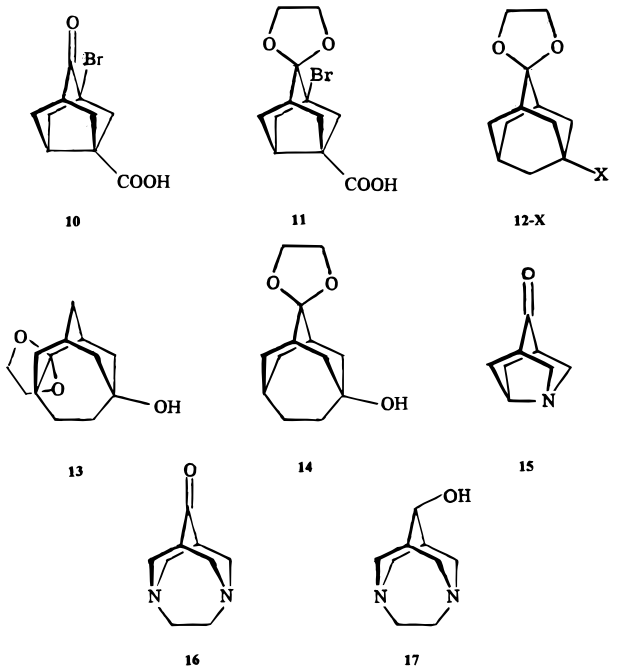


With these thoughts in mind, we studied various addition processes with **1-X**, **3-X**, **4**, **5**, and **6** for comparison with the known behavior of **2-X**, **7**, **8**, and **9**.



Synthesis

At the outset, compounds **1-X** were not known but derivative **10** had been reported.[10] After the keto function had been protected as the ketal **11**, hydrogenation with palladium on carbon followed by hydrolysis gave the keto acid **1**-COOH. Hunsdiecker decarboxylation converted this into **1**-Br, and treatment of the bromide with silver fluoride in hot cyclohexane yielded **1**-F. The synthesis of compounds **3-X** was based on the known[11] ester **12**-COOMe, previously reported by this laboratory. Lithium aluminum hydride reduction converted it into **12**-CH_2OH, and the corresponding alkoxide, generated by means of *tert*-butyllithium, upon treatment with tosyl chloride gave **12**-CH_2OTs. Hydrolysis in basic trifluoroethanol led to an equimolar mixture of **12**-CH_2OH and the ring-expanded homoadamantanols **13** and **14**, which are readily distinguished by means of their ^{13}C NMR spectra. Treatment of **14** with hydrofluoric acid gave **3**-F. Wittig reaction of this fluoride provided the methylene analogue **4**. Salt **5** was easily prepared from the known[12] parent **15**. Finally, since we had data[13] on 5,7-diazaadamantan-2-one *N*-oxide **9** and since the parent diazahomoadamantanone **16** is known,[14] we included **6** in our repertoire (see Experimental Section).



Experimental Section

General. IR spectra were measured in KBr pellets; absorptions are given in cm^{-1}. High and low resolution mass spectra were recorded by the Stony Brook Mass Spectrometry Facility. The signals are recorded below only where the identities of the nuclei are obvious. NMR spectra were measured in $CDCl_3$ except where noted, by means of 250 and 300 MHz spectrometers. ^{19}F Chemical shifts are given in ppm relative to $CFCl_3$. The ^{13}C NMR signals are assigned according to the outcome of DEPT experiments, on the basis of chemical shift values and on ^{19}F coupling constants (in some cases) as discussed in the text. The preparations of 1-bromo-9-noradamantan-3-carboxylic acid (**10**),[10] 5-carbomethoxyadamantan-2-one ethylene ketal (**12**-COOMe),[11] 3-azanoradamantan-9-one (**15**)[12] and 5,8-diazahomoadamantan-2-one (**16**)[14] have been described.

1-Bromo-9-noradamantan-3-carboxylic Acid Ethylene Ketal (11). A mixture of acid **10** (110 mg, 0.39 mmol), ethylene glycol (0.5 mL), and zinc chloride (15 mg) was heated in a commercial microwave oven (Samsung RE-552D) for 1 min. The mixture was allowed to cool to room temperature, diluted with 6.25 N aqueous sodium hydroxide and extracted with chloroform. The water layer was acidified with hydrochloric acid and extracted again; the combined extract was dried over sodium sulfate. Evaporation of solvent gave white solid **11** (100 mg, 85%), mp 145 °C. MS, *m*/*z* 304, 302 (1:1, M^+), 223 ($M^+ - Br$); HRMS, fd 304.0135; calcd 304.0135; IR, 3200−2500 (m), 2958 (m), 2886 (m), 1691 (s), 1147 (s) cm^{-1}; ^1H NMR, δ 10.15 (COOH), 4.26−4.12 (m, 2H), 4.10−3.96 (m, 2H), 2.72 (t, 1H, J = 5.5 Hz), 2.54−2.15 (m, 5H), 1.99 (s, 2H), 1.84−1.73 (m, 2H); ^{13}C NMR, δ 181.63 (COOH), 110.06 (OCO), 67.58 (C−COOH), 63.34 and 66.27 (CH_2O), 52.09, 49.66, 42.21 and 38.70 (CH_2), 46.56 and 43.89 (CH).

9-Oxo-noradamantane-3-carboxylic Acid (1-COOH). A solution of **11** (100 mg, 0.33 mmol) in absolute methanol (4 mL) containing potassium hydroxide (100 mg) was hydrogenated in the presence of 10% palladium on carbon (30 mg) at room temperature and 1.5 atm for 2.5 h. The mixture was filtered through Celite, and solvent was removed in vacuo. The residue was dissolved in a mixture of concentrated hydrochloric acid (0.5 mL) and acetic acid (1 mL) and heated to reflux for 1.5 h. The solution was concentrated to dryness and the residue extracted with acetone. Evaporation of solvent gave white solid **1**-COOH (50 mg, 84%), mp 128−129 °C (lit.[10b,10c] 133−7 °C, 132−4 °C). MS, *m*/*z* 180 (M^+), 162 ($M^+ - H_2O$); IR, 3100−2500 (w), 2962 (m), 1721 (s), 1693 (s), 1295 (m) cm^{-1};

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^{1}H NMR, δ 9.72 (COOH), 3.04 (t, 1H, J = 6.1 Hz), 2.79 (s, 2H), 2.36−1.80 (m, 8H); ^{13}C NMR, δ 212.36 (C-9), 181.88 (COOH), 52.62 (C-3), 52.14 (C-1,5), 46.42 (C-2,4), 43.56 (C-6,8), 43.13 (C-7).

