

Why Are Silyl Ethers Conformationally Different from Alkyl Ethers? Chair–Chair Conformational Equilibria in Silyloxycyclohexanes and Their Dependence on the Substituents on Silicon. The Wider Roles of Eclipsing, of 1,3-Repulsive Steric Interactions, and of Attractive Steric Interactions

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Abstract: An NMR study of the diaxial/diequatorial chair equilibrium in a range of silylated derivatives of *trans*-1,4- and *trans*-1,2-dihydroxycyclohexane is reported and discussed with a view to explaining unusually large populations of chair conformations with axial substituents, noted previously for some monosilyloxycyclohexanes and in some silylated sugars. X-ray diffraction studies of three *bis*-triphenylsilyloxycyclohexanes are reported and show both axial and equatorial silyloxy groups with the exocyclic bonds eclipsed. Eclipsing is also suggested by molecular mechanics (MM3) calculations on such derivatives. Both axial and equatorial tertiary silyl groups have 1,3-repulsive interactions with whatever substituents or hydrogen atoms are at the two adjacent equatorial positions, and these are relieved by rotation toward the eclipsed conformation of the exocyclic C–O bond. The three substituents on silicon interact *attractively* with the nine atoms at the 3, 4, and 5-positions of the cyclohexane ring and calculations suggest that these stabilizing interactions are significantly greater in the axial than in the equatorial conformation. An equatorial C–OSiR₃ bond with one or two equatorial neighbors has a restricted potential energy well that becomes much broader when the bond is axial without any equatorial neighbors in the alternative chair. Adjacent silyl groups in the 1,2-disubstituted series interact in a stabilizing way overall in all conformations, this being particularly marked in the diaxial conformation of the more complex ethers. These factors lead to unusually large axial populations.

Introduction

Trialkyl(or aryl)silyl [R¹R²R³Si-] derivatives of alcohol functions, henceforth called silyl derivatives, are of great practical use in protection strategies in organic synthesis.¹ Several aspects of the conformations of such derivatives of six-membered ring alcohols including pyranose sugars are strikingly unusual,^{2–8} and have been usefully exploited in synthesis.^{5,8}

A fundamental set of conformational results, which still awaits explanation, comes from the work of Eliel and Satici² on silyloxycyclohexanes **1** and their axial–equatorial equilibria (Scheme 1). The greater the bulk of the substituents on silicon, the greater the population of the chair conformation with the single silyloxy substituent *axial*. The authors reported that preliminary molecular mechanics calculations confirmed the trend of the results but gave no details.

The second conformational oddity is that of *O*-silylated sugar derivatives,^{4–8} where it is found that the chair conformation preferred is the one with several –O–SiR¹R²R³ and other groups axial, while the same sugar with hydroxy groups

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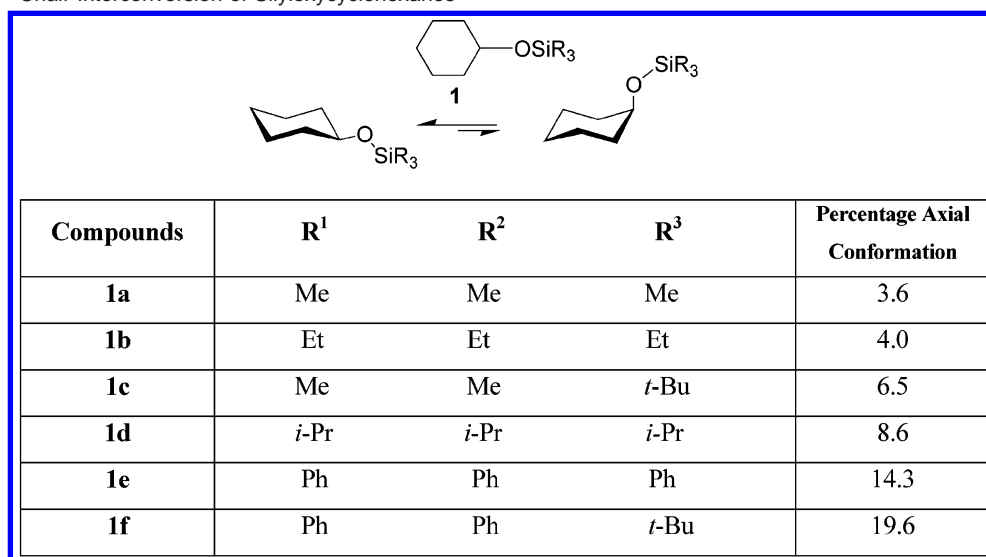
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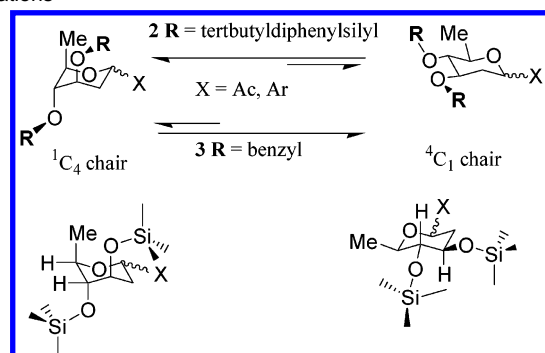
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Scheme 1. Chair–Chair Interconversion of Silyloxycyclohexanes^a

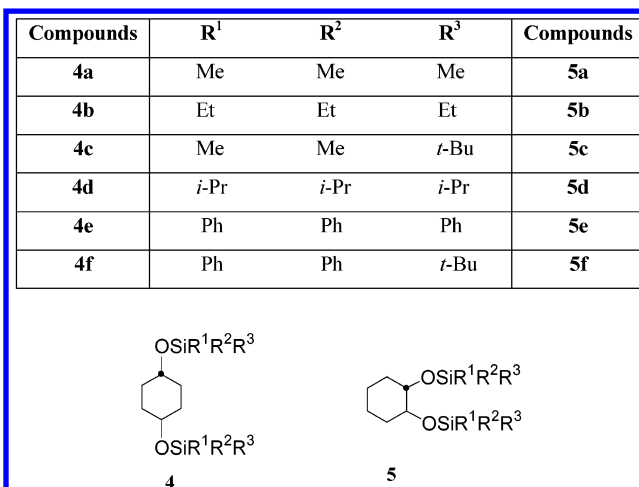
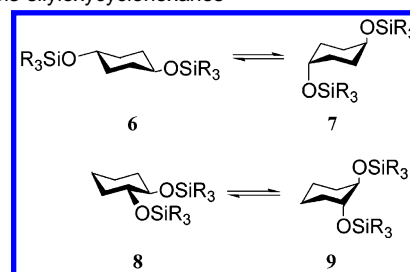
^a Conformational equilibrium in CD₂Cl₂ solution at about 200 K. The same trend is shown for toluene solutions but with a greater population of the axial conformation.²

Scheme 2. Preferred Ring Conformation of Different *O*-Protected Olivosides **2** and **3**, with Protecting Groups **R** in Plausible Locations⁴

protected by alkyl substituents adopts the other, ring-inverted, chair conformation with equatorial substituents. The contrasting equilibria of compounds **2** and **3** (Scheme 2), show an early example.⁴ The axial preference in **2** is attributed to the extra steric interaction of the three substituents on adjacent tertiary silyloxy groups when these are equatorial (as compared with the benzyl protecting group, which is primary). Clearly, however, the substituents on silicon in the ⁴C₁ chair need not be near each other, and the ¹C₄ chair has a methyl/oxygen and other 1,3-diaxial interactions; the essence of Eliel and Satici's results² is that even when there is a lone silyloxy group, increasing substituent bulk leads to more of the axial conformation.

