Rotation of the Allylselenic Intermediate in Moderating the Stereochemical Course of the Selenium Dioxide-Mediated Allylic Oxidation[†]

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Allylic oxidation adjacent to C = C bonds to produce allylic alcohols remains a reaction of considerable interest in organic chemistry and various methods for this purpose have been developed.[1,2] Among those the selenium dioxide-mediated oxidation is regarded as the most reliable and predictable method to introduce a hydroxy group into the allylic position for substituted alkenes regio- and stereo-selectively. The key mechanistic basis to induce a high regio- and stereo-selectivity in the allylic oxidation is the concerted and pericyclic process through two consecutive steps (an electrophilic 'ene' reaction followed by the [2,3]-sigmatropic rearrangement) (Scheme 1) as in a theoretical mechanism proposed by Sharpless[3] and a recent account concerning theoretical and experimental data.[4]

We reported the overall stereochemical pathways by elucidating both an 'ene' reaction and the [2,3]-sigmatropic rearrangement of the selenium dioxide-mediated oxidation of 2-methyl-2-butene.[5] Those efforts seem successful to explain regio- and stereo-selective aspects experimentally observed in the selenium dioxide-mediated allylic oxidation of several trisubstituted olefin compounds, particularly those where the concerted nature can be maintained during the whole process.

However, modes of selectivity in the allylic oxidation of substituted olefin compounds are found to depend strongly on the geometric features of the alkene substrates. In the case of the allylic oxidation of more general cyclic systems such as 1-*tert*-butyl-4-alkylidene cyclohexanes, where the system can avoid the concerted mode throughout two steps, an unexpected isomeric compound, cis-5-*tert*-butyl-2-ethylidenecyclohexanol was obtained. There should be involved a rotation of the allylselenic intermediate between two pericyclic steps.[6] The purpose of this note is to provide a clearer explanation for the mechanism of the selenium dioxide-mediated oxidation in the substituted alkenes how the rotation of the allylselenic
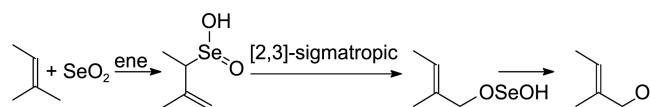
intermediate affects the stereochemical mechanism.

The Rotation of the Allylselenic Intermediate in the Allylic Oxidation of 1-*tert*-Butyl-4-alkylidene Cyclohexanes. In the allylic oxidation of 1-*tert*-butyl-4-alkylidene cyclohexanes, we observed a different stereo-selectivity mode compared to 2-methyl-2-butene.[6] Two important approaches of selenium dioxide toward the olefin function in the pericyclic 'ene' step of the allylic oxidation of 1-*tert*-butyl-4-ethylidene cyclohexane (1) are *trans-anti* approach (A) and *trans-syn* (B) approach (Figure 1). Thus, theoretical calculations show significant products obtained from the allylic oxidation of 1-*tert*-butyl-4-ethylidene cyclohexane should be ones *via* two approaches (A and B). The relative transition state energy of as shown in Figure 1, the *trans-anti* approach (A) is predicted moderately preferred than *trans-syn* approach (B), The TS energy of A has been calculated to be more stable than B by 0.633 and 0.577 kcal/mol in HF/3-21G and B3LYP/6-31G*, respectively.

According to the theoretical study of the reaction using HF/3-21G method,[6] the trans-isomer 2a is predicted as a major product (73%). The trans-isomer can be provided from the initial *trans-anti* approach (A) in the 'ene' step and *in situ* [2,3]-rearrangement. The allylselenic intermediate generated after *trans-anti* approach proceeds with a concerted mode, i.e., without C_3-C_4 bond rotation into a [2,3]-sigmatropic rearrangement. In this case, the position where the *'anti'* hydrogen (H_{anti} in Scheme 2) originally located is substituted by the OSeOH group after two concerted steps.

