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THE INFLUENCE OF SUBSTITUENT INDUCED ASYNCHRONICITY ON THE STEREOCHEMISTRIES OF INTRAMOLECULAR DIELS-ALDER REACTIONS

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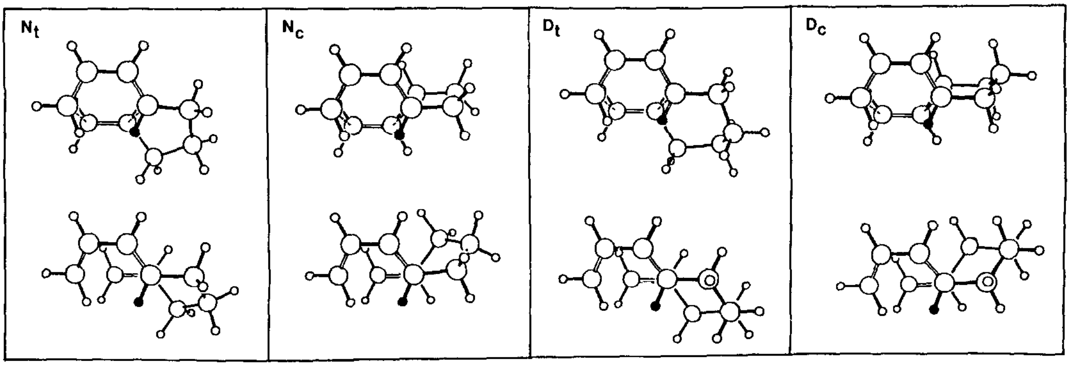
Abstract: Trends in stereoselectivities of intramolecular Diels-Alder reactions upon substitution are rationalized by a "twist-asynchronous" model, which is supported by MM2 model calculations.

The previous communication summarizes the stereoselectivities of nonatriene and decatriene intramolecular Diels-Alder cycloadditions, and trends in stereoselectivity induced by substituents.[1] Here, we provide a rationale of these results with computational support from MM2 model calculations.

Experimental evidence indicates that most Diels-Alder reactions have concerted mechanisms.[2] Theory,[3] rate measurements,[2] and stereochemical results on intermolecular cycloadditions,[4] indicate that Diels-Alder reactions of unsymmetrical addends proceed via asynchronous concerted mechanisms.[5] The alterations of stereoselectivities of intramolecular Diels-Alder reactions that occur upon substitution have been interpreted in terms of asynchronous transition states.[7-10] Here we show why nonatrienes and decatrienes respond so differently to unsymmetrical substitution.

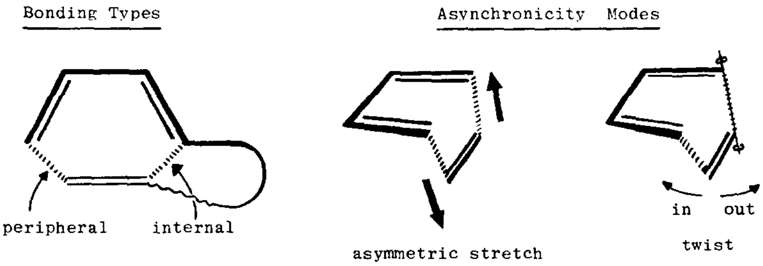
A qualitative rationale of the stereochemistries of reactions of the parent hydrocarbons may be gleaned from the approximate transition structures shown in Figure 1.

Figure 1: Top and Newman (along C_4-C_8 or C_9) views of synchronous MM2 transition states.



These structures were constructed beginning from our synchronous STO-3G transition structure for the butadiene-ethylene reaction.[6] The connecting polymethylene chains were substituted for appropriate hydrogens, and the side-chain conformations were optimized using normal MM2[11] parameters for connecting-chain atoms, sp^3 parameters for the atoms of the diene and alkene to which the connecting-chain is attached, and equilibrium angles obtained from the butadiene-ethylene transition state for these atoms. The butadiene and ethylene atoms were fixed at positions obtained for the unsubstituted transition structure. More flexible models under development in our laboratories give similar results.

Since the carbons undergoing "internal" bond formation (see definitions below) are alkyl substituted, this bond normally would be expected to be longer than the forming "peripheral" bond in the transition state. For the parent hydrocarbons, this substituent effect is cancelled out by the connecting-chain, which forces the termini forming the "internal" bond into relatively close proximity. Thus, the synchronous transition state models shown in Figure 1 give the correct relative energies of *cis* and *trans* transition states.

