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Silylation of Organic Compounds

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The mechanism of the silylation reaction and the methods of synthesis and properties of silylating agents are discussed together with the silylation of various classes of compounds in relation to the most characteristic substances. The bibliography includes 186 references.

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I. INTRODUCTION

The silylation reaction (particularly the trimethylsilylation reaction) is nowadays widely used in organic synthesis. "Silylation" is usually understood as the introduction of the silyl group in place of a labile hydrogen atom or a metal atom substituting the latter and it is essential that the group thus introduced can be readily removed with reintroduction of active hydrogen.

Silylation makes it possible to modify widely various properties of the starting materials: it alters the reactivity of the products and, in particular, makes it possible to block certain reaction centres, it improves the solubility of compounds in non-polar solvents and increases the volatility of products as the result of the disappearance of hydrogen bonds, thus permitting their analysis and separation by gas–liquid chromatography and mass spectrometry. Finally, in certain cases the stability of the initial substances increases after silylation, for example $(CH_3)_3SiN_3$ is more stable than HN_3.

Pierce's monograph[1] surveys data on the silylation of organic compounds up to 1967. Furthermore, there are a number of reviews dealing with individual aspects of silylation[2-6] and also with the use of silyl derivatives in gas–liquid chromatography[7,8]. However, we believe that, in view of the relative inaccessibility of the majority of the above sources to the Russian reader and also the publication in recent years of many new and interesting data, it is desirable to publish the present review.

II. THE MECHANISM OF THE SILYLATION REACTION

The majority of investigators believe that the silylation reaction is reversible and proceeds via a mechanism involving bimolecular nucleophilic substitution at the silicon atom[1]:

$$HY + R_3SiX \rightleftarrows \overset{\delta-}{Y}\cdots\overset{R\ R}{\underset{H\quad R}{Si}}\cdots\overset{\delta-}{X} \rightleftarrows HX + R_3SiY, \qquad (1)$$

where Y is the nucleophilic component of the molecule of the compound being silylated and X is the group substituted in the silylating compound.

According to another view[9], the silylation reaction proceeds via a many-centre transition state:

$$HY + R_3SiX \rightleftarrows \overset{R_3Si-X}{\underset{Y-H}{\vdots\ \vdots}} \rightleftarrows R_3Si-Y + HX. \qquad (2)$$

In many instances the rate-limiting stage of the reaction is believed to be the protonation of the silylating agent, preceding nucleophilic attack on the silicon atom[10]:

$$HY + R_3SiX \overset{\text{slow}}{\rightleftharpoons} [R_3SiX\cdots H]^+ \rightarrow \xrightarrow{Y^- \text{ or } HY} R_3SiY + HX. \qquad (3)$$

There are two criteria whereby it is possible to choose between particular silylation mechanisms. One of these is based on a kinetic study in which the order of the reaction with respect to the reactants and the rate-limiting stage are determined. The second is based on the study of silylation by agents containing an asymmetric silicon atom. This procedure for elucidating the mechanism has become possible as a result of detailed studies by Sommer[11], who obtained a set of optically active compounds with an asymmetric silicon atom and determined their true configurations.

The "optical" criterion makes it possible to investigate directly the mechanism of the substitution stage at the silicon atom even if it is not rate-determining. Sommer suggests[11] that silicon is capable of giving rise to transition structures in the silylation reaction as a result of the involvement of its vacant *d* orbitals. Three possible versions are considered.

1. The inversion of the optical configuration at the silicon atom (here and henceforth we shall designate this process, following Sommer[11], as S_N2–Si). In this case the group X is replaced by Y via a bimolecular mechanism and the transition state has the geometry of a trigonal bipyramid (Fig. 1).

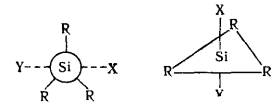


Figure 1. Geometry of the transition state in an S_N2–Si reaction.

2. The retention of the optical configuration at the silicon atom (we shall designate this process by S_Ni–Si)[11]. Here the reaction is also bimolecular but the geometry of the transition state changes. It is either a tetragonal

pyramid (Fig. 2*a*) or a trigonal bipyramid in which the relative positions of X and Y are not the same as in Fig. 1 (Fig. 2*b*).

3. The loss of optical activity. In this case the reaction either proceeds via the S_N1–Si mechanism involving the formation of a planar siliconium cation:

$$R_3Si{-}X \rightleftarrows R_3Si^+ + X^- \overset{HY}{\rightleftarrows} R_3SiY + HX\ ,$$

or it proceeds simultaneously via the S_N2–Si and S_Ni–Si mechanisms. Evidently a choice can be made between these two versions kinetically using the order of the reaction with respect to each reactant.

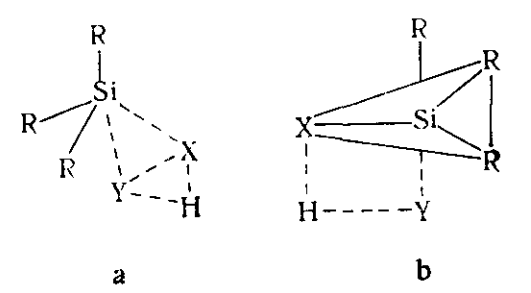


Figure 2. Geometry of the transition state in a S_Ni–Si reaction.

Since the siliconium cation R_3Si^+ is relatively unstable[12], and the silylation reaction is usually carried out in aprotic solvents of low polarity, we believe that "racemisation" is most probably a consequence of a bimolecular reaction mechanism intermediate between S_N2–Si and S_Ni–Si.

1. Reaction Kinetics

It has been shown that in many cases the rate determining stage in the silylation reaction is nucleophilic substitution at the silicon atom. Thus Grubb[13] established that silylation of trimethylsilanol in methanol proceeds with participation of the solvent and is catalysed by acids or bases. It was found that the reaction is of first order with respect to the silanol, chlorotrimethylsilane, and the catalyst. The following reaction mechanism was proposed:

$$(CH_3)_3SiOH + CH_3OH \rightleftarrows (CH_3)_3SiOCH_3 + H_2O\ .$$

Then, in the presence of an acid catalyst we have

$$(CH_3)_3SiOCH_3 + CH_3\overset{+}{O}H_2 \rightleftarrows (CH_3)_3Si\overset{+}{O}(H)CH_3 + CH_3OH,$$

$$(CH_3)_3SiOH + (CH_3)_3Si\overset{+}{O}(H)CH_3 \xrightarrow{slow} \left[(CH_3)_3Si\underset{H}{O} \cdots \overset{CH_3\ CH_3}{\underset{CH_3}{Si}} \cdots \underset{H}{O}CH_3\right] \rightleftarrows$$

$$\rightleftarrows [(CH_3)_3Si]_2O + CH_3\overset{+}{O}H_2\ ,$$

and in the presence of a basic catalyst

$$(CH_3)_3SiOH \overset{OH^-}{\rightleftarrows} (CH_3)_3SiO^- + H_2O,$$

$$(CH_3)_3SiO^- + (CH_3)_3SiOCH_3 \xrightarrow{slow} \left[(CH_3)_3SiO \cdots \overset{CH_3\ CH_3}{\underset{CH_3}{Si}} \cdots OCH_3\right] \rightleftarrows [(CH_3)_3Si]_2O + CH_3O^-.$$

The kinetics of the reaction of methanol with silylamines having the general formula $X{-}C_6H_4{-}NHSiR_3$

(where X = H, CH_3, OCH_3, C_2H_5, Cl, or F and R = alkyl) have been studied[14]. The reaction was carried out in an excess of methanol in the presence of or absence of acid catalysts. It was shown that it is irreversible and is of first order with respect to silylamine and the catalyst. For substituents X in the *meta*- and *para*-positions, a linear relation was observed between $\lg K = \lg(k_i/k_0)$ and the Hammett constants σ of the substituents (the sensitivity coefficient $\rho = -2.52$). Very rapid deuterium exchange between methanol and the silylamine was observed. Bearing in mind the data concerning the reaction order, the sign and magnitude of the sensitivity coefficient ρ, and the high activation entropy, the authors[14] suggested a mechanism for this process in which the rate-determining stage is the interaction of the protonated silylamine with methanol:

$$ArNHSi(iso\text{-}C_3H_7)_3 + (CH_3\overset{+}{O}H_2) \overset{fast}{\rightleftarrows} Ar\overset{+}{N}H_2Si(iso\text{-}C_3H_7)_3 + CH_3OH\ ,$$

$$Ar\overset{+}{N}H_2Si(iso\text{-}C_3H_7)_3 + \dot{C}H_3OH \rightarrow ArNH_2 + (iso\text{-}C_3H_7)_3Si\overset{+}{O}(H)CH_3\ , \qquad (4)$$

$$(iso\text{-}C_3H_7)_3Si\overset{+}{O}(H)CH_3 + CH_3OH \rightarrow (iso\text{-}C_3H_7)_3SiOCH_3 + CH_3\overset{+}{O}H_2\ .$$

Klebe[15] investigated the kinetics of the alcoholysis of many *N*-aryl- and *N*-trimethylsilyl-amides and determined the equilibrium constant for the interaction of these compounds with *N*-methylacetamide. The alcoholysis reaction is of first order with respect to the silylamide and the alcohol and is accelerated following the introduction of electronegative substituents at the nitrogen atom. The same substituents shift the equilibrium position towards the silylation of *N*-methylacetamide. Klebe believes that the rate-determining stage in both processes is bimolecular nucleophilic substitution at the silicon atom

$$ROH + CH_3CON[Si(CH_3)_3]C_6H_4{-}X \rightarrow \overset{R}{\underset{H}{O}} \cdots Si \cdots \underset{C_6H_4X}{N}COCH_3 \rightarrow$$

$$\rightarrow ROSi(CH_3)_3 + CH_3CONHC_6H_4{-}X\ ,$$

where X = *p*-OCH_3, *m*-OCH_3, *p*-CH_3, H, *p*-Cl, *m*-NO_2, or *p*-NO_2 and R = C_2H_5 or t-C_4H_9.

