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Local Conformer Control in Medium-Ring Olefin Epoxidation and Osmylation

E. Vedejs* and D. M. Gapinski

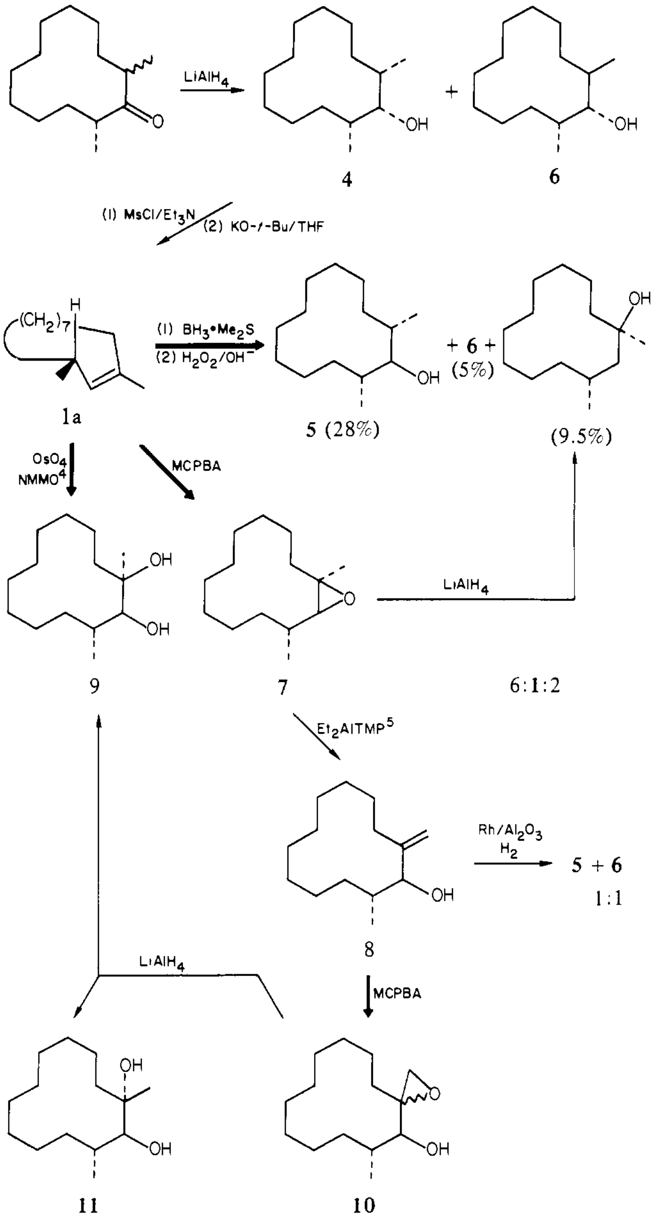
Contribution from the S. M. McElvain Laboratory of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received December 9, 1982*

Abstract: Epoxidation of di- or trisubstituted cyclic (*Z*)-alkenes of 10–15 members having an α-alkyl substituent occurs by least hindered attack on a geometry such as **1** having the allylic substituent pseudoequatorial. Similar selectivity is seen for α-branched *E*-trisubstituted cyclic alkenes. The *E*-disubstituted alkenes react with lower, but still useful, selectivity with MCPBA. However, osmylation of *E*-disubstituted cycloalkenes of 10, 12, and 15 members affords diastereomer mixtures with poor selectivity.

Medium- and large-ring alkenes are flexible molecules which have many conformational options. However, the local ring segment containing the alkene tends to adopt only certain geometries according to solid-state evidence.[1,2] Further restrictions in conformational options arise for molecules having an allylic alkyl branch point. In the case of (*Z*)-alkenes, a local conformation is favored where the allylic alkyl group can occupy a pseudoequatorial orientation, as in structure **1**.[1] Pseudoequatorial allylic alkyl is also observed in the (*E*)-olefin series, and the local olefin conformation can be described by a crownlike geometry as in **2**.[2] We have studied cis-addition reactions of representative cyclic alkenes having allylic methyl substituents to determine whether the stereochemistry of products can be correlated with transition-state geometries resembling **1** and **2**.

