Stereochemistry of Alkylation of α-Lithiopiperidines: Differing Effects of Formamidine and Urethane Activating Groups

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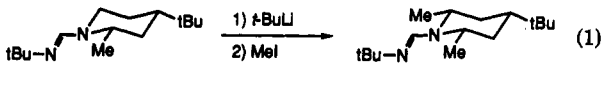
The stereochemistry of alkylation of α-lithio-*N*-(*N'-tert*-butylformimidoyl)-4-*tert*-butylpiperidines was studied. Monoalkylation proceeded to give equatorial 2-substituted piperidines, which in turn gave diequatorial 2,6-disubstituted piperidines when subjected to a second lithiation–alkylation procedure. The stereochemical result of the second alkylation is in contrast to α-lithio-2-substituted piperidines that are stabilized by the *N*-(*tert*-butoxycarbonyl) group; these gave the axial 6-substituted piperidine on treatment with electrophiles. A mechanistic rationalization of these results is given that invokes nonbonding interactions between the stabilizing groups and piperidine ring substituents.

The C-alkylation of amines α to nitrogen has been the subject of considerable effort among synthetic organic chemists.[1-3] One of the more generally applicable methods for this transformation is the metalation–alkylation of *N,N'*-alkyl formamides of secondary amines (eq 1) as reported earlier[2] from these laboratories. Recently, Beak[3] has reported that the *tert*-butoxycarbonyl group serves as an efficient activating group that allows facile α-lithiation of secondary amines (eq 2).



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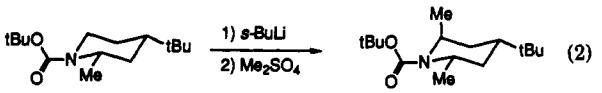


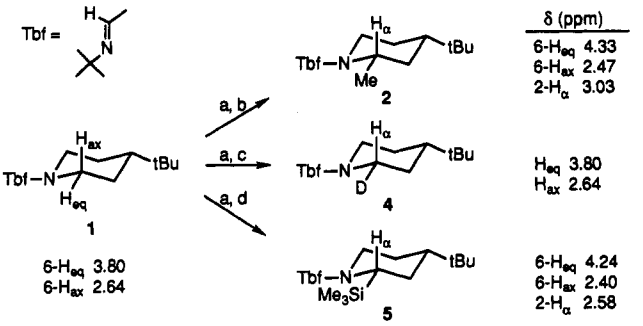
(2)

In his study of piperidine alkylations,[3a,c] Beak found that conformationally rigid 4-substituted piperidines alkylate initially in the equatorial 2-position, while subsequent alkylation occurs axially at the 6-position (eq 2). We reported[2b] earlier in our studies on formamidines an example in which only diequatorial substitution had taken place (eq 1). In order to better understand this apparent discrepancy and explore the generality of this substitution pattern, the present study was undertaken using *N*-(*N'-tert*-butylformimidoyl)-4-*tert*-butylpiperidine (**1**)[2b] as the substrate for sequential alkylations.

Metallation reactions of *N*-(*N'-tert*-butylformimidoyl)-4-*tert*-butylpiperidine (**1**) were carried out with use of an excess of *tert*-butyllithium in ether–THF, according to the earlier studies.[2b] The latter alkylation procedure was modified by the omission of HMPA and by maintaining the reaction mixture at −78 °C for an extended period after addition of the electrophile. This and a modified workup procedure (see Experimental Section) were found to produce useful yields of relatively clean material, free of added HMPA.

Under these conditions, simple, highly active electrophiles such as iodomethane, chlorotrimethylsilane, and deuteriomethanol were found to be effective traps for this α-lithiated derivative (Scheme I), while less active electrophiles such as *p*-anisaldehyde and allyl bromide gave complex mixtures of products. Thus, the 2-methyl **2**, 2-deuterio **4**, and 2-trimethylsilyl **5** formimidoylpiperidines were prepared in 88, 86, and 75% yields, respectively, and all demonstrated the same preference for equatorial products.

Scheme I[a]



[a] Key: a, *t*-BuLi/Et_2O–THF, −25 °C, 2 h; b, MeI/Et_2O, 88%; c, DOMe, 75%; d, Me_3SiCl, 86%.

The stereochemical assignments of formamidines **2**, **4**, and **5** were based on NMR evidence and chemical correlation with known compounds. It has been shown that axial protons in substituted cyclohexanes,[4] piperidines,[5] and quinolizidines[6] resonate at a higher field than their equatorial partners in substituted as well as unsubstituted cases. The vicinal coupling constants of these axial protons are characteristically near 3 (J_{ae}) and 12 Hz (J_{aa}) and can be distinguished from equatorial protons on the basis of the absence of the lower (3–4 Hz) diequatorial coupling constant.

