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Hyperconjugation as a Stereoinductive Factor in the Approach of Electrophiles to Trigonal Carbon

S. Srivastava and W. J. le Noble*

Department of Chemistry
State University of New York at Stony Brook
Stony Brook, New York 11794

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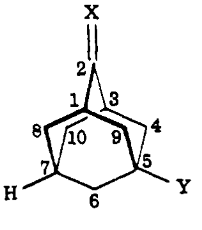
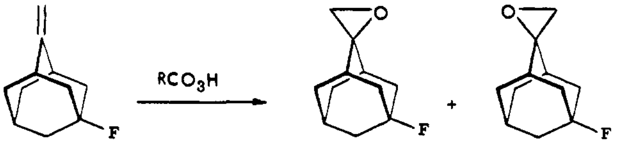
A recent report[1] from this laboratory described the virtues of 2,5-(or 1,4-)disubstituted adamantanes **1**-(X)(Y) in studies of the stereochemistry of addition to trigonal carbon: the rigid skeleton obviates questions arising from conformational uncertainty, the two faces of C_2 are sterically virtually equivalent, and the 5-substituent introduces a means of tuning these faces electronically. We found, for example, that electron-withdrawing groups Y direct nucleophiles to the syn side in carbonyl addition (X = O), and electron-donating groups direct them to the anti side. These facts provide strong support for the views of Cieplak, who holds[2] that the stereoselection of cyclohexanone reactions with nucleophiles is due to hyperconjugation: the ability of antiperiplanar σ bonds to delocalize into the newly developing σ^* orbital. Similar and even stronger stereoselection was found in 2-adamantyl carbocations—a fact that cannot be squared with any interpretation but neighboring carbon participation.



1-(X)(Y)

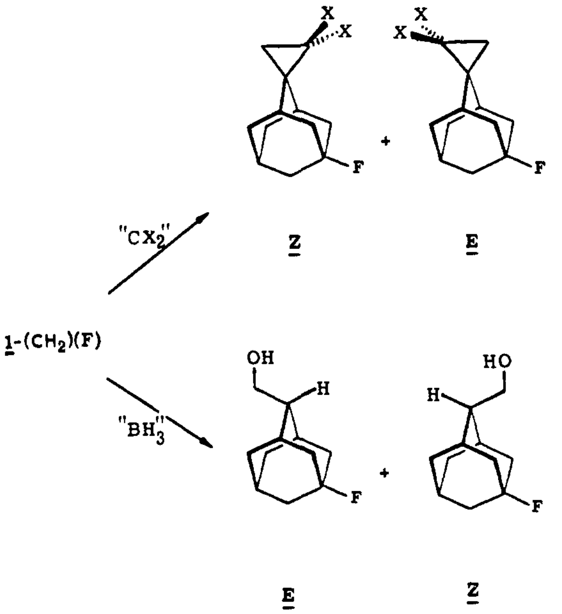
One might intuitively guess that electrophiles would exhibit the exact opposite face selectivity in their approach to trigonal carbon, but application of the Cieplak approach does not support this supposition. Regardless of which reaction partner contributes the bonding electrons, the σ^* orbital should attract electron density with the same directional preference as in the reaction of nucleophiles. We report here our findings with 5-fluoro-2-methyleneadamantane, **1**-(CH_2)(F), prepared via a Wittig reaction of **1**-(O)(F) (mp 124-5 °C; Anal. C, H).

Epoxidation of this compound with *m*-chloroperbenzoic acid gives a mixture of two oxiranes. The predominant isomer (66:34 ratio as determined by both GC and NMR integration) has the *Z* configuration. This was proved by means of the effect of $Eu(fod)_3$ on the ^{13}C NMR spectrum: in the *Z* product, C_5 is the bridgehead carbon atom subject to the far larger ^{19}F splitting *and* to the larger induced shift when compared to C_7.



1-(CH_2)(F) **Z** **E**

A 60/40 ratio was obtained in the addition of dichlorocarbene (chloroform and base under phase-transfer conditions); in this instance, strong NOE of the cyclopropyl hydrogens and the flanking pair at C_8 and C_{10} revealed the configuration of the predominant isomer to be *Z*. Similar results were also obtained with dibromocarbene (NOE) and in anti Markovnikov hydroboration (shift reagent shows that the product is predominantly the *E* alcohol resulting from syn approach).