Our approach assumes the local conformer effects will dominate the effect of remote substituents. We expect this assumption to hold in molecules that are sufficiently flexible to avoid serious transannular interactions. Still and Galynker have developed a computational method which can estimate the relative importance of many individual conformers of the entire molecule.[3b] This technique has been used to predict the effect of remote substituents on carbon bond forming reactions of medium-ring ketones and lactones and should also be helpful in evaluating olefin addition reactions. Our study is more specialized and deals only with the effect of allylic substitution, but the results show that predictions can be made in most instances without knowing the details of medium-ring conformation. Least hindered ("peripheral")[3b] attack

Scheme I. Selective Addition Reactions (Bold Arrows) of (*Z*)-1,3-Dimethylcyclododecene (1a) and Correlations (Light Arrows)



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[1] Dictiodiol: Finer, J.; Clardy, J.; Fenical, W.; Minale, L.; Riccio, R.; Battaile, J.; Kirkup, M.; More, R. E. *J. Org. Chem.* **1979**, *44*, 2044. Neolemnanes: Izac, R. R.; Fenical, W.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, 2569. Rubradirin: Hoeksema, H.; Mizsak, S. A.; Baczynski, L. *J. Antibiot.* **1979**, *32*, 773. Macbecins: Muroi, M.; Haibara, K.; Asai, M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123. Latrunculine A: Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, 3629.

[2] **Dollabella** diterpenes: Ireland, C.; Faulkner, D. J.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1976**, *98*, 4664. Kijanimycin: Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D. *Ibid.* **1981**, *103*, 3940. Avermectins: Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221. Kromycin: Tsai, C.; Stezowski, J. J.; Hughes, R. E. *Ibid.* **1971**, *93*, 7286. Whaley, H. A.; Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, 3659. Obtusallene: Cox, P. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Ibid.* **1982**, 579. Tetronolide: Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sada, Y. *Ibid.* **1980**, 2559. Euphoscopins: Yamamura, S.; Kosemura, S.; Ohba, S.; Ito, M.; Saito, Y. *Ibid.* **1981**, 5315. Euglobal: Sawada, T.; Kozuka, M.; Komiya, T.; Amano, T.; Goto, M. *Chem. Pharm. Bull.* **1980**, *28*, 2546. Cytochalasin H: Beno, M. A.; Cox, R. H.; Wells, J. M.; Cole, R. J.; Kirksey, J. W.; Christoph, G. G. *J. Am. Chem. Soc.* **1977**, *99*, 4123. Chaetoglobosins: Springer, J. P.; Clardy, J.; Wells, J. M.; Cole, R. J.; Kirksey, J. W.; Macfarlane, R. D.; Togerson, D. F. *Tetrahedron Lett.* **1976**, 1355.

[3] Examples of selective medium and large ring alkene addition reactions: (a) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (c) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774. (d) Doskotch, R. W.; Kelley, S. L., Jr.; Bufford, C. D. *J. Chem. Soc., Chem. Commun.* **1972**, 1137. (e) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654. (f) Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249. (g) Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127.

[4] Van Rheenen, V.; Kelly, R. C.; Chan, D. Y. *Tetrahedron Lett.* **1976**, 1973.

[5] Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1705.

[6] Minimum 20:1 selectivity; minor isomer not detected by 270-MHz NMR.

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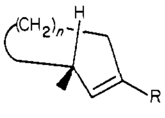
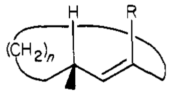
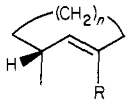
on local conformers **1** and **2** correlates very well with epoxidation or osmylation transition-state geometries inferred from the behavior of (*Z*)-olefins and trisubstituted (*E*)-olefins (R = alkyl). More ambiguous results are observed in the reaction of *E*-disubstituted olefins with the sterically demanding OsO_4 reagent. However, epoxidations occur as predicted from peripheral attack on local conformer **2**. Inspection of molecular models is sufficient to evaluate the relative importance of alternative local conformers such as **3**.



