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[14] For the comparison of solid-state structures the distortion parameters used by Taylor and Marder have been chosen: 1) the slip parameter (Δ) defined as the difference in the average bond lengths of the metal to the ring junction carbons C(3a), C(7a), and of the metal to adjacent carbon atoms of the five-membered ring, C(1), C(3); 2) the hinge angle (HA) defined as the angle between the planes defined by C(1), C(2), and C(3) and C(1), C(3), C(3a), and C(7a). a) S. A. Westcott, A. K. Kakkar, G. Stringer, N. J. Taylor, T. B. Marder, *J. Organomet. Chem.* **1990**, *394*, 777–794; b) A. K. Kakkar, S. F. Jones, N. J. Taylor, S. Collins, T. B. Marder, *J. Chem. Soc. Chem. Commun.* **1989**, 1454–1456. For (*S*,*S*)-**10**, the HA values of 3.5° and the Δ value of 0.12 Å clearly indicate a η^5 coordination of the indenyl ligand.

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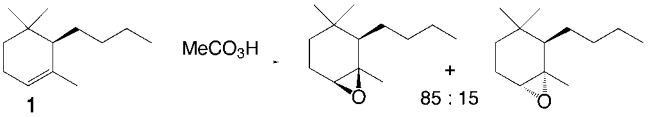
CH ··· O Hydrogen Bonding Influences π-Facial Stereoselective Epoxidations**

Ilyas Washington and K. N. Houk*

Epoxidations of *α*-cyclogeranyl systems,[1] such as **1** [Eq. (1)], occur *syn* to the alkyl group at C3, contrary to expectation based upon steric effects. To determine the origin and scope of this effect, transition structures have been located for oxygen transfer from peracetic acid to several substituted cyclohexenes (**2**–**4**) with quantum-mechanical methods. An explanation of the anomalous stereoselectivity of epoxidations of **1** was obtained and predictions were made about the



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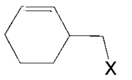
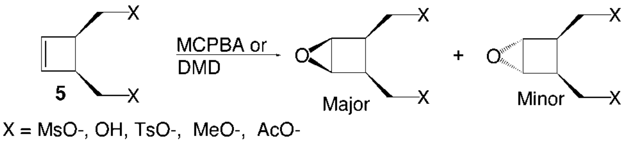
stereoselectivities of epoxidations of cyclohexenes **2**–**4** (OMs = methylenesulfonyloxymethyl). These predictions have been verified experimentally.



2: X= OMs, **3**: X = Br, **4**: X = CN

syn-Directing hydrogen-bonding groups that are able to differentiate diastereotopic faces of a C–C double bond for epoxidations have been widely used in synthesis.[2] Stabilizing hydrogen-bonding interactions between a –OH substituent on the alkene and the peracid oxygen atoms favor epoxidation *syn* to allylic and homoallylic alcohols.[3] A variety of other groups, such as, carboxamides,[4] sulfonamides,[5] carbamates,[6] amido,[7] urethano,[8] ureido,[9] unsaturated acetals,[10] sulfones,[11] sulfoxides,[12] phosphorus oxides,[13] and ammonium salts[14] have all been reported to show similar *syn*-directing effects. These observations have been associated with hydrogen bonding involving the alkene substituent and the peracid.

Surprisingly, the α-cyclogeranyl derivative **1**, which possesses no functionality near the reactive double bond, undergoes epoxidation by peracetic acid to yield the corresponding epoxides with a *syn* to *anti* ratio of 85:15 [Eq. (1)].[1] This observation has been rationalized based on the conformational preference for the axial half-chair conformation as well as on the electrostatic interactions between the peracid and the more electron-rich π face.[1] Similarly, *cis*-3,4(CH$_2$X)-substituted-cyclobutenes (**5**) [Eq. (2)] have also been reported to undergo selective *syn* epoxidation by *meta*-chloroperbenzoic acid (MCPBA) and dimethyldioxirane (DMD).[15] This has been explained by alkene pyramidalization and electrostatic interactions,[15a] as well as by attractive dipole–dipole interactions.[15b]



(2)

