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Theoretical Investigations on the Stereoselective Selenenylation Reaction of Alkenes

Martin Spichty, Gianfranco Fragale, and Thomas Wirth*

Contribution from the Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

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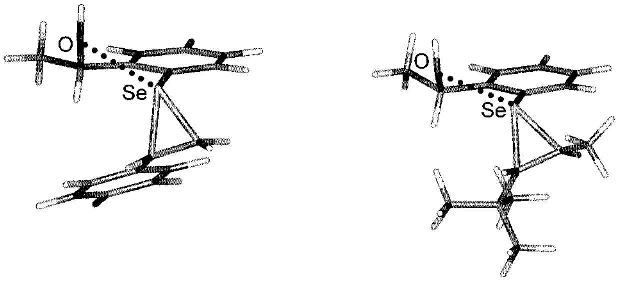
Abstract: Ab initio calculations have been performed to study the stereoselective selenenylation reaction of alkenes with chiral selenium electrophiles. The interaction of the heteroatom of the chiral side chain with the selenium atom in the reagent has been investigated by a detailed conformational analysis. Calculations of the seleniranium intermediates with different substituted alkenes have been performed as well. The reversal of selectivity changing from aromatic to aliphatic alkenes as substrates in the selenenylation reaction has already been proven by experiment and is now supported by the calculations described herein.

Introduction

Electrophilic selenenylation reactions of alkenes have been applied successfully in functionalizations of inactivated carbon−carbon double bonds.[1] This reaction and its mechanism have been studied since the 1970s and the reaction is known to occur by a two-step mechanism (see Scheme 1).[2] In the first step, seleniranium ions **1** are generated by the addition of an organoselenium electrophile to an alkene. These intermediates are then attacked by a nucleophile from the *anti* side leading to addition products of type **2**. Selenides **2** can undergo various subsequent reactions and are therefore versatile building blocks in organic synthesis.

Recently, various research groups have employed different chiral selenium electrophiles in this reaction.[1,3] Addition products **2** have been obtained in very high diastereomeric ratios. We have focused our interest mainly on aryl selenium electrophiles **3** with a chiral moiety in the *ortho* position to the selenium atom as shown in Figure 1. The coordination of the heteroatom of the chiral moiety with the selenium atom causes conformational rigidity in the electrophile, which seems to be important for an efficient transfer of chiral information in the selenenylation reaction.

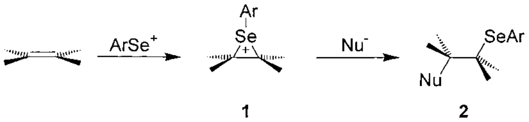
Herein we are discussing selenium electrophiles **4** and **5** (Scheme 2). Both electrophiles are efficient reagents in asymmetric alkoxyselenenylation and selenocyclization reactions, electrophile **5** leading to higher selectivities than electrophile **4**.[4] The stereoselectivity is also strongly dependent on the substitution pattern of the alkene. For example, with *(E)*-3-pentenol the reaction is not stereoselective, but with styrene derivatives diastereomeric ratios up to 50:1 have been observed. Because the role of the coordination between the oxygen atom of the chiral side chain and the selenium with respect to the selectivity in these reactions still remains unclear, ab initio calculations for the reactants and intermediates of the selenenylation reaction have been performed. The strong influence of the substitution pattern of the alkene on the stereoselectivity should become more clear as well.



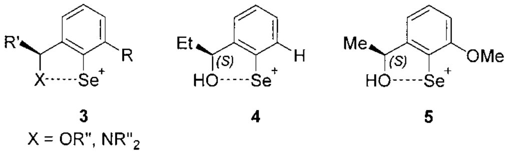
6a (R_1 = Ph, R_2 = H) **6a** (R_1 = *t*-Bu, R_2 = Me)

Figure 1. MP2/6-31G*-optimized structures of seleniranium intermediates **6a** of the selenenylation reaction of styrene (left) and 4,4-dimethyl-2-pentene (right) with electrophile **4**.

Scheme 1



Scheme 2



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* To whom correspondence should be addressed. New address: Cardiff University, Department of Chemistry, Cardiff CF10 3TB, United Kingdom. Phone and FAX: 0044-29-2087-6968. E-mail: wirtht@cf.ac.uk.