1



2



3

Results

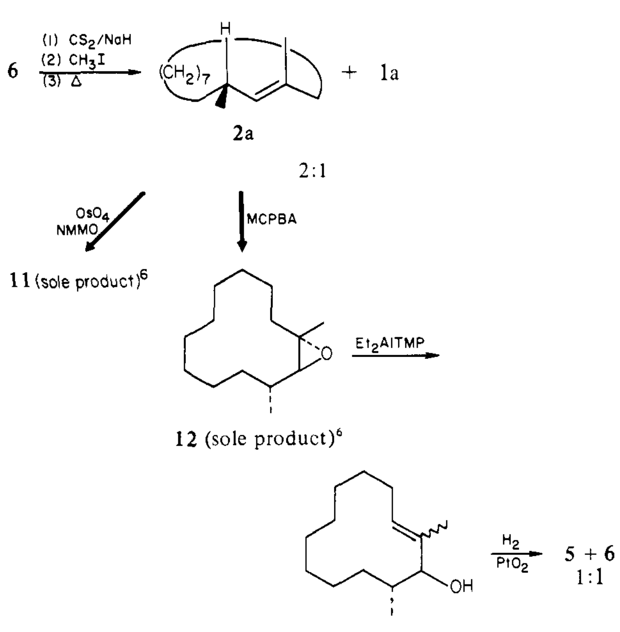
Addition reactions of 3-methyl-cyclododecenes **1a**, **2a**, **14**, and **15** have been examined in detail. In all cases where high selectivity has been observed, the stereochemistry of products has been proved by unambiguous synthesis. The geometry of alkenes has been confirmed by NOE studies for trisubstituted derivatives and by vicinal olefin coupling information in the case of disubstituted alkenes. Epoxidation and osmylation results are presented below in outline form, together with chemical correlation schemes to prove stereochemistry.

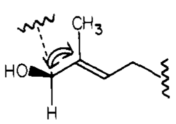
As shown in Scheme I, (*Z*)-1,3-dimethylcyclododecene (**1a**)[7] is attacked exclusively on the β-olefin face by *m*-chloroperbenzoic acid to give **7** and by OsO_4 to give **9**. Hydroboration occurs with approximately 9:1 β-face selectivity, but the products include an unusually large amount of tertiary alcohol and the total yield is only 43%. This reaction was done as part of the stereochemical correlation scheme and has not been investigated in other systems.

The correlations in Scheme I rest on the identity of dimethylcyclododecanols **4**, **5**, and **6**. *meso*-**5** is the only symmetrical isomer which can be formed by hydroboration from (*Z*)-olefin **1a**. The symmetrical isomer obtained by reduction of 2,12-dimethylcyclododecanone[8] must therefore be **4** which is formed together with *d,l* isomer **6**. Stereochemical assignments for epoxidation as well as osmylation use **8** as the key correlation compound. Of the two possible exocyclic alkene diastereomers, only **8** can give **5** by hydrogenation, and therefore **5**, **7**, and **8** must have two asymmetric centers of identical relative stereochemistry. Similarly, the mixture of epoxide diastereomers **10** must have the same methyl and hydroxyl stereochemistry at corresponding carbons as do **8**, **9**, and **11**. All of the addition reactions of **1a** occur with predominant or exclusive attack on the same olefin face.

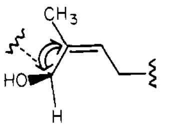
Correlations in Scheme II employ the same key reference structures as before. A comparison with results in Scheme I shows that the relative stereochemistry of attack at olefin C_2 with respect to olefin C_3 is the same in both (*E*)- and (*Z*)-alkenes. Only the stereochemistry at the carbon derived from olefin C_1 changes depending on olefin geometry. A similar analysis leads to the conclusion that allylic hydroxyl in the *E,Z* mixture **13** must not be sufficient to anchor either isomer into local conformations resembling **1a** or **2a**. Both **13**-*E* and **13**-*Z* would be expected to give **6** upon catalytic hydrogenation if the usual local conformers as shown above with pseudoequatorial hydroxyl were dominant in the transition state. This does not occur, partly because of unfavorable gauche or eclipsing interactions due to the adjacent olefinic methyl substituent, and a mixture of **5** and **6** results. Other factors may also be involved in this more complex substrate. These include the relatively small size of hydroxyl and the possibility that neighboring group participation by hydroxyl plays a role.

