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Cooperative Hydrogen-Bonding Effects in Silanediol Catalysis

Ngon T. Tran, Sean O. Wilson, and Annaliese K. Franz*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States

akfranz@ucdavis.edu

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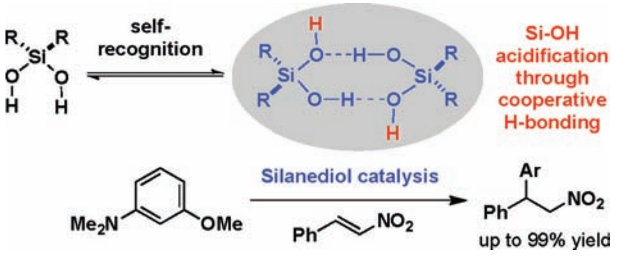
ABSTRACT



The importance of cooperative hydrogen-bonding effects and SiOH-acidification is described for silanediol catalysis. NMR binding, X-ray, and computational studies provide support for a unique dimer resulting from silanediol self-recognition. The significance of this cooperative hydrogen-bonding is demonstrated using novel fluorinated silanediol catalysts for the addition of indoles and *N,N*-dimethyl-*m*-anisidine to *trans-β*-nitrostyrene.

The versatile H-bonding capabilities of silanols and silanediols offer opportunities to discover new activating groups for organocatalysis.[1,2] Based on structural and NMR binding studies, silanediols such as **1** are known to bind anions such as acetate and chloride in a dual H-bonding mode.[3] As part of our program to explore and develop silanediols as a new class of H-bonding[4] catalysts, we recently reported the first example of silanediol catalysis.[5] We have demonstrated that silanediols bind strongly to neutral carbonyl compounds (e.g. DMF and benzaldehyde) and can catalyze a Diels–Alder reaction.[5a] Using computational and mass spectrometry studies, we have also shown that silanediols are comparable to known organocatalysts in acidity.[5b] Silanediols exhibit dual donor and acceptor properties through which new modes of activation and cooperative catalysis may be realized. To evaluate the catalytic activity of silanediols, we designed and synthesized new stable, isolable, and soluble silanediols **2**–**4** with electron-withdrawing fluoro groups (Figure 1).[5] Incorporating a mesityl group provides a general strategy to overcome problems related to condensation as well as solubility.

Here, we demonstrate a new class of stable, isolable silanediols (**2**–**4**) that catalyze the addition of heteroarenes to *trans-β*-nitrostyrene. The indole addition to nitrostyrene is an important C–C bond-forming reaction that is known to be catalyzed by silica gel,[6] as well as organocatalysts such as thioureas and 2-aminopyridinium ions.[7] This reaction provides an excellent system to study the cooperative H-bonding effects for silanediol catalysts.[8] Due to the self-recognition and cooperative H-bonding capabilities,[9] these silanediol catalysts provide exciting opportunities to

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(1) For reviews of silanols, see: (a) Chandrasekhar, V.; Boomishankar, R.; Nagendran, S. *Chem. Rev.* **2004**, *104*, 5847–5910. (b) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147–262. (c) For the first application of organosilanols as chiral ligands in asymmetric catalysis, see: Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407–1409.

(2) For examples describing the synthesis and H-bonding capabilities of chiral silanediols for the design of protease inhibitors, see: (a) Nielsen, L.; Skrydstrup, T. *J. Am. Chem. Soc.* **2008**, *130*, 13145–13151. (b) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035–10044. (c) Sieburth, S. M.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311–322. (d) Mutahi, M. W.; Nittoli, T.; Guo, L.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363–7375. (e) Sieburth, S. M.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812–814. For an example where the enhanced acidity of silanols can improve binding to a receptor, see: Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Warneck, J. B. H.; Tacke, R. *Organometallics* **2006**, *25*, 1188–1198.

(3) Kondo, S.-I.; Harada, T.; Tanaka, R.; Unno, M. *Org. Lett.* **2006**, *8*, 4621–4624.

(4) (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5419–5427.

(5) (a) Tran, N. T.; Min, T.; Franz, A. K. *Chem.—Eur. J.* **2011**, *17*, 9897–9900. (b) Liu, M.; Tran, N. T.; Franz, A. K.; Lee, J. K. *J. Org. Chem.* **2011**, *76*, 7186–7194.

