Effects of Substituent Modification on Face Selection in Reduction

Cheryl D. Jones,† Mira Kaselj,‡ Ralph N. Salvatore,§ and William J. le Noble*

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

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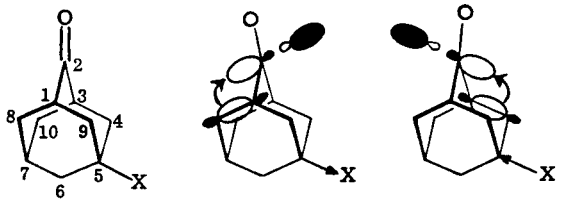
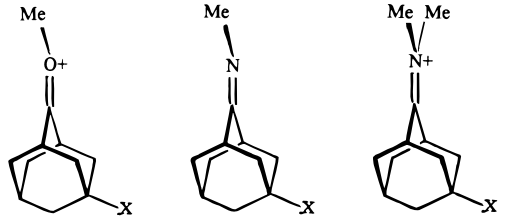
In our studies of the phenomenon of face selection in addition and elimination processes, we have made much use of 5-substituted adamantan-2-ones and their derivatives.[1] We have found it possible to account for our observations by assuming that the transition states are stabilized by hyperconjugative donation of electrons into the σ^* orbital of the newly forming or breaking bond by the antiperiplanar vicinal bonds.[2] When two of these vicinal bonds are adjacent to an electron-withdrawing substituent as in **1**-X, they are rendered electron-poor by it; the two transition states are then unequal in energy, and as a result, syn attack (as in **2**-*a*) is favored.



1-X **2**-*a* **2**-*b*

We have found that the ratios are larger when the electron demand of X is greater,[3] and that it can approach 10^3 or more in carbocations where the trigonal carbon carries a positive charge.[4] It therefore occurred to us that we might be able to increase the selectivity of ketones by modifying either the carbonyl function or the group X at C-5 so as to make them more electron demanding, and we report here several experiments to assess this idea.

The first of these experiments was based on an observation already in hand, namely, the binding of a formal cation to the carbonyl oxygen atom.[5] Thus, while the sodium borohydride reduction of 5-fluoroadamantan-2-one **1**-F leads-to-a ratio of 62:38 in favor of the *E*-alcohol, the capture of the 2-(2-methoxy-5-fluoroadamantyl) cation **3**-F gives the *E*-ether with a margin of 83:17. It is rarely practical in synthetic sequences to convert carbonyl groups into methoxy-substituted carbocations; hence, this observation is not very applicable. Instead, we decided to compare the *N*-methylimine **4**-Ph and *N*,*N*-dimethyliminium cation **5**-Ph, by reducing both with sodium borohydride in methanol. The latter species is of course readily obtainable from the former by means of gentle treatment with methyl iodide. In both cases, the assay was carried out by means of GC-MS; the assignment rested on a comparison of the observed ^{13}C NMR spectra of the mixture with that calculated, for example, from those of 2-*N*-methylaminoadamantane, 1-phenyladamantane, and adamantane itself.[6]



3-X **4**-X **5**-X

The experiment, carried out in methanol solution, produced two surprises. First, the ratio for imine **4**-Ph was found to be 67:33 in favor of the *E*-amine; thus, it is larger than that for 5-phenyladamantan-2-one **1**-Ph, which is 58:42.[1a] Second, the ratios for **4**- and **5**-Ph (68:32) are virtually identical, a finding quite unlike that observed for **1**- and **3**-F. It occurred to us that both of these observations would make sense if the species being reduced had not been **4**-Ph but rather its conjugate acid. However, the same result was obtained when the reduction was carried out in the presence of various concentrations of sodium methoxide, even up to 0.5 molar. While the concentration of the iminium cation must be minute under these conditions, its reduction is surely much faster than that of the free amine, and hence this experiment is not decisive. The use of carefully dried THF made no difference in the product ratio either, but it seemed possible that in the absence of a protic acid, the counterion introduced with the reducing agent complexes with the amine and thus accounts for the large ratio. Finally, even the use of tetra-*n*-butylammonium borohydride in THF did not alter the outcome; nevertheless, intervention by adventitious water cannot be ruled out.[7]