There is thus an unusual steric effect, and to examine it further, we now want to report chair–chair conformational equilibria in a range of *bis*-silyloxycyclohexanes, with the substituents either *trans*-1,4-, **4**, or *trans*-1,2-, **5** (Scheme 3).

The *trans*-1,4-disubstituted set **4a–4f** allows us to extend Eliel and Satici's work without concerns for steric interactions of the substituents, while the *trans*-1,2-disubstituted set **5a–5f** allows us to investigate interactions of adjacent silyloxy groups.⁹

Scheme 3. *trans*-1,4- and *trans*-1,2-*Bis*-silyloxycyclohexanes Derivatives**Scheme 4.** Chair–Chair Equilibria in *trans*-1,4- and *trans*-1,2-*Bis*-silyloxycyclohexanes

In both cases the chair–chair equilibrium is between the diequatorial conformation (**6** or **8**) and the diaxial conformation (**7** or **9**) (Scheme 4).

We report dynamic NMR measurements of the series **4** and **5** in deuteriodichloromethane solution, MM3 calculations of these and series **1**, and crystal structure data for three *bis*-silyloxy compounds.

We hope to clarify the nature of the steric effect by a systematic study of these two series, but clearly, disubstitution introduces perhaps quite subtle stereoelectronic effects. This is

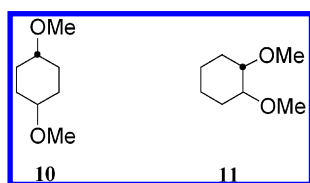
(9) Calculations for **5** are for the (*R,R*) configuration shown in Scheme 3, and drawings, torsion angles, and discussion will be in terms of this enantiomer, but experimental results are in fact for racemic **5a–f**.

Table 1. Chair–Chair Conformational Equilibria in Mono- and *trans*-1,4-Bis-silyloxycyclohexanes **4**

silyl ether	number of atoms in R ₃	monosilyloxycyclohexane (Eliel and Satici's experiments)		<i>trans</i> -1,4-bis-silyloxycyclohexane			
		% axial	A-value ^{a,d}	our calculation		our experiments	
				% diaxial ^b	difference in final steric energy ^c	% diaxial ^a	ΔG^d
4a OSiMe ₃	12	3.6	1.31	8	0.87	2.0	1.39
4b OSiEt ₃	21	4.0	1.26	12	0.70	0.8	1.72
4c OSiMe ₂ - <i>t</i> -Bu	21	6.5	1.06	23	0.44	0.7	1.77
4d OSi(<i>i</i> -Pr) ₃	30	8.6	0.94	22	0.46	19	0.52
4e OSiPh ₃	33	14.3	0.71	15	0.62	17	0.57
4f OSiPh ₂ - <i>t</i> -Bu	35	19.6	0.56	23	0.43	23	0.43

^a kcal/mol, free energy differences were determined experimentally at various low temperatures and have been standardized to give population values at 200 K by assuming $\Delta S^\circ = 0$. Solvent was CD₂Cl₂. ^b At 180 K, based on differences in the final steric energy, calculated assuming entropies are zero. ^c kcal/mol, for the most stable calculated axial and equatorial conformations, see text discussion on effect of conformations within the SiR₃ group. ^d kcal/mol at 180 K, axial less stable.

illustrated by the quite marked solvent dependence of the equilibrium in the obvious alkoxy analogues of the series **4** and **5**, the dimethoxycyclohexanes **10** and **11**, where nonpolar solvents favor diaxial conformations.^{10–12}

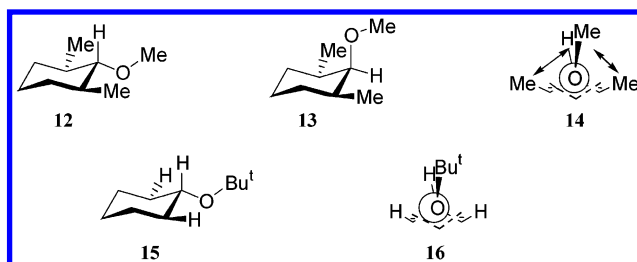


Results such as these are reminders that the equilibrium for vicinal disubstituted cyclohexanes **5** involves several factors that may differ between the two chair conformations.^{10–13} The inherent equatorial preference of a substituent and the stabilizing gauche effect in an O–C–C–O fragment both favor the diequatorial conformation. On the other hand, that conformation is disfavored by the steric repulsion of adjacent methoxy groups and the destabilizing interaction of carbon–oxygen bond dipoles. By observing our sets of compounds under uniform conditions, we hope to elucidate the particular, unusual steric factor in silyl ethers that is associated with the size of the substituents on silicon.

There are earlier results on substituted *mono*-alkoxycyclohexanes¹⁴ that particularly help an understanding of the results we now present. NMR coupling constant measurements show that methoxycyclohexanes **12** and **13** with equatorial substituents on either side of the methoxy group adopt an eclipsed conformation for the exocyclic C–O bond, with O–Me eclipsing C–H. Molecular mechanics calculations agree with this minimum energy bond conformation, and it has been suggested¹⁴ that it arises because *O*-methyl–*C*-methyl repulsions in the conventional staggered conformation are more substantial

than the H–methyl eclipsing interactions (see **14**, for example, an alternative view of **12**).

More interestingly for the present work, compound **15** with a *tert*-butoxy group, but only hydrogen atoms adjacent, also adopts an eclipsed conformation, (*O*-*tert*-butyl eclipsing C–H; see **16**), plausibly for the same reasons.¹⁵



Two other relevant features of the alkoxy-cyclohexane study^{14,16} are worth noting. When the alkoxy group has two equatorial neighboring substituents of different size, the rotational minimum has the alkoxy group somewhat displaced from eclipsed on the less-hindered side. Also, there is an intermediate level of neighboring interactions where the calculated potential energy diagram for the exocyclic C–O bond shows either inflections or even shallow minima on either side of eclipsed.¹⁶ Here, in the wider view, there is a broad potential well, centered on eclipsed.

Results

NMR Spectra. Each of the compounds **4a–4f** and **5a–5f** shows two sets of signals of different intensity at low temperatures when chair–chair interconversion is slow, both in the proton and carbon-13 NMR spectra. All population measurements for these series are from integration of proton NMR spectra recorded at $\sim -95^\circ\text{C}$ in deuteriodichloromethane solution. Carbon-13 NMR spectra were not used to determine the position of equilibria but showed changes in agreement with proton NMR spectra. No signals or other spectral changes were seen that might suggest that nonchair conformations contribute to the equilibria.

The 1,4-Disubstituted Cyclohexanes (Table 1). The low-temperature NMR data for the *trans*-1,4-bis-silyloxycyclohexanes **4a–4f** show the position of the equilibrium between the chair conformations **6** and **7** (Table 1).

