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α-Trialkylsilyl Amino Acid Stability

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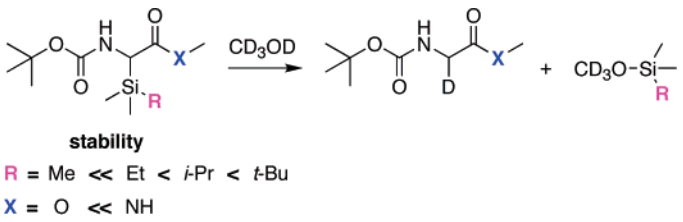
ABSTRACT



α-Trialkylsilyl amino acids have been evaluated for their stability toward methanolysis as a model for physiological conditions. The juxtaposition of amine and carbonyl groups significantly destabilizes the silicon–carbon bond, but changing a single methyl on silicon to an ethyl led to a dramatic stability enhancement. Converting the ester to an amide gave an additional jump in stability, suggesting broad potential for these novel amino acids in bioactive peptides and pharmaceuticals.

Ersatz amino acids are key elements of drug and peptide design and can also be used to alter the functionality and properties of proteins.[1] Their introduction can change conformations and add resistance to proteolytic enzymes. New amino acids additionally play an important role in the design of peptide-derived catalysts.[2]

Organosilicon amino acid components have taken several forms, such as β-silyl alanine **2**[3] and substituted phenylalanine **3**,[4] Figure 1. The proline analogue **4**[5] has recently been found to lend unique properties to neurotensin analogues,[6] and the useful latent reactivity of *N*-silylmethyl-substituted amino acid derivatives **5** has been described.[7]

α-Silyl amino acids **1**, in which the silicon is directly attached to the central carbon, are recent additions.[8] Unlike the more distantly substituted amino acids **2**−**5**, the proximity of the silicon to the carbonyl in **1** can lead to instability. We report here the first quantification of the stabilities of **1** toward methanolysis and a surprisingly subtle structure−stability relationship.

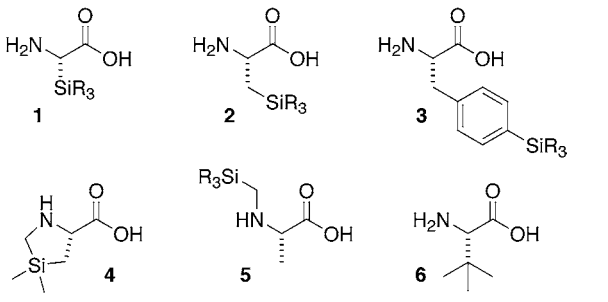


Figure 1. Silicon-substituted amino acids and the non-natural amino acid *tert*-leucine. Structures **1**, **4**, and **5** have been prepared only as derivatives.

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In general, α-amino silanes are very stable,[9] but α-silyl carbonyls have a degree of instability related to the type of carbonyl group.[10] α-Silyl esters are regarded as quite stable, however, with methyl trimethylsilyl acetate (**11**, Figure 2)

