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The SiOH-Containing α-Amino Acid $HOMe_2SiCH_2CH(NH_2)COOH$ and Its Immobilization on Silica via an Si−O−Si Linkage

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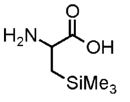
*Summary: The α-amino acid ester rac-$PhMe_2SiCH_2CH(NH_2)COOEt$ (rac-**4**) was transformed into the disiloxane $RMe_2SiOSiMe_2R$ (**5**; R = $CH_2CH(NH_2)COOH$) via an Si−C(Ph) cleavage in boiling hydrochloric acid. Upon dissolution of **5** in water, spontaneous formation of the racemic SiOH-containing α-amino acid $HOMe_2SiCH_2CH(NH_2)COOH$ (rac-**6**) occurred, which could be immobilized on silica via an Si−O−Si linkage between the α-amino acid and the silica support (characterization by solid-state NMR spectroscopy). The resulting silica-immobilized α-amino acid contains both characteristic functionalities: the COOH and the NH_2 group.*

Recently, we have reported on the synthesis of the silicon-containing α-amino acids *rac*-**1** and *rac*-**2**.[1] These compounds were synthesized in context with our studies on silicon-containing biologically active peptides[1,2] (in this context, see also ref 3). While *rac*-**1** could be prepared by hydrolysis of the α-amino acid ester *rac*-**3** in boiling hydrochloric acid and subsequent treatment of the resulting hydrochloride *rac*-**1**·HCl with propylene oxide, the analogous hydrolysis of *rac*-**4** did not lead to *rac*-**2**. Instead, in addition to the attempted hydrolysis of the ester moiety, an Si−C(Ph) bond cleavage was observed. To get more information about the nature of the Si−C(Ph) cleavage product (silanol versus disiloxane formation), the hydrolysis of *rac*-**4** was reinvestigated in more detail, and the synthetic potential of the resulting cleavage product for the development of a silica-bonded α-amino acid was evaluated.



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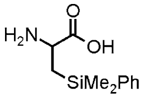

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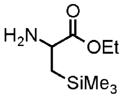

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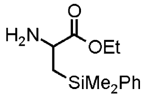

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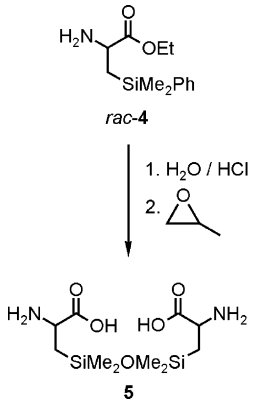
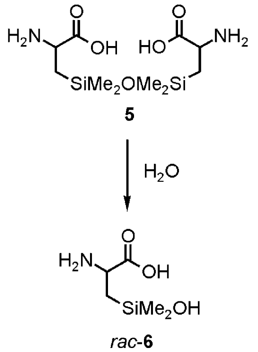
Treatment of *rac*-**4** with 6 M hydrochloric acid under reflux conditions and subsequent reaction of the resulting product with propylene oxide (to remove HCl) yielded the disiloxane **5** (yield 69%), which probably exists as a mixture of *rac*-**5** and *meso*-**5** (Scheme 1). The identitiy of **5** was established by elemental analyses and solid-state MAS NMR studies (^{13}C, ^{15}N, ^{29}Si). Due to the extremely poor solubility of **5** in organic solvents, all attempts to characterize it by solution NMR spectroscopy failed. However, the corresponding dihydrochloride **5**·2HCl could be characterized by NMR spectroscopy in solution (solvent $[D]_6DMSO$) and was shown to exist as a mixture of *rac*-**5**·2HCl and *meso*-**5**·2HCl (see below).

Scheme 1



Scheme 2



As shown by ^{1}H, ^{13}C, and ^{29}Si NMR studies and ESI-MS experiments, the Si−O−Si moiety of the disiloxane **5** reacts readily with water to form the silanol *rac*-**6** (Scheme 2). Upon dissolution of **5** in water, one very dominating set of resonance signals for the silanol was observed in the NMR spectra (Figure 1), and the protonated silanol was the dominating species in the ESI-MS spectrum as well (Figure 2); only traces of the disiloxane **5** were detectable.