A second possible way to influence diastereoselectivity is the deliberate addition of one of the more traditional Lewis acids. A good example is the complex of **1**-Ph with antimony pentachloride, which has been isolated in pure form and the crystal structure of which has been published by Laube.[8] The increased charge at C-2 is clear both from its deshielding (by 25 ppm relative to the pure ketone) and from the increased C═O bond length (by 0.045 Å). We furthermore found the carbonyl infrared frequency to be reduced by more than 40 cm^{-1}. The reduction of this complex indeed produced the *E*-alcohol

† Present address: Bristol-Meyers Squibb, 1 Squibb Drive, Bldg 97, New Brunswick, NJ 08903.

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

§ Present address: Department of Chemistry, University of South Florida, Tampa, FL 33620-5250.

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(7) It is perhaps of interest that the use of the ammonium salt led to a *reversal* of the ratio of **1**-Ph: the *Z*-alcohol prevailed by a margin of 57:43. We assume that long range hindrance in the ion-pair led to this result, as we have seen earlier with the use of another highly crowded reducing agent.[1a] For a related paper, see Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412.

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Table 1. Reduction of Adamantanone Derivatives

substrate	reducing agent	solvent	additive	*E*/*Z* product ratio	ref
3-F	$NaBH_4$	THF	–	83:17	5a
1-F	$NaBH_4$	Me_2CHOH	–	62:38	1a
1-Ph	$NaBH_4$	Me_2CHOH	–	58:42	1a
1-Ph	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O	–	49:51	1a
1-*t*-Bu	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O	–	42:58	1a
1-*t*-Bu	$LiAlH_4$	Et_2O	–	50:50	1a
4-Ph	$NaBH_4$	MeOH	–	67:33	–
5-Ph	$NaBH_4$	MeOH	–	68:32	–
4-Ph	$NaBH_4$	MeOH	3M MeO^-	65:35	–
4-Ph	$NaBH_4$	THF	–	66:34	–
4-Ph	$n\text{-}Bu_4NBH_4$	THF	–	68:32	–
1-Ph	$n\text{-}Bu_4NBH_4$	THF	–	43:57	–
1-Ph	$LiBH_4$	CH_2Cl_2	$SbCl_5$	64:36	–
1-Ph	$LiBH_4$	CH_2Cl_2	$TiCl_4$ (1M)	62:38	–
1-Ph	$LiBH_4$	CH_2Cl_2	$TiCl_3$	64:36	
1-Ph	$LiBH_4$	CH_2Cl_2	$MgCl_2$	61:39	–
1-Ph	$LiBH_4$	CH_2Cl_2	$NiBr_2$	61:39	–
1-Ph	$LiBH_4$	CH_2Cl_2	$SnCl_4$	62:38	–
1-Ph	$LiBH_4$	CH_2Cl_2	$BF_3{\cdot}Et_2O$	64:36	–
1-Ph	$LiBH_4$	CH_2Cl_2	$AlCl_3$	62:38	–
1-Ph	$LiBH_4$	CH_2Cl_2	Et_2AlCl	62:38	–
1-NMe_2	$NaBH_4$	D_2O	–	65:35	13
1-NMe_3 I	$NaBH_4$	D_2O	–	86:14	–
1-OMe	$NaBH_4$	D_2O or MeOH	–	64:36	13
1-OH	$NaBH_4$	MeOH	–	58:42	1a
1-OH	$NaBH_4$	THF	NaH	49:51	–
1-COOMe	$NaBH_4$	MeOH	–	57:43	–
1-COOH	$NaBH_4$	MeOH	NaOH	45:55	–
1-COOH	$NaBH_4$	MeOH	–	52:48	14

