# Rational vs Random Parameters in Transition State Modeling: MM2 Transition State Models for Intramolecular Hydride Transfers

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**Abstract:** An MM2 force field to model transition states of intramolecular hydride transfers from alkoxides to carbonyl compounds has been developed. On the basis of ab initio geometries of transition structures, the force field reproduces activation energies in a series of intramolecular hydride transfers. A previous force field based upon a similar philosophy reported by Menger and Sherrod gave a poor correlation; this has been found to be due to an abnormally large oxygen van der Waals term that was incorporated into the parameter set. An argument is presented for the use of rational, rather than random, parameters to study organic reactions.

## Introduction

Transition state modeling is a computational method to approximate the geometries and energies of transition states with an empirical force field. The method we have advocated is the use of quantum mechanics and experimental data to determine parameters of the force field.[1] The force field can then be used to predict reactivity within a closely related family of organic reactions.

We have studied a number of organic reactions by treating the transition state as an energy minimum rather than a saddle point. The underlying assumption is that the transition state for the simplest system is the ideal transition state geometry, and when bulky substituents or cyclic constraints are added, the resulting steric or strain effects distort the ideal structure and raise the energy of the system. The simplest transition structure is usually small enough that it can be studied at the *ab initio* quantum mechanical level. Available, well-tested force fields such as MM2 are used for all normal atoms and bonds.[2] Transition state geometric parameters such as bond lengths, angles, and dihedral angles are taken from the quantum mechanical structures. The atoms involved directly in bonding changes are given new atom types, and the corresponding force constants are derived from *ab initio* calculations or by analogy to related systems. The energy of the entire structure is minimized using standard molecular mechanics techniques. The difference in the steric energy change between the transition structure and the reactant structure corresponds to the change in activation energy.

This treatment has been criticized. The transition state is really a saddle point, not an energy minimum. Substitution which changes the energy of reaction is expected to alter the position of the transition state to an earlier or later geometry according to the experience summarized in the Hammond postulate.[3] Our models cannot easily cope with electronic effects involving stabilization of transition states. For that reason, our models have been limited to cases where relative activation energies are determined by the magnitude of strain effects on ground and transition states.

Others have tried to develop more general force field treatments of transition states. Jensen has proposed that the transition state be located by finding a minimum in the seam representing the lowest energy intersection of the reactant and product potential energy surfaces; these surfaces are described by the reactant and product force fields.[4] A modified version of Allinger's MM2 force field was used, in which a smaller (0.5–0.8 Å$^{-1}$ versus 2.0 Å$^{-1}$) cubic stretch constant was substituted in order to describe looser transition structures in a realistic fashion. This procedure is promising, although its success depends upon the transition state parameters being correctly represented by both reactant and product force fields.

Menger and Sherrod have criticized transition state modeling on more general grounds.[5] They questioned the utility of deriving geometric parameters and force constants from quantum mechanical calculations and expressed concern that empirical force fields include parameters which are to some extent arbitrary. They reported a case which demonstrated the failure of an apparently rational approach to parameter development.[5b] Menger and Sherrod also showed that ground state models which approximate the geometry and strain found in a transition state can be excellent transition state models.[5b] Sherrod subsequently developed a random approach to optimization of parameters.[5c] Instead of rational variations of parameters based upon physical principles and careful calibration, geometric terms and force constants were randomly altered, the transition structures were reoptimized, and a new correlation with experimental results was determined. Changes which increased the correlation were retained. This iterative process was continued until no further change in the correlation was achieved. In this way an improved correlation was achieved. Sherrod's skepticism of the transition state modeling is reflected in the name of his parameter optimization program, FUDGIT![5c]

Since there are hundreds of parameters in a force field for a reasonably-sized organic molecule, there is no doubt that excellent

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[1] (a) Houk, K. N.; Paddon-Row; M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (b) Houk, K. N.; Duh, J.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (d) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 2195. (e) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. (f) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (g) Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651. (h) Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656. (i) Thomas, B. E.; Loncharich, R. J.; Houk. K. N. *J. Org. Chem.* **1992**, *57*, 1354. (j) Brown, F. K.; Raimondi, L.; Wu, Y.-D.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 4405. (k) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439.