3-Bromonoradamantan-9-one (1-Br). A mixture of carboxylic acid **1**-COOH (100 mg, 0.56 mmol) and red mercuric oxide (254 mg, 1.12 mmol) in methylene bromide (50 mL) was heated to reflux, and bromine (50 μL, 1.12 mmol) was added. Heating was continued for 2 h; the solvent was removed by distillation and the residue purified by passage through a column of neutral alumina. Elution with petroleum ether containing chloroform (0−30%) gave white solid **1**-Br (80 mg, 67%), mp 119 °C. MS, m/z 216, 214 (1:1, M^+), 135 (M^+ − Br); HRMS, fd 215.9975, calcd 215.9974; IR, 2962 (s), 2877 (m), 1726 (s), 1716 (s), 877 (m) cm^{-1}; ^{1}H NMR, δ 2.94 (t, J = 6.22 Hz, 1H), 2.61 (s, 2H), 2.44−2.20 (m, 6H), 1.76 (d, J = 11.1 Hz, 2H); ^{13}C NMR, δ 210.20 (C-9), 60.36 (C-3), 54.27 (C-2,4), 53.10 (C-1,3), 47.62 (C-7), 43.19 (C-6,8).

3-Fluoronoradamantan-9-one (1-F). A mixture of 3-bromonoradamantan-9-one **1**-Br (75 mg, 0.35 mmol) and anhydrous silver fluoride (150 mg) in dry cyclohexane (4 mL) was heated to reflux for 5 days. After cooling, the silver salt precipitate was filtered and washed with warm cyclohexane. The solvent was removed by distillation and the residue passed through a column of neutral alumina with petroleum ether containing chloroform (30−50%) to give white solid **1**-F (35 mg, 65%), which sublimes in a sealed tube at 88 °C. MS, m/z 154 (M^+), 135 (M^+ − F); HRMS fd 154.0792, calcd 154.0794; IR, 2962 (s), 1730 (s), 1260 (s), 1072−1020 (bs), 800 (s) cm^{-1}. ^{1}H NMR, δ 2.75−2.63 (m, 3H), 2.33−2.16 (m, 6H), 1.77 (d, 2H, J = 11.2 Hz); ^{13}C NMR, δ 211.20 (C-9), 104.07 (J = 211.08 Hz, C-3), 51.72 (J = 8.52 Hz, C-1,5), 46.99 (J = 21.25 Hz, C-2,4), 42.31 (J = 3.48 Hz, C-6,8), 40.34 (J = 3.15 Hz, C-7); ^{19}F NMR, δ −168.34 (s, 1F).

5-(Hydroxymethyl)adamantan-2-one Ethylene Ketal (12-CH$_2$OH). A solution of **12**-COOMe (1.0 g, 4.0 mmol) in ether (10 mL) was added dropwise to a suspension of lithium aluminum hydride (0.130 g, 3.4 mmol) in dry ether (20 mL). The mixture was heated to reflux for 4 h. After cooling, a saturated aqeous ammonium chloride solution (30 mL) was added slowly with stirring which was continued for 30 min after the addition was complete. The mixture was filtered and the filtrate extracted with ether. The organic layer was dried over magnesium sulfate and evaporation of solvent gave colorless oil **12**-CH$_2$OH (0.87 g, 98%), bp 79 °C at 0.5 mmHg. MS, m/z 224 (M^+), 193 (M^+ − CH$_2$O); HRMS, fd 224.1412, calcd 224.1412; IR, 3550−3140 (m), 2904 (s), 2851 (s), 1120 (s). ^{1}H NMR, δ 3.93 (s, 4H), 3.21 (s, 2H), 2.03−1.30 (m, 14H). ^{13}C NMR, δ 111.10 (C-2), 72.36 (CH$_2$OH), 63.99 and 63.90 (CH$_2$O), 38.27 (C-6), 36.09 (C-4,9), 35.94 (C-1,3), 34.15 (C-8,10), 33.51 (C-5), 26.58 (C-7).

5-(Tosyloxymethyl)adamantan-2-one Ethylene Ketal (12-CH$_2$OTs). A 1.7 M solution of *tert*-butyllithium in hexane (2.9 mL, 4.9 mmol) was added to a solution of **12**-CH$_2$OH (1.0 g, 4.5 mmol) in dry ether (25 mL) at 0 °C. A white precipitate formed immediately. The mixture was stirred for 90 min after which a solution of prepurified *p*-toluenesulfonyl chloride (0.860 g, 4.5 mmol) in ether (12 mL) was added. The mixture was stirred for 2.5 h at 0 °C, quenched with water and extracted with ether. The ether solution was dried over magnesium sulfate; removal of solvent gave white solid **12**-CH$_2$OTs (1.77 g, 87%), mp 66−68 °C. HRMS, fd 378.1490, calcd 378.1501; IR, 2908 (s), 2857 (m), 1597 (m), 1358 (s), 1175 (s), 954 (s); ^{1}H NMR, δ 7.70 (d, 2H, J = 8.1 Hz), 7.26 (d, 2H, J = 8.1 Hz), 3.85 (m, 4H), 3.49 (s, 2H), 2.31 (s, 3H), 1.88−1.30 (m, 13H). ^{13}C NMR, δ 144.48, 132.78, 129.66 (2CH), 127.72 (2CH), 110.43 (C-2), 78.75 (CH$_2$OTs), 64.16 and 64.04 (CH$_2$O), 37.98 (C-6), 35.83 (C-4,9), 35.77 (C-1,3), 33.74 (C-8,10), 32.48 (C-5), 26.30 (C-7), 21.48 (CH$_3$).