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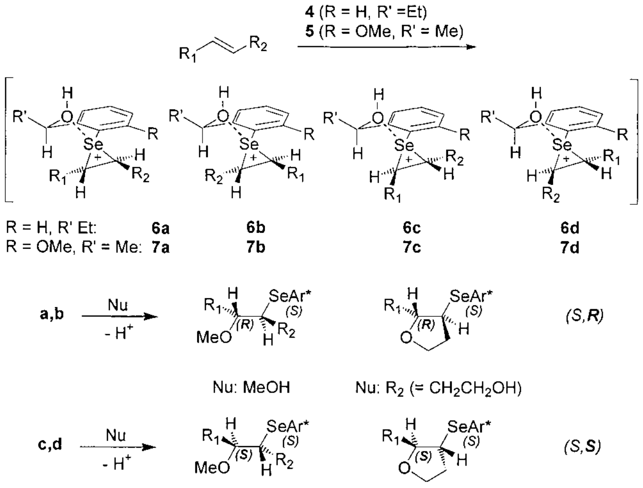
Table 1. Comparison of the Calculated Energy Difference *E*(Si) − *E*(Re) of the Intermediates (in kcal/mol) with the Diastereomeric Ratio *(S,**R**):(S,**S**)* of the Products for the Selenenylation Reactions of Electrophiles **4** and **5**

		calculation			experiment[a]		
entry	electrophile	R_1	R_2	*E*(Si) − *E*(Re)[b]	R_1	R_2	*(S,**R**):(S,**S**)*
1	**4**	Ph	H	+2.8;[c] +2.5 (**6d** − **6a**)	Ph	H	16:1
2	**4**	Ph	Me	+1.9; +1.6 (**6d** − **6a**)	Ph	Me	9:1
3	**4**	Me	Me	−0.5; −0.2 (**6c** − **6a**)	Et	CH_2CH_2OH	1:1
4	**4**	*t*-Bu	Me	−1.2; −0.7 (**6c** − **6b**)	*t*-Bu	CH_2CH_2OH	1:2.5[d]
5	**5**	Ph	H	+1.4; +1.9 (**7d** − **7a**)	Ph	H	50:1
6	**5**	Ph	Me	+0.8; +1.4 (**7d** − **7a**)	Ph	Me	12:1
7	**5**	Me	Me	−1.4; −0.7 (**7c** − **7a**)	Et	CH_2CH_2OH	1.5:1 or 1:1.5[e]

[a] Reference 4b. [b] A positive value for *E*(Si) − *E*(Re) indicates a higher stability of the Re intermediate. MP2/6-31G*//MP2/3-21G*; MP2/6-31G*//MP2/6-31G*. [c] Reference 8. [d] Reference 4a. [e] The absolute configuration could not be determined yet.

Scheme 3

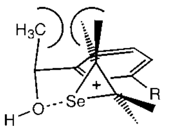


Methods

All calculations were performed on the second-order Møller−Plesset pertubation theory (MP2)[5] level. The geometry optimizations were carried out with the basis sets 3-21G* and 6-31G*. Relative energies were calculated with the basis set 6-31G*. To save computational time, the ethyl group in the electrophile **4** and in the intermediates **6a**−**d** was replaced by a methyl group. For the calculation of the rotation profiles, the dihedral angle γ was changed stepwise by 15° from 0° to 360°. At each step, the geometry of the electrophile was optimized (except dihedral angle γ which was kept constrained). All calculations were carried out with the program package Gaussian98[6] on HP N4000.

The Influence of the Alkene Substitution on the Stereoselectivity

The selenenylation of unsymmetrical *(E)*-substituted alkenes with electrophiles **4** and **5** leads to diastereomeric seleniranium intermediates **6a**−**d** and **7a**−**d**, respectively (see Scheme 3). The stabilizing interaction between the oxygen lone pair and the antibonding orbitals of the Se−alkene bonds forces these intermediates into a T-shaped arrangement of the O−Se−alkene bond system with respect to the Se−C_{aryl} bond.[7] This favorable T-shaped arrangement can also be achieved in a different manner as shown in intermediate **8** . Because of the high steric hindrance in intermediate **8** we will focus only on the seleniranium intermediates depicted in Scheme 3.



