Conformational Analysis of Cyclohexyl Silyl Ethers

Ernest L. Eliel* and Hikmet Satici

W. R. Kenan Laboratories, Department of Chemistry,
University of North Carolina,
Chapel Hill, North Carolina 27599-3290

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Silyl ethers are widely used in synthesis as protective groups for alcohols.[1] In previous publications[2] it was shown that the chelating ability of silyloxy groups, $R_2R'SiO$ in α-silyloxy ketones decreases with increasing size of the substituents: $Me_3SiO > Et_3SiO > t\text{-}BuMe_2SiO > t\text{-}BuPh_2SiO > (i\text{-}Pr)_3SiO$. The last group, "TIPS-O", is essentially nonchelating. In this study we set out to measure if a similar progression of size would be reflected in $-\Delta G°$ ("A-value") for these groups in the equilibrium shown in Scheme 1. A priori, it was not clear if a correlation would exist, since in $OSiR_3$ the bulky SiR_3 moiety would probably turn to the outside of the cyclohexane ring and might thus have little effect on the tendency of the group to avoid the axial position.

The values of $-\Delta G^\circ_{OSiR_3}$ with R = R′ = Me, Et, *i*-Pr, Ph and R′ = *t*-Bu, R = Me or Ph, as measured by low-temperature ^{13}C NMR spectroscopy,[3] are shown in Table 1. When values in one and the same solvent are compared, $-\Delta G°$ has no direct correlation with size; on the contrary, the values for $OSiMe_3$ and $OSiEt_3$ are slightly larger than values for $OSi(i\text{-}Pr)_3$, $OSiMe_2t\text{-}Bu$, $OSiPh_2t\text{-}Bu$ and $OSiPh_3$, suggesting that the alkyl groups attached to silicon are more sterically interfering when the $OSiR_3$ group is equatorial than when it is axial.[4] Values for R = Ph tend to be smaller than the values for R = alkyl.

Our first measurement involved the $OSiMe_3$ group in solvent CD_2Cl_2 and we were quite concerned to find that the value found, $-\Delta G° = 1.31$ kcal mol^{-1}, was quite different from the value 0.74 kcal mol^{-1} previously recorded[5] in solvent CF_3Cl. Suspecting that the apparent discrepancy might be due to the difference in solvents, we repeated the measurement in toluene-d_8 and found a value, 0.77 kcal mol^{-1}, consistent with that reported.[5] As shown in Table 1, the observed solvent difference is consistent for all four $OSiR_3$ groups for which measurements in both CD_2Cl_2 and $C_6D_5CD_3$ were carried out.

Table 1. $-\Delta G°$ Values for the Ring Inversion of Cyclohexyl Silyl Ethers (Scheme 1)

silyl ether	$-\Delta G°$ (kcal mol^{-1})[a] (toluene-d_8)	$-\Delta G°$ (kcal mol^{-1})[b] (CD_2Cl_2)
$OSiMe_3$	0.77 ± 0.04	1.31
$OSiEt_3$	0.73 ± 0.05	1.26
$OSi(i\text{-}Pr)_3$	0.51 ± 0.03	0.94
$OSiMe_2t\text{-}Bu$	*c*	1.06
$OSiPh_2t\text{-}Bu$	*c*	0.56
$OSiPh_3$	0.57 ± 0.07	0.71

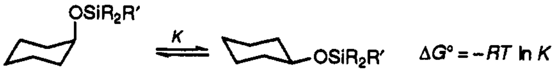
[a] At 178–188 K. [b] At 179–188 K. [c] Not determined.

