

fore, 0.57 mole of ozone sufficed to cause the disappearance of 1 mole of adduct III under these conditions. The solution was flushed with  $N_2$  for 10 min. and then was assayed for peroxide; found: 16% of peroxide ( $\pm 1\%$ ). Comparisons of the infrared spectrum of the solution with the spectra of solutions containing known mole ratios of acetyl peroxide, acetic anhydride, biacetyl, and trimethyl phosphite showed that the ozonization produced 16% peroxide, 14% anhydride, 70% diketone, and 100% phosphite ( $\pm 5\%$  for the anhydride and diketone).

(2) Other ozonizations were carried out in methylene chloride at  $20^\circ$ . The results are summarized in Table III. Examination of the infrared spectra of solutions after various ozone dosages showed that between 0.4 and 0.5 mole of ozone caused the disappearance of 1 mole of adduct. Examinations of the KI trap showed that this value also corresponds to the ozone which was utilized in the reaction.

(3) Ozonizations were carried out in hexane. The results are given in Table III. The products of the ozonization are sparingly soluble in hexane.

Biacetyl, acetyl peroxide, and acetic anhydride can be recognized by infrared bands at 5.82, 5.60, and 5.52  $\mu$ , respectively.

**Attempted Reaction between Benzoyl Peroxide and the  $\alpha$ -Diketone-Phosphite Adducts.**—The infrared spectrum of a solution containing equimolar amounts of benzoyl peroxide and the benzil adduct II in methylene chloride was examined at various times. After 3 hr. at  $20^\circ$ , there was little evidence for the formation of anhydride and  $\alpha$ -diketone. After 28 hr., the bands caused by these reaction products were detectable. The reaction was not investigated further; it appeared to be incomplete even after 28 hr.

**Reaction of the Benzil-Trimethyl Phosphite 1:1 Adduct (II) with Oxygen in Benzene Solution.**—(1) A solution of the benzil-phosphite adduct II (14.3 g.) in dry benzene (30 ml., 1.36  $M$ ) was stirred at  $20^\circ$  under an atmosphere of dry oxygen. After 5 days, the benzene was removed under vacuum and the residue was examined in the infrared: bands caused by benzoic anhydride (XII), benzil (XIII), and trimethyl phosphite were observed.

(a) A 3.02-g. aliquot of the residue was treated with saturated aqueous sodium bicarbonate and the mixture was kept 17 days at  $20^\circ$ . Benzil (1.21 g., 67%, m.p.  $87-92^\circ$ ) was filtered off, and the filtrate was made acidic with concentrated HCl. Benzoic acid (0.49 g., m.p.  $118-119^\circ$ ) was filtered off and the filtrate was extracted with ether. From the ether additional benzoic acid (0.11 g.) was obtained; total yield of benzoic acid: 30%.

(Benzil was recovered unchanged after 17 days in contact with saturated aqueous bicarbonate.)

(b) A 4.4-g. aliquot of the original residue was distilled under vacuum and gave 1.65 g. (94%) of trimethyl phosphite ( $114-118^\circ$  at 60 mm.).

(c) A 1.21-g. aliquot of the original residue was treated with 0.2 g. of aniline. The mixture was kept 15 min. at  $90^\circ$ , diluted with water, kept 2 hr. at  $20^\circ$ , and extracted with ether. The ether solution gave 0.13 g. of benzanilide, m.p.  $161-162^\circ$  (corresponds to 19% of benzoic anhydride).

**Reaction of the Benzil-Triphenyl Phosphite 1:1 Adduct (XVII) with Oxygen.**—A solution of the benzil-triphenyl phosphite adduct (7.2 g.) in benzene (25 ml., 0.54  $M$ ) was stirred at  $20^\circ$  under an atmosphere of oxygen. After 3 days the reaction seemed complete (the phenyl phosphite adduct appears to react faster than the methyl phosphite adduct). Benzanilide corresponding to 25% of benzoic anhydride was obtained by the procedure (1c) indicated above for the methyl phosphite adduct.

**Reactions of the Biacetyl-Trimethyl Phosphite 1:1 Adduct (III) with Oxygen in Benzene Solution.**—A solution of the biacetyl-phosphite adduct III (12.0 g.) in dry benzene (25 ml., 2.0  $M$ ) was stirred at  $20^\circ$ , under an atmosphere of dry oxygen, for 9 days. The mixture was submitted to fractional distillation. Benzene and most of the biacetyl were removed first. The second fraction was acetic anhydride (10–15%) identified by infrared spectrum and by conversion to acetanilide. The third fraction was trimethyl phosphite (70–75%). The fourth fraction (ca. 15%) was the adduct formed from biacetyl and the 1:1 biacetyl-trimethyl phosphite adduct (III), *i.e.*, the 2:1 biacetyl-trimethyl phosphite adduct XVIII (*meso*- and *rac*-2,2,2-trimethoxy-4,5-dimethyl-4,5-diacetyl-1,3-dioxaphospholane).<sup>10</sup>

The presence of biacetyl (about 60%) among the reaction products was determined by formation of the bis-2,4-dinitrophenylhydrazone.

**Attempts to Oxidize the Phenanthrenequinone-Trimethyl Phosphite 1:1 Adduct (I) with Molecular Oxygen.**—A solution of the quinone adduct I in dry benzene was stirred under 1 atm. of dry oxygen for 7 days. The adduct was recovered unchanged.

The pure adduct I was kept 4 days at  $110^\circ$  under an oxygen atmosphere. The product consisted of phenanthrenequinone (ca. 40%) and recovered adduct I (ca. 40%, separated by ether extraction.)

[CONTRIBUTION FROM THE GENERAL ELECTRIC RESEARCH LABORATORY, SCHENECTADY, N. Y.]

## The Addition of Silylamines and Silazanes to Isocyanates

By J. F. KLEBE, J. B. BUSH, JR., AND J. E. LYONS

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Addition reactions of secondary and tertiary silylamines and of silazanes with isocyanates were studied. Silylamine-isocyanate adducts (1:1) were obtained with secondary and tertiary silylamines. Spectroscopic evidence favors N-silylurea structures for these thermally stable, hydrolytically sensitive adducts. Silylureas containing at least one proton on nitrogen were found to undergo a rapid silyl-proton exchange. Reactions of disilazanes with isocyanates led to disilyl-substituted ureas and biurets. Isothiocyanates and silylamines formed analogous adducts which reverted to the starting materials at elevated temperatures.