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Table 2. Chair–chair Conformational Equilibria in *trans*-1,2-Bis-silyloxycyclohexanes **5**

silyl ether	no. of atoms in R ₃	<i>trans</i> -1,2-bis-silyloxycyclohexanes						
		our calculations					our experiments	
		% diaxial ^b	excess SiR ₃ /OSiR ₃ in eq cf ax ^f	difference in final steric energy ^c	H–C–O–Si, ^e deg		% diaxial ^a	Δ <i>G</i> ^d
					axial	equatorial		
5a OSiMe ₃	12	0.03	0.87	2.87	0.7, 1.1	12.2, 12.2	1	1.64
5b OSiEt ₃	21	0.04	1.21	2.25	19.4, 21.7	20.1, 15.7	5	1.05
5c OSiMe ₂ - <i>t</i> -Bu	21	0.03	1.44	2.61	0.2, 0.1	18.4, 18.4	11	0.75
5d OSi(<i>i</i> -Pr) ₃	30	28.0	0.73	0.33	6.4, 5.3	32.1, 32.1	95	−1.05
5e OSiPh ₃	33	6.4	−0.49	0.96	35.0, 34.8	6.1, 31.9	32	0.27
5f OSiPh ₂ - <i>t</i> -Bu	35	99.4	−2.49	−1.84	31.9, 34.8	29.7, 35.3	87	−0.66

^a kcal/mol, free energy differences were determined experimentally at various low temperatures and have been standardized to give population values at 200 K by assuming Δ*S*^o = 0. Solvent was CD₂Cl₂. ^b At 180 K, based on differences in the final steric energy, calculated assuming entropies are zero. ^c Diaxial and diequatorial, kcal/mol, the negative value means diaxial is more stable. See text discussion on effect of conformations within the SiR₃ group. ^d kcal/mol at 180 K, axial less stable. ^e Torsion angles for structures **8** (diequatorial) and **9** (diaxial).⁹ ^f These refer to net attractive interactions between silyl groups.

The chair conformation with equatorial substituents is preferred, but for the first three of the compounds, **4a–4c**, the tendency to populate the diaxial chair conformation is diminished compared with series **1**. For the remaining three compounds **4d–4f**, however, the diaxial tendency is enhanced. With the larger substituents on silicon, the population of the axially substituted chair conformation is uncommonly high, in keeping with the earlier work for monosilyloxycyclohexanes reported in the Introduction.

The 1,2-Disubstituted Cyclohexanes (Table 2). There is a surprising range of results for the equilibrium between chair conformations **8** and **9** for the *trans*-1,2-bis-silyloxycyclohexanes **5a–5f**.

The trimethylsilyl derivative **5a** is the only compound to show a decrease in the proportion of the diaxial conformation compared with monosubstituted. The remaining compounds **5** accentuate the results for the monosubstituted series **1**, showing an increased population of the diaxial conformation that is particularly striking for compounds **5d** and **5f**.

Elie and Satici reported² that the proportion of the axial conformation in series **1** is greater in toluene solution than in methylene chloride. We examined several compounds in the series **4** and **5** and observed similar relatively small increases. The proportion of diaxial conformation of compound **4d**, for example, increases from 19% in CD₂Cl₂ to 29% in toluene.

Since compound **5e** is crystalline at room temperature, CPDAS solid-state proton decoupled carbon-13 NMR spectra were recorded and, surprisingly, *five* signals of intensity ratio ~1:1:2:1:1 were seen at room temperature at around 68–78 ppm, the region of the silyloxygenated C1 and C2 carbon atoms. Less readily assigned multiple signals were seen in the remainder of the spectrum. This suggests that more than one conformation may be present in the crystal, so an X-ray diffraction study of the compound was carried out, and the results obtained confirm this.

Crystal Structures. The X-ray diffraction crystal structures of three *bis*-triphenylsilyloxycyclohexanes have been determined, namely, *trans*-1,4-*bis*-triphenylsilyloxycyclohexane **4e**, its *cis* epimer **17**, and the *trans*-1,2-isomer **5e**. Structures for the 1,4-disubstituted isomers are shown in Figures 1 and 2 and are described in detail in the Supporting Information. The *trans*-1,4-isomer **4e** adopts the chair conformation with two axial silyloxy substituents (i.e., the minor populated conformation in solution). The *cis*-1,4-disubstituted compound **17** has both axial

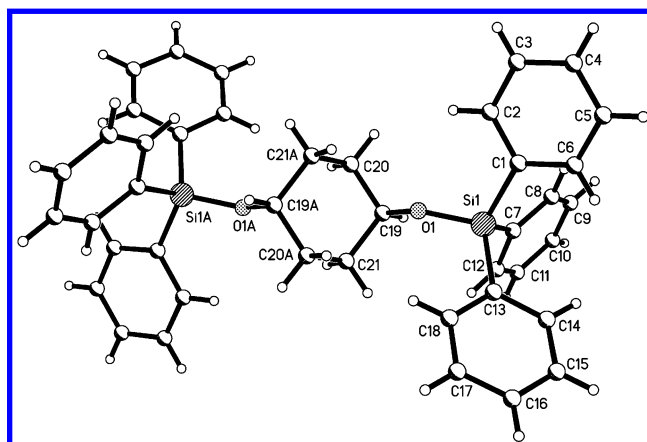
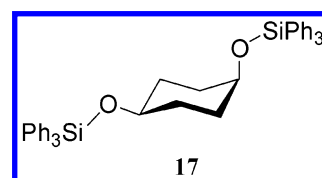


Figure 1. ORTEP diagram of the diequatorial conformation of *trans*-1,4-*bis*-triphenylsilyloxycyclohexane (**4e**).

and equatorial silyloxy groups, and two different molecules are found in the unit cell. For the *trans*-1,2-isomer **5e** whose CP MAS NMR is discussed above, the unit cell contains 12 molecules, and both diaxial and diequatorial chair conformations are found (see Supporting Information).⁹



When triphenylsilyloxy groups have no neighbors, as with the axial groups in **4e**, the exocyclic C–O bonds are nearly eclipsed with H–C–O–Si torsion angles of 13°. In the two different molecules of compound **17**, the torsion angles are 21° and 13° for axial silyl groups and 21° and 13° for equatorial silyl groups.

One other crystalline triphenylsilyloxy cyclohexane derivative with no adjacent substituents has been the subject of an X-ray diffraction study. In *O*-triphenylsilyl-17α-mercaptocholestan-3α-ol,¹⁷ the triphenylsilyloxy group is axial and the unit cell contains two different molecules, both of which show a marked eclipsing tendency with H–C–O–Si torsion angles of 4° and 12°. A search of the Cambridge Crystallographic Data Base¹⁸ yielded 36 further examples of other kinds of silyloxy groups

