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NMR and X-ray Studies of Hydrogen Bonding for Amide-Containing Silanediols

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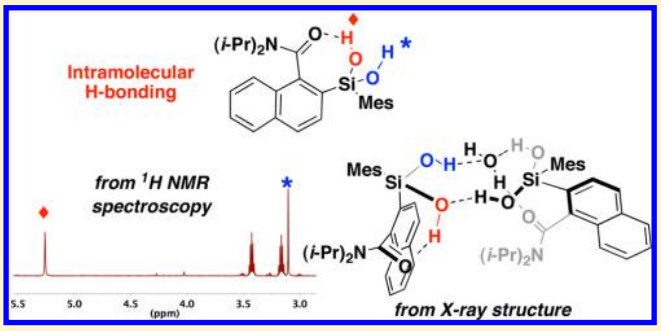
Supporting Information

ABSTRACT: The synthesis, isolation, and hydrogen-bonding properties of a series of amide-containing silanediols are described, including an enantioenriched silanediol. By incorporation of a 2,4,6-trimethylphenyl (mesityl) group, these functionalized silanediols are isolable by column chromatography and stable in the presence of standard acids (e.g., AcOH) and bases (e.g., NH_4OH). NMR spectroscopy and X-ray crystallography provide evidence for the conformational rigidity and binding properties of amido-silanediols based on the parameters (e.g., sterics, hybridization, and ring size of hydrogen bonding) that affect intra- and intermolecular hydrogen bonding. Pyridine binding studies demonstrate that these conformational effects have implications for the existence of single versus multiple modes of hydrogen bonding.



Inorganic and organic silanols exhibit unique hydrogen-bonding capabilities that are important for materials, surface chemistry, catalysis, and medicinal chemistry.[1] Organosilanols in several different forms have been investigated as isosteres in drug design and demonstrated to exhibit biological activity (Figure 1). For example, Tacke has reported silicon analogues

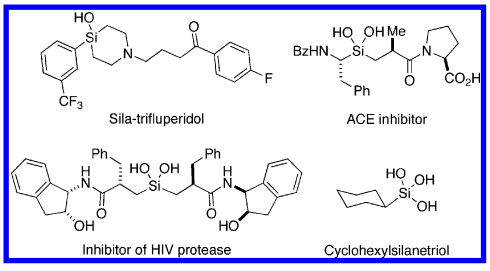


Figure 1. Biologically active silanols and silanediols.

of the dopamine (D_2) receptor antagonists,[2] and Sieburth has pioneered the synthesis and study of silanediol peptide analogues as protease inhibitors.[3] Silanetriols, which can be stabilized by the use of bulky substituents, have recently been found to provide reversible inhibition of acetylcholinesterase (AChE) activity.[4] Antimicrobial activities of trialkylsilanols have also been reported where silanols exhibit greater biocidal properties relative to carbon analogues, which is attributed to the enhanced hydrogen-bond acidity as well as the lipophilicity.[5] Our laboratory[6] and others[7] have also studied the hydrogen-bonding properties of silanols and silanediols for applications in molecular recognition and catalysis.

As with biomolecules such as peptides and carbohydrates, the intramolecular hydrogen bonding of bioactive silanediols is expected to play an essential role in their three-dimensional structure and biological function.[8] Research in this area often focuses on the development of synthetic methodology to access silanediol precursors;[3] therefore, very few studies have been reported that describe the intramolecular hydrogen bonding and conformational preferences for functionalized silanediols.[9] Computational studies of amide-containing silanediols demonstrate the effect of intramolecular hydrogen bonding on rigidity and conformation: if the correct conformation is obtained, a more rigid structure is expected to have better binding to a receptor due to a lower entropic penalty.[10] There is a need to access soluble silanediols that are stable toward condensation and desilylation in order to improve our understanding of the parameters affecting the conformational and hydrogen-bonding abilities of this class of compound.

Here we demonstrate the synthesis of a new series of stable and isolable amide-containing silanediols **1**−**4** for the purpose of understanding their intramolecular hydrogen bonding (Figure 2). This series of structurally related silanediols has been selected to compare different electronic effects, steric effects, the chiral center, the position of the silanediol, and ring size for intramolecular hydrogen bonding. The synthesis of new functionalized silanediols can be challenging because difficulties can be encountered due to self-condensation and oligomerization of the silanediol. Therefore, the ability to access more acidic aryl silanediols relies on the incorporation of bulky substituents surrounding the silicon atom in order to minimize self-condensation.[11] Previously, we have utilized a 2,4,6-trimethylphenyl (mesityl) group as a general strategy for steric

