pure state by recrystallization from ethanol-ethyl acetate: mp 184–185° dec; ir 700, 765, 1096, 1503, 1587, 2020, 2470–2800 cm^{-1}. *Anal.* Calcd for $C_{10}H_{13}ClN_2O$: C, 56.48; H, 6.16; N, 13.17. Found: C, 56.39; H, 5.86; N, 12.89.

A solution of **19** (316 mg, 1.795 mmol) in 6 *N* hydrochloric acid (4 ml) was stirred at 130° for 6.5 hr. The solution was concentrated, dried *in vacuo*, dissolved in concentrated aqueous ammonia (1 ml), and concentrated again giving the crystals which were recrystallized from ethanol–water–ether to afford 200 mg (57.1%) of **20**. The pure sample which showed mp 220–222° after a few recrystalliza-

tions from the same solvents was identified as DL-*threo-O*-methylphenylserine (mp 218–220°)[8] by the infrared spectrum (KBr) of the authentic specimen.

The Structure of Trimethylsilyl Amides

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Abstract: The structures of a series of bis(trimethylsilyl) amides have been investigated by nmr and ir spectroscopy. A study of the ^{15}N derivative of bis(trimethylsilyl)formamide provides definitive evidence for the amide structure and the free energy of activation for the rotational process is found to be 11.6 kcal/mol. The structures of the other amides were determined from their nmr characteristics, and all were found to have the imidate structure. The free energies of activation for the intramolecular exchange of trimethylsilyl groups range from 15.0 to 22.1 kcal/mol and are related to the electronic and steric properties of the substituent at the carbonyl carbon. The structures of mono- and bis(trimethylsilyl) amides, hindered rotation in the amide tautomers, and exchange of the trimethylsilyl group are discussed.

One of the interesting peculiarities of the trimethylsilyl group is its lability in many compounds in which alkyl groups are nonmobile. This is particularly well illustrated by the stereochemical nonrigidity of the popular silylating agent bis(trimethylsilyl)acetamide (BSA). Although this compound has been reported to have the amide structure (A)[1] and the imidate structure
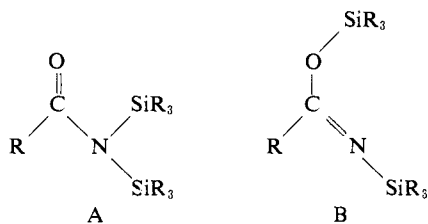
(B),[2] the imidate assignment has been confirmed by a spectroscopic study of the ^{15}N derivative.[3] The nmr spectrum of BSA at room temperature contains a singlet in the trimethylsilyl region which collapses to a doublet as the temperature decreases. This behavior is attributable to a temperature-dependent intramolecular exchange of trimethylsilyl groups. Recently, bis(trimethylsilyl)formamide has also been prepared, and its spectral behavior has been interpreted as evidence for the amide[4] and imidate forms.[5]

We report here: (a) the results of our investigation of the ^{15}N derivative of bis(trimethylsilyl)formamide,

and a series of bis(trimethylsilyl) compounds of the type $RCON[Si(CH_3)_3]_2$, where R $= C_2H_5$, $CH(CH_3)_2$, $C(CH_3)_3$, and CF_3, and (b) our conclusions regarding the determinants of the structure and exchange rate in both mono- and bis(trimethylsilyl) amides.

Experimental Section

Compounds. All reactions and operations were carried out under nitrogen in oven-dried glassware with dry solvents and compounds.

Bis(trimethylsilyl)formamide. The ^{14}N and ^{15}N isotopomers (96 atom % ^{15}N formamide was obtained from Merck, Sharpe and Dohme of Canada) were prepared by the reaction of 0.01 mol of formamide with 0.02 mol of trimethylchlorosilane and 0.022 mol of triethylamine in 5 ml of benzene at room temperature. After 1 hr of reflux the mixture was filtered and the filtrate distilled at reduced pressure through a 13-cm column packed with glass helices. Product was obtained at 68° (25 mm); a second fraction (which contained some trimethylsilylformamide) was obtained at 78° (25 mm) (lit.[4] bis(trimethylsilyl)formamide, 57° (13 mm)).

Bis(trimethylsilyl)propionamide was prepared by the treatment of propionamide with trimethylchlorosilane in triethylamine, bp 55° (10 mm). (*Anal.* Calcd for $C_9H_{23}NOSi_2$: C, 49.77; H, 10.59; N, 6.45. Found: C, 49.17; H, 10.67; N, 6.19.)

