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α-Alkyl-α-aminosilanes. 2. A ^{2}H NMR Study of Organolithium Stabilization by Silicon and by Phenyl in Solution

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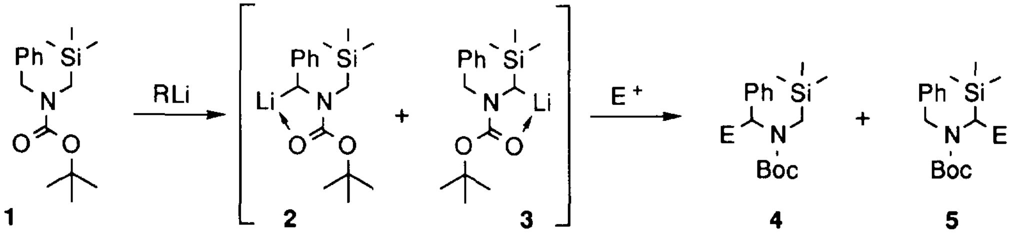
Abstract: *tert*-Butyl *N*-phenylmethyl-*N*-trimethylsilylmethyl carbamate is metalated at two positions: alpha to silicon and alpha to phenyl. The ratio of these metalation products was followed by deuteration and deuterium NMR. Kinetic deprotonation slightly favors the α-silyl anion but equilibrating conditions strongly favors the α-phenyl anion. Copyright © 1996 Elsevier Science Ltd

Silicon has long been known to stabilize α-carbanions, an effect initially ascribed to pπ-dπ bonding but now considered to be a result of polarization and negative hyperconjugation.[1,2] Carbanions alpha to silicon find many applications in synthesis, most notably the Peterson olefination[3], and occasionally an unanticipated metalation alpha to silicon has been reported.[4]

During a study of a metalation-alkylation sequence for the synthesis of α-alkyl-α-aminosilanes,[5] we prepared *tert*-butyl *N*-phenylmethyl-*N*-trimethylsilylmethyl carbamate **1** and studied its metalation chemistry. During this study we observed that metalation occurred alpha to both the phenyl group and the trimethylsilyl group, apparently in a ratio of 1:1 (vide infra), and gave a mixture of products **4** and **5**, the ratio of which varied with the electrophile.[5] We postulated that anions **2** and **3** might undergo equilibration under some of the alkylation conditions.

Studies by a number of groups have quantified the acidifying effect of silicon, both in the gas phase and in solution, and the observed values have been compared to the effect of a phenyl group. We are not aware of any case comparing phenyl and silicon in the same molecule. It was therefore of interest to know,



Scheme 1. Metalation of **1** occurs competitively next to phenyl and silicon.

from a synthetic standpoint as well as from a more fundamental vantage, what the kinetically derived ratios of **2** and **3** were and where the equilibrium ratio lay. As part of this investigation, we also wished to determine if the postulated equilibration occurred intermolecularly or could be occurring intramolecularly. Compound **1** proved to be an excellent substrate for these studies as it could withstand metalation and equilibration conditions without noticeable decomposition. For reasons that will be outlined below, we chose to study this chemistry using deuteration of the anions, and deuterium NMR to quantify the results.

BACKGROUND

Anion stabilization by Silicon. Calibration of silicon's ability to acidify adjacent protons has been addressed by a number of groups and in some cases compared to the acidity of protons adjacent to a phenyl group. In the gas phase, the acidity of tetramethylsilane has been determined by several different methods including pulsed FTICR and flowing afterglow techniques.[6] In all gas phase cases where a phenyl group has been compared with a trimethylsilyl group, the phenyl group stabilizes a carbanion to a greater degree. For example, Brauman et al. have used electron photodetachment and found the electron affinities of the trimethylsilylmethyl radical to be greater than that of the benzyl radical by 2 kcal/mol.[7]

In solution, acidities are heavily influenced by environmental effects that include solvation and the counter ion. An early study and provocative study by Eaborn[8] compared the effect of three trimethylsilyl groups (**6**) with three phenyl groups (**7**), measuring the rate of tritium loss on treatment with aqueous potassium hydroxide in DMSO. Under these conditions, **6** loses tritium 5-7 fold faster than **7**.