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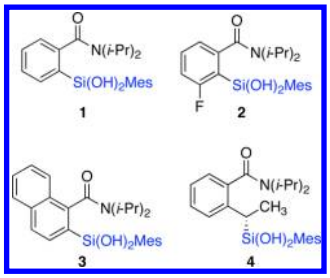
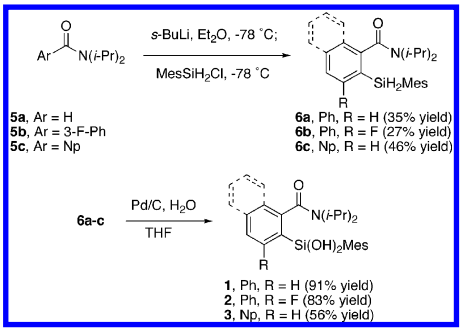


Figure 2. Silanediols synthesized and investigated here.

shielding in order to overcome self-condensation and improve the solubility of aryl silanediols.[6a−c]

Aryl amides **5a−c**, with different steric and electronic effects, were investigated to access silanediols **1−3** (Scheme 1). A

Scheme 1. Synthetic Route to Silanediols through Lithiation−Silylation Methodolgy



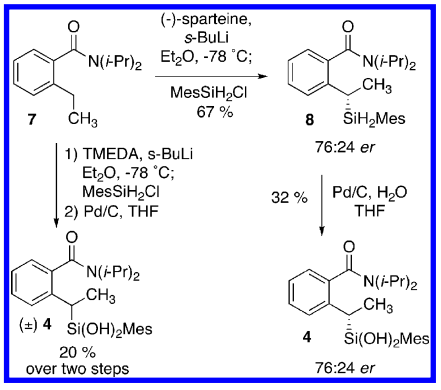
lithiation−silylation strategy with mesitylchlorosilane in the presence of TMEDA affords silanes **6a−c** in moderate yields following standard column chromatography procedures. Phenyl silicon electrophiles were not used because previous investigations resulted in lower yields of silanes and the products were more prone to decomposition without the shielding effect of the 2,4,6-trimethylphenyl (mesityl) group.

Metal-mediated hydrolysis of the Si−H bond affords silanediols **1−3** in good yields using catalytic Pd/C with H_2O in THF.[12] This hydrolysis method utilizes mild conditions that do not promote condensation of the silanediol product.[6a−c,13] Silanediols **1−3** can be purified using standard column chromatography conditions with no decomposition observed.[14] The silanediol structures have been confirmed using ^1H, ^{13}C, and ^{29}Si NMR spectroscopy, and HRMS.

Chiral, nonracemic silanediol **4** was accessed using an enantioselective lithiation−silylation strategy with benzylamide **7** (Scheme 2).[15] The (−)-sparteine-mediated asymmetric addition of mesitylchlorosilane to the benzylic position affords silane **8** with moderate enantioselectivity (76:24 er).[16,17] Silane **8** can be hydrolyzed to the enantioenriched, chiral silanediol **4** using Pd/C in the presence of 5 equiv of H_2O. The absolute stereochemistry was assigned by analogy to similar structures reported in the literature.[16] The racemic silanediol **4** is readily obtained by replacing (−)-sparteine with TMEDA.

We have utilized ^1H NMR spectroscopy to monitor the stability of silanediols **3** and **4** (i.e., toward condensation to afford siloxanes or desilylation).[2a,3a,18] Isolation of discrete silanediols is necessary for the accurate and reproducible study of hydrogen-bonding interactions. Understanding the stability of silanediols under various conditions provides insight into their potential utility as medicinal compounds and organo-

Scheme 2. Synthesis of Enantioenriched Silanediol 4



catalysts. Silanediols **3** and **4** (10 μM) exhibit no degradation when stored at room temperature in $CDCl_3$ solvent or a mixture of CD_3CN/D_2O after 7 days (see the Supporting Information). The stability in the presence of acid or base was also investigated. When silanediols **3** and **4** were monitored in the presence of AcOH (0.9 M) or excess NH_4OH (1.3 M), the ^1H NMR spectra also remained unchanged after 7 days. Upon addition of trifluoroacetic acid (0.1 M), rapid degradation (e.g., condensation and/or desilylation) of both silanediols is observed, on the basis of the disappearance of the characteristic peaks in the NMR spectra. The production of mesitylene along with broad, multiple new peaks suggests a combination of protodesilylation and condensation to form oligomeric siloxanes.