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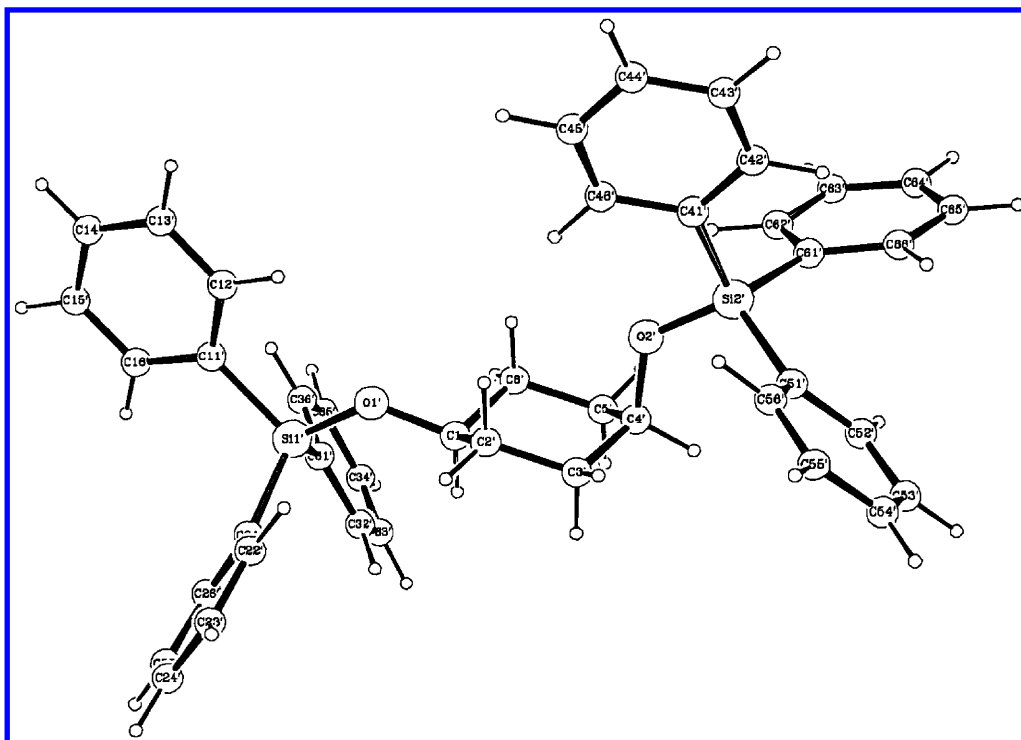


Figure 2. ORTEP diagram of *cis*-1,4-bis-triphenylsilyloxycyclohexane (17).

on a saturated six-membered ring with no adjacent equatorial substituents. Along with the seven examples from the present work, such silyloxycyclohexanes with a range of silicon substituents but no adjacent equatorial substituents on the ring have a mean torsion angle H—C—O—Si of 15.6°, with an average value almost 3° lower for axial silyloxy groups than for equatorial. The sample is large enough to suggest that such near-eclipsing of exocyclic C—O bonds is not an artifact of the crystalline state.

Trans-1,2-disubstituted compounds **5** are chiral,⁹ and the racemic form of compound **5e** crystallizes in the monoclinic system. The unit cell contains 12 molecules, four each of three kinds (Supporting Information). The first of these three is in a diaxial conformation with two molecules of each enantiomer. The H—C—O—Si torsion angles found for axial OSiPh₃ groups are 0° and 10°. The other two kinds of molecules have diequatorial conformations of opposite configuration, there being four of each in the unit cell.

The two diequatorial structures in the crystal of **5e** have bond lengths, bond angles, and torsion angles which are similar but different numerically.⁹ Equatorial triphenylsilyl groups have very different substituents at the two *neighboring* equatorial positions, hydrogen and triphenylsilyloxy, respectively, so none of the four different equatorial SiPh₃ groups are eclipsed but rather turned away from its neighboring OSiPh₃ group toward the unsubstituted ring position, with H—C—O—Si torsion angles all in the range |26|° – |31|°.

The Crystallographic Data Base yielded a further 22 examples of silyloxycyclohexanes or analogues with a single, adjacent, equatorial substituent,¹⁸ and in these cases the H—C—O—Si

torsion angle averages 31.3° with the silyl group turned away from the substituent, agreeing well with the four values reported for equatorial **5e**. The absence of one adjacent substituent thus produces torsion angles that are 15° further from eclipsing on average.

Molecular Mechanics Calculations. For molecular mechanics calculations of the *mono*- and *bis*-silyloxy cyclohexane series **1**, **4**, and **5**, we used Allinger's MM3(94) program whose parametrization for ethers and for silanes but not for silyloxy compounds has been discussed.^{19,20} Such calculations should be broadly reliable for indicating trends in the axial/equatorial population ratio along a series of compounds. The anti conformation for the exocyclic C—O bond in the equatorial conformation of compound **1a** (i.e., H—C—O—Si ~ 180°) is more than 3 kcal/mol less stable than the minimum-energy eclipsed conformation, while the anti, axial conformation is even more unstable than eclipsed, axial. Similar results are calculated for all silyl groups. Nonchair conformations of the cyclohexane ring are even less stable by calculation, so neither those conformations nor anti conformations about the C—O bond will be further discussed.

Finding the minimum energy structure for the *mono*- and *bis*-silyloxycyclohexanes requires that the conformation about each of the three or six Si—R bonds be properly investigated, so that a total energy for the molecule does not reflect a less-than-optimum conformation within an SiR₃ group. This is especially a problem in compounds with multiple ethyl, isopropyl, or phenyl groups. In **1d** for example, there are three staggered conformations for each isopropyl—silicon bond, so 3³ = 27 combinations of conformation, within a single *tris*-isopropylsilyl group. Such conformational possibilities have been discussed in detail previously.^{21a,b} Investigation of the *tert*-

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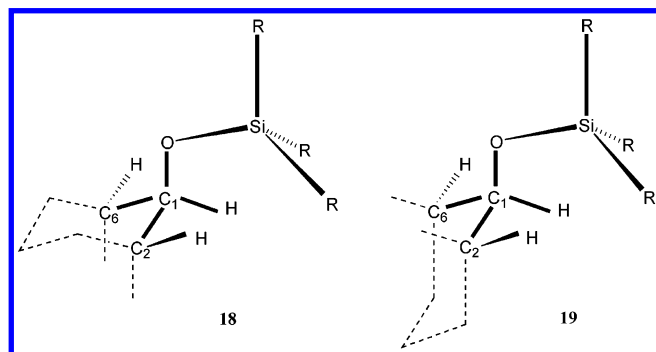
Table 3. Calculated Relative Energy ΔE_{Ax} (kcal/mol) of the Axial Chair Conformation of Silyloxycyclohexanes **1**, Equatorial = 0.0, and the Exocyclic Torsion Angles H–C–O–Si τ_{Eq} and τ_{Ax} , deg

substituent SiR ₃	$\tau_{\text{eq}}(\text{H}-\text{C}-\text{O}-\text{Si})$	ΔE_{Ax}		$\tau_{\text{ax}}(\text{H}-\text{C}-\text{O}-\text{Si})$
		MM3 calcd	experimental	
a, SiMe ₃	3.8	0.61	1.31	1.4
b, SiEt ₃	12.4	0.51	1.26	9.8
c, Si- <i>t</i> -BuMe ₂	5.8	0.41	1.06	3.7
d, Si(<i>i</i> -Pr) ₃	6.5	0.48	0.94	7.5
e, SiPh ₃	20.3	0.46	0.71	23.2
f, SiPh ₂ - <i>t</i> -Bu	25.9	0.42	0.56	26.7

Table 4. Calculated Relative Energy ΔE_{Ax} (kcal/mol) of the Diaxial Chair Conformation of *trans*-1,4-Bis-silyloxycyclohexanes **4**, Diequatorial = 0.0, and the Exocyclic Torsion Angles H–C–O–Si, τ_{eq} and τ_{ax} , deg

substituent SiR ₃	$\tau_{\text{eq}}(\text{H}-\text{C}-\text{O}-\text{Si})$	ΔE_{Ax}		$\tau_{\text{ax}}(\text{H}-\text{C}-\text{O}-\text{Si})$
		MM3 calcd	experimental	
a, SiMe ₃	4.4	0.87	1.55	1.9
b, SiEt ₃	14.1	0.70	1.91	11.4
c, Si- <i>t</i> -BuMe ₂	3.6	0.44	1.97	2.1
d, Si(<i>i</i> -Pr) ₃	3.8	0.46	0.49	7.3
e, SiPh ₃	25.2	0.62	0.63	27.1
f, SiPh ₂ - <i>t</i> -Bu	28.5	0.43	0.48	27.8

butyldimethylsilyl group and the *tert*-butyldiphenylsilyl group, as in **1c** and **1e**, consistently showed that the conformation with the *tert*-butyl group antiperiplanar to the O-cyclohexyl bond is most stable. Interestingly, the conformation **within** SiR₃ groups is essentially the same by calculation in the axial and equatorial minima. However, as the viewpoint used in **18** and **19** shows, the geometry of the interaction of SiR₃ with C2 and C6 and their attached equatorial hydrogens is similar in the two chair conformations.



