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A Transition State FMO Approach for Prediction of the Regioselectivity of the Diels-Alder Reaction

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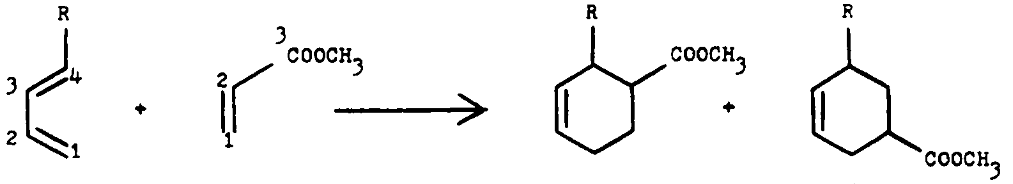
Abstract: The regioselectivity in the Diels-Alder reaction of 1-substituted-1,3-butadienes can be completely explained by FMO theory when the frontier molecular orbitals of the reactants in the concerted transition state are considered. This excellent agreement between theory and experimental results from the more realistic representation of the ionic polarization at the primary carbon sites.

Frontier Molecular Orbital(FMO) Theory has been used very successfully to explain the regioselectivity of the Diels-Alder reaction. However, conflicting results have been obtained with its application to the Diels-Alder reactions of 1-substituted-1,3-butadienes that contain electron withdrawing substituents. Several investigators[2-4] have reported that the FMO approach does not predict the preferred ortho regioisomer. In fact, Zhixing[3a] reported that the FMO approach does not predict the correct regioisomer for trans-2,4-pentadienoic acid(1) with HMO, CNDO/2, or MNDO molecular orbitals and that this failure was due to the inherent weakness in the FMO method. Other investigators have reported that the FMO method favored the preferred ortho regioisomer when generalized orbital coefficients were used,[5] secondary orbital interactions were considered,[6] or nonsynchronous bond formation was assumed.[7] None of these studies completely account for the regioselectivity of these dienes. In the addition of 1 to unsymmetrically substituted dienophile, the ortho regioisomer is preferred in both the endo and exo stereochemical modes of addition and the ortho/meta ratio is substantially greater in the endo addition (5.7:1) than in the exo addition (3.0:1)[8].



1, R = COOH
2, R = CN

Regioselectivity is determined in the transition state where the reactants have undergone significant changes in their molecular geometries.[9] These earlier studies used frontier molecular orbitals that were calculated with the unperturbed molecular geometries of the reactants. In this paper we show that improved agreement between FMO theory and experimental regioselectivities is obtained for 1-(electron-withdrawing substituted)-1,3-butadienes and other 1-substituted diene systems when the FMO's of the reactants in the concerted transition state are employed.

Theory

The details of FMO theory have been published.[10] The generalizations that are used to predict regioselectivity are as follows: (1) the pair of interacting FMO's which has the smaller energy difference makes the greater contribution to the stabilization of the transition state; (2) the atoms with the larger coefficients are bonded preferentially in the transition state. In the endo stereochemical mode of addition, the secondary interactions between the C-2 and C-3 atoms of the diene and the C-3 atom of the dienophile will also be considered along with the primary interactions.[6,11] In the exo stereochemical mode of addition, only the primary interactions are considered because secondary interactions are not possible.

As an approximation, the unperturbed geometries of the reactants are currently used to calculate FMO energies and coefficients.[3,5-7,10] However, an accurate geometry of the Diels-Alder transition state is now known through extensive ab initio calculations.[9,12] Since the regioselectivity of the Diels-Alder reaction is determined in the transition state, better agreement between FMO theory and experimental results is expected when the transition state FMO's of the reactants are used to predict regioselectivity. In this study the transition state FMO's of the dienes and the dienophiles are calculated for Salem's concerted transition state[12a] by the CNDO/2 method. The FMO's of the unperturbed reactants are determined with standard bond angles and bond lengths by the CNDO/2 method.[13] The ab initio FMO's of the unperturbed reactants are taken from the literature.[14]

Herdon has used a Diels-Alder transition state model to predict regioselectivity by simple valence bond theory.[15] Our FMO approach is more useful because of its detail, correlative ability.

