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Strong influence of intramolecular Si···O proximity on reactivity: Systematic molecular structure, solvolysis, and mechanistic study of cyclic *N*-trimethylsilyl carboxamide derivatives

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Dedicated to Dezső Knausz for his 80th birthday.

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ABSTRACT

A comparative alcoholysis study of *N*-silylated derivatives of simple heterocyclic carboxamides (lactams, imides, ureas) is presented. The second-order rate constant values span a range as wide as three orders of magnitude. On the basis of DFT calculations, a good correlation between reactivity and the Si···O distance was found within each family of compounds. The viability of two different reaction pathways was evaluated using a detailed computational mechanistic study of the methanolysis of cyclic urea homologues. Peculiarities in the single-crystal X-ray diffraction structures of the trimethylsilyl and trimethylsiloxy phthalimides are also discussed.

Introduction

Silylated carboxamide derivatives represent a notable group within organosilicon compounds[1] since they are extensively used as silylating agents for hydrogen-bonded, non-volatile analytes in gas-phase analytical techniques (e.g. gas chromatography and mass spectrometry)[2] and as protected/activated intermediates in multi-step organic syntheses.[3] Moreover, the unsilylated parent compounds (e.g. ureas) have gained increased interest in applications such as organocatalysis and supramolecular chemistry,[4] hence their controlled release from Si-protected (and lipophilic) precursors by protodesilylation reactions (e.g. hydrolysis, alcoholysis, fluoride-induced cleavage) under less conventional (e.g. biphasic, phase-transfer catalytic, micelle-forming) conditions may afford novel synthetic routes.[5]

In nucleophilic substitution reactions the increased reactivity of penta- and hexacoordinate silicon atoms over tetracoordinate ones has long been recognized.[6] One of the first reports concerning the unique reactivity of silylated amides, for example, over silyl amines, was published by Klebe who presumed a switch from the pentacoordinated configuration of the silicon center to the hexacoordinated one upon nucleophilic attack by a proton donor onto the Si atom.[7] In a later study, Lane and Frye determined the relative thermodynamic silylating abilities of trimethylsilylated *N*-alkyl amides and observed significantly different stability for the silylated pyrrolidone and ε-caprolactam, respectively; however this phenomenon was not fully rationalized.[8]

In our previous paper we reported the surprisingly different reactivity of *N*-silylated cyclic ureas with 5-(TMS_2Im), 6-(TMS_2Pyr), and 7-(TMS_2Diaz) membered rings during hydrolysis and alcoholysis reactions.[9] Both experimental (single-crystal X-ray diffraction) and quantum chemical studies revealed a strong relationship between the ground-state molecular structure of the substrates and their silylating power.[9,10] Herein, we present an extension of this study relating to silylated cyclic carboxamides, interpreting the new results in a wider perspective (Fig. 1). The octanolysis rate of a series of silyl lactams (TMSBL, TMSVL, TMSCL) and dicarboxylic acid imides (TMSSI, DMSBPI, TMSPI, TBDMSPI, TMSOPI, TMSGI, TMSNI) was determined under similar conditions as previously described[9] (Scheme 1).

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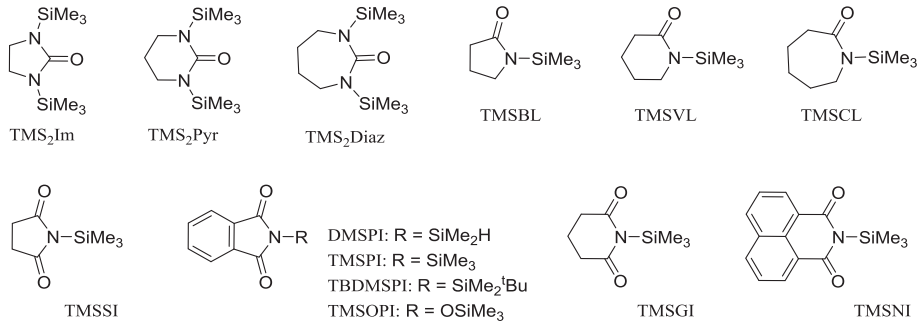
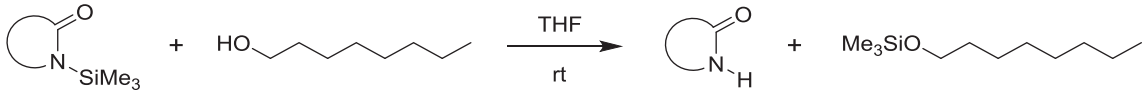


Fig. 1. Compounds concerned in this work.