Tables 3 and 4 show calculated overall energies for minimum energy axial and equatorial conformations for the series **1** and **4**, and the exocyclic H–C–O–Si torsion angles associated with these.

The axially substituted chair conformation is always calculated to be the less stable but the axial/equatorial energy difference is always underestimated compared with experimentally determined values. Along the series, however, the calculated and experimental trends match. In particular, the relative stability of the axial conformation is greater when the silicon substituents R contain a large number of atoms. The calculated diaxial/diequatorial energy differences for the *trans*-1,4-disubstituted series **4** are only a little greater than those of the

monosubstituted series, and in fact, in the trisisopropyl case the difference is slightly less. It is notable that the exocyclic torsion angle H–C–O–Si tends toward eclipsed, varying irregularly in size with the silyl group, and that it is similar in size in the axial and equatorial chair conformations of the same compound. The phenylsilyl compounds **1e**, **1f**, **4e**, and **4f** are calculated to have the least tendency toward eclipsing, although they are hardly staggered ($\tau = 20.3$ – 28.5°). Crystal structures reported above show torsion angles H–C–O–SiPh₃ much nearer eclipsed.

Molecular mechanics energy-minimized structures do not necessarily show the strain present in the idealized staggered chair conformations but rather show how the molecule has deformed to accommodate such strain. Nonetheless, calculations for series **1**, **4**, and **5** reproduce the trends of the experimental results; so to see if an explanation of the trends appears, we looked at the complete set of pairwise atom–atom interactions, repulsive or attractive, that MM3 provides. We report on each series in turn.

Calculations for Monosilyloxycyclohexanes 1a–f, Table 5. The parent silyloxycyclohexane **1**, SiR₃ = SiH₃, has been included, since it extends the trend in the series **1a–f** insofar as the overall axial/equatorial energy difference, 0.66 kcal/mol, is greater than that calculated for all the more substituted compounds.

The conventional explanation of the excess energy of the axial conformation over the equatorial is the interaction of the axial oxygen atom with C₃ and C₅ and the axial hydrogen atoms at these positions. These four interactions are indeed repulsive but are almost the same in all compounds **1a–f**, totalling in the narrow range 0.98–1.02 kcal/mol. This suggests that we examine whether differences along the series reflect the interaction of the ring with what is beyond the oxygen, i.e., with the atoms of the SiR₃ group. The interactions of C1 and H1 with SiR₃ are predominantly repulsive and are remarkably similar in both chair conformations. Their total is always more than 1 kcal/mol, but the difference between the two axial and equatorial chair conformations is always less than 0.1 kcal/mol and usually much less. Notably, the repulsions with C1 and H1 are *least* for **1e** and **1f**, but this plausibly reflects the fact that their minimum-energy conformations are quite far from eclipsed (Table 3).

There are remarkably few repulsive interactions of SiR₃ with the flanking CH₂ groups at positions 2 and 6, in the minimum energy conformations with near-to-eclipsing C–O bonds, illustrating how effective eclipsing is in relieving these. Once again the total of such interactions is very similar in the two chair conformations of any compound, differing by 0.00–0.07 kcal/mol in the series.

Thus overall, interactions of SiR₃ with C1, C2, and C6 and their attached hydrogens are repulsive, but as the second to last column of Table 5 shows, there is little difference in the total of these interactions in axial and equatorial conformations. Idealized structures **18** and **19** emphasize the geometric similarity of conformations, and while there are small differences in calculated bond lengths, bond angles, torsion angles, and interatomic distances, the net interaction of SiR₃ with this part of the molecule is very similar in the two conformations.

The remaining interactions of atoms of the SiR₃ group, which might produce differences between axial and equatorial con-

(21) (a) For discussion of the conformations within a trisisopropylsilyl group, for example: Anderson, J. E.; Casarini, D.; Lunazzi, L.; Mazzanti, A. J. *Org. Chem.* **2000**, 65, 1729–1737. (b) Anderson, J. E.; Koon, K. H.; Parkin, J. E. *Tetrahedron* **1985**, 41, 561–567.

Table 5. Difference in MM3-Calculated Interactions (kcal/mol) of SiR₃ with Parts of the Cyclohexane Ring in Minimum Energy Equatorial and Axial Conformations of Monosubstituted Compounds 1^a

monosilyloxycyclohexane (1a–f)					
silyl ether	no. of atoms in R ₃	difference between total energy of axial and equatorial conformations		difference between total energy of axial and equatorial conformations as to interactions of SiR ₃ atoms with C6H2C1HC2H2 atoms	difference between total energy of axial and equatorial conformations as to interactions of SiR ₃ atoms with C3H2C4HC5H2 atoms
		experimental ²	MM3 calcd		
OSiH ₃	3		0.66	0.04	−0.18
OSiMe ₃	12	1.31	0.61	0.00	−0.23
OSiEt ₃	21	1.26	0.51	0.09	−0.43
OSiMe ₂ - <i>t</i> -Bu	21	1.06	0.41	−0.05	−0.49
OSi(<i>i</i> -Pr) ₃	30	0.94	0.48	0.06	−0.48
OSiPh ₃	33	0.71	0.46	0.15	−0.35
OSiPh ₂ - <i>t</i> -Bu	35	0.56	0.42	−0.04	−0.37

^a A negative sign means that interactions are more stabilizing in the axial conformation.

formations, are with the atoms of the three methylene groups at the far end of the cyclohexane ring. Unsurprisingly, these pairwise interactions are all attractive though small. Even in the simplest trimethylsilyl compound **1a**, there are already 117 such interactions between the nine atoms of CH₂CH₂CH₂ and the thirteen atoms of Si(CH₃)₃, so their total may be substantial.

Viewing the diagrams **18** and **19**, the relative arrangements of these two fragments is different in the two chair conformations, and the calculation that such stabilization is greater in the more compact axial conformation than in the extended equatorial conformation confirms this. Over the six compounds **1a–f**, the average size of the attraction between one atom from each fragment is 4.4 and 2.7 cal/mol, respectively, in axial and equatorial conformations.

There are hundreds of such pairwise interactions, however, in each compound **1**, and the net results are shown in the right-hand column in Table 5. It is striking that these long-range attractive interactions contribute several hundred calories per mole toward stabilizing the axial conformation and the contribution increases erratically down the series. The corresponding calculations for series **4** and **5** yield similar results.

Calculations for 1,4-Bis-silyloxycyclohexanes 4a–f, Table 4. When the silyl group is SiMe₃ **4a**, SiEt₃ **4b**, and SiPh₃ **4e**, the excess energy of the diaxial conformation is calculated to be markedly higher than that of the corresponding monosilyl compound **1** shown in Table 3, but it is certainly not twice as large. In **4c**, **4d**, and **4f**, the excess energy in the diaxial conformation is much the same as that found for the corresponding monosilyl compounds.