### Introduction

The rapidly growing literature on the chemistry of silicon-nitrogen compounds contains a remarkably small number of reports dealing with an important type of reaction, the addition of silylamines to reactive functional groups and activated double bonds. No extensive study of any specific silylamine addition reaction, *e.g.*, to activated carbon-carbon double bonds, to isocyanates, etc., has been published. In several publications dealing with reactions of this kind, the silicon-nitrogen bond has been regarded as being analogous to a carbon-nitrogen bond; only structures of addition products have been considered which may be derived by cleavage of a hydrogen-nitrogen bond also con-

tained in the molecule. A few authors, however, report silylamine addition products whose structures show that cleavage of a Si-N bond has indeed taken place; this suggests that this bond may resemble in its reaction the H-N rather than the C-N bond. The factors governing the structure of addition products of secondary silylamines, R-N-Si≡, in which cleavage

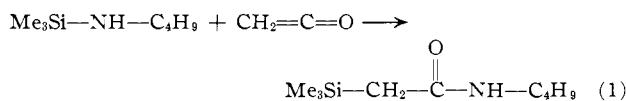
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of either Si-N or H-N can apparently occur, have not previously been investigated.

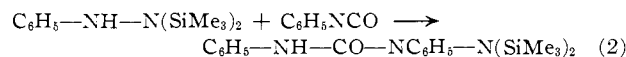
Additions of secondary silylamines to acrylonitrile,<sup>1</sup>

(1) V. G. Mironov, A. D. Petrov, and N. A. Pogonkina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 768 (1955).

ketene,<sup>2</sup> and phenyl isocyanate<sup>3-5</sup> have been shown to give products resulting from N-H bond cleavage. An exception is the addition of trimethylsilylbutylamine to ketene<sup>2</sup>

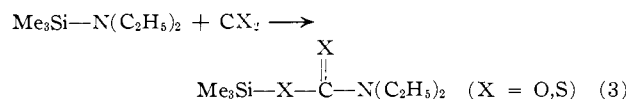


Where NH and NSiMe<sub>3</sub> on different nitrogens may react, it is reported that the product is that resulting from reaction of the NH bond



However, only the structure of the semicarbazide derived from the presumed product was established, and the proof of structure of the starting material is based on the assumption that N-H bond cleavage is the preferred course of the reaction.<sup>4a</sup>

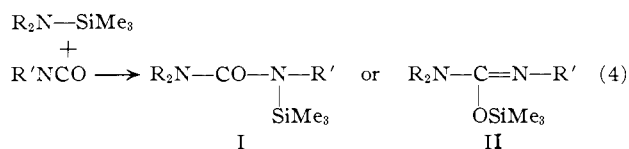
Prior to the completion of this work, only one class of reactions of tertiary silylamines involving Si-N bond cleavage was reported. Breederveld<sup>6</sup> has shown that tertiary silylamines add to carbon dioxide or carbon disulfide



After this work was completed, the preparation of adducts from trimethylsilyldiethylamine with ethyl isocyanate and phenyl isocyanate was published.<sup>7a,b</sup>

**Addition of Tertiary Silylamines to Isocyanates.**—We find that the addition of tertiary silylamines to isocyanates, a reaction which must involve N-Si cleavage, can be carried out with a wide variety of silylamines and isocyanates. The reaction is exothermic in many cases, proceeds under mild conditions, and leads to high yields of crystalline, hydrolytically sensi-

tive, and thermally stable products. A number of compounds prepared in this manner is listed in Table I. Elemental analyses show them to be 1:1 silylamine-isocyanate adducts.



An attempt was made to decide by spectroscopic means whether the addition products are N-trimethylsilylureas (I) or O-trimethylsilylisoureas (II). Comparisons of the infrared and ultraviolet spectra of the adducts with spectra of model compounds proved to be inconclusive.<sup>8</sup> Recently Pump and Rochow<sup>9</sup> have reported that the proton magnetic resonance spectra of a number of bistrimethylsilylamides show two trimethylsilyl absorptions which coalesce into a single absorption at temperatures from 28 to 88°. Their interpretation is that these compounds have N-silyl-silylimide structures, and that rapid intramolecular exchange of silyl groups between oxygen and nitrogen takes place at elevated temperatures. At the lowest temperature accessible with our equipment (213° K.) no evidence of splitting or broadening (other than viscosity broadening) can be detected in the single trimethylsilyl absorptions of bistrimethylsilyl-substituted ethyleneurea, N,N'-dimethylurea, and N,N'-diphenylurea. These results may be interpreted either as indicating that these compounds are O,N-bistrimethylsilyl-substituted isoureas and that trimethylsilyl exchange is rapid even at 213° K. or that the two trimethylsilyl groups are in equivalent environments. We favor the latter interpretation which requires that the compounds have N,N'-bistrimethylsilylurea structures. By analogy, we suggest that the monosilylated ureas are N-trimethylsilyl substituted (structure I). It has been reported that, based on spectroscopic evidence, silylamides exist in the iminoether form rather than the amide form.<sup>10</sup> Further work on the structure of silylamides and silylureas is indicated, in view of the discrepancy between these conclusions.