Scheme II. Selective Addition Reactions (Bold Arrows) of (*E*)-1,3-Dimethylcyclododecene and Correlations (Light Arrows)





13-*E*



13-*Z*

Correlations for the reactions of disubstituted 3-methylcyclododecenes in Scheme III are based on conversion of epoxides or diols into the known 2-methylcyclododecanol diastereomers **17** and **22**.[10] High selectivity for the same relative stereochemistry of epoxidation is observed as in Scheme I and Scheme II. Osmylation remains selective in the usual sense with (*Z*)-olefin **14**, but *E* isomer **15** reacts with low (1.9:1) and unknown selectivity. Among the reactions used for correlation purposes, the conversion of **20** into a 1:1 mixture of epoxides **24** and **25** is significant in the context of local conformer control. This result again suggests that allylic hydroxyl is not a reliable conformational anchor. The effect of allylic methyl remains dominant with disubstituted (*Z*)-olefin **14**, but the (*E*)-olefin **15** reacts with significant contributions from more than one transition-state geometry.

Because the behavior of disubstituted alkenes **14** and **15** suggests a more delicately balanced conformer population than for the trisubstituted alkenes, we have briefly explored two other ring sizes. As expected from the analogous reaction of **15**, osmylation selectivity is poor with (*E*)-3-methylcyclodecene (1:1 mixture) and (*E*)-3-methylcyclopentadecene (2:1 mixture). Product stereochemistry has not been proved in any of these marginally selective reactions.

Epoxidation of (*E*)-3-methylcyclodecene results in a 5.5:1 preference for the same relative stereochemistry as in **15** → **18**. In the more flexible (*E*)-3-methylcyclopentadecene, the analogous epoxidation preference falls to 3:1. In all three cases studied (10-, 12-, and 15-membered (*E*)-3-methylcycloalkene epoxidations) the NMR spectrum of the major epoxide has a singlet (!) for the C_3 methyl group due to accidental equivalence with strongly shielded C_3 methine hydrogen. Comparison of chemical shifts in the spectra of **18** and **19** (Scheme III) suggests that each epoxide adopts that crownlike local conformation which places epoxide oxygen "outside" the ring. Neighboring pseudoaxial substituents are

