J. Am. Chem. Soc. **2000,** *122,* 2948−2949

Transition States and Origins of Stereoselectivity of Epoxidations by Oxaziridinium Salts

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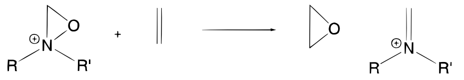
Received October 18, 1999
Revised Manuscript Received January 24, 2000

Oxaziridinium salts are highly reactive sources of electrophilic oxygen (eq 1)[1] and are promising candidates for asymmetric epoxidation reagents, a topic of great interest.[2] Chiral oxaziridiniums can react with facial selectivity with prochiral alkenes, and several iminium salts have been used as asymmetric epoxidation catalysts:[3] Oxone (potassium peroxymonosulfate) oxidizes an iminium salt to the oxaziridinium intermediate, which then transfers oxygen to an alkene. Iminium salts **1**[3a] and **2**[3b] afford *R,R*-stilbene oxide in 33−42 and 31% ee, respectively, and salt **3**[3d] gives stilbene oxide in 68−78% ee. An efficient and stereoselective iminium catalyst would be an attractive alternative to other available epoxidation methods, such as catalytic reactions with ketones.[4]



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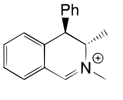

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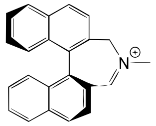

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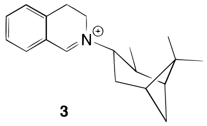

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To understand how stereoselective epoxidations by oxaziridiniums work and to design efficient catalysts, we have located transition structures (TS) for oxygen transfer from oxaziridinium salts to alkenes with quantum mechanical methods. We also examined the factors leading to stereoselective epoxidation for iminium salts **1** and **2**, as well as the highly asymmetric intramolecular epoxidation of **4**.[5]

Figure 1 shows B3LYP/6-31G*[6,7] calculated TSs for the epoxidation of ethylene by oxaziridinium (**A**), *N,N*-dimethyloxaziridinium (**B**), *C*-methyloxaziridinium (**C**), and *C,N,N*-trimethyloxaziridinium (**D**). The TS constrained to be planar is overlayed on the spiro TS in **B**. The activation energy for structure **A** is 1.4 kcal/mol, and the TS is very early. The two forming bonds are 2.6 Å, much longer than those in epoxidations by performic acid, dioxirane, and oxaziridine.[8] The methyl substituents on the oxaziridinium make the TS more advanced, due to cation stabilization in the reactant. Like the transition states found for alkene epoxidation by performic acid, dioxirane, and oxaziridine,[8] all transition structures for epoxidations by oxaziridiniums are spiro and synchronous. Structure **D** shows the calculated TSs for ethylene epoxidation by *C,N,N*-trimethyloxaziridinium in the gas phase and in a continuum solvation model[9] for dichloromethane ($\epsilon = 9.08$). The latter predicts a slightly later TS and a substantially higher activation energy.

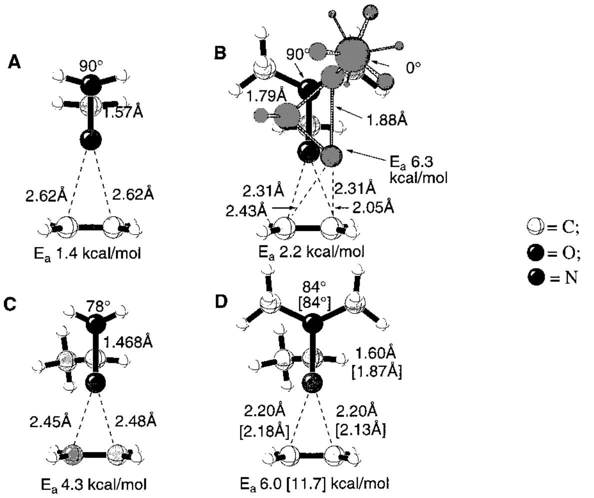

Figure 1. B3LYP/6-31G TS for epoxidation of ethylene by substituted oxaziridiniums. Numbers in brackets are for dichloromethane. Angles are dihedral angles formed by the planes of oxaziridinium of the forming oxirane ring.