**Addition of Secondary Silylamines to Isocyanates.**—In view of the demonstration that N-Si cleavage may take place during addition to isocyanates, the question of the direction of bond cleavage in the addition of secondary silylamines to isocyanates was examined. The properties of these adducts resemble those of the products of isocyanates with tertiary silylamines: they are easily soluble even in aliphatic hydrocarbons, relatively stable thermally but very sensitive to hydrolysis. Iminoether structures analogous to those considered for the adducts of tertiary silylamines and isocyanates are possible also for the trisubstituted

TABLE I  
SILYLUREAS FROM TERTIARY SILYLAMINES

Structure	M.p., °C. or b.p. (mm.)	Car- bon, %		Hy- dro- gen, %		Nitro- gen, %		Sili- con, %	
		Found Calcd.	Found Calcd.	Found Calcd.	Found Calcd.				
$\text{C}_6\text{H}_5\text{NCON}(\text{CH}_3)_2$   SiMe <sub>3</sub>	46-49	60.9 61.0	8.4 8.5	12.0 11.9	11.6 11.9				
$\text{C}_6\text{H}_5\text{NCONC}_6\text{H}_{10}$   SiMe <sub>3</sub>	42-44 95-96 (3)	65.3 65.2	8.6 8.7	10.1 10.1					
$\text{C}_6\text{H}_5\text{NCONCH}_3$   CH <sub>3</sub> SiMe <sub>3</sub>	35-38	60.9 60.9	8.7 8.5	11.8 11.9	12.4 11.9				
$\text{C}_6\text{H}_5\text{NCONC}_6\text{H}_5$   CH <sub>3</sub> SiMe <sub>3</sub>	56-60	68.7 68.4	7.3 7.4	9.3 9.4	9.8 9.4				
$\text{CH}_3-p\text{-C}_6\text{H}_4\text{-NCON}(\text{CH}_3)_2$   SiMe <sub>3</sub>	80-82 (0.5)			11.4 11.2	11.4 11.2				

(2) W. W. Limburg and H. W. Post, *Rec. trav. chim.*, **81**, 430 (1962).

(3) U. Wannagat and H. Niederprüm, *Z. anorg. allgem. Chem.*, **308**, 307 (1961).

(4) (a) U. Wannagat and C. Krüger, *Monatsh. Chem.*, **94**, 63 (1963); (b) U. Wannagat and J. Pump, *ibid.*, **94**, 141 (1963).

(5) U. Wannagat, H. Bürger, C. Krüger, and J. Pump, *Z. anorg. allgem. Chem.*, **321**, 208 (1963).

(6) H. Breederveld, *Rec. trav. chim.*, **81**, 276 (1962).

(7) (a) G. Oertel, H. Malz, and H. Holtschmidt, *Chem. Ber.*, **97**, 891 (1964);

(b) W. Fink, *ibid.*, **97**, 1433 (1964).

(8) Comparison of the ultraviolet spectra (maxima indicated) of (a) with (b) and (f) shows that introduction of a double bond in conjugation with phenyl results in a shift of the absorption maximum to longer wave lengths in these cases, whereas the maximum of one of the silylureas in question (d) appears at the same wave length as the parent urea (c). However, compounds (e) and (g) do not show this bathochromic shift, so that no definite conclusions can be drawn from the ultraviolet spectra: (a)  $\text{C}_6\text{H}_5\text{CH}_2\text{CO}-\text{NC}_6\text{H}_5$  (220 mμ, tailing off toward longer wave length), (b)  $\text{C}_6\text{H}_5\text{CH}=\text{C}(\text{OSiMe}_3)\text{NC}_6\text{H}_5$  (280 mμ), (c)  $\text{C}_6\text{H}_5\text{NHCONC}_6\text{H}_5$  (242 mμ), (d)  $\text{C}_6\text{H}_5\text{N}(\text{SiMe}_3)\text{CONC}_6\text{H}_5$  or  $\text{C}_6\text{H}_5\text{N}=\text{C}(\text{OSiMe}_3)\text{NC}_6\text{H}_5$  (243 mμ), (e)  $\text{C}_6\text{H}_5\text{N}=\text{C}(\text{OCH}_3)\text{NC}_6\text{H}_5$  (235 mμ, weak shoulder at 270 mμ), (f)  $\text{C}_6\text{H}_5\text{CH}=\text{NC}_6\text{H}_5$  (262 mμ, shoulder at 310 mμ), (g)  $\text{C}_6\text{H}_5\text{C}(\text{OSiMe}_3)=\text{NSiMe}_3$  (230 mμ).

(9) J. Pump and E. G. Rochow, *Chem. Ber.*, **97**, 627 (1964).

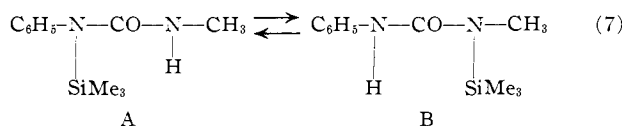
(10) E. Frainnet, A. Bazouin, and R. Calas, *Compt. rend.*, 1304 (1963).



