

DFT Calculation on the Stereochemistry of the Allylic Oxidation. Selenium Dioxide-Mediated Oxidation of an Exocyclic Olefinic Hydrindane Compound

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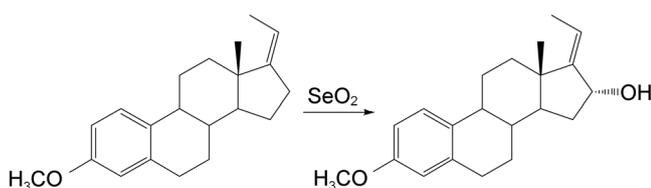
Selenium dioxide-mediated oxidation is among the most important transformations for introducing an hydroxy group into the allylic position in the substituted alkenes in organic^{1,2} and biochemical³ pathways. A unique mode of highly stereoselective interaction of selenium dioxide with olefins, resulting in allylic alcohols, is well exemplified for the preparation of a steroid compound as shown Scheme 1.⁴

Since Sharpless and Lauer proposed a mechanism, generally accepted, for this process in 1972 as resulting from an initial ene reaction followed by a [2,3]-sigmatropic rearrangement,⁵ there have been considerable efforts on particularly clarifying the stereo-selectivity of this reaction. For example, Singleton and Hang clarified a concerted aspect of the ene step in the allylic oxidation of 2-methyl-2-butene with selenium dioxide (**1** → **2** in Scheme 2).⁶ Recently we have elucidated the overall pathways in detail by treating theoretically both an 'ene' reaction and the 2,3-sigmatropic rearrangement involved in this selenium dioxide-mediated oxidation of **1**: the allylic oxidation occurs by complex mechanisms via two competing paths such as *anti*-approach

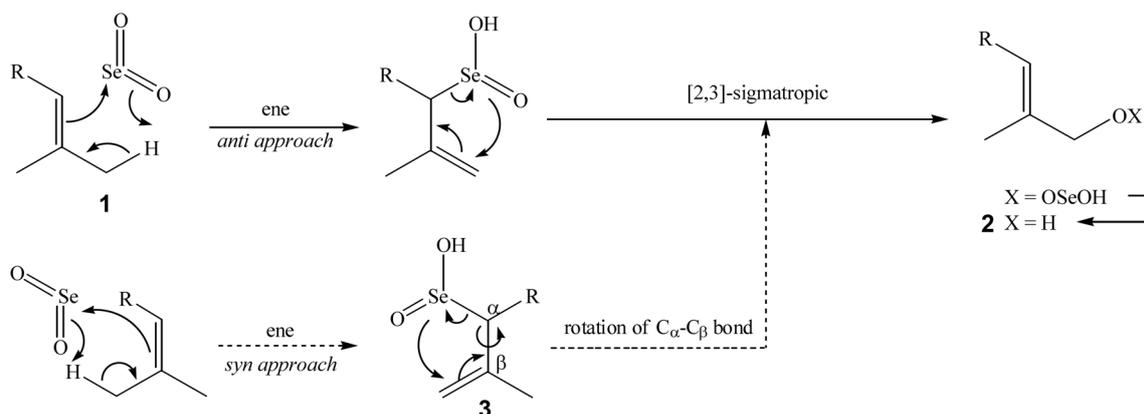
and *syn*-approach in the 'ene' reaction to produce the (E)-allylic alcohol **2**, where it has been first noticed the C_α-C_β bond rotation in 2,3-rearrangement step plays an important part for the stereo-selectivity of the reaction.⁷

Now our attention is brought to understand the consequence of the C_α-C_β bond rotation in the selenic acid intermediate produced from the ene step as to whether it may affects the stereochemical course of the allylic oxidation of a hydrindane compound **5**, where an exocyclic olefinic structure is crafted (Scheme 3). Here, we report the results of ab initio studies of the allylic oxidation of **5**, focusing on analyzing whether the conformational change *via* bond rotation in selenic acid intermediate **6** may give rise to produce **9**.