Table 2. $\Delta G°$ Values for the Ring Inversion of *cis*-4-Methylcyclohexyl Silyl Ethers (Scheme 2)

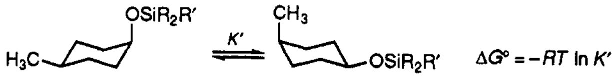
silyl ether	temperature (K)	solvent	$-\Delta G°'$ (kcal mol^{-1})	$-\Delta G°' + 1.74$[a] (kcal mol^{-1})
$OSiMe_3$	178.7	CD_2Cl_2	-0.44 ± 0.01	1.30
$OSiMe_3$	183.6	CD_3OD	-0.80 ± 0.02	0.94
$OSiEt_3$	179.8	CD_2Cl_2	-0.43 ± 0.03	1.31
$OSi(i\text{-}Pr)_3$	194.8	CD_2Cl_2	-0.82 ± 0.02	0.92
$OSiMe_2t\text{-}Bu$	179.0	CD_2Cl_2	-0.61 ± 0.02	1.13
$OSiPh_2t\text{-}Bu$	183.7	CD_2Cl_2	-1.12 ± 0.01	0.62
$OSiPh_3$	183.6	CD_2Cl_2	-0.99 ± 0.09	0.75

[a] See text.

Scheme 1



Scheme 2



Since such sizable solvent differences for solute molecules containing but a single dipole in solvents which are not strong hydrogen bond donors seem unprecedented, we decided to check the results by also measuring conformational equilibria for the same $OSiR_3$ groups in a cis-1,4-disubstituted cyclohexane derivative (Scheme 2). The results (Table 2) can be compared with those in Table 1 by assuming[3] that the A-values in cis-1,4-disubstituted cyclohexanes are subtractive, i.e. that $\Delta G°'$ for such compounds may be set equal to $\Delta G° + 1.74$, the latter being the $-\Delta G°$ or A-value for methyl.[6] It follows that $-\Delta G° = -\Delta G°' + 1.74$ kcal mol^{-1}. Comparison of $\Delta G°$ values so computed (last column in Table 2) with ΔG^0 for the same substituent in Table 1 shows excellent agreement.

To exclude the possibility that the larger $-\Delta G°$ values in CD_2Cl_2 (as compared to toluene-d_8) might be due to (weak) hydrogen bonding in the former solvent, we carried out a measurement for $OSiMe_3$ in methanol-d_4 (Table 2, entry 2). However, the equilibrium, rather than being displaced to the equatorial $OSiMe_3$ conformer, was displaced to the axial one relative to CD_2Cl_2. This excludes either solvent dielectric ($\epsilon = 32.6$ for methanol, 8.9 for methylene chloride[7]) or hydrogen-bonding effects.

We have no explanation for the unexpected solvent effect observed except to suggest that some specific interaction involving silicon is involved, in as much as only very minor solvent effects are seen in the conformational equilibria of cyclohexyl fluoride, chloride, and bromide.[8]

Experimental Section

All compounds used in this study were prepared by standard methods[1] using commercially available alcohols and chlorosilanes and were purified by alumina column chromatography. Low-temperature ^{13}C NMR spectra were measured with a Varian XL-400 spectrometer equipped with a variable temperature controller at 100.59 MHz. Temperatures of the probe and the sample were found to be equilibrated to ±0.2 °C within 0.5 h as established by calibration with the ^1H NMR spectrum of methanol, but in the actual measurements, 1 h was allowed for equilibration in

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[4] This is also suggested by preliminary molecular mechanics calculations. Gordillo, B., unpublished results.

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Table 3. Low-Temperature Chemical Shifts (ppm) of Cyclohexyl Silyl Ethers[a]