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A recent theoretical study has suggested that the stereoselective outcome of selenenylation reactions can be deduced from the steric and from the $\pi-\pi$ interactions of the alkene substituents with the electrophile part in the intermediates.[8] We assume that the diastereomeric ratio of the products reflects the stability of the preceding seleniranium intermediates. Ab initio calculations[9] for the reaction of electrophile **4** with styrene (R_1 = Ph, R_2 = H) support this assumption: intermediate **6a** which yields after nucleophilic attack the major product is 2.8 kcal/mol more stable than intermediate **6c** leading to the minor diastereomer. The other two intermediates **6b** and **6d** are both higher in energy. To probe the influence of the substitution pattern of the alkene, we calculated the relative energies of the seleniranium ions **6** and **7** for several different substituted alkenes as shown in Table 1.

The computational methods, MP2/6-31G*//MP2/3-21G* and MP2/6-31G*//MP2/6-31G*, are comparable. With both electrophiles, the seleniranium ions resulting from a Re attack to aromatic alkenes are lower in energy than the seleniranium ions resulting from a Si attack. With aliphatic alkenes, however, the most stable seleniranium ions are formed by a Si attack. This means that the change from an aromatic to an aliphatic alkene should result in a reversal of selectivity. The experimental proof for that behavior was the detailed investigation of the selenocyclization of various homoallylic alcohols and the determination of the absolute configuration of the newly generated stereocenters.[4a] A comparison of the computational results with the experimental observations is shown in Table 1. The energy difference between the most stable seleniranium ions of the Si and the Re attack, *E*(Si) − *E*(Re), is compared with the diastereomeric ratio (*S*,***R***):(*S*,***S***) of the products. Focusing on

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electrophile **4** (Table 1, entries 1−4), a remarkable correlation between the calculated energy differences and the experimentally observed diastereomeric ratios can be noted. For (*E*)-*β*-methylstyrene (R_1 = Ph, R_2 = Me; entry 2) the energy difference is considerably less positive than that for styrene (R_1 = Ph, R_2 = H; entry 1). This would argue for a lower (*S*,***R***)-selectivity for (*E*)-*β*-methylstyrene in comparison to styrene which in fact is observed experimentally. For (*E*)-2-butene (R_1 = Me, R_2 = Me; entry 3), a model system for (*E*)-3-hexenol (R_1 = Et, R_2 = CH_2CH_2OH), the energy differences decreases even more becoming slightly negative. Indeed, the experiment shows that with (*E*)-3-pentenol the diastereomeric ratio drops to 1:1. For (*E*)-4,4-dimethyl-2-pentene (R_1 = *t*-Bu, R_2 = Me; entry 4) the energy difference *E*(Si) − *E*(Re) now becomes largely negative which means that the intermediate of the Si attack is much more favorable. This is fully in agreement with the experimentally observed, inverted diastereomeric ratio for (*E*)-5,5-dimethyl-3-hexenol (R_1 = *t*-Bu, R_2 = CH_2CH_2OH). The question arises why aromatic and aliphatic alkenes behave differently. The MP2/6-31G*-optimized diastereomers **6a** resulting from a Re attack of **4** to the aromatic alkene styrene (R_1 = Ph, R_2 = H) and to the aliphatic alkene (*E*)-4,4-dimethyl-2-pentene (R_1 = *t*-Bu, R_2 = Me) are shown in Figure 1. With styrene this diastereomer is the most stable one, whereas with (*E*)-4,4-dimethyl-2-pentene **6a** is the most instable diastereomer. In the case of styrene, diastereomer **6a** is stabilized by a *π*−*π* interaction between the phenyl ring of the alkene and the aromatic moiety of the electrophile. The replacement of the phenyl group at this specific position by an alkyl group causes strong steric interactions between the alkyl group and the electrophile part. It is therefore apparent that this position is preferentially occupied by a phenyl group in the case of the aromatic alkenes (Re attack intermediate **6a**, R_1 = Ph, R_2 = H/Me) or by a hydrogen atom in the case of the aliphatic alkenes (Si attack intermediate **6c**, R_1 = *t*-Bu/Me, R_2 = Me).

