An Evaluation of σ-σ^* and Torsional Effects in the Osmylation and Epoxidation of 4-*tert*-Butylmethylenecyclohexane Derivatives

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Received July 8, 1988

Several axially selective additions of methylenecyclohexane derivatives are known, including (1) epoxidation with peracids,[1a-c,2] (2) cycloaddition of $ClSO_2NCO$[1d] or $Cl_2C{=}C{=}O$,[1d,e] and intermolecular capture reactions of (3) cationic[1f-h,2] or (4) radical[1i] intermediates. Some of these results have been attributed to a stabilizing interaction between axial C_2-H σ-orbitals with the developing C_1 σ^* orbital in "anti" attack,[2,3] but there are other rationales[1b,4] as well as many examples of equatorial attack[5] that raise questions regarding the importance of the σ,σ^* effect.

We have studied epoxidations and osmylations of 4-*tert*-butylcyclohexane derivatives **1**[6] and **2**[2,6] to determine if selectivity patterns will reveal σ,σ^* interactions within a family of related substrates. Our experiments did not detect evidence of such trends. The results of Table I indicate a small increase in axial epoxidation of allylic ethers **2d** or **2e** vs the parent alkene **1a**, even though bonding anti to the best acceptor (X = OCH_3) is necessary. Only the axial alcohols (entries I-**2b,c**) deviate from the pattern of favored axial epoxidation, due to the familiar syn-directing effect of hydroxyl.[9] Especially revealing is the comparison of **1d** with **2e**; the product ratio is barely perturbed by the interchange of C_2 axial vs equatorial methyl and methoxy groups and there is no indication of specific σ,σ^* effects.

The analogous osmylations (Table II) are more complex and show a greater bias for equatorial attack. This pattern is observed for the parent alkene **1a**, for derivatives having an equatorial heteroatom (Table II, entries **1b-f**), and also for the axial alcohols (**2b,c**).[10] However, osmylation selectivity is inverted for all of the substrates **2** having axial 2-methoxy, 2-acetoxy, or 2-methylthio groups. Axial attack dominates, anti to the C_2 heteroatom. The switch to an axial preference is most striking in the case of the secondary ethers (entry II-**1c** vs II-**2d**) and sulfides (entry II-**1f** vs II-**2g**). The general trend for avoidance of ether or sulfide heteroatoms correlates with late transition state variants of the empirical Kishi model[12a] that maintain maximum separation of electron pairs[12b] but not with the "inside oxygen" model.[13]

Table I. Epoxidation (MCPBA/CH_2Cl_2) of Alkenes **1-2**

alkene	X	R	ax:eq (**3**:**4**)	alkene	X	R	ax:eq (**5**:**6**)
1a (**2a**)	H	H	69:31[a]				
1b	OH	H	60:40[b]	**2b**	OH	H	11:89[b]
1c	OCH_3	H	60:40	**2c**	OH	CH_3	13:87
1d	OCH_3	CH_3	88:12	**2d**	OCH_3	H	83:17
1e	OAc	H	75:25	**2e**	OCH_3	CH_3	83:17

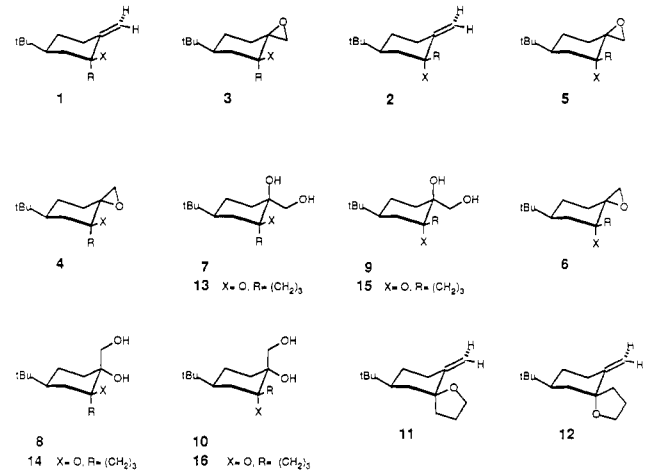
[a] Reference 1a. [b] Only the axial isomer was reported using *p*-nitroperbenzoic acid in chloroform (ref 19).