Figure 1 shows four B3LYP/6-31G(d)[16, 17] calculated transition states for the epoxidation of 2,3,4,4-tetramethylcyclohexene (a model for **1**) by peracetic acid. The tetrasubstituted cyclohexene has two half-chair conformations, with the C3 methyl group in axial or equatorial conformations. The conformation with an equatorial methyl group was calculated to be 0.7 kcal mol^{-1} higher in energy than that with an axial methyl group, which was attributed to A^{1,2} strain.[18] In **A**, attack *syn* to the methyl group at C3 has the lowest activation energy, in accord with the experimental preference for the analogous reaction of **1**. In **A** the oxygen that is transferred (O1) is 2.57 Å from a hydrogen atom on the C3 methyl group. The sum of O and H van der Waals radii is 2.6 Å. Transition states with shorter H···O distances (**B** and **C**) or with an equatorial methyl group (**D**) and no H···O contact are higher in energy than **A**.

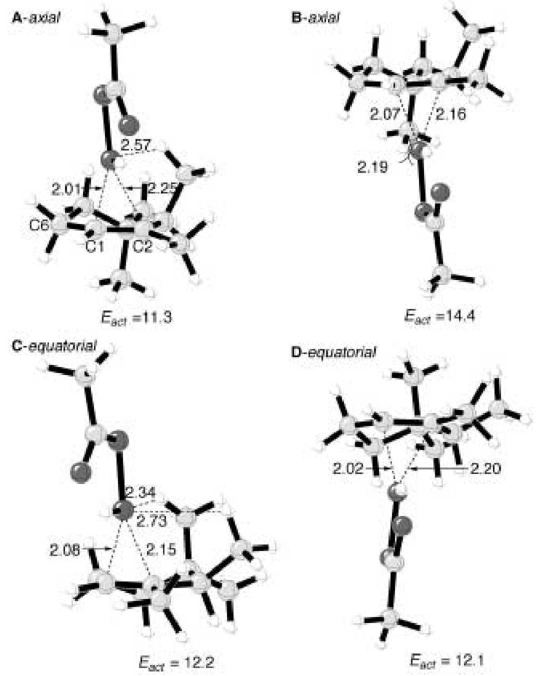
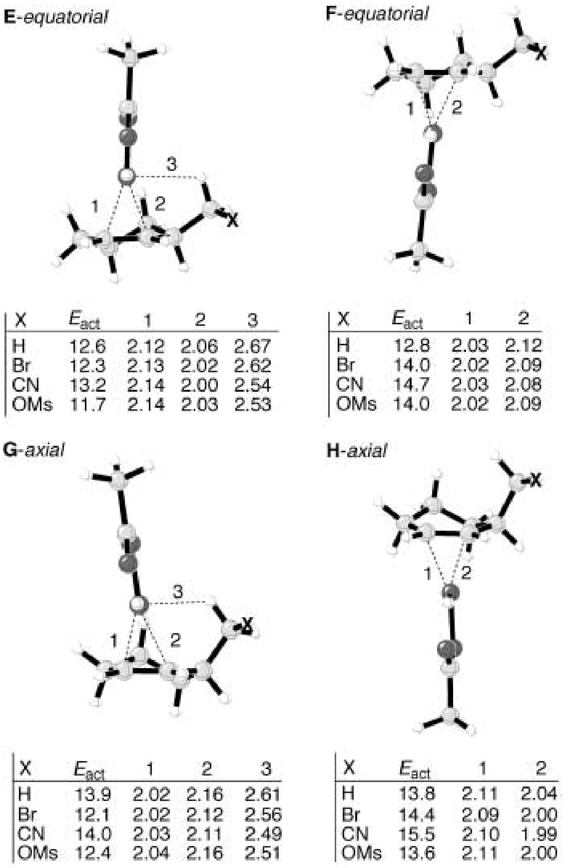


Figure 1. B3LYP/6-31G(d) transition states for epoxidation of 2,3,4,4-tetramethylcyclohexene by peracetic acid. Distances in Angstroms. Energies in kcal mol^{-1}.