Attractive interactions between SiR₃ groups and the far end of the ring favor the diaxial conformation even more markedly than in the series **1**, but details are not shown. Conformations with both SiR₃ groups on the same side of the H1, C1, C4, H4 plane are more stable by over 100 cal/mol than those with groups on opposite sides of the plane. This shows that there is some residual attractive steric interaction between silyl groups, even when they are separated by the ring and two oxygen atoms.

Calculations for 1,2-Bis-silyloxycyclohexanes 5a–f. The calculations, shown in Table 2, reproduce the trend of the experimental results without closely matching absolute values. It is particularly encouraging that the significant diaxial populations found in the NMR spectra of the three compounds **5d–f** are also predicted by the calculations. The torsion angles calculated for the now-adjacent exocyclic C–OSiR₃ bonds are interesting. In diequatorial conformations, SiR₃ groups are turned away from each other and thus away from the near-to-eclipsing

values found in series **1**; this minimizes repulsive interactions. The diaxial conformations, **5a** and **5c** are eclipsed, but for the other compounds (**5b**, **5e**, and **5f**), the silyl groups are turned *toward* each other, presumably to maximize attractive interactions.

We do not show the numbers, but the sum of attractive interactions of silyl groups with the far end of the cyclohexane ring is once again greater in the diaxial conformation, is more marked than in the monosubstituted series, and makes an increasing contribution to the equilibrium along the series **5a–f**.

What is more inconsistently variable is the interaction of a silyl group with its neighboring silyloxy group in the two conformations. Calculations suggest that the sum of these interactions is always substantially attractive in the optimized, diequatorial, and diaxial conformations, although there is at least one repulsive interaction in every conformation of each member of the series. Summing all pairwise interactions of this type shows that the net silyl/silyloxy attraction is greater in the diequatorial conformation for **5a–d** but in the diaxial conformation for **5e** and **5f**.

The sum of the attractive interactions of silyl atoms with silyloxy atoms ranges up to 3.4 kcal/mol for trialkylsilyl groups and up to 7.2 kcal/mol for arylsilyl groups. Repulsive interactions are never more than 0.7 kcal/mol in total. With such conformational energies in play, it is little wonder that the conventional equilibrium of cyclohexane chairs with equatorial or axial substitution (with *A* values of 0.56–1.31 kcal/mol in series **1**) can be overwhelmed by two, many-atomed, silyl substituents arranging their relative positions to best effect.

The calculations reported were carried out assuming a dielectric constant of 1.5, the MM3 default value. The value used might affect results, particularly in the series **4** and **5**, with two silyloxy groups. Changing the constant to 5 produced a fairly uniform increase of 0.2 kcal/mol in the calculated axial/equatorial energy difference (and insignificant changes in geometric parameters), thus improving agreement with experiment. Further increasing the constant to 10 or 20 produced much smaller additional changes for all compounds.²²

Calculations of Rotational Potentials. Molecular mechanics allows the calculation of the molecular energy as the H–C–O–Si torsion angle is changed through a range of values. This should approximate the rotational potential for the bond, if

(22) A referee has pointed out that the dielectric constant of dichloromethane is given as 9 at 293 K and 16 at 180 K in the CRC Handbook, so the improved agreement with experiment may be valid, but it is not clear whether solvent can dominate the dielectrics within a single molecule.

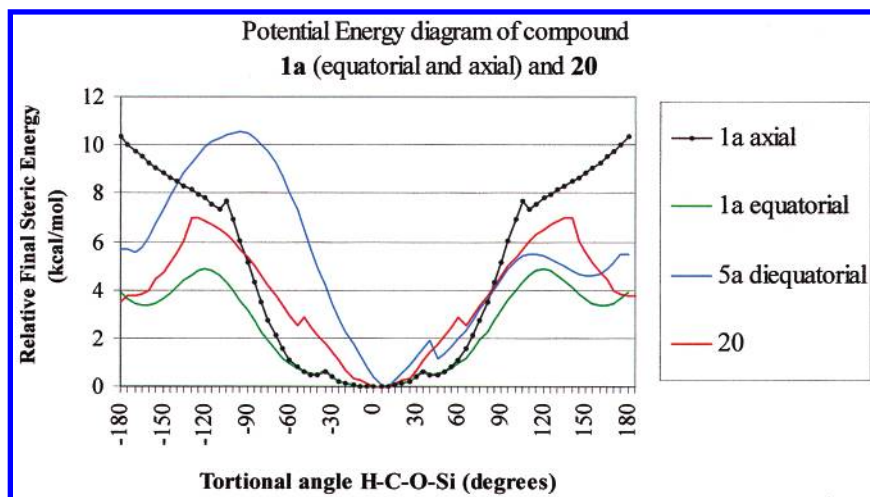


Figure 3. Potential energy diagrams of compounds **1a** (equatorial and axial), **5a** (diequatorial), and **20**.

rotation is a simple process as it probably is for at least trimethylsilyloxycyclohexane, **1a**. Rotation about the C–O bond is complex in most other molecules with significant changes within silyl groups, so we seldom tried to calculate these.

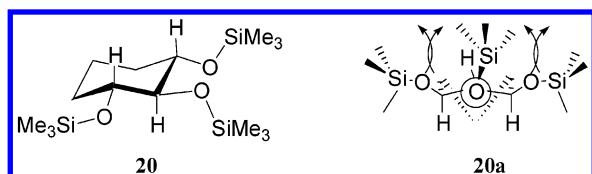
For both equatorial and axial forms of **1a** (see Figure 3), a similar potential curve is obtained for H–C–O–Si torsion angles between -60° and 60° . The energy minimum is close to 0° , but the striking consequence of a preferred eclipsed conformation is that the potential minimum is flat-bottomed and 240° wide. Maxima occur about 120° on either of the minimum when the O–Si bond eclipses a ring C–C bond. Whether the trimethylsilyloxy group is axial or equatorial, rotation from the minimum to a torsion angle of 60° increases the energy by less than 1 kcal/mol.

A much steeper sided potential well results when an equatorial silyloxy group has two equatorial neighbors; see Figure 3. This shows a plot for compound **20**, which has three equatorial trimethylsilyloxy groups and is thus a model for a silylated sugar. For an alternative view, see **20a**.

When a trimethylsilyloxy group has only one equatorial neighbor (e.g., diequatorial **5a**), the potential has a narrower, skewed minimum which is a combination of those for **1a** and **20**.

Calculations with full matrix minimization quantified the vibrational entropy of both diaxial and diequatorial conformations in series **4** and **5**. The results obtained vary greatly, but on average, such entropy is lowest in the diequatorial conformation of the series **5** when silyloxy groups are most able to constrain each other. Thus, both aspects of the calculations suggest that reduced entropy of a chair conformation with adjacent equatorial substituents of the type OSiR_3 may favor the axial chair conformation.

It is significant that for **5a** and **20** in the ring-inverted form when all substituents are axial and thus not interfering, the overall enthalpy is greater, but the potential well is broad again.



Discussion

Conformation of the Exocyclic Bond and the Axial-Substituted Chair Conformation. The tendency of a silyloxy group on a six-membered ring to adopt eclipsed conformations for the exocyclic C–O bond is so marked that such an eclipsed conformation should be the point of departure for a discussion of more complicated molecules. Rotation away from a staggered conformation minimizes marked 1,3-repulsive steric interactions of the tertiary silyl group with the adjacent equatorial positions, even when the latter are not substituted. Eclipsing is equally likely for axial and equatorial silyloxy groups, since both have a similar geometric relationship to the adjacent equatorial positions and calculations of the repulsions involved confirm this.