(6) Shumaila, A. M. A.; Kusurkar, R. S. *Synth. Commun.* **2010**, *40*, 2935–2940.

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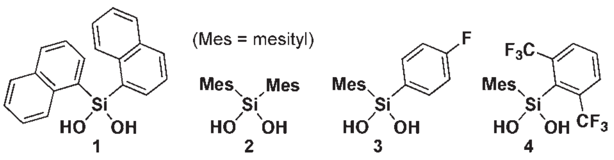
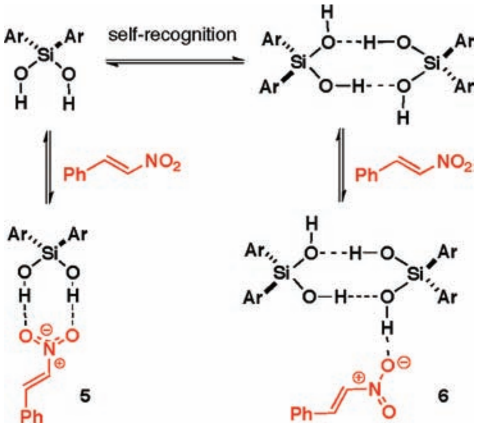


Figure 1. Silanediol catalysts studied here.

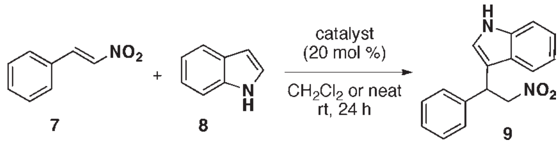
investigate new modes of H-bonding activation that are distinct from other dual H-bonding organocatalysts such as thioureas. Here we have investigated the mode of H-bonding with silanediols **1**–**4** and propose that the primary activation of *trans*-β-nitrostyrene proceeds through single-point H-bonding with a unique dimeric structure in a complex such as **6** (Scheme 1). Our previous structural and NMR binding studies have demonstrated that silanediols **2**–**4** bind strongly to neutral carbonyls through single point H-bonding[5a] activation. While self-association has been studied for other bifunctional organocatalysts, in these cases, the formation of a dimer often blocks the available H-bonding positions, thus reducing catalytic activity and lowering enantioselectivity.[10]

Scheme 1. Monomeric vs Dimeric Active Species



Initially we investigated the Friedel–Crafts addition of indole to nitrostyrene to compare the catalytic activity of silanediols **1**–**4** (Table 1).[11,12] With a monosilanol (e.g., triphenylsilanol), no catalysis was observed and the reaction yield matches that of the background rate (entries 1–2). Diphenylsilanediol and aryl silanediols such as **1** and **2** also showed low catalytic activity (entries 3–5). The enhanced solubility of silanediol **2** may explain why this silanediol shows equal or greater catalytic activity compared to the phenyl and naphthyl derivatives, even though they are calculated to be more acidic.[13] Silanediols **3** and **4**, which maintain the mesityl group while also incorporating electron-withdrawing groups, provided the highest catalytic activity (entries 6–7). Silica gel is also known to catalyze this reaction with a high yield (entry 8),[6] and this is attributed to the fact that the silica surface contains silanols and silanediols that exhibit cooperative H-bonding, thus providing enhanced activation.[14] From these results, we conclude that the catalytic ability is dependent on the acidity as well as the solubility of the silanediol, which dictates the level of association and cooperative H-bonding.

Table 1. Indole Addition^{a}



entry	catalyst	pK_a^{b}	yield in DCM (%)^{c}	solvent-free yield (%)
1	none	–	10	32
2	Ph_3SiOH	11.7	10	45
3	$Ph_2Si(OH)_2$	11.4	19	52
4	**1**	11.8	33	65^{e}
5	**2**	12.4	40	73
6	**3**	11.9	68	83
7	**4**	11.6	92^{d}	92^{e}
8	silica gel^{f}	6.8 ± 0.2	91	78

[a] All reactions performed at 2.0 M with 1.5 equiv of indole. [b] See ref 13. [c] Yields are reported as an average of 2–4 replicates. See the Supporting Information for a table with standard deviations and experimental procedures. [d] The reaction with *N*-methyl indole proceeds with 99% yield with catalyst **4**. [e] Reaction run for 4 h. [f] 20 wt % catalyst loading, see ref 6.

