

Stereoselectivity Control by Torsional Steering in an Intramolecular Diels–Alder Reaction of Vinyl Oxocarbenium Ions

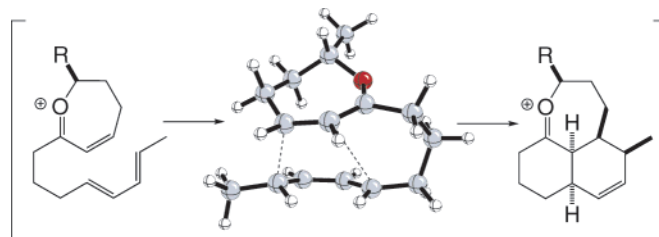
Robert G. Iafe and K. N. Houk*

Department of Chemistry and Biochemistry, University of California,
Los Angeles, California 90095-1569

houk@chem.ucla.edu

Received May 3, 2006

ABSTRACT



Density functional theory (B3LYP/6-31+G*) has revealed the origin of stereoselectivity in intramolecular Diels–Alder reactions of vinyl oxocarbenium ions. The cycloaddition has endo preference and occurs with remote stereocontrol syn to the substituent at the stereogenic center. Torsional steering, the preference for the staggered conformation about forming σ -bonds, dictates the preferred transition structure.

The Diels–Alder (DA) reactions of vinyl oxocarbenium ions have been the subject of recent interest.¹ Under conditions similar to those used in the Noyori ketalization reaction,² compound **1** undergoes an intramolecular ionic DA reaction via the intermediate vinyloxocarbenium ion **2** with remote stereocontrol to afford cycloadducts **4** and **5** each as a 9:1 mixture of diastereomers (Scheme 1).³ Structures **4** and **5** are formed presumably from intermediate **3** either by loss of a proton or by trapping of the oxocarbenium ion by the extended TMS ether, respectively. *trans*-Enone **6** is the isomerization product of **1** and cannot form a cyclic oxocarbenium ring; therefore, **6** does not provide any cycloadducts.

The intermediacy of a vinyl oxocarbenium ion in an intramolecular DA reaction was first proposed by Roush and co-workers⁴ in the hydrofluoric acid catalyzed DA reactions

of certain enoates. The proposed mechanism for this reaction involves the reversible formation of a vinyl oxocarbenium ion which can cyclize irreversibly to the cycloadduct. This concept was further extended by several groups.¹ Sammakia and co-workers³ observed a difference in the behavior of bis-TMS-protected **1** and bis-TIPS-protected **1**; bis-TIPS-protected **1** cannot form an oxocarbenium ion under the reaction conditions ($\text{Al}(\text{OTf})_3/\text{TfOH}$, CH_2Cl_2 , $-20\text{ }^\circ\text{C}$) and provides an 85:15 mixture of bis-TIPS-protected *trans*-alkene and bis-TIPS-protected DA cycloadducts as a mixture of diastereomers. The decreased reactivity and selectivity of bis-TIPS **1** compared to that of **1** suggest that these compounds react via different mechanisms, specifically that **1** reacts via an oxocarbenium ion.

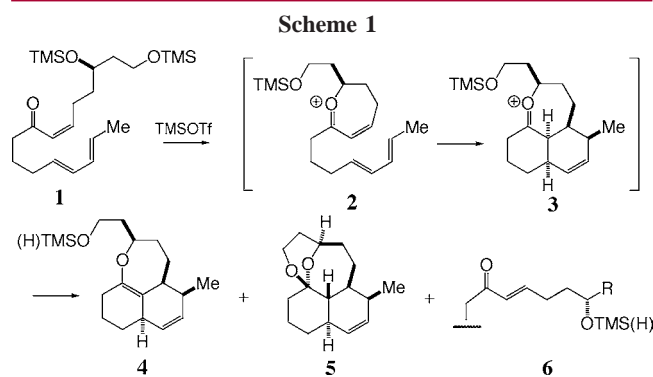
Conformational searches by Sammakia et al. on model reactants using the AM1 method led to the hypothesis that the contrasteric product is formed due to steric interference from the pseudoaxial hydrogens, H_a and H_b , on the vinyl-

(1) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371.