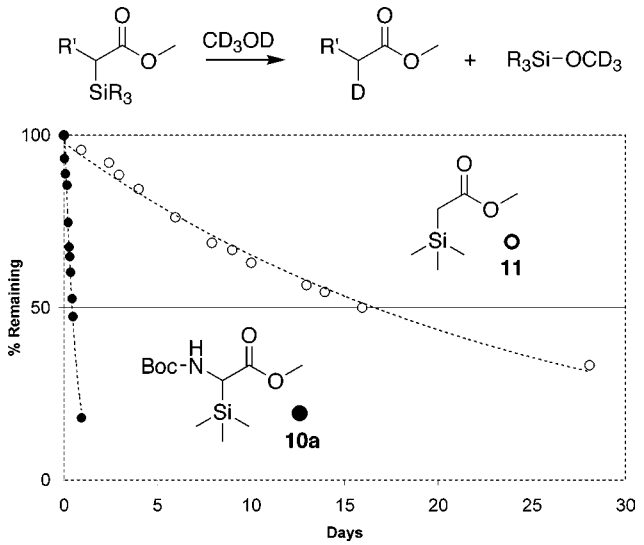


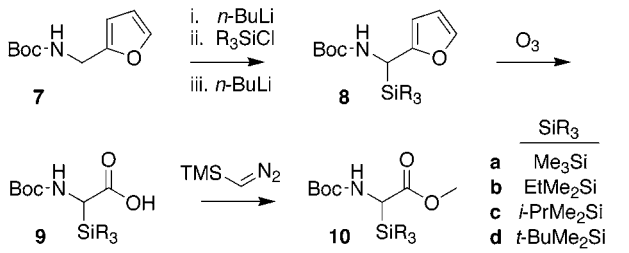
Figure 2. Methanolysis of the methyl esters of α-trimethylsilyl acetate and Boc-protected α-trimethylsilyl glycine at 20 °C.

available commercially. The stability of **1** is also a function of R in the SiR_3.

The simplest trialkylsilyl **1**, $R_3 = Me_3$, would be analogous to *tert*-leucine **6**, a rare, naturally occurring amino acid[11] with α-helix destabilizing properties[12] that can be found in several recently developed pharmaceutical agents.[13] The steric and lipophilic properties of **6** can inoculate peptide sequences against proteolysis and has led to peptides that can cross the blood−brain barrier.[13b] α-Trialkylsilyl amino acids might be expected to exhibit equally interesting properties. Trialkylsilyl groups are larger and more lipophilic than similarly substituted carbon: trimethylsilane has a volume of 89 Å^3, 20% larger than isobutane (74 Å^3). Nevertheless, the length of the Si−C bond lends a substantially smaller apparent steric bulk to the structure, a property reflected by the *A* values for Me_3Si and *tert*-butyl groups, of 2.5 and 4.9 kcal mol^{-1}, respectively.[14,15] If the α-silyl amino acids **1** were adequately stable under physiological conditions, they could become valuable peptide and pharmaceutical components.

To evaluate the stability of α-trialkylsilyl amino acids, methyl esters **10** were prepared using a modification of our recently described reverse-aza-Brook rearrangement route,[8d] starting with furfurylamine, Scheme 1. For the purposes of this study, racemic amino acids were employed.

Scheme 1. Preparation of α-Silyl Amino Acid Esters



Methanolysis of the methyl esters **10** was chosen as a barometer of stability because of the intrinsic simplicity of the chemistry and its similarity to aqueous biological conditions. The reaction was followed by ^{1}H NMR spectroscopy until at least one half-life was established; samples of the esters in methanol-d_4 were held at 20 °C and monitored periodically. Methanolysis under these conditions gave a clean conversion of the α-silyl esters to α-deutero esters and a new set of silane signals corresponding to the silyl methyl ethers. For esters with half-lives of more than a month, some ester exchange was also observed, with the appearance of methanol-*O*-*d*.

The dramatic effect of amine substitution can be seen in Figure 2. A commercial sample of methyl trimethylsilyl acetate **11** methanolyzed over a period of weeks, with a half-life of 16 days at 20 °C. In contrast, the *N*-Boc α-trimethylsilyl glycine **10a** underwent a surprisingly rapid methanolysis, with a half-life of approximately 11.5 h.

Despite the instability of the trimethylsilyl ester **10a**, the more sterically shielded α-*tert*-butyldimethylsilyl amino acid had been subjected to standard peptide coupling conditions without difficulty.[8b,8d] To probe this effect systematically, the methyl ester series **10a**−**d** was completed with the ethyl and isopropyl analogues. Under identical methanolysis conditions, Figure 3, these homologues demonstrated increasing stability as the steric shielding of the silane increased. While this trend was expected, the dramatic stability enhancement that accompanied the change of one methyl group in **10a** to an ethyl group, **10b**, was particularly striking. The half-life for the ethyldimethylsilyl derivative **10b** was 23 days, more