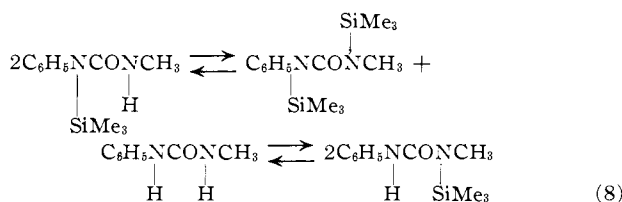
TABLE V  
 DISILYL-SUBSTITUTED UREA AND BIURET DERIVATIVES

Structure	M. p. or b. p. (mm.), °C.	Carbon, %		Hydrogen, %		Nitrogen, %		Silicon, %	
		Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
$\begin{array}{c} \text{CH}_3-\text{N}-\text{CO}-\text{N}-\text{CH}_3 \\   \quad   \\ \text{SiMe}_3 \quad \text{SiMe}_3 \end{array}$	22-23								
	56 (0.1)	46.5	46.4	10.6	10.4	12.3	12.0	23.9	24.2
	$n_D^{20}$ 1.4523								
$\begin{array}{c} \text{C}_6\text{H}_5-\text{N}-\text{CO}-\text{N}-\text{H} \\   \quad   \\ \text{SiMe}_3 \quad \text{SiMe}_3 \end{array}$	69-71							20.1	20.0
$\begin{array}{c} \text{C}_6\text{H}_5-\text{N}-\text{CO}-\text{N}-\text{CH}_3 \\   \quad   \\ \text{SiMe}_3 \quad \text{SiMe}_3 \end{array}$	$n_D^{20}$ 1.5005	56.6	57.0	8.9	8.9	9.8	9.5	19.3	19.1
$\begin{array}{c} \text{C}_6\text{H}_5-\text{N}-\text{CO}-\text{N}-\text{C}_6\text{H}_5 \\   \quad   \\ \text{SiMe}_3 \quad \text{SiMe}_3 \end{array}$	57-59	64.1	64.0	8.2	7.9	8.1	7.9	16.0	15.7
$\begin{array}{c} \text{CH}_3-\text{N}-\text{CO}-\text{N}-\text{CO}-\text{N}-\text{CH}_3 \\   \quad   \quad   \\ \text{SiMe}_3 \quad \text{CH}_3 \quad \text{SiMe}_3 \end{array}$	95-98 (0.1)	45.2	45.6	9.4	9.4	14.9	14.5	19.4	19.4
	$n_D^{20}$ 1.4729								
$\begin{array}{c} \text{C}_6\text{H}_5-\text{N}-\text{CO}-\text{N}-\text{CO}-\text{N}-\text{C}_6\text{H}_5 \\   \quad   \quad   \\ \text{SiMe}_3 \quad \text{CH}_3 \quad \text{SiMe}_3 \end{array}$	104-105	61.0	61.3	7.6	8.2	10.2	10.6	13.6	13.6

tion, a new singlet at 2.83 p.p.m. is observed. In mixtures of  $\text{DCCl}_3$  and  $(\text{D}_3\text{C})_2\text{SO}$  the intensity of the 2.83 p.p.m. signal is proportional to the concentration of  $(\text{D}_3\text{C})_2\text{SO}$ . When the dimethyl sulfoxide is evaporated



from these solutions and the residue is dissolved in deuteriochloroform, only the original signals at 2.69 p.p.m. ( $J = 4.5$  c.p.s.) and 0.20 p.p.m. are observed. We conclude that a solvent-dependent equilibrium of the species A and B is observed. The mechanism of the silyl transfer may be intramolecular as indicated by eq. 7 or intermolecular involving disilylated and unsilylated intermediates as shown by eq. 8. That disilylated ureas are possible reaction intermediates has

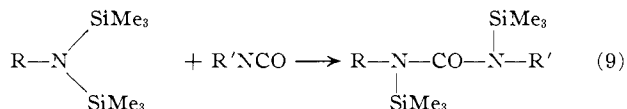


been shown by the synthesis of a number of representatives of this previously unreported class of compounds (see below).

In view of the demonstration that silylureas may undergo rapid silyl-proton exchange, we feel that the question of the direction of preferential cleavage in the addition of secondary silylamines to isocyanates cannot be answered with the evidence presently available. We have shown that this question is of no consequence for the structures of the products. In addition, structure proofs for silylated hydrazines<sup>4a</sup> and hydroxylamines<sup>4b</sup> which have been based on the structure of hydrolysis products of the adducts with phenyl isocyanate now appear to be open to question.

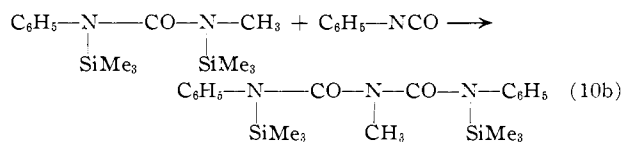
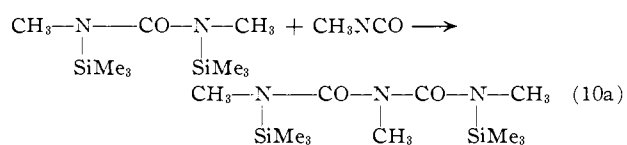
**Addition of Silazanes to Isocyanates.**—The first step of the reaction of N-alkyl- and aryl-substituted disilazanes with isocyanates follows the pattern observed with tertiary silylamines: an Si-N bond is cleaved and 1:1 adducts are obtained which can be shown to be N,N'-disilyl-substituted urea derivatives (Table V).

The reaction of N-methylhexamethyldisilazane with phenyl or methyl isocyanate is smooth although not exothermic and the adducts are obtained in high yield after 24 hr. at slightly elevated temperatures. N-



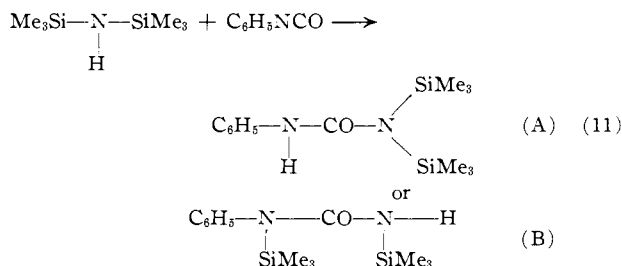
Phenylhexamethyldisilazane is less reactive; in mixture with phenyl isocyanate it has to be heated at temperatures above  $100^\circ$  for several days in order to lead to good yields of the disilylurea; above  $150^\circ$ , decomposition into diphenylcarbodiimide and hexamethyldisiloxane is observed.

In contrast to monosilylurea derivatives, disilylureas containing at least one alkyl group will add a second isocyanate molecule as demonstrated by eq. 10a and 10b.<sup>11a</sup> These reactions too proceed at room



temperature to give high yields of the disilylbiurets.

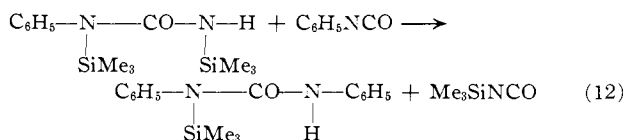
The addition of hexamethyldisilazane to phenyl isocyanate offers the possibility of two tautomeric products, analogous to the products obtained with secondary silylamines



(11a) NOTE ADDED IN PROOF.—It was recently reported<sup>7b</sup> that under more vigorous conditions monosilylureas will add a second mole of isocyanate.