Table II. Catalytic Osmylation (NMMO/H_2O/Acetone)[18] of Alkenes **1-2**

alkene	X	R	ax:eq (**7**:**8**)[a]	alkene	X	R	ax:eq (**9**:**10**)[a]
1a (**2a**)	H	H	14:86[b]				
1b	OH	H	<5:95	**2b**	OH	H	33:67
1c	OCH_3	H	<5:95	**2c**	OH	CH_3	14:86
1d	OCH_3	CH_3	20:80	**2d**	OCH_3	H	88:12
1e	OAc	H	8:92	**2e**	OCH_3	CH_3	90:10
1f	SCH_3	H	<5:95[c,d]	**2f**	OAc	CH_3	67:33
				2g	SCH_3	H	92:8[c]

[a] Conversion to diols was >80% unless otherwise noted. Ratios were determined by NMR, and assignments were established by ^{13}C NMR (ref 7) after conversion to acetonides using $(MeO)_2CMe_2$/TsOH. [b] Reference 5a. [c] Equimolar OsO_4 in ether/pyridine was used to minimize sulfoxide formation. [d] Conversion of diol sulfide into sulfoxide (ca. 30%) was observed.

Chart I



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(6) Allylic alcohols were prepared via MCPBA epoxidation of enol silanes of 4-*tert*-butylcyclohexanone or the 2-methyl derivative to give diastereomeric 2-hydroxy-4-*tert*-butylcyclohexanones. Wittig methylenation of the acyloins and O-methylation gave **1c-e** and **2d-f**. A similar route via cis or trans 2-((*tert*-butyldimethylsiloxy)propyl)-4-*tert*-butylcyclohexanones gave **11** or **12** after deprotection and Mitsunobu cyclization. Thioethers were made by Wittig olefination of 2-(methylthio)-4-*tert*-butylcyclohexanone. Stereochemistry was established by ^{13}C chemical shift comparisons of cyclohexane ring carbons (C_3, C_5) in the epoxides **3-6** and in acetonides derived from the diols **7-10**.[7] The epoxides **3-6** were also correlated by cleavage to the corresponding **7-10** with hydroxide.

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(9) See: Berti, G., ref 1b, pp 130-152.

(10) Osmylation selectivity of **2c** increased to 5:95 (**5c**:**6c**) in dichloromethane, suggesting a role for hydrogen bonding in the directive effect.[11]

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Axial selectivity with **2d** is the result of unusually slow equatorial attack. Thus, a 1:1 mixture of equatorial **1c** and axial **2d** was subjected to osmylation with 0.1 equiv of OsO_4/pyridine. Diols derived from **2d** could not be detected by NMR analysis of the product (≥20:1 **8c**:**9d**). Since **9d** is formed ca. seven times faster than **10d** (Table II), the axial CH_3O group decreases the rate of *equatorial* osmylation of **2d** by at least two orders of magnitude relative to **1c**. Axial attack on **2d** is retarded less, and this is the source of the selectivity.

The trend for avoidance of ether oxygen is smaller when conformational restrictions are imposed on the C–O bond. Spirocyclic ethers **11** and **12** (prepared by Mitsunobu cyclization of the corresponding diols)[6] were subjected to catalytic osmylation. Isomer **11** was unexceptional and gave the normal preference for equatorial attack (ca. 4:1 **14**:**13**, >90%),[6] but **12** reacted nonselectively and afforded a 1.1:1 mixture of diols (>90%). Higher selectivity in the unconstrained methoxy analogues **2** is therefore related to alkoxy rotamer issues and bears no simple relationship to the nature of anti σ orbitals.