(2) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(3) Sammakia, T.; Johns, D. M.; Kim, G.; Berliner, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 6504.

(4) Roush, W. R.; Gillis, H. R.; Essinfeld, A. P. *J. Org. Chem.* **1984**, *49*, 4674.



oxocarbenium ring, which preferentially blocks one face of the dienophile (Figure 1).³ The formed product involves attack syn to the ethyl group.

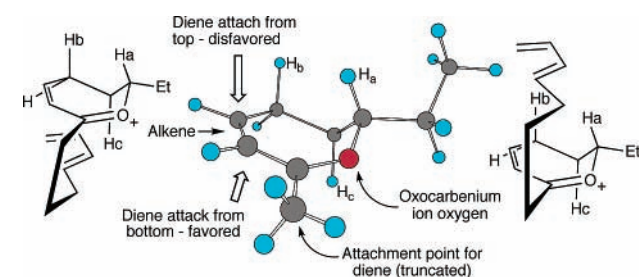


Figure 1. AM1 optimized model reactant (center) and cycloaddition transition states (left and right) proposed by Sammakia and co-workers.³

We have previously shown that reactions tend to occur with staggered arrangements about bonds to the reacting centers.⁵ For that reason, a different transition state for the disfavored approach was expected. Consequently, we undertook a theoretical investigation of the reaction. B3LYP/6-31+G* density functional theory calculations as implemented in Gaussian 03⁶ were used to locate the transition states for model systems of **1** and to provide a more detailed explanation of the stereochemistry.

Four transition structures (TSs) were located for the intramolecular ionic DA reaction of a model for **1**: endo syn (**7**) and anti (**8**) with respect to the methyl group (modeling the TMSOCH₂CH₂ group in **1**) and exo syn (**9**)

and anti (**10**). The endo syn TS is preferred ($\Delta H_{\text{exo-endo}} = 0.9$ kcal/mol), and the difference in enthalpy for the two endo DA TSs is 1.9 kcal/mol. All TSs (Figure 2) are fairly asynchronous; the forming σ -bonds fall in the range of 2.05–2.06 and 2.86–2.90 Å. This asynchronicity is a result of electron withdrawal from the oxocarbenium group in conjugation with the dienophile.

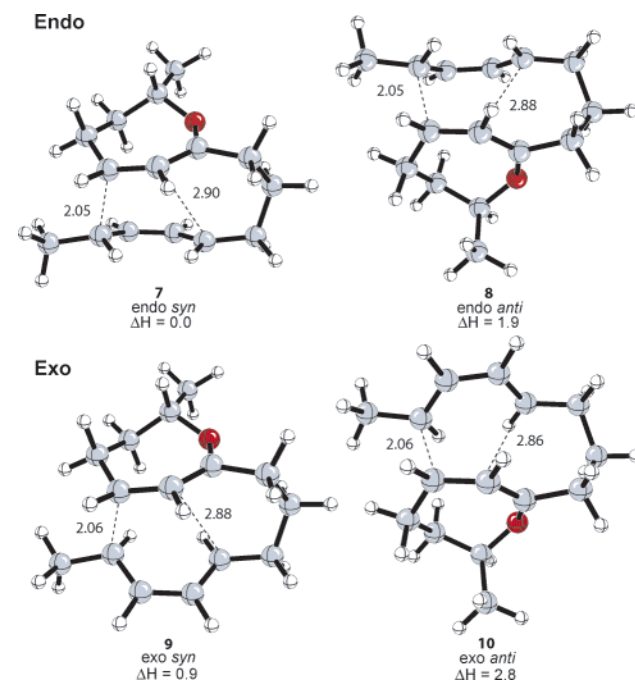


Figure 2. B3LYP stationary points for four transition structures of the intramolecular Diels-Alder reaction of model **1**. Distances are in Å. Relative enthalpies are in kcal/mol.