The rate of methanolysis of menthyloxysilanes[16] and of solvolysis of trialkylphenoxysilanes[17,18] in the presence of basic catalysts is also determined by the S_N2–Si stage. Each reaction is of second order overall: it is of first order with respect to the catalyst and the triorganosiloxane. The kinetic data for these acid-catalysed processes do not allow an unambiguous determination of the rate-limiting stage, which may be both substitution at the silicon atom:

$$R_3SiOR' + CH_3\overset{+}{O}H_2 \xrightarrow{slow} R_3SiOCH_3 + R'\overset{+}{O}H_2,$$

$$R_3SiOC_6H_4{-}X + C_2H_5\overset{+}{O}H_2 \xrightarrow{slow} R_3SiOC_2H_5 + X{-}C_6H_4\overset{+}{O}H_2;$$

and the protonation of the silylating agent:

$$R_3SiOR' + CH_3\overset{+}{O}H_2 \rightleftarrows R_3Si\overset{+}{O}R'H + CH_3OH,$$

$$R_3SiOC_6H_4{-}X + C_2H_5\overset{+}{O}H_2 \rightleftarrows R_3Si\overset{+}{O}H(C_6H_4{-}X) + C_2H_5OH,$$

where R = CH_3, C_2H_5, iso-C_3H_7 or C_6H_5, R′ = menthyl group, and X = H, *m*-Cl, *p*-Cl, *p*-OCH_3, or *p*-CH_3 (for X = H, R = CH_3, C_2H_5, C_3H_7, C_4H_9, *t*-C_4H_9, or C_6H_5).

It has been established that the silanolysis of silylamines[9]

$$R_3SiOH + R'_3SiNR''_2 \rightarrow R_3SiOSiR'_3 + NHR''_2$$

$$(R{=}C_2H_5,\ n\text{-}C_3H_7;\ R'{=}CH_3,\ C_2H_5,\ n\text{-}C_4H_9;\ R''{=}H,\ C_2H_5,\ t\text{-}C_4H_9)$$

and the silylation of nitroalcohols by chlorotrimethylsilane[19] are second-order reactions overall, but the rate-limiting stages of these processes cannot be determined on the basis of the literature data.

2. Stereochemistry of the Reaction

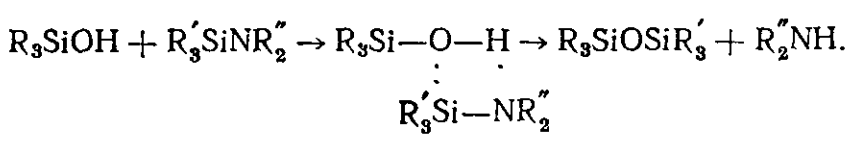
The silylation of compounds containing a mobile hydrogen atom with the aid of optically active trialkylhalogenosilanes proceeds as a rule with almost complete inversion of the configuration of the R_3Si fragment[20–25]. The silylation of water and methanol by silylamines[25–27] and the silylation of methanol by alkoxycarbonylsilanes proceed similarly[28]. On the other hand, the interaction of organic acids and HCl with silylamines can proceed both with and without inversion of optical configuration[26,29]†.

Examination of the kinetic and stereochemical data for the silylation reaction shows that it usually proceeds via the S_N2–Si mechanism. The silylating agent can interact in both neutral and protonated forms, the latter being apparently preferable. The silylated compound reacts either as an anion or as a neutral molecule. However, in many instances the silylation reaction proceeds via the S_Ni–Si mechanism or simultaneously via the S_N2–Si and S_Ni–Si mechanisms.

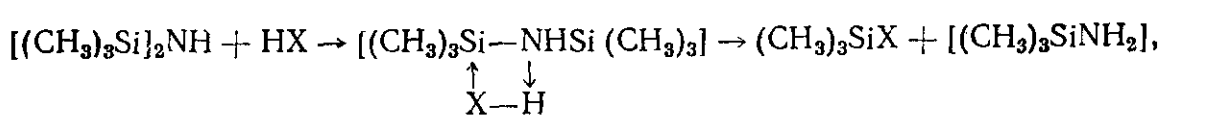
3. Additional Data on the Silylation Mechanism

In addition to the kinetic and stereochemical studies already discussed, it is necessary to consider certain investigations which also provide information about the mechanism of the silylation reaction.

A hypothetical S_Ni–Si mechanism involving a many-centre transition state has been postulated for some reactions. In particular, such a mechanism has been suggested for the silanolysis of silylamines[10]:

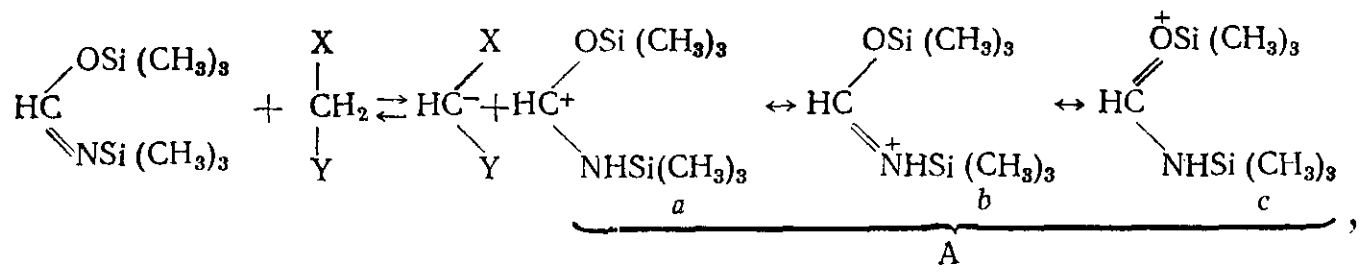


According to Becke-Goehring and Wunsch[30], the interaction of hexamethyldisilazane with compounds containing a mobile hydrogen atom may be accompanied by the formation of an intermediate complex‡:



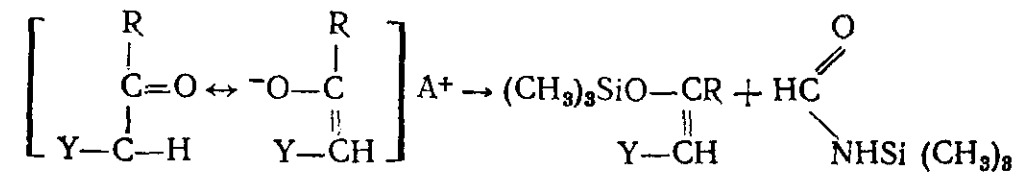
where X = Cl, OC_2H_5, or OC_6H_5.

In their study of the silylation of weak C–H acids by *N,O*-bis(trimethylsilyl) formamide Kentlenner et al.[10] suggested that the silylating agent is initially protonated with formation of an ambident cation A§:



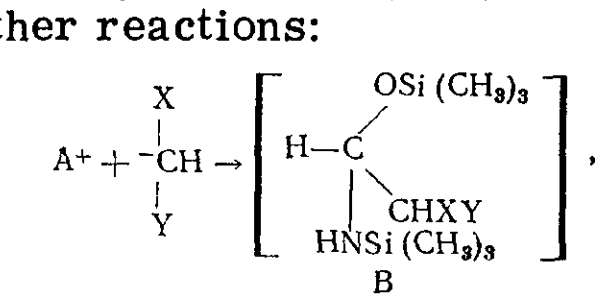
where X = RCO for R = CH_3 or C_6H_5 and Y = $CO_2C_2H_5$, for R = CH_3OCOCH_2 and Y = CO_2CH_3, or for R = C_6H_5 and Y = $COCH_3$ and X = CN for Y = CN, $CO_2C_2H_5$, or CO_2CH_3.

When the anion formed from the C–H acid is capable of tautomerism, the ambident cation A reacts with it in form (*b*) or (*c*), giving rise to an *O*-silylation product:



where Y = $COOC_2H_5$, $COOCH_3$, or $COCH_3$.

When the anion of the C–H acid is incapable of tautomerism, the cation A reacts with this "hard" anion in form (*a*) to form compounds of type C, which are unstable and undergo further reactions:



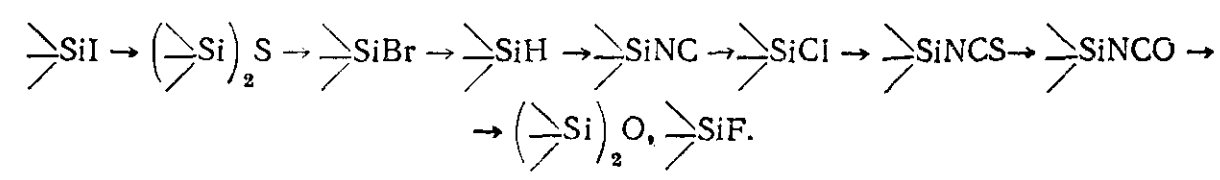
where X = CN and Y = CN, $COOCH_3$, or $COOC_2H_5$.

Thus several different mechanisms have been proposed for the silylation reaction¶. We believe that this process should not be always treated from the standpoint of any one mechanism, since the reaction mechanism can probably change under the influence of many factors.

4. The Influence of the Nature of the Group X Substituted in the Silylating Agent R_3SiX

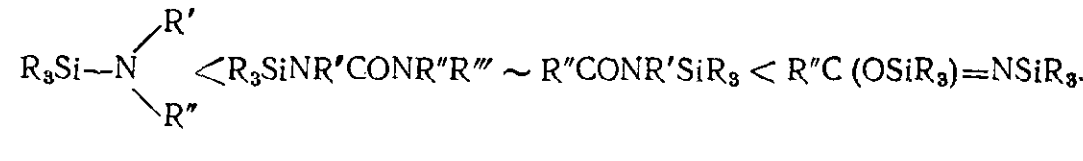
Examination of Eqn. (1) shows that the rate of silylation must depend on the properties of the substituent X as the group to be eliminated†. Firstly, it is desirable that X should be capable of delocalising the negative charge arising on it in the transition state. Secondly, the weaker the $(d-p)_\pi$ interaction between the silicon atom and the group X, the greater the ease of nucleophilic attack on the silicon atom and the dissociation of the Si–X bond. In many cases the rate of the silylation reaction depends on the ease of protonation of the compound R_3SiX [Eqn. (3)] and the role of protonation should become more important as X becomes more difficult to eliminate.