These results provide strong support for the Cieplak view and contradict predictions by Klein.[3] It may be noted also that these reactions are among a number applied to norbornene.[4] In that case, exo approach is strongly favored, a fact that is often used to cast doubt upon the usefulness of exo reactivity as an argument for σ delocalization during the formation of the 2-norbornyl cation. The present demonstration that electrophiles and nucleophiles draw similar benefit from hyperconjugation leads us to precisely the opposite view.[5]

The effect is most pronounced with those electrophiles that become bound to the methylene carbon, so that the stereochemistry is then determined by the collapse of C_2 with a nucleophile. Thus, oxymercuration with mercuric acetate produces >95% *Z* alcohol, trifluoroacetic acid furnishes >99% *Z* ester, and HCl gas gives $\gg$99% *Z* dihalide. It is interesting that the selectivity is far less (~5:1) when the tertiary methyl alcohol (X = Me, OH) is used to generate the cation with HCl; evidently, it is strongly affected by the presence of a water molecule in the activated complex. We conclude by stating the simple rule that both nucleophiles *and* electrophiles, approach trigonal carbon from the direction anti parallel to the electrorichest single bond. There are indications both in the literature and in the results of our own further laboratory work that the proposition is valid also in pericyclic reactions. Whether this generalization is best understood with Cieplak's simple model or in alternative terms will undoubtedly

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[1] Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. Unfortunately, the *E* and *Z* entries for 5-OH in Table I in this paper were reversed (erratum submitted).

[2] Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

[3] Klein, J. *Tetrahedron* **1974**, *30*, 3349.

[4] Brown, H. C. *The Nonclassical Ion Problem*; Plenum: New York, 1977; with comments by P. v. R. Schleyer; see p 125.

[5] The same substituent effect has been reported in a few other reactions: (a) The singlet oxygen ene reaction to 7-isopropylidenenorbornenes (Okada, K.; Mukai, T. *J. Am. Chem. Soc.* **1978**, *100*, 6509. Results are attributed to π orbital distortion.). (b) Several electrophilic reagents with 7-isopropylidenenorbornenes and -benzonorbornenes (Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Böhm, M. *J. Am. Chem. Soc.* **1978**, *100*, 6510. Several possible reasons are analyzed.). (c) The NCS chlorination of 7-azabenzonorbornenes (Malpass, J. R.; Walker, M. P. *J. Chem. Soc., Chem. Commun.* **1979**, 585. Results are attributed to an electrostatic interaction between the succinimide and benzo rings.). (d) Singlet oxygen cycloaddition to substituted adamantylideneadamantanes (Hummelen, J. C. Thesis, University of Groningen, 1985, 76. Nelsen, S. F.; Kapp, D. L.; Akaba, R.; Evans, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6863. No explanations were offered.).

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be the subject of future discussions.[6]

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(6) Theoretical work pertinent to the chemistry reported here has been reported by the following: (a) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7396. (b) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908. (c) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703. (d) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328.

Effects of Sterically Remote Substituents on π-Facial Stereoselectivity in Additions to Methylenecyclohexanes

Carl R. Johnson,*[†] Bradley D. Tait,[†] and
Andrzej S. Cieplak*[‡]

Department of Chemistry, Wayne State University
Detroit, Michigan 48202
Department of Chemistry, Fordham University
Bronx, New York 10458

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Changes in electronic properties of a stereogenic center without accompanying changes in steric interactions at that site offer an important method to probe stereoelectronic effects. Recently the first comprehensive study of the impact of electronic modifications of the inducing center on stereoselectivity of nucleophile capture by either a carbonyl group or a carbonium ion has been reported by le Noble and co-workers.[1] By using the sterically nonbiased system of 5-substituted 2-adamantanones, these researchers addressed the fundamental problem of the nature and importance of hyperconjugative σ assistance in such reactions. The surprisingly large effects of remote substitution observed in these studies are consistent with the model of Cieplak.[2]

We have been interested in exploitation of the same approach in an attempt to address basic questions raised by theories of π-facial stereoselection. We were particularly intrigued by the generality of stereoelectronic control in reactions of diverse mechanisms and the importance of σ assistance in sterically biased systems. For this purpose, we have carried out an investigation of various reactions of methylenecyclohexanes substituted at C(-3) by groups of varying electronegativity and large steric bulk.