For electrophile **5** (Table 1, entries 5−7) the same tendencies as for **4** can be pointed out. But the values of the energy difference *E*(Si) − *E*(Re) for the aromatic alkenes are lower with electrophile **5** than with **4**, although **5** yields higher stereoselectivities in the experiments. This cannot be explained by the calculations above, the comparison of the energy differences for **4** and **5** would rather suggest an opposite result (better selectivities with **4** than with **5**). However, for the aliphatic alkene (*E*)-2-butene the calculated energy difference with **5** is larger than that with **4**. Indeed, electrophile **5** yields the higher stereoselectivity with the aliphatic alkene (*E*)-3-hexenol. But the energy difference of −1.4 (MP2/6-31G*//MP2/3-21G*) or −0.7 kcal/mol (MP2/6-31G*//MP2/6-31G*) is far too large for the quite moderate diastereomeric ratio of 1:1.5, whereas the absolute configuration of the products could not be determined yet.

The Role of the Side-Chain Coordination

The higher stereoselectivities obtained with electrophile **5** in comparison to **4** might result from a stronger coordination of the side-chain oxygen atom to the selenium and, accordingly, a better transfer of chiral information in the selenenylation reaction is observed. To verify this assumption, the strength of the oxygen−selenium interaction in electrophiles **4** and **5** was investigated. Therefore, we calculated the energy profile for the variation of dihedral angle *γ* (1,2,3,4) from 0° to 360° (see Figure 2). The calculations were performed with the method MP2/6-31G*//MP2/3-21G* which lead to matching results with the method MP2/6-31G*//MP2/6-31G* in the case of the seleniranium intermediates.

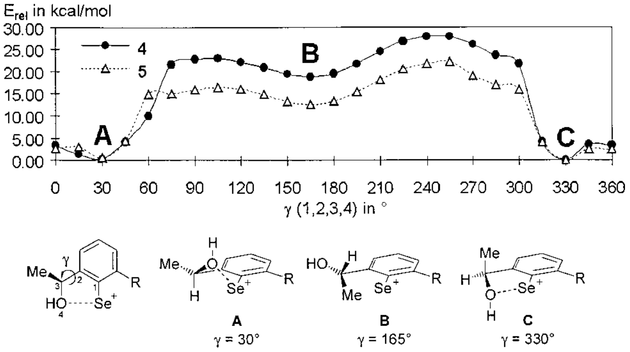

Figure 2. Rotation profiles of electrophiles **4** and **5** calculated on the MP2/6-31G*//MP2/3-21G* level.

The rotation profiles of **4** and **5** look very similar. In both profiles energy minima are found at 30° (**A**), 165° (**B**), and 330° (**C**). The minima **A** and **C** with oxygen−selenium coordination show a Se−O distance of 1.93 (**4**) and 1.97 Å (**5**), respectively. At the minimum **B** the selenium and oxygen atom are separated more than 4.5 Å from each other (**4** and **5**). The dissociation energy for electrophile **5** is smaller than that for **4**. The energy difference between the two minima **A** and **B** is 12.5 kcal/mol for **5** and 18.7 kcal/mol for **4**. The +M effect of the *o*-methoxy group is obviously overriding the −I effect in **5**. Accordingly, the strength of the coordination does not correlate with the stereoselectivities obtained with electrophiles **4** and **5**.

Conclusion

We have performed detailed ab initio calculations for the stereoselective selenenylation reaction with different electrophiles and alkenes. From the computational results we can conclude that the diastereomeric ratio of the products reflects the stability of the intermediates of the selenenylation reaction. The conformational analysis of the chiral side chain revealed that the coordination of the oxygen atom to the selenium is necessary to obtain high stereoselectivities. The higher experimental diastereomeric ratios with electrophile **5** in comparison to **4** can be explained neither by the stability of the seleniranium intermediates nor with the strength of the side chain coordination and require further investigations.

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Supporting Information Available: Computational details and Cartesian coordinates for **6a−d** and **7a−d** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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