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# 2,6-Bis(triisopropylsilyl)pyridine, An Extreme Example of the Effect of Strong Steric Screening on Basicity

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***Abstract:*** *2,6-Bis(triisopropylsilyl)pyridine (**1**) has been synthesized from 2,6-dibromopyridine. It is a very weak base in water since it does not dissolve in 6N hydrochloric acid, but does undergo protonation in nonaqueous media by triflic acid.* 

Steric crowding in amines results in interesting changes in molecular structure, basicity, and chemical properties. Thus, triisopropylamine[1] shows essentially planar bonding to nitrogen (<C–N–C 119.2°) and an unusual electron transfer reaction with $SbF_5$ to form $R_3N^{+\bullet}$.[2] Di-*tert*-butylamine,[3] although basic ($pK_A$ 10.1 in 9 : 1 EtOH–$H_2O$[4]) does not react appreciably at 25 °C with methyl iodide or dimethylsulfate after several days,[3] due to steric screening.[5] Sterically hindered nitrogen bases now constitute a family of valuable synthetic reagents, for example, 2,6-di-*tert*-butylpyridine,[6] 1,8-bis(dimethylamino)naphthalene,[7] 1,1,2,3,3-pentaisopropylguanidine,[8,9] and of course, Hunig's base diisopropylethylamine, probably the most commonly used of all. This paper describes the preparation and unusual properties of the super hindered amine 2,6-bis(triisopropylsilyl) pyridine (**1**).

The synthesis of **1** was carried out in two steps from 2,6-dibromopyridine: (1) metal-halogen exchange with 1 equivalent of *n*-butyllithium in THF at -90 °C followed by reaction with triisopropylsilyl triflate (TIPSOTf) to form 2-bromo-6-triisopropylsilylpyridine (**2**) (83%) and (2) sequential treatment of **2** with *n*-butyllithium and TIPSOTf at -78 °C in THF to provide **1** as a colorless solid, mp *ca* 29 °C, in 76% yield.[10] Purification of **1** was effected by rapid chromatography on silica gel using *pentane* for elution, an indication of the profound steric shielding by the TIPS groups adjacent to nitrogen. Even more impressive was the finding that **1** did not dissolve in 6*N* hydrochloric acid, indicating that it must be less basic than water, i.e. not basic in aqueous solution. This finding takes on additional meaning after comparison with pyridine and 2,6-di-*tert*-butylpyridine which have well defined $pK_A$ values in 70% aqueous ethanol of 3.69 and 2.70, respectively.[11] $^1H$ NMR analysis of a 1 : 1

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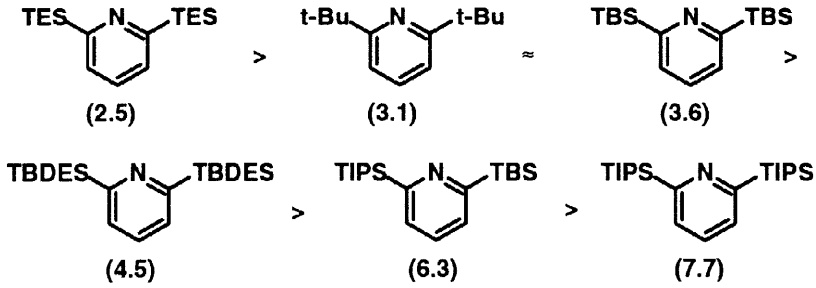
mixture of **1** and trifluoroacetic acid in $CDCl_3$ indicated the presence of substantial amounts of free **1** and $CF_3CO_2H$ as well as the conjugate acid of **1**. Complete conversion of **1** to the conjugate acid required the addition of *ca.* 7.7 equiv of $CF_3CO_2H$ to $CDCl_3$ solution as determined by $^1H$ NMR titration.

A series of 2,6-bis(trialkylsilyl) pyridines was prepared from 2,6-dibromopyridine by the method described for **1** above, including bistriethylsilyl (TES), bis-*tert*-butyldimethylsilyl (TBS), bis-*tert*-butyldiethylsilyl (TBDES), and 2-triisopropylsilyl-6-*tert*-butyldimethylsilyl. The relative order of basicity of these 2,6-disubstituted pyridines in $CDCl_3$ was then determined by $^1H$ NMR monitored titration with $CF_3CO_2H$. The numbers of equivalents of $CF_3CO_2H$ required to fully protonate the pyridine ring at nitrogen are summarized in Scheme 1 which is arranged in descending order of basicity. Interestingly, bis(triethylsilyl) pyridine is the only base in this series which shows any $^1H$ NMR chemical shift in the presence of 40 equivalents of HOAc in $CDCl_3$.




