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Axial Preference of Bulky Group- and Electron-Withdrawing Group-Substituted Oxygen Atom on the Chair-Type -Cyclohexanone, -Glutaric Anhydride, and -Glutarimide

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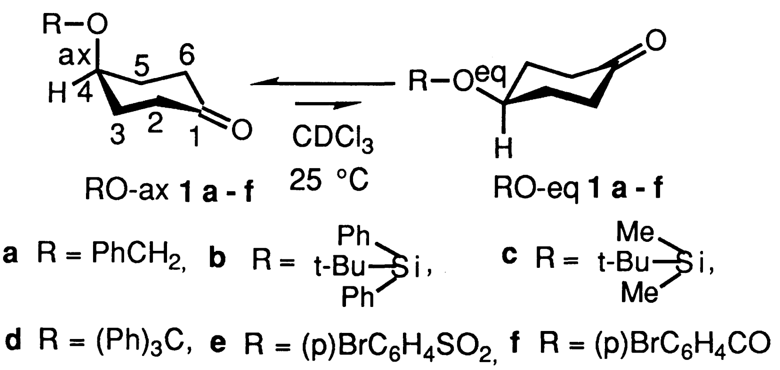
Axial preference (>ca. 70% at 25 °C) of alkoxy and silyloxy groups of the chair-type six-membered cyclic compounds has been clarified by the ^{1}H-NMR bandwidth mesurement method. Based on the X-ray analysis of 4-substituted cyclohexanones, it has been disclosed that the cyclohexanone ring adopts chair form and the 4-substituent occupies the axial site in all cases.

There have been examples that one cannot estimate the stable molecular conformation only from viewpoint of the conventional bulk-repulsive concept.$^{1)}$ Djerassi et al. published interesting papers on the axial preference of electron-withdrawing groups substituted at C(3) on the cyclohexanones.$^{2)}$ Allinger and Bowen commented about the Djerassi's papers in terms of the molecular mechanic treatment of the various 3-heteroatom-substituted cyclohexanones.$^{3)}$ The axial preference of hydroxy, methoxy, and benzyloxy groups and halogens substituted at C(4) on the cyclohexanone in the solution were recorded only by Stolow et al.$^{4)}$ and Kirk$^{5)}$ utilizing ^{1}H-NMR analysis. However, conformational analysis of the 3-substituted glutaric anhydride and glutarimide and of the cyclohexanones possessing bulky-group [*t*-butyldimethylsilyl(TBDMS), *t*-butyldiphenylsilyl, and triphenylmethyl groups]- and electron-withdrawing group [*p*-bromobenzenesulfonyl and *p*-bromobenzoyl]- substituted oxygen atom at the C(4) position has never been documented. We describe herein axial-conformer preference of the various substituents of **1a-f** and **2-4** in their $CDCl_3$ solution and the first example of the crystallographic structure **1b,d-f** bearing the axial substituent.



RO-ax **1 a - f** RO-eq **1 a - f**

a R = $PhCH_2$, **b** R = $t\text{-Bu}\!-\!Si(Ph)_2$, **c** R = $t\text{-Bu}\!-\!Si(Me)_2$,

d R = $(Ph)_3C$, **e** R = $(p)BrC_6H_4SO_2$, **f** R = $(p)BrC_6H_4CO$

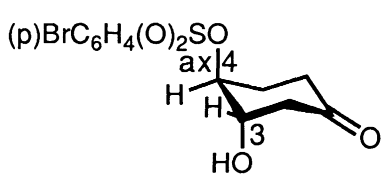
First, we attempted to determine the dynamic 400 MHz ^{1}H-NMR of **1a-f** at low temperature (-80 - -100 °C). However, in all cases of **1a-f**, we could not recognize any two kinds of peaks corresponding to the both conformers with axial- and equatorial-substituents. Thus, approximate probability(%) of the axial conformer (RO-ax **1a-f**) preference in $CDCl_3$ at 25 °C was tentatively determined by a simple calculation2,4) based on each 4-H ^{1}H-NMR bandwidth of compounds **1a-f** and axial- and equatorial-4-TBDMSoxy-2,6-cis-dimethyl cyclohexanones6) (Table 1). Surprisingly, the compounds **1b-d** possessing bulky groups can predominate the 4-substituent-axial conformer, RO-ax **1b-d** in an unexpectably high percentage($\approx$80%). The compounds **1a** and **1e,f** substituted with electron-withdrawing groups exhibited ca. 70% of axial-conformer preference, respectively. On the basis of the above ^{1}H-NMR bandwidth mesurement method, preferential conformation of compounds **2-4** seemed to be estimated. ^{1}H-NMR(400 MHz) bandwidth of 3-H (W = 22.7 Hz) and 4-H (W = 20.2 Hz) of bis-substituent cyclohexanone **2**7) suggested high preference (ca. 82%) of its 3,4-diaxial conformer. Similarly, 3-TBDMSoxy-glutaric anhydride (**3**)8) (W = 17.5 Hz) and -glutarimide (**4**)9) (W = 17.5 Hz) were shown to be 3-TBDMSoxy-axial conformer in a high percentage (> 90%).10)

Table 1. Axial preference of alkoxy(or silyloxy) group of 4-alkoxy(or silyloxy)cyclohexanones **1a-f**

Compound	^{1}H-NMR Bandwidth$^{a)}$ W(Hz) of C4-H	Calcd/%$^{b)}$ of RO-ax conform
1a	22.5	71
1b	20.7	80
1c	20.3	82
1d	20.0	83
1e	22.6	71
1f	22.2	73

a) Determined by 400 MHz ^{1}H-NMR analysis ($CDCl_3$, 25 °C).

b) Calculated on the basis of the data [W(C(4)-Hax)=16.4 Hz and W(C(4)-Heq)=37.5 Hz] of 4-TBDMSoxy-2,6-cis-dimethyl cyclohexanone in $CDCl_3$ at 25 °C.



