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Transition State Stereoelectronics in Alkene Epoxidations by Fluorinated Dioxiranes

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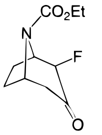
Dioxiranes derived from chiral ketones are highly promising reagents for the catalytic asymmetric epoxidation of alkenes.[1−16] Among chiral ketones that have been examined as dioxirane precursors, some of the most successful are substituted cyclohexanones bearing an electronegative heteroatom α to the carbonyl group.[2,4,13] The fluoro and other electronegative groups have been found to be strong activators in catalyzed epoxidations[17] involving **1**,[9] **2**,[13] **3**,[6] **4**,[4] and **5**[12] as catalysts. The electronegative substituent activates the ketone toward attack by the stoichiometric co-oxidant, $KHSO_5$, and also increases the reactivity of the resulting dioxirane. The heteroatom has also been implicated in the asymmetric induction.



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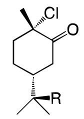

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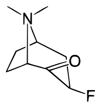

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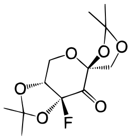

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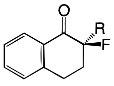

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Studies of conformationally fixed 4-*tert*-butyl-2-fluorocyclohexanones have revealed an interesting stereoelectronic effect: in general, equatorial fluoroketones are found to be more reactive than the corresponding axial isomers.[5,6] However, these studies are complicated by the fact that the monofluorocyclohexanones undergo Baeyer−Villiger decompositions at different rates, and by the strong tendency of the axial isomers to form stable hydrates.

The asymmetric epoxidation of stilbene by **1** was explained by a *spiro* transition state (TS) where the hydrogen substituent of the alkene occupies the region of the fluorine.[9] Similarly, asymmetric epoxidation of stilbene with **2** has been rationalized by *spiro*-attack *syn* to the axial chlorine atom.[13] Shi has proposed equatorial attack in his fructose-derived dioxirane, which has both equatorial and axial α-CO bonds.[15,16]

An understanding of the stereoelectronic effects operating in oxygen transfer would contribute greatly to the understanding of the role of the fluoro group (and other electronegative heteroatoms, or groups, Z) in these systems, and aid in the design of improved catalysts. We have explored stereoelectronic preferences in alkene epoxidations by fluorinated dioxiranes with quantum mechanical methods and report a dramatic conformational preference in the transition states.

The dioxirane derived from fluoroacetaldehyde is predicted to have three staggered minima: two are shown in Figure 1; the third is the enantiomer of **A**. B3LYP/6-31G(d)[18,19] calculations predict a 1.6 kcal/mol preference for conformation **A**, where the fluorine atom is anti to one of the dioxirane oxygens, over **B**, where the fluorine is gauche to both dioxirane oxygens. Simple Z−C−C−O groups prefer gauche conformations,[20] but there is too much electrostatic repulsion between F and *two* gauche oxygens held close together in the dioxirane.

Figure 2 shows the transition state computed for the epoxidation of ethene by methyldioxirane (**C**) and three transition states for epoxidation of ethene by fluoromethyldioxirane (**D**, **E**, **F**) all characterized by significant O−O bond breaking. The C−O bond to the transferring O is stretched, while the other C−O bond is shortened. The fluoro group is predicted to lower the activation energy compared to **C**. Remarkably **D** is preferred over **E** and **F** by 4.5 kcal/mol. Optimization with a bigger basis set (6-311++G(d,p)) gave relative energies of 0.0, 4.3, and 3.6 kcal/mol for **D**, **E**, and **F**, respectively. In **D** the fluorine atom is approximately anti to the dioxirane oxygen that is not transferred (F−C−C−O dihedral 172°). This arrangement minimizes electrostatic repulsion between the oxygen with greater developing negative charge and the fluorine (Mulliken charges: $O2 = -0.44$; $O3 = -0.32$; $F = -0.32$). A natural bond orbital analysis confirms the electrostatic origin of this conformational preference: there are no significant differences between bond orders of the C−O, O−O, and O−C bonds in the various transition states. In **D**, the inductive effect of the F lowers the E_a, and no electrostatic repulsion is introduced. In **E** and **F**, F−O repulsions counteract the inductive electron-withdrawal. Single-point calculations with a 6-31G(d) basis set in a continuum solvation model[21] for tetrahydrofuran ($\epsilon = 7.58$) and water ($\epsilon = 78.39$) gave activation energies of 11.0, 14.1, and 13.1 (THF) and 11.0, 12.7, and 10.9 kcal/mol (water) for **D**, **E**, and **F**, respectively.

There is also a close contact and potential weak interaction in **D** (2.30 Å) between the fluorine and an olefinic H (Mulliken charge = 0.20); the sum of the van der Waals radii of H and F

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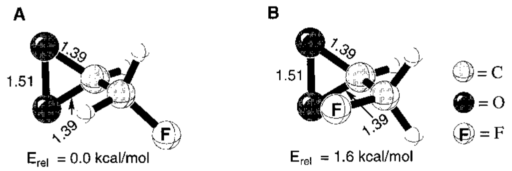

Figure 1. B3LYP/6-31G(d) optimized geometries for fluoromethyldioxirane. Distances are in angstroms.