**Scheme 1.** Number of equivalents of $CF_3CO_2H$ required to protonate fully the pyridine substrate in $CDCl_3$ solution by $^1H$ NMR analysis.

Treatment of **1** with 1 equivalent of triflic acid in ether and removal of solvent afforded a colorless triflate salt of **1**. Single crystal X-ray diffraction analysis of this salt revealed the structure shown in Figure 1. The $NH^+$---O(3) (triflate) distance of 2.92 Å is approximately that of a normal hydrogen bond. The triflate counterion fits easily into the molecular cleft comprised by the pyridinium NH and the adjacent TIPS groups.

The super hindered pyridine **1** does not react with $CH_3I$ or $CH_3OTf$. Nor does it form complexes with $Cu(OTf)_2$, AgOTf or $BF_3$. In the case of these electrophiles the bulky triisopropylsilyl substituents are simply too large to allow coordination to nitrogen. The greatly attenuated basicity of **1** is probably the result of much lower solvation energies of the conjugated acid because of extreme steric shielding.[11]

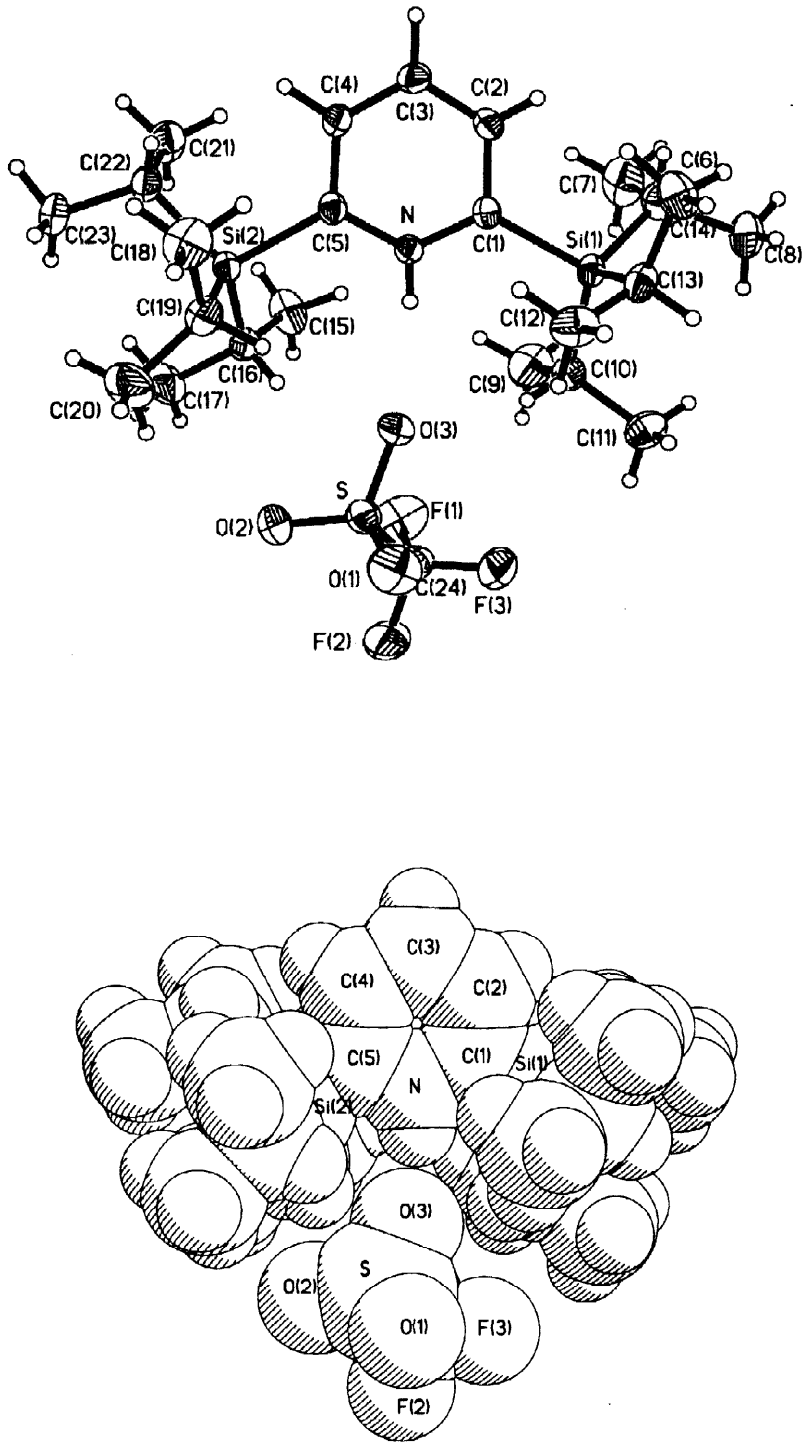



**Figure 1.** X-ray structure of the triflate salt of 2,6-bis(triisopropylsilyl)pyridine. The distance between N(1) and O(3) of the triflate is 2.918 Å; the distance between N(1) and H(1) is 0.835 Å; and the distance between O(3) and H(1) is 2.115 Å.

The following procedure provides detail for the preparation of **1**.

**2,6-Bis(triisopropylsilyl)pyridine**: To a solution of 2,6-dibromopyridine (1 g, 4.2 mmol) in THF (10 mL) at -90 °C (liq. $N_2$/methanol bath) under $N_2$, a solution of *n*-BuLi in hexanes (1.6 M, 2.9 mL, 4.6 mmol) was added dropwise. The resulting light brown homogeneous solution was stirred at -90 °C for 15 min. A precooled solution of TIPSOTf (1.3 mL, 4.8 mmol) in THF (2 mL) was added. The reaction mixture was stirred at -90 °C for 4 h, and them gradually warmed up to 23 °C. THF was removed, and the residue was treated with pentane, and then filtrated through a Celite pad. The crude product was purified by Kügelrhor distillation (150 °C/ 0.5 mm Hg, 1.1 g, 83%). 