3-Hydroxyhomoadamantan-7-one Ethylene Ketal (13) and 3-Hydroxyhomoadamantan-9-one Ethylene Ketal (14). A solution of **12**-CH$_2$OTs (1.0 g, 2.65 mmol) and sodium carbonate (0.7 g, 6.5 mmol) in aqueous trifluoroethanol (20% water by volume, 80 mL) was heated at 180 °C for 15 h. The solvent was removed in vacuo and the residue extracted with chloroform and dried over magnesium sulfate. Evaporation yielded 0.47 g (80%) of a 1:1:1 mixture of **12**-CH$_2$OH, **13**, and **14**; column chromatography (neutral alumina, petroleum ether:ether = 11:9) gave pure samples of all three compounds, in that order. Compound **13**, mp 91−92 °C. MS, m/z 224 (M^+); HRMS, fd 224.1411; calcd 224.1412; IR, 3550−3150 (m), 2900 (s), 1455 (m), 1105 (s), 1040 (m), 1012 (m). ^{1}H NMR, δ 3.83 (m, 4H), 2.05−1.30 (m, 16H); ^{13}C NMR, δ 112.37 (C-9), 72.24 (C-3), 64.31 and 63.91 (CH$_2$O), 46.69 (CH$_2$), 41.12 (CH$_2$), 40.98 (CH$_2$), 40.39 (CH), 36.75 (CH), 35.83 (CH$_2$), 33.07 (CH$_2$), 26.77 (CH), 23.86 (CH$_2$). Compound **14**: mp 91−9 °C. MS, m/z 224 (M^+). HRMS, fd 224.1414, calcd 224.1412; IR, 3400−3100 (m), 2905 (s), 1445 (m), 1115 (s), 1035 (m), 1015 (m). ^{1}H NMR, δ 3.92 (s, 4H), 2.30−2.15 (m, 4H), 2.06−1.63 (m, 10H), 1.44 (d, J = 13.5, 2H). ^{13}C NMR (benzene), δ 110.62 (C-9), 71.67 (C-3), 64.11 and 63.96 (CH$_2$O), 45.05 (C-2,11), 42.05 (C-4), 35.93 (C-1,8), 35.75 (C-7,10), 30.28 (C-6), 30.08 (C-5).

3-Fluorohomoadamantan-9-one (3-F). Solid **14** (200 mg) was added to a solution of 70% poly-hydrogen fluoride/pyridine (Aldrich, 4 mL) and ammonium bifluoride (160 mg, 2.81 mmol) in a polyethylene bottle at 0 °C. The mixture was stirred for 20 min, quenched with ice and water, and extracted with pentane. The pentane solution was dried over magnesium sulfate; removal of solvent gave white solid **3**-F (100 mg, 61%), mp (with dec) 240 °C. MS, m/z 182 (M^+); HRMS, fd 182.1111, calcd 182.1107; IR, 2910 (s), 2860 (m), 1739 (s), 1711 (s), 1450 (m), 1012 (m). ^{1}H NMR, δ 2.42−2.15 (m, 11H), 1.90−1.80 (m, 4H); ^{13}C NMR, δ 217.40 (C-9), 94.45 (J = 170.32 Hz, C-3), 44.33 (J = 23.6 Hz, C-2,11), 43.67 (J = 12.60 Hz, C-1,8), 39.87 (C-7,10), 38.20 (J = 25.27 Hz, C-4), 29.83 (C-6), 27.29 (J = 16.9 Hz, C-5); ^{19}F NMR, δ −122.43 (bs, 1F).

5-Fluoro-9-methylenehomoadamantane (4). Triphenylmethylphosphonium bromide (490 mg, 1.37 mmol, vacuum-dried over phosphorus pentoxide) in THF (5 mL) was treated dropwise with *n*-butyllithium (0.88 mL, 1.6 M, 1.4 mmol) under nitrogen. After 30 min, a solution of **3**-F (250 mg, 1.37 mmol) in THF (3 mL) was added dropwise; the mixture was heated to reflux for 2 h, allowed to cool to room temperature, and quenched with water. The precipitate (phosphonium salt) was filtered and washed with ether. The aqueous part of the filtrate was extracted with ether. The organic solution was dried over magnesium sulfate. Removal of solvent gave white solid **4** (175 mg, 71%), mp 94 °C. MS, m/z 180 (M^+); HRMS, fd 180.1311, calcd 180.1314; IR, 3070 (w), 2977 (w), 2908 (s), 2853 (m), 1658 (m), 1446 (m), 1010 (s), 887 (s). ^{1}H NMR, δ 4.61 (s, 2H), 2.50 (s, 2H), 2.18−1.88 (m, 9H), 1.84−1.60 (m, 4H); ^{13}C NMR, δ 154.71 (C-9), 102.65 (=CH$_2$), 96.55 (J = 168.01 Hz, C-3), 45.52 (J = 20.57 Hz, C-2,11), 39.68 (C-7,10), 38.57 (J = 25.41 Hz, C-4), 37.08 (J = 12.76 Hz, C-1,8), 30.59 (C-6), 27.64 (J = 17.81 Hz, C-5); ^{19}F NMR, δ −117.22 (s, 1F).

3-Azanoradamantan-9-one (15) was prepared in seven steps from 4-hydroxypiperidine as described.[12] Its ^{1}H and ^{13}C NMR spectra were observed in methanol-d_4; in this medium, it is in equilibrium with the *E*- and *Z*-hemiketals.[15] ^{1}H NMR (CD$_3$OD) δ 3.88 (t, 1H, J = 6.0 Hz), 3.58 (t, 1H, J = 6.0 Hz), 3.20−3.00 (m, 8H), 2.80−2.67 (m, 6H), 2.33−2.16 (m, 6H), 2.04−1.68 (m, 10H); ^{13}C NMR (CD$_3$OD), δ 98.63 (C), 67.15, 63.30 and 63.00 (CH$_2$), 61.29, 61.21, 60.77, 53.14, 45.50 and 45.28 (CH), 44.74, 39.64 and 39.39 (CH$_2$); C=O was not observed.