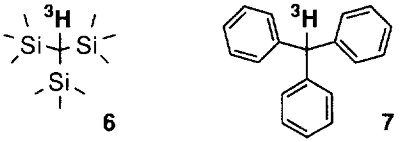


Figure 1. Under basic conditions, **6** loses tritium faster than **7** by a factor of 5-7.[8]

The acidity of silylated fluorenes **9** - **11** have been studied by two groups.[9,10] Bordwell found **9** and **10** to be more acidic in DMSO than the parent fluorene **8** by 2.2 kcal/mol, while the triphenylsilyl group had a greater effect (5.9 kcal/mol).[2] In terms of p*K*a units, 9-trimethylsilylfluorene was found to have a p*K*a of 21.7, compared to 22.6 for **8**. Phenyl is even more stabilizing: **12** has a p*K*a of 17.9.[10] Under similar conditions, sulfones **13** and **14** were found to be more acidic than the parent methyl phenyl sulfone by 4.2 and 12.5 kcal/mol, respectively.[2]

Streitweiser et al.[9] found that trimethylsilyl substitution lowered the p*K*a of a fluorenyl anion in THF by only 1 unit (**9** versus **8**). With the more localized charge in benzyltrimethylsilane **15**, the effect of silicon is greater and the p*K*a is lowered by 3.4 units relative to toluene. Similar results were found for 2-trimethyl-

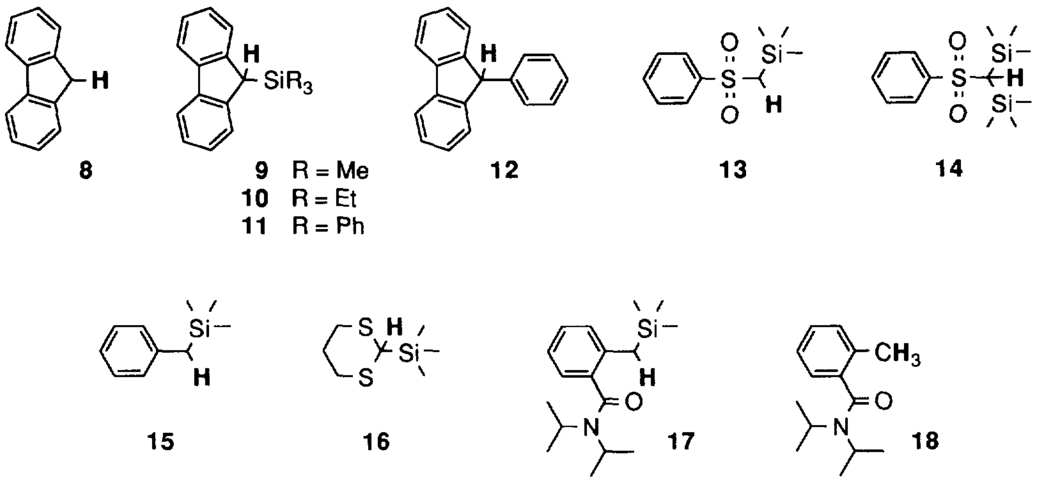
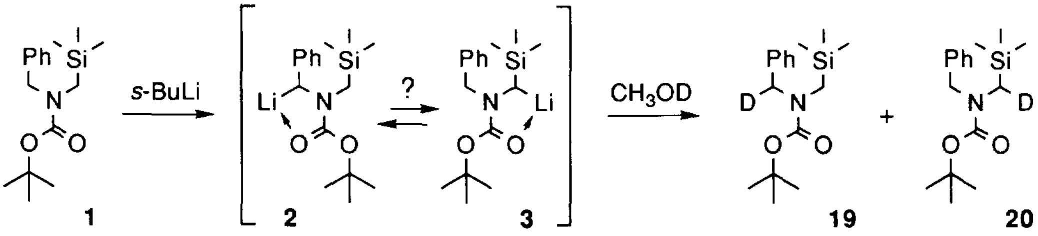


Figure 2. Substrates used to study acidification due to substitution of a trialkylsilyl group.

silyl-1,3-dithiane **16** relative to the parent 1,3-dithiane. In a related study, Miah and Fraser[11] reported p*K*a values for amides **17** and **18**, finding that the silane lowered the p*K*a of **17** by 4.3 units relative to **18**.