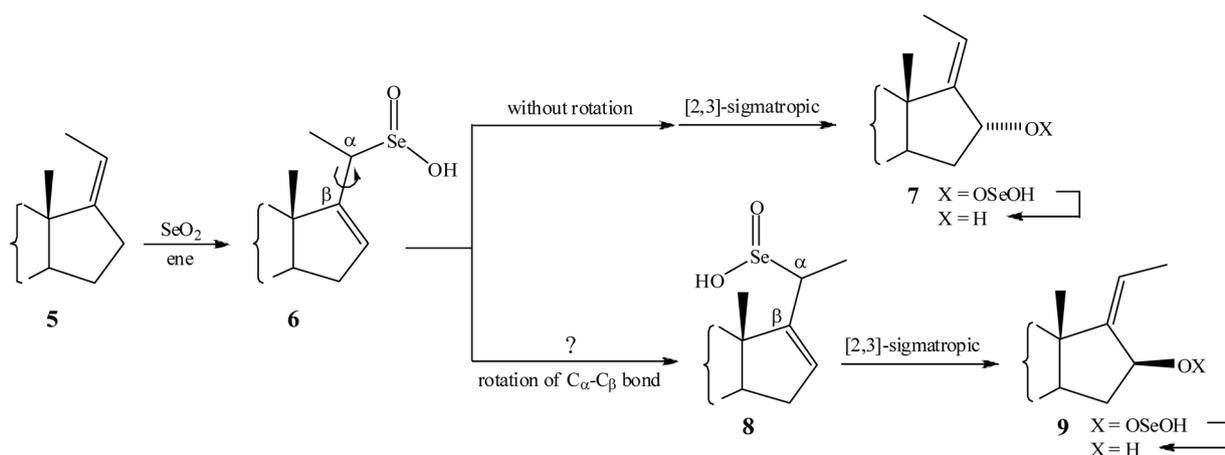
To study the reaction pathway with relative stabilities for possible transition states during the allylic oxidation of model compound **5** (Scheme 4 and Table 1), we have investigated the energy of possible transition states in SeO₂ oxidation of **5** by b3lyp/6-31G* calculation. In ene reaction step, the anti approach of selenium dioxide is energetically favored than the syn one by 1.82 kcal/mol (entry 2 and 3 in Table 1). In the following 1,3-rearrangement step, the O=Se-group approach to the α face of double bond is more favorable than the β face by 2.28 kcal/mol (entry 4 and 5 in Table 1). The compound **7** as a major product should be obtained by the pathway of **ts-1a** and **ts-1a-2α**. The other isomer **9** can be formed through the pathway of **ts-1a** and **ts-1a-2β**, where a C_α-C_β bond rotation of the 'ene' reaction



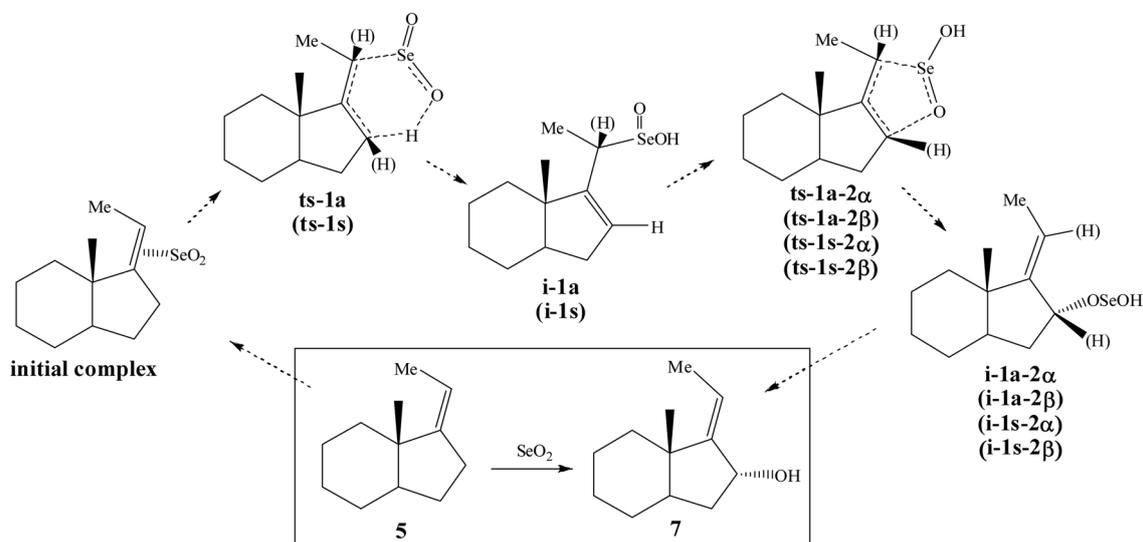
Scheme 1



Scheme 2



Scheme 3



ts (transition state), i (intermediate), a (anti approach of Se to Me group), s (syn approach of Se to Me group), α (α -face attack), β (β -face attack)