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[1] Merget, M.; Günther, K.; Bernd, M.; Günther, E.; Tacke, R. *J. Organomet. Chem.* **2001**, *628*, 183−194.

[2] Tacke, R.; Merget, M.; Bertermann, R.; Bernd, M.; Beckers, T.; Reissmann, T. *Organometallics* **2000**, *19*, 3486−3497.

[3] Review on silicon-based drugs that also deals with silicon-containing α-amino acids and peptides: Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526−543.

10.1021/om040127n CCC: $30.25

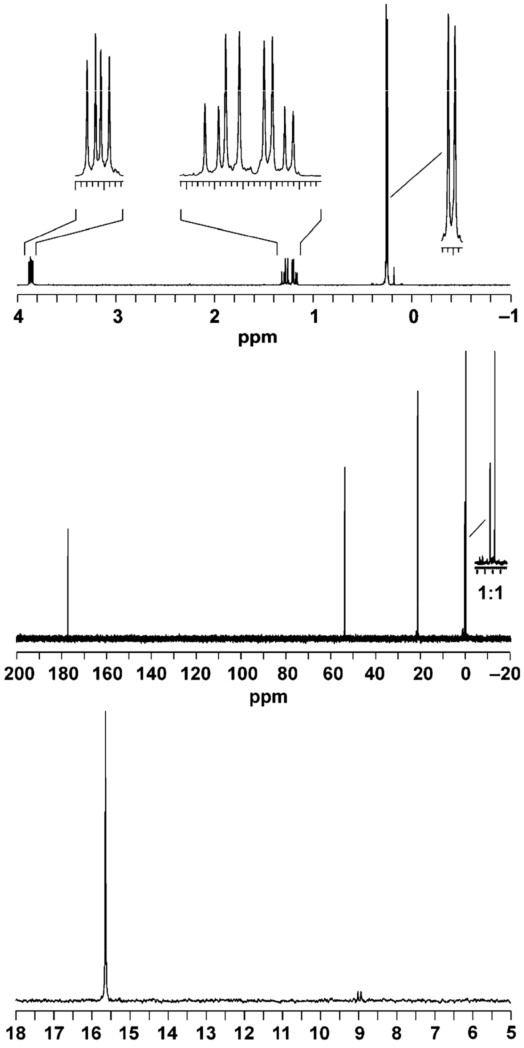

Figure 1. ^{1}H (top), ^{13}C (middle), and ^{29}Si (bottom) NMR spectra of a 32 mM aqueous solution of *rac*-**6** (22 °C; 400.1 MHz (^{1}H), 100.6 MHz (^{13}C), 79.5 MHz (^{29}Si)). The spectra were recorded immediately after dissolution of **5** in D_2O. Integration of the two resonance signals for the two diastereotopic $SiCH_3$ groups in the ^{13}C NMR spectrum revealed the intensity ratio 1:1.

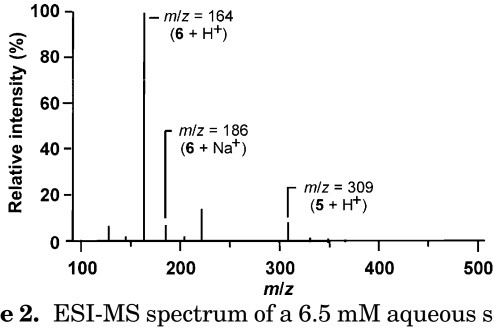

Figure 2. ESI-MS spectrum of a 6.5 mM aqueous solution of *rac*-**6**. The spectrum was recorded immediately after dissolution of **5** in water at 20 °C (for details, see Experimental Section).