Deuterium NMR. In considering methods for directly quantifying the ratio of anions **2** and **3**, we elected to employ the deuteron, as the most reactive and quantitative of electrophiles (after the proton). The α-phenyl and α-silyl methylene groups in **1** (and **19** and **20**) are well separated in the proton NMR and could be simply integrated (see Figure 3A). Proton integration is this system is, however, of inherently low precision as the measurement involves the reduction of four proton signals to at most three protons (100% deuterium incorporation). At 100% deuterium incorporation (Scheme 2), a ratio of 3:1 for **19**:**20** would involve measuring a proton integration ratio of 1.25:1.75, or 42:58. If deuterium incorporation was only 50% this ratio deteriorates to 1.63:1.88, or 46:54. A ratio less pronounced than 3:1 would be proportionately more difficult to measure.



Scheme 2. Deuteration of metalation intermediates **2** and **3**.

An alternative to proton integration is to directly integrate the deuterium in the product.[12-14] Although the deuteron is a less sensitive NMR nucleus than the proton by a factor of 100, it is routinely available using the lock coils of almost any spectrometer. Natural abundance of deuterium is very low (0.015%), and so the ratio of **19**:**20** can directly measured. Chemical shifts within the deuterium NMR spectra are nearly identical to the proton spectra[15] and therefore assignment is unambiguous.[16]

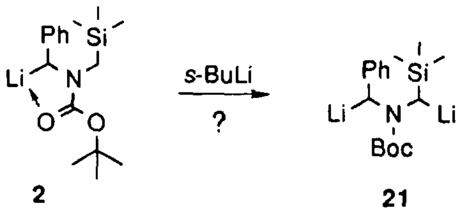
RESULTS AND DISCUSSION

Deuterium NMR. Spectra were run in 95:5 chloroform/deuterochloroform mixtures, using the deuterochloroform for chemical shift calibration. Spectra were run unlocked and without decoupling at ambient temperature, with the 5 mm deuterium lock channel used for acquisition of the signal. While these conditions (and the presence of two amide rotamers) led to rather broad signals, baseline separation was readily achieved. To calibrate the sensitivity of the method, solutions containing mixtures of benzene-d_6 and acetone-d_6 in ratios of 95:5 and 98:2 were prepared in chloroform, in concentrations that mimicked the expected amount of deuterium from the metalation experiments. These samples confirmed that ratios of 95:5 could be accurately quantified and that ratios of 98:2 could not. Although a ratio of 98:2 could not be quantified with precision, the smaller quantity of deuterium in this sample was easily discerned.

Kinetic deprotonation. To minimize the possibility of equilibration during the metalation, a solution of the urethane **1** was added dropwise to three equivalents each of *sec*-butyllithium and TMEDA in ether at -78 °C. Immediately following the addition, methanol-d_1 (30 equivalents) was added rapidly and workup gave a 97% recovery of urethanes **19** and **20** (100% deuterium incorporation by MS). The ratio of **19**:**20** was slightly in favor of the alpha-silyl anion at 0.90:1.00. The deuterium NMR result can be seen in Figure 3B.

Thermodynamic results. When **1** is treated with 0.8 equivalents each of *sec*-butyllithium and TMEDA at -78 °C, and then rapidly quenched with methanol-d_1, a mixture of **19** and **20** is produced that is similar to the kinetic results described above. If this mixture is allowed to warm to 0 °C for one hour however, recooling to -78 °C and addition of methanol-d_1 yields only deuteration next to the phenyl group (Figure 3C). It is apparent that much less than 2% of the alpha-silyl anion remained under these conditions. Deuterium incorporation for this experiment was 41%.

Anion Stability. To further test the stability of the anions under the equilibration conditions used (0 °C), urethane **1** was treated with 3 equivalents of *sec*-butyllithium and TMEDA in ether at -78 °C and then warmed to 0 °C for one hour. On recooling and quenching with methanol-d_1, deuterium NMR found the product to be a mixture of **19** and **20**. Mass spectroscopy indicated a monodeuteration level of 90%, along with 3% undeuterated and 7% di-deuteration. This confirms the stability of the anions under the equilibrating conditions, and largely rules out equilibration by intramolecular proton transfer. The measured ratio of **19** and **20** by deuterium NMR is somewhat confusing, as the ratio now favors the α-silyl anion by 1:1.8 (Figure 3D). The higher deuteration adjacent to silicon may reflect the presence of dilithio species **21**. This makes sense in view of the dideuteration found by mass spectroscopy and would most likely occur by metalation of **2** where the initially formed anion is delocalized (and would lead to a higher proportion of α-silyl deuteration).