Scheme 1. Octanolysis reaction of silylated cyclic carboxamides.

In order to gain a deeper insight into the ring-size dependent solvolytic reactivity, a detailed computational mechanistic study of the methanolysis of three *N,N′*-disilylated urea homologues (TMS_2Im, TMS_2Pyr, TMS_2Diaz) is also discussed.

Results and discussion

Syntheses

The silylated lactams (TMSBL, TMSVL, TMSCL) and TMSPI were obtained from the reaction between the corresponding N—H compound and trimethyl chlorosilane in the presence of triethylamine as a proton scavenger. Unlike aromatic (benzene, toluene) or ether (Et_2O, dioxane) solvents commonly used for such reactions,[11] CH_2Cl_2 was selected as being one of the best solvents for silylation.[12] DMSPI and TBDMSPI were similarly prepared from phthalimide and dimethyl or *tert*-butyldimethyl chlorosilane. In the case of TMSNI, naphthalimide was first converted into its sodium salt using $NaNH_2$, then silylated using a THF solution of Me_3SiCl in excess.

Both alicyclic silyl imides (TMSSI and TMSGI) were synthesized by silylation of the corresponding imide with *N,O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA). Several attempts with commonly used basic silylating agents (e.g. Me_3SiCl/Et_3N, hexamethyl disilazane, trimethylsilyl *N,N*-dimethyl carbamate) failed to give TMSOPI in satisfactory yield since the reversibly formed red-coloured ammonium salt of the deprotonated *N*-hydroxy phthalimide precipitated out of the mixture and therefore could not be efficiently silylated. Using the more powerful reagent BSTFA led to the desired product. To the best of our knowledge, TMSNI and TMSOPI are novel compounds.

Octanolysis study of silylated lactams and imides

Rate measurements were carried out at room temperature in 1-octanol/THF mixtures containing the substrate in 100 times dilution compared to the alcohol. Solvolysis reactions could be conveniently followed using gas chromatography by monitoring the relative peak area of the trimethylsiloxy octane (OctOTMS) formed (Fig. 2).

The peak intensity *vs* time data were evaluated surmising a pseudo-first order kinetic model:

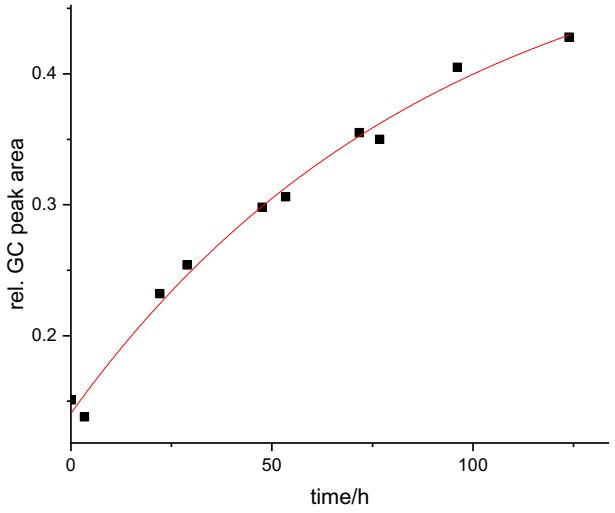


Fig. 2. GC peak area of OctOTMS *vs* time for the octanolysis reaction of TMSPI.

$$X = X_\infty\left(1 - ae^{-k_{exp}t}\right),$$

where X, X_∞, k_{exp}, t and a denote the actual and final peak area of the OctOTMS (normalised to the internal standard), the pseudo-first order rate constant, the reaction time and a constant parameter, respectively (see the literature for a physical interpretation of the latter parameter[9]). The bimolecular rate constant (k_2) independent of the alcohol concentration was determined in order to characterise the reactivity of substrates where $k_2 = k_{exp}/[OctOH]$. Considering the wide range of several orders in magnitude spanned by k_2s, the $pk_2 \equiv -\log_{10}(k_2/h^{-1}\,mol^{-1}\,dm^3)$ values are instead listed, together with the Gibbs free energies of activation calculated from the Eyring–Polányi equation wherein the transmission coefficient is taken as the unity (Table 1).

Firstly, it should be mentioned, for example, that the difference of 1.7 kcal mol^{-1} between the $\Delta^{\ddagger}G$ values for the five-membered (TMSBL) and the six-membered (TMSVL) silyl lactams is reflected in the 16 times faster alcoholysis of the latter compound, whereas the difference of at least 3.4 kcal mol^{-1} between the corresponding ring-membered silyl ureas indicates a 300 times difference in reaction rates. Upon considering the pk_2 values themselves, it should