Scheme 4

Table 1. Calculation Results for SeO_2 oxidation of 5 using b3lyp/6-31G* methods

entry		E_{total} (hartree)	ΔE (kcal/mol)	
1	initial complex	-3019.075	0.000	
2	ts-1a	-3019.058192	10.751	
3	ts-1s	-3019.055287	12.573	
4	ts-1a-2 α	-3019.065456	6.1923	7
5	ts-1a-2 β	-3019.061821	8.4735	9
6	ts-1s-2 β	-3019.067317	5.0249	
7	ts-1s-2 α	-3019.065866	5.9351	

E_{tot} reactants (hartree): -2549.738633 for SeO_2 ; -469.31309 for 5; -3019.083792 for i-1a; -3019.083519 for i-1s. -3019.093728 for i-1a-2 α ; -3019.101031 for i-1a-2 β ; -3019.094984 for i-1s-2 α ; -3019.100764 for i-1s-2 β .

intermediate should be involved. The overall profiles concerning the above stereochemical issues including structures of significant transition states are depicted in Figure 1 and 2. Thus, the $C_{\alpha}-C_{\beta}$ bond rotation necessary for the formation of

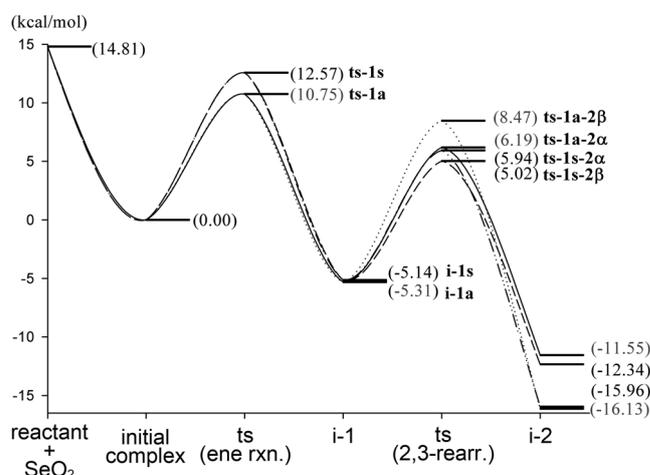


Figure 1. Reaction profile for SeO_2 oxidation of 5.

ts-1a-2 β , leading to 9 should be hampered severely due to a steric effect by the presence of the Me group on the fused