The dominant option after *trans-syn* 'ene' approach is to

Scheme 1

(*d1*=2.305/*d2*=1.422/*d3*=1.422/
d4=1.305/*d5*=1.334/*d6*=1.707)

(*d1*=2.300/*d2*=1.422/*d3*=1.421/
d4=1.313/*d5*=1.340/*d6*=1.709)

E_{rel} (kcal/mol)	0.000	HF/3-21G	0.636
	0.000	B3LYP/6-31G*	0.577

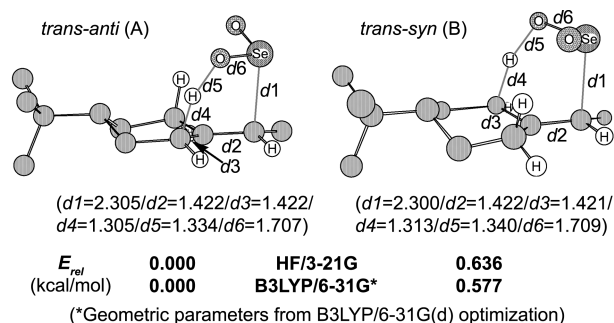(*Geometric parameters from B3LYP/6-31G(d) optimization)

Figure 1. Optimized structures of transition states of 'ene' reaction for *trans-anti* (A) approach and *trans-syn* (B) approach. (geometric parameters are obtained from B3LYP/6-31G* optimization).

Scheme 2
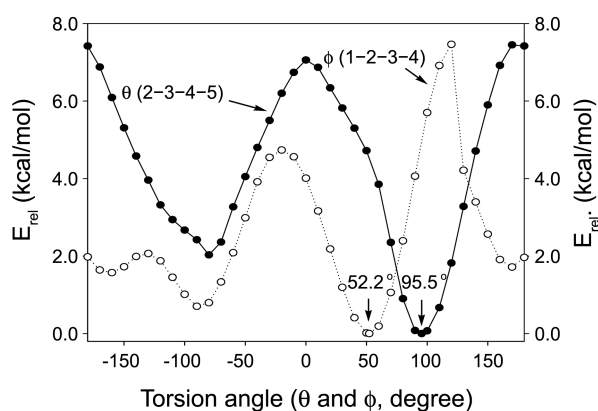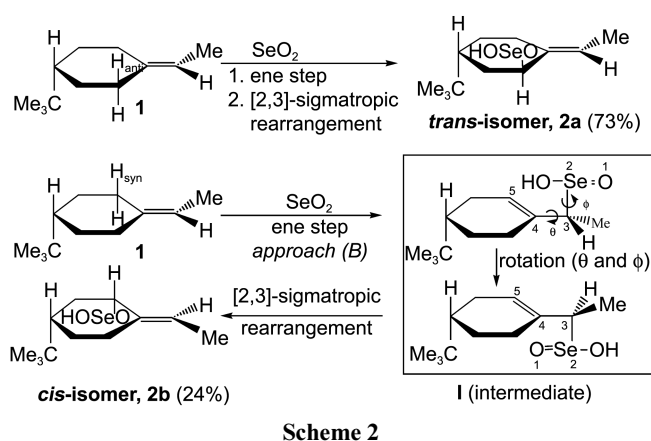
Figure 3. Torsion energies for **I** with θ and ϕ.