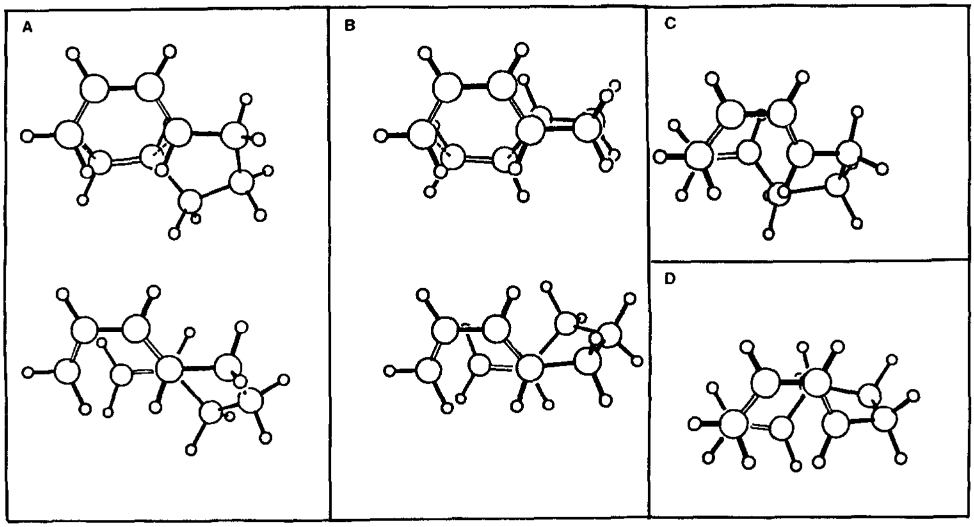


In the nonatriene case, the developing cyclopentane ring is equally strained in both transition states. The *trans* transition structure, $\underline{N}_t$, has an *exo* alkyl substituent, while the *cis*, $\underline{N}_c$, has an *endo* alkyl substituent. The former is sterically disfavored due to interaction of the connecting-chain with the "inside" (darkened on the drawings) hydrogen at C-4.[6] Thus, $\underline{N}_t$ is 1 kcal/mol less stable than $\underline{N}_c$. In the decatriene case, both *cis* and *trans* transition states have nearly perfectly staggered chair conformations of the developing cyclohexane rings. The *cis* transition state, $\underline{D}_c$, has one formal axial substituent (the butadiene moiety), and although this group is nearly flat, 1,3-diaxial interactions destabilize $\underline{D}_c$ by 0.7 kcal/mol, partially counteracting the 1 kcal/mol preference for $\underline{D}_c$ due to repulsions in $\underline{D}_t$ due to the *exo* alkyl substituent. Thus, the *cis* transition state is 0.3 kcal/mol more stable than the *trans*. If the hydrogen on C-3 of butadiene is replaced by an alkyl substituent, larger 1,3-diaxial interactions strongly destabilize the *cis* transition state.[12]

Substitution of a donor on the diene terminus, or acceptor on the alkene terminus, should lead to an asynchronous transition state with more advanced bonding "internally" than "peripherally".[3,7,10] Most qualitative arguments focus on the "asymmetric stretch" mode of asynchronicity,[8,10] but several lines of reasoning suggest that the "twist" mode is more important. First, the lowest energy real vibrational frequency associated with the synchronous butadiene-ethylene transition state[6] corresponds to a twist. It has even been suggested that this twisted mode is preferred for synchronous reactions.[13,14] Second, if asynchronous transition states involved the asymmetric stretch mode, then the donor-diene, acceptor-alkene cases should approach a disubstituted cycloalkane geometry in the transition state, and there should be a stronger preference for *trans* product in the decatriene case than in the nonatriene case (cf. energies of 1,2-disubstituted cycloalkanes).[15] This is not found experimentally.

We postulate that as one proceeds down the cases listed in Table 1 of the previous Communication,[1b] the degree of "twist" mode asynchronicity increases, when there is a torque applied by the connecting-chain. This torque is relatively large with a trimethylene connecting-chain, since the $C_5C_4C_8C_7$ dihedral angle would be ideally 0° in a "stretched cyclopentane", with the C_4-C_8 bond length equal to the transition state distance of 2.2Å.[16] By contrast, a "stretched cyclohexane" remains in a nearly perfect chair conformation, so there is little torque around the forming internal bond. Thus, the connecting-chain has a much greater affect on the nonatriene transition states than on the decatriene transition states. Figure 2 shows examples of the twist mode asynchronicity which we postulate should occur in substituted nonatrienes. These models were constructed by twisting the vinyl moiety by 10° in the sense shown, and reoptimizing the positions of the connecting-chain atoms with our MM2 model.

Figure 2: Model "10°-twist" asynchronous MM2 model transition states for 1,3,8-nonatriene reactions.
A: 10° "out-twist" about C_4-C_8 in trans TS. B: 10° "in-twist" in cis TS.
C: 10° "in-twist" about C_1-C_9 in trans TS. D: 10° "out-twist" about C_1-C_9 in cis TS.



As an acceptor is substituted at C_9, or a donor at C_1, the trans transition state should twist as shown in A in Figure 2, in order to relieve strain in the developing cyclopentane ring. This decreases the dihedral angle in the cyclopentane about the forming internal bond. This torque causes the C_9 terminus to move outside, or in an exo direction. B shows the twist distortion expected for the substituted cis transition state. Here, the C_9 terminus moves inside, or in an endo direction. We postulate that the outside movement of the C_9 terminus is easier than the inside movement, due to greater diene-alkene steric repulsions in the latter. Antibonding secondary orbital interactions of the coefficient at C_3 of the diene HOMO, and C_9 of the dienophile LUMO, may also destabilize this inside twist. The more potent the substituents, the more this distortion will occur, resulting in higher trans stereoselectivity. Both cis and trans decatriene transition states have nearly perfect chair-cyclohexane rings formed by the connecting-chains. Consequently, there is very little torque about C_4-C_9, and only slight changes in stereoselectivity occur upon substitution.

The twist asynchronicity which occurs upon internal acceptor substitution (at C_8), and should also occur upon C_2 or C_4 donor substitution of the diene, is demonstrated in C and D. Here, the C_1C_9 peripheral bond is more fully formed in the transition state, so twisting about this bond occurs. Now the *cis* product is preferred, since the corresponding transition state, *D*, is stabilized by outward motion of C_8, while *C* is destabilized by inward motion of C_8. The nonatriene gives moderate *cis*-stereoselectivity, since only small outward motion is permitted in the developing nine-membered ring. Greater motion is permitted in the decatriene case, and *cis*-stereoselectivity is higher.[1]

Quantitative versions of these models will be reported at a later date.

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