Certain ideas about the influence of the nature of the group X on the ease of substitution are provided by the series of conversions deduced by Eaborn[33] and Anderson and Fischer[34] on the basis of studies of the reactions of certain silver salts with triorganosilanes:



In this series the reactions of the compounds $\geqslant$SiX with the salt AgY proceed only from left to right.

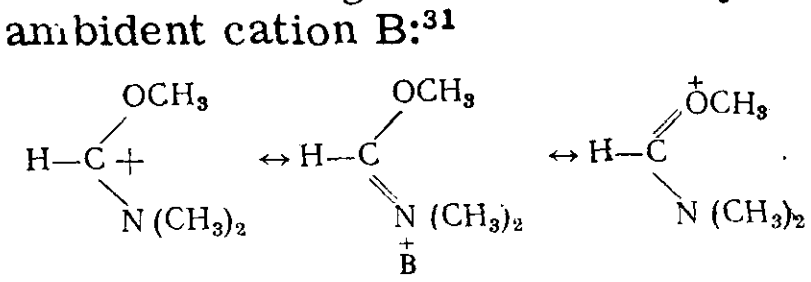
The most thoroughly investigated silylating agents are compounds with an Si–N bond. These organosilicon derivatives have been arranged in the following sequence in terms of their silylating capacity[1,15]:



† These results are explained in the next section of this review.

‡ However, the authors do not rule out also other reaction mechanisms.

§ The cation A can be regarded as the silylated analogue of the ambident cation B:[31]



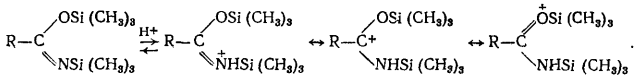
¶ In addition to the foregoing, we may mention that a radical-anion mechanism has been put forward for the silylation of ketones in the presence of an alkali metal[32].

† X must be more electronegative and less nucleophilic than Y in the compound HY being silylated. Otherwise HX must be removed from the reaction sphere in order to shift the equilibrium towards the silylation products.

Silylamines are less effective donors of the trimethylsilyl group than silylated ureas and amides. *NO*-Bis-(trimethylsilyl)amides are the best silylating agents for the majority of compounds to be silylated, among those known at the present time.

The explanation is that, firstly, the introduction of the carbonyl group at the nitrogen atom linked to the silicon atom weakens the $(p - d)_\pi$ interaction between them and facilitates nucleophilic attack on the silicon atom. The introduction of a second trimethylsilyl group into silylated amides weakens still further the double-bond character of the linkage between the silicon atom and the group X to be substituted. Secondly, on passing from silylamines to silylated amides and ureas, there is an increase of the capacity of the group X being eliminated for the delocalisation of the negative charge due to the carbonyl group.

Furthermore, *NO*-bis(trimethylsilyl)amides are more readily protonated than silylamines and silylureas, since the resulting positive charge is more effectively stabilised:



The substituent at the nitrogen atom in the group $-CO-N(X)-Si$ also influences the reactivity of *N*-silylamides.

The study of the methanolysis of *N*-methyl-*N'*phenyl-*NN'*-bis(trimethylsilyl)urea showed that the trimethylsilyl group at the nitrogen atom linked to the more electronegative substituents is more mobile[15]:

$$C_6H_5N[Si(CH_3)_3]CON(CH_3)Si(CH_3)_3 \xrightarrow{CH_3OH} C_6H_5NHCON(CH_3)Si(CH_3)_3.$$

It is noteworthy that the ease of protonating of silylamides depends very markedly on the contribution of the amide formed to the structure of the amide and on the energy barrier between the amide and imide forms (see Section III). A decrease of the barrier and an increase of the content of the form C in the mixture should facilitate the protonation of silylamines (in consequence of the resonance stabilisation of the cation $R-C(OSi<)(\overset{+}{N}HR')$) and hence improve the silylating capacity of these compounds.

In conclusion we shall consider briefly the influence of the group X being substituted in silylating agents with an Si–O bond. Sommer et al.[23] investigated the rate of solvolysis of alkoxy- and acyloxy-silanes R_3SiOR' and $R_3SiOCOR'$. Trialkylacyloxysilanes are more reactive, owing to the greater stabilisation of the charge by the group $(-OCOR')^-$ compared with $(OR')^-$ and the smaller amount of double bond character of the linkage between the silicon atom and the group being substituted in acyloxysilanes compared with alkoxysilanes.

5. The Influence of the Nature of the Compound HY Being Silylated

The silylation mechanism may be also determined by the properties of the compound being silylated. If the compound HY has pronounced nucleophilic properties, then reaction (1) should be favoured. An increase of the acidity of HY with retention of fairly marked nucleophilic properties should lead to a many-centre cyclic transition state, in accordance with Eqn. (2). Under these conditions, when the acidity of HY is of decisive importance, the rate-limiting stage becomes the protonation of the silylating agent [Eqn. (3)].

Hydroxy-compounds are known to be more readily silylated than compounds with an N–H bond[35]. Possibly this is because alcohols are stronger acids than amines. For this reason, they, on the one hand, protonate more readily the silylating agent (see acid catalysis) and, on the other hand, they are themselves more readily deprotonated, the anion RO^- being more nucleophilic than the amine.

The rate of silylation decreases in the series of alcohols $CH_3OH > n\text{-}C_3H_7OH > n\text{-}C_6H_{13}OH$ in parallel with the decrease of their acidity[36,37]. The decrease of the rate of silylation in the series $RNH_2 > R_3CONH_2 > RCONHSi(CH_3)_3$ takes place in parallel with the decrease of the nucleophilicity of these compounds[35].

6. Steric Effects

In many cases the mechanism and rate of silylation are determined by the steric factors associated with the silylating agent or the compound being silylated. Thus, in the interaction of organic acids with silylamines, the change in reaction mechanism may be caused by the steric hindrance in the compound being silylated. In particular, the silylation of benzoic acid proceeds via the S_Ni–Si mechanism. When substituents are introduced into the *ortho*-position, the mechanism changes to S_N2–Si.[26]

Secondary amines with a branched chain in the α-position relative to the nitrogen atom are silylated with greater difficulty than primary amines, which is due to steric hindrance[38]. Bulky substituents in certain primary amines and aminoacids preclude the introduction of a second trimethylsilyl group at the nitrogen atom when the starting materials are treated with diethyltrimethylsilylamine in the presence of ammonium sulphate[39].

According to some investigators[36,37], the decrease of the rate of hydrolysis and alcoholysis of chlorotriorganosilanes in the series water > methanol > propanol > 1-hexanol > isopropyl alcohol is due to the steric hindrance in the compound being silylated.

A study of the rate of hydrolysis of various disilazanes showed that bulky substituents at the silicon atom retard the reaction[40]. The same causes are probably responsible for the resistance to hydrolysis of alkoxyisopropyldimethyl- and alkoxy-t-butyldimethyl-silanes[41,42]. A steric effect of the substituents at the nitrogen atom was also observed in a study of the rate of methanolysis of silylamines: $C_6H_5(C_2H_5).NSi(C_2H_5)_3$ silylates methanol more slowly than does $C_6H_5NHSi(C_2H_5)_3$.[14]

7. The Influence of Catalysts

The role of the acid catalyst in the silylation reactions proceeding via Eqns. (1) and (3) reduces to the protonation of the silylating agent R_3SiX, which in its turn weakens the $(p - d)_\pi$ interaction between the silicon atom and the group X. Examples of acid-catalysed silylation reactions are quoted below.

Alcoholysis of silylamines is as a rule an acid-catalysed reaction[14,26]. Grubb showed[13] that the condensation of a silanol in ethanol is catalysed by acids (see Subsection 1 of the present Section).

The following mechanism has been proposed for the silylation of alcohols and amines by hexamethyldisilazane[43]:

$$[(CH_3)_3Si]_2NH \overset{H^+}{\rightleftarrows} [(CH_3)_3Si]\overset{+}{N}H_2-Si(CH_3)_3;$$

$$[(CH_3)_3Si]_2\overset{+}{N}H_2 + HY \rightleftarrows \{(CH_3)_3SiNH_2-Si(CH_3)_3\cdots Y-H\} \rightarrow (CH_3)_3SiY + (CH_3)_3Si\overset{+}{N}H_3,$$

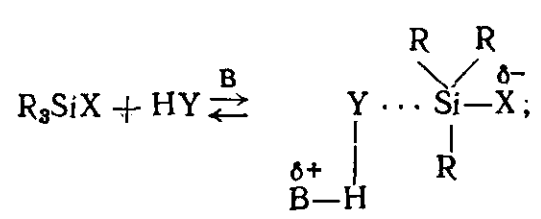
where Y = OR or NHR (R = alkyl).

Langer et al.[43] believe that the interaction of an alcohol with hexamethyldisilazane is accelerated by chlorotrimethylsilane (CTMS) only because the reaction of CTMS with the alcohol results in the formation of hydrogen chloride.

Proton-donating compounds[44] catalyse the attainment of equilibrium:

$$\gt SiNR_2 + R'NH_2 \overset{H^+}{\rightleftarrows} \gt SiNHR' + NHR_2.$$

Many silylation reactions involving the S_N2–Si mechanism [Eqn. (1)] are catalysed by bases. In the first place the role of bases may reduce to binding the proton from HY in the transition state[36,37,45]:



where B is the base.

In the second place bases can promote the dissociation of HY.[13,46]

In the silylation with the aid of CTMS of a hydroxy-group in certain monosaccharides pyridine is used as the base. The formation of an intermediate pyridine–CTMS complex has been assumed[47,48]‡. Bases sometimes inhibit the silylation reaction. Evidently in this case they prevent the protonation of the silylating agent [see Eqn.(3)]. For example, hexamethyldisilazane is resistant to hydrolysis in an alkaline medium[50]. The alcoholysis of many silylanilines is inhibited in the presence of basic catalysts[14]§.