in excess by a margin of 65:35, compared with that of 57:43 for the free ketone.[1a] However, the Lewis-acid enhanced reaction also led to side products: a mixture of 2-chloro-5-phenyladamantanes is present as well as two other components that were not identified. Similar results were obtained by adding titanium tri- or tetrachloride; stannic, magnesium, aluminum, or diethylaluminum chloride; nickel bromide; or boron trifluoride etherate; the quantities of side products (but not the *E*/*Z* ratio) varied from negligible to serious depending on the counterion, medium, reaction time, and so on, but we did not undertake a systematic investigation (see Table 1). We assume that the similarity of the ratios regardless of the strength of the Lewis acid is due to the more rapid reaction of the complexed ketone, so that the proportion of this species is not important.

Finally, we were interested in modifying 5-substituent X itself as a way to influence selectivity. We showed earlier that replacing C-5 by positive nitrogen greatly increased *E*/*Z* ratios,[9] and that replacing it by negative boron inverted the ratio of deuterium atom capture by 2-adamantyl radicals.[10] The question considered here is how this effect diminishes as the charged atom resides at a greater distance. To that end, we compared the reduction ratio of 5-(dimethylamino)adamantan-2-one **1**-NMe_2 with that of its methyl iodide salt, and indeed we found a still sizable increase in the *E*/*Z* ratio, from 65:35 to 86:14. Conversely, while the reduction of 5-methoxyadamantan-2-one **1**-OMe with sodium borohydride in either methanol or D_2O gives an *E*/*Z* ratio of 64:36, and that of alcohol **1**-OH gives a ratio of 58:42 (with or without added base), the reaction of **1**-OH in THF in the presence of sodium hydride gave a ratio of 49:51. Similarly, the ratio of the keto ester **1**-COOMe (57:43) is inverted to 45:55 if the acid itself (**1**-COOH) is reduced in the presence of sodium hydroxide in methanol. No such inversion occurred if D_2O was used, and intermediate compositions resulted if mixtures of these solvents were employed.

In conclusion, it appears in principle possible to raise the selectivity in addition reactions by introducing or augmenting positive charge at either the trigonal atom being added to or at the remote substituent, and to diminish it by means of negative charge in the substituent. The failure to observe such an effect in the borohydride reduction of imine **4**-Ph may well be an indication that the nitrogen atom in this species is bound to or paired with a cation prior to reaction.

Experimental Section

2-(*N*-Methylimino)adamantane (4-H). This compound was prepared as a pale yellow oil in 98% yield by stirring a solution of adamantanone (100 mg, 0.67 mmol) in a mixture of dry THF (1.5 mL) and methylamine (2.0 M in THF, 1 mL) and 4A molecular sieves (1.0 g) at room temperature under nitrogen overnight. After centrifugation, the solvent was evaporated; a GC of the residue showed only a single peak. ^{1}H NMR (C_6D_6), δ 3.08 (s, 3H), 2.88 (bs, 1H), 2.76 (bs, 1H), 1.80−1.56 (m, 12H); ^{13}C NMR, δ 177.92 (CN), 43.91 (CH_3), 39.25 (2C, CH_2), 38.13 (2C, CH_2), 36.95 (CH), 36.81 (CH_2), 32.15 (CH), 28.29 (2C, CH). Imine **4**-H is very sensitive to hydrolysis and is best kept in ether solution if it must be stored.

2-(*N,N*-Dimethyliminiumadamantane iodide (5-H iodide). Freshly prepared imine **4**-H (50 mg, 0.31 mmol) in dry THF (1.5 mL) is treated with 4A molecular sieves (0.5 g), and methyl iodide (0.10 mL, 1.6 mmol) is added in portions over 30 min. After 6 h, the drying agent is removed and the solvent evaporated; the salt is dissolved in acetonitrile, reprecipitated by adding ether, and washed with ether to give an off-white solid (87 mg, 93%); mp 144−5 °C. ^{1}H NMR (CD_3OD), δ 3.57 (s, 6H), 3.38 (bs, 2H), 2.21−1.94 (m, 12H); ^{13}C NMR, δ 166.45 (C=N), 45.61 (2C, CH_3), 39.32 (4C, CH_2), 38.14 (2C, CH), 35.53 (CH_2), 26.98 (2C, CH). This compound is also sensitive to hydrolysis.

