

THEORETICAL STUDIES OF THE STEREOSELECTIVITIES OF ORGANIC REACTIONS

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Abstract: Transition structures for additions to propene confirm the general preference for allylic bonds to be staggered with respect both to partially formed bonds and to the partially pyramidalized carbons undergoing attack. The significance of these results are discussed for models of asymmetric induction, Huisgen's factor "x", the stereoselectivities of additions to bicyclic alkenes, and the stereochemistry of the S_N2' reaction.

During the last few years, my colleagues and I have undertaken the theoretical investigation of the factors which influence the stereoselectivities of organic reactions. Here, I would like to present a progress report on the interesting discoveries which we have made during that time.

The origin of asymmetric induction has been of continual interest, but theoretical attention on this subject is now unusually high, spurred by the considerable practical import that such processes have gained for the stereospecific synthesis of natural products. Various empirical models have been proposed to rationalize the preference for attack on the "top" or "bottom" of an alkene with diastereotopic faces. Three common models of this type are summarized in Fig. 1.¹⁻¹⁰

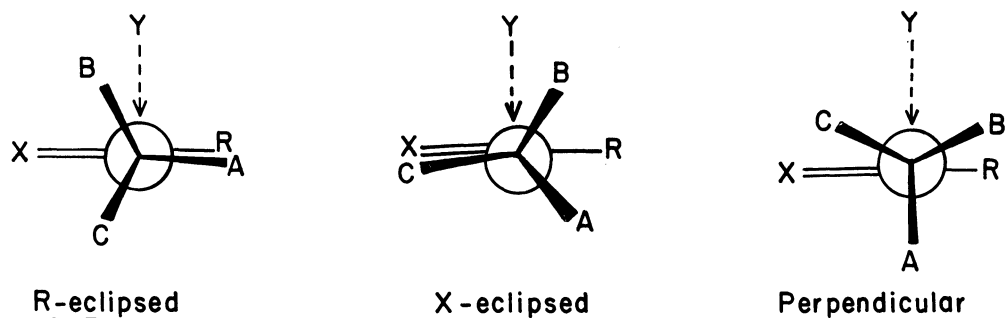


Fig. 1. Models of asymmetric induction.

These models differ by the choice of the conformation of the chiral center with respect to the center at which a new bond is being made, and by the positioning of large (L), medium (M), and small (S) allylic substituents on the chiral center. In the epoxidation of allylic alcohols, the hydrogen-bonding potential of the allylic hydroxyl substituent, rather than the size of the group, is frequently invoked to rationalize the preferred position of the hydroxyl group. The "X-eclipsed" (double-bond eclipsed) model is based on the assumption that a conformation similar to that of the isolated alkene or carbonyl is maintained in the transition structure.^{3,6a,8,10} The "R-eclipsed" (single-bond eclipsed) model incorporates a conformation which is an energy maximum in the reactants.^{2,6b} An intermediate geometry is assumed for the "perpendicular" model.^{4,5,7,9}

Anh's calculations on model geometries for the transition structures for attack of nucleophiles on carbonyls,⁵ and ours for the attack of nucleophiles, radicals, and electrophiles on substituted alkenes¹³ indicate that allylic bonds are staggered with respect to partially formed bonds in the transition states of addition reactions. Such conformations also allow staggering of the partially pyramidalized carbon¹³ undergoing attack with respect to the allylic bonds. The arrangement of allylic bonds is dictated by the trajectory of the forming bond, indicating that the exact conformation of the chiral center in the transition structure varies for different reagents.^{14,15}

Transition structures for reactions which are representative of nucleophilic, radical, and electrophilic additions to substituted alkenes were obtained by gradient searches with ab

initio calculations and the 3-21G basis set.¹⁶⁻¹⁸ BH_3 represents a mildly electrophilic species, the addition of the hydrogen atom to propene is an example of a radical addition, while hydride represents a nucleophile. The transition structures for the attack of H^- and H^\cdot at the substituted carbon of propene, and BH_3 in both orientations are shown in Fig. 2.¹⁷ The transition structures for the different types of attack are quite varied. This has important bearing on Baldwin's rules for ring closure,¹⁴ which are based upon the trajectories of attack on various types of bonds. In particular, the nucleophilic reagent attacks with a CC-H angle of 126° , somewhat larger than has been deduced previously for the attack of nucleophiles on carbonyls.¹⁵ We have reported a similar trajectory for the attack of hydride on ethylene.²⁰ Radical (H^\cdot) attack is at a much less obtuse angle, while the mildly electrophilic borane B-C bond-forming process occurs at an acute angle. Other electrophiles are expected to attack at an acute angle, via bridged intermediates.