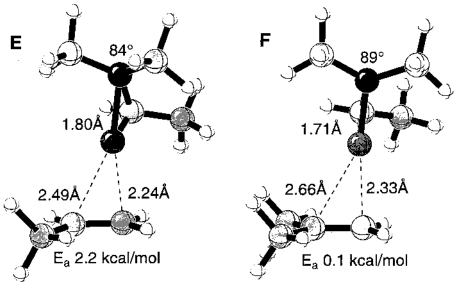

Figure 2. B3LYP/6-31G* TS for epoxidation of propene and isobutene by *C,N,N*-trimethyloxaziridinium.

Figure 2 shows the TSs for the epoxidations of propene and isobutene by *C,N,N*-trimethyloxaziridinium. The activation energies for epoxidations of the more nucleophilic, substituted alkenes are lower than that of ethylene. For isobutene (**F**) the gem-dimethyl group make the TS highly asynchronous.

Structures **G** and **H** (Figure 3) depict the two TS for attack on *trans*-2-butene. For structure **H**, there is steric repulsion between the substrate and an oxaziridinium methyl group. The TS is

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[6] Studies of performic acid, dioxirane, peroxynitrous acid, and oxiziridine epoxidations has shown that B3LYP/6-31G* calculations provide transition structure and energies in accord with available experimental data and QCI calculations.[8]

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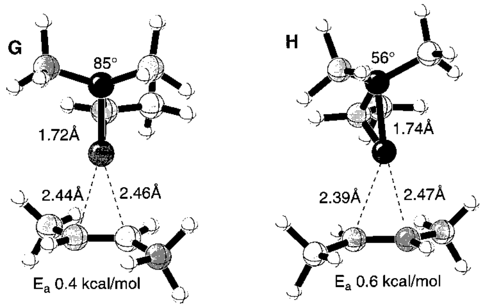


Figure 3. B3LYP/6-31G* TS for epoxidation of *trans*-2-butene by *C*,*N*,*N*-trimethyloxaziridinium.

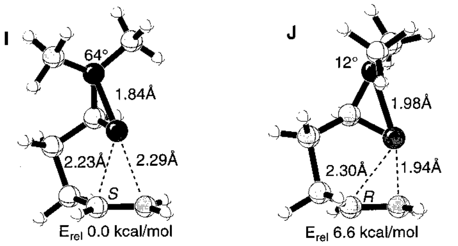
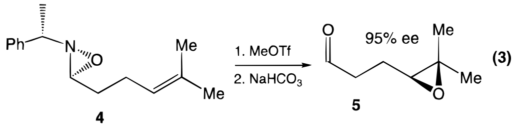


Figure 4. B3YLP/6-31G* TSs for intramolecular epoxidation.

twisted to an angle of 56°, and the forming O−C bond on the hindered side is stretched to relieve steric strain. The twisted structure **H** is only 0.2 kcal/mol above **G**. This small energy difference implies that there is conformational flexibility in the spiro TS. This is in contrast to the tighter TS found for epoxidation by dioxirane.[10] The flexibility of the spiro TS is a result of the early TS for epoxidation. Calculations for ethylene epoxidation by *N*,*N*-dimethyloxaziridinium (**B**) in which the geometry was constrained to be planar gave a structure that was 4.1 kcal/mol higher in energy than the spiro TS.

Compound **4** undergoes intramolecular epoxidation to yield the *S*-epoxide **5** in 94% ee beginning from **4** of >90% de (eq 3).[5]



This reaction has been modeled using *N*,*N*-dimethyl-*C*-(3-butenyl)-oxaziridinium. Structures **I** and **J** are the calculated TS leading to the *S*- and *R*-epoxides, respectively (Figure 4). The tether in **I** forces a synchronous TS in contrast to that found for propene. Structure **J** leading to the minor isomer is nearly planar, highly asynchronous, and is 6.6 kcal/mol higher in energy than **I**.

The TS for epoxidation by the oxaziridiniums of **1** and **2** were modeled at the B3LYP/6-31G*//AM1[11] level. AM1 was found to reasonably reproduce the TS geometries found at the B3LYP/6-31G* level. For epoxidation of ethylene by *C*,*N*,*N*-trimethlyoxaziridinium, AM1 gives a 90° TS, 2.00 Å for the two forming bonds, 1.66 Å for the C−N bond and a planar geometry that is 8.7 kcal/mol higher in energy. The TS is tighter, but similar to the B3LYP/6-31G* geometry (**D**).