For example, the proton (H_α) adjacent to the methyl group in **2** occurs at 3.03 ppm (ddq; J_{ae} = 2.7, J_{aa} = 10.9 Hz) and correlates more closely in terms of the chemical shift with the axial 6-proton of **2**, occurring at 2.47 ppm, than with the equatorial proton at 4.33 ppm. The downfield shift of the equatorial 6-proton (from 3.80 in **1** to 4.33 ppm in the case of **2**) has been shown to occur in certain *N* (electron-withdrawing)-substituted piperidines[5a-d] and

(1) (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (b) Logusch W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. (c) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (d) Katritzky, A. R.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 2571. (e) Ahlbrecht, M.; Kornetzky, D. *Synthesis* **1988**, 775.

(2) (a) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59 and references cited therein. (b) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.

(3) (a) Beak, P.; Lee, W.-K. *J. Org. Chem.* **1990**, *55*, 2578. (b) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, 1197. (c) Beak, P. Personal communication.

(4) (a) Eliel, E. L.; Gianni, M. H.; Williams, Th. H. *Tetrahedron Lett.* **1962**, 741. (b) Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 1053.

(5) (a) Fraser, R. R.; Grindley, T. B.; Passannati, S. *Can. J. Chem.* **1975**, *53*, 2473. (b) Chow, Y. L.; Colon, C. J. *Can. J. Chem.* **1968**, *46*, 2728. (c) Duquet, D.; Callens, R. E. A.; Borremans, F. A. M.; Anteunis, M. J. O. *Bull. Chem. Soc. Belg.* **1985**, *94*, 51. (d) Palasz, P. D.; Utley, J. H.; Hardstone, J. D. *Acta Chem. Scand.* **1984**, *B38*, 281. (e) Gossinger, E. *Monatsch. Chem.* **1982**, *113*, 339.

(6) (a) Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Lett.* **1965**, 2705. (b) Bohlmann, F.; Schumann, D. *Tetrahedron Lett.* **1965**, 2435.

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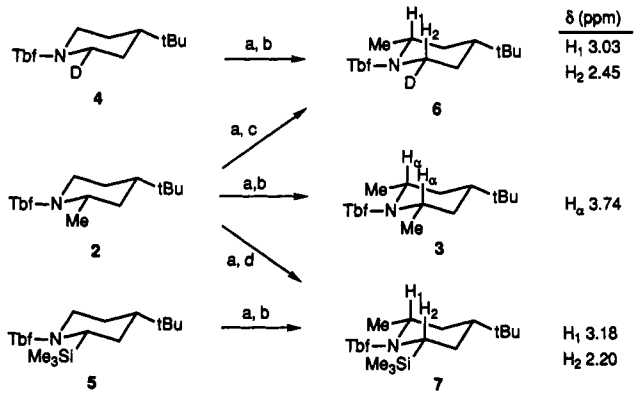
Scheme II[a]



[a] Key: a, *t*-BuLi/Et_2O–THF, −25 °C, 2 h; b, MeI/Et_2O; c, DOMe, d, Me_3SiCl. Yields: a, b (to give **6**), 81%; a, b (to give **3**), 75%; a, c (to give **6**), 93%; a, d (to give **7**), 97%; a, b (to give **7**), 45%.

related compounds.[6b] Similar chemical shift and vicinal coupling arguments can be made regarding the stereochemistry of silyl derivative **5**, in which the methine proton (H_α) at 2.58 ppm (dd, J_{ae} = 2.7, J_{aa} = 11.6 Hz) better resembles the axial methylene proton at 2.40 ppm than the equatorial methylene proton (C-6) at 4.24 ppm. In both cases, coupling constants are typical of axial protons coupled vicinally to a methylene group.

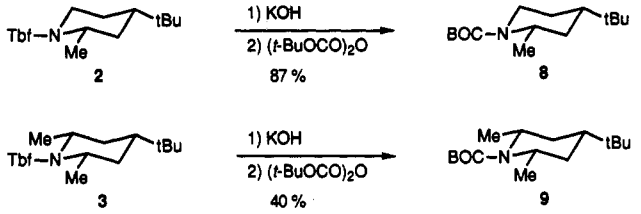
Further evidence of the assigned stereochemistry was made by the removal of the *tert*-butylformamidino group and introduction of the BOC group, providing a direct correlation with a result of Beak and Lee (vide infra).[3a]

The second alkylation (Scheme II) was performed with use of the same conditions as utilized for monoalkylation, with the order of electrophile addition being varied in order to test the effect of different groups on the alkylation stereochemistry. The results of these reactions are shown in Scheme II and consistently demonstrated the same preference for diequatorial alkylation. Thus, the same product **7** was obtained by silylation of the monomethylpiperidine **2** as by methylation of the silylpiperidine **5**, and those obtained by alternating deuteration and methylation (**6** and **3**, respectively) were also the same.

As with monoalkylated formimidoylpiperidines **2**, **4**, and **5**, a combination of spectroscopic and chemical evidence was used to assign the stereochemistry of alkylation of these dialkylated materials. In addition to chemical shift and vicinal coupling constant arguments, an NMR-discernable symmetry element (a plane of symmetry) was central to the assignment of dimethylpiperidine **3**. In this case, the symmetry of the molecule should simplify the proton and carbon NMR spectra by introducing degeneracy among the resonances of symmetrical atoms; this was indeed observed. For example, the ^{13}C DEPT spectrum (135° tip angle) of **3** demonstrated only one methylene (CH_2) group at 31.60 ppm, corresponding to the two symmetrically equivalent ring methylenes. In the proton spectrum of **3**, the methine protons showed a single resonance (3.74 ppm, dq, J_{aa} = 13.8 Hz) having coupling constants and a chemical shift typical of such angular protons, thus fixing the configuration of the methyl groups as equatorial.