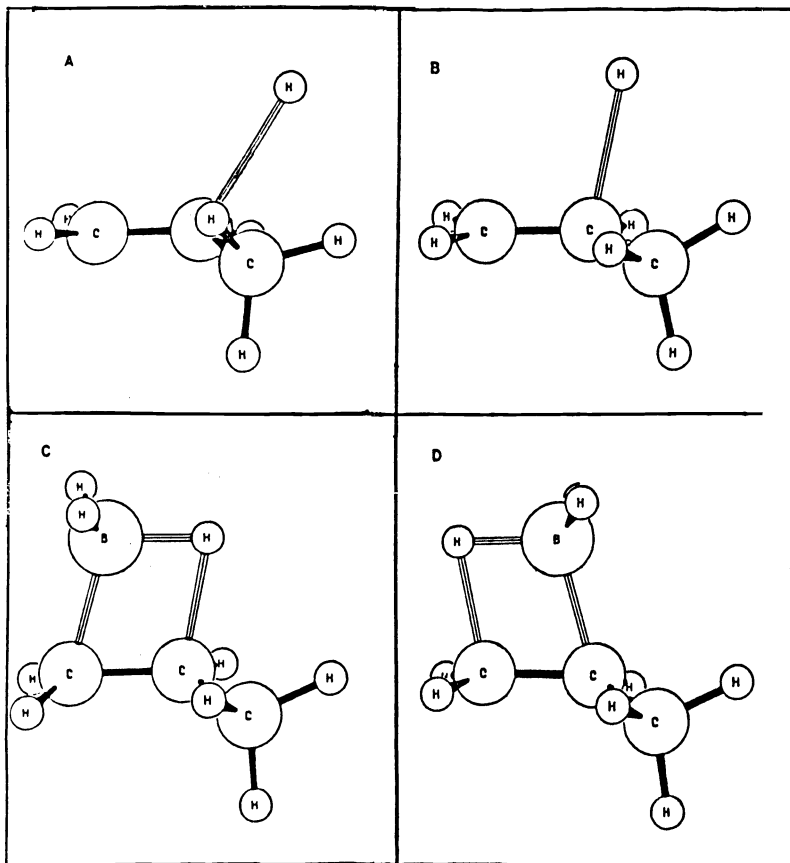


Fig. 2. Transition structures for additions to alkenes.

The trajectories of attack are quite compatible with qualitative predictions of frontier molecular orbital theory.²¹ In particular, the attack of an electrophile at an acute X---C=C angle may be attributed to the favorable interaction of the electrophile LUMO with the alkene HOMO, which is a bonding orbital. This interaction is maximized when the electrophile LUMO approaches the center of the double bond, unless powerful unsymmetrical donor substitution makes the HOMO appreciably unsymmetrical. The obtuse angle of nucleophilic attack occurs in order to maximize interaction of the nucleophile HOMO with the alkene LUMO, and to minimize overlap of the nucleophile HOMO with the alkene HOMO. The radical attack occurs in a more nearly perpendicular fashion, since the interactions of the singly-occupied orbital of the radical with both the HOMO and the LUMO of the alkene are stabilizing. Radicals seek a compromise between maximization of overlap with the HOMO and with the LUMO.

Although the transition structure represents the highest energy point along the lowest energy transit from reactants to products, reactants are expected to select a variety of geometries if they are reasonably close in energy to the transition structure.¹⁹ We have carried out computations¹⁷ which show that for hydride attack, a 10° bend of the attack trajectory away from the ideal causes an increase in energy of about 1.4 kcal/mol, so that a reaction forced to go through such a trajectory would be 10 times slower than the ideal at room temperature. For H^\cdot , a 15° bend away from the ideal trajectory takes 1.4 kcal/mol.¹⁷

As suggested in the introduction, in each transition structure the methyl group has rotated into a conformation which is staggered with respect both to the partially formed bond, and to the partially pyramidalized carbon undergoing attack. The staggering is coupled to the direction of attack, so that the conformations of allylic substituents will be significantly different with respect to the alkene for nucleophiles, radicals, and electrophiles.