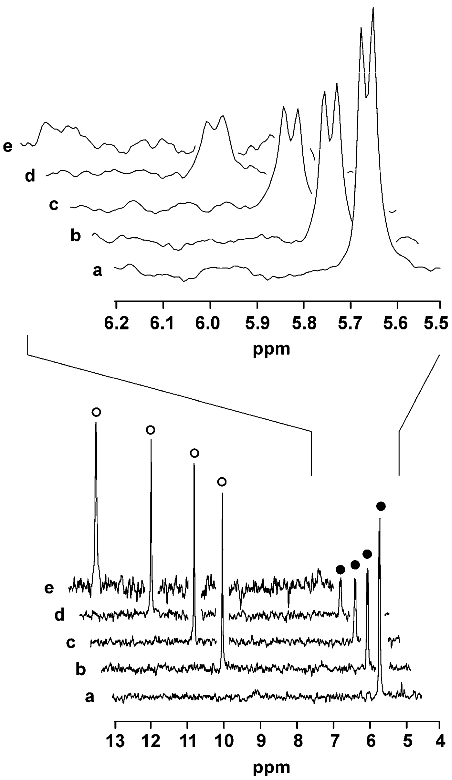

Figure 3. ^{29}Si NMR spectra obtained for solutions of *rac*-**5**·2HCl/*meso*-**5**·2HCl in [D$_6$]DMSO and [D$_6$]DMSO/D_2O mixtures ([D$_6$]DMSO (a); [D$_6$]DMSO/D_2O, 80:1 (b), 40:1 (c), 20:1 (d), 10:1 (e) (v/v); 22 °C, 59.6 MHz). The solutions were prepared by dissolution of *rac*-**5**·2HCl/*meso*-**5**·2HCl in [D$_6$]DMSO, followed by addition of D_2O. Two resonance signals were observed for *rac*-**5**·2HCl/*meso*-**5**·2HCl (●), and one resonance signal was observed for *rac*-**6**·HCl (○).

To the best of our knowledge, *rac*-**6** (which represents a sila-analogue of the α-amino acid *rac*-4-hydroxyleucine, *rac*-$HOMe_2CCH_2CH(NH_2)COOH$)[4] is the first SiOH-containing α-amino acid to be reported in the literature. However, this silanol only exists in aqueous solution and water-containing organic solvents and cannot be isolated: upon evaporation of the water, again the disiloxane **5** was obtained.

The silanol–disiloxane equilibrium was also studied for solutions of the dihydrochlorides *rac*-**5**·2HCl/*meso*-**5**·2HCl (prepared by dissolution of **5** in 6 M hydrochloric acid and subsequent removal of the solvent in vacuo) in [D$_6$]DMSO and [D$_6$]DMSO/D_2O. As shown in Figure 3, two resonance signals were observed in the ^{29}Si NMR spectrum of *rac*-**5**·2HCl/*meso*-**5**·2HCl in [D$_6$]DMSO. After addition of a small amount of D_2O (→ [D$_6$]DMSO/D_2O, 80:1 (v/v)), a third resonance signal appeared, that can be assigned to *rac*-**6**·HCl. After addition of further portions of D_2O (→[D$_6$]DMSO/D_2O, 40:1, 20:1, 10:1 (v/v)), a decrease of intensity of the two resonance signals for the disiloxane was observed, whereas the intensity of the resonance signal for the silanol increased, which was the only detectable species at a [D$_6$]DMSO/D_2O ratio of 10:1 (v/v). These results clearly demonstrate that the Si–O–Si linkage of *rac*-**5**·2HCl and *meso*-**5**·2HCl reacts easily with water to form the silanol *rac*-**6**·HCl, the disiloxane/silanol ratio being dependent on the water content of the [D$_6$]DMSO/D_2O mixture.

The existence of the silanol *rac*-**6** in aqueous solution (and in mixtures of DMSO and water as well) offers the possibility of using this SiOH-containing α-amino acid for synthetic purposes in solution. As an example, we

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[4] Synthesis of racemic 4-hydroxyleucine: (a) Wieland, T.; Mannes, K. *Liebigs Ann. Chem.* **1958**, *617*, 152–162. (b) De Kimpe, N.; Sulmon, P.; Brunet, P. *J. Org. Chem.* **1990**, *55*, 5777–5784.