***N*-Methyl-3-azanoradamantan-9-one Iodide (5).** Iodomethane (0.4 mL) was added to a solution of **15** (42 mg, 0.3 mmol) in methylene chloride (5 mL). A white precipitate formed in the next 0.5 h. Evaporation of solvent gave white solid **5** (76 mg, 90%). NMR analysis of a D$_2$O solution of the salt showed it to be present in the form of a diol. ^{1}H NMR (D$_2$O), δ 4.26 (t, 1H, J = 6.6 Hz), 3.76 (d, 2H, J = 10.5 Hz), 3.26 (d, 2H, J = 11.7 Hz), 3.13 (s, 3H), 2.51 (s, 2H), 2.26−2.02 (m, 4H); ^{13}C NMR (D$_2$O), δ 92.06 (C-9), 75.76 (C-7), 69.91 (C-2,4), 48.02 and 46.67 (C-1,5 or CH$_3$), 46.22 (C-6,8).

3,6-Diazahomoadamantan-9-one (16). This compound was prepared as described.[14] The authors' ^{1}H NMR spectrum

(15) This was also the case with **5**; see Hahn, J.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916.

was confirmed. ^{13}C NMR, δ 214.5 (C=O), 59.9 (C-2,7,10,11), 57.72 (C-4,5), 53.7 (C-1,8).

3,6-Diazahomoadamantan-9-ol (17). This compound was prepared as described.[16] ^{1}H NMR, δ 3.74, (s, 1H, H-9), 3.61 (d, J = 14 Hz, 2H), 3.15 (d, J = 13.5 Hz, 2H), 3.00 (s, 4H, H-4,5), 2.79 (d, J = 14 Hz, 2H), 2.40 (d, J = 13.5 Hz, 2H), 1.69 (s, 2H, H-1,8); ^{13}C NMR, δ 71.0 (C-9), 57.9, 57.7 (C-4,5), 57.5 (C-7,10), 50.7 (C-2,11), 37.1 (C-1,8).

3,6-Diazahomoadamantan-9 *N*-Oxide (6). This compound was prepared by means of the procedure used for compound **9**.[13] ^{1}H NMR (D_2O, pH adjusted to 13), δ 4.06 (d, J = 13 Hz, 2H), 3.66 (d, J = 13 Hz, 2H, H-2,11, overlaps with t, J = 8 Hz, 2H, H-5), 3.38 (d, J = 14.5 Hz, 2H), 3.02 (t, J = 8 Hz, 2H, H-4), 2.86 (d, J = 14.5 Hz, 2H, H-7,10), 1.72 (s, 2H, H-1,8); ^{13}C NMR (D_2O), δ 74.7 (C-4), 72.4 (C-2,11), 52.9 (C-7,10), 48.9 (C-5), 40.4 (C-1,8); C=O was not detected.

Selectivity Studies. Reduction of 1-Br. Sodium borohydride (0.2 mmol) was added to a stirred solution of ketone **1**-Br (0.2 mmol) in methanol (1 mL) at 0 °C. After 3 h, the mixture was poured into an aqueous ammonium chloride solution and extracted with chloroform. The extract was dried over sodium sulfate; evaporation of solvent gave a mixture of alcohols *E*- and *Z*-3-bromonoradamantan-9-ol (*E*- and *Z*-**18**). The ratio of the isomers was obtained from ^{1}H NMR spectra measured in the presence of 0.15 eq of Eu(fod)$_3$; the broad singlet at δ3.84 is well resolved into two singlets at δ5.7 and 6.2 under these conditions. This ratio was found to be in excellent agreement with the one deduced from GC analysis. IR, 3450−3100 (m), 2960 (s), 1460 (m), 1073 (s), 785 (s) cm^{-1}. ^{1}H NMR, δ 3.84 (bs, 2H-9), 2.70−2.52 (m, 4H), 2.25−1.83 (m, 16H), 1.57−1.43 (m, 4H). *E*-**18**: MS, *m*/*z* 137 (M^+ − Br), 119 (M^+ − Br−H_2O); ^{13}C NMR, δ 71.36 (C-9), 63.91 or 63.74 (C-3), 51.68 (C-2,4), 47.87 (C-7), 44.21 (C-1,5), 38.23 (C-6,8). *Z*-**18**: MS, *m*/*z* 137 (M^+ − Br), 119 (M^+ − Br−H_2O); ^{13}C NMR, δ 70.47 (C-9), 63.91 or 63.74 (C-3), 50.22 (C-2,4), 46.61 (C-7), 44.68 (C-1,5), 39.61 (C-6,8). The chemical shift assignments are based unambiguously on DEPT experiments, the effects of Eu(fod)$_3$ on the chemical shifts and on the well-known effect of the oxygen atom at C-9 on the signals of C-2,4 and C-6,8 (see also text below). The major isomer is assigned on the basis of ^{13}C signal intensities.

Reduction of 1-F. The reaction was carried out in precisely the same way as that of **1**-Br, to give a mixture of *E*- and *Z*-3-fluoronoradamantan-9-ol (*E*- and *Z*-**19**). The ratio of the isomers was determined by means of integration of both the ^{1}H and the ^{19}F NMR signals; the two were in excellent agreement. IR, 3550−3100 (m), 2958 (s), 2874 (m), 1321 (s), 1050 (s), 730 (s) cm^{-1}; ^{1}H NMR, δ 3.86 (s, *E*-H-9), 3.80 (s, *Z*-H-9), 2.36−2.27 (m, 8H), 2.05−1.09 (m, 14H), 1.42 (d, J = 11.40 Hz, 2H). *E*-**19**: MS, *m*/*z* 156 (M^+), 138 (M^+ − H_2O); ^{13}C NMR, δ106.48 (J = 207.81 Hz, C-3), 72.63 (C-9), 44.61 (J = 20.13 Hz, C-2,4), 43.23 (J = 8.34 Hz, C-1,5), 40.48 (J = 23.23 Hz, C-7), 37.89 (J = 2.91 Hz, C-6,8); ^{19}F NMR, δ −168.63 (d, J = 12.00 Hz, 1F). *Z*-**19**: MS, *m*/*z* 156 (M^+), 138 (M^+ − H_2O); ^{13}C NMR, δ 105.47 (J = 208.75 Hz, C-3), 71.50 (J = 1.70 Hz, C-9), 44.08 (J = 7.53 Hz, C-1,6), 43.73 (J = 19.20 Hz, C-2,4), 39.18 (J = 23.31 Hz, C-7), 39.12 (J = 3.16 Hz, C-6,8); ^{19}F NMR, δ −161.36 (q, J = 12.71 Hz, 1F). The ^{13}C assignments are facilitated in this case by the ^{19}F splittings which are steeply dependent on the number of intervening bonds.

