Regioselective Synthesis of Allylic Alcohols Using the Mislow–Evans Rearrangement: A Theoretical Rationalization

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During investigation of the [2,3]-sigmatropic rearrangement of allylic sulfoxides to sulfenates,[1] Mislow *et al.* found that the S to C oxo-transfer occurred stereoselectively.[1a] It was also observed that substituents on the allylic moiety exerted regioselective control over the resultant olefin geometry.[2] Thus, both the sulfoxide stereochemistry and allylic group substituents control the relative energetics of competitive transition structures and hence the ratios of the final products.[3]

The synthetic potential of the allylic sulfoxide rearrangement was recognized by Evans *et al.*[4] as an effective method of preparing allylic alcohols. Thiophilic reagents are used to trap cleanly the sulfenate resulting from rearrangement of allylic sulfoxides. The methodology exploited both stereochemical facets of the rearrangement: (1) transfer of chirality from S to C, thus controlling the configuration of the newly formed stereogenic center, and (2) control of the olefin geometry in the allylic alcohol product. Stereoselective synthesis of a series of trisubstituted allylic alcohols demonstrated the general utility of this methodology.[5] In all cases, *E* olefinic geometry predominates. For example, 1,2-dimethylallyl phenyl sulfoxide (**1**, Scheme 1) was prepared by α-methylation of the racemic sulfoxide, yielding a mixture of the four diastereomers of **1** differing in configuration at S and C_α. Then, upon rearrangement of the mixture a 97/3 *E*/*Z* ratio of allylic alcohols **2** was obtained in the presence of trimethyl phosphite.

Recently, we demonstrated the effectiveness of ab initio and Monte Carlo calculations in the elucidation of reaction paths and solvent effects on the Mislow–Evans rearrangement.[6] The observed preferences for *endo* over *exo* transition structures (TS's), which control π-facial selectivity for the rearrangement, were reproduced for simple allylic sulfoxides. A natural extension of this work was to investigate the origins of the observed control of olefin geometry in substituted systems. The stereochemical course of [2,3]-Wittig rearrangements has also been clarified by similar ab initio calculations.[7]

During the rearrangement of the diastereomeric mixture of sulfoxide **1**,[5] both diastereomers **1a** and **1b**, which differ in configuration at the C-α position, may undergo rearrangement through either an *endo* or *exo* TS.[8] Four mirror-image transition structures arise from the sulfoxide structures that are epimeric at sulfur. To enable a direct comparison with the experimental observations, the four unique TS's were located via ab initio calculations with the 3-21G(*) basis set along with low-energy conformers of the reactants and products (Figure 1).[9] Vibrational frequency calculations verified the nature of the stationary points. Previously, the validity of using the 3-21G(*) basis set was supported through application to the rearrangement of allyl methyl sulfoxide to allyl methanesulfenate.[6] Modest effects of basis set and correlation energy were found on the structures and relative energetics of the rearrangement. The computed activation energies of 27.8 and 30.0 kcal/mol for the *endo* and *exo* TS's at the 3-21G(*) level are similar to our highest-level results (MP3/6-31+G*//6-31+G*) of 25.9 and 27.4 kcal/mol and to experimental values.[6]

Assuming nonselective reaction of the thiophile, the relative amount of each sulfenate produced is reflected in the final *E*/*Z* product distribution for the allylic alcohol. A key point from Figure 1 is that although the *(E)*-

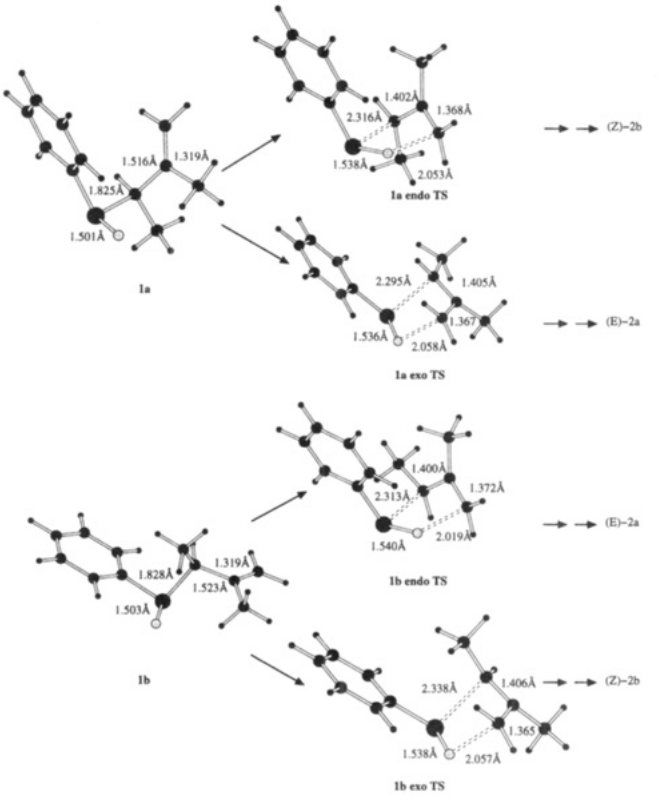

Figure 1. Computed 3-21G(*) structures for the [2,3]-sigmatropic rearrangement of **1a** and **1b**.