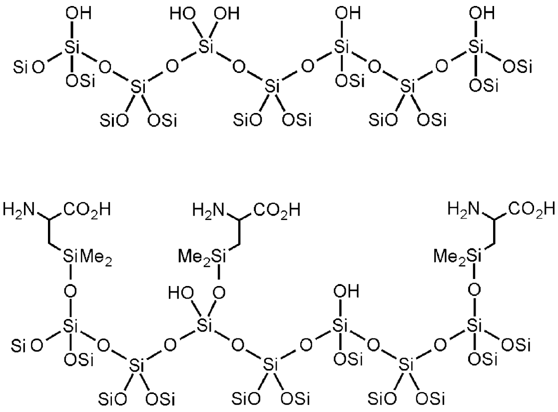

Figure 4. Schematic representation of surfaces of untreated silica (top) and silica treated with *rac*-**4** in boiling hydrochloric acid, followed by treatment with propylene oxide (bottom), showing the transformations $Q_2 \rightarrow Q_3$ and $Q_3 \rightarrow Q_4$.

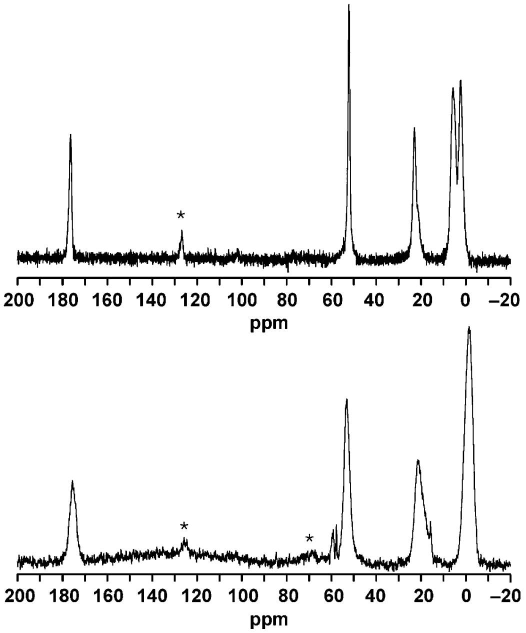

Figure 5. Solid-state ^{13}C VACP/MAS NMR spectra of *rac*-**5**/*meso*-**5** (top) and silica treated with *rac*-**4** in boiling hydrochloric acid, followed by treatment with propylene oxide (bottom) (for details, see Experimental Section).

have tried to immobilize *rac*-**6** on silica surfaces via an Si−O−Si linkage by condensation of the SiOH group of *rac*-**6** with silica-bonded SiOH groups to give materials of the type shown in Figure 4. In fact, hydrolysis of *rac*-**4** in boiling hydrochloric acid (→ formation of *rac*-**6**), in the presence of silica and subsequent treatment with propylene oxide gave the desired material, as is evident from the solid-state ^{13}C and ^{29}Si NMR spectra depicted in Figures 5 and 6. The solid-state ^{29}Si single-pulse MAS NMR spectrum of the product obtained shows a significant increase of intensity for the Q_4 (−111 ppm) signal and a decrease of intensity for the Q_3 (−102 ppm) and Q_2 (−92 ppm) signals in comparison with the untreated silica starting material (Figure 6). This is in accordance with the transformation of the SiOH moieties of the silica surface into Si−O−Si bridges ($Q_2 \rightarrow Q_3$, $Q_3 \rightarrow Q_4$; see also Figure 4). Treatment of silica with 6 M hydrochloric acid under reflux conditions in the absence of *rac*-**4**, followed by treatment with propylene oxide, did not change the ^{29}Si MAS NMR spectrum.