Reduction of 3-F. Sodium borohydride (8.5 mg, 0.22 mmol) was added to a stirred solution of ketone **3**-F (40 mg, 0.22 mmol) in methanol (1 mL) at 0 °C. After 3 h, the mixture was poured into saturated aqueous ammonium chloride and extracted with methylene chloride. The organic layer was dried over magnesium sulfate, and removal of solvent gave a white solid mixture (34 mg, 83%) of *E*- and *Z*-5-fluorohomoadamantan-9-ol (*E*- and *Z*-**20**). Analyses by means of GC, ^{1}H NMR (H-9), and ^{19}F NMR gave virtually identical ratios. IR, 3050−3600 (m), 2911 (s), 1458 (m), 1068 (s), 1014 (s), 744 (s); ^{1}H NMR, δ 3.84 (s, H-9E), 3.63 (q, J = 3.50 Hz, *Z*-H-9), 2.50−1.55 (m, 30H), 1.27 (d, J = 13.76 Hz, 2H). *E*-**20**: GCMS, *m*/*z* 184 (w, M^+), 166 (M^+ − H_2O); ^{13}C NMR, δ 96.39 (J = 167.74 Hz, C-3), 72.20 (J = 1.62 Hz, C-9), 43.47 (J = 21.71 Hz, C-2,11), 38.40 (J = 25.52 Hz, C-4), 32.89 (J = 12.37 Hz, C-1,8), 30.24 (C-7,10), 29.87 (C-6), 27.74 (J = 18.82 Hz, C-5); ^{19}F NMR, δ −119.45 (m, 1F). *Z*-**20**: GCMS, *m*/*z* 184 (w, M^+), 166 (M^+ − H_2O); ^{13}C NMR, δ 96.62 (J = 166.89 Hz, C-3), 72.01 (J = 1.74 Hz, C-9), 38.40 (J = 25.52 Hz, C-4), 37.53 (J = 21.76 Hz, C-2,11), 36.96 (C-7,10), 33.97 (J = 1.51, C-1,8), 29.78 (C-6), 27.82 (J = 17.77 Hz, C-5); ^{19}F NMR, δ −114.34 (bs, 1F). The ^{13}C signals were assigned on the basis of DEPT experiments, ^{19}F couplings, and the effect of the C-9 oxygen atom on the chemical shifts of C-2,11 and C-7,10.

Methylation of 3-F. Methyllithium (0.17 mL,1.4 M, 0.24 mmol) was added to a solution of **3**-F in ether (2 mL) at 0 °C. After 12 h, the mixture was treated with saturated aqueous ammonium chloride and extracted with ether; the organic layer was dried over magnesium sulfate. Removal of solvent gave a white solid mixture (37 mg, 85%) of *E*- and *Z*-5-fluoro-9-methylhomoadamantan-9-ol (*E*- and *Z*-**21**) which was analyzed by means of GC and of ^{19}F NMR. IR, 3100−3600 (m), 2927 (s), 1455 (m), 1381 (m), 1017 (m); ^{1}H NMR, δ 2.72−1.20 (m). *E*-**21**: MS, *m*/*z* 183 (M^+ − CH_3); ^{13}C NMR, δ 96.54 (J = 167.27 Hz, C-3), 71.45 (C-9), 42.14 (J = 21.99 Hz, C-2,11), 39.25 (J = 25.40 Hz, C-4), 37.41 (J = 11.80 Hz, C-1,8), 32.89 (C-7,10), 29.02 (C-6), 28.03 (J = 18.23 Hz, C-5), 27.42 or 26.21 (J = 1.92) (CH_3). ^{19}F NMR, δ −118.31 (m, 1F). *Z*-**21**: MS, *m*/*z* 183 (M^+ − CH_3). ^{13}C NMR, δ 96.43 (J = 166.52 Hz, C-3), 71.24 (J = 1.62 Hz, C-9), 39.82 (J = 21.91 Hz, C-2,11), 38.79 (J = 26.29 Hz, C-4), 38.03 (J = 11.95 Hz, C-1,8), 35.45 (C-7,10), 29.21 (C-6), 28.58 (J = 18.11 Hz, C-5), 27.42 or 26.21 (J = 1.92 Hz) (CH_3). ^{19}F NMR, δ −116.40 (m, 1F). The ^{13}C NMR assignments were made in the same way as those described above for compounds **20**.