We have assessed the degree of preference of these staggered transition structures by computing the relative energies of other transition state conformations, at various computational levels.¹⁷ For each transition structure, the methyl rotational barrier is 2-4 kcal/mol. This is nearly as large as that in the final product, even though the partially formed bonds are quite long, and the carbon to which bonding occurs is only partially pyramidalized! About half of the methyl conformational preference is due to the pyramidalization of C-2 in the transition state, while the remainder arises from avoidance of eclipsing with the partially formed bonds. For hydride attack, the avoidance of eclipsing of allylic substituents with the partially formed bond is the dominant effect. We attribute these larger barriers to the especially pronounced closed-shell repulsion between allylic bonds and the partially formed bond from the electron-rich reagent to the alkene. Thus, the factors which cause ethane to be staggered are manifest even when bonds are relatively long and weak!

The preference for staggering of the allylic bonds with respect to the forming bond and the bonds to the partially pyramidalized carbon, is just that deduced in 1968 by Felkin for nucleophilic attack on carbonyls.⁴ In all of the structures shown in Fig. 2, the allylic carbon hydrogen bond which is *anti*-periplanar to the partially formed bond is stretched by 0.002-0.017Å²² relative to the bonds to the other two hydrogens, but this hyperconjugative interaction²² is most likely insignificant compared to the obviously different steric requirements of the three allylic positions.

I would like to demonstrate the utility of these generalizations by describing applications to understanding of (a) the stereochemistry of hydroboration, (b) the origin of Huisgen's "factor x" and the *exo* stereoselectivity of additions to norbornenes, and (c) the stereochemistry of the S_N2' reaction.

Kishi has devised a model to rationalize the observed stereoselectivities of hydroborations of chiral alkenes.⁸ Fig. 3 shows this model on the left.

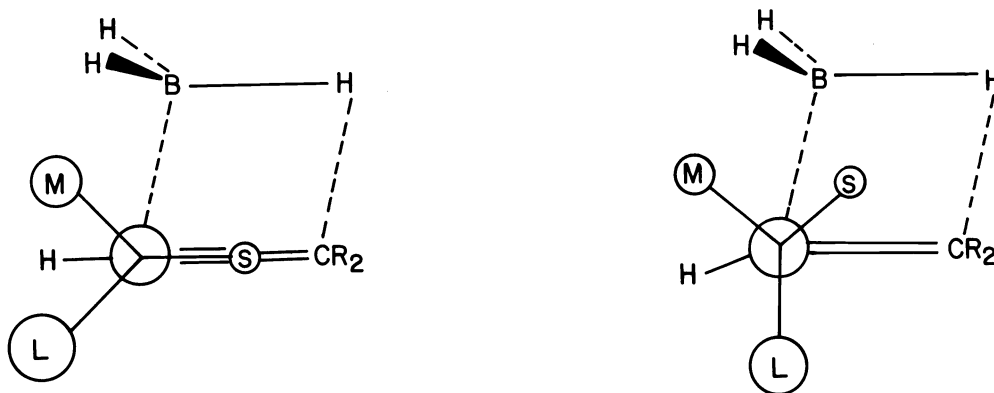


Fig. 3. The "X-eclipsed" and staggered models for hydroboration.

This is an "X-eclipsed" model, but for the hydroboration of propene, we calculate that this model transition structure is 1.3 kcal/mol higher in energy than the staggered transition structure shown in Fig. 2. Through computations, or by inspection of models, we can show that the position which is *anti*-periplanar to the partially formed bond is least crowded, the "outside" is the second least crowded, and the "inside" is most crowded. This leads to the general model shown at the right of Fig. 3 to rationalize the stereoselectivity that Kishi has observed for a variety of hydroborations. Our model and the Kishi model lead to the same rationalization of hydroboration stereochemistry.

It is interesting to compare this model for hydroboration to the Felkin-Anh model for nucleophilic attack on carbonyl compounds.^{4,5} For the latter, the allylic position *anti*-periplanar to the attacking reagent is least crowded once again, but the relative steric requirements of "outside" and "inside" positions are opposite to those for hydroboration. The trajectory of hydride attack makes the "outside" position more crowded than the

"inside" because the "outside" position is sandwiched between the hydrogen attached to the carbonyl carbon and the attacking reagent. An increase in size of either of these groups should further crowd the "outside" position. By contrast, the "inside" is most crowded for hydroboration, since a group here is trapped between the attacking reagent, the partial double-bond, and the breaking BH bond.