Bis(trimethylsilyl)dimethylacetamide was obtained from the reaction of isobutyramide with trimethylchlorosilane in the presence of triethylamine, bp 52° (9 mm). (*Anal.* Calcd for $C_{10}H_{25}NOSi_2$: C, 51.88; H, 10.89; N, 6.05. Found: C, 52.07; H, 10.78; N, 6.92.)

Bis(trimethylsilyl)trimethylacetamide was obtained from the reaction of the lithium salt of hexamethyldisilazane with trimethylacetyl chloride in hexane, bp 72–74° (15 mm) (lit.[2b] 79–80° (16 mm)).

Bis(trimethylsilyl)trifluoroacetamide was a commercial sample.

Nmr and Ir Measurements. Nmr spectra were obtained on a Varian A-60D spectrometer equipped with variable-temperature accessory V-4341/V-6057. Temperatures were measured with methanol and ethylene glycol samples and the equations of Van Geet.[6] Variables used in the determination of free energies of

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activation are averages of at least three scans at the appropriate temperatures.

Chlorobenzene, toluene, and methylene chloride were dried over molecular sieves (type 4A).

Infrared spectra were obtained on a Perkin-Elmer 621 spectrophotometer.

Results

Bis(trimethylsilyl)formamide. The infrared spectra obtained from the neat ^{14}N and ^{15}N isotopomers of this compound were identical except for the shift of two peaks: a medium intensity peak at 1210 cm^{-1} in the ^{14}N derivative appeared at 1189 cm^{-1} in the ^{15}N derivative and a somewhat less intense peak at 983 cm^{-1} in the ^{14}N derivative appeared at 961 cm^{-1} in the ^{15}N isotopomer. The very intense absorption at 1659 cm^{-1} remained unchanged by isotopic substitution. This is in direct contrast to the infrared behavior of the bis(trimethylsilyl)acetamide (which exists in the imidate form) in which the peak at 1698 cm^{-1} in the ^{14}N derivative shifts to 1675 cm^{-1} in the ^{15}N compound. The 1659-cm^{-1} absorption of bis(trimethylsilyl)formamide can therefore be assigned to the carbonyl function and is good evidence for the existence of this compound in the amide form (A).

This conclusion is also supported by the nmr spectra: the protons of the trimethylsilyl group of the ^{14}N isotopomer give rise to a singlet at 0.3 ppm in methylene chloride which splits into a doublet below $-46°$. The trimethylsilyl protons of the ^{15}N isotopomer, on the other hand, appear as a doublet ($J = 0.6$ Hz) at room temperature which then splits into a doublet of doublets below $-46°$. The room temperature doublet of the ^{15}N formamide is a result of the 3 bond $^{15}N-^1H$ coupling, while the low temperature doublet of doublets is attributable to the splitting by ^{15}N of the magnetically nonequivalent protons of the rotational isomers. This behavior can also be contrasted with that of the acetamide, where the low-temperature spectrum showed a singlet due to the O-trimethylsilyl group and a doublet due to the N-trimethylsilyl group.[3] A summary of the nmr assignments of bis(trimethylsilyl)-formamide neat and in CH$_2$Cl$_2$ as well as the assignments for the monosubstituted derivative as a 15% solution with the bis compound are given in Table I.

Table I. Nmr Data for Bis(trimethylsilyl)formamide and Trimethylsilylformamide

			δ (ppm)	m[a]
Bis				
	Neat	Si(CH$_3$)$_3$	0.26	d, $J(^{15}N-H) = 0.66$ Hz[b]
		COH	8.62	d, $J(^{15}N-H) = 15.0$ Hz
	CH$_2$Cl$_2$, 20%,	Si(CH$_3$)$_3$	0.29	d, $J(^{15}N-H) = 0.64$ Hz
		COH	8.55	d, $J(^{15}N-H) = 14.9$ Hz
Mono[c]				
		Si(CH$_3$)$_3$	0.21	d, $J(^{15}N-H) = 0.9$ Hz
		N-H	6.83	dd, $J(^{15}N-H) = 80.0$ Hz
				$J(H-H) = 2.8$ Hz
		COH	8.43	dd, $J(^{15}N-H) = 13.1$ Hz
				$J(H-H) = 2.8$ Hz

[a] Multiplicity: d, doublet; dd, doublet of doublets. [b] Measured at 0°. [c] As 15% solution in bis derivative; measured at 0°.