A series of cyclohexanones were converted to the methylenecyclohexanes by using Corey's procedure[3] for the Wittig reaction. The reagents chosen for study with these substrates were those which gave products readily transformable to methyl carbinols allowing straightforward structure assignments[4] (Scheme I).

Reaction of the exocyclic methylenes with mercuric acetate in water effected oxymercuration of the alkene.[5] Sodium borohydride in 3 N NaOH resulted in reductive demercuration giving the methyl carbinols.[6] Oxidation of the methylenecyclohexanes with *m*-chloroperoxybenzoic acid (*m*CPBA) afforded the epoxides. The mixtures of epoxides were converted into the methyl carbinols by reduction with lithium aluminum hydride.

Scheme I

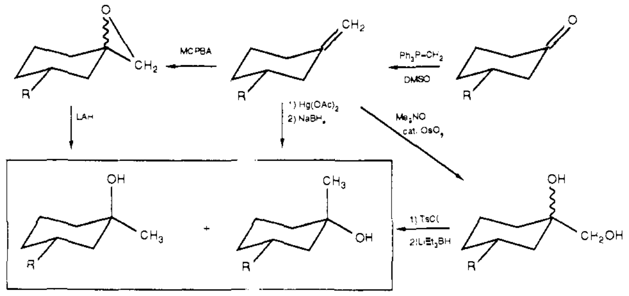

Table I. Percentage of Axial Attack in Reactions of C-3 Substituted Methylenecyclohexanes

entry	 R =	% 1[h] (0 °C)	2[i] (0 °C)	3[j] (25 °C)
a	Si(CH$_3$)$_3$	40	52	7
b	*t*-Bu	58,[b] 58[c]	60[d]	
c	H[a]	69,[b] 70[e]	69[f]	14[g]
d	C$_6$H$_5$	67	70	15
e	C$_6$H$_4$–CF$_3$-*p*	70	75	14
f	CF$_3$	92		

[a] The 4-*tert*-butyl derivative is used as the surrogate for the 3-*H* derivative. [b] Reference 5c. [c] Jasserand, D.; Granger, R.; Girard, J. P.; Chapat, J.-P. *C. R. Acad. Sci.* **1971**, *272C*, 1693. [d] Sevin, A.; Cense, J. M. *Bull. Soc. Chim. Fr.* **1974**, 963. [e] Jasserand, D.; Girard, J. P.; Rossi, J. C.; Granger, R. *Tetrahedron* **1976**, *32*, 1535. [f] Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363. [g] Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628. [h] Hg(OAc)$_2$, H$_2$O. [i] *m*CPBA, CH$_2$Cl$_2$ [j] OsO$_4$/Me$_3$NO, THF/H$_2$O.

Catalytic osmylation[7] of the methylenecyclohexanes afforded mixtures of diastereomeric vic diols. The assignments of the stereoisomers were assured by conversion of the diols to the methyl carbinols. This was accomplished by a two-step procedure. The primary alcohol was selectively tosylated, and the tosylate was removed by reduction with lithium triethylborohydride.

Oxymercuration occurs through the intervention of a mercurinium ion, apparently formed in a readily reversible process; CO bond formation (oxygen nucleophile attack) is the rate-limiting and product-determining step.[8] Peracid epoxidation[9] and cis hydroxylation with osmium tetroxide[10] are considered to occur by one step, irreversible synchronous additions to the alkene. Peracid epoxidations, in particular, are recognized to be electrophilic in nature; rates correlate with the nucleophilicity of the alkene.

Our results are presented in Table I, where C(-3) groups are listed according to the Charton's preferred σ_I values.[11] The ratios of diastereomeric products for 4-*tert*-butylmethylenecyclohexane are used as the surrogate reference point for the hypothetical 3-H substituted compounds. In each reaction series there is an increase in the proportion of axial attack with increase in the electronegativity of the remote 3-equatorial substituent; indeed, a plot of the logarithm of the ratio of isomers versus σ_I for five oxymercurations where the σ_I values are available reveals a reasonable

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[†] Wayne State University.

[‡] Fordham University.

(1) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

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(11) Charton, M. *J. Org. Chem.* **1964**, *29*, 1222.

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