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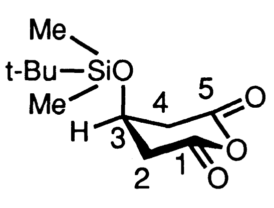

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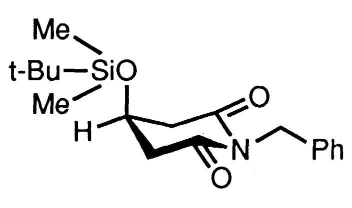

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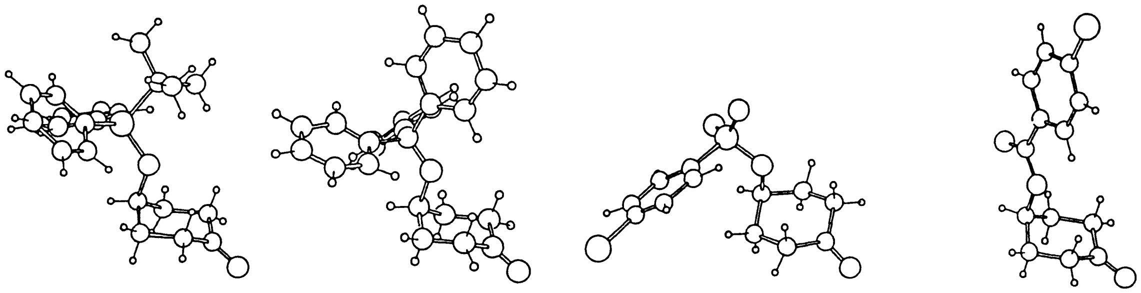
In order to provide the conformational details of the 4-substituted cyclohexanones, X-ray analyses of **1b,d-f** were carried out.11) The crystal of **1d** contains three crystallographically independent molecules. For **1d**, the reflections of the higher order were not observed because of large thermal motions of the molecules.[11] The respective molecular geometries finally obtained were irregular and not adequate to be compared with those of **1b**,**1c**, and **1f** in details.[11] Perspective views of the molecules **1b**,**d**-**f** are depicted in Fig. 1. The cyclohexanone ring adopts chair form and the RO group occupies the axial site in all cases, respectively. The positions of hydrogen atoms located in difference electron density maps are not far from those optimized by energy minimization using the MNDOC program.[12] The interatomic distances between 4-O and the axial hydrogen atoms at the 2- and 6-positions are nearly equal to the sum of van der Waals radii, 2.6 Å. For **1b**,**1e**, and **1f**, the corresponding bond lengths in the cyclohexane rings which exhibit approximate Cs molecular symmetry agree within experimental errors: average bond lengths of C(1)-C(2), C(2)-C(3), and C(3)-C(4) are 1.496(3), 1.530(3), and 1.512(2) Å, respectively. The bond length of C(4)-OR is 1.492(5) Å for **1b**, 1.465(4) Å for **1e**, and 1.429(4) Å for **1f**, the differences among them being statistically significant. It can be suggested that the C(4)-OR bond of the molecule having an electron-withdrawing substituent (R group) tends to be more elongated. The bond angles of C(3)-C(4)-C(5) [112.4(4)°, 111.4(3)°, and 110.3(3)° for **1b**,**1e**, and **1f**, respectively] are also affected by the substituents.



1b **1d** **1e** **1f**

Fig. 1. Perspective view of the crystallographic structure of cyclohexanones **1b**,**d**-**f**.

Thus, axial preference of the bulky group- and electron-withdrawing group-substituted oxygen on the cyclohexanone, glutaric anhydride, and glutarimide has been unequivocally demonstrated by utilizing 400 MHz ^{1}H-NMR and X-ray analysis. This axial-preference nature of RO and SiO groups in the molecules **1a**-**f** and **2**-**4** may be understood in terms of the space-through interaction such as an electrostatic attraction[2,13] $[\mathrm{Si(or\ R)}\overset{\delta-}{\mathrm{O}}\cdots\overset{\delta+}{\mathrm{C}}\mathrm{=O}]$ and/or an n, π* orbital overlap between Si(or R) oxygen atom and carbonyl group. These characteristic prochiral compounds **1a**-**f**, **3**, and **4** will be attractive for new chiral design.

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6) Axial- and equatorial-4-TBDMSoxy-2,6-cis-dimethylcyclohexanones (colorless oil) were derived from the compounds obtained by methylation of 4-hydroxycyclohexanone with methyl iodide in the presence of lithiumdiisopropyl amide in THF-HMPA.

7) Compound **2** (colorless oil) was selectively prepared by (*p*)-bromobenzenesulfonylation of trans -3,4-dihydroxycyclohexanone obtained from acidic treatment of 3,4-epoxycyclohexanone with H_2SO_4 in acetone.

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9) Glutarimide **4** [colorless needles (hexane), mp 96-96.5 °C] was synthesized by aminolysis of glutaric anhydride **3** with benzylamine in CH_2Cl_2 followed by dehydration with acetylchloride.

10) On the basis of crystallographic structure of the glutarimide moiety of sesbanimide (See: R. G. Powell, C. R. Smith Jr., D. Weisleder, G. K. Matsumoto, J. Clardy, and J. Kozlowski, *J. Am. Chem. Soc.*, **105**, 3739 (1983)), the chair conformations **3** and **4** were tentatively assigned for 3-TBDMSoxy-glutaric anhydride and -glutarimide, respectively.

11) Details of the X-ray diffraction analysis of compounds **1b,d-f** should be soon reported elsewhere.

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