J. Am. Chem. Soc. **1995,** *117,* 9077−9078

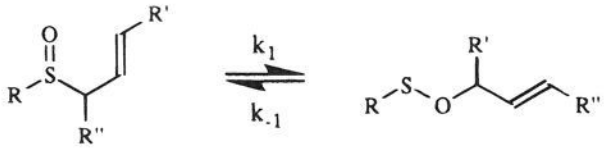
Elucidation of Transition Structures and Solvent Effects for the Mislow−Evans Rearrangement of Allylic Sulfoxides

Deborah K. Jones-Hertzog and William L. Jorgensen*

Department of Chemistry, Yale University
New Haven, Connecticut 06520-8107

Received May 1, 1995

The facile conversion of allylic sulfoxides to sulfenates, characterized by Mislow *et al.*[1] as a [2,3]-sigmatropic rearrangement, was developed by Evans and co-workers[2] into a valuable method for the synthesis of allylic alcohols.[3] The



forward reaction is notably decelerated in polar solvents, e.g., by factors of 29 and 332 at 60.7 °C ($\Delta\Delta G^\ddagger = 2.2$ and 3.9 kcal/mol) in going from methylcyclohexane to ethanol and to 2,2,3,3-tetrafluoro-1-propanol for allyl *p*-tolyl sulfoxide (ATS).[1a] Coupled with the insensitivity of the reverse reaction rate to solvation, this was taken to indicate that (1) the transition state resembles the sulfenate and (2) the rate changes for the forward reaction reflect more favorable solvation of the more polar sulfoxide in more polar solvents.[1] Though a linear correlation was obtained between log k_1 for ATS and the solvent polarity index E_T,[1] the rate effects could be expected to be even larger since in hydrogen-bonding solvents much weaker hydrogen bonding to a sulfenate, and presumably the transition state, than a sulfoxide is anticipated. For example, with ab initio 6-31G* optimizations, we obtain optimal hydrogen-bond strengths of 10.2 and 5.8 kcal/mol for a water molecule with dimethyl sulfoxide and dimethyl sulfenate.[4] The present study was carried out to characterize the transition structures for the rearrangement and details on the changes in solvation along a reaction path in an alcohol solvent.

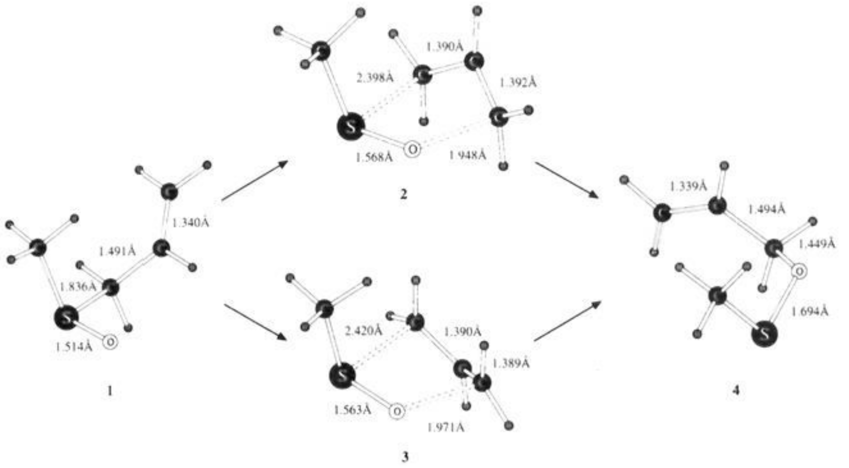


Figure 1. Computed MP2/6-31G* structures for the rearrangement of allyl methyl sulfoxide **1**.

Table 1. Computed Energies (kcal/mol) Relative to Sulfoxide **1**

level	*endo*-TS **2**	*exo*-TS **3**	product **4**
3-21G(*)//3-21G(*)	27.8	30.0	−16.3
6-31G*//6-31G*	36.7	38.4	−13.1
6-31+G*//6-31+G*	37.0	38.5	−11.6
MP2/6-31G*//6-31G*	18.2	20.0	−5.5
MP2/6-31G*//MP2/6-31G*	18.5	20.1	−5.9
MP2/6-31+G*//6-31+G*	18.6	20.1	−3.0
MP3/6-31G*//6-31G*	25.4	27.0	−9.6
MP3/6-31+G*//6-31+G*	25.9	27.4	−7.6