Favored transition states **A** and **D** are more asynchronous than **B** and **C**. The C2 methyl group causes C1 to be more nucleophilic in all cases, but in **B** and **C** the forming O1–C1 bond and the axial C6–H bond are eclipsed, resulting in lengthening of the forming O1–C1 bond and a more synchronous transition state.[19] Calculations of the transition states for epoxidation of 1-methylcyclohexene, where the same eclipsing-synchronous and noneclipsing-asynchronous transition states were found, gave activation energies of 11.1 kcal mol^{-1} for the two transition states.

The lower energy of transition states **A** and **C** suggests that there is a slight attractive interaction between the C3 methyl group with the O1 atom of the peracid. Presumably, in **B** the H···O distance of 2.19 Å leads to repulsion. The C3 methyl group contains the C–H bond nearest to the atom O1; this C–H bond is 0.3 mÅ shorter than the other two C–H bonds of the methyl group. C–H bond contraction on the order of 0.2–0.5 mÅ is observed in documented cases of CH···O hydrogen bonding.[20]

Further support for a small attractive CH···O interaction was found in transition states calculated for the epoxidation of 3-methylcyclohexene by peracetic acid at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d)[21] level of theory (Figure 2). The half-chair conformation with an equatorial methyl group for the reactant is favored by 0.8 kcal mol^{-1} over the conformation with an axial methyl group. The transition state involving s*yn* attack (**E**) on the conformation with an equatorial methyl group is 0.2 kcal mol^{-1} lower in energy than **F**. The energy difference of 0.2 kcal mol^{-1} in favor of **E** over **F** is similar to estimates of attractive interactions between CH···O in other systems (0.3–0.7 kcal mol^{-1}).[22] The effect is very small, and a nearly equal mixture of the *cis* and *trans* epoxides are formed experimentally.[23]



E-*equatorial*

X	E_{act}	1	2	3
H	12.6	2.12	2.06	2.67
Br	12.3	2.13	2.02	2.62
CN	13.2	2.14	2.00	2.54
OMs	11.7	2.14	2.03	2.53

F-*equatorial*

X	E_{act}	1	2
H	12.8	2.03	2.12
Br	14.0	2.02	2.09
CN	14.7	2.03	2.08
OMs	14.0	2.02	2.09

G-*axial*

X	E_{act}	1	2	3
H	13.9	2.02	2.16	2.61
Br	12.1	2.02	2.12	2.56
CN	14.0	2.03	2.11	2.49
OMs	12.4	2.04	2.16	2.51

H-*axial*

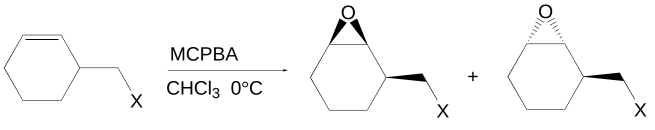
X	E_{act}	1	2
H	13.8	2.11	2.04
Br	14.4	2.09	2.00
CN	15.5	2.10	1.99
OMs	13.6	2.11	2.00

Figure 2. B3LYP/6-31 + G(d,p)//B3LYP/6-31G(d) transition states for epoxidation of 3-substituted cyclohexenes by peracetic acid. The structures shown are from the calculations for X = H.

The $CH_3 \cdots$ peracid hydrogen bonding in the epoxidation of 3-methylcyclohexene is not strong enough for significant differentiation of the two faces of the π bond. However, electronegative substituents on the methyl group could increase the attractive $CH \cdots$ peracid interaction to allow asymmetric epoxidation. Transition states were computed for epoxidations of the electronegatively substituted derivatives of 3-methylcyclohexenes. The results are shown in Figure 2. The conformation containing an equatorial bromomethyl group is favored by 0.1 kcal mol^{-1} over that containing an axial bromomethyl group. The preference for *syn* attack (**E** and **G**) over *anti* attack (**F** and **H**) is now very large (see Figure 2). In the *syn* transition state of **3**, the distances between the methyl hydrogen atom and the oxygen atom of the peracetic acid are 0.05 Å shorter than for 3-methylcyclohexene. The bromine atom increases the electronegativity at the carbon atom making it a better hydrogen bond donor.[24]