This reaction was reported by Wannagat and co-workers,<sup>5</sup> and structure A was proposed by these authors. We find that the proton magnetic resonance spectrum of the adduct shows two trimethylsilyl signals (0.13 and 0.18 p.p.m.) which do not coalesce at temperatures up to 150°. These results are consistent with structure B with two trimethylsilyl groups in different environments.<sup>7b</sup> This conclusion is supported by the observation that N-methyl-N'-phenyl-N,N'-bis(trimethylsilyl)urea shows two similarly spaced trimethylsilyl signals (0.18 and 0.21 p.p.m.), whereas N,N-dimethyl-N',N'-bis(trimethylsilyl)urea shows a single signal at 0.21 p.p.m.

Phenylbis(trimethylsilyl)urea will also undergo reaction with a second molecule of phenyl isocyanate at room temperature; the product, however, is not the expected biuret derivative but trimethylsilyl-N,N'-diphenylurea along with trimethylsilyl isocyanate.



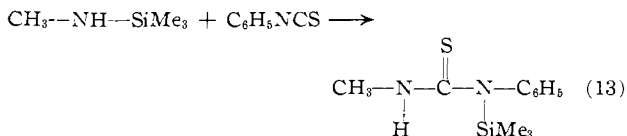
#### Addition of Silylamines to Phenyl Isothiocyanate.—

The addition of silylamines to phenyl isothiocyanate leads to the silylated thioureas. A number of compounds prepared in this manner is listed in Table VI.

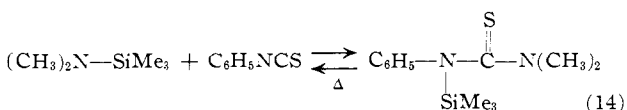
TABLE VI  
SILYLTHIOUREAS

Structure	M.p., °C.	Carbon, %		Hydrogen, %		Nitrogen, %		Silyl, %		Sulfur, %	
		Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
$\text{C}_6\text{H}_5\text{N}-\text{CSNCH}_3$	132-134	55.8	55.5	7.9	7.9	11.9	11.9	11.9	11.8	13.3	13.4
$\begin{array}{c} \text{SiMe}_3 \quad \text{H} \\   \qquad   \\ \text{C}_6\text{H}_5\text{NCSN}(\text{CH}_3)_2 \end{array}$	52-53	57.5	57.2	8.2	7.9	11.3	11.1	11.1	11.1	12.4	12.7
$\begin{array}{c} \text{SiMe}_3 \\   \\ \text{C}_6\text{H}_5\text{NCSNC}_4\text{H}_9 \\   \\ \text{SiMe}_2\text{C}_6\text{H}_5 \end{array}$	87-88	67.4	66.7	8.1	7.6	8.1	8.2	8.3	8.2	8.9	9.3

The proton magnetic resonance spectrum of N-trimethylsilyl-N'-methyl-N-phenylthiourea prepared according to eq. 13 shows a doublet ( $J = 4.5$  c.p.s.) at 2.98 p.p.m. due to the N-methyl protons.

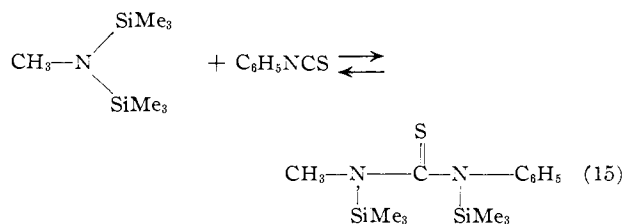


In contrast to the thermally stable silylureas, silylthioureas revert to the starting materials at elevated temperatures

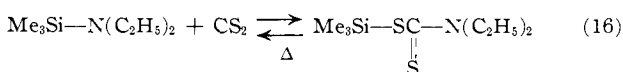


When the infrared spectrum of N,N-dimethyl-N'-phenyl-N'-trimethylsilylthiourea is taken in benzene, chloroform, or carbon tetrachloride at 80°, a strong band appears at 4.9  $\mu$ , indicative of the  $-\text{N}=\text{C}=\text{S}$  function. This band is absent in the spectrum before heating and after cooling the solution. Attempts to obtain thio-

ureas with two silyl substituents by reaction of silazanes with phenyl isothiocyanate failed; the mixture of N-methylhexamethyldisilazane and phenyl isothiocyanate after several hours at 35° showed a moderately intense  $\text{C}=\text{S}$  absorption at 1710  $\text{cm}^{-1}$  in the infrared spectrum, indicating that some addition product may have been formed



Disappearance of this band at 60° points at the thermal instability of this structure. Breederveld has noted a similar phenomenon with the adducts of silylamines and carbon disulfide. Upon distillation the adducts decompose into the starting materials



Carbon dioxide, on the other hand, forms thermally stable addition products with silylamines.<sup>6</sup>

Further experiments have shown that addition reactions with silylamines are not confined to the systems described in this paper. Acid anhydrides, for example, will readily undergo reaction with silylamines. These reactions will be the subject of a future publication.

#### Summary

The reactions of secondary and tertiary silylamines and of silazanes with isocyanates and isothiocyanates have been investigated. It is shown that N-silylated ureas or thioureas are produced in high yield. Ureas with two silyl substituents add further isocyanate to form disilylbiurets. A rapid intermolecular exchange between trimethylsilyl groups and protons, proceeding under very mild conditions, has been demonstrated.

#### Experimental

Chemical shifts were measured in p.p.m. from internal tetramethylsilane using a Varian H-60 analytical spectrometer. Spectra were taken on 10-30% solutions in  $\text{CDCl}_3$ ,  $\text{CCl}_4$ , or  $(\text{CD}_3)_2\text{SO}$ .

1. **N,N-Bistrimethylsilylaniline.**—To a solution of 33 g. (0.2 mole) of N-trimethylsilylaniline in 100 cc. of dry tetrahydrofuran was added with stirring under anhydrous conditions 200 cc. of a 10% solution of butyllithium in hexane. Butane was evolved and the mixture warmed up to reflux temperature during the addition which was completed within 30 min. To the resulting clear orange-colored solution was then slowly added 33 g. (0.3 mole) of trimethylchlorosilane. The reaction was exothermic and a white precipitate of lithium chloride was formed. The mixture was filtered after 15 hr. of stirring at room temperature and the filtrate distilled. Bis(trimethylsilyl)aniline distilled at 72° (2.6 mm.) as a colorless mobile liquid ( $n_D^{20}$  1.4840), yield 38 g., 80%. *Anal.* Calcd.: C, 60.7; H, 9.7; N, 5.5; Si, 23.7. Found: C, 60.7; H, 9.8; N, 6.0; Si, 23.8.