8. Effect of Solvents

Polar solvents as a rule accelerate the silylation reaction and promote its occurrence via the S_N2–Si mechanism. For example, the methanolysis of optically active alkoxysilanes $R_3\overset{*}{S}iOR'$ in non-polar solvents takes place with retention of the configuration (the S_Ni–Si mechanism). On the other hand, when the solvent is changed to methanol, the reaction proceeds with inversion of optical configuration[51].

Triethylamine or pyridine, which bind the hydrogen chloride formed, are sometimes used as solvents (particularly in silylation with the aid of CTMS).[2,52]

‡ However, other investigators[49] showed that the complex $(CH_3)_3SiClC_5H_5N$ is not formed and the effect of pyridine probably reduces to binding the hydrogen chloride liberated.

§ It is interesting that benzylsilanes are hydrolysed under the same conditions, although the anion $C_6H_5NH^-$ is more readily eliminated than $C_6H_5CH_2^-$.[14]

III. METHODS OF SYNTHESIS AND PROPERTIES OF SILYLATING AGENTS

Much space is devoted to the characteristics of silylating agents in the published reviews and monographs[1-6]. In addition to these publications, one may also quote the paper by Plueddemann[53]. A reference has also been made to a brochure published by Pierce Chemical Company[54] in which 23 silylation methods are described, reagent standards and prices are quoted, etc. CTMS, silylated amines, hexamethyldisilazane, *N*-trimethylsilylimidazole, silylated ureas and amides, trimethylvinyloxysilanes, and dialkyl trimethylsilyl *N*-trimethylsilylphosphorimidates are normally employed as silylating agents.

Chlorotrimethylsilane is obtained by treating silicon with hydrogen chloride in the presence of catalysts[55]. It is a liquid (b.p. 57.3°C), which readily hydrolyses in air.

Silylamines. The general method for the synthesis of these compounds, which contain an Si–N bond, is the silylation of primary and secondary amines with the aid of CTMS in the presence of tertiary amines[2].

Hexamethyldisilazane is formed when ammonia is silylated with CTMS:[50]

$$NH_3 + (CH_3)_3SiCl \rightarrow [(CH_3)_3Si]_2NH.$$

It is a liquid (b.p. 125–126°C), which hydrolyses in the presence of acids. Alkaline and neutral hydrolysis is slow.

N-Trimethylsilylamidazole is obtained[56] by treating imidazole with CTMS. This silylating agent is a liquid boiling at 91°C at 12 mmHg which has the refractive index n_D^{20} = 1.4756.

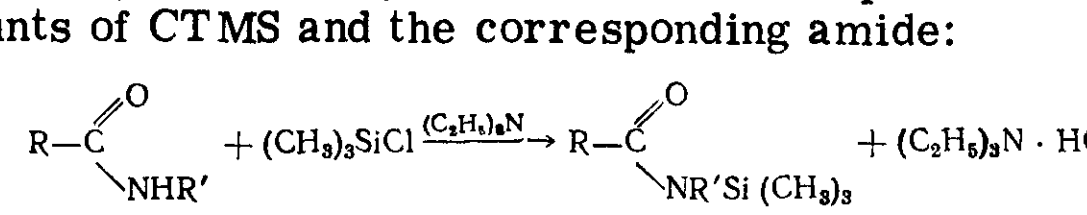
Organosilicon derivatives of ureas are formed when silylamines or alkylsilazanes react with organic isocyanates[57-59]:

$$R_2N-Si(CH_3)_3 + R'NCO \rightarrow R_2NCONR'Si(CH_3)_3.$$

When phenyl isocyanate reacts with hexamethyldisilazane, *N*-phenyl-*NN'*-bis(trimethylsilyl)urea is formed[58].

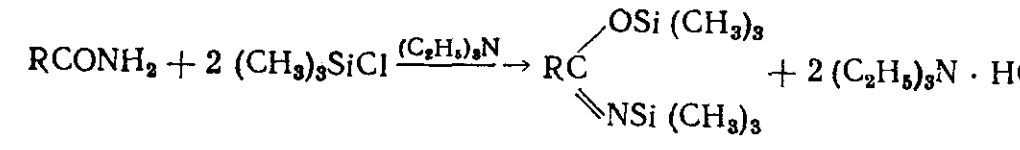
NN'-Diphenyl-*N*-trimethylsilylurea (it is a crystalline substance readily hydrolysed in air) has some advantage over other silylating agents, since silylation with its aid leads to the formation of *NN'*-diphenylurea, which is sparingly soluble in organic solvents and this facilitates the isolation of the silylation products from solutions in a pure form.

NO-Organosilicon derivatives of amides are readily obtained by the interaction of equimolar amounts of CTMS and the corresponding amide:



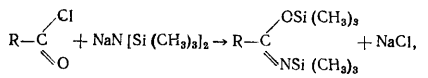
where R = CF_3 and R' = CH_3,[60] R = R' = H, R = R' = CH_3,[61] or R = CH_3 and R' = H.[62]

In the presence of a twofold excess of the silylating agent and under more severe conditions, *NO*-bis(trimethylsilyl) derivatives of amides are produced:

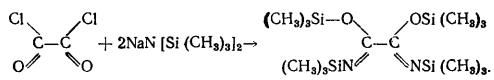


where R = H,[10] CH_3, vinyl[63], or CF_3.[64]

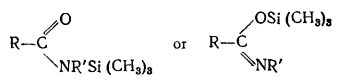
Another method for the synthesis of *NO*-bis(trimethylsilyl)amides was proposed by Pump and Rochow[65]:



where R = C_6H_5, C_5H_4N, or $(CH_3)_3C$. A trimethylsilyl derivative of oxalic acid diamide was obtained similarly[65]:

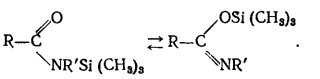


The structure of silylated amides. Silylation of amides can result in the formation of two isomeric products:



A B

^{1}H NMR data for a number of monotrimethylsilylated amides indicate the migration of the $(CH_3)_3Si$ group between oxygen and nitrogen atoms[15,66]:

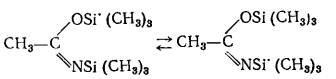


The equilibrium position in this process depends on the electronegativity of the substituents R and R′. The rate of migration of the $(CH_3)_3Si$ group varies in the following sequence of a function of R (R′ = C_6H_5):[66]

$$CF_3 \simeq CCl_3 < CHCl_2 < CH_2Cl < CH_3 \leqslant C_2H_5 < \text{iso-}C_3H_7 \ll \text{t-}C_4H_9 .$$

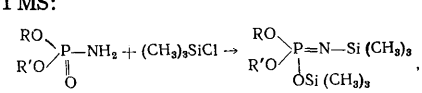
With increase of the electronegativity of the substituent at the nitrogen atom, the content of the *O*-trimethylsilyl imidate rises[15].

A study of the ^{1}H NMR and infrared spectra of bis(trimethylsilyl)acetamide (BSA) led Pump and Rochow[65] to the conclusion that this compound is *NO*-bis(trimethylsilyl)acetamide and that there is a rapid intramolecular exchange of $(CH_3)_3Si$ groups¶.



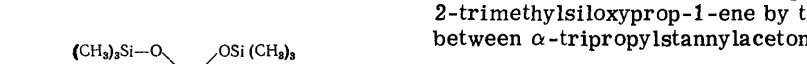
In recent years studies of the infrared and ^{1}H NMR spectra of mono- and bis-(trimethylsilyl)amides enriched in ^{15}N established rigorously that BSA and other bis(trimethylsilyl) derivatives having the general formula $[RCON][Si(CH_3)_3]_2$, where R = iso-C_3H_7, t-C_4H_9, or CF_3, exist exclusively in the imidate form, while bis(trimethyl)formamide and the monosilylacetamides CH_3CONR–$Si(CH_3)_3$ (R = H or alkyl) are true amides[67–69].

Dialkyl trimethylsilyl *N*-trimethylsilylphosphorimidates are formed on silylation of the corresponding amides of dialkyl phosphoric acids with an excess of CTMS:[70]



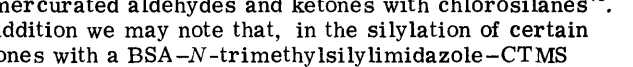
where R = R′ = CH_3; R = C_2H_5, R′ = CH_3; R = n-C_4H_9; R′ = CH_3. These compounds are very sensitive to moisture.

Vinyloxysilanes are formed when the corresponding enolates are acted upon by CTMS:[71]†



where R = H and R′ = C_6H_5, R = H and R′ = CH_3, R = CH_3 and R′ = $COCH_3$, or R = H and R′ = HC = $C(CH_3)_2$.

Lutsenko and coworkers[72] reported the synthesis of 2-trimethylsiloxyprop-1-ene by the exchange reaction between α-tripropylstannylacetone and CTMS:



Certain vinyloxysilanes have been obtained by treating α-mercurated aldehydes and ketones with chlorosilanes[73]. In addition we may note that, in the silylation of certain ketones with a BSA–*N*-trimethylsilylimidazole–CTMS mixture, trimethylvinyloxysilanes are also formed[74].

Silylating agents were already compared to some extent in the discussion of the mechanism of the silylation reaction. The most convenient are the trimethylsilyl derivatives of ureas and amides. To some extent, this can be accounted for by the fact that, as a result of the silylation reaction, ureas and amides, compounds which are usually inert with respect to silylation products, are formed. To investigate substances containing the NH,, OH, and SH groups with the aid of gas–liquid chromatography (GLC), they are silylated with trifluoro-*N*-methyl-*N*-trimethylsilylacetamide[57] and trifluoro-*NO*-bis(trimethylsilyl)acetamide[61], since the fluorinated derivatives are more volatile than their non-fluorinated analogues. Mixtures of several silylating agents have been recommended in several studies, CTMS being added to such compositions as the catalyst[7,75–77]. This version of the silylation reaction is used particularly frequently in GLC.