NMR spectroscopy demonstrates that structurally related silanediols **1−4** exhibit intramolecular hydrogen bonding with different conformational rigidities (Figure 3). ^1H NMR spectra

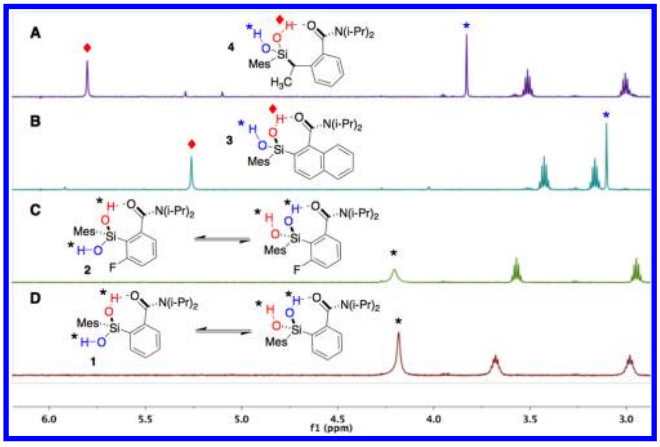


Figure 3. Hydroxyl peaks of silanediols **1−4** (10 mM in C_6D_6) as visible by ^1H NMR spectroscopy. Silanediols **3** and **4** contain chemically inequivalent hydroxyl peaks at room temperature, suggesting rigid intramolecular hydrogen bonding under ambient conditions.

of silanediols **4** and **3** each exhibit two distinct hydroxyl signals with a large chemical shift difference (2.16 and 1.97 ppm, respectively, Figure 3A,B), which is attributed to a single conformation of intramolecular hydrogen bonding. For silanediols **1** and **2**, the same intramolecular hydrogen bonding is proposed between the amide and one of the hydroxyl groups; however, only a single broadened peak is observed, suggesting that a rapid equilibrium exists between conformers (Figure 3C,D). In the case of silanediol **4**, the single conformation is

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attributed to the ring size of intramolecular hydrogen bonding and hybridization of the carbon attached to silicon. In the case of silanediol **3**, the enhanced rigidity and preference for a single conformation is attributed to the increased steric effect of the naphthyl group relative to the phenyl derivatives.[19] When ^{1}H NMR spectroscopy is performed at low temperature for silanediol **2** in $CDCl_3$, the geminal silanol peaks are resolved at −40 °C and a single conformation can be observed (see Figure S1 in the Supporting Information). Additional analysis of silanediols **1**−**4** using IR spectroscopy suggests that several modes of hydrogen bonding exist (in the solid state), on the basis of the observation of a single broad O−H peak.[20]

Understanding the parameters affecting the intra- and intermolecular hydrogen-bonding properties of silanediols is important for specificity in both biological applications and organocatalysis. Using pyridine binding studies, we have monitored the adoption of various binding motifs based on chemical shifts of silanediols **2**−**4** using ^{1}H NMR spectroscopy in the presence of varying equivalents of pyridine (see Figure S1 in the Supporting Information).[21] For each silanediol, significant chemical shifts (up to 1.23 ppm) are observed for the silanol signal, demonstrating the presence of intermolecular hydrogen-bonding interactions with pyridine; however, distinctive peak shape and broadening patterns are observed for each silanediol. Peak shape in NMR spectroscopy is often used as evidence of single-mode binding between small molecules and proteins.[22] In the case of silanediols **3** and **4**, for which two distinct silanol peaks are observed, the upfield silanol proton has a significantly greater change in chemical shift ($\Delta\delta$ = 1.23 ppm for **3** and 0.88 ppm for **4**) in comparison to the downfield silanol proton ($\Delta\delta$ = 0.37 ppm for **3** and 0.40 ppm for **4**). With silanediol **4** a significant initial broadening of both silanol peaks is observed up to the addition of 4 equiv of pyridine. Upon addition of an excess of pyridine (5 equiv), both silanol peaks sharpen, suggesting the transition to a single mode of pyridine binding (Figure 4). Although a similar change in chemical shift was also observed for silanediol **3**, the peak shape remains constant at various amounts of pyridine (see Figure S3 in the Supporting Information), which is attributed to a more rigid system that generally favors a single mode of binding. In the case of silanediol **2**, the silanol peak progressively broadens upon increasing the amount of pyridine (see Figure S2 in the Supporting Information), suggesting multiple modes of intra- and intermolecular binding. The difference in binding behavior between these comparable silanediols demonstrates how intramolecular hydrogen-bonding ring size, hybridization, and steric effects each play a role to affect intermolecular interactions and therefore all have important implications for the design of silanol-based medicinal compounds and hydrogen-bonding catalysts.