Because silanediols such as **1**–**4** exist in a H-bonded dimer or polymeric network in the crystalline form,[1,5] we hypothesized that a solvent-free reaction would also proceed efficiently. Thus, the indole addition reaction was also examined under solvent-free conditions where the two solid reagents were stirred directly with the silanediol catalyst. This solvent-free reaction proceeds efficiently, which indicates the importance of cooperative H-bonding in the crystalline form, or resulting from concentration effects, to enhance catalysis.

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(7) Selected examples: (a) Schneider, J. F.; Falk, F. C.; Fröhlich, R.; Paradies, J. *Eur. J. Org. Chem.* **2010**, 2265–2269. (b) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464–16465. (c) Takenaka, N.; Sarangthem, R. S.; Seerla, S. K. *Org. Lett.* **2007**, *9*, 2819–2822. (d) Gu, Y.; Ogawa, C.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 175–178. (e) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.

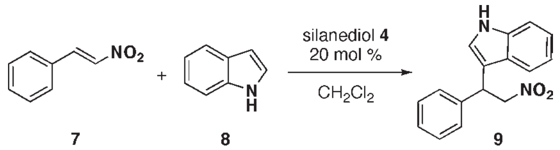
(8) While this manuscript was in preparation, the indole addition to nitrostyrene was reported to be catalyzed by silanediol **1** and Ph_3SiOH; see: Schafer, A. G.; Wieting, J. M.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 5228–5231. We cannot reproduce these results with multiple replicates examined. We attribute the difference in reactivity to the presence of trace acid (i.e. HCl produced upon hydrolysis of the silyl chloride) in their synthesis of silanediol **1**. Our synthetic route utilizes a silane precursor to avoid production of HCl. See Supporting Information.

(9) Based on NMR binding experiments, we have calculated self-association constants for silanediols to be 4.6–7.7 M^{-1}. These NMR studies show that self-association increases significantly with concentration: see Supporting Information and ref 5a.

(10) (a) Jang, H. B.; Rho, H. S.; Oh, J. S.; Nam, E. H.; Park, S. E.; Bae, H. Y.; Song, C. E. *Org. Biomol. Chem.* **2010**, *8*, 3918–3922. (b) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208–1210.

A study of concentration and temperature effects also provides evidence that the dimer is an active catalytic species. Due to silanediol self-recognition, the dimer is the predominant species in solid state and in solution $\geq$0.4 M.[5a] A significant increase in reaction yield occurs at concentrations where catalyst self-association is observed, while negligible activation occurs at catalyst concentrations $<$0.2 M (Table 2). Decreasing the reaction temperature to 0 °C, where self-association is also favored, produced similar yields at 48 h compared to room temperature.

Table 2. Temperature and Concentration Effects[a]

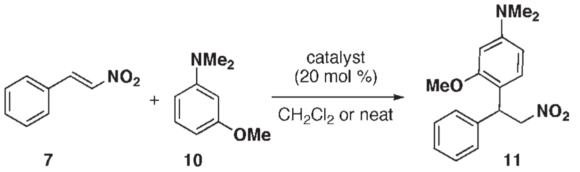


entry	concn of reaction (M)	catalyst concn (M)	temp	time (h)	yield (%)[b]
1	2.0	0.4	rt	24	91
2	1.0	0.2	rt	48	42
3	0.50	0.1	rt	48	29
4	0.05	0.01	rt	48	23
5	2.0	0.4	40	24	99
6	2.0	0.4	4	24	48
7	2.0	0.4	4	48	80
8	2.0	0.4	−20	48	19

[a] All reactions performed with 1.5 equiv of indole. [b] Without catalyst, the yield is 4% at 4 °C (24 h) and 21% at 40 °C (48 h).

Similar patterns of reactivity were observed for the Michael reaction with a more challenging Michael donor, *N*,*N*-dimethyl-*m*-anisidine (Table 3).[7c] Simple silanols and silanediols provide low catalytic activity at both 24 and 48 h, and only silanediol **4** is active enough to catalyze the reaction in good yield at 48 h. It is notable in this case that the solvent-free conditions with silanediol **4** provide a significant increase in catalytic activity, affording a 99% yield for the addition product **11** in less than 24 h.