Regarding the unsymmetrical alkylation products **6** and **7**, chemical shift data were also consistent with equatorial substitution, taking into account their respective field effects such as the downfield shift of the silyl α-proton of **7** to 2.20 ppm. Vicinal couping constants are also in the range expected for axial protons (J_{aa} large, J_{ae} small) with the exception of the 2-methyl-6-silyl derivative **7**, in which

Scheme III



they are shifted to the intermediate values of 4.0 and 5.9 Hz. Furthermore, treatment of silylpiperidine **5** with *t*-BuLi under the conditions for alkylation at −78 °C followed by an aqueous quench resulted in a high recovery of unchanged **5**, thus precluding any base-induced epimerization of the silyl group. A slight change in the conformation of the piperidine ring of **7** with the bulky α-silyl substituent may account for the observed coupling,[5a] though the exact nature of such a conformation is presently unknown.

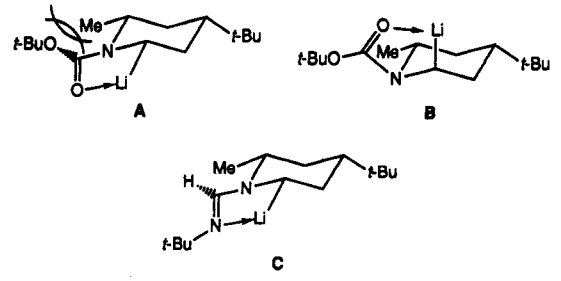
To further substantiate the stereochemical assignment, chemical correlation was established with two of the methylated piperidines described earlier by Beak.[3a] Hydrolysis of the formamidino groups of the mono- and dimethylated piperidines **2** and **3** followed by introduction of the BOC group[7] gave **8** and **9** corresponding to the derivatives reported by Beak (Scheme III). Although **8** was identical with Beak's monomethyl urethane, **9** did not correspond to his reported dimethylated BOC derivative.

The proton and carbon-13 NMR spectra of these BOC derivatives, **8** and **9**, confirms that the initial formamidine substitution occurred to give equatorial products whereas the second alkylation also gave equatorial products. In the latter case, single resonances for **9** were observed for the methyl groups and piperidine ring atoms bisected by the plane of symmetry, that is, the methine and methylene carbons and attached protons. In the proton NMR, a single methyl group and methine proton were seen (1.19 ppm, d, 6 H; 4.12 ppm, dq, 2 H) for diequatorial compound **9**, while Beak's 2-equatorial-6-axial dimethyl derivative (eq 2) showed two signals corresponding to each of these structural features (CH_3, 1.12, 1.23 ppm; CH, 3.56, 4.10 ppm). The same result was seen in the carbon NMR and DEPT experiments with the overall number of resonances for the diequatorial compound **9** reduced by three due to the symmetry element (to 9 resonances), while Beak's unsymmetrical dimethyl BOC piperidine gave 12 resonances.[3a]

To account for the diequatorial products of formamidines and the equatorial–axial products of the BOC derivatives, we may offer an explanation of these results in terms of the differing steric requirements for the stabilizing groups. In the BOC system, coordination of the carbonyl oxygen to the lithium atom requires an orientation by the *tert*-butyl group of BOC in which contact can occur between it and the equatorial methyl group A. This destabilizing interaction makes the generation of an axial lithio species B more favorable, resulting in alkylation that is generally accepted to proceed with retention producing the axial methyl product.

In the case of the *tert*-butylformamidine C, the *tert*-butyl group resides on a nitrogen that is on the same side of the molecule as the lithio carbanion and is, therefore, quite distant from the 6-methyl substituent. Furthermore, only the hydrogen on the imine is in proximity to the 6-methyl substituent, which is of minor steric concern. Equatorial alkylation is now possible, leading to the ob-

(7) Bhat, K. L.; Flanagan, D. M.; Joullie, M. M. *Synth. Commun.* **1985**, *15*, 587.



served diequatorial products. It should be noted that these considerations ignore any role played by coordinating solvent molecules or aggregation among different lithiated species. These would appear to have little effect on the disposition of the bulky *tert*-butyl groups, given the requirement of lithium–heteroatom coordination in each case.

With the discovery of these interesting and complementary steric effects, it is now possible to choose the relative stereochemistry of alkylation reactions α to nitrogen in more complex systems. In order to apply this effect to an asymmetric synthetic scheme, such systems would be governed by two considerations, namely, the rigidity of the nitrogen-containing ring (to prevent inversion) and the preexistence of substitution in the α′ position (to control regiochemistry as well as to bias the stereochemistry).