***n*-Butylation of 3-F.** *n*-Butyllithium (0.18 mL, 1.6 M, 0.29 mmol) was added to a solution of **3**-F (50 mg, 0.27 mmol) in THF (2 mL) at room temperature. After 2 h, aqueous workup as described above provided a white solid mixture (56 mg, 85%) of *E*- and *Z*-*n*-butyl-5-fluorohomoadamantan-9-ol (*E*- and *Z*-**22**). Column chromatography (silica, 200−400 mesh, pentane:ether = 9:1) gave initially pure *E*-**22**; later fractions were mixtures of *E*- and *Z*-**22**. The ratio of isomers was determined from the ^{19}F NMR spectrum of the crude product as well as by GC analysis. IR, 3200−3600 (s), 2921 (s), 1468 (m), 1023 (s); ^{1}H NMR, δ 2.66−1.15 (m, 5H), 0.97−0.88 (m, 45H). *E*-**22**: MS, *m*/*z* 183 (M^+ − Bu); IR: 3190−3530 (s), 2949 (s), 2923 (s), 1461 (m), 1170 (m), 1028 (s). ^{1}H NMR, δ 2.42−1.95 (m, 7H), 1.86−1.60 (m, 8H), 1.40−1.18 (m, 7H), 0.97−0.88 (m, 3H); ^{13}C NMR, δ 96.50 (J = 167.74 Hz, C-3), 72.18 (C-9), 41.71 (J = 21.83 Hz, C-2,11), 39.36 (J = 25.57 Hz, C-4), 37.71 (C-12), 35.26 (J = 11.59 Hz, C-1,8), 32.93 (C-7,10), 29.64 (C-6), 28.06 (J = 18.09 Hz, C-5), 24.28 (C-13), 23.22 (C-14), 14.15 (CH_3); ^{19}F NMR, δ-117.59 (m, 1F). *Z*-**22**: MS, *m*/*z* 183 (M^+ − Bu). ^{13}C NMR, δ 96.93 (J = 166.49 Hz, C-3), 71.96 (C-9), 39.88 (J = 21.59 Hz, C-2,11), 38.85 (J = 26.32 Hz, C-4), 36.85 (C-12), 35.89 (J = 1.89 Hz, C-1,8), 34.90 (C-7,10), 29.04 (C-6), 28.79 (J = 18.07 Hz, C-5), 24.46 (C-13), 23.28 (C-14), 14.15 (CH_3); ^{19}F NMR, δ −115.56 (m, 1F). The ^{13}C NMR signals were assigned on the basis of DEPT experiments, the effect of the oxygen atom at C-9 on the chemical shifts of the flanking carbons, and the application of Eu(fod)$_3$ as described in the text.

Epoxidation of 4. Olefin **4** (80 mg, 0.44 mmol) was dissolved in methylene chloride (4 mL), and *m*-chloroperbenzoic acid (95 mg, 80−85%) was added. After 24 h, the excess of peracid was destroyed by adding a 10% aqueous solution of sodium sulfite. The mixture was extracted with methylene chloride and the organic layer washed successively with 5% sodium bicarbonate, water, and saturated aqueous sodium chloride; drying over sodium sulfate and removal of solvent gave 70 mg (80%) of a mixture of *E*- and *Z*-5-fluoro-9-methylenehomoadamantane epoxide (*E*- and *Z*-**23**). The ratio of isomers was determined from the ^{1}H NMR signals of the oxirane protons in the presence of 0.15 equiv of Eu(fod)$_3$ as well as from the ^{19}F spectrum and by GC analysis. IR, 2924 (s), 2870 (m), 1456 (m), 1017 (s); ^{1}H NMR, δ 2.58 (t, J = 15.0

(16) Kuznetsov, A. I.; Vladimirova, I. A.; Serova, T. M.; Moskovkin, A. S. *Chem. Heterocycl. Comput. (Engl. Transl.)* **1991**, *27*, 631.

Hz, 2H), 2.32−0.75 (m with s at 2.30 and 2.23, 32H). *E*-**23**: GCMS, *m*/*z* 196 (M^+), 181 ($M^+ - CH_3$). ^{13}C NMR (C_6D_6), δ 95.22 (J = 170.08 Hz, C-3), 62.23 (C-9), 53.68 (CH_2O), 41.88 (J = 21.98 Hz, C-2,11), 38.61 (J = 25.89 Hz, C-4), 36.97 (C-7,10), 35.02 (J = 12.33 Hz, C-1,8), 30.12 (C-6), 27.68 (J = 16.84 Hz, C-5); ^{19}F NMR, δ −117.25 (bs, 1F). *Z*-**23**: MS, *m*/*z* 196 (M^+), 181 ($M^+ - CH_3$). ^{13}C NMR (C_6D_6), δ 95.50 (J = 169.44 Hz, C-3), 62.31 (C-9), 54.07 (CH_2O), 43.80 (J = 20.00 Hz, C-2,11), 38.69 (J = 25.67 Hz, C-4), 34.76 (C-7,10), 34.34 (J = 12.62 Hz, C-1,8), 29.91 (C-6), 27.56 (J = 17.05 Hz, C-5); ^{19}F NMR, δ-119.40 (m, 1F).

Reduction of 15. The reductions were carried out under conditions similar to those described above, in methanol-d_4 and in THF-d_8. The resulting mixtures of *E*- and *Z*-3-azanoradamantan-2-ol (*E*- and *Z*-**24**) were analyzed by integrating the H-9 signals, and the assignments of configuration based on the chemical shifts of the flanking carbons in the ^{13}C NMR spectrum. ^{1}H NMR (CD_3OD) δ 4.00 (bs, *E*-H-9), 3.92 (bs, *Z*-H-9), 3.76 (t, *Z*-H-7, J = 6.1 Hz), 3.65 (t, *E*-H-7, J = 6.7 Hz), 3.46 (d, 2H, J = 10.9 Hz), 3.15−2.70 (m, 6H), 2.29 (bs, 4H), 2.17 (d, 2H, J = 11.3 Hz), 2.05−1.71 (m, 6H). *E*-**24**: ^{13}C NMR (CD_3OD), δ70.43 (C-9), 63.56 (C-2,4), 62.26 (C-7), 44.03 (C-1,5), 38.79 (C-6,8); *Z*-**24**: ^{13}C NMR (CD_3OD), δ 70.38 (C-9), 62.46 (C-2,4), 61.43 (C-7), 43.76 (C-1,5), 39.90 (C-6,8). The composition depended on the solvent used in the reduction; see text.

Reduction of 5. This reaction was done with sodium borohydride at room temperature in D_2O to give a mixture of *E*- and *Z*-*N*-methyl-3-azanoradamantan-9-ol iodide (*E*- and *Z*-**25**), which was analyzed by means of integratable ^{13}C NMR (INVGATE). *E*-**25**: ^{1}H NMR (D_2O) δ 4.36 (bs, 1H), 4.27 (bs, 1H), 3.83 (d, 2H, J = 10.3 Hz), 3.49 (d, 2H, J = 10.8 Hz), 3.30 (s, 3H), 2.74 (bs, 2H), 2.35 (m, 2H); ^{13}C NMR (D_2O) δ 80.16 (C-7), 73.69 (C-2,4), 69.88 (C-9), 51.43 (CH_3), 45.89 (C-1,5), 38.99 (C-6,8). *Z*-**25**: ^{1}H NMR (D_2O) δ4.22 (bs, 1H), 4.15 (d, 2H, J = 10.4 Hz), 3.10 (d, 2H, J = 10.8 Hz), 3.26 (s, 3H), other signals overlap those of the *E*-isomer; ^{13}C NMR (D_2O) δ 78.49 (C-7), 72.69 (C-2,4), 68.90 (C-9), 51.48 (CH_3), 45.00 (C-1,5), 40.25 (C-6,8).