Scheme 1

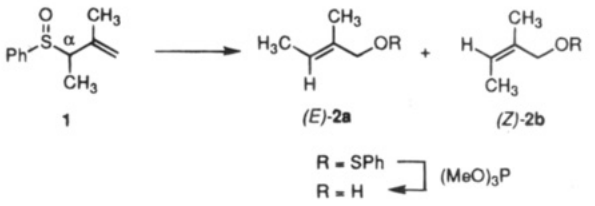

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Table 1. Computed 3-21G(*) Energies for the *exo* and *endo* TS's

TS	electronic energy (au)	rel energy (kcal/mol)	E_a (kcal/mol)
1a *endo*	−892.346 94	2.5	30.5[a]
1a *exo*	−892.350 87	0.0	28.0[a]
1b *endo*	−892.350 35	0.0	29.4[b]
1b *exo*	−892.344 45	3.7	33.1[b]

[a] Electronic energy of reactant **1a** = −892.395 47 au. [b] Electronic energy of reactant **1b** = −892.397 15 au.

product arises from the *endo* TS for **1b**, it requires the *exo* TS for **1a**. In fact, the 3-21G(*) results in Table 1 assert that the *endo* TS is favored over the *exo* one for **1b** by 3.7 kcal/mol and the *exo* TS for **1a** is favored by 2.5 kcal/mol over the *endo* alternative. The corresponding predicted *E*/*Z* product ratios at room temperature are 98.5/1.5 for **1a** and 99.8/0.2 for **1b**, which are similar to the observed 97/3 *E*-selectivity.[5]

Several factors can be identified that contribute to the relative stabilities of the four TS's: (1) the intrinsic ca. 1.5 kcal/mol preference for *endo* TS's,[6,7b] (2) eclipsing 1,2-phenyl/methyl interactions, (3) eclipsing 1,3-phenyl/methyl interactions, and (4) 1,3-interactions in the allylic fragment of the TS. In an attempt to quantify the energetic contribution of (4), specifically 1,3-H/H (**1a** *exo* TS and **1b** *endo* TS) *vs* 1,3-H/methyl (**1a** *endo* TS and **1b** *exo* TS), the sulfoxide moiety was removed from each TS and a single-point 3-21G(*) calculation was carried out on the remaining allylic fragment. In both examples, the 1,3-H/H conformation is ~2 kcal/mol lower in energy than the 1,3-H/methyl arrangement in spite of the 1,2-methyl/methyl interaction in the former case. The effect of 1,3-allylic strain in a variety of systems was studied by Houk *et al.*;[10] it was found analogously that "1,3-allylic strain is a much larger factor in determining the conformations of alkenes than 1,2-strain".

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For the rearrangement of diastereomer **1a**, the *exo* TS does not have eclipsing phenyl/methyl interactions and the 1,3-allylic interaction is H/H. In contrast, the *endo* TS of **1a** is destabilized by both a 1,3-phenyl/methyl interaction and the 1,3-allylic H/methyl interaction. Assuming the latter cancels the ca. 2 kcal/mol *endo* advantage, the 1,3-phenyl/methyl interaction appears to be destabilizing by 2−3 kcal/mol. For the rearrangement of diastereomer **1b**, the *endo* TS has a destabilizing 1,3 phenyl/methyl interaction and the favorable 1,3-allylic H/H arrangement. The higher-energy *exo* TS from **1b** suffers from both an eclipsing 1,2-phenyl/methyl interaction and the 1,3-allylic H/methyl interaction. Assigning 2−3 kcal/mol to the 1,2-phenyl/methyl interaction coupled with the other energy terms rationalizes the computed ca. 4 kcal/mol preference for the *endo* TS of **1b**. Though the two disfavored TS's have the C1-methyl group in an axial-like position, the associated energetic effect is dependent on the disposition of the other substituents about the five-membered ring, especially the group on sulfur.

Thus, the observed *(E)*-selectivity for the Mislow−Evans rearrangement of **1** is reproduced in ab initio calculations and requires passage through the *endo* TS for one diastereomeric sulfoxide (*R*,*S* or *S*,*R*) and through the *exo* TS for the C1 epimer (*R*,*R* or *S*,*S*). This dichotomy can be rationalized by analysis of the constituent interactions in the alternative transition structures.

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Supporting Information Available: Complete specifications of the optimized geometries of the diastereomeric reactants, TS's, and products for **1** in *Z*-matrix format (4 pages).

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