Scheme 3. Higher temperatures and concentrations of *sec*-butyllithium may lead to dianion formation.

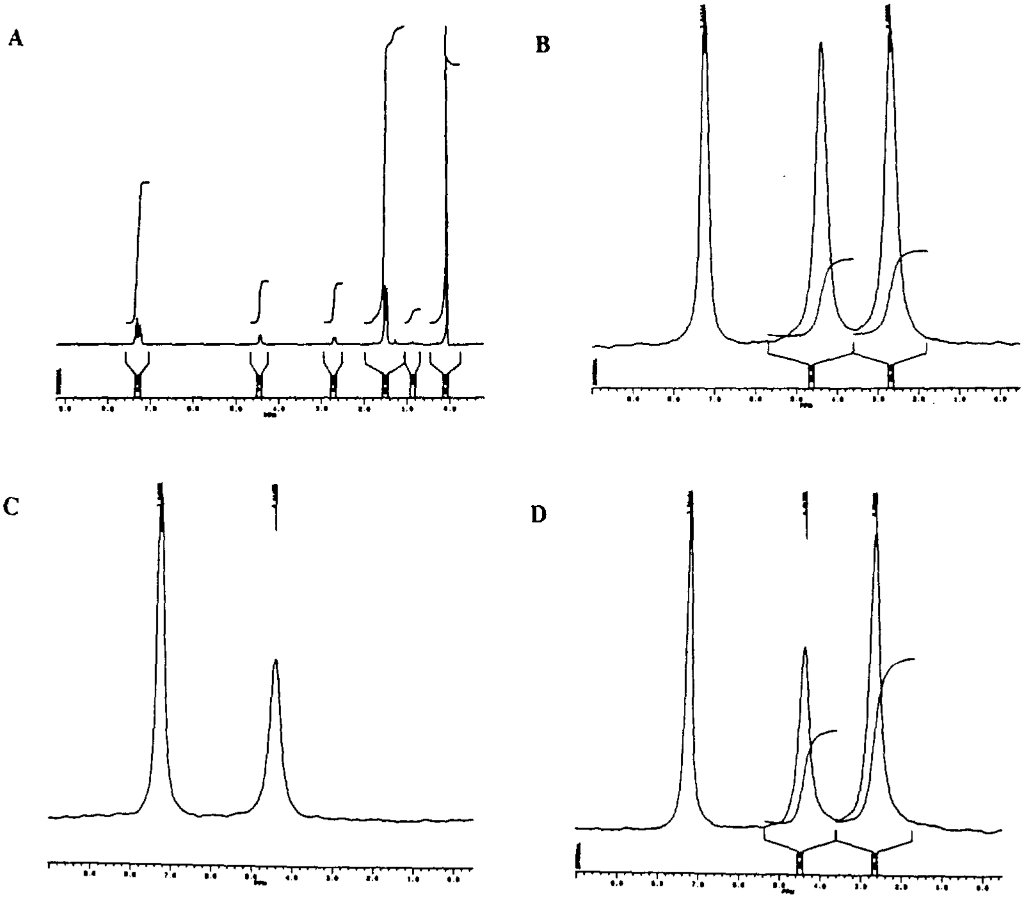


Figure 3. All deuterium NMR spectra contain deuterochloroform as a reference.

A. Proton NMR spectrum of the deuterated product from kinetic metalation.

B. Deuterium NMR spectrum of the kinetic metalation product (compare with A).

C. Deuterium NMR spectrum of the equilibrated metalation product.

D. Deuterium NMR spectrum following metalation with excess base at 0 °C.

In the deprotonation of **1**, competing silicon and phenyl, there is a very slight preference for kinetic metalation alpha to silicon. Nevertheless, thermodynamics clearly favors the α-phenyl anion. The stability of the benzyl anion **2**, relative to the α-silyl anion **3**, requires that a reactive electrophile be used if the α-silyl anion is to be efficiently intercepted. If the reaction of the lithiated species is slow relative to proton equilibration, the products **19** and **20** can become a source of protons and an avenue for equilibration to the α-phenyl anion.