Table 1. The calculation results for torsion energy for torsion angle[a]

torsion angle[b]	θ (< 2-3-4-5)		ϕ (< 1-2-3-4)	
	E_{tot} (hatree)[c]	E_{rel} (kcal/mol)[d]	E_{tot}(hatree)[c]	E_{rel} (kcal/mol)[d]
−180	−3020.289958	7.42	−3020.298632	1.98
−170	−3020.290827	6.88	−3020.299171	1.64
−160	−3020.292074	6.09	−3020.299279	1.57
−150	−3020.293324	5.31	−3020.299037	1.72
−140	−3020.294488	4.58	−3020.298615	1.99
−130	−3020.295471	3.96	−3020.298493	2.07
−120	−3020.296494	3.32	−3020.298793	1.88
−110	−3020.297099	2.94	−3020.29947	1.45
−100	−3020.297526	2.67	−3020.300172	1.01
−90	−3020.297927	2.42	−3020.300666	0.7
−80	−3020.298552	2.03	−3020.300514	0.8
−70	−3020.298030	2.36	−3020.299662	1.33
−60	−3020.296567	3.27	−3020.298458	2.09
−50	−3020.295330	4.05	−3020.297023	2.99
−40	−3020.294138	4.80	−3020.295546	3.91
−30	−3020.293021	5.50	−3020.294539	4.55
−20	−3020.291910	6.20	−3020.294236	4.74
−10	−3020.291046	6.74	−3020.294514	4.56
0	−3020.290537	7.06	−3020.295395	4.01
10	−3020.290830	6.87	−3020.296743	3.16
20	−3020.291673	6.34	−3020.298306	2.18
30	−3020.292508	5.82	−3020.299882	1.19
40	−3020.293336	5.30	−3020.301135	0.41
50	−3020.294260	4.72	−3020.301761	0.01
60	−3020.295647	3.85	−3020.30148	0.19
70	−3020.298033	2.35	−3020.300098	1.06
80	−3020.300348	0.90	−3020.297969	2.39
90	−3020.301660	0.08	−3020.295312	4.06
100	−3020.301666	0.07	−3020.292698	5.7
110	−3020.300713	0.67	−3020.290761	6.92
120	−3020.298876	1.82	−3020.289891	7.46
130	−3020.296563	3.28	−3020.29507	4.21
140	−3020.294272	4.71	−3020.296375	3.39
150	−3020.292380	5.90	−3020.297698	2.56
160	−3020.290753	6.92	−3020.298744	1.91
170	−3020.289907	7.45	−3020.299048	1.72
180	−3020.289958	7.42	−3020.298654	1.96

[a]It has been optimized relaxed potential energies surface at torsion angle and of INT from −180° to 180° with increment by 10°.
[b]Torsion angle (degree).
[c]Total energy value (hartree) obtained by b3lyp/6-31g* method.

choose the energetically a favorable path involving a C_3-C_4 bond rotation. Then the system cannot maintain the concerted nature anymore in overall. Thus, the '*syn*' hydrogen (depicted as H_{syn}) abstracted in its first step will not be substituted by the OSeOH group (Scheme 2). The overall streochemical outcome results in a *cis*-isomer **2b**.

To rationalize the stereochemical course shown in Scheme 2, we have compared relative energies between the rotational barriers and transition states of [2,3]-sigmatropic rearrangement of the allylselenic intermediate **I**, which is obtained from '*trans-syn*' approach in 'ene' step. Table 1 summarized the optimized relaxed potential energies of the intermediate **I** at torsion angles (ϕ, θ) from −180° to +180° with increment by 10° using B3LYP/6-31G(d) method. Figure 3 shows the energy profile of the states between the 'ene' step and the [2,3]-sigmatropic rearrangement step versus two torsion angles (ϕ, θ), where ϕ and θ are for torsion angle C_1-C_2-C_3-C_4 and C_2-C_3-C_4-C_5, respectively. We noticed the shape of the curve in the Figure is not symmetrical as expected for the diastereoisomeric states corresponding to two minima, where Se_2-C_3 and C_4-C_5 bonds are orthogonal.

Figure 4 shows geometric structure and relative energies for the optimized intermediate **I**, and two transition states (**TS-A** & **TS-B**) for [2,3]-sigmatropic rearrangement. For the optimized intermediate **I**, the minimum energy structure shows at θ = 95.5° and ϕ = 52.2°, and the relative energy is

defined by 0.00 kcal/mol. The relative energies of transition states **TS-A** and **TS-B** show 15.6 and 14.4 kcal/mol, respectively. Those indicate the activation energies for [2,3]-sigmatropic rearrangement.

