A POSSIBLE EXPLANATION FOR PREFERENTIAL STABILIZATION OF THE SUBSTITUENT AXIAL CONFORMATION IN ALKOXY- OR SILOXY-SUBSTITUTED SIX-MEMBERED CYCLIC COMPOUNDS BY THE $\sigma \rightarrow \sigma^*$ ORBITAL OVERLAP: REMARKABLE EFFECT OF ELECTRON-WITHDRAWING GROUPS

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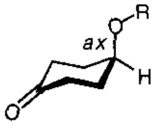
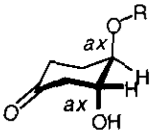
Abstract- The substituent axial conformation in alkoxy- or siloxy-substituted six-membered cyclic compounds must be stabilized by the existence of an electron-withdrawing group or a double bond in their molecules, which can be rationalized in terms of the σ(C-H)$\rightarrow\sigma^*$(C-OR) or π(C=C)$\rightarrow\sigma^*$(C-OR) orbital overlap concept. The basicity of the oxygen atom of alkoxy and siloxy substituent groups may effect the relative stability of the substituent axial conformer.

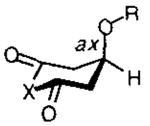
We demonstrated earlier that the benzyloxy and siloxy groups in the chair-type cyclohexanones (**1**) and (**2**), glutaric anhydride (**3**,X = O), and glutarimide (**3**,X = NCH_2Ph) exist preferentially (>70% at 25 °C) in the axial (*ax*) orientation.[1] Stolow et al. reported a similar anomaly in the equilibrium of the Cl- or OH-substituted cyclohexanone derivatives (**4**) in which the *ax* conformer is stabilized over the corresponding equatorial (*eq*) one.[2] Djerassi and coworkers documented that 3-heteroatom-substituted 2,2-dimethylcyclohexanones (**5**) predominantly adopt the heteroatom-substituent *ax* conformer and the extent of *ax* preference essentially follows electronegativity: F>OH~OMe>OAc>Cl >Br~SEt>Me.[3] Recently, we clearly demonstrated the preferential *ax* orientation (95-98%) of the heteroatom substituent in the chair-type 4-benzyloxy- and 4-siloxythiane 1,1-dioxides (**9a-c**) by utilizing dynamic ^{1}H nmr analysis.[4] Thus, one can readily realize that the degree of *ax* conformer preference of the heteroatom substituent in the six-membered cyclic compounds must be deeply concerned with the existence of strong electron-withdrawing group(s) such as carbonyl and sulfonyl groups and with electronegativity and basicity of the heteroatom substituents. There have been many postulations including the familiar examples such as the anomeric[5] and gauche[6] effects and the halo ketone effect[7] for explanation of the preferential conformation of the flexible molecules involving heteroatom(s) and unsaturated system(s). The *ax* preference nature of heteroatom substituent in the cyclohexanones has been explained by a through-space interaction based on the electrostatic attraction or the dipole-dipole interactions and by an orbital overlap between lone-pair orbital of the heteroatom substituent and π* of carbonyl group.[8] Bowen and Allinger carried out *ab initio* calculations which support the Djerassi's finding[3] of the conformational analysis of compound (**5**) by utilizing the parameters obtained from the MM2 program.[9] Although we do not deny the previous proposals described above, we wish to argue about the *ax* or *pseudoax* conformer preference of compounds (**1-10**) in terms of the σ→σ* or π→σ* orbital overlap concept similar to that (n→σ* orbital overlap one) for the generalized anomeric effect.[10] In a conformational equilibria in compounds (**1-9**), the σ(C-H)→σ*(C-OR) orbital overlap interaction may considerably contribute to the stability of RO-*ax* conformers, while the σ(C-



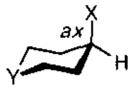
1a-g



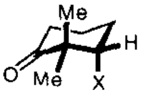
2f



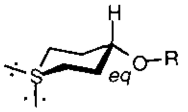
3b X = O, NCH$_2$Ph



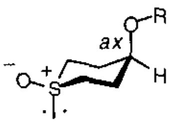
4 X = OH, Cl
Y = CO, CCl$_2$,



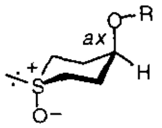
5 X = F, Cl, OH,
OMe, OAc, etc.