Results and Discussion

For the reaction of 1 with acrylic acid, the primary HOMO coefficients of the transition state FMO's favor the meta regioisomer and the primary LUMO coefficients favor the ortho regioisomer (Table I). Since the difference between the primary LUMO coefficients is much larger than the difference between the primary HOMO coefficients, the primary interactions favor the ortho regioisomer (Figure 1). This prediction agrees with the experimental results of 3.0:1 preference for the ortho regioisomer in the exo mode of addition.[8]

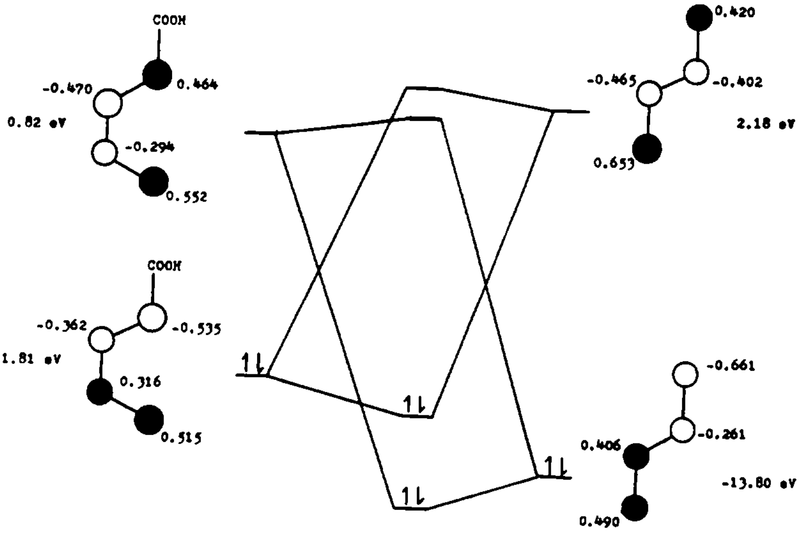
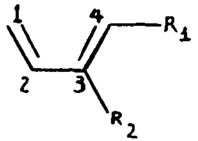


Figure 1. CNDO/2 Frontier Molecular Orbital Interactions for the Diels-Alder Reaction Between Trans-2,4-pentadienoic acid and Acrylic Acid in the Concerted Transition State.

Table I

Frontier Orbital Coefficients and Energies of 1,3-Butadienes



			MO	HOMO Coefficients					LUMO Coefficients				
R_1	R_2	Geometry	Method	C-1	C-2	C-3	C-4	HOMO, eV	C-1	C-2	C-3	C-4	LUMO, eV
$COOH(CH_3)$	H	Standard	CNDO/2	-0.462	-0.313	0.393	0.488	-12.72	0.477	-0.277	-0.508	0.445	1.74
			ab initio	-0.498	-0.366	0.384	0.525	-6.78	0.542	-0.311	-0.523	0.505	4.95
COOH	H	Transition State	CNDO/2	-0.514	-0.316	0.362	0.535	-11.81	0.552	-0.294	-0.470	0.464	0.82
CN	H	Standard	CNDO/2	-0.497	-0.327	0.435	0.507	-12.55	0.501	-0.322	-0.488	0.510	2.20
CN	H	Transition State	CNDO/2	-0.541	-0.317	0.396	0.533	-11.57	0.552	-0.323	-0.448	0.521	1.20
CH_3	H	Standard	CNDO/2	-0.531	-0.342	0.462	0.524	-12.16	0.532	-0.391	-0.434	0.560	3.27
			ab initio	-0.533	-0.373	0.428	0.528	-6.31	0.617	-0.451	-0.436	0.629	6.31
CH_3	H	Transition State	CNDO/2	-0.577	-0.325	0.424	0.539	-11.10	0.554	-0.375	-0.400	0.579	2.21
H	CH_3	Standard	CNDO/2	-0.498	-0.340	0.417	0.621	-12.51	0.549	-0.404	-0.427	0.561	3.25
H	CH_3	Transition State	CNDO/2	-0.541	-0.331	0.382	0.636	-11.52	0.577	-0.389	-0.400	0.572	2.22
H	CN	Standard	CNDO/2	-0.484	-0.336	0.404	0.599	-12.95	0.478	-0.323	-0.431	0.606	2.47
H	CN	Transition State	CNDO/2	-0.536	-0.337	0.375	0.616	-11.99	0.529	-0.329	-0.403	0.610	1.53
CH_3	CH_3	Standard	CNDO/2	-0.468	-0.284	0.456	0.561	-11.72	0.517	-0.372	-0.433	0.555	3.14
CH_3	CH_3	Transition State	CNDO/2	-0.526	-0.282	0.420	0.572	-10.80	0.549	-0.365	-0.399	0.568	2.16