[2] (a) Allinger, N. L.; Yuh, Y. *QCPE* **1980**, *12*, 395. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. The MM2(87) parameter set is used.

[3] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

[4] Jensen, F. *J. Am. Chem. Soc.* **1992**, *114*, 1597.

[5] (a) Menger, F. M.; Sherrod, M. J. *J. Am. Chem. Soc.* **1989**, *111*, 2611. (b) Menger, F. M.; Sherrod, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8071. (c) Sherrod, M. J. *Tetrahedron Lett.* **1990**, *31*, 5085.

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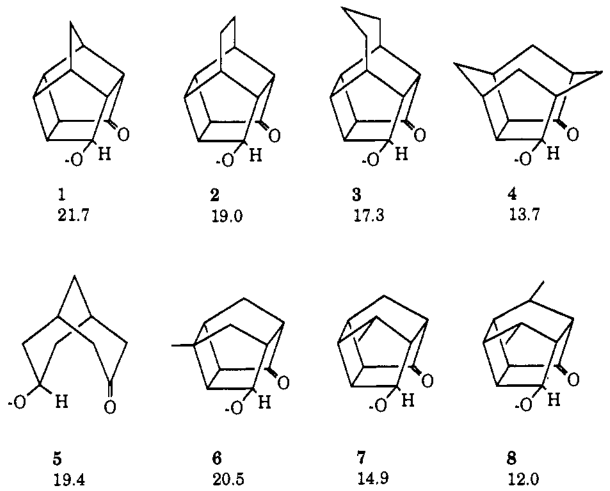
**Table 1.** Models and Correlations for Hydride Transfer Reactions

| author | model | ref | compds | correl coeff |
|---|---|---|---|---|
| Jensen | intersecting seam | 4 | 1–5 | 0.39 |
| | ab initio-based transition state | 4 | 1–5 | 0.89 |
| Menger and Sherrod | ab initio-based transition state, “TS1” | 5a | 1–5 | 0.89 |
| | methylene-bridged ground state, “TS2” | 5a | 1–5 | 0.99 |
| | diketone ground state, “TS3” | 5a | 1–5 | 0.97 |
| | distorted ground state, “TS4” | 5a | 1–5 | 1.00 |
| | ab initio-based transition state, “TS1” oxygen van der Walls radii 2.20 Å | 5a | 1–8 | 0.61 |
| | ab initio-based transition state, “TS1” FUDGIT optimization of parameters | 5c | 1–8 | 0.96 |
| | ab initio-based transition state, “TS1” oxygen van der Walls radii 1.74 Å | 5a and this work | 1–8 | 0.83 |
| Eurenius and Houk | ab initio-based transition state | this work | 1–5 | 0.99 |
| | ab initio-based transition state | this work | 1–8 | 0.97 |



1 21.7

2 19.0

3 17.3

4 13.7

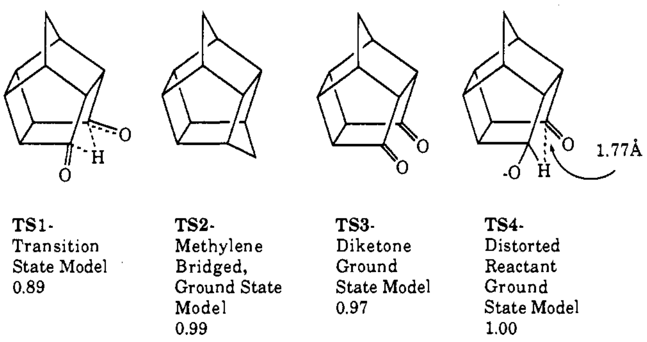
5 19.4

6 20.5

7 14.9

8 12.0

**Figure 1.** Experimental activation energies (kcal/mol) determined using dynamic NMR techniques for hydride transfers.[6]



TS1- Transition State Model 0.89

TS2- Methylene Bridged, Ground State Model 0.99

TS3- Diketone Ground State Model 0.97

TS4- Distorted Reactant Ground State Model 1.00

**Figure 2.** Four models for hydride transfer and the correlation coefficients calculated for reactions of compounds **1** to **5**.[5a] TS1 is based on a RHF/3-21G transition structure. TS2 and TS3 are gound state models that approximate the strain of the transition structure. TS4 is a distorted ground state model with the H/C(=O) distance constrained to 1.77 Å.