Neighboring equatorial substituents other than hydrogen interact more strongly, so that in the minimum energy diequatorial conformation of the 1,2-disubstituted compounds **5**, silyl groups rotate away from each other somewhat (i.e., away from eclipsing).

When there are equatorial substituents on both sides of a silyloxy group, as in many silylated sugars, there is a rather more marked steric compression with a reduced possibility of relief by such a rotation. However, ring inversion to give the alternative chair, having axial silyloxy groups with hydrogen atoms as the adjacent equatorial substituents, is still a possible relief, although with a conventional axial-substituent penalty. In fact, in the diaxial conformation, the simpler alkylsilyl groups remain eclipsed but otherwise, particularly in **5b**, **5e**, and **5f**, they rotate *toward* each other to maximize attractive interactions to the point where the first repulsive interaction is encountered.

Whenever a trimethylsilyloxy substituent has no equatorial neighbors, a broad potential energy well is calculated, and many slightly different conformational states of similar energy can presumably be populated. When an equatorial silyloxy group has one or two equatorial neighbors, the potential energy well has steeper sides, and fewer states are accessible. The entropy of such a conformation is reduced. A different broad minimum with a wide choice of states can be reached, however, by ring inversion to give axial groups with no equatorial neighbors. There is again an enthalpic penalty in changing to an axially substituted chair, but there is a counterbalancing entropic gain.

Role of Attractive Interactions in the Extended Equatorial Conformation and the Folded Axial Conformation. Since the

three R groups are distant from the ring, due to long C—Si and O—Si bonds, steric repulsion is significant for only two of the conformational points at issue. The first is the tendency toward eclipsed exocyclic bonds discussed above. The second is the consequence of an oxygen substituent being axial. Within a given series, this is always the same, being the conventional repulsion of that oxygen atom by two axial hydrogen atoms. Nonetheless, the position of chair–chair equilibria ranges widely down each series, so interactions less obvious than these repulsions need to be considered.

The silyl group locates antiperiplanar to the cyclohexane ring along the O—C bond, so the axial silyloxycyclohexane is a more compact molecule than the equatorial alternative. In particular, SiR₃ when axial is nearer to the nine atoms making up the methylene groups at positions 3, 4, and 5 in the cyclohexane chair, than when it is equatorial.²⁴ This results in greater attractive stabilization of the molecule in the axial conformation by several hundred calories per mole. The relative stabilization increases with the number of atoms in the SiR₃ group, but not in a linear fashion, since not all SiR₃ atoms can locate at the positions that maximize attractive stabilization (see Table 5). The fit would be better or worse depending on whether molecular mechanics under- or overestimates attractive interactions. None of the model conformational results used in the parametrization of MM3 specifically focused attention on attractive interactions.

With the *trans*-1,2-disubstituted series **5**, two further points have to be considered. First, there are interactions *between the side chains* which are substantially attractive in total in all conformations, which increase with the bulk of the side chain, and which while they favor the diequatorial conformation for simpler silyl groups, favor the diaxial conformation for the bulkier. Second, the diaxial conformations are favored by higher entropy since equatorial substituents reduce the surface of each other's potential energy well.

In polysilyloxy compounds such as protected sugars, poly-equatorial conformations are disfavored since a third equatorial substituent prevents two vicinal substituents from optimizing their interactions by moving apart. Polyaxial conformations still have their entropic advantage and neighboring substituents retain their freedom to optimize attractive interactions.

Contrast with Alkyl Ethers. The conformational behavior of the silyloxycyclohexanes is *not unusual* compared with that of alkoxy analogues, when it is realized that comparisons up to now have involved primary alkoxy derivatives. A more realistic comparison is with *tert*-alkoxycyclohexanes. A long-known NMR study of *tert*-butoxycyclohexane and associated molecular mechanics calculations both suggest an axial/equatorial equilibrium that places the steric effect of the *tert*-butoxy group between that of the methoxy and the ethoxy groups.²³ The experimental *A*-values under standard conditions are OMe, 0.60, OEt, 0.90, and *O*-*t*-Bu, 0.75. It has also been noted from calculations of minimum energy conformations^{14,15} that while methoxycyclohexane has an H—C—O—Me torsion angle of about 42°, the C—O bond of *tert*-butoxycyclohexane is eclipsed

both when axial and equatorial. NMR observations bear out this last point. Finally, the same calculations show that the *tert*-butyl fragment has attractive interactions with the far end of the ring that are 0.21 kcal/mol greater in the axial chair than in the equatorial.

tert-Butoxycyclohexane thus behaves like the bulkier silyloxycyclohexanes despite having significantly shorter bonds and thus suffering relatively more steric compression. We expect that the odd conformational behavior of silylated sugars will also be observed for any poly-*O*-*tert*-alkylated sugars that can be prepared.

The importance of 1,3-interactions in cyclohexane conformational analysis thus extends beyond that of the axial substituent with axial hydrogen atoms at positions 3 and 5 on the ring. Our results show that, for OX both axial and equatorial, the attached X-group when it is quaternary, such as SiR₃ or *tert*-butyl, has significant 1,3-interactions with the adjacent *equatorial* hydrogen atoms.²⁴ The consequence is that rotation about the exocyclic C—O bond minimizes this particular 1,3-interaction, which seems thus to be more important than the bond eclipsing which results.

We do not conclude that the present work totally explains the “silyl effect”, but it sheds light on two important aspects that can be taken forward to a discussion of polysilyloxy compounds.

Care must be exercised in interpreting small sets of interactions extracted from molecular mechanics calculations. Thus, the exocyclic C—O bond is calculated to be eclipsed in both conformations of compound **1a** (and in many others). Inspection of the detail of these minimum energy conformations of **1a** shows that the interactions between the atoms of SiMe₃ and the equatorial hydrogen atoms at C2 and C6 *are all attractive*. We can aver confidently, however,¹⁴ that such a bond is eclipsed because of *repulsion* between SiMe₃ and these equatorial hydrogens *in the conventional staggered conformation*. Calculations show only what the molecule has done to relieve what plausibly are the determining repulsive interactions in the molecule.

This can be confirmed by examining the calculations for the equatorial conformation of compound **5a**, where the second trimethylsilyloxy group forces the first to rotate toward the C6 position with an H—C—O—Si torsion angle of 12°. Here the repulsive methyl—CH₂ pairwise interactions total 0.13 kcal/mol whereas in the equatorial conformation of **1a**, with a torsion angle of 4°, there are no such repulsive interactions.

Trans-1,2-disubstituted Cyclohexanes as Models for More Complex Molecules. The series **5** presents a simple model for the interactions of two complex silyloxy groups, in the light of the conformational features that have emerged from the series **1** and **4**. There would be repulsive interactions between SiR₃ groups in an undistorted diequatorial conformation, and to that extent, the simple rationalization is correct, but, in the minimum energy diequatorial conformation, the two silyl groups rotate away from each other to minimize repulsions. In a polysilylated sugar, for example, a β -D-glucose derivative with potentially four equatorial silyloxy groups, two adjacent silyloxy-groups rotating away from each other encounter further equatorial substituents opposing this movement. In the alternative chair

(23) Senderowitz, H.; Abramson, S.; Aped, P.; Schleifer, L.; Fuchs, B. *Tetrahedron Lett.* **1989**, 30, 6765–6768.

