

# Conformational Searching and Modeling of Transition States

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Received August 18, 1995<sup>®</sup>

The application of the WIZARD method for conformational search to Houk's transition state modeling method shows significant improvements in the ability to predict and understand the diastereoselectivity of the reaction of nucleophiles with carbonyl groups.

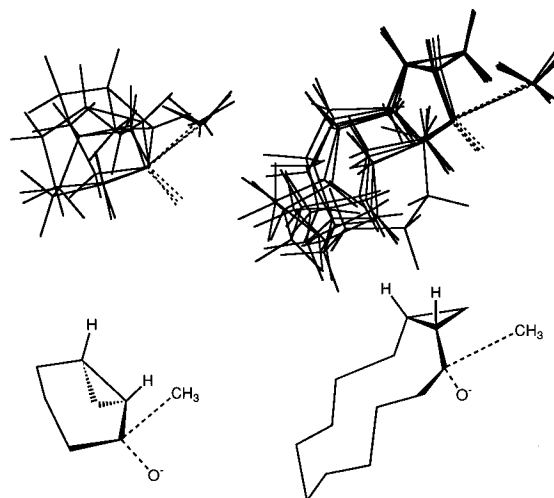
In 1987 Wu and Houk introduced a new method for modeling the structures and energies of transition states (TS) based on the utilization of molecular mechanics programs (such as MM2) to reproduce the results found by quantum mechanical (QM) methods.<sup>1</sup> The TS geometries found by the QM programs were treated as if they were minimal energy conformations and were converted to MM2 parameters. MM2 can then optimize the geometries of TSs utilizing standard methods. Houk compared the results of this method to the experimental results for the addition of LAH to acyclic molecules originally reported by Felkin<sup>2</sup> in 1968, as shown in Table 1. In most cases the theoretical predictions are within a few percent of the experimental values, with an average error of only 7.75%. In a few cases the predictions are notably in error; e.g., up to 18%.

Recently we reported an adaptation of Houk's method for performing conformational searches on transition state geometries for nucleophilic addition to bicyclo[*m*.1.0]alkan-2-ones.<sup>3</sup> The results from the combined use of WIZARD to perform a conformational search and calculation of the energies using MM2 augmented with the Houk parameters was in good agreement with the experimental results found by Mash.<sup>4</sup> During these studies bicyclo[*m*.1.0] systems ranging from *n* = 4 to *n* = 14 were examined. It was noted that different ring systems exhibited different behavior: The energetic difference between the successive TS conformations for the [4.1.0] systems was high (about 1 Kcal/mol), so that the majority of the reaction products arose from the first few conformations. In these systems the geometrical changes between the conformations is large, and the R/S diastereoselectivity changes dramatically from conformation to conformation. The diastereoselectivity predicted from the best two TS conformers is substantially different from the prediction based on the ensemble of TS conformers. On the other hand, as the size of the ring increased the energetic differences became progressively smaller until the difference became less than 0.2 kcal/mol for the [14.1.0] systems. With such a small difference the less stable conformations contributed significantly to the final product mixture. However, all of the low energy TS conformations for these large rings exhibit roughly the same local conformation around the carbonyl, as shown for bicyclo[10.1.0]tridecan-2-one in Figure 1. In addition, each diastereomeric TS exhibits an ensemble of conformations with roughly the same energy distribution. Thus, the diastereomer ratio predicted from the

**Table 1.** Comparison of Felkin's Experimental Data, Houk's Predictions, and Predictions Made by Performing a Conformational Search on the Transition States

	L	R	expt <sup>a</sup>	Houk <sup>b</sup>	$\Delta$ %	ensemble	$\Delta$ %	# conf <sup>c</sup>
1	cyclohexyl	Me	62:38	69:31	7	65:35	3	138
2	cyclohexyl	Et	67:33	72:28	5	65:35	2	365
3	cyclohexyl	<i>i</i> -Pr	80:20	79:21	1	80:20	0	387
4	cyclohexyl	<i>t</i> -Bu	62:38	80:20	18	62:38	0	114
5	phenyl	Me	74:26	60:40	14	69:30	5	7
6	phenyl	Et	76:24	67:33	9	74:26	2	23
7	phenyl	<i>i</i> -Pr	83:17	79:21	4	83:17	1	26
8	phenyl	<i>t</i> -Bu	98:02	94:06	4	94:06	4	8
av error					7.8		2.0	
std dev					5.3		1.8	

<sup>a</sup> Reference 2. <sup>b</sup> Reference 1. <sup>c</sup> Including high energy twist boat conformations for L = cyclohexyl.



**Figure 1.** Superimposition of the lowest energy transition state conformations for the methyl anion addition to bicyclo[4.1.0]alkan-2-one (left) and bicyclo[10.1.0]alkan-2-one (right), along with drawings of the lowest energy conformations (below).

lowest energy conformations of the two transition states is essentially the same as that derived by summing over the weighted contributions of the entire ensemble.

These observations led to the hypothesis that Houk's method might not be at fault, per se, but that the errors could arise due to contributions from one or more TS conformations which had not been accounted for. This hypothesis is in agreement with the observations of Anh and Eisenstein<sup>5</sup> in their *ab initio* (STO-3G) studies of the model proposed by Felkin. In their study of the reaction of hydride with 2-chloropropanal they found only two important TS conformations.

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<sup>®</sup> Abstract published in *Advance ACS Abstracts*, March 1, 1996.