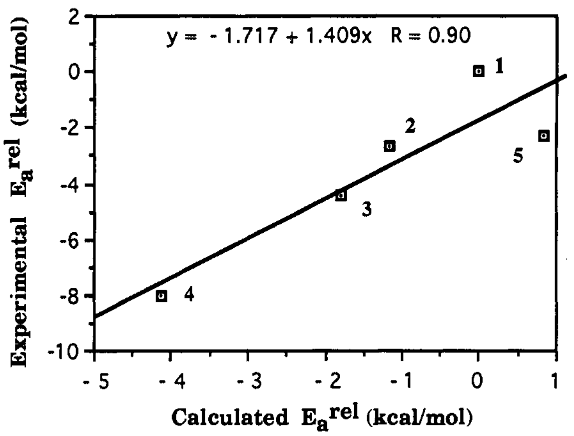


**Figure 3.** Menger and Sherrod's transition state modeling correlation with experimental relative activation energies (kcal/mol).

correlations can be obtained with limited experimental data sets using the FUDGIT approach. When parameters have been altered from values known to be correct for similar molecules, however, any hope for physical meaning is lost, and predictions are made only with the greatest trepidation. Thus, it is important to learn why the Menger–Sherrod rational approach failed.

Both Jensen, and Menger and Sherrod demonstrate their transition state modeling approaches by application to a series of hydride transfers. Watt's dynamic NMR data for anionic hydroxy ketone hydride transfers in DMSO with sodium as the counterion provide activation energies for eight hydride transfers.[6] Figure 1 shows the compounds that have been included in hydride transfer transition state modeling studies.

Jensen's transition state modeling reproduced the general trends, but Table 1 shows that the correlation with experiment was low (0.39). Compound **5** is especially problematical. His implementation of the ab inito-based modeling approach resulted in a significantly better correlation of 0.89. This might reflect the inadequacy of ground state MM2 parameters to describe the potential surface in the region of the transition state, which would give a poor approximation to transition state geometry and energy.

Menger and Sherrod also modeled the hydride transfer with an ab initio-based transition state modeling approach, **TS1**, and three “ground state” models, a methylene bridge hydrocarbon, **TS2**, a diketone, **TS3**, and a distorted hydroxy ketone, **TS4**. Figure 2 shows the four models that Menger included in his study and the correlation coefficient found for each.[5a]

Menger and Sherrod's implementation of the rational approach, based upon a RHF/3-21G transition structure, gave a lower correlation than the three ground state structure models (Table 1). The correlation is shown in Figure 3. Again, compound **5** is a problem; the remaining four compounds lie on a straight line. When Sherrod subjected the rational parameters to the FUDGIT routine, he was able to significantly increase the correlation coefficient to 0.96.[5c]

Menger's ground state models provide excellent correlations with experimental data. Each involves conversion of the ground state hydroxy ketone into a more strained species, and the increase in strain energy which also occurs in the hydride transfer transition state is reflected remarkably well in these simple models.

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[6] (a) Craze, G.; Watt, I. *J. Chem. Soc., Chem. Commun.* **1980**, 147. (b) Craze, G.; Watt, I. *J. Chem. Soc., Perkin Trans. II* **1981**, 175. (c) Cernik, R.; Craze, G.; Mills, O. S.; Watt, I. *J. Chem. Soc., Perkin Trans. II* **1982**, 361. (d) Cernik, R.; Craze, G.-A.; Mills, O. S.; Watt, I.; Whittleton, S. N. *J. Chem. Soc., Perkin Trans. II* **1984**, 685. (e) Watt, I.; Whittleton, S. N.; Whitworth, S. M. *Tetrahedron* **1986**, *42*, 1047. (f) Hillier, I. H.; Smith, S.; Mason, S. N.; Whittleton, C.; Watt, I. F.; Willis, J. *J. Chem. Soc., Perkins Trans. II* **1988**, 1345.