As indicated in Table I, the one bond $^{15}N-H$ coupling constant in the mono derivative is 80.0 Hz, somewhat lower than the 88–93 Hz range reported for other

amides, but very similar to the value of 77.5 Hz obtained for trimethylsilylacetamide.[3] The signals from the less abundant rotamer were not observed.[7]

The free energy of activation for the rotational process in bis(trimethylsilyl)formamide was calculated by applying the Eyring equation (transmission coefficient $= 1$) to the rate constant obtained at the coalescence temperature (T_c) by the approximate method ($k_c = \pi \Delta \nu_c / \sqrt{2}$). The chemical shift difference, $\Delta \nu_c$, was obtained by extrapolation of a least-squares plot of four slow exchange region values to the coalescence temperature. This method has been shown to yield values of $\Delta G^{\pm}$ which are probably within ± 0.2 kcal/mol of the total line shape result when $\Delta \nu_c > 3$ Hz.[8] The coalescence parameters are summarized for bis-(trimethylsilyl)formamide as well as a series of other bis(trimethylsilyl) amides in Table II. The coalescence

Table II. Activation Parameters for Bis(trimethylsilyl) Amides[a]

	Compound	T_c (0°)	$\Delta \nu_c$, Hz	$\Delta G^{\pm}$, kcal/mol
I	HCON[Si(CH$_3$)$_3$]$_2$	-46	12.1	11.6
II	CH$_3$CON[Si(CH$_3$)$_3$]$_2$[b]	11	8.1	15.3
III	CH$_3$CH$_2$CON[Si(CH$_3$)$_3$]$_2$	10	6.9	15.0
IV	(CH$_3$)$_2$CHCO[Si(CH$_3$)$_3$]$_2$	11.5	5.8	15.2
V	(CH$_3$)$_3$CCO[Si(CH$_3$)$_3$]$_2$	59	1.3	18.8
VI	CF$_3$CO[Si(CH$_3$)$_3$]$_2$	125	2.8	22.1

[a] 20% in ClC$_6$H$_5$. [b] Reference 7.

of the trimethylsilyl resonances in bis(trimethylsilyl)-formamide was observed in three solvents—chlorobenzene, toluene, and methylene chloride—and the resultant standard free energies of activation are the same within experimental error (± 0.3 kcal).

Other Bis(trimethylsilyl) Amides. The structure of bis(trimethylsilyl)acetamide has been shown to be that of type **B**, and the free energy of activation for the exchange of trimethylsilyl groups as determined by the total line-shape procedure was found to be 15.3 kcal/mol.[7] The nmr spectra of this compound and the other derivatives listed in Table II exhibit the same behavior in the trimethylsilyl region as that noted above for the formamide, i.e., a low-temperature doublet which coalesces at a higher temperature to a singlet. If compounds III, IV, and V were N,N-substituted (type A), the greater size of the substituent attached to the carbonyl carbon should produce a lower rotational barrier than that found for compound I (as is observed for the series RCON(CH$_3$)$_2$ where the barrier varies H $>$ CH$_3$ $>$ C$_2$H$_5$ $>$ C(CH$_3$)$_3$.[9] The higher free energies of activation (we assume throughout that $\Delta G^{\pm}$ parallels E_a) are evidence for the imidate structure, and the observed coalescence behavior can be attributed therefore to intramolecular exchange of the trimethylsilyl groups.

The room temperature nmr spectrum of bis(trimethylsilyl)trifluoroacetamide (VI) as a 20% solution in chlorobenzene exhibits a sharp singlet (δ 0.235 ppm) and a quartet (δ 0.185 ppm, $J = 0.6$ Hz) in the trimethylsilyl region which coalesce to a single peak at

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125°. The unequal coupling between ^{19}F and the protons of the magnetically nonequivalent $Si(CH_3)_3$ groups could be a consequence of coupling to cis and trans trimethylsilyl groups of the N,N tautomer. A better interpretation in view of the nmr of N-methyl-N-trimethylsilyltrifluoroacetamide (a singlet for the Si-$(CH_3)_3$ group, two quartets for the NCH_3 group)[10] is that the compound has the imidate structure and that the coupling of the ^{19}F across the C=N bond to the protons of the N-trimethylsilyl group is greater (because of the greater s character in the intervening bonds) than that to the O-trimethylsilyl group. The high free energy of activation is also best rationalized by exchange in the imidate structure, rather than hindered rotation in the amide structure. The free energy of activation for the rotational process in N,N-dimethyltrifluoroacetamide is 2 kcal/mol lower than that for N,N-dimethylformamide.[11] Thus, replacement of H by CF_3 probably should result in a lower $\Delta G^{\pm}$ for VI *if* it existed in the amide form.