Chirality transfer from S to C is controlled by the relative energies of proposed *endo* and *exo* transition structures (TS).[3] Indeed, such transition structures for the rearrangement of allyl methyl sulfoxide **1** were located via MP2/6-31G* optimizations, as illustrated in Figure 1 along with the lowest energy conformers of the six located for both **1** and allyl methyl sulfenate **4**. The energetic results in Table 1 reveal that the *endo* TS **2** is favored by 1.5−2.2 kcal/mol. The *exo* TS **3** appears to be disfavored by the exocyclic C−S bond eclipsing a hydrogen on C1. Experimentally, *endo* transition states have been indicated to be preferred for simple systems,[1a,3] e.g., by 0.5−1.5 kcal/mol for 3-alkylallyl aryl sulfoxides.[5] The computed activation energies are not sensitive to extension of the basis set from 6-31G* to 6-31+G*; however, they are sensitive to the inclusion of correlation energy. Vibrational frequency calculations at the 6-31G* level verified the nature of the stationary points and yielded $\Delta H^\ddagger$ (MP3/6-31G*//6-31G*) values of 24.0 and 25.6 kcal/mol and $\Delta S^\ddagger$ values of −4.5 and −4.2 eu for the *endo* and *exo* transition structures at 60.7 °C. The predicted $\Delta H^\ddagger$ of 24−25 kcal/mol at the highest levels is consistent with the experimental values of 21−23 kcal/mol for various allyl aryl sulfoxides and 25.9 kcal/mol for **1** in benzene at 60.7 °C.[1] Also, the observed $\Delta S^\ddagger$ values of −4 to −8 eu concur with the computed results.[1] The transition structures show modest basis set and correlation dependence; the C- - -S and C- - -O distances for **2** are 2.241 and 1.984 Å (3-21G(*)), 2.337 and 1.988 Å (6-31G*), 2.368 and 2.002 Å (6-31+G*), and 2.398 and 1.948Å (MP2/6-31G*).

In order to make direct comparisons with the observed solvent effects for ATS, a minimum energy reaction path (MERP) was generated for its rearrangement via the *endo* TS at the 3-21G(*) level.[6] Reaction path following[7] yielded an 86-frame "movie". Utilizing established procedures,[8] partial atomic charges for each frame were obtained from single-point 6-31G* calculations by fitting to the electrostatic potential surface (EPS).[9] Changes in the free energies of solvation (ΔG_{sol}) along the MERP were computed via Monte Carlo simulations with the BOSS program.[10] Free energy perturbations were performed between 59 of the frames in periodic solvent boxes containing 396 methanol[11] or 260 methylcyclohexane molecules.[12] Each individual simulation with double-wide sampling entailed 10^6 configurations of equilibration followed by $2-4 \times 10^6$ configurations of averaging. The intermolecular interactions are represented by Coulomb and Lennard-Jones (LJ) terms with all solute atoms explicit; no intramolecular degrees of freedom were

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[1] (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.

[2] Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

[3] For an extensive review, see: Braverman, S. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley: London, 1988; Chapter 14.

[4] Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegal, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart J. J. P.; Pople, J. A. *Gaussian92*, Revision A; Gaussian, Inc.: Pittsburgh, PA, 1992.

[5] Goldman, S.; Hoffmann, R. W.; Maak, N.; Geueke, K.-J. *Chem. Ber.* **1980**, *113*, 831.

[6] The *exo* TS was found to be 1.4 kcal/mol higher in energy at this level.

[7] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

[8] (a) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 7430. (b) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966.

[9] Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

[10] Jorgensen, W. L. *BOSS*, Version 3.5; Yale University: New Haven, CT, 1994.

[11] Jorgensen, W. L. *J. Phys. Chem.* **1986**, *90*, 1276.

[12] Jorgensen, W. L.; Madura, J. D.; Swenson, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 6638.