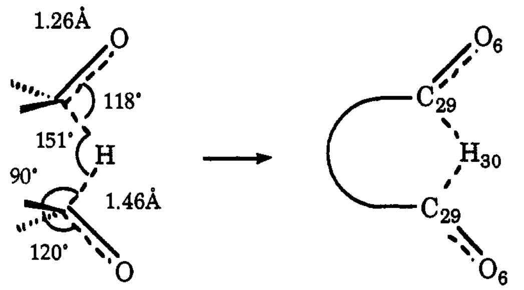

**Figure 4.** The transition state for the hydride transfer from methoxide to formaldehyde structure calculated at the RHF/3-21G level[7] is shown on the left. On the right, the model force field transition structure with the new atom types labeled is shown.

**Table 2.** Parameter List for the Hydride Transfer Transition State Model

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 | 2 | 0 | 4 | | | |
| 1 | 1 | 29 | 30 | 0.0 | 0.0 | 0.140 |
| 5 | 1 | 29 | 30 | 0.0 | 0.0 | 0.120 |
| 1 | 1 | 29 | 6 | 0.1 | 0.1 | 0.18 |
| 5 | 1 | 29 | 6 | 0.0 | 0.0 | 0.180 |
| 1 | 29 | 30 | 29 | 0.0 | 0.0 | 0.0 |
| 6 | 29 | 30 | 29 | 0.0 | 0.0 | 0.0 |
| 29 | 30 | 2.3 | 1.463 | | | |
| 6 | 29 | 8.05 | 1.261 | | | |
| 1 | 29 | 30 | 0.18 | | 90.47 | |
| 1 | 29 | 6 | 0.35 | | 120.59 | |
| 30 | 29 | 6 | 0.27 | | 118.16 | |
| 29 | 30 | 29 | 0.0 | | 151.41 | |

**Table 3.** Bond Parameters Developed from the RHF/3-21G Transition Structure

| bond | $L_0$(Å) | $k_S$ (mdyn $Å^{-1}$) |
|---|---|---|
| 29–30 | 1.463 | 2.30 |
| 6–29 | 1.261 | 8.05 |

Because the Menger–Sherrod work casts doubt on the utility of rational ab initio force field modeling, we have reinvestigated this problem. We have applied our transition state modeling approach to the same series of hydroxy ketone hydride transfers. We obtain a high correlation using a rational approach based upon the ab initio transition state and simple assumptions about force constants. We have also discovered why the Menger–Sherrod attempt at rational modeling gave a poor correlation with experiment.

**Development of the Force Field.** The ab initio RHF/3-21G transition state for hydride transfer upon which our force field is developed is shown schematically in Figure 4. Parameters for the new atom types $C_{29}$, $O_6$, and $H_{30}$ were developed. The force field is flexible, with all atoms free to relax into the minimum energy geometry. Parameters were developed for any terms which include a portion of the breaking or forming bond. Any atom, bond, angle, or dihedral angle that is not directly involved in the hydride transfer is treated according to the standard MM2 force field. No additional lone pairs are added to the oxygens. All parameters are given in Table 2.

Angles and dihedrals that contain one, but not both, of the forming bonds are assigned one-half the standard MM2(87) parameter values, based on the assumption that these forming and breaking bonds are more flexible than fully formed bonds.[1c] Force constants describing breaking bonds and the included angles and dihedrals are derived from ab initio calculations[4a,6] or are based on reasoning discussed in the following section. Dipole and van der Waals terms are standard MM2(87) parameters.

**Bonds.** Table 3 lists the bond parameters implemented in our transition state force field. The ab initio $C_{29}$–$H_{30}$ and $C_{29}$–$O_6$ distances are used for the equilibrium bond distance, $L_0$, in the parameter set. The force constant for the C–O bond is 8.05 mdyn $Å^{-1}$, the average of force constants for double and single C–O bonds. The force constant for $C_{29}$–$H_{30}$ is set to 2.3 mdyn $Å^{-1}$, one-half the C–H standard value. The $sp^3$ $C_1$–$C_{29}$ bonds are treated as standard $sp^3$–$sp^3$ bonds.