These conclusions—that is, that all of the amides studied except the formamide have the imidate structure—are substantiated by the absence of a medium intensity peak within 30 cm^{-1} of 983 cm^{-1} in the infrared spectra of all derivatives except I (V exhibits a weak peak at 978 cm^{-1}). As mentioned above, this absorption is almost certainly associated with the Si-N grouping and is in the region previously assigned to the Si-N-Si asymmetric stretch.[4,12]

Discussion

The change in structure that results from a change in substituent from H to CH_3 in the bis(trimethylsilyl) derivatives is not easily rationalized. The difference in free energies of the amide and imidate forms is probably not great for most derivatives and is some function of steric and electronic differences. While there is clearly a difference in steric requirements for H and CH_3, an examination of space-filling models of the Stuart–Briegleb type does not reveal any major difference in steric hindrance between the amide and imidate forms for both I and II.

One of the electronic differences between formamides and acetamides is the greater π character in the ground state of the formamide.[9] An increase in the π character in the amide should lead to stabilization of that form if the substituent responsible for the increase does not invoke a similar stabilization of the imidate form. This dependence of structure on the π character in the C-N bond seems to receive support from the structures of trimethylsilyl-N-alkylformamides and -acetamides which exist in solution as amides[3,7] and the trimethylsilylacetanilides which are tautomeric mixtures of amide and imidate.[13] Thus, when the substituent attached to nitrogen is phenyl, which conjugates with nitrogen and consequently decreases the carbonyl-nitrogen π character, the relative stability of the amide form decreases. Moreover, electron-releasing substituents on the phenyl ring of the acetanilides increase the percentage of amide present, presumably by increasing the π character in the C-N bond.[13]

The change in structure from trimethylsilyl-N-alkyl-

acetamides to bis(trimethylsilyl)acetamide can be interpreted in the same way. The decrease in the π-bond order produced by the trimethylsilyl group can be appreciated by a comparison of the *rotational* free energies of activation for N-*tert*-butylformamide (average $\Delta G^{\pm}$, 30% ClC_6H_5, 20.1 kcal/mol[7]), N,N-diisopropylformamide ($\Delta G^{\pm}$, o-$Cl_2C_6H_4$, 20.6 kcal/mol[14]), N-trimethylsilylformamide (average $\Delta G^{\pm}$, 30% ClC_6H_5, 17.8 kcal/mol[7]), and bis(trimethylsilyl)formamide ($\Delta G^{\pm}$, 30% ClC_6H_5, 11.6 kcal/mol). Since the *tert*-butyl and trimethylsilyl groups have similar steric requirements,[7] the difference of 2 kcal/mol in $\Delta G^{\pm}$ between the mono derivatives can be attributed to the electronic effect of silicon. Two trimethylsilyl groups attached to nitrogen produce a decrease in $\Delta G^{\pm}$ relative to the *tert*-butyl analog (bis(*tert*-butyl)formamide should have a $\Delta G^{\pm}$ similar to that of bis(isopropyl)formamide[14]) of considerably more than twice that due to one trimethylsilyl group.

While the structural changes that result from a change in substituents attached to nitrogen can be successfully rationalized by variations in the π character of the C-N bond, a similar rationalization of the effect of substituents attached to the carbon is unsuccessful. Electron-withdrawing substituents such as CF_3 do not favor the imidate form. Hence, the reason for the difference in structure between I and the other bis-substituted amides is not clear.

The free energies of activation for the *exchange* process which occurs in compounds II-VI can be roughly correlated (except for V) with the electron-withdrawing effect of the R group. The same dependence of exchange rate on the electronic character of the carbonyl substituent has been observed in bis(trimethylsilyl)-benzamides[15] and trimethylsilylanilides.[16]

