$$\log K = 0.62(\pm 0.12) \log P - 0.28(\pm 0.34) \quad (2)$$
$$n = 5; r = 0.995; s = 0.060$$

Equations 1 and 2 for the simple model enzyme systems can be compared with the more complex interaction of ligands with proteins. Equation 3 correlates binding of miscellaneous organic compounds by bovine serum albumin. C in eq 3 is the molar concentration of ligand necessary to produce a 1:1 complex of albumin and ligand; hence, it can be regarded as a binding constant. The slope of eq 3 (as well as eq 2) is a little higher than that of eq 1. This is at least in part due to the fact that the system on which eq 1 is based is not pure water, but instead contains 11% ethanol and 1% dioxane. The solubilizing effect of these solvents would lower the effective partition coefficients of the esters in comparison to the π constants obtained in pure water and octanol. In fact, Murakami et al. noted that as one increased the ethanol content of the hydrolysis solution, the catalytic effect decreased; hence, one expects a slightly lower slope because of the alcohol.

$$\log 1/C = 0.75(\pm 0.07) \log P + 2.30(\pm 0.15) \quad (3)$$
$$n = 42; r = 0.960; s = 0.159$$

A more complex example is that of the formation of a complex between X-$C_6H_4CONH_2$ and the enzyme alcohol dehydrogenase.[12] In eq 4, π_4 and E_{s4} refer to the hydrophobic and steric effects of substituents in the 4 position of the benzamide inhibitors, while σ refers to the electronic effect of both the 3 and 4 substituents. Apparently, 3 substituents do not contact the enzyme but may promote their electronic effect through the framework of the benzene ring. The hydrophobic effects of 4 substituents binding to the enzyme are similar to those of eq 1 (i.e., similar coefficients indicate similar hydrophobic effects).

$$-\log K = 0.45(\pm 0.28)\pi_4 - 0.80(\pm 0.30)\sigma + 0.23(\pm 0.17)E_{s4} - 2.37 \quad (4)$$
$$n = 14; r = 0.953; s = 0.168$$

The results of eq 1 and 2 show that substituent constants and regression analysis can be used to study ligand interactions of various model enzyme systems and that the resulting correlation equations can be compared quantitatively with those which are now being generated with the natural macromolecules and enzymes. Much more complex comparisons can be made; for example, instead of using $RCOOC_6H_4$-p-NO_2 to develop eq 1, one could use $RCOOC_6H_4$-X. For such a set of congeners, the electronic effect of X, as well as its hydrophobicity, could be included in the correlation equation. By making a better selection of R for which E_s values are known, one could also assess the importance of steric effects around the reaction center. By making more sterically restricting cyclophanes, one could study steric effects such as those brought out by the E_s term of eq 4.

This is the first instance, to our knowledge, where π constants have been used to correlate the interaction of small organic compounds (not micelles) hydrophobically.

It must be noted that micelle formation with some of the very hydrophobic molecules used in this study is a serious problem. Murakami et al. were well aware of the possible complications which could result from micelle formation and took precautions to work below critical micelle concentrations. There is the possibility that some micelle formation may have occurred; however, if it did it would probably have little effect on the shape of eq 1. Equation 1 is very similar to eq 2, in which hydrolysis is occurring in micelles.

Through such comparative studies of model enzymes using correlation equations to disentangle the multiple effects of substituents, our understanding of the enzymic process will be greatly increased.

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Structure–Reactivity Relationships of *N*-Alkyl(trimethylsilyl)amides[1]

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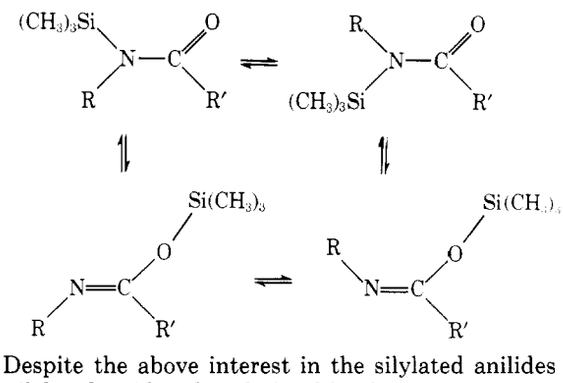
Silylating agents play an important role in both academic and industrial applications because of their ability to alter solubility, affect the course of some chemical reactions, increase volatility, etc. One important class of silylating agent, the silylamides, has sparked considerable interest because of their structural complexity and high chemical reactivity.[2,3]