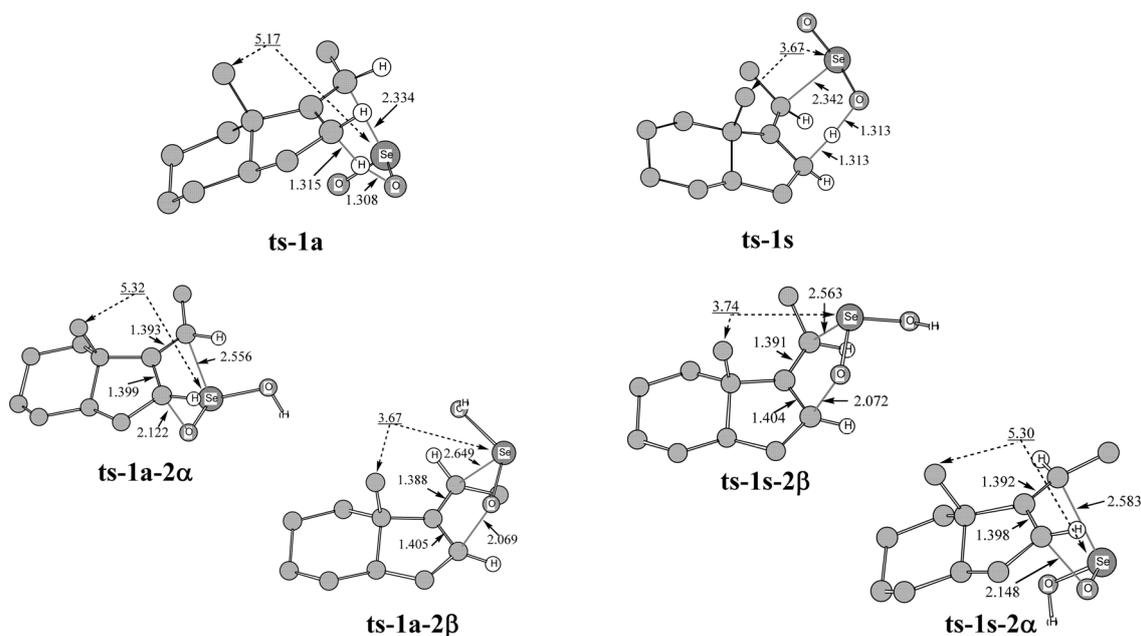


Figure 2. Structures of Transition States in SeO_2 oxidation of **5**.

ring.

Assuming the compound ratio, A/B depends on the relative energies of the transition states, E_A^\ddagger and E_B^\ddagger , then $A/B = \exp[(E_B^\ddagger - E_A^\ddagger)/RT]$. Based on the calculation (Table 1), the ratio of two isomeric products **7** and **9** has been predicted by the relative energies of TSs in this reaction. The distribution ratio of **ts-1a/ts-1s** and **ts-1a-2 α /ts-1a-2 β** have been predicted by 95.6/4.4 and 97.9/2.1 at 298.15 K, respectively. The compound **7** should be obtained from **ts-1a-2 α** via **ts-1a**, and its yield is predicted with 93.6% by 0.956×0.979 . The yield of **9** from **ts-1a-2 β** via **ts-1a** is calculated by 2.0% in a similar method. So it may be expected the compound **7** is exclusively obtained in the allylic oxidation of **5**. The above results well agree with the experimental observation, producing a single compound in the allylic hydroxylation of a steroid compound using selenium dioxide (Scheme 1).⁴ What lies behind the tendency of this process to show such a high stereo-selectivity? Appreciable relationship exists between the geometric distances and calculated energies of significant transition states. The methyl group at the fused ring junction seems to play an important role in controlling the global geometry including the selenium moiety during the reaction. Energies of transition states for the allylic hydroxylation decrease as the geometric distances between the angular methyl group on fused ring and selenium atom increase. The observed $\text{C}\cdots\text{Se}$ distances in the optimized TS structure are 5.17 Å for **ts-1a** and 3.67 Å for **ts-1s**, and **ts-1a** is predicted lower energy than **ts-1s** by 1.82 kcal/mol. In a similar pattern, **ts-1a-2 α** is predicted lower energy than **ts-1a-2 β** by 2.28 kcal/mol, where the $\text{C}\cdots\text{Se}$ distances are shown by 5.32 Å for **ts-1a-2 β** , 3.74 Å for **ts-1a-2 α** (shown in Figure 1 and 2).

In conclusion, the present work has rationalized the stereochemical issues associated with ene step and 2,3-sigmatropic rearrangement in SeO_2 oxidation of **5**. In the

allylic oxidation of **5**, the $\text{C}_\alpha\text{-C}_\beta$ bond rotation in 2,3-rearrangement step does not come into play and the overall reaction demonstrates an extremely high stereo-selectivity.

Computational Methods

All ab initio calculations have been carried out using the Gaussian 98 program.⁸ The structures of the intermediates and transition states were then fully optimized using the density functional theory B3LYP/6-31G*.⁹ Harmonic vibrational frequencies calculated at the same level were used for the characterization of stationary points. TS optimizations with the keyword 'opt = ts, calcfc' are carried out. The compound ratio A/B was predicted from the relative energies of the transition states, E_A^\ddagger and E_B^\ddagger , by $A/B = \exp[(E_B^\ddagger - E_A^\ddagger)/RT]$ (hence we can to make a comparison with experimental data).¹⁰

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