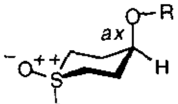
6a-d



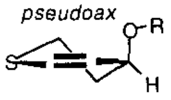
7a-c



8a-c



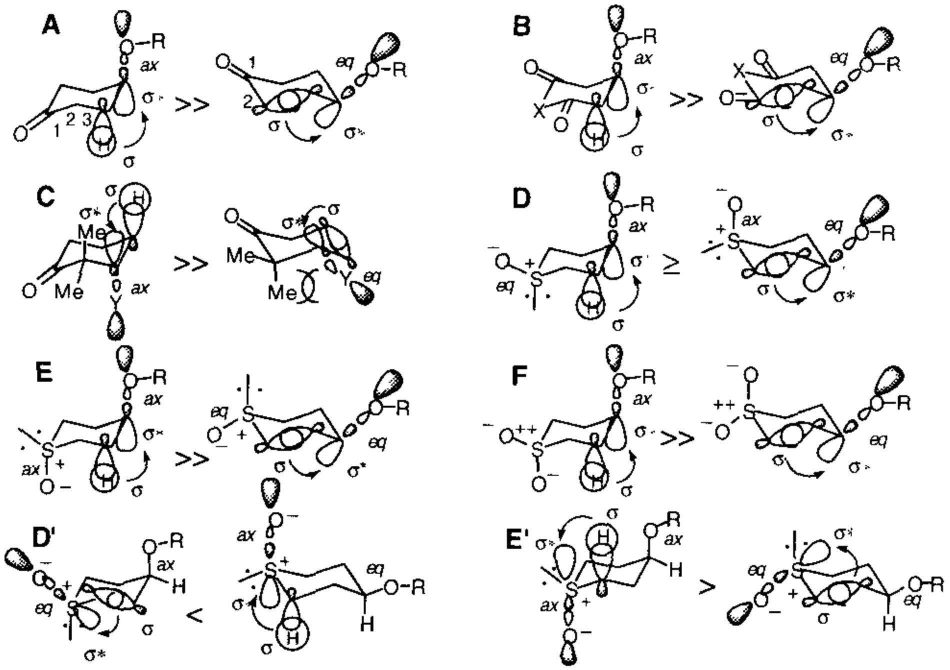
9a-c



10a,c

a = CH$_2$Ph, **b** = Si(Me)$_2$*t*-Bu, **c** = Si(Ph)$_2$*t*-Bu,
d = Si(Me)$_3$, **e** = C(Ph)$_3$, **f** = SO$_2$C$_6$H$_4$*p*-Br,
g = COC$_6$H$_4$*p*-Br

C)→σ*(C-OR) orbital overlap one may similarly stabilize their corresponding RO-*eq* conformers as shown in Figure 1 (**A-F**).[11]



R = CH_2Ph, $Si(Me)_2t$-Bu, $Si(Ph)_2t$-Bu, $Si(Me)_3$, etc. ; X = O, NCH_2Ph; Y = F, Cl, OH, OMe, OAc, etc.

Figure 1. Preferential stabilization of axial or equatorial conformer by σ→σ* orbital overlap.