In all of the examples described so far, the alkene is acyclic and free to adopt whatever conformation is dictated by the attacking reagent. However, in bicyclic systems, the conformations of allylic bonds are fixed by the skeleton of the molecule. In general, attack which can occur staggered with respect to allylic bonds should be favored by 1-3 kcal/mol as compared to attack which must occur eclipsed with respect to allylic bonds. A particularly interesting application of this is in understanding stereoselectivity and reactivity of norbornene and related polycyclic molecules.

Huisgen has shown that the rates of reaction of norbornene with dienes and 1,3-dipoles are anomalously rapid. After estimating the amount of strain-relief acceleration that can be expected to be important, Huisgen concluded that a yet-to-be understood factor, named "factor x", was responsible for this rapid rate of reaction.²³ We believe that this factor is the nearly ideal arrangement of allylic substituents on the exo face of norbornene, as demonstrated in Fig. 4.²⁴

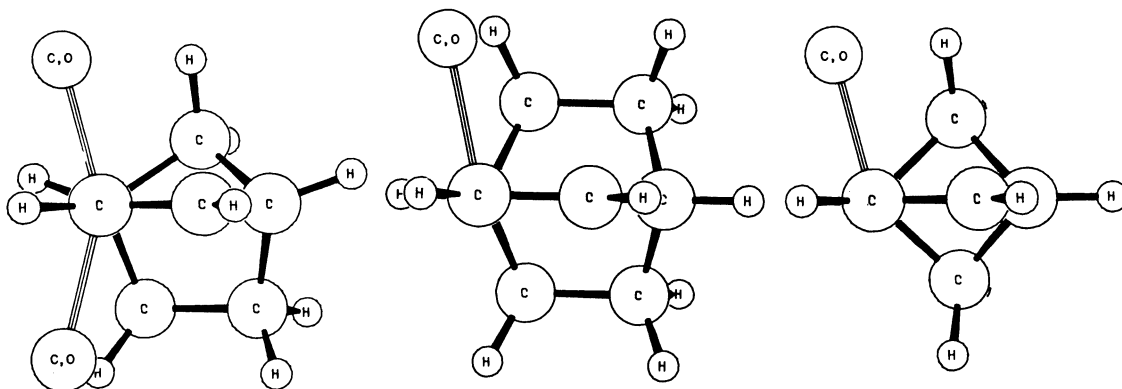


Fig. 4. Newman projections for bicyclic [2.2.1], [2.2.2], and [2.1.1] alkenes.

The "extra bonds" placed on the Newman projections of three bicyclic alkenes correspond to the direction of bonding inferred from a transition structure for fulminic acid cycloadditions.²⁵ Other 1,3-dipolar cycloadditions and Diels-Alder reactions reported by Huisgen should have similar bonding directions. Even without consideration of differences in strain release, it is clear that the attack on the exo face of norbornene, and on bicyclo[2.1.1]hexene should be facile, due to the nearly perfectly staggered arrangement of allylic bonds with respect to forming bonds, whereas the attack on the endo face of norbornene, or on bicyclo[2.2.2]octene should be less favorable due to the near eclipsing present in transition structures for cycloadditions.

In spite of the beauty of this explanation, we were concerned about the possibility that hyperconjugative electron-donation by the anti-periplanar 1,6 and 4,5 σ bonds of norbornene might be facilitating attack on this molecule. However, Jiri Mareda suggested the following experimental test of our staggering theory and alternative hyperconjugative mechanisms. According to a MM2 optimization, bicyclo[3.2.1]oct-6-ene has the ideal staggered arrangement of allylic bonds upon cycloaddition to the double bond. Our theory predicts that this molecule should be as reactive on the exo face as norbornene. On the other hand, this alkene is less strained than norbornene, and the 1,2 and 4,5 σ bonds do not hyperconjugate as well as the 1,6 and 4,5 σ bonds of norbornene. Strain and hyperconjugative theories would predict lower reactivity for the [3.2.1] system. Paul Mueller studied the cycloaddition of mesitonitrile oxide to bicyclo[3.2.1]oct-6-ene, and found that norbornene is only 1.3 times more reactive.²⁴ We feel that this result is strong support for the staggering theory.