Experimental Section

Solvents used in these experiments were prepared by refluxing over the appropriate drying agent with storage over molecular seives (3 Å) under a blanket of argon. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled under argon from calcium hydride (CaH_2). Diethyl ether and tetrahydrofuran were distilled under an atmosphere of argon from sodium–benzophenone ketyl. Chromatographic solvents (hexanes, ether) were redistilled prior to use. Aldrich Grade 951 silica gel refers to item 34,333-1, silica catalyst support. Metalation–alkylations were routinely carried out under a positive pressure of argon that had been passed through a calcium sulfate drying tube and a deoxygenation column consisting of a BASF copper-based catalyst operating at 200–220 °C and stirred by means of a Teflon-coated magnetic stirring bar, unless otherwise noted.

***N*-(*N*′-*tert*-Butylformimidoyl)-2-methyl-4-*tert*-butylpiperidine (2).** Into a flame-dried 50-mL round-bottom flask equipped with a magnetic stirring bar was weighed 1.911 g (8.51 mmol) of formimidoylpiperidine 1,[2b] which was then degassed by two evacuation–argon purge cycles by use of a vacuum dessicator, followed by flushing with deoxygenated argon through a syringe needle. The starting material was dissolved in 14.3 mL of diethyl ether and 3.6 mL of tetrahydrofuran and cooled to below −78 °C with an acetone–dry ice bath, and 6.7 mL (13 mmol, 1.5 equiv) of a 1.9 M solution of *tert*-butyllithium in pentanes (Aldrich) was added. This resulted in the formation of a yellow-white precipitate that dissolved when the cooling bath was replaced with a CCl_4–dry ice bath (−25 °C). During 2 h at −25 °C, a yellow-white precipitate again formed and the reaction mixture was cooled to below −78 °C prior to addition of the electrophile. Methyl iodide (Fisher) was passed through a plug of basic alumina (Aldrich, Brockmann I), and 1.6 mL (26 mmol, 3.0 equiv) was taken in a flame-dried round-bottom flask, dissolved in 2 mL of diethyl ether, cooled to below −78 °C, and added to the reaction mixture by rapid cannulation. Immediate whitening and thickening of the reaction mixture was observed, and the reaction was stirred 12 h under argon at −73 to −78 °C (Neslab Cryocool).

The reaction mixture was transferred into 150 mL of hexanes in a separatory funnel and the remaining white solid treated with a few milliliters of a 4:1 mixture of saturated sodium chloride solution and water, made 2 N in NaOH by the addition of solid NaOH, and rinsed in with hexanes. The organic layer contained a copious white precipitate that was digested by the addition of 10 mL of basic brine and vigorous shaking. The organic layer was washed with an additional 5 mL of basic brine, and the aqueous layer was back-extracted with a little hexanes. Drying (Na_2SO_4) of the organic phase, filtration, and concentration to 0.2 mmHg provided 1.9894 g (98.0%) of a very pale gold oil that was determined by integration of formamidine protons in the proton NMR to consist of 90% of the desired material, 6% recovered starting material, and 3% of an unidentified substance, assumed to be the single-electron reduction product.[2b]

Purification of the desired material was accomplished by column chromatography as follows. A sample (1.35 g) of the crude mixture of products was applied to a column of silica gel (60 g, Aldrich grade 951) that had been deactivated as a slurry with triethylamine (5% v/v in hexanes) and rinsed with 50 mL of 2.5% triethylamine in hexanes, eluting with same. The desired material eluted later than the starting material; concentration of the appropriate fractions (^1H NMR assay) afforded 792.8 mg of **2** having a purity of 97% by ^1H NMR assay, contaminated with starting material, as a clear colorless oil: IR (CH_2Cl_2) 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.85 (s, 9 H), 1.15 (s, 9 H), 1.32 (d, 3 H, J = 6.5 Hz), 2.47 (m, 1 H), 3.03 (ddq, 1 H, J = 2.7, 6.4, 10.9 Hz), 4.33 (m, 1 H), 7.62 (s, 1 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 32.16, 53.25, CH 46.48, 53.90, 147.79, CH_2 25.54, 36.59, 43.95, CH_3 19.88, 27.24, 31.31. Attempts to purify this material by other means such as radial chromatography or column chromatography with TLC grade silica gel (Merck Silica Gel G) led to decomposition of the formamidine. Fractional distillation was attempted by use of a 6-in. Vigreux column at reduced pressure, though the first drop of distillate showed no enrichment in either component of the mixture. Repeated chromatography as described previously led to the recovery of material having a purity of 99% by analytical GLC. Anal. Calcd for $C_{15}H_{30}N_2$: C, 75.57; H, 12.68; N, 11.75. Found: C, 75.32; H, 12.53; N, 11.74.

***N*-(*N*′-*tert*-Butylformimidoyl)-2,6-dimethyl-4-*tert*-butylpiperidine (3).** By the same procedure employed for the preparation of monomethylformimidoylpiperidine **2**, 300.8 mg (1.26 mmol, 1.0 equiv) of piperidine **2** was treated with 0.90 mL (1.9 mmol, 1.5 equiv) of a 2.1 M solution of *tert*-butyllithium in pentane (Aldrich), followed by addition of 0.24 mL (3.9 mmol, 3.0 equiv) of methyl iodide in 0.5 mL of dry diethyl ether.