The employment of 2-trimethylsiloxyprop-1-ene for the silylation of compounds with the OH, NH, COOH, and SH groups showed that it is less effective than BSA and silylation with its aid is not always satisfactory[78]. *N*-Trimethylsilylimidazole, which readily silylates oxygen linked to mobile hydrogen, is at the same time relatively unsuitable for the silylation of the N–H bond[76].

The usefulness of a particular silylating agent is determined by the nature of the compound to be silylated. For this reason, examples illustrating conditions governing the silylation of various functional groups are quoted below.

IV. METHODS FOR THE SILYLATION OF VARIOUS CLASSES OF ORGANIC COMPOUNDS

1. Silylation of Amines

A general method for the silylation of amines involves their reaction with CTMS [2] (Table 1). An excess of the initial amine or tertiary amines are used to combine with the hydrogen chloride liberated. In the silylation of amines their alkali metal salts are sometimes used.

¶ We believe that the evidence supporting intramolecular rather than intermolecular exchange of $(CH_3)_3Si$ group is inadequate.

† The review does not deal with the synthesis of vinyloxysilanes by the reaction of hydrogen-containing silanes with αβ-unsaturated aldehydes and ketones.

Another method for the silylation of amines involves the transamination of silylamines, first investigated by Larson and coworkers[86]:

$$(CH_3)_3SiNR_2 + R'NH_2 \rightleftarrows (CH_3)_3SiNHR' + NHR_2.$$

Table 1. Silylation of amines by chlorotrimethylsilane.

Amine	Reaction product	Yield, %	Refs.
Ammonia	Hexamethyldisilazane	45-70	51,79
Methylamine	Methyltrimethylsilylamine	38-55	51
Ethylamine	Ethyltrimethylsilylamine	25	51
Diethylamine	Diethyltrimethylsilylamine	32	51
Aziridine	*N*-Trimethylsilylaziridine	44	80,81
Pyrrolidine	*N*-Trimethylsilylpyrrolidine	65	82
Piperidine	*N*-Trimethylsilylpiperidine	72	82
Pyrrole (K salt)	*N*-Trimethylsilylpyrrole	71	82,83
Indole (K salt)	*N*-Trimethylsilylindole	55	82
Aniline	*N*-Trimethylsilylaniline	60-80	84,85

Hexamethyldisilazane, trimethylsilylamine, and diethyltrimethylsilylamine are usually employed as donors of the trimethylsilyl group (Table 2). The rate of this reaction increases following the distillation of the amine NHR_2 formed or after the addition of catalytic amounts of ammonium salts, CTMS, or $ZnCl_2$, which promote the condensation to silazanes of the silylamines formed initially[38] (Table 3):

$$2\,(CH_3)_3SiNHR' \xrightarrow{(NH_4)_2SO_4} [(CH_3)_3Si]_2NR' + R'NH_2\ .$$

For sterically hindered amines, only the monosilyl derivatives have been obtained[38].

Table 2. Transamination of silylamines.

Amine	Silylating agent	Reaction product	Yield, %	Refs;
Imidazole	$[(CH_3)_3Si]_2NH$	*N*-Trimethylsilylimidazole	85	82
Pyrazole	$(C_2H_5)_3SiNH_2$	*N*-Trimethylsilylpyrazole	72	82
3,5-Dimethylpyrazole	$(C_2H_5)_3SiNH_2$	3,5-Dimethyl-*N*-trimethylsilylpyrazole	59	82
1,2,4-Triazole	$(C_2H_5)_3SiNH_2$	*N*-Trimethylsilyl-1,2,4-triazole*	81	82
Benzimidazole	$(C_2H_5)_3SiNH_2$	*N*-Trimethylsilylbenzimidazole	81	82
Indazole	$(C_2H_5)_3SiNH_2$	*N*-Trimethylsilylindazole	79	82
Pyrrolidine	$(C_2H_5)_3SiNH_2$	*N*-Trimethylsilylpyrrolidine	72	82
Piperidine	$(C_2H_5)_3SiNH_2$	*N*-Trimethylsilylpiperidine	42	82
Tetramethylenediamine	$[(CH_3)_3Si]_2NH$	*NN*-Bis(trimethylsilyl)tetramethylenediamine	89	87

*The position of the $(CH_3)_3Si$ group in the ring is not indicated.

The silylation of primary amines containing a branched alkyl substituent in the α-position with *N*-methyl-*N*-trimethylsilylacetamide yields monosilyl-substituted products[38]. In other cases silylation with this agent leads to the corresponding silazanes.

N-Methyl-*N*-trimethylsilylamides have been used to silylate secondary amines when the latter were analysed by GLC:[88]

$$RCON(CH_3)Si(CH_3)_3 + R'_2NH \rightarrow RCONHCH_3 + (CH_3)_3SiNR'_2,$$

where R = H or CH_3.

At an elevated temperature primary amines can be silylated by a trialkyl- or triarylsilane in the presence of catalytic amounts of metal hydrides[89]:

$$RNH_2 + R'_3SiH \xrightarrow[\sim 100^\circ]{\text{Met-H}} RNHSiR'_3 + H_2,$$

where R and R' is an alkyl or aryl group. Triarylsilanes react more readily in this process than trialkylsilanes. Likewise alkylamines are silylated less effectively than arylamines.

Table 3. Transamination of silylamines in the presence of catalysts[39].

Amine	Silylating agent	Catalyst	Reaction product	Yield, %
Ethylamine	$(CH_3)_3SiN(C_2H_5)_2$	$(NH_4)_2SO_4$	*N*-Ethylhexamethyldisilazane	85
n-Propyltrimethylsilylamine	ditto	ditto	Hexamethyl-*N*-(n-propyl)-disilazane	93
n-Butylamine	"	"	*N*-(n-butyl)hexamethyldisilazane	90
Aniline	"	"	Hexamethyl-*N*-phenyldisilazane	89
n-Butylamine	$[(CH_3)_3Si]_2NH$	"	*N*-(n-butyl)hexamethyldisilazane	33
Isopropylamine	$(CH_3)_3SiN(C_2H_5)_2$	"	Isopropyltrimethylsilylamine	95
n-Butylamine	ditto	$ZnCl_2$	n-Butyltrimethylsilylamine	90
t-Butylamine	"	$(NH_4)_2SO_4$	t-Butyltrimethylsilylamine	79
Cyclohexylamine	"	ditto	Cyclohexyltrimethylsilylamine	95

2. Silylation of Alcohols

Alcohols are usually silylated with the aid of CTMS (in the presence of tertiary amines) or hexamethyldisilazane. The reactions have comparatively low rates, but the desired products are formed in high yields. Best results were obtained when monosilylacetamides, BSA, and *N*-trimethylsilylimidazole were used. The rate of silylation of alcohols depend on their acidity and on steric factors (see Section II, Subsections 5 and 6).

Individual examples of the silylation of polyhydric alcohols and alcohols with other functional groups are quoted below. Prey and Gump[48], who silylated certain monosaccharides with CTMS in the presence of pyridine, obtained bis-, tris-, and tetrakis(trimethylsilyl)derivatives of monosaccharides. Schwartz et al.[52] reported the synthesis of incompletely silylated D-glucose with chlorotriethylsilane in pyridine. In the presence of a deficiency of the silylating agent the product is *O*-tris(triethylsilyl)-D-glucose, while in the presence of an excess of the silylating agent a mixture of tris- and tetrakis-(triethylsilyl)-D-glucoses is formed. Pentakis(trimethylsilyl)-glucose can also be obtained by silylating glucose with CTMS.[47]

Derivatives with all the hydroxy-groups trimethylsilylated were obtained by treating uronic acids with CTMS in the presence of pyridine[90]. Alcohols with sulphur-containing functional groups, for example $(C_3H_7S)_2C(CH_3).CH_2OH$, were silylated with CTMS in the presence of triethylamine[91]. Halogenophenols react with CTMS to form the corresponding trimethylsilyl derivatives[92]. Acetone cyanohydrin is also silylated with CTMS.[93,94]

Certain nitro- and halogeno-alcohols were recently silylated with the aid of halogenosilanes[19,95,96]:

$$(CH_3)_3SiCl + ROH \xrightarrow{C_5H_5N} (CH_3)_3SiOR,$$
$$R=CH_2CH_2NO_2,\ CH(CH_3)CH_2NO_2,\ CH_2NO_2,$$
$$CH(NO_2)C_2H_5,\ C(CH_3)_2CH_2NO_2,\ CH(CH_3)C(NO_2)(Br)CH_3,$$
$$CH_2C(Br)(NO_2)CH_3,\ CH(CH_2Cl)CH_2NO_2.$$

The silylation of sugars[97] and phenols[46,98] by hexamethyldisilazane gave high yields of the corresponding derivatives with all the hydroxy-groups trimethylsilylated. The silylation of alcohols, including steroid alcohols[77], by the BSA–CTMS–*N*-trimethylsilylimidazole mixture has been investigated at 60–80°C in several studies[74,77]. The resulting trimethylsilyl derivatives were analysed by GLC. It was found that this mixture of silylating agents is in some cases more effective than BSA.