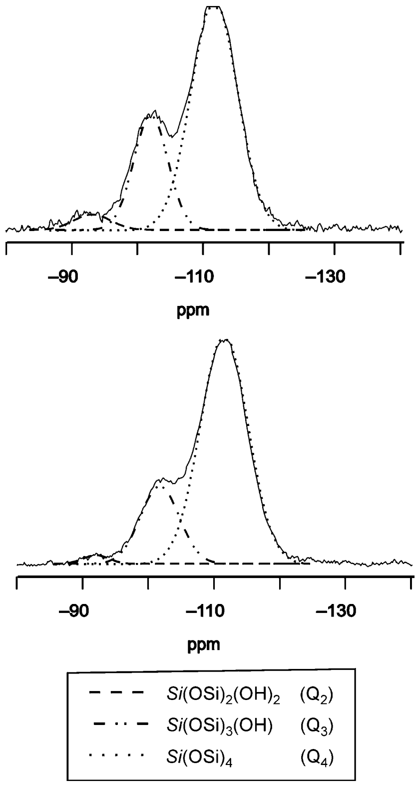

Figure 6. Solid-state ^{29}Si single-pulse MAS NMR spectra of untreated silica (top) and silica treated with *rac*-**4** in boiling hydrochloric acid, followed by treatment with propylene oxide (bottom) (for details, see Experimental Section). The areas for the Q_2, Q_3, and Q_4 moieties were calculated by a Gaussian line-shape deconvolution using the program WIN-NMR (version 6.2.0.0).

These preliminary results are quite promising, because an immobilization of the optically active α-amino acids (*R*)-**6** and (*S*)-**6** should also be possible, starting from the respective α-amino acid esters (*R*)-**4** and (*S*)-**4** (for the synthesis of (*R*)-**4** and (*S*)-**4**, see ref 1). Silica-immobilized α-amino acids are of great interest for a variety of applications in chromatography,[5−7] preferably with optically active α-amino acid residues. In addition, immobilized α-amino acids on solid supports are used for metal remediation.[8]

In contrast to silica-bonded α-amino acids, where immobilization was accomplished via the COOH or the NH_2 group of the α-amino acid, we report here on a silica-immobilized α-amino acid that still contains both characteristic functionalities: the COOH *and* the NH_2 group. Upon extensive washing of this material with water, partial removal of the α-amino acid was observed (hydrolytic cleavage of the Si−O−Si linkage as shown by solid-state single-pulse ^{29}Si MAS NMR spectroscopy). Future studies will have to elucidate the potential of silica-immobilized α-amino acids of the formula type $HOR^1R^2SiCH_2CH(NH_2)COOH$ (R^1, R^2 = substituted and

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(5) Gübitz, G.; Jellenz, W.; Santi, W. *J. Chromatogr.* **1981**, *203*, 377−384.

(6) Gaida, A. V.; Monastyrskii, V. A.; Magerovskii, Y. V.; Staroverov, S. M.; Lisichkin, G. V. *J. Chromatogr.* **1988**, *424*, 385−391.

(7) Nesterenko, P. N. *J. Chromatogr.* **1992**, *605*, 199−204.

(8) Malachowski, L.; Stair, L.; Holcombe, J. A. *Pure Appl. Chem.* **2004**, *76*, 777−787.

unsubstituted alkyl; including optically active α-amino acids) for practical applications.

Experimental Section

Preparation of *rac*-2-Amino-3-(dimethylphenylsilyl)-propanoic Acid Ethyl Ester (*rac*-4). This compound was synthesized according to ref 1.

Preparation of 3,3'-(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(2-aminopropanoic acid) (5). A solution of *rac*-**4** (1.00 g, 3.98 mmol) in 6 M hydrochloric acid (10 mL) was heated under reflux for 1 h and then cooled to 20 °C. The solvent was removed in vacuo, and the residue (consisting of *rac*-**5**·2HCl and *meso*-**5**·2HCl) was dissolved in ethanol (5 mL), followed by addition of propylene oxide (4 mL). The resulting mixture was heated under reflux for 10 min, and the precipitate was isolated by centrifugation and washed successively with ethanol (2 × 10 mL) and diethyl ether (2 × 10 mL) to give **5** in 69% yield as a colorless solid (422 mg, 1.37 mmol). ^{13}C VACP/MAS NMR: δ 2.3 (br, SiCH_3), 5.6 (br, SiCH_3), 22.9 (br, SiCH_2CH), 52.2 (br, SiCH$_2$$C$H), 176.4 (br, C=O). ^{15}N VACP/MAS NMR: δ −327.9 (br). ^{29}Si MAS NMR: δ −1.2 (br). Anal. Calcd for $C_{10}H_{24}N_2O_5Si_2$: C, 38.94; H, 7.84; N, 9.08. Found: C, 38.5; H, 7.4; N, 9.1.