When a search for transition structures involving eclipsing around forming bonds was performed, four higher energy TSs were located. All these eclipsed TSs (Figure 3) are similarly asynchronous; the forming σ -bonds falling in the range of 2.03–2.06 and 2.81–2.83 Å. The alkene hydrogen and H_b (from Sammakia's model) on the oxocarbenium ring are nearly eclipsed in each case, with the dihedral angles in a range of 3.0–17.0°.

If the seven-membered ring maintained its lowest energy conformation, the difference between endo syn and eclipsed

(5) (a) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971. (b) 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. (c) Evanseck, J. D.; Houk, K. H. *J. Am. Chem. Soc.* **1990**, *112*, 9148. (d) Wu, Y.-D.; Houk, K. N.; Paddon-Row, M. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1019. (e) Wu, Y.-D.; Li, Y.; Na, J.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 4625. (f) Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchinson, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 2204. (g) Ando, K.; Green, N. S.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 5334. (h) Behnam, S. M.; Behnam, S. E.; Ando, K.; Green, N. S.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 8970. (i) Cheong, P. H.-Y.; Yun, H.; Danishefsky, S. J.; Houk, K. N. *Org. Lett.* **2006**, *8*, 1513.

(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

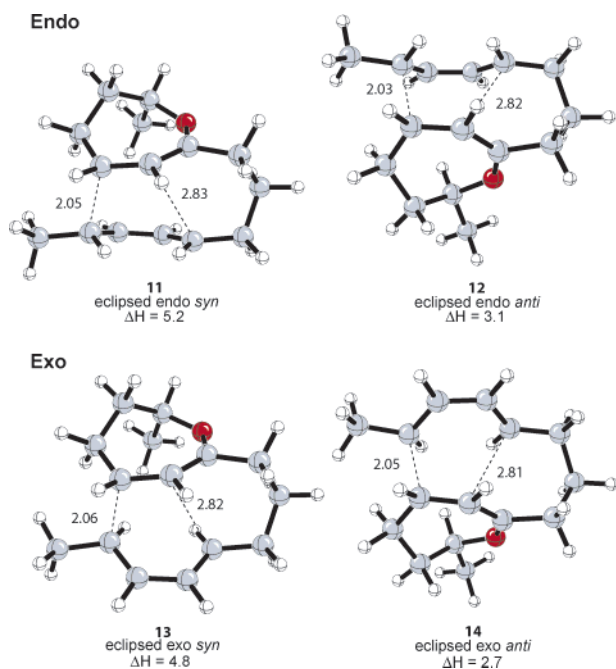


Figure 3. B3LYP stationary points for four eclipsed transition structures of the intramolecular Diels–Alder reaction of model **1**. Distances are in Å. Relative enthalpies are in kcal/mol and compared to **7**.

endo anti attack would be 3.1 kcal/mol. In fact, both go through staggered conformations (Figure 2), and the endo syn and endo anti difference is predicted to be only 1.9 kcal/mol, in good agreement with experiment.

How can the direction of attack be influenced by the apparently minor differences between the two faces of this alkene? The stereochemical outcome of this reaction arises from attack of the diene on the same face as the methyl

substituent in the oxocarbenium ring. This apparently con-
trasteric result can be best understood by considering the
preferred staggered conformation of the forming σ -bonds
with respect to the allylic bonds. Long recognized by Felkin⁷
for nucleophilic additions, transition state staggering, which
we have called torsional steering,⁵ determines the stereo-
selectivity of addition reactions. In the preferred TS conformer,
there is nearly perfect staggering with respect to the two
forming C–C bonds. When calculations are performed on
the model system lacking the methyl substituent on the seven-
membered ring, the eclipsed TS is 3.3 kcal/mol higher in
energy than the staggered. Similarly, the eclipsed transition
state conformations of the seven-membered oxocarbenium
ring suffer from torsional strain from eclipsed forming
bonds and are disfavored, as shown in Figure 3. The alkyl
substituent of the syn TS adopts a pseudoaxial conforma-
tion on the seven-membered oxocarbenium ring, repre-
sented in Figure 2. On the other hand, the same substituent
on the anti TS is pseudoaxial since the difference between
the staggering and eclipsing around the forming bonds is
greater than the difference between pseudoaxial and
pseudoequatorial methyl conformations.