To obtain the *cis*-isomer from the intermediate **I**, it should be noted the [2,3]-rearrangement step undergo *via* transition state **TS-B**. Based on the above results, the minimum required rotational energy for arrangement to possible [2,3]-rearrangement seems not to be over 8 kcal/mol (see Figure 3 & Table 1). The activation energy of the [2,3]-sigmatropic
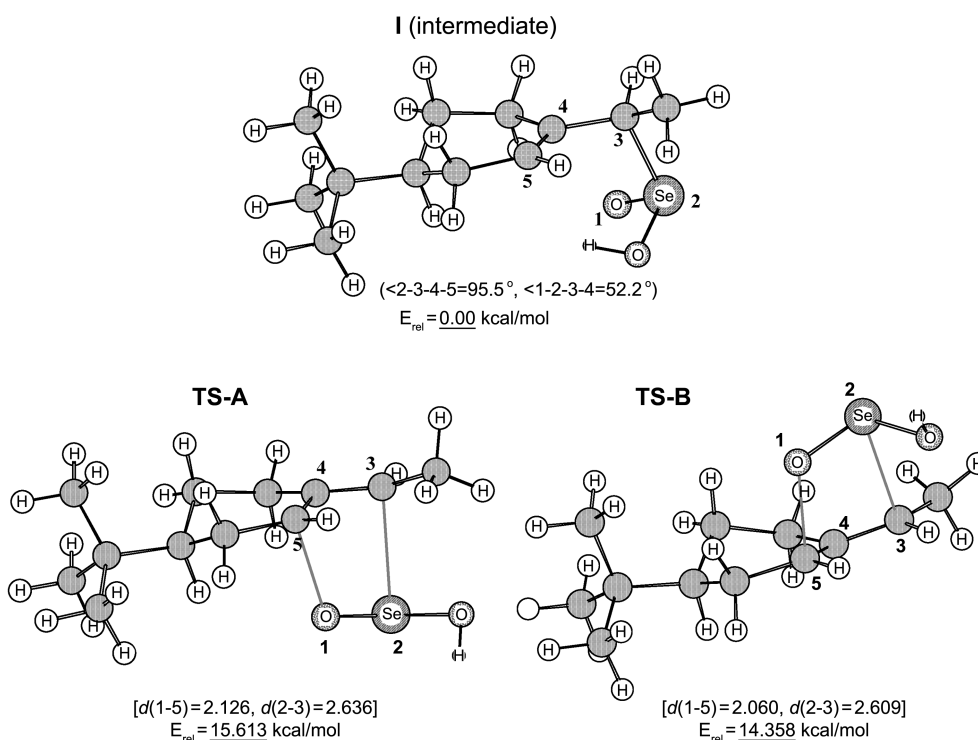
I (intermediate)

(<2-3-4-5=95.5°, <1-2-3-4=52.2°)
E_{rel} = 0.00 kcal/mol

TS-A

[d(1-5)=2.126, d(2-3)=2.636]
E_{rel} = 15.613 kcal/mol

TS-B

[d(1-5)=2.060, d(2-3)=2.609]
E_{rel} = 14.358 kcal/mol

Figure 4. Optimized structure for intermediate **I**, **TS-A** and **TS-B** of [2,3]-rearrangement.

rearrangement is predicted more than 14 kcal/mol, which is larger than those values for the rotation (see Figure 4). The system for [2,3]-sigmatropic rearrangement locates energetically quite strained, so other possible route can be allowed to other conformation *via* rotation. Regarding the relative energy of two transition states (**TS-A** & **TS-B**) from the intermediate **I**, it predicts moderately preferential to form the cis-isomer *via* **TS-B**.