A plausible mechanism for this concentration-independent exchange is depicted by the following scheme.[15]
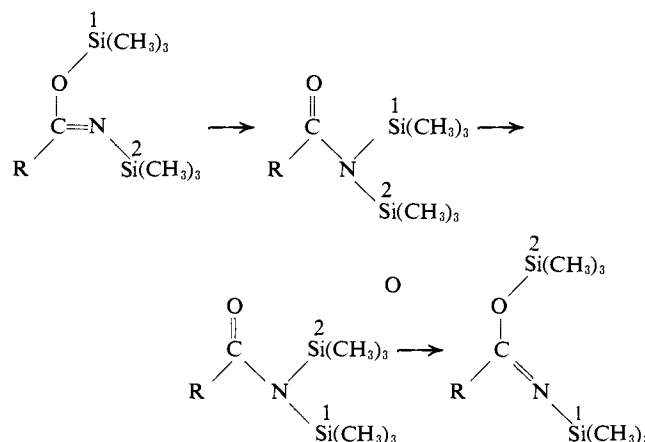
Migration of a trimethylsilyl group from oxygen to nitrogen with a concomitant rearrangement of electronic structure to the amide form is followed by rotation about the carbonyl–nitrogen bond of the intermediate amide. Finally, the other trimethylsilyl group which is now cis to oxygen migrates and the imidate form is regenerated.

There are several noteworthy aspects of this se-

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quence. First, the ground state is probably the imidate with the trimethylsilyl groups trans to one another. Only in this conformation is the nitrogen lone pair accessible to the O-Si(CH$_3$)$_3$ group. Moreover, when R is not large this conformation seems to minimize steric repulsions.

Second, if this is indeed the mechanism, the migration step is rate determining. This follows from the argument that the free energy of activation for rotation in the intermediate should be about the same as or lower than that of compound I (*vide supra*). Since the free energies of activation for the exchange processes are considerably higher, they must correspond to the rate-determining migration step.

Finally, an examination of space-filling models reveals that an increase in the *size* of the carbonyl substituent R probably results in slightly greater steric hindrance in the imidate ground state than in the intermediate amide. Therefore, an increase in size of R should destabilize the ground state more than the intermediate, thereby resulting in a slight decrease in activation energy. Indeed, when R = C(CH$_3$)$_3$ the hindrance in the trans imidate conformation is so severe that the ground state may become the cis isomer. Migration of Si(CH$_3$)$_3$ would probably be preceded by rotation about the C=N bond to produce the reactive trans isomer. This may account for the high $\Delta G^{\ddagger}$ for this derivative. (The low 1.3 Hz $\Delta \nu_c$ for V produces an error of no more than 0.4 kcal/mol for $\Delta G^{\ddagger}$.[8])

Conformational Analysis by Lanthanide Induced Shifts. *N*-Nitrosopiperidines

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Abstract: A method of conformational analysis based on measured lanthanide induced shifts (LIS) for a series of compounds is proposed and shown to give acceptable conformational analyses for the *N*-nitroso derivatives of piperidine, 4-methylpiperidine, 2-methylpiperidine, 2-ethylpiperidine, and 2-propylpiperidine. The method uses LIS Δ values relative to an internal standard common to all members of a series, and these relative Δ values are used to calculate the equatorial and axial populations of a given proton signal, taking the relative Δ values of the proton in an axial and equatorial orientation from a conformationally rigid model compound.

L anthanide induced shift (LIS) values observed in the nmr spectra of complexes between organic substrates and lanthanide shift reagents have been extensively used[1] in determination of the molecular geometry of conformationally rigid systems; however, the use of LIS values in the quantitative stereochemical analysis of a conformationally mobile system has not been reported. Two approaches to the problem of interpreting experimental LIS values for molecules known to exist as mixtures of conformers have been proposed. The first method[2] uses the known or estimated population of the different conformers to calculate an average value of G, the geometric factor in the McConnell equation, which is then used to calculate LIS values. In cases where the position of the conformational equilibrium is unknown, a comparison of observed shifts with those calculated for different conformers, assuming a value of the metal–ligand distance, is used[3–6] to determine the preferred conformation. Several authors[7,8] have

pointed out the possibility that the addition of the lanthanide shift reagent may alter the position of the conformational equilibrium. We wish to report a method by which a quantitative estimate of the population of different conformers can be made directly from observed LIS values. This method has been applied to the conformational analysis of a number of *N*-nitrosopiperidines, some of which had been subjected to conformational analysis by other nmr methods.

Rationale of the Method

In a conformationally mobile system the observed Δ value (slope of a plot of the lanthanide induced shift *vs.* molar ratio of shift reagent to substrate) for a proton is the weighted average of the Δ values of this proton in the contributing conformers, where N_i is the mole frac-

$$\Delta = \Sigma_i N_i \Delta_i \tag{1}$$

tion of conformer i and Δ_i is the Δ value of this proton in conformer i. For six-membered rings, such as cyclohexanes and piperidines, where there are only two major conformers, eq 1 reduces to

$$\Delta = N_e \Delta_e + N_a \Delta_a \tag{2}$$

where (e) refers to the conformation in which the proton

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