Reduction of 6 and Oxidation of 17. The reduction was carried out in methanol as described above to give a mixture of *E*- and *Z*-3,6-diazahomoadamantan-9-ol *N*-oxide (*E*- and *Z*-**26**). These compounds were also formed in the oxidation of **17** with *m*-chloroperbenzoic acid. Since the isomer ratios in the two reactions were very different, the ^{1}H NMR signals of the mixtures were readily sorted. *E*-**26**: ^{1}H NMR (D_2O, pH adjusted to 13): δ 4.15 (s, 1H, H-9), 3.88 (d, J = 13 Hz, 2H), 3.78 (m, 4H), 3.44 (d, J = 14.5 Hz, 2H), 3.07 (t, J = 7 Hz, 2H), 2.77 (d, J = 14.5 Hz, 2H), 1.89 (s, 2H, H-1,8); ^{13}C NMR (D_2O), δ 74.3 (C-4), 73.7 (C-2,11), 67.2 (C-9), 48.5 (C-5), 48.3 (C-7,10), 33.8 (C-1,8). *Z*-**26**: ^{1}H NMR (D_2O), δ 4.0−3.6 (m, 11H), 3.08 (m, 2H), 2.01 (s, 2H); ^{13}C NMR (D_2O), δ 74.2 (C-4), 67.7 (C-2,11), 66.4 (C-9), 54.4 (C-7,10), 48.3 (C-5), 34.8 (C-1,8).

In the presence of a 2-fold excess of *m*-chloroperbenzoic acid, *N*,*N*′-dioxide **27** is formed from alcohols **26**. ^{1}H NMR (D_2O, pH adjusted to 13), δ 4.01 (m, 3H), 3.89 (d, J = 13 Hz, 2H), 3.77 (s, 4H), 3.70 (d, J = 14 Hz, 2H), 3.62 (d, J = 14 Hz, 2H), 2.19 (s, 2H); ^{13}C NMR (D_2O), δ 71.8 (C-7,10), 66.0 (C-9), 65.2 (C-2,11), 65.1 and 64.9 (C-4,5), 37.3 (C-1,8). Efforts to reduce **27** back to the mono-*N*-oxides **26** were unsuccessful.

Results and Discussion

As noted in the Experimental Section, several analytical approaches were available to assay the mixtures: GC and ^{1}H, ^{13}C, and ^{19}F NMR. In some cases, Eu(fod)$_3$ was used to separate signals. Most of the crude mixtures were analyzed by more than one technique, and the results differed by no more than one percentage point in all instances.

The assignment of the major components of these mixtures was made virtually exclusively on the basis of the ^{13}C NMR spectra. As we have noted elsewhere, a singly bound oxygen atom at C-2 in adamantanes (or C-9 in nor- or homoadamantanes) tends to polarize the axial C−H bonds "underneath" it, so that the protons appear at lower field than normal[17a] and the ^{13}C atoms show up at higher field.[17b] An electron-withdrawing group at C-5 in adamantanes (C-3 in nor- and homoadamantanes) shifts the signals of the neighboring carbons to lower field, and as a result of the combined influence of these two substituents, the *Z*- isomers have the signals of the flanking carbons between them (C-4,9 in adamantanes) fairly close together, whereas those of the *E*- isomers are relatively far apart. In *Z*-5-bromoadamantan-2-ol, for example, the C-4,9 and the C-8,10 signals appear at δ 42.54 and δ 34.28, respectively, whereas the same signals in the *E*-isomer appear at δ 47.63 and δ 29.13, respectively.[18] These patterns reappear in virtually every reaction we study, and hence the result is usually clear at a glance. Comparison of the inner and outer signals then reveals which isomer is the major one. This approach was used throughout this study; it was backed up in several cases by the use of Eu(fod)$_3$, which shifts the pair of carbons proximal to the oxygen much more strongly to lower field than the distal pair. In those cases where the remote substituent is fluoro, the ^{19}F splittings of the signals of all carbon atoms within three bonds were also very helpful. The results are given in Table 1.

Table 1. Product Ratios in Addition Processes of Adamantane Derivatives

substrate	reaction	conditions	analysis	*E*:*Z*	ref
1-Br	$NaBH_4$	MeOH, 0 °C	GC	59:41	
			^{1}H NMR	60:40	
2-Br	$NaBH_4$	MeOH, 0 °C	^{1}H NMR	59:41	3a
1-F	$NaBH_4$	MeOH, 0 °C	^{1}H NMR	60:40	
			^{19}F NMR	60:40	
2-F	$NaBH_4$	MeOH, 0 °C	^{1}H NMR	62:38	3a
3-F	$NaBH_4$	MeOH, 0 °C	^{19}F NMR	67:33	
			^{1}H NMR	66:34	
			GC	66:34	
2-F	MeLi	Ether, 0 °C	GC	70:30	3a
3-F	MeLi	Ether, 0 °C	GC	66:34	
			^{19}F NMR	67:33	
3-F	*n*-BuLi	THF, 0 °C	^{13}C NMR	67:33	
7	*m*CPBA	CH_2Cl_2, rt	GC	66:34	19
			^{1}H NMR	66:34	19
4	*m*-CPBA	CH_2Cl_2, rt	^{1}H NMR	58:42	
			^{19}F NMR	58:42	
			GC	58:42	
15	$NaBH_4$	MeOH-d_4, 0 °C	^{1}H NMR	66:34	
		THF-d_8, 0 °C	^{1}H NMR	46:54	
a	$NaBH_4$	MeOH, 0 °C	^{1}H NMR	62:38	20
	MeLi	THF, 0 °C	^{1}H NMR	45:55	20
5	$NaBH_4$	D_2O, rt	^{13}C NMR	87:13	
8	$NaBH_4$	D_2O, rt	^{1}H NMR	96:4	20
9	$NaBH_4$	MeOH, 0° C	^{1}H NMR	88:12	13
6	$NaBH_4$	MeOH, 0 °C	^{1}H NMR	83:17	
17	*m*-CPBA	CH_2Cl_2, rt	^{1}H NMR	28:72	
b	*m*-CPBA	CH_2Cl_2, rt	^{1}H NMR	31:69	13

[a] 5-Azaadamantan-2-one. [b] 5,7-Diazaadamantan-2-ol.