**Preparation of Silylureas.**—The addition reactions of silylamines with isocyanates were carried out in carefully dried hexane, benzene, ether, acetone, acetonitrile, or without solvent. The reactions are nonexothermic in the case of secondary aromatic silylamines or silazanes in combination with methyl isocyanate and no solvent was generally used in these cases; the reactants were mixed in stoichiometric proportions in an anhydrous atmosphere and agitated on a magnetic stirrer at 35° for 2 to 24 hr. which generally led to nearly complete conversion. Heating proved to be advantageous in case of phenyldimethyl-

silyl-substituted amines. Combination of tertiary aliphatic silylamines with phenyl isocyanate represent the other end of the reactivity scale, the reactions being highly exothermic in these cases so that an anhydrous solvent was used as diluent and the addition of one reactant to the other was carried out slowly in order to moderate the reaction. Strictly anhydrous conditions have to be maintained during the preparation and isolation procedures. Several silylamines used for the addition reactions have not been described previously; their preparation was straightforward using the corresponding amine and chlorosilane with triethylamine as acid acceptor in benzene or toluene: *N*-(dimethylphenylsilyl)aniline, b.p. 140° (3.3 mm.),  $n_D^{20}$  1.5829. *N*-trimethylsilyl-*N*-methylaniline, b.p. 77° (5.5 mm.),  $n_D^{20}$  1.5212; *N*-trimethylsilyl-*m*-toluidine, b.p. 108° (12 mm.),  $n_D^{20}$  1.5180. The following preparations are given as examples.

**2. Trimethylsilyl-*N*-methyl-*N'*-phenylurea. A.**—To the stirred solution of 10.3 g. of trimethylsilylmethylamine (0.1 mole) in 20 cc. of anhydrous hexane was added dropwise 11.9 g. (0.1 mole) of freshly distilled phenyl isocyanate. The addition was completed within 10 min.; the temperature of the mixture rose to about 70°. The product was obtained as colorless crystals after cooling to room temperature. The silylurea is fairly soluble even in cold hexane; a nearly quantitative yield of pure material was obtained by evaporation of the solvent and sublimation at 70° and 0.1 mm. pressure.

**B.**—Freshly distilled methyl isocyanate (5.7 g., 0.1 mole) was mixed with 16.5 g. (0.1 mole) of *N*-trimethylsilylaniline. No solvent was used; a very slight spontaneous temperature rise was detected. The mixture was stirred magnetically at 35° for 24 hr. The resulting colorless viscous fluid was slowly distilled in a molecular still at 35° (0.1 mm.); the product crystallized in the cold parts of the apparatus. The isolated yield of crystalline product was about 80%; a small amount of by-products was formed. The products obtained by methods A and B were identical according to melting point (72–75°; mixture melting point undepressed), infrared, and proton magnetic resonance spectrum. *N*-Methyl-*N'*-phenylurea was obtained in quantitative yield upon hydrolysis with ethanol. *Anal.* Calcd.: C, 63.9; H, 6.8; N, 18.6. Found: C, 64.0; H, 6.7; N, 18.6.

**3. *N*-Trimethylsilyl-1-piperidinecarboxanilide.**—To 15.7 g. of *N*-trimethylsilylpiperidine (0.1 mole) dissolved in 50 cc. of anhydrous ether was slowly added with mechanical stirring 11.9 g. (0.1 mole) of freshly distilled phenyl isocyanate. The dropwise addition of the isocyanate resulted in vigorous boiling of the ether. The solvent was distilled off after completion of the addition and the colorless viscous reaction product was distilled in a micro-distillation apparatus without column. The silylurea distilled at 96–97° (0.1 mm.) and solidified in the receiver. The material melted at 42–44° after vacuum sublimation at 35° (0.1 mm.). Hydrolysis with ethanol yielded quantitatively 1-piperidinecarboxanilide. *Anal.* Calcd.: C, 70.6; H, 7.9; N, 13.7. Found: C, 70.4; H, 8.0; N, 13.7.

**4. *N*-(Dimethylphenylsilyl)-*N,N'*-diphenylurea.**—A mixture of 2.27 g. (0.01 mole) of *N*-(dimethylphenylsilyl)aniline and 1.19 g. (0.01 mole) of phenyl isocyanate was placed in an oil bath heated at 150° in an atmosphere of dry nitrogen and agitated with a magnetic stirrer. The mixture solidified when it was removed from the oil bath after 1 hr. The product was recrystallized from dry hexane-benzene, 1:1; m.p. 111–113°.

**5. *N,N'*-Dimethyl-*N,N'*-bis(trimethylsilyl)urea and 1,3,5-trimethyl-1,5-bis(trimethylsilyl)biuret.**—A mixture of 4.0 g. of *N*-methylhexamethyldisilazane<sup>12</sup> and 1.6 g. of freshly distilled methyl isocyanate (20% excess) was stirred magnetically for 24 hr. at 35° in an anhydrous atmosphere. The resulting moderately viscous colorless fluid was distilled. The fractions boiling at 55–58° (0.1 mm.) (A) and 96–98° (0.1 mm.) (B) were collected separately. The colorless disilyldimethylurea (A) is a crystalline solid, m.p. 22–23°,  $n_D^{20}$  1.4523. Its proton magnetic resonance spectrum shows a signal at 2.72 p.p.m. due to  $-N-CH_3$  and a signal at 0.22 p.p.m. due to  $Me_2Si-$  in a ratio of 1.0:3.2 (required 1:3). Addition of ethanol and evaporation of volatile material resulted in a solid, m.p. 98–102°; after recrystallization from benzene, m.p. 102–103°. The mixture melting point with *N,N'*-dimethylurea was undepressed.