Workup, followed by filtration through a plug of silica gel (1 g, Aldrich Grade 951) deactivated with 5% triethylamine in hexanes and eluted with same, gave 302.2 mg of crude material consisting of 80% of the desired dimethylpiperidine (76% overall yield), along with 14% of recovered starting material and 6% of the electron transfer reduction product,[2b] *cis*-4-*tert*-butyl-6-methyl-3,4,5,6-tetrahydropyridine (^1H NMR assay of formamidine C*H* singlets). A cleaner sample of the desired product (98.6% by analytical GLC) and an enriched sample of the tetrahydropyridine were obtained by repeated chromatography on silica gel, first with 15 g of silica (Aldrich Grade 951) deactivated and eluted with 3% triethylamine in hexanes followed by chromatography of enriched fractions (250 mg; 94% **3** by GLC) on 20 g silica gel as previously. In this way, 134.6 mg (42.3%) of **3** was obtained: IR (CH_2Cl_2) 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.84 (s, 9 H), 1.15 (s, 9 H), 1.23 (d, 6 H, J = 6.7 Hz), 3.74 (dq, 2 H, J = 6.9, 13.8 Hz), 7.35 (s, 1 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 31.96, 52.97, CH 42.15, 50.33, 149.59, CH_2 31.60, CH_3 24.60, 26.98, 31.30. Anal. Calcd for $C_{16}H_{32}N_2$: C, 76.13; H, 12.78; N, 11.10. Found: C, 76.10; H, 12.99; N, 11.23.

The major resonances of the tetrahydropyridine were discernable in the proton NMR of appropriate fractions: ^1H NMR ($CDCl_3$, 300 MHz, $CDCl_3$ = 7.240 ppm) δ 0.86 (s, 9 H), 1.15 (s, 9 H), 1.38 (d, 3 H, J = 6.3 Hz), 3.55 (ddq, 1 H, J = 3.0, 6.2, 11.4 Hz), 4.77 (dm, 1 H, J = 8.4 Hz), 6.92 (dd, 1 H, J = 2.5, 8.5 Hz), 7.55 (s, 1 H).

***N*-(*N*′-*tert*-Butylformimidoyl)-2-deuterio-4-*tert*-butylpiperidine (4).** By the same procedure used for the preparation of methylpiperidine **2**, 402.9 mg (1.80 mmol, 1.0 equiv) of formimidoylpiperidine **1** was treated with 1.1 mL (2.6 mmol, 1.5 equiv) of a 2.4 M solution of *tert*-butyllithium in pentanes (Aldrich). The lithio derivative was quenched at −78 °C by the direct addition of deuteriomethanol (Aldrich 99.5%, 0.4 mL, 9.8 mmol, 5.5 equiv) and stirred in the cold for 30 min, whereupon workup gave 374.5 mg of the crude product. Proton NMR analysis of the crude material showed the presence of a small amount of the free

base resulting from hydrolysis of the formamidine. Chromatography on silica gel (15 g, Aldrich Grade 951) deactivated with 5% triethylamine in hexanes, eluting with the same solvent mixture followed by 25% ether in hexanes (5% triethylamine), gave 302.0 mg (74.6%) of the desired material as a clear, colorless oil. Proton NMR analysis of this material showed the presence of 12% of undeuterated material by integration of the equatorial (1 H) and axial (2 H) protons: IR (CH_2Cl_2) 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.86 (s, 9 H), 1.16 (s, 9 H), 2.63 (app t, 2 H, J = 11.8 Hz), 3.79 (dm, 1.1 H, J = 14.1 Hz), 7.29 (s, 1 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 31.96, 52.50, CH 45.73 (t, J = 20.8 Hz), 46.84, 150.00, CH_2 26.15, 26.28, 46.07, CH_3 27.05, 31.02.

***N*-(*N'-tert*-Butylformimidoyl)-2-(trimethylsilyl)-4-*tert*-butylpiperidine (5).** By the same procedure used for the preparation of the mono- and dimethylpiperidines **2** and **3**, 400.9 mg (1.787 mmol, 1.0 equiv) of formimidoylpiperidine **1** was treated with 1.1 mL (2.6 mmol, 1.5 equiv) of a 2.4 M solution of *tert*-butyllithium in pentanes (Aldrich). Addition of chlorotrimethylsilane (0.68 mL, 5.4 mmol, 3.0 equiv) to the reaction mixture at −78 °C and stirring at −78 °C overnight was followed by workup as described previously. This yielded 487.2 mg of the crude product (R_f = 0.7; 5% Et_3N in hexanes; R_f starting material = 0.3 with streaking), which was purified by column chromatography on silica gel (24 g, Aldrich Grade 951), deactivated with 5% triethylamine in hexanes, washed, and eluted with 2% triethylamine in hexanes. In this way was obtained 455.5 mg (86.0%) of the desired material as a clear, colorless oil: IR (CH_2Cl_2) 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.13 (s, 9 H), 0.84 (s, 9 H), 0.9–1.2 (m, 3 H), 1.15 (s, 9 H), 2.40 (dd, 1 H, J = 2.1, 12.2 Hz), 2.58 (dd, 1 H, J = 2.7, 11.6 Hz), 4.24 (dm, 1 H, J, = 12.1 Hz), 7.40 (s, 1 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 32.36, 52.94, CH 48.70, 51.26, 149.23, CH_2 25.92, 27.68, 47.03, CH_3 −1.29, 27.12, 31.35. Anal. Calcd for $C_{17}H_{36}N_2Si$: C, 68.85; H, 12.24; N, 9.45. Found: C, 68.58; H, 12.34; N, 9.50.