carbon[b]	OSiMe$_3$[c]		OSiEt$_3$[c]		OSi(i-Pr)$_3$[c]		OSiPh$_3$[c]		OSit-BuMe$_2$[d]	OSit-BuPh$_2$[d]
C1	70.4	71.2	70.5	71.3	70.9	71.8	72.0	72.4	71.2	71.8
C1*	66.1	66.4	65.9	66.3	65.8	66.7	67.4	67.7	65.9	66.9
ratio	48.8	9.30	35.0	7.47	11.0	3.97	8.15	5.27	19.0	4.99
C2	35.4	36.7	35.7	36.8	36.0	37.1	35.4	36.4	35.7	35.5
C2*	32.4	33.4	32.8	33.7	33.0	34.0	32.3	33.0	32.9	32.5
ratio[e]	37.8	7.72	32.4	7.39	15.26	3.76	6.69	4.00	19.35	4.60
C3	24.3	25.0	24.4	25.1	24.5	25.4	24.2	24.8	25.4	24.3
C3*	19.6	f	19.7	f	19.7	20.7	19.8	f	19.7	19.9
ratio[e]	41.1	–	36.2	–	15.0	–	6.73	–	19.20	–
C4	24.6	25.4	24.7	25.5	24.8	25.8	24.6	25.4	24.8	24.7
C4*	?	26.4	25.5	26.5	25.7	26.8	25.5	26.3	25.7	25.7
ratio[e]	–	13.4	–	–	–	–	–	4.55	–	–

[a] Shifts in ppm downfield from TMS, temperatures 179–189 K. [b] Carbons marked with an asterisk belong to the axially substituted cyclohexane ring. [c] Left column: solvent CD_2Cl_2; right column: solvent toluene-d_8. [d] Solvent CD_2Cl_2. [e] Ratio of signal areas of equatorial/axial conformers for the carbon indicated. [f] Signal is buried under toluene peaks at 19.9–21.0 ppm.

the low-temperature probe, with the decoupler on. The number of scans ranged from 3000 to 20000 with a 39° pulse angle; data point size varied from 8–32K bites. Signal area ratios were determined by both digital integration and direct measurement methods; the $\Delta G°$ values reported are averages of several such measurements, in most instances for two or three different pairs of signals. Standard deviations were computed accordingly. Chemical shift assignments were checked by recording the ^{13}C NMR spectra of *cis*- and *trans*-4-(*tert*-butylcyclohexyl)- and *trans*-4-(methylcyclohexyl)silyloxy compounds and effecting parametric corrections[9] for the *tert*-butyl or methyl substituents so as to obtain the shifts of the ring carbons for the pure conformers shown in Schemes 1 and 2. The low-temperature chemical shifts are displayed in Table 3.

General Method for the Preparation of Silyl Ethers. Preparation of the silyl ethers is well established in the literature.[1] In a typical preparation of the silyl ethers used in this study 2.0 mmol of cyclohexanol compound was dissolved in 4 mL of DMF. To this solution were added 3.0 mmol of chlorosilane, 4.0 mmol of imidazole, and a catalytic amount of 4-(dimethylamino)-pyridine. The resulting solution was stirred at room temperature overnight. Water (20 mL) and 1:1 mixture of ether:hexanes (30 mL) were added and the phases were separated. The organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by alumina column chromatography (hexanes/ether) gave the silyl ethers in 75–95% yield.

[(Triphenylsilyl)oxy]cyclohexane: ^1H NMR (CD_2Cl_2) δ 7.25–7.75 (m, 15 H), 3.85 (m, 1 H), 1.10–1.82 (m, 10 H); ^{13}C NMR (CD_2Cl_2) δ 135.76, 135.48, 130.25, 128.17, 72.24, 35.99, 26.00, 24.31.

***cis*-4-Methylcyclohexyl triphenylsilyl ether:** ^1H NMR (CD_2Cl_2) δ 7.35–7.85 (m, 15 H), 4.22 (m, 1 H), 1.39–1.85 (m, 9 H), 1.02 (d, 3 H); ^{13}C NMR (CD_2Cl_2) δ 135.78, 135.63, 130.28, 128.22, 68.97, 33.24, 32.09, 29.70, 22.38.

[(*tert*-Butyldiphenylsilyl)oxy]cyclohexane: ^1H NMR (CD_2Cl_2) δ 7.25–7.75 (m, 10 H), 3.65 (m, 1 H), 1.08–1.80 (m, 10 H), 1.00 (s, 9 H); ^{13}C NMR (CD_2Cl_2) δ 136.23, 135.38, 129.87, 127.91, 71.86, 35.98, 27.28, 26.18, 24.23, 19.55.