The epoxidations of **1a–e** and **2d,e** are qualitatively consistent with a variation of the torsional explanation of Cherest and Felkin.[4a] The developing C_1---O bond must be longer than the partially rehybridized exocyclic methylene bond in the transition state (TS), and the latter should make the dominant contribution to the *steric component* (repulsion of filled orbitals) of torsional effects (1,2-interactions).[14] Comparison of *reactant-like* TS geometries shows that equatorial bonding encounters substantial eclipsing interactions, while axial bonding results in a more staggered arrangement of adjacent bonds. The result is an advantage for the axial product, provided that the reagent can avoid 1,3-interactions with the axial C–H bonds. This requirement is easily met in the epoxidations because asynchronous bonding of oxygen should be advanced at the methylene terminus vs C_1, placing the reagent far from cyclohexane substituents. The other axially selective additions of **1a** can be interpreted in a similar way by comparing 1,2-interactions of existing and developing bonds.[1,2] Caution is recommended because the torsional effect depends on the degree of rehybridization and on other details of TS geometry, but the concept is useful when the reagents are compact.

In the osmylations, the TS should be more product-like, and both the equatorial and axial bonding modes would have staggered geometries. Under these circumstances, 1,3-interactions due to osmate ligands can play the dominant role, and the equatorial TS is favored.[15] However, this trend is easily overcome by the oxygen avoidance phenomenon mentioned earlier.

Torsional barriers are proposed to contain a substantial σ,σ^* component as well as components due to filled orbital interactions.[14a] Their relative importance in the ground state is controversial,[14] but Tables I and II show no TS correlation between donor–acceptor properties of axial substituents and epoxidation or osmylation stereochemistry. The σ,σ^* contribution to $\Delta\Delta G^*$ must therefore be small. Hyperconjugative interactions may control stereochemistry in the absence of steric bias,[16] but other variables become more important in typical substrates, especially when heteroatoms are present.

The early TS concept of dominant 1,2-interactions by the existing bond vs the developing bond provides a simple explanation for other stereochemical results, such as the preferred axial addition of compact nucleophiles to cyclohexanones.[17] Solvation of the partial negative charge at oxygen (or coordination by bulky Lewis acids)[17b] may increase the effective bulk of the existing C–O bond and would further destabilize a partially eclipsed early TS for equatorial bonding.

Our discussion emphasizes repulsive terms of the torsional effect (steric repulsions, etc). Further investigations are under way to clarify the magnitude and geometric dependence of the 1,2- vs 1,3-interactions.

Acknowledgment. This work was supported by the National Science Foundation.

Supplementary Material Available: Spectral data (R_f, MS, IR, and ^{13}C NMR) for **1c–f**, **2c–g**, **11**, **12**, **3c–f**, **4c–e**, **5d,e**, **6d,e** and acetonides of **7c,d**, **8b–e**, **9c–g**, **10c–g**, and **13** (8 pages). Ordering information is given on any current masthead page.

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Kinetics of the Reaction of β-Methoxy-α-nitrostilbene with Thiolate Ions. First Direct Observation of the Intermediate in a Nucleophilic Vinylic Substitution

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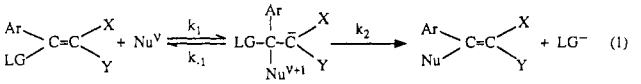
Received May 4, 1989

Nucleophilic vinylic substitution on substrates such as **1**, where XY are strongly electron-withdrawing groups and LG is a relatively sluggish leaving group, is believed to proceed by the addition–elimination mechanism[1] shown in eq 1. The evidence



(1)

1 2 3

includes the observation of base catalysis with amine nucleophiles,[2] k_{Br}/k_{Cl} ratios close to unity and k_F/k_{Cl} ratios ≫ 1[1a,d,e] (Br, Cl, F = LG), and the observation of stereoconvergence[1d,3] (both E and Z substitution products formed starting from either E or Z precursor). We now report the first example where **2** can be directly observed under conditions conducive to substitution. The

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