**Table 2.** Distribution of the Transition State Conformations for **4**

minor		major	
energy above lowest (kcal/mol)	%	energy above lowest (kcal/mol)	%
0.5	20.4	0	46.9
1.198	6.4	0.994	9.0
1.235	6.0	1.59	3.3
1.928	1.9	1.943	1.8
2.034	1.6	2.957	0.3
2.129	1.3	2.976	0.3
2.488	0.7	>3.0	<0.3

mations (*R* and *S*), the rest lying more than 4 Kcal/mol above the most stable conformation. However, in their studies of the more sterically hindered 2-methylbutanal they found five transition state conformations within 2.7 Kcal/mol of the most stable one (for a total of six). This reduction of the difference in conformational energies with increasing steric hindrance is well-known for ground state molecules. Two effects have been seen: increasing importance of less stable conformations in the equilibrium mixture and a lowering of the barrier to rotation. For example, while butane shows a 0.9 Kcal/mol difference between the *anti* and *gauche* forms, 2,3-dimethylbutane exhibits less than 0.1 Kcal/mol.<sup>6</sup> Although the rotational barrier for the *tert*-butyl group in 2,2,3-trimethylbutane is 6.9 Kcal/mol, the barrier for the equivalent bond in the more sterically hindered 2,2,3,4-tetramethylpentane is only 6.0 Kcal/mol.<sup>7</sup> Since the molecules chosen by Felkin and modeled by Houk are much more complex than those calculated by Ahn, it seemed reasonable to assume that the conformational complexity would be even greater and that the minor conformations would be more important than previously assumed.

The combination of WIZARD and MM2 augmented with Houk's parameters was used to test this hypothesis. The general WIZARD method and the method used to augment WIZARD's structural axioms with axioms pertaining to TSs have been described previously.<sup>3a</sup> In brief, WIZARD is based in symbolic logic and uses axioms of structure and a theorem proving method to logically infer a complete set of conformations for a given molecule. Combined with a good method for calculating energy (MM2 + Houk parameters) this method provides the chemist with a rapid and comprehensive method for examining the conformational analysis of complex systems.

The results for the eight molecules are shown in Table 1. In each case WIZARD was used to find a complete ensemble of all TS conformations. MM2 was used to calculate the energies, and the population distributions were calculated using a Boltzmann distribution. The ability to predict the experimental ratios is substantially improved. While Houk's results for these molecules had an average error of 7.75% with  $\sigma = 5.33\%$ , the average error based on the complete ensemble is 2.00%, with  $\sigma = 1.80\%$ . More importantly, the three maximal errors are 5%, 4%, and 3% based on the ensemble, while they are 18%, 14%, and 9% in Houk's original calculations.

The low energy conformations for molecule **4**, where L = cyclohexyl, M = methyl, S = hydrogen and R = *tert*-butyl, are shown in Table 2. This molecule has eight TS conformations within the first 2 Kcal/mol and 23 conformations within 5 Kcal/mol. These conformations are unequally distributed between the two diastereomers: The most stable

**Table 3.** Distribution of the Transition State Conformations for **1**

minor		major	
energy above lowest (Kcal/mol)	%	energy above lowest (Kcal/mol)	%
0.776	13.7	0	51.2
0.8263	12.6	1.159	7.2
1.854	2.2	1.676	3.0
1.981	1.8	1.957	1.9
2.115	1.4	2.14	1.4
2.24	1.1	2.213	1.2
2.607	0.6	2.85	0.4
2.98	0.3	>3.0	<0.3

TS conformation leads to the major diastereomer. The ratio based on the two most stable TS conformations is 70:30, which is too much contribution for the major isomer. When all the conformations are considered, the most stable TS conformation is calculated to contribute only 47% of the overall product, while the most stable TS conformation of the minor diastereomer is only expected to contribute 20% of the overall product. The remaining major TS conformations should contribute an additional 14% major diastereomer, and the minor TSs should give an overall contribution of 18% more product. The dual effect is to dilute the contribution from the most stable conformations and give more minor diastereomer from higher energy conformations. Overall the ratio is predicted to be 38.2:61.8, which is very close to the reported value of 38:62.

The results for molecule **1**, where L = cyclohexyl, M = methyl, S = hydrogen, and R = methyl, are shown in Table 3. In this case the first and second TS for the minor diastereomer are nearly equal in energy (0.776 and 0.826 Kcal/mol relative to the most stable conformation), while the first and second TS for the major diastereomer are quite different in energy (0.0 and 1.159 Kcal/mol relative). Thus the second best minor TS is expected to contribute nearly as much final product as the best minor TS (12.6% versus 13.7% of the overall ensemble). The predicted based on the entire ensemble is 65:35, while experimental data is 62:38, which is not as good as the previous example but better than predictions based on the most stable TS (71:29) or Houk's choice of TSs (69:31).

Examination of the two best conformations also points up an interesting fact—the two most stable TSs do not always arise from the Felkin–Ahn major and minor predictions. This has some interesting ramifications for the Felkin–Ahn model, namely, that while the model does make good qualitative predictions, it is not always the best starting point for quantitative studies. Modeling a few transition states obtained from the Felkin–Ahn model using either Houk's method or a quantum mechanical method can give percentages which are in worse agreement with experiment than a prediction based on the full conformational ensemble. Thus a full conformational search should be performed to obtain maximal predictive power, no matter what method is used to calculate the relative energies of the TSs themselves. Such searches could be performed with WIZARD,<sup>3</sup> stochastic methods,<sup>8</sup> torsion angle driving,<sup>9</sup> distance geometry methods,<sup>10</sup> or other methods.<sup>11</sup>

#### ACKNOWLEDGMENT

We would like to thank U of A President Manuel T. Pacheco, whose promise of support has helped the author to go far.

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CI9500952