The disilylbiuret derivative (B) is a colorless viscous fluid,  $n_D^{20}$  1.4729. The proton magnetic resonance spectrum shows

signals at 2.74, 3.00, and 0.28 p.p.m. in a ratio of 1.0:2.03:6.0. Hydrolysis with ethanol led to a white solid, m.p. 120–124°; after recrystallization from benzene, m.p. 125–126° (reported m.p. of 1,3,5-trimethylbiuret: 126°). *Anal.* Calcd.: C, 41.3; H, 7.6; N, 29.0. Found: C, 41.5; H, 7.6; N, 28.8.

**6. *N*-Methyl-*N'*-phenyl-*N,N'*-bis(trimethylsilyl)urea.**—To 8.7 g. (0.05 mole) of *N*-methylhexamethyldisilazane was added with stirring 6.0 g. (0.05 mole) of phenyl isocyanate. The dropwise addition resulted in exothermic reaction and was completed within 20 min. Stirring was continued at 35° for 15 hr. The colorless, slightly viscous, clear liquid was subjected to molecular distillation, which was completed within 3 hr. at 60–65° bath temperature and 0.1 mm. pressure; almost no residue remained. The proton magnetic resonance spectrum of the distillate showed, in addition to aromatic protons, a signal at 2.25 p.p.m. due to  $>N-CH_3$  and two signals at 0.22 and 0.18 p.p.m. resulting from the two unequivalent trimethylsilyl groups. The ratio of aromatic to *N*-methyl to combined trimethylsilyl protons was 5:2.83:18 as compared with 5:3:18 required.

**7. 1,5-Diphenyl-3-methyl-1,5-bis(trimethylsilyl)biuret.**—A mixture of 2.37 g. of *N*-methyl-*N'*-phenyl-*N,N'*-bis(trimethylsilyl)urea and 0.95 g. of phenyl isocyanate was allowed to stand at 35° for 20 hr. under anhydrous conditions. A white solid was formed after this time which was recrystallized from dry *n*-hexane and melted at 99–101°. The n.m.r. spectrum shows peaks at 2.55 and 0.13 p.p.m. in addition to two groups of aromatic protons; the ratio is 2.8:10:19.4 (required: 3:10:18). Hydrolysis afforded *N,N'*-diphenyl-*N'*-methylbiuret. *Anal.* Calcd.: C, 66.9; H, 5.6; N, 15.2. Found: C, 67.1; H, 5.5; N, 15.2.

**8. *N,N'*-Diphenyl-*N,N'*-bis(trimethylsilyl)urea.**—Bis(trimethylsilyl)aniline, 12.9 g., was mixed with 9.6 g. of phenyl isocyanate (50% excess) and heated at 145° under an atmosphere of dry nitrogen for 48 hr. Vapor phase chromatographic analysis of the mixture showed that 76% of the aniline derivative had been converted to the product. The mixture crystallized partially on cooling; 5 cc. of dry hexane was added which dissolved the product, a small amount of insoluble material was filtered off, and the product allowed to crystallize at  $-15^\circ$ . The disilylurea was washed with a few cc. of dry hexane, dried, and purified by vacuum sublimation at 55° (0.01 mm.); yield 12.7 g., 65%, m.p. 56–58°.

**9. *N,N*-Dimethyl-*N,N'*-bis(trimethylsilyl)urea.**—To a magnetically stirred suspension of 1.6 g. of *N,N*-dimethyl-*N'*-trimethylsilylurea, prepared by reaction of trimethylchlorosilane with *N,N*-dimethyl-*N'*-lithiurea, m.p. 126–129°, in 5 cc. of dry tetrahydrofuran was slowly added with ice cooling in an atmosphere of dry  $N_2$  6.4 g. of a solution of 15% butyllithium in hexane. A fine white precipitate was formed. After the addition was complete, 2.0 g. of trimethylchlorosilane (30% excess) was slowly added to the ice-cooled stirred suspension of *N,N*-dimethyl-*N'*-trimethylsilyl-*N'*-lithiurea. Stirring at 0° was continued for 1 hr., volatile material was then removed at 0° *in vacuo* (1 mm.), the residue treated with cold hexane (about 0°), filtered, and the filtrate concentrated in a rapid stream of dry nitrogen. A colorless oil remained which was subjected to a vacuum of 0.1 mm. for 15 min. at room temperature in order to remove residual solvent. The proton magnetic resonance spectrum in  $CDCl_3$  showed a signal at 2.95 p.p.m. due to methyl on nitrogen and a signal at 0.21 p.p.m. due to trimethylsilyl (ratio 6:19.1). The solution had been kept in Dry Ice until the recording of the spectrum. After 1 hr. at room temperature, infrared and n.m.r. spectra of the solution showed indication for partial decomposition into trimethylsilyl isocyanate and trimethylsilyldimethylamine; 75% of the material (20% in  $DCCl_3$ ) had decomposed after 15 hr. at room temperature. The *N,N*-dimethyl-*N,N'*-bis(trimethylsilyl)urea solidified at  $-15^\circ$  in a freezer but liquefied slowly after about 3 days, indicating slow decomposition even at this temperature.

**10.  $\alpha$ -(1-Piperidino)- $\beta$ -phenyl-O-trimethylsilylvinyl Ether.**—Krüger and Rochow showed that sodium bis(trimethylsilyl)amide reacts with carbonyl compounds with  $\alpha$ -protons giving the sodium enolate and subsequently with chlorosilane with O-silyl substituted enol.<sup>13</sup> This reaction scheme was applied to an amide: 1-phenylacetyl-piperidide, (20.3 g., 0.1 mole) was mixed with 19 g. of sodium bis(trimethylsilyl)amide (0.1 mole) in 100 cc. of dry benzene in an anhydrous atmosphere. The suspension became

(12) R. C. Osthoff and S. W. Kantor, *Inorg. Syn.*, **5**, 55 (1957).

(13) C. R. Krüger and E. G. Rochow, *Angew. Chem.*, **76**, 793 (1963).

warm and very thick. It was placed in an oil bath, heated at 90°, and 12 g. (0.11 mole) of trimethylchlorosilane were slowly added with mechanical stirring. The mixture was filtered after 2 hr. at 90°, the filtrate was concentrated on a rotating evaporator at 60°. The product crystallized in large colorless crystals on cooling to room temperature after most of the solvent was removed; after two recrystallizations from dry hexane, m.p. 53–56°. *Anal.* Calcd.: C, 69.8; H, 9.1; N, 5.1. Found: C, 70.0; H, 9.4; N, 5.0.