Two Examples where the Stereochemical Outcome seems not to be Affected by the Rotation of the Allylselenic Intermediate. The selenium dioxide-mediated allylic oxidation of acyclic olefinic systems, for example, 2-alkylsubstituted-2-butenes (**4**) may be one example of this category. As shown in Scheme 3, off-mode of the C_3-C_4 bond rotation (*anti*-approach) and on-mode of the C_3-C_4 bond rotation (*syn*-approach) during the allylic oxidation of **4** give the same product, (*E*)-allylic alcohol **5**.
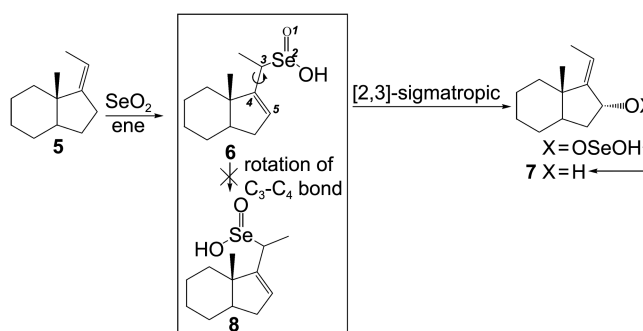
The allylic hydroxylation of the stereochemically congested olefinic system with selenium dioxide is an example where the effect of the rotation may be excluded. A special example such as a hydrindane olefin compound is considered as shown in Scheme 4.[7] The compound **7** as a major product is obtained *via* two concerted reactions, i.e., the 'ene' step and off-rotation mode rearrangement. A minor isomer can be formed from the intermediate **8** produced by the bond rotation of the intermediate **6**. The predicted ratio of two products is calculated to be 98:2 at 298.15 K. Actually, the C_3-C_4 bond rotation necessary for the formation of **8**, leading to the minor product is hampered severely due to a steric effect by the presence of the -Me group on the fused ring.

Allylic oxidation adjacent to C = C bonds to produce allylic

alcohols is among the most important processes in many biochemical systems, e.g. the oxidative process catalyzed by cytochrome P450 enzymes with high regio- and stereoselectivity.[11] It is intriguing to elucidate how biochemical systems can manage to interact very selectively with the olefin moiety in case of substrates which have no intrinsic stereospecificity in the molecule of 1-*tert*-butyl-4-alkylidene cyclohexanes discussed earlier. Such biochemical systems may have options with minimum rotation of the C_3-C_4 bond
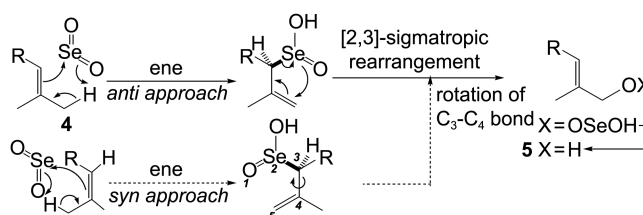
Scheme 3

Scheme 4

of the allylic intermediates to achieve the goal as the allylic oxidation.

In summary, we have studied the stereochemical course of the selenium dioxide-mediated oxidation for several substituted alkenes by analyzing the rotation of the C_3-C_4 bond of the allylselenic intermediate. We have shown how the C_3-C_4 bond rotation of the allylselenic intermediate prior to the [2,3]-sigmatropic rearrangement moderates the stereochemical course of the selenium-dioxide mediated allylic oxidation of substituted alkenes by a combinational analysis of calculation and experimental data. Thus, we provide a clear and rational explanation for the stereochemical mechanism of the selenium dioxide-mediated oxidation in the substituted alkenes.

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. The number of imaginary frequencies (0 or 1) indicates whether a minimum or a transition state has been located. In Starting with approximate TS structures of an 'ene' and a '[2,3]-rearrangement' step, by fixing corresponding bond distances for forming and breaking on that TS pathway, 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 make a comparison with experimental data).[10]

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