***N*-(*N'-tert*-Butylformimidoyl)-2-deuterio-4-*tert*-butyl-6-methylpiperidine (6). (a) By the Methylation of Deuteriopiperidine 4.** By the utilization of the procedure for the preparation of methylpiperidine **2**, 213.6 mg (0.9464 mmol, 1.0 equiv) of deuteriopiperidine **4** was treated with 0.59 mL (1.4 mmol, 1.5 equiv) of a 2.4 M solution of *tert*-butyllithium in pentanes (Aldrich) and alkylated with 0.18 mL (2.9 mmol, 3.0 equiv) of methyl iodide in 0.5 mL of diethyl ether. Workup followed by filtration through a plug of silica gel (1 g, Aldrich Grade 951) deactivated and eluted with 5% triethylamine in hexanes provided 203.4 mg (89.6%) of crude material consisting of 90% of the desired product along with 7% recovered starting material and 3% of the single electron transfer reduction product[2b] (integration of formamidine singlets, ^1H NMR). Integration of the axial and equatorial protons indicated the presence of 5.3% of the undeuterated methylpiperidine **1**: IR (CH_2Cl_2) 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.85 (s, 9 H), 1.32 (d, 3 H, J = 6.5 Hz), 1.56 (s, 9 H), 2.45 (dm, 1 H, J = 10.0 Hz), 3.03 (ddq, 1 H, 2.6, 6.5, 11.0 Hz), 4.33 (m, 5 × 10^{-2} H), 7.61 (s, 1 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 32.15, 53.20, CH 43.70 (t, J = 21.3 Hz), 43.98, 53.87, 147.77, CH_2 25.43, 36.59, CH_3 19.85, 27.22, 31.30.

(b) By the Deuteration of Methylpiperidine 2. By the same method used for the preparation of methylpiperidine **2**, 185.5 mg (0.78 mmol, 1.0 equiv) of deuteriopiperidine **4** was treated with 0.67 mL (1.2 mmol, 1.5 equiv) of a 1.75 M solution of *tert*-butyllithium in pentanes (Aldrich) and deuterated by the direct addition of 0.10 mL (2.5 mmol, 3.2 equiv) of deuteriomethanol at −78 °C. Workup after 20 min at −78 °C and filtration through a plug of silica gel (2 g, Aldrich grade 951) deactivated and eluted with 5% triethylamine in hexanes provided 173.8 mg (93.3%) of the desired material as a clear, colorless oil, which contained 7% of the undeuterated (starting) material by integration of the axial and equatorial protons in the NMR spectrum. The proton NMR spectrum of this material corresponded in all respects to the material prepared by method (a) described previously for the methylation of deuteriopiperidine **4**.

***N*-(*N'-tert*-Butylformimidoyl)-2-(trimethylsilyl)-6-methyl-4-*tert*-butylpiperidine (7). (a) By the Silylation of Monomethylpiperidine 2.** By the same method used for the preparation of monomethylpiperidine **2**, 245.3 mg (1.03 mmol, 1.0 equiv) of monomethylpiperidine **2** was treated with 0.64 mL (1.5 mmol, 1.5 equiv) of a 2.4 M solution of *tert*-butyllithium in pentanes (Aldrich). Silylation was accomplished by the direct addition of chlorotrimethylsilane to the reaction mixture at −78 °C followed by overnight stirring at the same temperature.

Workup and filtration through a plug of silica gel (1 g, Aldrich Grade 951) deactivated and eluted with 5% triethylamine in hexanes provided 308.3 mg (96.5%) of material, which was homogeneous by analytical TLC (silica; 2% Et_3N in hexanes, R_f = 0.6); IR (CH_2Cl_2) 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.05 (s, 9 H), 0.7–0.9 (m, 1 H), 0.82 (s, 9 H), 1.11 (s, 9 H), 1.2–1.4 (m, 2 H), 1.30 (d, 3 H, J = 6.9 Hz), 2.20 (dd, 1 H, J = 4.0, 5.9 Hz), 3.18 (ddq, 1 H, J = 2.7, 6.8, 11.0 Hz), 7.31 (s, 1 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 32.51, 53.72, CH 48.97, 52.52, 57.68, 145.36, CH_2 23.69, 35.99, CH_3 0.38, 20.66, 27.23, 31.21. Anal. Calcd for $C_{18}H_{38}N_2Si$: C, 69.61; H, 12.33; N, 9.02. Found: C, 69.71; H, 12.43; N, 9.14.