Although bis(trimethylsilyl)amides[5] and (trimethylsilyl)-acetanilides[3,6,7] are thought to consist of a mixture of *N*-silylated amide and the *O*-silylated imidate tautomeric structures, the *N*-alkyl(trimethylsilyl)amides have been reported to be totally in the *N*-silylated amide form.[4] There is the possibility of additional structural complexity arising from restricted rotation or cis–trans isomerization for amide and imidate forms as illustrated below:



Despite the above interest in the silylated anilides and bissilylated amides, the relationship of structure to reactivity in the simple silylated *N*-alkylamides has been largely ignored.

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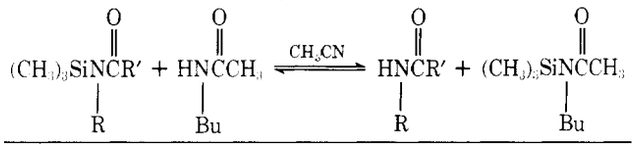
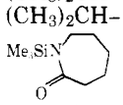
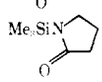
Table I. Influence of *N*- and *C*-Alkylation on the Relative Chemical Stability of Selected Silylamides

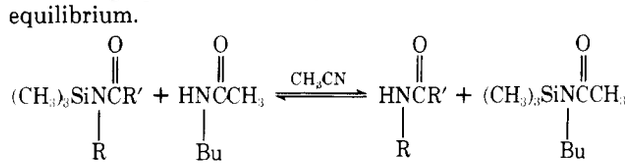


R	registry no.	R′	K_{eq}
$(CH_3)_3C$–	67969-42-9	CH_3–	1.1×10^2
$(CH_3)_3Si$–	10416-58-7	CH_3–	2.2×10^1
n-C_4H_9	23138-73-0	CH_3–	1.0
CH_3–	7449-74-3	CH_3–	3.0×10^{-1}
$(CH_3)_2CH$–	67969-43-1	CH_3–	9.3×10^{-4}
$(CH_3)_2N$–	67969-44-2	CH_3–	$<1.0 \times 10^{-5}$
$(CH_3)_3C$–	67200-04-8	H–	1.0×10^{-1}
CH_3–	13889-02-6	H–	$<4.2 \times 10^{-3}$
CH_3–	67969-45-3	$(CH_3)_3C$–	5.0×10^{-1}
CH_3–	67969-46-4	CH_3CH_2	3.3×10^{-1}
CH_3–		CH_3–	3.0×10^{-1}
CH_3–	24589-78-4	CF_3	2.2×10^{-1}
CH_3–	65768-03-8	$N(CH_3)_2$–	5.0×10^{-3}
CH_3		H	$<4.2 \times 10^{-3}$
$(CH_3)_3C$–		CH_3	1.1×10^2
$(CH_3)_2CH$–	67969-47-5	CH_3CH_2–	2.0×10^{-2}
$(CH_3)_2CH$–		CH_3–	1.0×10^{-3}
	3553-94-4		1.1×10^{-1}
	14468-90-7		$<3.0 \times 10^{-6}$

Our interest in this question was first stimulated by the knowledge that silylated derivatives of pyrrolidone and ϵ-caprolactam exhibit grossly different reactivity. Suspecting that the silylated pyrrolidone's markedly lower reactivity might be related to effects on the above tautomeric and topomeric equilibria, we decided to further examine the relationship of structural features on amidosilane reactivity. Although we have not yet fully rationalized the observed differences, we have found the very interesting reactivity pattern spanning seven orders of magnitude reported herein.

Results and Discussion

A series of *N*-alkyl(trimethylsilyl)amides was prepared and their relative chemical reactivity determined by careful gas chromatographic (GLC) analysis of the following systems at equilibrium.