Table 3. Anisidine Addition[a]



entry	catalyst	time (h)	yield in DCM (%)[b,c]	solvent-free yield (%)
1	none	24	5	3
2	Ph_3SiOH	24	9	4
3	$Ph_2Si(OH)_2$	24	4	–
4	**1**	24	20	21
5	**1**	48	21	–
6	**2**	24	24	29
7	**4**	24	40[d]	99[c]
8	**4**	48	74	–
9	silica gel[e]	24	88	84

[a] All reactions performed with 1.5 equiv of indole at room temperature. [b] Reaction is 2.0 M in DCM. [c] Yields reported as an average of 2 or more replicates. See the Supporting Information for a table with standard deviations and experimental procedures. [d] Performing this reaction in toluene for 24 h affords a similar yield (35%). [e] 20 wt % catalyst loading.

NMR binding studies were performed to investigate the H-bonding of nitrostryene with silanediol **4** compared with other Lewis bases.[15] We have previously reported strong molecular recognition between silanediols and carbonyl compounds; however, NMR studies show that silanediols bind weakly to nitrostyrene based on the SiOH shift (Figure 2). At concentrations below the level of self-association (e.g. $\leq$0.01 M), no significant binding is observed. Binding is only detectable (SiOH $\Delta\delta$ = 0.48 ppm) upon increasing the concentration of silanediol to a level where significant catalyst self-association is observed (e.g., $>$0.2 M). This is in direct contrast to stronger silanediol binding effects observed for neutral Lewis bases (e.g., DMF) and anions (e.g., acetate and halide) where SiOH shifts range from $\Delta\delta$ = 1.6 to 3.9 ppm.[3,5] NMR shifts also indicate that silanediols exhibit strong self-associative H-bonding to form a dimer. This evidence is consistent with the hypothesis that a dimeric complex (e.g., **6**) exhibits stronger H-bonding to activate the nitrostyrene. Crystallization of silanediol **1** with diethyl ether demonstrates the favorable formation of the dimeric complex in the presence of a Lewis base.[16] This cooperative mode of H-bonding is an important distinction from the mode of activation proposed for a thiourea and has important implications for catalyst design.[17]

Computational studies were performed to model the cyclic dimer and to evaluate the enhanced acidity of complex **13**. Performing studies with B3LYP/6-31+G(d)

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(11) The addition of indole was selected for an accurate comparison of catalytic ability due to the low background rate. Using methoxyindole proceeds with a background rate of 35–40% yield in CH_2Cl_2.

(12) Silanediols **1**–**4** were prepared from the corresponding diarylsilanes. See Supporting Information for details.

(13) Acidity calculations were conducted with B3LYP/6-31+G(d) using Gaussion03. The geometries were fully optimized, frequencies were calculated, and pK_a values were verified by comparison to experimental data for known acids, including orthosilicic acid, dimethylsilanediol, and triethylsilanol. See Supporting Information for complete details.

(14) (a) Hair, M. L.; Hertl, W. *J. Phys. Chem.* **1969**, *73*, 4269–4276. (b) Hair, M. L.; Hertl, W. *J. Phys. Chem.* **1970**, *74*, 91–94.

(15) For 0.01 M in C_6D_6, we have calculated the binding constant between silanediol **4** and DMF to be 90.8 ± 0.4 M^{-1} while that with *trans*-β-nitrostyrene is $\leq$6.5 ± 5.2 M^{-1}. See ref 5 and Supporting Information.

(16) Attempts to crystallize nitrostyrene with silanediols were unsuccessful. Searching the Cambridge Structural Database (October 26, 2011) provides no X-ray evidence supporting binding to nitrostyrene in a dual hydrogen-bonding fashion.

(17) Kinetic studies are currently underway. For examples where kinetic studies of catalytic systems have been used to elucidate reaction mechanisms and improve catalyst design, see: (a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014. (b) Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925.