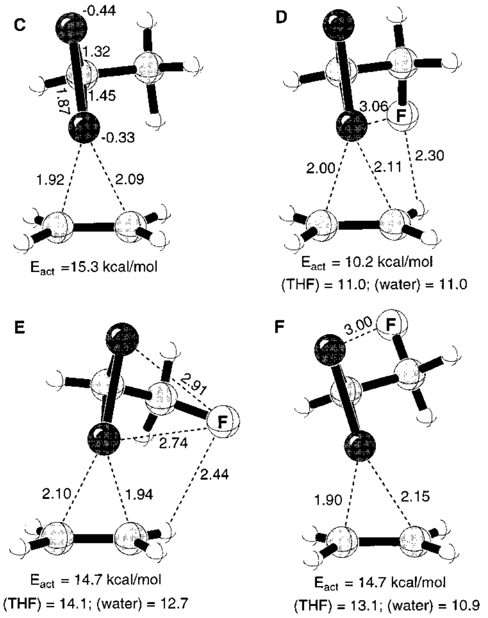

Figure 2. B3LYP/6-31G(d) TS for (C) epoxidation of ethene by methyldioxirane, and (D, E, F) epoxidation of ethene by fluoromethyldioxirane. Activation energies for D−F in THF and water used the CPCM[21] model.

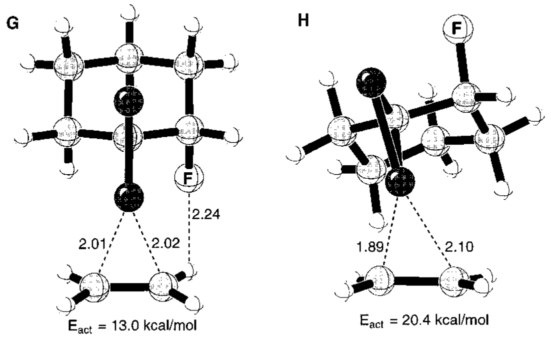

Figure 3. B3LYP/6-31G(d) TS for epoxidation of ethene by axial-2-fluorocyclohexanone dioxirane: (G) equatorial attack and (H) axial attack.

is ca. 2.5−2.7 Å.[22] When **D** was re-optimized with the inclusion of diffuse functions (B3LYP/6-31++G(dp)), the H−F distance was longer (2.44 Å), but still within the sum of the van der Waals radii.

The transition states for epoxidation of ethene by cyclohexanone dioxirane may involve transfer of either an equatorial oxygen or an axial oxygen. Equatorial attack is calculated to be preferred by 2.4 kcal/mol (18.2 vs 20.6 kcal/mol), since axial attack is disfavored by steric interactions between the ethene and the C3 and C5 axial hydrogens of the cyclohexanone.

Figure 3 shows B3LYP/6-31G* transition states for axial and equatorial attack by ethene on axial-2-fluorocyclohexanone dioxirane. The preference for equatorial attack is increased to 7.4 kcal/mol. This energy difference is largely due to the 5.2 kcal/mol stabilization of the TS for equatorial attack (compared to the TS for cyclohexanone dioxirane and ethene) due to inductive activation, unfettered by electrostatic repulsions. The activation energy for axial attack (**H**) is only very slightly lower in energy than that for cyclohexanone itself, since F inductive and O···F repulsion balance. The huge difference here will be effective in guiding the reaction to a single transition state.

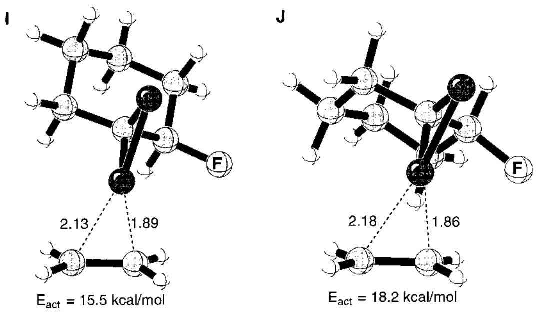

Figure 4. B3LYP/6-31G(d) TS for epoxidation of ethene by equatorial-2-fluorocyclohexanone dioxirane: (I) equatorial attack and (J) axial attack.

Transition states were also located for epoxidation of ethene by the dioxirane derived from equatorial-2-fluorocyclohexanone (Figure 4). Here the CF is held gauche to both oxygens. Equatorial (**I**) and axial (**J**) attack have only 2.5 kcal/mol lower activation energies than the corresponding reactants with cyclohexanone dioxirane. Structures **I** and **J** are highly asynchronous presumably due to electrostatic attractions and nonbonded repulsions.

Experimentally, chiral fluoroketone (*R*)-**1** reacts with (*E*)-5-decene to give (*E*)-(2*R*,3*R*)-2,3-dibutyloxirane in 44% ee.[23] Our calculations suggest that this occurs by equatorial attack *syn* to the fluorine.

Calculations suggest a marked stereoelectronic preference in alkene epoxidations by fluorinated dioxiranes. The transition state with fluorine anti to the dioxirane oxygen that becomes the carbonyl oxygen is preferred, placing the fluorine syn to the alkene. In addition, we have noted a preference for attack on the equatorial oxygen in cyclohexanone-derived dioxiranes. When combined, these effects predict that axial-substituted fluorocyclohexanones are more reactive than equatorial ones, and reaction should take place selectively via the dioxirane oxygen syn to the fluorine. However, the overall efficiency of a ketone catalyst will depend not only on the reactivity of the dioxirane in the oxygen transfer step, but also on the control of potential competing processes such as hydration and Baeyer−Villiger decomposition. For a series of ketones showing moderate hydration equilibrium constants, Yang has reported that there is no apparent correlation between tendency to form a hydrate and catalytic efficiency,[24] suggesting that controlling the Baeyer−Villiger reaction is the major problem. Interestingly, Shi has recently demonstrated that the degree of Baeyer−Villiger decomposition relative to dioxirane formation can be influenced by variation of the substituents β to the carbonyl group.[14] Providing that such competing pathways can indeed be controlled, the TS conformational preferences revealed in this work will be valuable in the design of improved catalysts, and efforts to exploit them are underway.

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Supporting Information Available: Energies and Cartesian coordinates of all structures reported here, and charges and dipole moments of structures in Figures 2−4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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