Finally let us turn to the stereochemistry of the S_N2' reaction, an interesting phenomenon which has been studied theoretically many times.²⁶ Of the two possible stereochemistries of reaction, the syn is usually preferred, in which the leaving group leaves from the same side of the plane of the allyl group as the nucleophile enters. Although we have not

obtained a transition structure for this reaction, we do have indirect evidence for the origin of the syn preference in this reaction. Fig. 5 shows the transition structure for the attack of hydride, a model nucleophile, on atom 1 of propene. As described earlier, the alkene is trans bent in this transition structure, and as a result the methyl group rotates so as to become staggered with respect to the partially pyramidalized carbon-2.

One of the CH bonds has rotated into a conformation where it is more or less syn to the attacking hydride. This should be the position into which an electronegative atom (leaving group) will rotate, since this will maximize the overlap of the "partial lone-pair" at C-2 and the low-lying σ^* orbital of the leaving group.

Indirect information on this point can be obtained from calculations on radical anions, which resemble structurally the alkene portion of the S_N2' transition state. Fig. 6 shows the radical anions of ethylene and allyl alcohol, obtained by ab initio calculations with the STO-3G basis by Michael N. Paddon-Row. Both species are highly trans bent, and the hydroxyl group, a model for a leaving group, rotates into the conformation shown. Here, there is strong overlap of the orbital at C-2 and the σ^*_{CO} orbital which leads eventually to scission of this bond. Even in this radical anion, the CO bond has been stretched substantially by this interaction. Thus, the syn- S_N2' transition state is favored because (i) the alkene bends in a trans-fashion upon interaction with a nucleophile at C-1, (ii) the allylic bonds at C-3 rotate so as to become staggered with respect to the partially pyramidal C-2, and (iii) the allylic bond to the most electronegative group (the leaving group) rotates into the syn conformation to maximize stabilization of the transition state by anti-overlap of the orbital at C-2 with the σ^*_{CX} orbital.

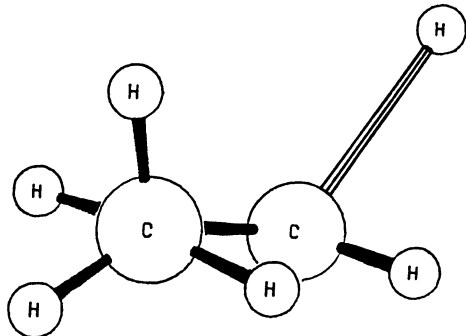


Fig. 5. Transition structure for attack of hydride on C-1 of propene.

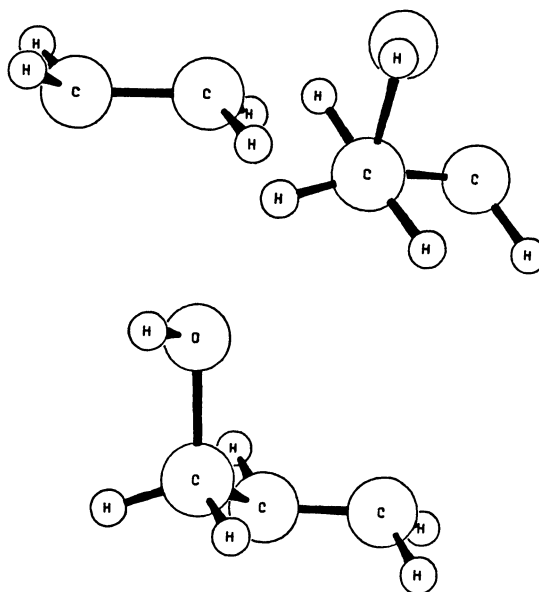


Fig. 6. The STO-3G radical anions of ethylene and allyl alcohol (two views).

I hope that these examples demonstrate the power of relatively simple torsional ideas as applied to transition structures. Our investigations to date have concentrated on torsional and steric interactions involving non-polar allylic groups. Studies are in progress to determine how electronic factors which may develop with polar allylic bonds may cause different types of substituents to prefer one or another of the three non-equivalent allylic conformations in addition transition structures.

ACKNOWLEDGEMENTS. I am grateful to the brilliant scientists, gentlemen, and good friends who carried out the research I have described. They are Nelson G. Rondan, Michael N. Paddon-Row (New South Wales Institute of Technology), Pierluigi Caramella (University of Catania), Jiri Mareda, and Paul Mueller. The National Science Foundation and the National Institutes of Health have provided generous financial support of our research.