Cyano and methylenesulfonyloxymethyl (OMs) groups showed a similar effect (Figure 2). The conformations containing an equatorial cyanomethyl or an equatorial methylenesulfonyloxymethyl group are favored by 0.5 and 0.3 kcal mol^{-1}, respectively, over the axial conformations. For the equatorial and axial cyanomethyl half-chair conformations, *syn* attack is favored by 1.5 kcal mol^{-1} over *anti* attack. For **2**, *syn* attack is preferred by 2.3 kcal mol^{-1} in the equatorial conformation and by 1.2 kcal mol^{-1} in the axial conformation. While the calculated $CH \cdots O$ interaction energies are smaller than that of similar $OH \cdots$ peracid interaction energies (which were calculated to be 2.8 kcal mol^{-1} for epoxidation of 2-cyclohexene-1-ol at the B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)[25] level) the difference in predicted activation energies between *syn* and *anti* attack for **2**–**4** are substantial enough for π-facial selectivity.

The predictions were tested by experimental epoxidations of **2**–**4** with MCPBA. Epoxidation of **2**–**4** gave quantitative yields of epoxides, stereochemical results are shown in Scheme 1. Compounds **3** and **4** gave *cis* and *trans* epoxide isomers in a ratio of 70:30 and 80:20, respectively, as measured by GC/MS of the crude reaction mixture. The stereochemistry of the major and minor epoxides was assigned by comparison of GC/MS retention times and ^{1}H NMR and ^{13}C NMR data for the reaction mixtures with data for the pure *cis*-3-bromomethyl-1,2-epoxycyclohexane and *trans*-3-cyanomethyl-1,2-epoxycyclohexane synthesized independently (see Experimental Section and Supporting Information). Epoxidation of **2** gave a *cis*:*trans* epoxide ratio of 93:7 as measured by GC/MS of the crude reaction mixture. The stereochemistry of the products was determined by ^{1}H NMR spectroscopy on the isolated epoxides.[26] Although the predicted stereoselectivity is overestimated, the experimentally determined preference for the *cis* epoxide is consistent with $CH \cdots O$ interactions in the transition state.



	X = H[23]	50	50
3:	X = Br	70	30
4:	X = CN	80	20
2:	X = OMs	93	7

Scheme 1. Ratios of stereoisomers obtained from epoxidations of 3-substituted cyclohexenes with MCPBA.

We have shown a new general effect that peracids prefer to attack *syn* to a homoallylic methyl group, a result of $CH \cdots O$ hydrogen-bonding. Although, the preference is small in the case of the unactivated methyl group, this *syn* preference increases for alkenes with electron-withdrawing substituents. With appropriate electron-withdrawing groups, this interaction may be exploited for stereoselective synthesis.

Experimental Section

General procedure for epoxidation of **2**–**4**: To a flask was added **2**, **3**, or **4**, dry $CHCl_3$, and MCPBA (0.9 equivalents, washed with pH 7 phosphate buffer, crystallized from diethyl ether/hexanes (1:3) and dried at 0.5 mmHg for 12 h). The mixture was stirred for 12 h at 0 °C. Additional MCPBA (0.3 equiv) was added and the mixture was stirred for 2 h at 0 °C, and then KF (to precipitate remaining MCPBA and *meta*-chlorobenzoic acid (MCBA),[27] 1.4 equiv) was added. Epoxide ratios were determined by

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Use of a Perfluoroalkylsulfonyl (PFS) Linker in a "Traceless" Synthesis of Biaryls through Suzuki Cleavage

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Solid-phase synthesis has attracted increasing attention from the scientific community and particularly from the pharmaceutical industry in an effort to speed up drug discovery.[1] A key component in solid-phase synthesis is the linker that is used to attach the molecules to the solid support. There has been significant interest in recent years to develop "traceless" linkers[2] which afford compounds suitable for biological assays lacking any extraneous functionality that may limit their usefulness as drug leads.

We recently reported the preparation of a perfluoroalkylsulfonyl (PFS) fluoride resin, **1** (see Scheme 1, in essence a triflate resin), and its application for the traceless synthesis of arenes using a palladium-mediated reductive deoxygenation.[3] We sought to extend application of this linker to a

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