To assess how larger substituents may influence the
stereoselectivity, single point calculations were performed
using B3LYP/6-31+G* density functional theory on pseudo-
axial and pseudoequatorial conformations for various alkyl
groups on the truncated oxocarbenium ring. Table 1 shows
the relative energies of these structures. Bulkier alkyl groups
lead to greater differences in enthalpy. The bulkier *tert*-butyl
group has greater 1,3-diaxial interactions in the pseudoaxial
position and is thermodynamically disfavored in this con-
formation. We predict that a bulkier substituent will show a
greater preference for a syn transition state with the sub-
stituent in a pseudoaxial conformation. A maximum
activation energy difference of 3.1 kcal/mol will be achieved

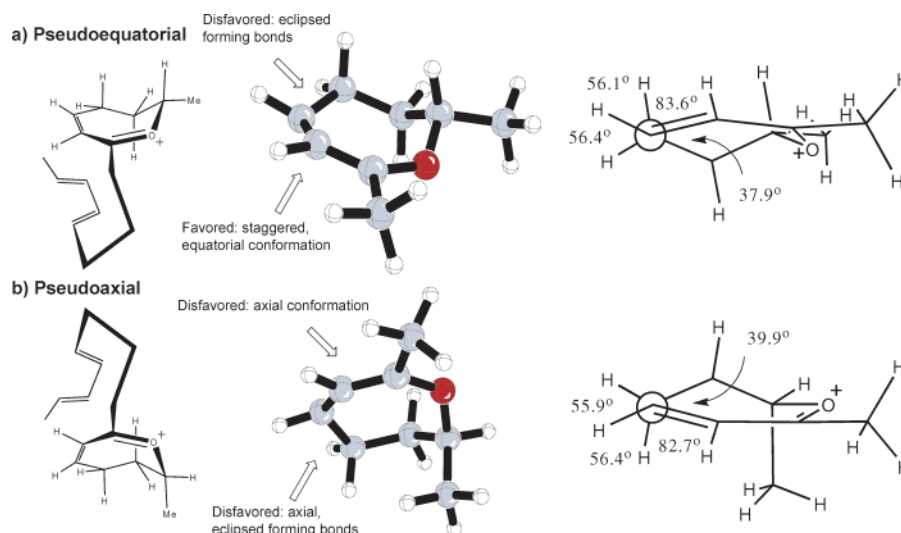


Figure 4. Transition structures of model reaction **1**, B3LYP optimized model reactants, and Newman projections of oxocarbenium rings.

Table 1. B3LYP Enthalpies for Pseudoequatorial and Pseudoaxial Conformations of Different Alkyl Groups on the Seven-Membered Oxocarbenium Ring

entry	R	pseudo-equatorial	pseudo-axial	$\Delta H_{\text{as-eq}}$ (kcal/mol)
1	Me			1.3
2	Ph			1.6
3	<i>t</i> -Bu			3.3

when the substituent is locked in the pseudoequatorial conformation.

These results provide another powerful example of the impact of torsional steering upon the stereoselectivities of additions to π -bonds, specifically in [4 + 2] cycloadditions. The new explanation of the origin of stereochemistry is shown in Figure 4. Torsional steering directs attack to occur

in a staggered formation. In the favored conformation of the oxocarbenium ring, this leads to a preference for attack syn to the methyl. Staggered attack anti to the methyl requires a ring flip to a higher energy conformation with a pseudoaxial methyl. The preference for a staggered conformation with respect to forming bonds controls stereoselectivity.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health for financial support of this research. The computations were performed on the UCLA Academic Technology Services (ATS) Hoffman Beowulf cluster. We thank Professors Tarek Sammakia, University of Colorado at Boulder, and William Roush, The Scripps Research Institute, Florida, for discussions and helpful comments on the manuscript.

Supporting Information Available: Cartesian coordinates, electronic energies, and zero-point vibrational energies of optimized structures of ground states and transition states. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL061085X

(7) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205.