When the results for the haloadamantanone derivatives **1**-X−**3**-X are compared, it is at once obvious that syn approach by the nucleophile to the carbonyl group is preferred in all cases. The length of the bridge between the remote bridgehead atoms makes at most a minor difference. The same thing can be said about the single

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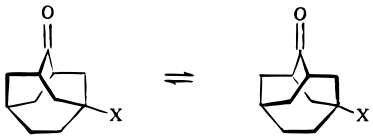
(18) (a) Mukherjee, A. K.; le Noble, W. J. *J. Org. Chem.* **1993**, *58*, 7955. (b) Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.

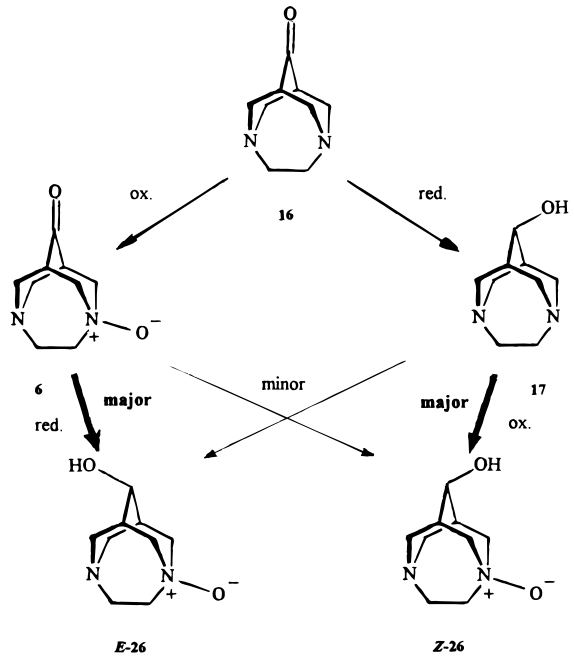
example of electrophilic addition (**4** *vs* **7**). No trend is visible in any of these data that might reflect a gradual response to the placement of the hominal hydrogen atoms. One might wonder whether the homoadamantane skeleton is indeed as rigid as pictured above, and whether a deformation is introduced by the extra methylene. In that case, the substrate would be subject to a conformational equilibration of the type shown in eq 1, which would presumably raise one axial hydrogen and lower the other. In these enantiomeric forms, the nucleophile will seek out a path away from the plane perpendicular to that of the carbonyl group, and favoring the less hindering hydrogen. If that were so, the homoadamantane skeleton would be more similar to the noradamantane framework than to the adamantane parent itself. Indeed, one observes that the adamantane derivatives generally show somewhat larger ratios than either of the analogues.



Schleyer[21] has examined the conformation of homoadamantane by means of NMR as well as on a computational basis. As he pointed out, the c_{2V} symmetrical structure suffers from a pair of eclipsed methylene groups (C-4 and C-5); while this interaction is relieved in the equilibrating structures, the relief is achieved at the cost of increased strain throughout the rest of the molecule. Both the spectral evidence and the calculations favored the symmetrical structure. It should be pointed out that whatever the positions of the axial hydrogens at C-2 and C-11 may be, they are repeated with the axial hydrogens at C-7 and C-10: the two faces are identical in that respect. As a result of these considerations, we favor the viewpoint that the higher ratios with the adamantane skeleton are the result of the more perfect antiperiplanar alignment of the bonds, which allows the remote substituent to make its influence felt more strongly. This also accounts for the fact that when the substituent is placed at the equatorial position of C-4 rather than at C-5 in the adamantanone,[3b] its effect is not significantly stronger, and even two bromine atoms at C-4 and C-9 cause only a modestly larger preference for syn approach than does a single bromine atom at C-5.

Since the differences between conpounds **1**−**3** were small, we decided to expand the investigation by incorporating a quaternary nitrogen atom in the remote bridgehead position(s); we have shown elsewhere[16,20,22] that this greatly magnifies the ratios. The keto amines **15** and 5-azaadamantan-2-one themselves are not very informative because the ratios are solvent dependent: in hydrogen-bonding solvents, the *zu* face is favored, and in others, the *en* face.[23] This is easily explained: a hydrogen-bonded nitrogen atom carries an increased positive charge, whereas a nonbonded one can use its unshared pair to serve as an electron donor. A comparison of compounds **5** and **8** shows a larger ratio for the latter. We do not have information on 3-azahomoadamantan-9-one, but comparing the diaza analogues **6** and **9** again shows the adamantane analogue to exhibit the larger ratio.

Scheme 1



Finally, it may be noted that compounds **6** and **17**, when treated with sodium borohydride and *m*-chloroperbenzoic acid, respectively, give the same products *E*- and *Z*-**26**, but in very different ratios. Thus, the major stereoisomer of **26** differs depending on which of the two sequences is followed in Scheme 1. In both cases, hyperconjugation involving a remote substituent is the determining factor, as we have reported earlier[13] in another case. We do not know of any basis other than transition state hyperconjugation on which these facts could have been confidently predicted.

We conclude as follows. Our experiments do not support the notion that ring flattening and the related repositioning of axial hominal hydrogens are important determinants in the stereochemistry of addition to cyclohexanone and its derivatives. Rigidly enforced antiperiplanarity of the intervening bonds is preferred in the transmission of remote substituent effects on the stereochemistry of addition and elimination.

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Supporting Information Available: NMR spectra of **1**-COOH, **1**-Br, **1**-F, **3**-F, **4**−**6**, **11**, **12**-CH_2OH, **12**-CH_2OTs, **13**−**17**, **27**, and *E*,*Z*-mixtures of **18**−**26** (119 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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