6-Bromo-2-triisopropylsilylpyridine: $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.40 ppm (m, 2H); 7.35 (m, 1H); 1.44 (sept, $J$ = 7.4 Hz, 3H); 1.09 (d, $J$ = 7.4 Hz, 18H). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 168.0 ppm, 142.9, 135.8, 129.6, 126.7, 18.5, 10.8. IR ($cm^{-1}$): 882.4, 1017.8, 1097.9, 1110.4, 1418.2, 1536.8, 1561.2, 2864.0, 2943.2, 2958.6. MS (CI): cal'd for $C_{14}H_{25}{}^{79}BrNSi$ (M + $H^+$) = 314.0940, found: 314.0948.

To a solution of 2-bromo-6-triisopropylsilylpyridine (1.0 g, 3.2 mmol) in THF (10 mL) at -78 °C under $N_2$, a solution of *n*-BuLi in hexanes (1.6 M, 2.3 mL, 3.7 mmol) was added dropwise. The resulting orange solution was kept at - 78 °C for 10 min, and then warmed to -40 °C for 15 min. After recooling the reaction mixture to -78 °C, a precooled solution of TIPSOTf (1.0 mL, 3.7 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 5 h at -60 to -70 °C, and then gradually warmed to 23 °C. THF was removed, and the residue was treated with pentane. The mixture was filtrated and concentrated. The crude product was purified by column chromatography ($SiO_2$, pentane, 950 mg, 76%): $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.42 ppm (dd, J = 8.4, 7.0 Hz, 1H); 7.34 (d, $J$ = 7.4 Hz, 2H); 1.48 (sept, $J$ = 7.5 Hz, 6H); 1.08 (d, $J$ = 7.5 Hz, 36H). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 164.6 ppm, 130.3, 129.1, 18.7, 10.9. IR ($cm^{-1}$): 883.0, 1016.3, 1463.3, 2865.7, 2890.0, 2943.2. MS (EI): cal'd for $C_{23}H_{45}NSi_2$ ($M^+$) = 391.3091, found: 391.3081.

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