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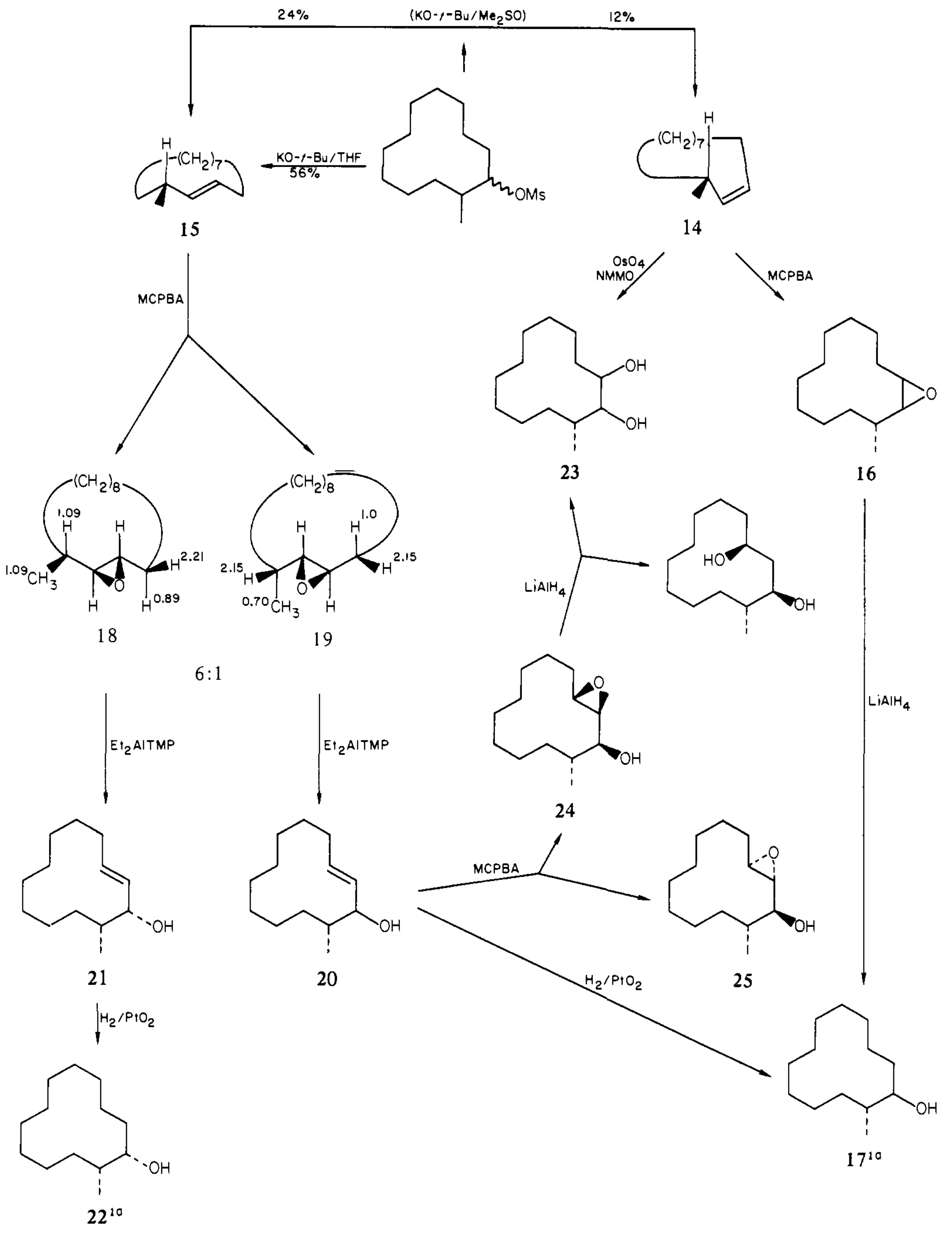
[7] Prepared by mesylate elimination from 4. The mesylate of 6 did not eliminate under the same conditions.

[8] Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076.

[9] Results for 2 and 14 are derived from studies using enriched *E*:*Z* mixtures. Product mixtures were assayed by 270-MHz NMR. Excellent peak resolution of methine and methyl signals allows detection of <5% isomer contaminants.

[10] Sicher, J.; Svoboda, M.; Pankova, M.; Zavada, J. *Coll. Czech. Chem. Commun.* **1971**, *36*, 3633.

Scheme III. (*E*)- and (*Z*)-3-Methylcyclododecenes



significantly shielded relative to their pseudoequatorial counterparts, an effect which is also seen in the *CH*OH proton of **25** (2.98 ppm) vs. **24** (3.63 ppm) and in simpler analogues.[11b]

In the (*Z*)-olefin series, epoxidation of 3-methylcyclooctene,[14a] 3-methylcyclodecene, and 3-methylcyclopentadecene occurs with high selectivity[6] as in the 12-membered ring case. Osmylation affords a single diol with the 8- and 10-membered rings and a 4:1 mixture with the 15-membered analogue. The stereochemistry of osmylation products in these examples has not been rigorously proved, but the usual preference as in **14** → **23** can be assumed by analogy to the (*Z*)-alkene epoxidations. Correlations in the epoxidation experiments have been performed by the same methods used in Scheme III.