REFERENCES AND NOTES

1. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, N.Y., (1971); P.A. Bartlett, Tetrahedron, 36, 2 (1980).
2. D.J. Cram and F.A. Abd Elhafez, J. Am. Chem. Soc., 74, 5828 (1952).
3. G.J. Karabatsos, J. Am. Chem. Soc., 89, 1367 (1967).
4. M. Cherest, H. Felkin and N. Prudent, Tetrahedron Lett., 2199, 2205 (1968).
5. N.T. Anh and O. Eisenstein, Nouveau J. Chim., 1, 61 (1977); N.T. Anh, Fort. Chem. Forschung, 88, 145 (1980).
6. (a) P. Chautemps and J.-L. Pierre, Tetrahedron, 32, 549 (1976); (b) an alternative to the Chautemps-Pierre model has apparently been described: R.K. Boeckman, Jr., and E.W. Thomas, J. Am. Chem. Soc., 100, 987 (1979).
7. P. Chamberlain, M.L. Roberts and G.H. Whitham, J. Am. Chem. Soc., (B), 1374 (1970).
8. Y. Kishi, Aldrichimica Acta, 13, 23 (1980); M.R. Johnson and Y. Kishi, Tetrahedron Lett., 4347 (1979); I. Hasan and Y. Kishi, Tetrahedron Lett., 4229 (1980); See also, A.S. Narula, Tetrahedron Lett., 22, 2017 (1981); Sharpless has proposed a similar model for t-BuOOH/VO(acac)₂ peroxidations: K.B. Sharpless and T.R. Verhoeven, Aldrichimica Acta, 18, 63 (1979).
9. T. Itoh, K. Jitsukawa, K. Kaneda and S. Teranishi, J. Am. Chem. Soc., 101, 159 (1979). These authors also propose a transition state for t-BuOOH/VO(acac)₂ epoxidations like the perpendicular model, but with A = OH and attack occurring eclipsed to the OH group.
10. G. Schmid, T. Fukuyama, K. Akasaka and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979); M.R. Johnson, T. Nakata and Y. Kishi, Tetrahedron Lett., 4343 (1979); H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M.R. Johnson and Y. Kishi, J. Am. Chem. Soc., 102, 7962 (1980).
11. E. Toromanoff, Tetrahedron, 36, 2809 (1980) follows changes in torsional angles for formation of products, which is in effect equivalent to an assumption of a product-like transition structure.
12. P. Caramella, N.G. Rondan, M.N. Paddon-Row and K.N. Houk, J. Am. Chem. Soc., 103, 2438 (1981).
13. N.G. Rondan, M.N. Paddon-Row, P. Caramella and K.N. Houk, J. Am. Chem. Soc., 103, 2436 (1981).
14. J. Baldwin, J. Chem. Soc., Chem. Comm., 734, 738 (1976).
15. H.B. Burgi, J.D. Dunitz, J.M. Lehn and G. Wipff, Tetrahedron, 30, 1563 (1974).
16. J.S. Binkley, J.A. Pople and W.J. Hehre, J. Am. Chem. Soc., 102, 939 (1980).
17. M.N. Paddon-Row, N.G. Rondan and K.N. Houk, J. Am. Chem. Soc., (1982), in press.
18. J.S. Binkley, R.A. Whiteside, R. Krishnan, R. Seeger, D.J. DeFrees, H.B. Schlegel, S. Topiol, L.R. Kahn and J.A. Pople, Carnegie-Mellon University, Pittsburgh, PA.
19. S. Scheiner, W.N. Lipscomb and D.A. Kleier, J. Am. Chem. Soc., 98, 4770 (1976).
20. R.W. Strozier, P. Caramella and K.N. Houk, J. Am. Chem. Soc., 101, 1340 (1979).
21. G. Klopman in "Chemical Reactivity and Reaction Paths", G. Klopman, Ed., Wiley-Interscience, New York, 1974, Chapter 4, pp. 55-166.
22. This factor has recently been discussed for nucleophilic addition to carbonyls: A.S. Cieplak, J. Am. Chem. Soc., 103, 4540 (1981).
23. R. Huisgen, P.H.J. Ooms, M. Mingin and N.L. Allinger, J. Am. Chem. Soc., 102, 3951 (1980); R. Huisgen, Pure Appl. Chem., 53, 171 (1981).
24. N.G. Rondan, M.N. Paddon-Row, P. Caramella, J. Mareda, P.H. Mueller and K.N. Houk, submitted for publication.
25. J. Goddard, A. Komornicki and H.F. Schaefer III, J. Am. Chem. Soc., 102, 1763 (1980).
26. R.M. Magid, Tetrahedron, 36, 1901 (1980).