**Table 4.** Bond Angle Parameters Developed from the RHF/3-21G Transition Structure

| angle | $q_0$ (deg) | $k_B$ (mdyn $deg^{-2}$) |
|---|---|---|
| 1–29–30 | 90.47 | 0.180 |
| 1–29–6 | 120.59 | 0.350 |
| 30–29–6 | 118.16 | 0.270 |
| 29–30–29 | 151.41 | 0.000 |

**Table 5.** Dihedral Angle Parameters Developed from the RHF/3-21G Transition Structure

| dihedral angle | $V_1$ (kcal/mol) | $V_2$ (kcal/mol) | $V_3$ (kcal/mol) |
|---|---|---|---|
| 1–1–29–30 | 0 | 0 | 0.140 |
| 5–1–29–30 | 0 | 0 | 0.120 |
| 1–1–29–6 | 0.100 | 0.100 | 0.180 |
| 5–1–29–6 | 0 | 0 | 0.180 |
| 1–29–30–29 | 0 | 0 | 0 |
| 6–29–30–29 | 0 | 0 | 0 |

**Angles.** Equilibrium values, $q_0$, for angles 1–29–30, 1–29–6, 6–29–30, and 29–30–29 are taken directly from the ab initio calculation. Force constants for 1–29–30 and 6–29–30 are one-half that of standard, 0.180 and 0.270 mdyn $deg^{-2}$. The 1–29–6 angle is given half the normal MM2 force constant of 0.350 mdyn $deg^{-2}$. The force constant of the 29–30–29 angle was set to 0.0 mdyn $deg^{-2}$, based upon calculations of Williams[7b] who calculated a very low frequency vibration for bending of this angle. These parameters are shown in Table 4.

**Dihedral Angles.** Dihedrals 1–1–29–30 and 5–1–29–6 are given normal force constants, whereas dihedrals 1–1–29–6 and 5–1–29–30 are assigned one-half the normal values. Values for the 1–29–30–29 and 6–29–30–29 torsions are determined from Williams' potential energy surface.[7b] Rotation around the 29–30 bond occurs freely, and so all $V_n$ are set to 0 kcal/mol. Table 5 lists these parameters.

**Dipole and van der Waals Terms.** Normal MM2 dipole and van der Waals terms are used as the default parameters. Changes in van der Waals terms are unnecessary since both $sp^2$ and $sp^3$ carbons and oxygens have nearly identical van der Waals radii (1.90 Å versus 1.94 Å for $sp^3$ versus $sp^2$ carbons). Atom type 29 was set to a default $sp^3$ carbon. Both carbonyl and alkoxy oxygens have radii of 1.74 Å in the standard MM2 parameter set. The van der Waals radius of the migrating hydride was set to a normal values, and the default dipole terms were maintained.

## Results and Discussion

Figure 5 shows the correlation of relative activation energies calculated using this transition state force field with experimental activation energies for compounds **1–8**. The correlation coefficient is 0.97, or 0.99 when only compounds **1–5** are included (Table 1).

A simple, rational approach gives an excellent correlation with experiment without additional arbitrary adjustments of parameters. Why then did Sherrod and Menger come to the conclusion that such a rational procedure fails?

Many of the parameters presented above are the same or similar to those used in the Menger–Sherrod treatment. Two major differences between their force field and ours are in their handling

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(7) (a) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 906. (b) Williams, I. H.; Miller, A. B.; Maggiora, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 530. (c) Field, M. J.; Hillier, I. H.; Smith, S.; Vincent, M. A.; Mason, S. C.; Whittleton, S. N.; Watt, C. F.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* **1987**, 84.

(8) MODEL, Clark Still, Columbia University, Version KS 2.92. The authors thank Dr. K. Steliou at the Department of Chemistry, University of Montreal, for providing MODEL parameters.

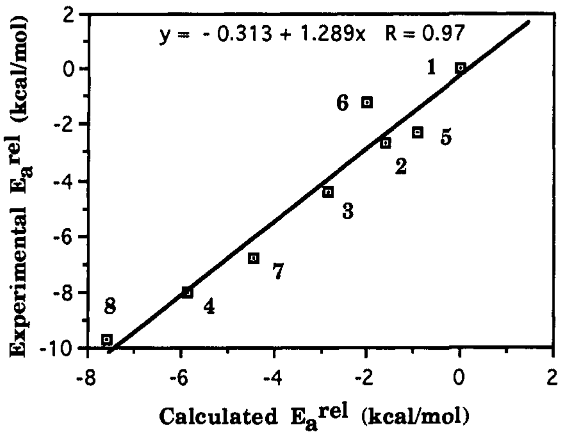

**Figure 5.** Comparison of calculated relative activation energies using the transition state force field and experimental relative activation energies.