2-(*N*-Methylamino)adamantane. This known amine[11] was obtained by reducing the imine **4**-H (50 mg, 0.31 mmol) with sodium borohydride (0.46 mg, 1.2 mmol, in four portions) in methanol (2.0 mL) during 20 min. Stirring was continued for 6 h. The pH was adjusted to 1 with concentrated hydrochloric acid to decompose unreacted borohydride and then to 12 with concentrated sodium hydroxide to liberate the amine. After evaporation to dryness, the amine was isolated by extraction of the residue with ether and evaporation of solvent to give a white solid (46 mg, 91%); mp 86 °C, lit.[11] 87 °C. ^{1}H NMR (C_6D_6), δ 2.46 (s, 1H), 2.34 (s, 3H), 2.16 (s, 1H), 2.11 (s, 1H), 1.80−1.61 (m, 11 H), 1.44 (s, 1H), 1.39 (s, 1H); ^{13}C NMR, δ 64.24 (CH), 38.40 (CH_2), 37.69 (2C, CH_2), 33.99 (CH_3), 32.26 (2C, CH), 31.56 (2C, CH_2), 28.41 (CH), 28.30 (CH).

2-(*N,N*-Dimethylaminoadamantane. This known amine[11] was obtained by reducing the iminium salt (50 mg, 0.16 mmol) exactly as described for the monomethylamine. Mp 30−31 °C, lit.[11] 30−31 °C. ^{1}H NMR (C_6D_6), δ 2.30 (bs, 1H), 2.25 (bs, 1H), 2.10 (s, 6H), 1.96 (bs, 2H), 1.82−1.55 (m, 9H), 1.43 (bs, 1H), 1.38 (bs, 1H); ^{13}C NMR, δ 70.02 (CH), 43.05 (2C, CH_3), 38.19 (CH_2), 37.54 (2C, CH_2), 31.64 (2C, CH_2), 30.20 (2C, CH), 28.05 (CH), 27.67 (CH).

2-(*N*-Methylimino-5-phenyladamantane (4-Ph). This compound was prepared from the ketone[12] in 97% yield in exactly the same way as the parent imine (see above). Mp 45−8 °C. ^{1}H NMR (C_6D_6), δ 7.37−7.10 (m, 5H), 3.11 (s, 3H), 2.95 (bs, 1H),

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2.85 (bs, 1H), 2.06−1.48 (m, 11H). ^{13}C NMR, δ 177.32 (C═N), 149.56, 128.46 (CH), 126.11 (CH), 125.11 (CH), 44.46 (CH_2), 43.92 (CH_3), 43.55 (CH_2), 42.26 (CH_2), 38.38 (CH_2), 37.28 (CH_2), 37.16 (CH), 36.37, 32.14 (CH), 28.97 (CH).

2-(*N,N*-Dimethyliminium)-5-phenyladamantane iodide (5-Ph iodide). The preparation was identical to that of **5**-H iodide. Mp 136−8 °C. ^{1}H NMR (CD_3CN), δ 7.41−7.20 (m, 5H), 3.59 (s, 6H), 3.50 (bs, 2H), 2.39−2.14 (m, 11H); ^{13}C NMR, δ 166.46 (C═N), 148.06, 129.38 (CH), 127.33 (CH), 125.79 (CH), 45.70 (2C, CH_3), 43.92 (2C, CH_2), 41.47 (CH_2), 38.68 (2C, CH_2), 38.46 (2C, CH), 35.89, 28.03 (CH).