Solution NMR Data for *rac*-6 Obtained after Dissolution of 5 in D$_2$O. ^{1}H NMR (D$_2$O, 400.1 MHz): δ 0.13 (s, 3 H, SiCH_3), 0.14 (s, 3 H, SiCH_3), 1.08 (δ_A), 1.16 (δ_B), and 3.75 (δ_X) (Si$CH_AH_BCH_X$, $^2J_{AB}$ = 14.7 Hz, $^3J_{AX}$ = 6.0 Hz, $^3J_{BX}$ = 9.8 Hz). ^{13}C NMR (D$_2$O, 100.6 MHz): δ −0.7 (SiCH_3), −0.3 (SiCH_3), 20.7 (SiCH_2CH), 53.2 (SiCH$_2$$C$H), 176.2 ($C$=O). ^{29}Si NMR (D$_2$O, 79.5 MHz): δ 15.8.

Preparation of *rac*- and *meso*-2,2'-(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(1-carboxyethanaminium chloride) (*rac*-5·2HCl/*meso*-5·2HCl). A solution of **5** (300 mg, 973 μmol) in 6 M hydrochloric acid (1 mL) was stirred at 20 °C for 5 min, and the solvent was then removed in vacuo to give *rac*-**5**·2HCl/*meso*-**5**·2HCl in 100% yield as a colorless solid (370 mg, 970 μmol). ^{1}H NMR ([D$_6$]DMSO, 400.1 MHz): δ 0.12 (s, 6 H, SiCH_3), 0.14 (s, 6 H, SiCH_3), 1.05−1.27 (m, 4 H, SiCH_2CH), 3.75−3.78 (m, 2 H, SiCH$_2$CH), 8.4 (br s, 6 H, NH), 13.7 (br s, 2 H, OH). ^{13}C NMR ([D$_6$]DMSO, 150.9 MHz): δ 0.62 (SiCH_3), 0.63 (SiCH_3), 1.2 (SiCH_3), 20.66 (SiCH_2CH), 20.68 (SiCH_2CH), 49.74 (SiCH$_2$$C$H), 171.28 ($C$=O), 171.29 ($C$=O). ^{29}Si NMR ([D$_6$]-DMSO, 79.5 MHz): δ 5.42, 5.44. The ^{13}C and ^{29}Si NMR data of *rac*-**5**·2HCl/*meso*-**5**·2HCl could not be assigned to the single stereoisomers. According to the intensities of the resonance signals, the molar ratio of *rac*-**5**·2HCl and *meso*-**5**·2HCl was ca. 1:1. Anal. Calcd for $C_{10}H_{26}Cl_2N_2O_5Si_2$: C, 31.49; H, 6.87; N, 7.34. Found: C, 30.1; H, 6.4; N, 7.2.

Immobilization of *rac*-6 on Silica. A mixture of *rac*-**4** (440 mg, 1.75 mmol), silica (1.14 g; particle size, 30−60 μm; J. T. Baker, 7024−01), and 6 M hydrochloric acid (10 mL) was heated under reflux for 1 h and then cooled to 20 °C. The solvent was removed in vacuo, and ethanol (5 mL) and propylene oxide (5 mL) were added to the residue. The resulting mixture was heated under reflux for 10 min, and the remaining solid was isolated by centrifugation and washed successively with water (2 × 10 mL), ethanol (2 × 5 mL), and diethyl ether (10 mL) to give a white solid (902 mg). ^{13}C VACP/MAS NMR: δ −1.6 (br, SiCH_3), 21.3 (br, SiCH_2CH), 53.0 (br, SiCH$_2$$C$H), 174.9 (br, C=O). ^{15}N VACP/MAS NMR: δ −328.1 (br). ^{29}Si MAS NMR: δ 11.3 (br, SiCH$_3$), −92.3 (br, SiO_2 (Q$_2$)), −101.7 (br, SiO_2 (Q$_3$)), −111.5 (br, SiO_2 (Q$_4$)) (intensity ratio, 5:2:21:77; Q$_2$/Q$_3$/Q$_4$ intensity ratio of the silica starting material, 3:27:70).