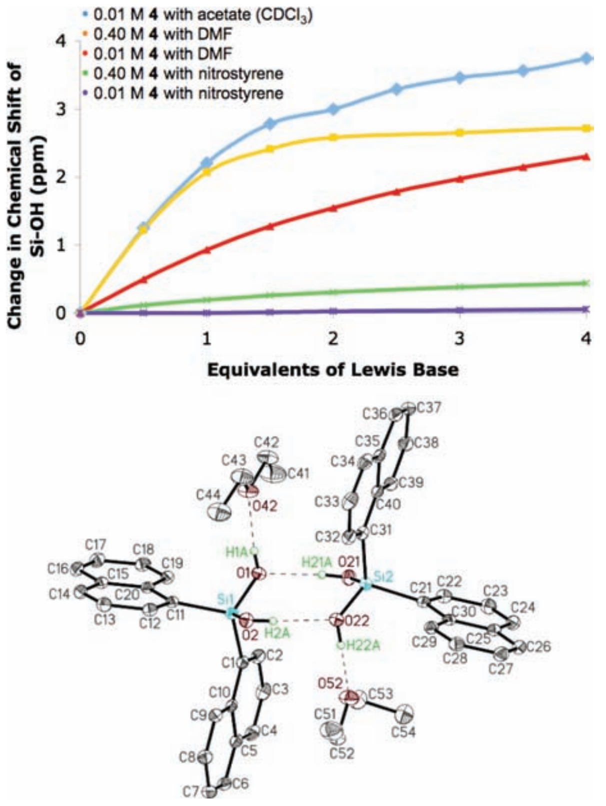
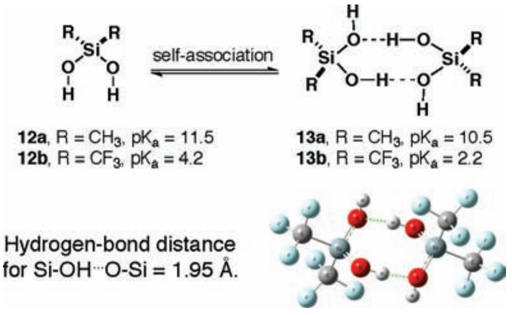


Figure 2. NMR binding studies (400 MHz, in C_6D_6) with silanediol **4** and X-ray crystal structure of silanediol **1** binding to a Lewis base (e.g., diethylether). H-bond distances for Si−OH···O−Si = 1.95 Å (average) and Si−OH···OEt$_2$ = 1.80−1.96 Å.

demonstrates that the formation of the cyclic dimer enhances the acidity of the SiOH by 1−2 pK_a units through a type of "OH-acidification" (Scheme 2).[13,18] Thus, at concentrations of significant catalyst self-recognition, the cyclic dimer is the dominant catalytic species due to its greater acidity and consequently stronger activation. Overall, the catalytic ability of silanediols is attributed to a balance between the SiOH acidity, the solubility of the silanediol, and access to the cyclic dimer with enhanced H-bonding capabilities.

Scheme 2. Computational Study of Dimer Formation and Acidity for pK_a in H_2O Using B3LYP/6-31+G(d)



In conclusion, we have demonstrated the importance of cooperative H-bonding effects and SiOH-acidification for silanediol catalysis. The self-recognition of the silanediol creates a unique dimeric structure with enhanced H-bonding capabilities that is not observed with most organocatalysts. We propose that this cyclic dimer is the predominant catalytic species capable of activating carbonyls and Lewis bases (e.g., nitro groups) as electrophiles. Evidence for this mode of H-bonding activation is based on concentration effects observed, NMR binding, structural studies, computational studies, and enhanced activity observed for solid-state reactions (i.e., solvent-free conditions). Based on the cooperative H-bonding, silanediols provide a new mode of activation for catalyst design as well as a model to study SiOH acidification and surface reactivity of silica gel for organic transformations. These studies also provide important insight for catalyst design, particularly for consideration of asymmetric catalysis, which must take into consideration the self-recognition properties of silanediols.

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Supporting Information Available. Experimental procedures, spectral data for all compounds, NMR binding studies, crystallography, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] The effect of OH-acidification by H-bonding catalysis has been previously reported for TADDOL molecules. When cooperative intramolecular H-bonding is prevented, then the acidity is dramatically reduced; see: (a) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846–5850. (b) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem.—Eur. J.* **2011**, *17*, 8524–8528.