The silylation of glucose and its derivatives by *N*-trimethylsilylacetamide has been reported[99]. The reactions proceed at high rates and with satisfactory yields. The silylation of polyhydric alcohols and sugars by *N*-methyl-*N*-trimethylsilylacetamide makes it possible to separate these compounds by GLC.[88] BSA readily silylates 2′-hydroxy-*m*-terphenyl, while 2,6-di-t-butylphenol reacts with BSA only on refluxing in acetonitrile[100]‡. The silylation of alcohols by trimethylvinyloxysilanes takes place with high yields in the presence of catalytic amounts of CTMS.[78]

3. Silylation of Aminoalcohols

Aminoalcohols are silylated by CTMS (in the presence of triethylamine)[101], hexamethyldisilazane[102], or dimethyltrimethylsilylamine[39]. These reactions have been mainly investigated for ethanolamine, the hydroxy-group being silylated first[101,102]:

$$HOCH_2CH_2NH_2 \xrightarrow[(C_2H_5)_3N]{(CH_3)_3SiCl} (CH_3)_3SiOCH_2CH_2NH_2$$

or

$$HOCH_2CH_2NH_2 \xrightarrow{[(CH_3)_3Si]_2NH} (CH_3)_3SiOCH_2CH_2NH_2.$$

Under more severe conditions and in the presence of an excess of the silylating agent, the *NO*-bis(trimethylsilyl) derivative of ethanolamine is produced[101]:

$$HOCH_2CH_2NH_2 \xrightarrow[(C_2H_5)_3N]{(CH_3)_3SiCl} (CH_3)_3SiOCH_2CH_2NHSi(CH_3)_3.$$

Ethanolamine has been silylated to *NN*-bis(trimethylsilyl)-*O*-trimethylsilylethanolamine with the aid of diethyltrimethylsilylamine in the presence of $(NH_4)_2SO_4$ as the catalyst[39].

It has been shown that the BSA–*N*-trimethylsilylimidazole mixture can silylate selectively the OH group in aminoalcohols in the presence CTMS.[74]

4. Silylation of Organic Acids

Trimethylsilyl esters of organic acids are usually obtained when the acids are treated with hexamethyldisilazane[98] or CTMS in the presence of pyridine[103]. For example, bis(trimethylsilyl) esters of terephthalic, fumaric, and sebacic acids have been obtained by treating the dibasic acids with CTMS.[103] Trimethyl acetate, propionate, and adipate have been synthesised with the aid of hexamethyldisilazane[98]. The silylation of derivatives of certain hydroxyacids has been studied[103].

When sodium tartrate is acted upon by CTMS, a mixture of products is formed: 2,3-bis(trimethylsilyl) derivatives of tartaric acid, polytartrate esters, trimethylsilanol, and hexamethyldisiloxane. The reaction of CTMS with strontium lactate results in the formation of polylactate esters, trimethylsilanol, and α-trimethylsiloxylactic acid, which the authors believe is obtained as a result of a rearrangement of monotrimethylsilyl lactate[103]:

$$\left[\begin{matrix}HOCHCOO\\ |\\ CH_3\end{matrix}\right]_2 Sr + 2(CH_3)_3SiCl \rightarrow SrCl_2 + 2\{CH_3CH(OH)COOSi(CH_3)_3\}$$
$$\downarrow$$
$$(CH_3)_3SiOCH(CH_3)COOH\ (65\text{—}70\%) + [-CH(CH_3)COO]_n + n(CH_3)_3SiOH.$$

In order to identify certain acids, their trimethylsilyl esters, which are suitable for infrared spectroscopic studies, are prepared with the aid of dialkyl trimethylsilyl *N*-trimethylsilylphosphorimidates[70]§:

$$RCOOH + (C_2H_5O)_2P[OSi(CH_3)_3]{=}NSi(CH_3)_3 \rightarrow (C_2H_5O)_2P(O)NHSi(CH_3)_3 + RCOOSi(CH_3)_3.$$

5. Silylation of Aminoacids

Aminoacids can be silylated by various agents: CTMS, hexamethyldisilazane, silylamines, and silylamides. In many cases best results were obtained when CTMS was used in the presence of triethylamine[104].

CTMS reacts with both the free acids and with their derivatives. The hydrogen of the carboxy-group is the first to be substituted in free aminoacids. It was found that monoaminoacids are converted into the corresponding hydrochlorides of their trimethylsilyl esters after only brief heating in the presence of an excess of CTMS.[105]:

$$H_2NCHRCOOH + (CH_3)_3SiCl \rightarrow HCl \cdot H_2NCHRCO_2Si(CH_3)_3,$$

where R = CH_3 or $CH_2CH(CH_3)_2$.

Aminoacids with several functional groups also form the hydrochlorides of *O*-trimethylsilyl esters on interaction with CTMS.[105] In particular, the hydrochlorides of the trimethylsilyl esters of glutamic acid, serine, and cystine have been obtained[105]. It is noteworthy that under these conditions lysine forms a mixture of mono- and tris(trimethylsilyl) derivatives[105]:

$$3H_2NCH_2(CH_2)_3CH(NH_2)COOH + 5(CH_3)_3SiCl \rightarrow 2\begin{matrix}CH_2(CH_2)_3CHCO_2Si(CH_3)_3\\ |\quad\quad\quad\quad |\\ NH_2\cdot HCl\quad NH_2\cdot HCl\end{matrix} +$$
$$+\begin{matrix}CH_2(CH_2)_3CHCO_2Si(CH_3)_3\\ |\quad\quad\quad\quad |\\ NHSi(CH_3)_3\quad NHSi(CH_3)_3\end{matrix}.$$

The difficulty of silylating certain free aminoacids by chlorosilanes has been explained in a review[5] by the existence of inactive betaines. *O*-Trialkylsilyl esters of aminoacids sometimes disproportionate on heating[106]:

$$2RCH(NH_2)COOSiR'_3 \rightarrow RCH(NHSiR'_3)COOSiR'_3 + RCH(NH_2)COOH.$$

When the hydrochlorides of trimethylsilyl esters of aminoacids are treated with CTMS and triethylamine, *NO*-bis-(trimethylsilyl) derivatives of the aminoacids can be isolated in low yields[105].

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‡ CTMS and hexamethyldisilazane do not enter into this reaction[100].

§ The use of silylamides for this purpose is ruled out, because the reaction results in their conversion into carbonyl compounds[70].

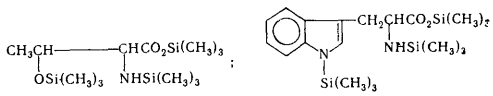
The silylation of aminoacids by hexamethyldisilazane leads to the formation of *NO*-bis(trimethylsilyl) derivatives and in this case too the hydrogen of the carboxy-group is the first to be substituted[106,107]§. A mixture of diethyltrimethylsilylamine, CTMS, and triethylamine is sometimes used to synthesis *NO*-bis(trimethylsilyl) derivatives of aminoacids[106].

Satisfactory results were obtained in the silylation of aminoacids by diethyltrimethylsilyl- or dibutyltrimethylsilyl-amines in the presence of catalytic amounts of $(NH_4)_2SO_4$. *NO*-Bis(trimethylsilyl) derivatives of valine, alanine, phenylalanine, leucine, and isoleucine were isolated in this way[39,108]. It was possible to introduce three $(CH_3)_3Si$ groups only into the sterically unhindered glycine molecule[39]:

$$H_2NCH_2COOH + 3(CH_3)_3SiN(C_2H_5)_2 \xrightarrow{(NH_4)_2SO_4} [(CH_3)_3Si]_2NCH_2CO_2Si(CH_3)_3 + 3NH(C_2H_5)_2.$$

A number of aminoacids with functional groups and their hydrochlorides have been silylated with the aid of diethyltrimethylsilylamine. In particular, derivatives of glutamic acid, sarcosine, alanine, histidine, proline, norvaline, tyrosine, hydroxyproline, and aspartic acid with all the functional groups trimethylsilylated have been obtained[109].

Klebe et al.[110] separated aminoacids by gas–liquid chromatography after silylating them with the aid of BSA. They investigated the silylation of more than 20 aminoacids, including alanine, valine, and serine. They were the first to describe the fully silylated threonine and tryptophan:



Trifluoro-*NO*-bis(trimethylsilyl)acetamide has also been proposed as a silylating agent for aminoacids[64]. Because of its volatility, it is more suitable for the gas–liquid chromatographic analysis of aminoacids than BSA.

The effects of silylating agents of different classes on certain aminoacids (phenylalanine, lysine, and tyrosine) were compared under the conditions of gas–liquid chromatography[76]. They were arranged in the following sequence in terms of the rate of silylation: dialkyltrimethylsilylamines > BSA ≫ monosilylacetamide. *N*-Trimethylsilylimidazole proved to be inactive under these conditions. It is interesting that the addition of dimethylformamide or dimethylformamide and CTMS to BSA impaired the silylating capacity of the latter, while pyridine facilitated silylation. Trifluorobis(trimethylsilyl)-acetamide was regarded as equal to BSA in its silylating capacity. The authors arranged in the following sequence the aminoacids investigated in terms of the rate of silylation: tyrosine ≥ phenylalanine > lysine. The above series do not involve the absolute kinetic characteristics of the process, since they reflect not only the rate of silylation but also the stability of the derivatives formed in solution.

It has been shown[75] that properties of the solvent have a significant influence on the degree of silylation of polyfunctional aminoacids. With increase of solvent polarity the degree of silylation of these products usually rises.

By treating alkyl esters of aminoacids with CTMS, Birkofer and Ritter[111,112] obtained their *N*-trimethylsilyl derivatives:

$$H_2NCHR(CH_2)_nCO_2C_2H_5 \xrightarrow{(CH_3)_3SiCl} (CH_3)_3SiNHCHR(CH_2)_nCO_2C_2H_5,$$

where $n = 0$ and R = H, n-C_3H_7, or s-C_4H_9 and $n = 1$ and R = H or CH_3.

N-Benzoyl derivatives of aminoacids react with CTMS to form *N*-benzoyl-substituted trimethylsilyl esters[113]:

$$C_6H_5CONHCHRCO_2H + (CH_3)_3SiCl \xrightarrow{C_5H_5N} C_6H_5CONHCHRCO_2Si(CH_3)_3,$$

where R = H, CH_3.

On silylation with CTMS in the presence of pyridine and formamide, glutamic acid gives rise only to the mono-*O*-trimethylsilyl derivatives, because (according to the authors) the amino-group and the second carboxy-group form an inner salt[113].

Ruhlmann[114] obtained trimethylsilyl-substituted aminoacids by treating alkali metal salts of the aminoacids with CTMS and triethylamine. He then isolated fully trimethylsilylated glycine, alanine, phenylalanine, and ϵ-aminocaproic, *p*-aminobenzoic, anthranilic, and glutamic acids. Treatment of glycine, alanine, and isoleucine hydrochlorides with CTMS and triethylamine led to the formation of the corresponding *NO*-bis(trimethylsilyl) derivatives of the aminoacids[115].