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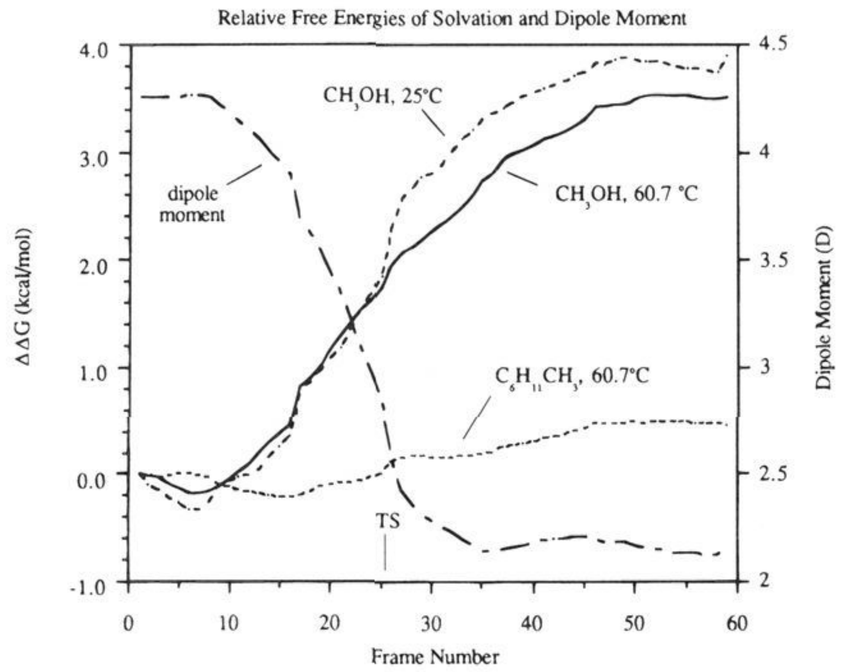

Figure 2. Computed changes in free energies of solvation and dipole moment along the MERP for ATS.

sampled. OPLS parameters were used for the solvents[11,12] along with the EPS charges and standard OPLS LJ parameters[13] for the solutes.

The computed changes in ΔG_{sol} are shown in Figure 2 for methanol at 25 and 60.7 °C and for methylcyclohexane at 60.7 °C; the corresponding $\Delta\Delta G^{\ddagger}$ values are 2.3, 2.0, and 0.1 kcal/mol on progressing from ATS to the TS at frame 26.[14] Continuing to the product, the overall $\Delta\Delta G_{\mathrm{sol}}$ values are 3.9, 3.5, and 0.5 kcal/mol, respectively.[14] Experimentally , $\Delta G^{\ddagger}$ for ATS increases by 2.8 kcal/mol at 60.7 °C in going from methylcyclohexane to methanol.[15] The computed solvent effect is in reasonable accord. However, the calculations also predict that the reverse reaction should be accelerated in methanol with $\Delta\Delta G^{\ddagger} \approx -1.2$ kcal/mol, while the experimental data for the sole case of allyl *p*-(trifluoromethyl)benzenesulfenate give a $\Delta\Delta G^{\ddagger}$ of ca. -0.3 kcal/mol at 25 °C.[1b]

The solvent effects and computed dipole moments (Figure 2) indicate that the TS is more product-like than reactant-like. It was then remarkable to note the distributions of individual solute−methanol interaction energies obtained for the reactant, TS, and product at 60.7 °C (Figure 3). The hydrogen-bonding peak at low energy changes little between sulfoxide and TS, but is nearly eliminated for the sulfenate. With an energetic cutoff of -3.5 kcal/mol, the average number and strength of the hydrogen bonds are 1.3 and -6.4 kcal/mol for the reactant, 1.0 and -6.4 for the TS, and 0.1 and -3.9 for the product (Figure 4). The EPS charges for the oxygen are consistent with this pattern being closer for the sulfoxide (-0.47) and TS (-0.43) than sulfenate (-0.36), and the corresponding S−O bond lengths are 1.495, 1.540, and 1.653 Å for the ATS reaction at the 3-21G(*) level and 1.514, 1.568, and 1.694 Å in Figure 1. Thus, although the overall polarity of the TS as measured by the dipole moment is more product-like, the oxygen in the TS maintains sulfoxide-like character including strong hydrogen-bond-accepting ability. Without this dichotomy the observed solvent effects for the Mislow−Evans reaction would be even more striking. Enhanced hydrogen bonding for transition states is emerging as an important factor controlling solvent effects on pericyclic reactions.[8] For both the Claisen[8b] and Mislow−Evans rearrangements, the charge on the oxygen in the TS is closer to that for the unsaturated (S=O or C=O) reactant or product than the saturated one, which contributes to the strong hydrogen bonding.