Reduction of 4-Ph. Sodium borohydride reduction as described above gave a mixture (96%) which was analyzed by means of GC-MS; both components had *m/z* $M^+ = 241$. The GC ratio was 33:67. ^{1}H NMR (C_6D_6), δ 7.36−7.09 (m, 5H), 2.45 and 2.41 (s and s, 1H, *E* and *Z*, respectively), 2.32 (s, 1H), 2.25 and 2.23 (s and s, 3H, *E* and *Z*, respectively), 2.16 (s, 1H), 2.11 (s, 1H), 1.91−1.32 (m, 11H); ^{13}C NMR, *E*-amine, 150.88, 128.44 (CH), 125.90 (CH), 125.23 (CH), 63.56 (CH), 43.89 (CH_2), 43.14 (2C, CH_2), 36.31, 34.07 (CH_3), 32.77 (2C, CH), 30.63 (2C, CH_2), 28.94 (CH); *Z*-amine, 150.88, 128.39 (CH), 125.82 (CH), 125.23 (CH), 63.21 (CH), 43.68 (CH_2), 37.07 (2C, CH_2), 36.66 (2C, CH_2), 36.09, 33.96 (CH_3), 33.00 (2C, CH), 29.02 (CH). The assignments of configuration were made as described in the text; the proton integrations both gave the *E*:*Z* ratio of 67:33.

Reduction of 5-Ph. The reduction in this case also produced a mixture in 97% yield which consisted of two components in a 32:68 ratio as shown by means of GC-MS; both had *m/z* $M^+ = 255$. ^{1}H NMR (C_6D_6), δ 7.39−7.10 (m, 5H), 2.42−2.25 (m, 2H), 2.13 and 2.10 (s and s, 6H, *E* and *Z*, respectively), 2.07−1.32 (m, 12H); ^{13}C NMR, *E*-amine, δ 150.87, 128.46 (CH), 125.92 (CH), 125.26 (CH), 69.53 (CH), 43.78 (CH_2), 43.18 (2C,CH_3), 42.98 (2C, CH_2), 35.84 (c), 30.99 (2C, CH), 30.76 (2C, CH_2), 28.81 (CH); *Z*-amine, δ 151.23, 128.36 (CH), 125.80 (CH), 125.26 (CH), 69.17 (CH), 43.48 (CH_2), 43.02 (2C, CH_3), 37.24 (2C, CH_2), 36.48 (2C, CH_2), 35.57, 30.91 (2C, CH), 28.43 (CH). The proton and GC analyses were in good agreement; the configurational assignments were made as described in the text.

Reduction with Lewis Acids. 5-Phenyladamantan-2-one was reduced with lithium borohydride and sodium borohydride in the presence of the various Lewis acids mentioned in the text, at temperatures from room temperature to −80 °C. The acids were obtained from Aldrich and used as received. The ketone (0.1 mmol) was dissolved in methylene chloride or 2-propanol (2−3 mL), and the acid (0.1 mmol) was added with stirring. Complex formation was confirmed by means of infrared spectra. The borohydride (20 mg) was dissolved in the same solvent and added slowly; stirring was continued for 2 h before quenching with aqueous ammonium chloride. After workup, the residues were examined by means of ^{1}H NMR and HPLC. In all instances, small enhancements in the *E*/*Z* ratio of alcohols were seen; in most cases, the two 2-chloro-5-phenyladamantanes and other side products were also present.

Reduction of Adamantanones with Charged 5-Substituents. 5-(*N*,*N*-Dimethylamino)-,[13] -hydroxy-,[1a] -methoxy-,[13] and carbomethoxyadamantan-2-ones[13,14] were synthesized as described in the references. The free carboxylic acid[14] was also prepared, as was the 5-trimethylammonium salt (by reaction of the amine with methyl iodide). All were reduced with sodium borohydride and the products analyzed as described in the text.

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Supporting Information Available: GC-MS and ^{1}H and ^{13}C NMR spectra of compounds **4**- and **5**-Ph and the corresponding alcohols (65 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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