Summary

Epoxidation selectivity is good with medium-sized-ring 3-methyl (*E*)-alkenes and can be rationalized by least hindered (peripheral)[3b] attack on a crownlike local conformer such as **2** (pseudoequatorial allylic methyl).[11] The same transition-state geometry can be invoked for the reaction of OsO_4 with *E*-trisubstituted **2**[12] but not with disubstituted 10-, 12-, or 15-membered (*E*)-alkenes. Significant osmylation of both olefin faces suggests that pseudoequatorial C_3 methyl in **15** may interfere with approach by bulky $OsO_4(L)_2$. Alternative geometries where the C_3 methyl is in the olefin plane may become more reactive. For disubstituted *E* olefins, reasonable possibilities include the crownlike local conformer **3** (R = H) with CH_3 in a pseudoaxial orientation or noncrown variants where the CH_3 group remains eclipsed with the olefin β-substituent. Such local conformers are unlikely for trisubstituted (*E*)-alkenes (**3**, R = alkyl), and transition-state geometry **2** is strongly favored. It may be significant that a

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[11] Other examples: (a) Corey, E. J.; Weigel, L. O.; Chamberlin, R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613 (allylic methyl and OH substituents). (b) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *Ibid.* **1979**, *101*, 159. (c) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670 (allylic OH substituent only).

[12] Other examples: Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979; also, ref 3g.

crownlike geometry with pseudoaxial methyl is observed as the preferred local conformation of the minor epoxides (**19**, for example) obtained from *E*-disubstituted 3-methylcycloalkenes.

Transition-state geometries resembling any of these (*E*)-olefin conformers will encounter considerable transannular interactions as rehybridization proceeds. Thus, several factors complicate the correlation of favored ground-state and transition-state local conformation in reactions involving *E*-disubstituted cycloalkenes and bulky reagents. As noted earlier, our generalization is intended for use only with (*E*)-olefins having allylic *alkyl* substitution. Although there are examples in the literature where allylic OH directs epoxidations in the same stereochemical sense as in our system with allylic CH_3,[11b,c] the effect is smaller and not as reliable. This is evident from the nonselective epoxidation of **20**. Predictions in the (*E*)-olefin series must be made with caution.[13]

On the other hand, the behavior of medium-ring (*Z*)-alkenes having an allylic (C_3) branch point is easily predicted as long as olefin C_2 does not have additional substituents. In all such cases described in this paper or in earlier work,[3g,11b,c,14] the major product can be rationalized by least hindered attack on a local conformer similar to **1**. Similar results have been observed for systems having either allylic hydroxyl or alkyl substitution, so the effect must be relatively large.

We believe that consistently high selectivity results from a good match between preferred local ground-state and transition-state geometry. Both CH_3 and R occupy innocuous locations near the olefin plane in conformers such as **1**, and there is sufficient flexibility to minimize transannular effects as rehybridization occurs. The selectivity is often large enough (>20:1 product ratios) to justify stereochemical predications based on the dominant local conformer even in more complex systems where other important conformational factors may not be known.

Acknowledgment. This work was supported by a grant from the National Science Foundation (Grant CHE-8113026).

Supplementary Material Available: Table I, reduction of 2-methylcycloalkanones with $LiAlH_4$, Table II, formation of medium-ring cycloalkene by mesylate elimination, Table III, epoxidation of allylically substituted medium-ring olefins with mCPBA, Table IV, osmylation of allylically substituted *Z* medium-ring olefins, and Table V, osmylation of medium-ring allylically substituted (*Z*)-olefins, and complete experimental details and spectra data (44 pages). Ordering information is given on any current masthead page.

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(13) We have described an example of osmylation of an *E*-trisubstituted alkene which occurs with high selectivity *opposite* to what is predicted using a local geometry as in **2**.[3g] A transannular electron-deficient π-system appears responsible for the anomaly.