Figure 5 shows the calculated TSs for epoxidation of *trans*-stilbene by the oxaziridinium of **1**. The oxaziridinium shown is the result of oxidation of **1** *cis* to the methyl, which occurs to minimize torsional strain, as established in related dihydroanthracenes.[12] The TS leading to the *R*,*R*-epoxide, shown in **K**, is favored by 4.2 kcal/mol, corresponding to higher selectivity than observed experimentally, but in the experimentally observed direction. In the disfavored TS (**L**), a phenyl group of stilbene is in a sterically crowded position under the fused arene ring. This is in contrast to the planar TS model that has been proposed to rationalize stereoselectivities for epoxidation of *trans*-stilbene by **1**.[3a]

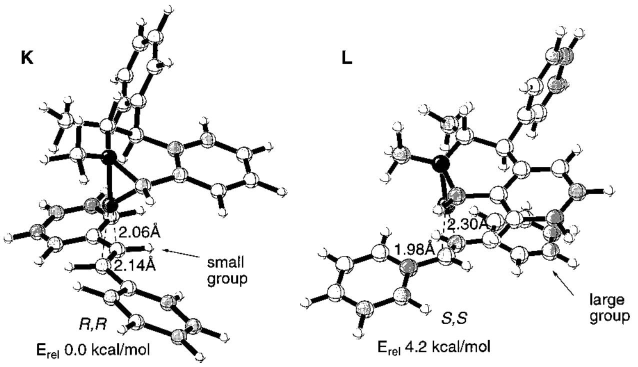


Figure 5. B3YLP/6-31G*//AM1 TS for epoxidation of *trans*-stilbene by the oxaziridinium of **1**.

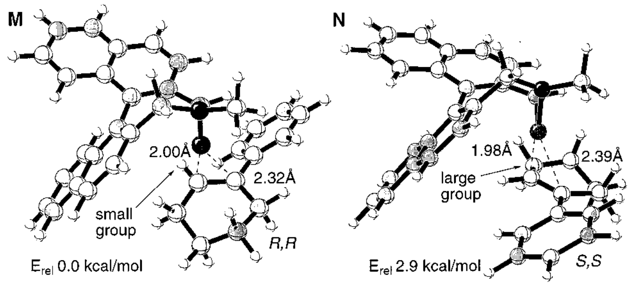


Figure 6. B3YLP/6-31G*//AM1 TS for epoxidation of 1-phenylcyclohexene by the S_C,R_N-oxaziridinium of **2**.

For iminium **2** it has been proposed that the stereochemistry of the oxaziridinium ring formed by Oxone oxidation or by peracid oxidation of the imine followed by alkylation is R_C,S_N. Although we could not locate the TS, the intermediates formed by nucleophilic attack of peroxymonosulfate anion on the iminium of **2** were located.[13] The intermediate leading to formation of the R_C,S_N isomer was 8.1 kcal/mol higher in energy than the intermediate leading to the S_C,R_N isomer, due to steric repulsion between the arene hydrogen and an oxygen.

Epoxidations of *trans*-stilbene and 1-phenylcyclohexene were modeled with both the R_C,S_N and S_C,R_N-oxaziridinium isomers. The R_C,S_N-oxaziridinium favored formation of the *S*,*S*-epoxides, while the S_C,R_N formed the *R*,*R* products. Experimentally the *R*,*R* product is formed in 31 and 71% ee respectively, from *trans*-stilbene and 1-phenylcyclohexene. For the S_C,R_N-oxaziridinium (Figure 6) the TS leading to the *(R,R)*-1-phenylcyclohexene oxide was 2.9 kcal/mol lower in energy than the TS leading to the *(S,S)*-stilbene oxide. In the disfavored TS (**N**), the CH_2 group of the cyclohexene ring is on the same side as the arene ring of the oxaziridinium oxidant. Although the stereoselectivity is overestimated, the direction of oxidation is that expected for steric control in the spiro TS.

The flexible spiro transition state provides a semi-quantitative account of the experimental stereoselectivities. These methods are being applied to the design of new oxaziridinium epoxidation reagents.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health (GM-36700) for financial support of this research and the National Computational Science Alliance (Illinois) for computer time and support. We thank Jian Liu and Nick DeMello for preliminary studies and Professor Dan Yang for discussions.

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[11] AM1 and PM3 calculations were preformed using SPARTAN V5.0; Wavefunction, Inc.

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