NMR Studies. The solution ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded at 22 °C on a Bruker DRX-300 (^{29}Si, 59.6 MHz), Bruker DRX-400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{29}Si, 79.5 MHz), or Bruker DRX-600 NMR spectrometer (^{13}C, 150.9 MHz) using [D$_6$]DMSO, [D$_6$]DMSO/D$_2$O, or D$_2$O as the solvent. Chemical shifts (ppm) were determined relative to internal [D$_5$]DMSO (^{1}H, δ 2.49; [D$_6$]DMSO), internal HDO (^{1}H, δ 4.70; D$_2$O), internal [D$_6$]DMSO (^{13}C, δ 39.5; [D$_6$]DMSO), or external TMS (^{13}C and ^{29}Si, δ 0; D$_2$O) (^{29}Si, δ 0; [D$_6$]DMSO). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H COSY experiments and by simulations using the WIN-DAISY software package (version 4.05, Bruker). Assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C,^{1}H COSY experiments. Solid-state ^{13}C and ^{15}N VACP/MAS NMR spectra were recorded at 22 °C on a Bruker DSX-400 NMR spectrometer (^{13}C, 100.6 MHz; ^{15}N, 40.6 MHz) with bottom layer rotors of ZrO$_2$ (diameter 7 mm) containing ca. 200 mg of sample. Chemical shifts (ppm) were determined relative to external TMS (^{13}C, δ 0) or glycine (^{15}N, δ −342.0); spinning rate, 5 kHz; contact time, 1 ms (^{13}C) or 3 ms (^{15}N); 90° ^{1}H transmitter pulse length, 3.6 μs; repetition time, 4 s. Solid-state ^{29}Si single-pulse MAS NMR spectra were recorded at 22 °C on a Bruker DSX-400 NMR spectrometer (79.5 MHz) with bottom layer rotors of ZrO$_2$ (diameter 7 mm) containing ca. 200 mg of sample. Chemical shifts (ppm) were determined relative to external TMS (δ 0); spinning rate, 5 kHz; ^{29}Si transmitter pulse length, 4 μs; repetition time, 120 s. The areas extracted from the ^{29}Si single-pulse MAS NMR experiments were calculated by a Gaussian line-shape deconvolution using the program WIN-NMR (version 6.2.0.0, Bruker).

ESI-MS Studies. (a) Chemicals. Water (HPLC gradient grade) was purchased from Acros.

(b) Sample Preparation. A 6.5 mM aqueous solution of *rac*-**6** was prepared by dissolving **5** (1.00 mg, 3.24 μmol) in water (1.00 mL), and the sample was then analyzed instantaneously by ESI-MS.

(c) ESI-MS Analysis. Analysis was performed with a Finnigan MAT triple-stage quadrupole TSQ 7000 mass spectrometer with an ESI interface. Data acquisition and evaluation were conducted on a Digital Equipment Personal DECstation 5000/33 using Finnigan MAT ICIS 8.1 software. Nitrogen served as both sheath and auxiliary gas. The electrospray ionization parameters were as follows: temperature of the heated capillary, 200 °C; electrospray capillary voltage, 2.6 kV; sheath gas, 70 psi (1 psi = 6894.74 Pa); auxiliary gas, 10 units. For measurement, the sample solutions were continuously delivered at a flow rate of 20 μL min^{-1} by means of a syringe pump system (Harvard apparatus, No. 22). Positive ions were detected by scanning from *m/z* 100 to 500 with a total scan duration of 1.0 s; 60 scans were collected within 1 min. The multiplier voltage was set to 1.3 kV.

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