In general, electron donation from an *ax* C-H bond toward σ* of the *ax* C-OR bond under the antiperiplanar relation may be preferred over that from a C-C bond toward σ* of the *eq* C-OR bond under the similar antiperiplanar relation.[11] However, in the RO-monosubstituted cyclohexanes, each RO-*eq* conformer is predominant over each corresponding RO-*ax* conformer bearing 1,3-diaxial steric repulsion between *ax*-OR and *ax*-protons.[12] In case that the location of the σ(C-C) orbital bond is closer to the electron-withdrawing group(s) (*i.e.*, carbonyl, sulfonyl, dichloromethylene, sulfinyl, sulfur,[13] etc) than that of the σ(C-H) orbital bond, the σ(C-C) orbital must be more stabilized than the σ(C-H) orbital in energy.[14] Thus, the σ(C-H)→σ*(C-OR) interaction should be more strongly effective than the σ(C-C)→σ*(C-OR) one, which assure the *ax* conformer preference of the heteroatom substituent in the six-membered cyclic chair-type compounds(**1-9**) overcoming the 1,3-diaxial steric repulsion. This σ(C-H)→σ*(C-OR) orbital overlap concept seemes to be applied to the dynamic system such as a stereoselective anti-elimination reaction and the Pummerer type reaction in an antiperiplanar or anticoplanar manner as shown in Figuer 2.[15, 16]

A big difference between extreme RO-*ax* conformer preferences (89-98%)[4] in the *trans*-4-RO-thiane 1-oxides (**8a-c**) and 1,1-dioxides (**9a-c**) and significant RO-*ax* conformer preferences (**7a** = 45%, **7b** = 66%, and **7c** = 67%)[4] in the *cis*-4-RO-thiane 1-oxides can be rationalized by considering both the usual strong σ(C-H)→σ*(C-OR) interactions (**D**, **E**, and **F**) and another corresponding weak σ(C-H)→σ*(S-O) ones (**D'** and **E'**).

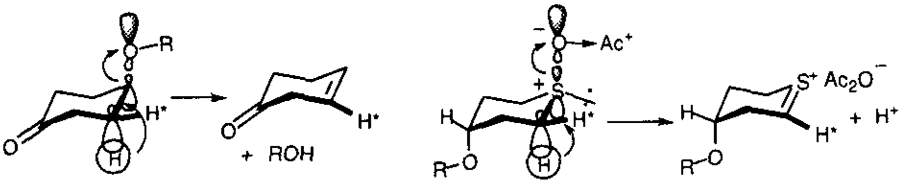
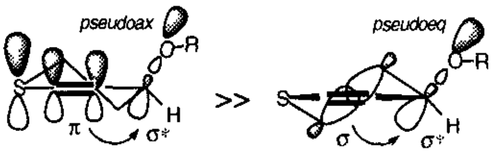


Figure 2. Stereoselective anti-elimination mode.

The order of RO-*ax* conformer preferences [**7c**>**7b**>**7a** and **6c**(53%)>**6b**(31%)>**6a**(24%)>**6d**(11%)] in *cis*-4-RO-thiane 1-oxides and 4-RO-thianes seemed to be proportional to the bulky size of R groups and inversely proportional to the oxygen atom basicity of RO groups.[4] Thus, the relative basicity of the oxygen atom of benzyloxy and siloxy groups[17] was estimated on the basis of up-field shift (Δδ ppm) of ^{119}Sn-peak of Me_2SnCl_2 in the presence of the corresponding cyclohexanol ether.[4] The basicity order, TMS-O>$PhCH_2$-O>TBDMS-O>TBDPS-O determined by our method, was well consistent with the order of the RO-*eq* comformer preferences in the compounds (**6**) and (**7**) as demonstrated by us.[4] Electron withdrawal [n→σ*(Si-C) interaction] from oxygen atom of RO group by silyl groups (but not by TMS group) may cause a lowering of σ*(C-OR) in energy, which would be a little responsible for increasing the RO-*ax* conformation.

The *pseudoax* conformer preferences of 4-RO-dihydrothiine derivatives (**10a,c**), described in the recent paper,[4] are rationalized in terms of more preferential π(C=C)→σ*(C-OR) stabilization[18] than the σ(C-C)→σ*(C-OR) one for the RO *pseudoeq* conformation as depicted in Figure 3.



R = CH_2Ph, $Si(Ph)_2t$-Bu

Figure 3. Pseudoaxial conformer stabilization by π→σ* orbital overlap.

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