EXPERIMENTAL

NMR. ^2H NMR spectra were recorded at 38.4 MHz on a Brüker AC-250 spectrometer using 512 scans, a pulse width of 11.5 ms, and a 1.3 s data acquisition of 2048 points. The spectrometer was operated unlocked using the broad band preamplifier and the 5 mm proton probe deuterium lock channel. Samples were prepared in 5 mm tubes with a 400 μL solution of 5% $CDCl_3$ in $CHCl_3$ (v/v).

Kinetic Reaction. To a -78 °C mixture of *sec*-butyllithium (1.3 M, 3.0 eq) and TMEDA (0.33 mL, 2.2 mmole, 3.0 eq) in ether (1 mL) was added dropwise a solution of **1**[5] (212 mg, 0.72 mmole) in ether (1 mL) over a period of 5 min. The resulting mixture was quenched by rapid addition of methanol-d_1 (0.88 mL, 30 eq) and then poured into sat. NH_4Cl solution (25 mL). The aqueous phase was extracted five times with ether, the combined organics were washed with sat. NaCl solution (25 mL) and dried over $MgSO_4$, and concentrated to give 206 mg (97%) of a crude mixture of **19** and **20**: ^1H NMR ($CDCl_3$) δ 7.35-7.19 (m, 5 H), 4.43 & 4.40 (2bs, 1.4 H), 2.70 & 2.66 (2bs, 1.6 H), 1.50 & 1.44 (2bs, 9H), 0.04 (s, 9H). ^2H NMR (5% $CDCl_3$ in $CHCl_3$) δ 4.38 (bs, 0.476 D), 2.68 (bs, 0.524 D). MS (NH_3/CI) *m/z* (relative intensity) MH^+ 296 (48), 295 (100), 256 (17), 240 (23), 239 (50), 238 (12), 196 (23), 195 (57), 194 (7).

Thermodynamic Reaction. To a -78 °C solution of **1** (204 mg, 0.70 mmol) and TMEDA (0.09 mL, 0.6 mmol, 0.8 eq) in ether (2 mL) was added dropwise *sec*-butyllithium (0.46 mL of a 1.3 M solution in cyclohexane, 0.6 mmol). After 5 min the reaction mixture was transferred to a 0 °C bath for one hour. After cooling to -78 °C, rapid addition of methanol-d_1 (0.85 mL, 30 eq) was followed by addition of sat. NH_4Cl solution (25 mL). After extraction of the aqueous phase with five portions of ether, the combined organics were washed with sat. NaCl solution (25 mL), dried over $MgSO_4$, and concentrated to give 198 mg (ca. 97%) of a mixture of **1** and **19**. ^2H NMR (5% $CDCl_3$ in $CHCl_3$) δ 4.42 (bs). MS (NH_3/CI) *m/z* (relative intensity) MH^+ 296 (24), 295 (92), 294 (100), 239 (45), 238 (54), 195 (48), 194 (53).

Stability of metalation products (2) and (3). To a -78 °C solution of *sec*-butyllithium (2.04 mL of a 1.1 M solution in cyclohexane, 2.25 mmol, 3 eq) and TMEDA (0.34 mL, 2.25 mmol, 3 eq) in ether (1 mL) was added dropwise a solution of **1** (220 mg, 0.75 mmol) in ether (1 mL). After 10 min the reaction flask was transferred to a 0 °C bath and stirred for 1.5 h. The resulting solution was poured into methanol-d_1 (25 mL), diluted with sat. NH_4Cl solution (50 mL) and extracted five times with ether. The combined organics were washed with sat. NaCl solution, dried over $MgSO_4$, and concentrated to give a faintly yellow oil. ^2H NMR (5% $CDCl_3$ in $CHCl_3$) δ 4.40 (bs, 0.357 D) and 2.69 (bs, 0.643 D). MS (NH_3/CI) *m/z* (relative intensity) 296 (17), 295 (69), 294 (2), 256 (46), 240 (22), 239 (98), 238 (14), 196 (20), 195 (100), 194 (6). HRMS calcd.for $C_{16}H_{27}DNO_2Si$ 295.1952, found 295.1945.

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