(b) By the Methylation of Silylpiperidine 5. By the same method used for the preparation of monomethylpiperidine **2**, 253.6 mg (0.8551 mmol, 1.0 equiv) of silylpiperidine **5** was treated with 0.53 mL (1.3 mmol, 1.5 equiv) of a 2.4 M solution of *tert*-butyllithium in pentanes (Aldrich). The reaction mixture was treated with methyl iodide (0.16 mL, 2.6 mmol, 3.0 equiv) in 0.5 mL of dry diethyl ether at −78 °C and stirred overnight at −78 °C. Workup afforded 268.8 mg of crude material that was determined (^1H NMR) to consist of roughly equal amounts of the methylated material and starting silylpiperidine along with several unidentified minor components. Gas chromatographic analysis showed the two major components to comprise 91% of the total composition of the mixture.

***N*-(*tert*-Butoxycarbonyl)-2-methyl-4-*tert*-butylpiperidine (8).** In a 25-mL round-bottom flask was taken 408 mg (^1H NMR assay; 85%, 1.45 mmol) of 2-methylformimidoylpiperidine **2**, which was dissolved in 15 mL of a 2:1 MeOH–H_2O solution and to which was added 1.1 g (Baker 87.5%, 17 mmol, 12 equiv) of solid KOH. The reaction mixture became heterogeneous upon heating (oil bath, 55 °C) and was stirred overnight in a closed vessel purged with argon.

The reaction mixture was cooled and extracted with three 15-mL portions of methylene chloride, which were diluted with 50 mL of hexanes prior to drying (Na_2SO_4) and concentration. The resulting gold oil (270.8 mg, 102% of theoretical yield) was used in the next step without further purification: ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.85 (s, 9 H), 1.07 (d, 3 H, J = 6.3 Hz), 1.65 (m, 2 H), 2.58 (m, 2 H), 3.13 (m, 1 H).

The crude piperidine described previously (ca. 1.71 mmol) was added to a dry round-bottom flask and dissolved in 1.1 mL of dry methylene chloride and 0.48 mL (3.4 mmol, 2.0 equiv) of dry triethylamine. The resulting solution was cooled with an ice–acetone bath (−10 °C), and 460 mg (2.11 mmol, 1.2 equiv) of di-*tert*-butyl dicarbonate (Aldrich) was added in a single portion. The reaction was left to stir overnight and warm to room temperature, whereupon saturated aqueous citric acid (1 mL) was added and the reaction mixture diluted with methylene chloride (40 mL). Water (5 mL) was added to wash the organic phase, followed by brine (5 mL) and drying (Na_2SO_4) prior to concentration, which afforded 460 mg of crude material.

The desired material was isolated by column chromatography on silica gel (20 g, Aldrich Grade 951), eluting with 5% ether in hexanes initially, followed by 10% ether in hexanes. The material exhibited an R_f of 0.15 (silica; 10% ether in hexanes, visualized by *p*-anisaldehyde in ethanol with mild heating) and 321.7 mg (86.6% over two steps, based on 85% starting material purity) was obtained as a clear colorless oil having spectral characteristics identical with those described by Beak:[3c] IR (CH_2Cl_2), 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.84 (s, 9 H), 1.14 (d, 3 H, J = 6.2 Hz), 1.46 (s, 9 H), 2.90 (dq, 1 H, J = 5.9, 10.8 Hz), 3.78 (m, 2 H); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 32.23, 78.71, 155.23, CH 41.73, 50.25 CH_2 24.53, 30.94, 36.89, CH_3 19.89, 26.88, 28.47.

***N*-(*tert*-Butoxycarbonyl)-2,6-dimethyl-4-*tert*-butylpiperidine (9).** In a 25-mL round-bottom flask was added 167 mg (^1H NMR assay; 80.5%, 0.53 mmol) of 2,6-dimethylformimidoylpiperidine **3**, which was dissolved in 6 mL of a 2:1 MeOH–H_2O solution and to which was added 0.42 g (Baker 87.5%,

6.5 mmol, 12 equiv) of solid KOH. The reaction mixture became hetereogeneous upon heating (oil bath, 55 °C) and was stirred overnight in a closed vessel purged with argon.

The reaction mixture was cooled and extracted with three 10-mL portions of methylene chloride, which were diluted with 30 mL of hexanes prior to drying (Na_2SO_4) and concentration. The resulting gold oil (97.9 mg, 108% of theoretical yield) was used in the next step without further purification: ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.85 (s, 9 H), 1.09 (d, 6 H, J = 6.3 Hz), 1.63 (m, 2 H), 2.64 (dq, 2 H, J = 2.3, 6.2 Hz).