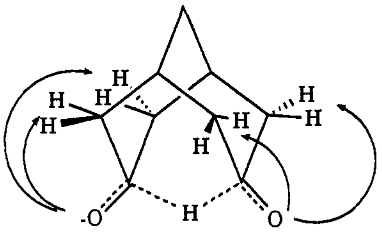

**Figure 6.** Schematic representation of the large oxygen-vicinal H interactions which cause **5** to deviate from the correlation.

of dipole and van der Waal terms. We have found that the dipole terms did not affect the correlation achieved, but the van der Waals term for oxygen which they used does significantly affect the correlation as discussed below.

Using the Menger and Sherrod force field for compounds **1** through **8**, van der Waals interactions dominate the overall change in steric energy. There are four interactions of this type for each compound and these interactions contribute the most to the overall steric energy. Compound **5**, which deviates drastically from the original Menger correlation involving **1**–**5**, has particularly large interactions between the oxygens and the hydrogens on the adjacent carbons as shown in Figure 6.

Menger's parameter set contains a MODEL-Version 2.92[8] default alkoxide van der Waals radii of 2.20 Å. The MM2(87) parameter set contains a van der Waals default term for either an $sp^2$ or $sp^3$ oxygen of 1.74 Å. When the 2.20 Å radius is used, the O–H interactions, shown in Figure 6, destabilize the transition state for compound **5**. When all eight compounds are included in the force field study, the correlation coefficient is only 0.61. Compounds **5**, **7**, and **8** are all predicted to have much larger activation energies than are found experimentally. When the ordinary 1.74 Å van der Waals radius is incorporated for oxygen and the rest of the Menger–Sherrod parameters are used, a considerably better correlation of 0.83 is found (Figure 7).

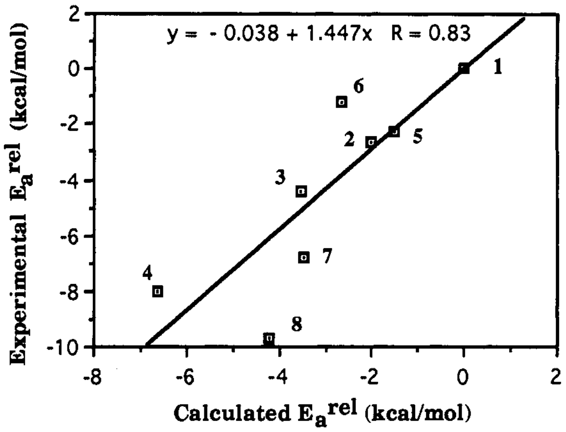

**Figure 7.** Comparison of calculated $E_a^{rel}$ using Menger and Sherrod's parameter set except for the MM2 default oxygen 1.74 Å van der Waals radius and experimental $E_a^{rel}$.

Sherrod later subjected the transition state bond and angle stretch parameters to optimization with the program FUDGIT. The flexible $C_{29}$–$H_{30}$–$C_{29}$ angle opened from 151° to 176° while the $O_6$–$C_{29}$–$H_{30}$ angle decreased 15°. Most interestingly, the oxygen–carbon partial double bond length stretched from 1.26 to 1.42 Å. Clearly, FUDGIT forced the offending oxygen further from the reaction site in order to alleviate the strain that the abnormal van der Waals parameter imposed in compound **5**. The result makes no sense chemically. Two abnormal parameters fix the problem with **5**, but the results will be unpredictable for new compounds.

Comparison of the various hydride transfer models reveals several interesting points. First, transition state modeling works well when rational parameters are used, but some care and testing must go in to making these choices. Second, Menger et al. have demonstrated that transition state modeling can be achieved even by ground state models which incorporate the appropriate geometry and strain mimicking those in the transition state.[5]

**Acknowledgment.** We are grateful to the National Science Foundation for financial support of this research and to Dr. Yundong Wu for extensive discussions.