(14) (a) Cope, A. C.; Wood, G. L. *J. Am. Chem. Soc.* **1963**, *85*, 3601 (allylic methyl). (b) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *Ibid.* **1969**, *91*, 6892. (c) Friedrich, E. C.; Biresaw, G. *J. Org. Chem.* **1982**, *47*, 2426. (d) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *Ibid.* **1977**, *42*, 3031 (allylic OH).

(15) Brown, H. C.; Varma, V. *J. Org. Chem.* **1974**, *39*, 1631.

Description of Conjugation and Hyperconjugation in Terms of Electron Distributions

R. F. W. Bader,*† T. S. Slee,† D. Cremer,‡ and E. Kraka‡

Contribution from the Department of Chemistry, McMaster University, Hamilton, Ontario, Canada L8S 4M1, and the Lehrstuhl für Theoretische Chemie, der Universität zu Köln, 5000 Köln 41, West Germany. *Received January 10, 1983*

Abstract: This paper presents a description of CC bonds in hydrocarbons in terms of the properties of the charge density ρ at a bond critical point. This is the point ($\mathbf{r}_c$), where ρ attains its minimum value along the path of maximum density (the bond path) linking the nuclei of neighboring atoms. A bond order is defined in terms of ρ_b, the value of ρ at $\mathbf{r}_c$. A measure of the deviation of the charge distribution of a bond path from axial symmetry is provided by the bond ellipticity $\epsilon = \lambda_1/\lambda_2 - 1$, where λ_1 and λ_2 ($|\lambda_1| > |\lambda_2|$) are the two negative curvatures of ρ at r_c. The value of ϵ is zero for the CC bond in ethane of order 1 and attains some maximum value for CC bonds of order 2. The ellipticity thus provides a quantitative measure of the π character of these bonds and the plane of the π distribution is uniquely specified by the direction of the axis associated with the curvature of smallest magnitude, λ_2. The values of ρ_b and ϵ enable one to translate the electronic effects predicted by orbital models into observable properties of ρ. Conjugative interactions between single and double bonds are reflected by $n > 1$ and $\epsilon > 0$ for the CC bonds of formal order 1. The major axes of the ellipticities induced in the single bonds are parallel to the corresponding axes of the double bonds. The largest effects are found for systems with an aromatic delocalization of π electrons. Antiaromaticity is reflected by a decrease in the value of n and ϵ for the intervening single bonds. Hyperconjugation is also reflected by a value of $n > 1$ and an $\epsilon > 0$ for the participating CC single bond. The CC bonds of a cyclopropyl fragment also exhibit substantial ellipticities as a consequence of the proximity of a ring critical point to the bond critical points in three-membered ring systems. The conjugative interaction of a three-membered ring with an unsaturated system as rationalized in terms of the Walsh orbitals for cyclopropane is here given a physical basis in terms of the topological properties of the charge density.

The topology of a molecular charge distribution yields a single unified theory of molecular structure, one that defines atoms, bonds, structure, and the mechanisms of structural change.[1,2] The same theory defines all average properties of an atom in a molecule.[3]

One may unambiguously assign a chemical structure to a molecule by determining the number and kind of critical points in its electronic charge distribution, points where $\nabla\rho = 0$. The same information enables one to determine whether or not the structure is topologically stable with respect to the making and/or breaking of chemical bonds. If it is unstable, one may predict the possible ensuing structural changes. The determination of

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† McMaster University.

‡ Universität zu Köln.

(1) (a) Bader, R. F. W.; Anderson, S. G.; Duke, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 1389–1395. (b) Bader, R. F. W.; Nguyen-Dang, T. T.; Tal, Y. *J. Chem. Phys.* **1979**, *70*, 4316–4329.

(2) Bader, R. F. W.; Nguyen-Dang, T. T.; Tal, Y. *Rep. Prog. Phys.* **1981**, *44*, 893–948.

(3) (a) Bader, R. F. W. *J. Chem. Phys.* **1980**, *73*, 2871–2883. (b) Bader, R. F. W.; Nguyen-Dang, T. T. *Adv. Quantum Chem.* **1981**, *14*, 63–124.

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