6. Silylation of Peptides

Like aminoacids, peptides have been silylated by treatment with CTMS,[111] hexamethyldisilazane[116], silylamines[117], and silylamides[104]. Both the carboxy- and amino-groups were silylated in the resulting products. When hexamethyldisilazane was used, only dioxopiperazines were isolated from the reaction mixture[116].

7. Silylation of Ketoximes and Aldoximes

These compounds are silylated by CTMS in pyridine[118-120]:

$$RR'C{=}NOH + (CH_3)_3SiCl \xrightarrow{C_5H_5N} RR'C{=}NOSi(CH_3)_3$$

R=R′=CH_3; R=R′= iso-C_5H_7; R=C_6H_5, R′=CH_3; R=H, R′=CH_3; R=H, R′=C_6H_5; R=H, R′=*o*-C_6H_4OH; R=H, R′=*o*-$(CH_3)_3SiOC_6H_4$.

8. Silylation of Hydroxylamine

When hydroxylamine is silylated by an equimolar amount of CTMS, *O*-trimethylsilylhydroxylamine is formed[121]. When the reaction is carried out in the presence of triethylamine and an excess of CTMS, the product is *NO*-bis(trimethylsilyl)hydroxylamine[121]:

$$NH_2OH + 2(CH_3)_3SiCl \xrightarrow{(C_2H_5)_3N} (CH_3)_3SiNHOSi(CH_3)_3.$$

The second hydrogen atom at the nitrogen atom can be substituted by the trimethylsilyl group only via the lithio-derivative[121]:

$$(CH_3)_3SiNH \xrightarrow[OSi(CH_3)_3]{C_4H_9Li} (CH_3)_3SiNOSi(CH_3)_3 \xrightarrow[Li]{(CH_3)_3SiCl} [(CH_3)_3Si]_2NOSi(CH_3)_3.$$

When CTMS was allowed to react with *O*- and *N*-alkyl derivatives of hydroxylamine, products with both one and two hydrogen atoms substituted by the $(CH_3)_3Si$ group were obtained[122].

¶*O*-Trimethylsilyl derivatives of aminoacids can be obtained by treating the *NO*-bis(trimethylsilyl) derivatives with ammonia of the free aminoacid[107].

9. Silylation of Hydrazines

When *O*- and *N*-alkyl derivatives of hydroxylamine are treated with CTMS, the product is 1,2-bis(trimethylsilyl)-hydrazine[123,124]. Under more severe conditions, a mixture of 1,2- and 1,1-bis(trimethylsilyl)hydrazines is isolated[124-126]. It has been suggested[124] that both isomers are formed as a result of the interaction of CTMS with intermediate monosilylated hydrazine. It has also been found that 1,2-bis(trimethylsilyl)hydrazine rearranges to 1,1-bis(trimethylsilyl)hydrazine in boiling benzene in the presence of N_2H_4.HCl or triethylamine.

1-Methyl-2-trimethylsilylhydrazine was obtained from methylhydrazine and CTMS.[127] Other trimethylsilyl derivatives of hydrazine were synthesised from this compound[126]:

$$CH_3NHNHSi(CH_3)_3 \xrightarrow[2.(CH_3)_3SiCl]{1.C_4H_9Li} CH_3N[Si(CH_3)_3]NHSi(CH_3)_3 + CH_3NHN[Si(CH_3)_3]_2.$$

On heating above 100°C in the presence of $N_2H_3(CH_3)$.HCl, the resulting mixture isomerises[127]:

$$(CH_3)_3SiN(CH_3)NHSi(CH_3)_3 \rightleftarrows CH_3NHN[Si(CH_3)_3]_2 .$$

10. Silylation of Acetylenes

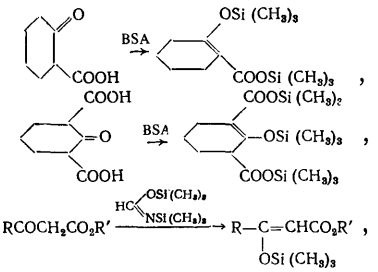
The silylation of free acetylenes has not been described, but there have been a number of studies dealing with the silylation of lithium, sodium, or magnesium derivatives of acetylenes by trialkylhalogenosilanes. Since it is comparatively difficult to remove the trialkylsilyl group from the acetylene silylation products, the term "silylation" is not used in the present sections strictly in the sense employed elsewhere in the review. However, since silylation is nowadays widely used to protect the terminal C≡C bond in order to use the resulting derivatives as intermediates in organic synthesis, we thought it desirable to include some information on this problem. The main data on the silylation of acetylenes up to 1960 have been compiled in a monograph[128]. Later a series of studies dealing with the silylation of metallated arylacetylenes (see for example, Eaborn et al.[129]), halogenoacetylenes[130], and unsubstituted acetylene (see, for example, Eastmond and Walton[131] and Krüerke[132]) were carried out.

11. Silylation of Ambident Systems

Bearing in mind the appreciable hardness of silyl cations[133], the interaction of silylating agents with ambident compounds may be expected to result in the silylation of the hardest anionic centre in these systems. However, in view of the relative lability of the silicon–element bonds, one can also postulate that both kinetically and thermodynamically favoured products of the silylation reaction should be detected in this case.

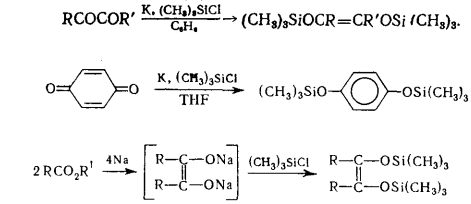
Silylation of ketones. As already mentioned, when carbonyl compounds are treated with a mixture of *N*-trimethylsilylimidazole with BSA and CTMS at an elevated temperature, the hardest centre in the ambident system—the oxygen atom—is silylated[74,77].

Silylation of α- and β-keto-acids and β-ketoacid esters. When these compounds were silylated by *NO*-bis(trimethylsilyl)amides, the corresponding *O*-trimethylsilyl derivatives were obtained[10,80]:

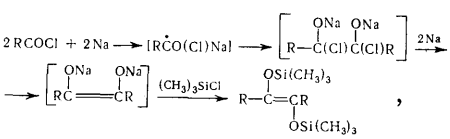


where R = CH_3, C_6H_5, or CH_3OCOCH_2 and R′ = CH_3 or C_2H_5.

Silylation of *O*- and *C*-metallo-derivatives of carbonyl compounds. The silylation of enolates usually leads to the formation of *O*-silylated products. When hydroxyketones[134], diketones[135], and carboxylic acid esters and chlorides[136-140] react with CTMS in the presence of alkali metals, it is suggested that the corresponding enolates are formed initially and then give rise to *O*-silylation products having the general formula $R'C[OSi(CH_3)_3]=CR[OSi(CH_3)_3]$, where R and R′ are alkyl substituents in the initial compounds. Several examples of this reaction are given below:

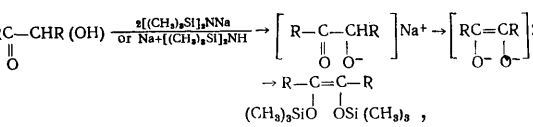


where R = CH_3, C_2H_5, C_3H_7, iso-C_3H_7, n-C_4H_9, $(CH_3)_2CH(CH_2)_2$, or n-C_7H_{15} and R′ = C_2H_5 or n-C_4H_9;



where R = H, CH_3, C_2H_5, or C_3H_7.

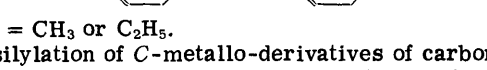
The sodium salt of hexamethyldisilazane may be used to synthesise *O*-metallo-derivatives of α-hydroxyketones[134]:



where R = H, CH_3, C_6H_5 or β-furyl and R′ = H, CH_3, C_6H_5, or β-furyl.

The interaction of carbonyl compounds capable of enolisation with the sodium salt of hexamethyldisilazane or of sodium enolates of carbonyl compounds with CTMS leads to the corresponding *O*-trimethylsilyl derivatives[71,141]. The reactions of alkyl- and alkylalkoxy-halogenosilanes with the sodio-derivatives of acetoacetic ester[142-144] or acetylacetone[145] leads to the formation of the corresponding *O*-silylated derivatives. The exchange reaction

of trialkylchlorosilanes with tributylstannoxycyclohex-1-ene provides a convenient method for synthesising trialkylsiloxycyclohex-1-enes[146,147]:



where R = CH_3 or C_2H_5.

The silylation of *C*-metallo-derivatives of carbonyl compounds also involves the formation of *O*-silylated products[148-151]. The reaction of *C*-metallo-derivatives of acetone with trialkylhalogenosilanes led to the formation of the corresponding alkoxysilanes[72,151]:

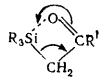
$$R_M CH_2COCH_3 \xrightarrow{R_3SiHal} CH_2=C(CH_3)OSiR_3 + R_MHal,$$

where R_M = $HgCH_2COCH_3$, HgCl, HgI, $(C_4H_9)_3Sn$, $(C_3H_7)_3Sn$, or $(C_3H_7)_3Ge$, R = CH_3, C_2H_5, or C_3H_7, and Hal = Cl, Br, or I.