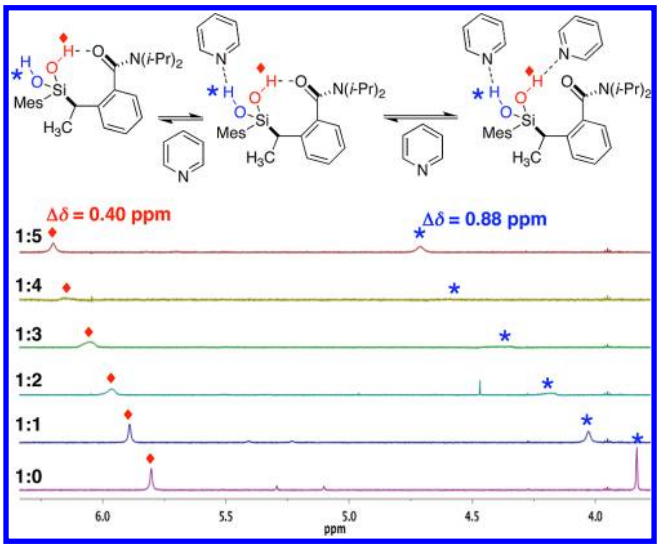

Figure 4. ^{1}H NMR spectroscopy binding studies of silanediol **4** (10 mM in C_6D_6) with increasing equivalents of pyridine.

The X-ray structure of amide silanediol **3** confirms intramolecular hydrogen bonding between the amide and silanol group, with additional intermolecular hydrogen-bonding interactions affording a dimeric complex with a bridging water molecule (Figure 5). An additional hydrogen bond is also observed between the amide and water molecule. The bridging water molecule is incorporated into the dimeric species through absorption of atmospheric water. We have previously observed that bulky diaryl silanediols self-associate through intermolecular hydrogen bonding to form a cyclic dimer, which exhibits strong hydrogen bonding with neutral Lewis bases (e.g., DMF, Et_2O, PhCHO) on the basis of X-ray and NMR binding studies.[6a−c,23] Here, the amide functionality and bridging water molecule contribute to a unique network of hydrogen bonding observed in the X-ray structure for silanediol **3**. This combination of intramolecular and cooperative hydrogen bonding provides valuable insight for the design of medicinal compounds and also has implications for understanding the interactions of water and organic molecules with heterogeneous silica.[24]

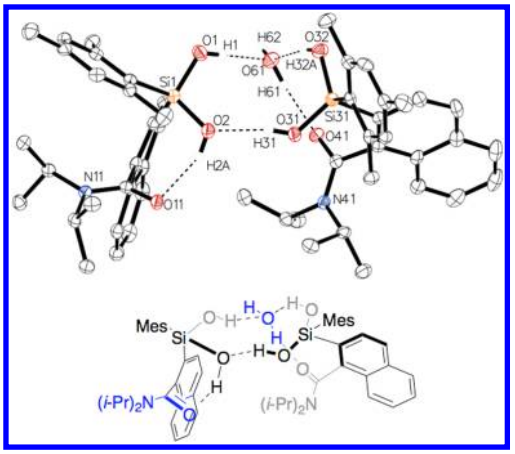

Figure 5. X-ray crystallographic analysis of silanediol **3**, affording a dimeric complex that confirms amide intramolecular hydrogen bonding and incorporates a bridging H_2O molecule.

In conclusion, we have demonstrated the effect of intramolecular hydrogen bonding on molecular conformation and intermolecular binding modes for a series of structurally related silanediols. Through incorporation of a bulky mesityl substituent, amide silanediols are soluble in organic solvents, are readily isolated through column chromatography, and are stable under standard acidic or basic conditions. Using NMR spectroscopy, a comparison of silanediols **1**−**4** demonstrates that steric effects, silanol attachment (e.g., sp^2 vs sp^3), ring size of intramolecular hydrogen bonding, and temperature all play an important role in dictating the conformational rigidity of amide-containing silanediols. These conformational effects have

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implications in the existence of single- versus multiple-mode intermolecular hydrogen bonding, as demonstrated through binding studies with pyridine. X-ray crystallography demonstrates the ability of amide silanediols to form a unique hydrogen-bonding network with intramolecular hydrogen bonding and incorporation of a bridging water molecule. It is expected that the results of this study can be used to design and study the hydrogen-bonding preferences of new peptidomimetic silanediols and organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, figures, and a CIF files giving experimental procedures, spectral data for all compounds, NMR and IR spectra, pyridine binding studies for silanediols 2 and 3, and crystallographic data for **3** (CCDC 884477). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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