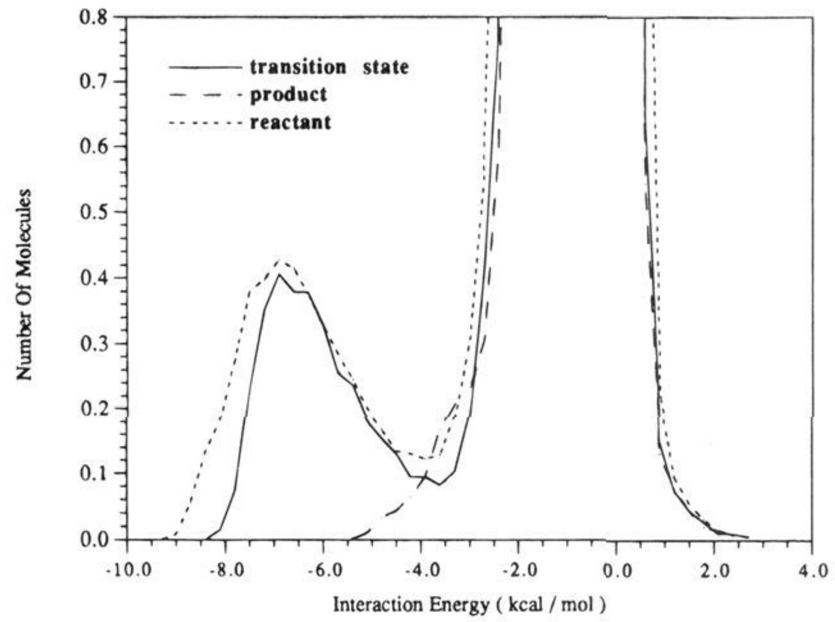

Figure 3. Computed distributions of individual solute−methanol interaction energies from the Monte Carlo simulations at 60.7 °C.

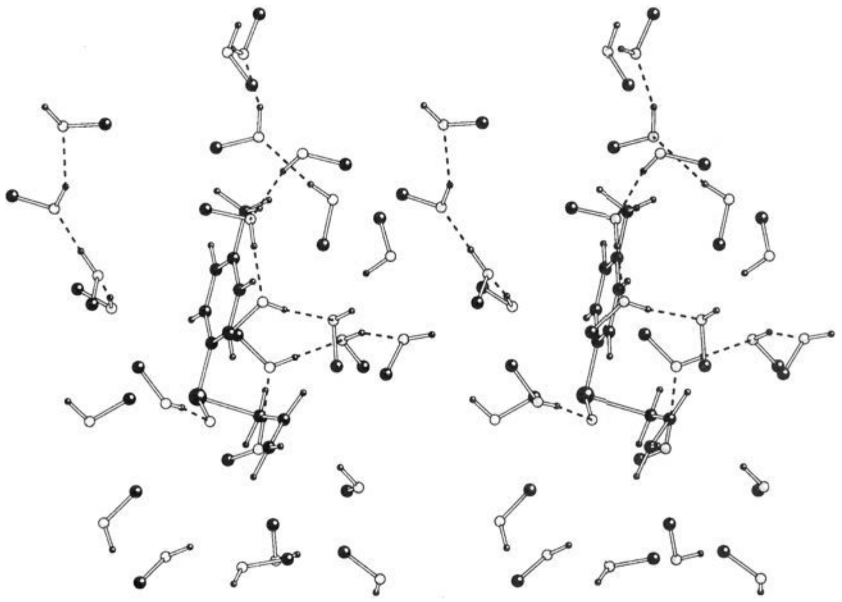

Figure 4. Stereoplot of a configuration for the TS of ATS in methanol. Only solvent molecules within 5 Å are shown. There is one hydrogen bond to the oxygen of the TS.

Acknowledgment. Gratitude is expressed to the National Science Foundation and to Bayer Pharmaceutical Division for support of this research and to Dongchul Lim for computational advice.

Supporting Information Available: Complete specifications of the optimized geometries of the reactant, TS's, and product for both the methyl- and *p*-tolyl-substituted systems in Z-matrix format and the potential function parameters (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) (a) Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657. (b) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768. (c) Jorgensen, W. L.; Nguyen, T. B. *J. Comput. Chem.* **1993**, *14*, 195.

(14) Uncertainties (1σ) in the computed values are 0.1 kcal/mol from the batch mean procedure.

(15) Extrapolated from the data for ethanol and 2,2,3,3-tetrafluoro-1-propanol using the correlation with E_{T}.