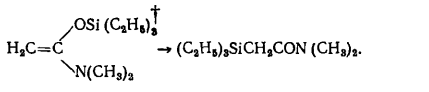
When trialkylhalogenosilanes were allowed to react with α-metallated carboxylic acid esters, only the *O*-silylation products were also isolated[72,151,152]:

$$(C_2H_5)_3SiI + Hg(CH_2COOCH_3)_2 \rightarrow CH_2=C(OCH_3)OSi(C_2H_5)_3 + IHgCH_2COOCH_3;$$
$$(C_2H_5)_3SnCH_2COOCH_3 + (C_3H_7)_3SiI \rightarrow (C_2H_5)_3SnI + CH_2=C(OCH_3)OSi(C_3H_7)_3.$$

There is an equilibrium between the *O*- and *C*-silyl derivatives of carbonyl-containing compounds, which is usually displaced towards one of the products[150]. Isomerisation of silyl derivatives of carbonyl-containing systems can be an intramolecular[153-155] or an intermolecular[153,156] process. Since in the former case the optical configuration at the silicon atom is retained[155], it has been suggested that the reaction proceeds via a four-unit cyclic transition state:



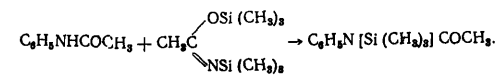
Intermolecular isomerisation is accelerated by trialkyliodosilanes or mercury salts[153-156]. The rate of isomerisation and the equilibrium position depend on the nature of the carbonyl compound and the substituents at the silicon atom. The introduction of electronegative substituents at the silicon atom facilitates the conversion into *C*-silylated products[157]. Substituents at the carbonyl group with a positive mesomeric effect also promote the rearrangement of *O*-derivatives into *C*-derivatives[158]:



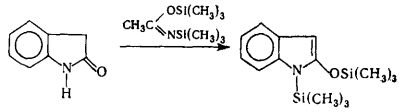
O-Silyl-derivatives are comparatively more favoured by thermodynamic factors, probably because of the $(p-d)\pi$ interaction between the oxygen and silicon atoms[150].

Silylation of amides, ureas, and urethanes. The silylation of amides has already been discussed. It was noted that the formation of these products is reasonable on thermodynamic grounds. Depending on the nature of the substituents at the carbonyl groups and at the nitrogen atom, the amide or imide form of the products predominates or their equilibrium mixture is formed.

In addition we may quote the study by Klebe et al.[100], who showed that amides can be silylated by BSA:



Under these conditions oxindole is immediately converted into the bis(trimethylsilyl) derivative[100]:



The silylation of phenyl esters of phosphoramidic acids with the aid of hexamethyldisilazane or methyltrimethylsilylamine yielded the corresponding trimethylsilyl derivatives[30,159]:

$$RN[Si(CH_3)_3]H + (NH_2)_nP(O)(OC_6H_5)_{3-n} \rightarrow [(CH_3)_3SiNH]_nP(O)(OC_6H_5)_{3-n},$$

where R = CH_3 or $Si(CH_3)_3$ and n = 1 or 2.

Some data on the silylation of ureas were presented above. Only the *N*-silylation products have been isolated. In addition to the foregoing, we may mention that urea can be silylated also by hexamethyldisilazane[88]:

$$CO(NH_2)_2 + [(CH_3)_3Si]_2NH \rightarrow [(CH_3)_3SiNH]_2CO + NH_3.$$

Mono-*N*-trimethylsilyl derivatives have also been obtained by treating the corresponding ureas with BSA.[100]

A number of studies have been made on the silylation of various urethanes by CTMS in the presence of triethylamine[160-162]:

$$RNHCOOR' \xrightarrow[(C_2H_5)_3N]{(CH_3)_3SiCl} RN[Si(CH_3)_3]COOR',$$

where R = alkyl[160,161] or C_6H_5 [162] and R' = CH_3, [160] $(CH_3)_3Si$, [161] or C_2H_5. [162] Kricheldorf[162] demonstrated rigorously by spectroscopic investigations that the products isolated are exclusively *N*-trimethylsilyl derivatives.

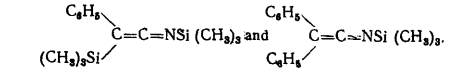
Silylation of compounds in which the mobile hydrogen atom has been replaced by a metal. When halogenosilanes react with silver cyanide[163-165], mixtures of silyl-substituted cyanides and isocyanosilanes, in equilibrium with one another, are formed. According to infrared spectroscopic data[166], the cyanide formed predominates the usual temperature, but with increase of temperature its content in the mixture falls.

The silylation of the corresponding silver salts by bis(trimethylsilyl) sulphide yielded $(CH_3)_3SiNC$ and $(CH_3)_3SiNCO$.[34] Trimethylsilyl nitrite is formed from silver nitrite and CTMS.[167]‡ The reaction of CTMS with silver cyanamide yields *NN*-bis(trimethylsilyl)carbodiimide, $(CH_3)_3SiN=C=NSi(CH_3)_3$, which is isomeric with cyanohexamethyldisilazane[169].

The tris(trimethylsilyl) derivative was obtained from the trisodium salt of acetonitrile and CTMS:[140]

$$Na_3[N\equiv C-C \leftrightarrow C=C=N] \xrightarrow{(CH_3)_3SiCl} [(CH_3)_3Si]_2C=C=N-Si(CH_3)_3.$$

The corresponding trimethylsilylated products were isolated similarly after the reaction of the sodium salts of phenylacetonitrile and diphenylacetonitrile with CTMS:[140]



Similar results were obtained by Klebe[170] in the silylation of malonotrile.

†H_2C = $CNR'_2(OSiR_3)$ is obtained by the interaction of $R_3SiNR'_2$ with keten[158].

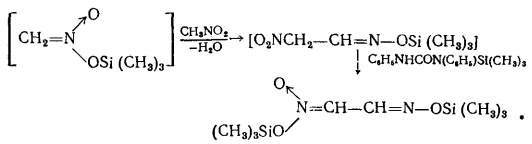
‡ $(CH_3)_3SiONO_2$ was obtained similarly[168].

Silylation of diazoacetic ester. Schollkopf and coworkers[171,172] obtained diazo-*C*-trimethylsilylacetic ester by the interaction of diazoacetic ester salts with CTMS or bis(trimethylsilyl) sulphide:



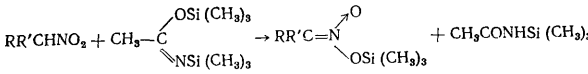
Silylation of nitro-compounds. Since nitro-compounds exhibit a dual reactivity[153], the formation of *O*-silylation products may be expected in their silylation reactions.

After allowing nitromethane to react with *NN'*-diphenyl-*N*-trimethylsilylurea, Klebe[170] isolated the bis(trimethylsilyl) derivatives of methazonic acid. The author suggests that this product is formed via the intermediate trimethylsilyl ester of methanenitronic acid:

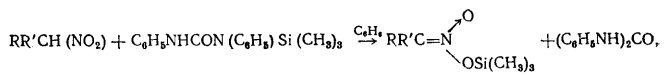


After the reaction of nitromethane with CTMS in pyridine, Manzur and Zamudio[174] isolated hexamethyldisiloxane, which they believe is also formed via the intermediate trimethylsilyl ester of methanenitronic acid. However, no evidence is adduced[170,174] in support of the formation of this intermediate.

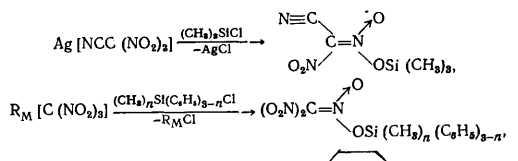
The first clear-cut experimental confirmation of the *O*-silylation of nitro-compounds was obtained by Tartakovskii and coworkers[155-159]. On silylation of nitroalkanes (nitromethane, nitroethane, etc.) by BSA, these investigators isolated (or detected) the trimethylsilyl esters of the corresponding alkanenitronic acids in nearly quantitative yields[175]:

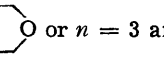


where R = R' = H (20°C)§, R = CH_3 and R' = H (60°C), R = C_2H_5 and R' = H (80°C), R = R' = CH_3 (100°C), or R = C_6H_5 and R' = H (20°C). *O*-Trialkylsilyl derivatives of aliphatic nitro-compounds with other functional groups have been obtained by treating the free nitro-compounds with *NN'*-diphenyl-*N*-trimethylsilylurea[176-179]:



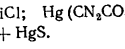
where R = R' = $COOCH_3$, R = $COOCH_3$ and R' = H, R = NO_2 and R' = H, or R = R' = NO_2, or by the interaction of the silver or mercury salts of the nitro-compounds with alkylchlorosilanes[176-179]:

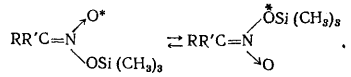


where *n* = 0, 1, or 3 and R_M = Ag.  or *n* = 3 and R_M = $Hg[C(NO_2)_3].CH_3NO_2$.

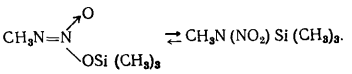
§ The silylation temperature is indicated in brackets.

The structure of the silyl esters of nitronic acids has been confirmed by making them undergo the 1,3-dipolar cycloaddition reaction with olefins and also by infrared, ultraviolet, and NMR spectroscopic data[176-180].

It has been shown[180] that there is a rapid intramolecular exchange of the $(CH_3)_3Si$ group between the oxygen atoms in the  fragment:



The silylation of methylnitramine by methyltrimethylsilylamine, BSA, or *NN'*-diphenyl-*N*-trimethylsilylurea as well as the silylation of the silver salt of methylnitramine by CTMS leads to a tautomeric mixture of *O*- and *N*-trimethylsilyl derivatives of methylnitramine[181]:



The presence of tautomers is indicated by low-temperature NMR data for the products[182]. It has been shown that, with increase of temperature, the equilibrium is displaced towards the *O*-trimethylsilyl derivative. The introduction of bulky substituents at the silicon atom has the same influence on the equilibrium position[182].

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The present review does not have as its aim the discussion of the problem of the applications of trimethylsilyl derivatives in organic synthesis. However, it is necessary to emphasise yet again that silylation makes it possible to expand significantly and modify the sphere of applications of particular products in organic reactions.

As examples, one can quote the interaction of silyldiamines with phosgene[87,183], the use of trimethylsilyl azide in the synthesis of tetrazoles[184,185], the thermal decomposition of silylated urethanes with formation of isocyanates[161], and the involvement of nitroalkane derivatives in dipolar 1,3-cycloaddition[175]. Furthermore, the uses of silyl derivatives in peptide synthesis[1,5] and in the synthesis of nucleosides and nucleotides[186] have been examined in detail.

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