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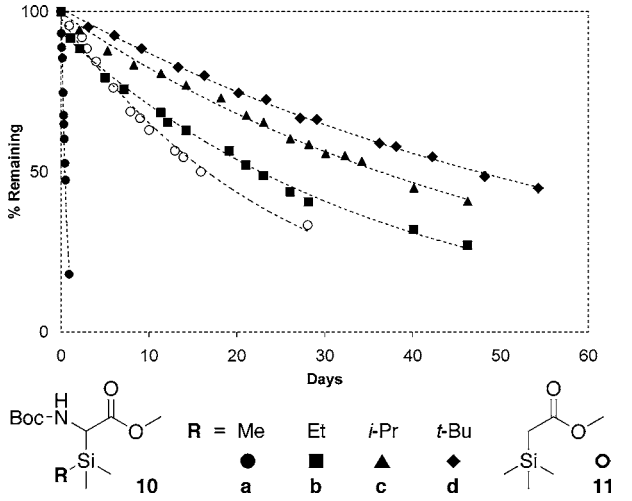

Figure 3. Methanolysis at 20 °C as a function of silane substitution.

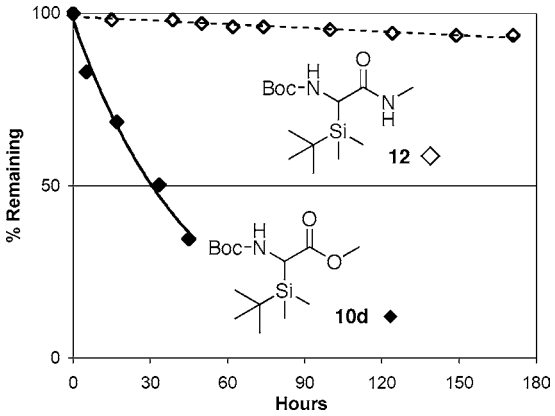

Figure 4. Methanolysis at 57 °C for the methyl ester and methyl amide.

than 40 times that of the trimethylsilyl amino acid ester **10a**. This incremental steric shielding more than compensated for the destabilizing effect of the amino group. For the *tert*-butyldimethylsilyl-substituted **12d**, the half-life for methanolysis at 20 °C was 56 days and the isopropyl group was intermediate in stability with a half-life of 36 days.

The enhanced stability of the ethyldimethylsilane **10b** over the trimethylsilane **10a** is most likely attributable to a steric effect, although an effect of this magnitude has not been observed previously. The ethyldimethylsilyl group is not stable enough to be employed as a protecting group in organic synthesis,[16] although its mass spectral properties have been profitably employed in analytical settings.[17]

The systems most structurally analogous to amino acid derivatives **10** are the *N*-silyl amides. Their dynamic equilibration with the corresponding *O*-silyl imidates gave nearly identical ratios for the trimethylsilyl and ethyldimethylsilyl groups, and a substantially different ratio with the dimethylisopropylsilyl group.[18]

Alcoholysis of chlorosilanes has been reported to be exclusively influenced by the steric effect of alkyl substitution; only modest differences are found for the relative reaction rates of lithium isopropoxide with trimethyl, ethyldimethyl and isopropyldimethyl chlorosilanes.[19] Similar results have been found for aqueous hydrolysis,[20] acetolysis,[21] and self-condensation.[22]

The reactivities of trimethylsilyl and ethyldimethylsilyl enol ethers in Mukaiyama aldol reactions is nearly identical.[23] Investigations of silane steric effects that include both trimethylsilyl and ethyldimethylsilyl groups have not found significant differences for vinylsilanes[24] or allylsilanes.[25] Methyl/ethyl/*tert*-butyl exchange on silenes has led to only minor rate differences for reactions with alcohols.[26]

One might anticipate that an amide derivative of **1** would be more stable than the methyl esters **10**. To evaluate this conjecture, the *N*-methyl amide **12** was prepared and subjected to methanolysis conditions. Based on the stability expectations, the methanolysis temperature was raised to 57 °C (refluxing acetone bath). Under these conditions, the half-life for **10d** dropped from 56 days to 33 h, Figure 4. The methanolysis of amide **12**, however, was very slow, with 93% of **12** unchanged after one week. Extrapolation of these data indicate that the half-life of **12** is approximately 56 days.

These trends have been demonstrated here for Boc-protected amino acid derivatives, we anticipate that they will translate to full peptide structures: that a small incremental steric adjustment of the trialkylsilyl group of α-silyl amino acids can yield stable silane-containing peptides with unique steric, electronic and lipophilic properties, and new opportunities for peptide and pharmaceutical modifications.

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Supporting Information Available: Experimental procedures, compound characterization, and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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