These chromatographic data were used to calculate equilibrium constants (K_{eq}) which were correlated with structural features in these materials. The chemical equilibria studied and the equilibrium constants obtained are shown in Table I.

Several trends are evident in the observed relative thermodynamic silylating power of these silylamides. Increasing the steric bulk of the nitrogen substituent of the silylamide serves to enhance the relative silylating ability of these agents. The relative reactivity (with R′ equal to methyl) as R goes from methyl to *tert*-butyl changes by three orders of magnitude. Overall, changes in the nitrogen substituent resulted in relative silylating powers which differed by over seven powers of ten (10^7) in the series of acetamides shown.

Altering the steric bulk or electron-donating ability of the carbonyl substituent, R′, also produced changes in the relative chemical stability of the *N*-alkyl(trimethylsilyl)amides. Although these changes were less dramatic, Table I shows differences of over two orders of magnitude in the silylating power of these materials as R′ is varied from hydrogen to *tert*-butyl for a series of *N*-methyl derivatives. Somewhat larger changes were noted when R was *tert*-butyl and the substituent on the carbonyl carbon, R′, was changed from hydrogen to methyl.

There is one anomaly in this structure–reactivity series, the *N*-isopropyl(trimethylsilyl)amides. Instead of lying between the *tert*-butyl and *n*-butyl examples the *N*-isopropyl compounds are markedly less reactive than would be expected. In fact, the *N*-isopropyl derivatives were less reactive than even the *N*-methyl(trimethylsilyl)amides. This finding has not been explained but may be related to topomeric differences in these compounds. Additional studies are underway which hopefully will correlate the relative chemical reactivity of these silylamides with any topomeric differences indicated by appropriate NMR and infrared spectroscopic measurements.

Experimental Section

Reagents and Chemicals. All organic and inorganic materials were used only after drying, distillation, or standardization to insure purity and dryness.

Gas–Liquid Chromatography (GLC). All gas–liquid chromatograms were recorded with an Infotronic Model 2400 series gas chromatograph equipped with a Model 68 linear temperature programmer and a 6 ft × ⅛ in. SP2401 column. The injection port temperature was maintained at 160 °C and the detector (TC–He) at 310 °C. The column was linearly programmed at 20 °C/min from 100 to 200 °C.

Equilibrium Constants. Equilibrium constants were determined by the following method.

Dried vials fitted with septum closures were charged with equimolar amounts of *N*-alkyl(trimethylsilyl)amide, *N*-butylacetamide, and CH_3CN (the solvent and internal standard). Samples were removed periodically for GLC analysis and equilibrium constants calculated by classical methods.

Response factors for reactants and products were calculated by methods described by L. F. Hanneman[8] relative to acetonitrile.

Silylamides. All of the silylamides were prepared in a similar fashion and each material was characterized by NMR and infrared analysis. All operations were carried out in an inert atmosphere to prevent inadvertent hydrolysis of these extremely moisture sensitive materials. The preparation of *N*-*tert*-butyl(trimethylsilyl)acetamide is typical of the procedure used.

***N*-*tert*-Butyl(trimethylsilyl)acetamide.** A flask fitted with a reflux condenser, thermometer, and septum was evacuated, dried, and flushed with dry nitrogen. The system was protected from atmospheric moisture via a series of dry ice–acetone cold traps and nitrogen. The flask was charged with 20.0 g (0.17 mol) of *N*-*tert*-butylacetamide, 118.29 g (1.17 mol) of triethylamine, and 50 mL of dry pentane. Then 37.73 g (0.35 mol) of trimethylchlorosilane was added to the stirring mixture via syringe. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate fractionally distilled at reduced pressure. Distillation resulted in 20.1 g (0.11 mol) of the desired product, bp 62 °C (22 mm Hg) (65% yield).

Registry No.—*N*-Butylacetamide, 1119-49-9; *N*-*tert*-butylacetamide, 762-84-5; trimethylchlorosilane, 75-77-4.

Supplementary Material Available: A table summarizing the boiling points and the NMR data for the *N*-alkyl(trimethylsilyl)-amides listed in Table I (2 pages). Ordering information is given on any current masthead page.

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