(24) In compound **1a**, calculations suggest that the maximum and minimum separation of two hydrogen atoms H—C—Si···C4—H is 9.04 and 6.25 Å in the equatorial conformation, whereas these limits are only 8.00 and 5.92 Å in the axial conformation.

conformation, in contrast, each axial silyloxy group is quite free of vicinal restrictions on obtaining its optimum local conformation.

To this discussion of repulsive interactions in such compounds must be added the attractive interactions that we have demonstrated in the model series. Axial SiR_3 groups have enhanced attractive interactions with the far end of the sugar ring compared with equatorial groups, while the mutual attraction of neighboring, polyatomic, SiR_3 groups and entropy favor diaxial conformations.

The overall picture that emerges from this work is thus of a different kind of conformational analysis from all-carbon systems. Oxygen–silicon and silicon–carbon bonds are quite long compared with the carbon–for–silicon analogues—the standard values used in MM3 for example are O–Si 1.64 Å, O–C 1.42 Å; C–Si 1.87, C–C 1.53 Å, so repulsive interactions play a lesser role. On the other hand, readily available silyl chlorides allow the introduction of quite complex trialkylsilyl groups with many atoms, which if they are too far from the ring to repel, must attract. Much that is observed in conformational terms can be attributed to enhanced attractive interactions of one or more silyl groups in the axial conformation. This is certainly the rationalization that applies to Eliel and Satıcı's work on monosilyloxycyclohexanes.

The conventional axial/equatorial equilibrium of simple compounds depends on repulsive interactions of a few atoms at positions 1, 3, and 5 on the ring. Polysilylated six-membered rings have many hundreds of attractive interactions totalling several kilocalories per mole, so it not surprising that in many cases, these dominate the overall molecular equilibrium observed.

We have tried not to place too much emphasis on the exact sums of attraction and repulsion between groups. Molecular mechanics calculations do not address the possible influence of undoubted differences in the electronic nature of the substituents on silicon,¹ but we doubt if the correct balance between steric and electronic factors can be obtained and related to the single experimental number we have obtained for each compound. We believe that the broader indications as to the relative importance of steric attraction and repulsion and conformational entropy are nonetheless quite credible.

Conclusions

A range of silylated derivatives of *trans*-1,2- and *trans*-1,4-dihydroxycyclohexane have been studied by NMR spectroscopy, X-ray diffraction studies, and molecular mechanics (MM3) calculations, to explain unusually large populations of chair conformations with axial substituents. For both axial and equatorial, tertiary, silyloxy groups, eclipsed conformations for the exocyclic C–O bond relieve parallel-1,3-interactions between the SiR_3 group and the adjacent equatorial hydrogen atoms. The axial silyloxycyclohexane has a more compact shape than the equatorial alternative. While its oxygen has a conventional repulsive interaction with C3 and C5, the atoms of the SiR_3 group have only attractive interactions with the methylene groups at positions 3, 4, and 5 in the ring, and these are greater than in the extended equatorial conformation and increase down each series **1**, **4**, and **5**, as the number of atoms in SiR_3 increases.

When two silyloxy groups are next to each other, the exocyclic bond conformation can adjust so that the two sets of

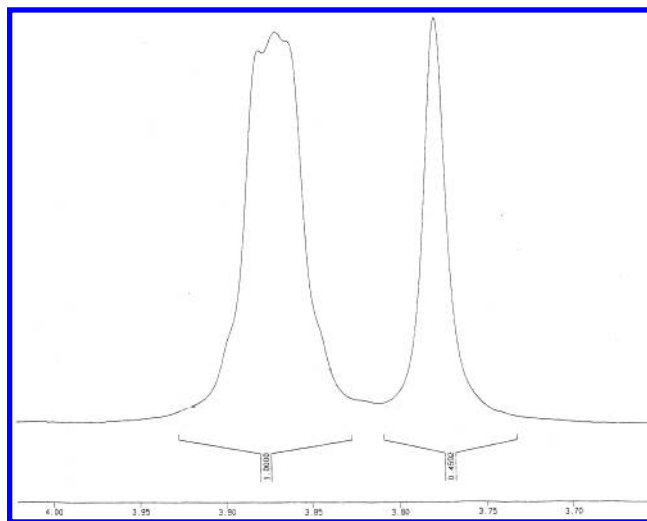


Figure 4. Methine proton NMR signals for compound **5e** at 178 K.

SiR_3 atoms attract each other overall, and for bulkier silyl substituents, this attraction is greater in the diaxial. In addition, in the axial conformation, the two silyloxy groups enjoy a broad rotational potential minimum with a greater range of states than in the diequatorial conformation.

Experimental Section

Crystal Structures. Hydrogen atoms were not located directly in the determination. For the purpose of determining the H–C–O–Si torsion angles reported, the methine hydrogen atoms were assumed to be located on the external bisector of the ring C–C–C bond angles. For the purpose of determining closest approach of silyl groups in the crystal of **1e**, hydrogen atoms were located conventionally on the observed benzene rings.

NMR Spectra. Spectra were recorded for solutions ~5 mM in CD_2Cl_2 using a Bruker DRX-500 MHz spectrometer with a gradient unit system with variable temperature control or using a Bruker AMX 300-MHz spectrometer. Solid-state spectra were recorded on a Bruker MSL 300-MHz solid-state spectrometer. To measure populations at low temperatures, the methine proton signals were electronically integrated. These signals were assigned on the basis of their width at half-height, since coupling was not always clearly resolved (Figure 4). The diequatorial conformation has a much broader signal (~20 vs ~7 Hz) since the axial methine proton has large couplings to adjacent axial protons. In **5e** and **5f**, in contrast to **5a–d** and **4a–f**, axial protons are downfield from equatorial protons, since they are deshielded by an anisotropic, equatorial substituent at C2.

For compounds **4**, methine proton signals are not first order (i.e., not triplets of triplets) due to a large coupling between isochronous axial protons at C2 and C3 and at C5 and C6.

Barriers to ring inversion appear to be about 11.6 kcal/mol in all compounds. For several compounds of series **4** and **5**, populations were also measured for toluene- d_6 solution, and in agreement with Eliel and Satıcı's observations for series **1**, the population of the diaxial conformation was found to be somewhat higher than in dichloromethane- d_2 solution.

Molecular Mechanics Calculations. Molecular mechanics calculations were carried out using Allinger's MM3 (94) program.^{19,20} Both the dihedral drive option and the stochastic search option were used to supplement chemical intuition in locating overall minima for each ring conformation. The rest of the parameters were used as default parameters in the program and run on a Silicon Graphics work station. Interaction of groups, e.g., the trimethylsilyl groups of **5a**, was determined by summing the 169 atom–atom pairwise interactions listed in the MM3 (94) output.

Acknowledgment. C.M. would like to gratefully acknowledge the Clare Boothe Luce Fund for a Professorship and the ACS Petroleum Research Fund for partial support of this research. J.G.O. is grateful for a Bogue Research Fellowship (UCL) for his partial support during this project. We would also like to thank to Dr. Abil Aliev from UCL NMR services for his help in the acquisition of the spectra and his very useful comments regarding the interpretation of the NMR data.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (**5a–f**, **4a–f**, **17**). Tables of crystallographic data for compounds **4e**, **5e**, and **17**. Unit cell diagram for compound **5e**. This material is available free of charge via the Internet at <http://pubs.acs.org>. See any current masthead page for ordering information and Web access instructions.

JA035936X