***cis*-4-Methylcyclohexyl *tert*-butyldimethylsilyl ether:** ^1H NMR (CD_2Cl_2) δ 3.92 (m, 1 H), 1.30–1.68 (m, 10 H), 1.38 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (CD_2Cl_2) δ 67.49, 33.62, 32.10, 29.59, 26.06, 22.32, 18.43, −4.70.

***cis*-[(*tert*-Butyldiphenylsilyl)oxy]-4-methylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 7.68–7.80 (m, 4 H), 7.35–7.50 (m, 6 H), 4.05 (m, 1 H), 1.30–1.78 (m, 9 H), 1.11 (s, 9 H), 0.9 (d, 3 H); ^{13}C NMR (CD_2Cl_2) δ 136.23, 135.31, 129.87, 127.91, 68.48, 33.35, 32.29, 29.72, 27.29, 22.60, 19.67.

***cis*-[(Trimethylsilyl)oxy]-4-methylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 3.89 (m, 1 H), 1.30–1.65 (m, 9 H), 0.90 (d, 3 H), 0.10 (s 9 H); ^{13}C NMR (CD_2Cl_2) δ 67.89, 33.32, 31.61, 29.66, 21.84, 0.25.

***cis*-[(Triethylsilyl)oxy]-4-methylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 3.92 (m, 1 H), 1.35–1.70 (m, 9 H), 0.88–1.02 (m, 12 H), 0.59 (q, 6 H); ^{13}C NMR (CD_2Cl_2) δ 67.64, 33.79, 32.06, 29.79, 22.23, 7.23, 5.46.

[(Triethylsilyl)oxy]cyclohexane: ^1H NMR (toluene-d_8) δ 3.62 (m, 1 H), 1.10–1.85 (m, 10 H), 1.01 (t, 9 H), 0.60 (q, 6 H); ^{13}C NMR (CD_2Cl_2) δ 71.09, 36.57, 26.07, 24.74, 6.98, 5.29.

[(Triisopropylsilyl)oxy]cyclohexane: ^1H NMR (CD_2Cl_2) δ 3.73 (m, 1 H), 1.18–1.85 (m, 13 H), 1.05 (s, 18 H); ^{13}C NMR (CD_2Cl_2) δ 70.93, 36.40, 26.21, 24.38, 18.34, 12.84.

***cis*-[(Triisopropylsilyl)oxy]-4-methylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 4.07 (m, 1 H), 0.85–1.85 (m, 33 H); ^{13}C NMR (CD_2Cl_2) δ 67.47, 33.89, 32.31, 29.65, 22.51, 18.41, 12.85.

***cis*-[(Trimethylsilyl)oxy]-4-*tert*-butylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 3.98 (m, 1 H), 0.90–1.78 (m, 9 H), 0.88 (s, 9 H), 0.10 (s, 9 H); ^{13}C NMR (CD_2Cl_2) δ 66.34, 48.29, 34.33, 32.55, 27.43, 21.21, 0.00.

***cis*-[(Triisopropylsilyl)oxy]-4-*tert*-butylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 4.08 (m, 1 H), 0.95–1.85 (m, 30 H), 0.90 (s, 9 H); ^{13}C NMR (CD_2Cl_2) δ 66.80, 48.34, 34.70, 32.86, 27.66, 21.32, 18.36, 12.80.

***trans*-[(Triisopropylsilyl)oxy]-4-*tert*-butylcyclohexane:** ^1H NMR (CD_2Cl_2) δ 3.57 (m, 1 H), 0.93–1.98 (m, 30 H), 0.85 (s, 9 H); ^{13}C NMR (CD_2Cl_2) δ 72.31, 47.67, 37.14, 32.53, 27.80, 26.20, 18.31, 12.81.

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[9] cf. Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; p 67.