11. *N,N*-Dimethyl-*N'*-phenyl-*N'*-trimethylsilylthiourea.—Phenyl isothiocyanate (6.75 g., 0.05 mole) in 20 ml. of anhydrous ether was added dropwise over a 15-min. period to a magnetically stirred solution of 5.85 g. (0.05 mole) of *N*-trimethylsilyl-*N,N*-dimethylamine in 20 ml. of anhydrous ether. After stirring under a blanket of dry nitrogen for 7 hr., the ether was pulled off at room temperature, leaving a crystalline white solid which was recrystallized from *n*-hexane giving white needles melting at 52–53°

[CONTRIBUTION FROM THE INSTITUTE OF MOLECULAR BIOLOGY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON, EUGENE, OREGON]

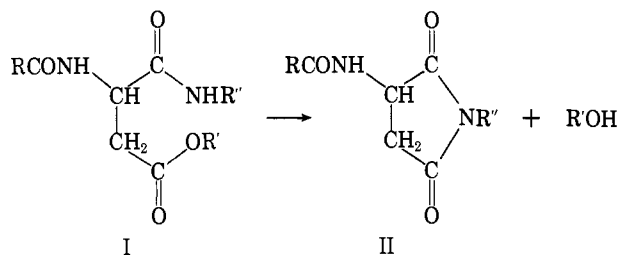
## The Reaction of Formohydroxamic Acid with Acyl Derivatives in Neutral Aqueous Solution

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A peculiar reaction of a  $\beta$ -alkyl ester of an aspartylserine peptide with neutral hydroxylamine, yielding formohydroxamic acid (FHA) in nearly stoichiometric quantities, has been observed. The reaction of FHA with acylating agents has been studied. Acylation occurs readily with formohydroxamate anion, the rate of acylation being unusually rapid for an anionic nucleophile with this  $pK_a$  (8.70). The acylation of hydroxamic acids by acylimidazoles involves the complementary charged species acylimidazolium<sup>+</sup> + hydroxamate<sup>-</sup>, to the apparent exclusion of other conjugate acid–base species. These latter acylation reactions are extremely rapid; the product of the reaction is the *N,O*-diacylhydroxylamine. In contrast to other *N,O*-diacylhydroxylamines, *N*-formyl-*O*-acylhydroxylamines deacylate rapidly at neutral pH. This reaction involves elimination of acylate<sup>-</sup> rather than hydrolysis.

In a previous communication,<sup>2a</sup> it was reported that derivatives of the dipeptide *L*-aspartyl-*L*-serine exhibited chemical reactivity which was not anticipated on the basis of the well-investigated reactivities of the aggregate constituent monofunctional side chains. One such noteworthy chemical phenomenon is the ease with which  $\beta$ -esters of aspartyl peptides (I) cyclize to form 5-membered imide rings (II). The imide ring was found to undergo facile (hydroxyl ion catalyzed) hydrolysis to a mixture of the corresponding  $\alpha$ - and  $\beta$ -carboxylates.



Another notable reaction of the above-mentioned aspartylserine peptide is the hydroxylaminolysis of the  $\beta$ -ester at neutral pH. Formation of the *N*-hydroxamate from the ester in 1 *M* hydroxylamine at pH 6 (50% aqueous dioxane) occurs at a rate far in excess of the rate of formation of the cyclic imide II from the ester in the absence of  $\text{NH}_2\text{OH}$ , under the otherwise similar conditions. From the hydroxylaminolysis reaction mixture (see Experimental) a hydroxamic acid product was isolated which appeared to catalyze the hydrolysis of acyl derivatives in aqueous solution. The purified product was shown to be formohydroxamic acid. The apparent catalytic reactivity of formohydroxamic acid was found to be typical of hydroxamic acids. The formation of acylate anion was found

to proceed *via* a two-step "acylation–deacylation" mechanism, characteristic of the hydrolysis of acyl derivatives catalyzed by tertiary bases (and imidazoles) and by proteolytic enzymes.<sup>2b</sup>

### Results and Discussion

The utility of cinnamoyl derivatives as models for the study of acylation reactions has been elegantly demonstrated by Bender and co-workers.<sup>3</sup> Cinnamoyl-imidazole (CI), and other chromophoric acylating agents, have been employed in this study (following, in essence, the method of Bender),<sup>3</sup> in order to characterize any intermediates which might form in a catalyzed acylation reaction. Since in the experiments reported herein the formation of cinnamate from cinnamoylating agents was found to be promoted by formohydroxamic acid *via* a cinnamoyl intermediate, a number of cinnamoylhydroxamate derivatives were prepared, and their ultraviolet spectra recorded. Pertinent data are listed in Table I.

**The Reaction of Cinnamoylimidazole with Formohydroxamic Acid (FHA).**—The reaction of formohydroxamic acid (FHA) with cinnamoylimidazole (CI) was followed spectrophotometrically. Figure 1 shows a typical run at 25°, pH 6.86 (0.05 *M* phosphate buffer). Under these conditions (excess FHA) there is a rapid disappearance of CI with a concomitant increase of a cinnamoyl intermediate with an ultraviolet absorbance maximum ( $\lambda_{\text{max}}$ ) at 282  $m\mu$ . This intermediate subsequently undergoes deacylation at a relatively slower rate to yield cinnamate ion ( $\lambda_{\text{max}}$  269.5  $m\mu$ ). The rate of the first step (acylation) is first order in FHA concentration, whereas the second step (deacylation) is independent of the concentration of free FHA. Both reactions were studied as a function of pH. The dependencies of the first-order rate constants on pH are illustrated in Fig. 2. Both acylation and deacylation steps are optimally rapid near neutrality,

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(2) (a) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962); (b) M. L. Bender, *ibid.*, **84**, 2582 (1962).

(3) M. L. Bender, G. R. Schonbaum, and B. Zerner, *ibid.*, **84**, 2540 (1962).