The crude piperidine described previously (ca. 0.53 mmol) was added to a dry round-bottom flask and dissolved in 0.5 mL of dry methylene chloride and 0.16 mL (1.15 mmol, 2.2 equiv) of dry triethylamine. The resulting solution was cooled with an ice-acetone bath (-10 °C), and 156 mg (0.715 mmol, 1.3 equiv) of di-*tert*-butyl dicarbonate (Aldrich) was added in a single portion. The reaction was left to stir overnight and warm to room temperature, whereupon saturated aqueous citric acid (1 mL) was added and the reaction mixture diluted with methylene chloride (30 mL). Water (5 mL) was added to wash the organic phase, followed by brine (5 mL) and drying (Na_2SO_4) prior to concentration, which afforded 188 mg of crude material.

The desired material was isolated by column chromatography on silica gel (10 g, Aldrich Grade 951), eluting with 5% ether in hexanes initially, followed by 10% ether in hexanes. The desired material demonstrated an R_f of 0.15 (SiO_2; 10% ether in hexanes, visualized by *p*-anisaldehyde in ethanol with mild heating), and 57.9 mg (40.4%, based on 80.5% starting material purity over two steps) were obtained as a clear colorless oil: IR (CH_2Cl_2) 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, Me_4Si = 0.00 ppm) δ 0.82 (s, 9 H), 1.45 (s, 9 H), 1.19 (d, 6 H, J = 6.7 Hz), 1.95 (m, 2 H), 4.12 (dq, 2 H, J = 7.0 Hz); ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz, $CDCl_3$ = 77.00 ppm) δ C 31.92, 78.77, 155.41, CH 41.61, 47.65, CH_2 30.97, CH_3 24.73, 26.92, 28.55. Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.43; H, 11.59; N, 5.16.

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Zwitterionic Quaternary Ammonium Alkoxides: Organic Strong Bases

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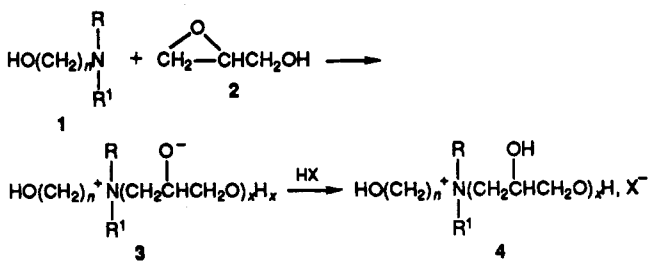
Stable quaternary ammonium alkoxides, a new type of organic strong base, were obtained from unhindered tertiary alkanolamines and glycidol. At elevated temperatures, the 2-hydroxyethyl derivatives underwent intramolecular rearrangements and deoxyalkylation to form tertiary amine terminated 1,4-poly(3-hydroxyoxetanes). Demethylation was also observed. The 3-hydroxypropyl derivative underwent disproportionation and Hofmann elimination in addition.

Bases play a very important role in organic chemistry as reagents and catalysts. In earlier work, we[1] and others[2] observed the formation of strong bases from reactions of tertiary alkanolamines **1** and epoxides. We have now characterized the addition compounds derived from **1** and glycidol (**2**) as monomeric and oligomeric zwitterionic quaternary ammonium alkoxides **3** and report their preparation and properties. As potential substitutes for alkali metal alkoxides, they are easily prepared without evolution of hydrogen and their water solubility facilitates separation from organic substrates. Addition compounds have been postulated as intermediates in the amine-catalyzed polymerization of epoxides,[3,4] but only one isolation has been reported.[5] A hexane-insoluble substance obtained from the reaction of 1,2-epoxyoctane with **1a** at 75 °C was assigned a quaternary ammonium alkoxide structure on the basis of identification of its thermal decomposition products.

Results and Discussion

Formation of **3** from alkanolamines and glycidol, an exothermic reaction, was readily followed by the appearance of quaternary methyl groups in the ^1H NMR spectra and quantified by titration (Table I). Neutralization with HCl enabled isolation and characterization of the major product as the chloride salt (**4**, x = 1, X = Cl). The balance of products were di- and triglycidyl ethers of **3** (x > 1) in which the ether linkages were predominantly 1,4.[6] No O-alkylated amines were formed, thus the strong base content measures the percent quaternization and also provides an average value of x.



The percent of quaternization was dependent on the structure of the amine. Both increasing the number of 2-hydroxyethyl groups and substitution of 3-hydroxypropyl for 2-hydroxyethyl decreased the percent of quaternization.

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(1) Buriks, R. S.; Lovett, E. G. *J. Org. Chem.* **1987**, *52*, 5247.
(2) McKelvey, J. B.; Benerito, R. R.; Ward, T. L. *Ind. Eng. Chem. Prod. Res. Dev.* **1967**, *6*, 115.
(3) Shechter studied the catalysis of many glycidyl ether reactions. Shechter, L.; Wynstra, J. *Ind. Eng. Chem.* **1956**, *45*, 86.
(4) Vasquez, A.; Matějka, L.; Spaček, P.; Dušek, K. J. *Polym. Sci. Polym. Chem. Ed.* **1990**, *28*, 2305.
(5) Tobler, E. *Helv. Chim. Acta* **1969**, *52*, 408.
(6) Vandenberg, E. E. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 915.

0022-3263/91/1956-2755$02.50/0