When the secondary interactions of the transition state FMO's are considered, greater preference for the ortho regioisomer is predicted by the theory. The largest secondary coefficient is located at the C-3 carbon of the diene in both HOMO and LUMO; thus interaction between this secondary carbon and the carbonyl carbon of the dienophile will provide the greater stabilization of the transition. In agreement with the theory the preference for the ortho regioisomer increased to 5.7:1 in the endo addition.

The agreement between FMO theory and the experimental results is not as good when the FMO's of the unperturbed reactants are used. The primary HOMO coefficients still favor the meta regioisomer and the primary LUMO coefficients favor the ortho regioisomer; however, the differences between the coefficients are similar. In this situation, the primary HOMO coefficients are predicted to the control the regioselectivity because (1) the difference between the primary LUMO coefficients of the dienophile is two times greater than the difference between the primary HOMO coefficients and (2) the energy difference for HOMO(diene)-LUMO(dienophile) is slightly smaller than the energy difference for HOMO(dienophile)-LUMO(diene). Thus, FMO theory favors the incorrect regioisomer when the primary interactions of the unperturbed reactants are considered. The previous studies which reported the failure of FMO theory in this case only considered these FMO interactions.[2,3] The secondary interactions of the unperturbed reactants favor the ortho regioisomer and agree with the higher ortho/meta ratio in the endo addition.[6]

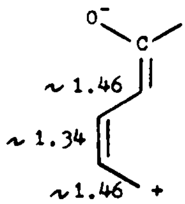
Anh's nonsynchronous bond approach[7] doesn't predict the correct regioisomer for this case when the primary interactions of the unperturbed reactants are considered. The initial bond formation is predicted to be between the diene C-4 and the dienophile C-1 positions. The correct ortho regioisomer is favored by Anh's approach when the transition state FMO's are used. However, Anh's FMO approach can not account for the different regioselectivities in the endo and exo additions.

The FMO predictions for the 1-cyano-1,3-butadiene(2) are essentially the same as those for 1. The primary and secondary interactions of the transition state FMO's favor the ortho regioisomer(Table I). When the FMO's of the unperturbed reactants are used, the primary HOMO/LUMO coefficients favor the meta regioisomer and the secondary HOMO/LUMO coefficients favor the ortho regioisomer. Experimentally, the ortho regioisomer is preferred;[16] however, the regioisomer ratios in the endo and exo additions are not known.

The use of the transition state FMO's can also improve the agreement between experimental and FMO theory for dienes with 1-electron-donating substituents. The high ortho selectivity(9:1)[17] of 1-methyl-1,3-butadiene is consistent with the transition state FMO's but not with the FMO's of the unperturbed reactants. The primary and secondary HOMO coefficients of the diene in the concerted transition state are significantly different and favor the ortho regioisomer(Table I). However, the primary HOMO coefficients of the unperturbed diene are nearly equal and only slightly favor the ortho regioisomer.

The FMO predictions for 2-substituted-1,3-butadienes are not changed when the transition state FMO's are used instead of the FMO's of the unperturbed reactants. The only significant change in their FMO coefficients was a small reduction in the differences between the coefficients(Table I). Thus, a slightly smaller regiochemical effect by the 2-substituent is predicted. This prediction is consistent with the strong regiochemical control exerted by 1-substituents in 1,2-disubstituted dienes. For example, the strong regiochemical control (6:1)[18] exerted by the 1-methyl substituent in the cycloadditions of 1,2-dimethyl-1,3-butadiene is better explained with the transition state FMO's. In this case, the secondary HOMO interactions of the diene control the regioselectivity and the primary HOMO coefficients favor the incorrect regioisomer (Table I). The difference between the primary HOMO coefficients of the diene is much smaller (0.046) than the difference (0.138) between the secondary HOMO coefficients; thus, strong regiochemical control by the secondary orbital interactions is expected.

The changes in the primary FMO coefficients of the 1-substituted-1,3-butadienes in the transition state are consistent with an increase in the ionic polarization at the primary carbon sites. The ionic polarization in the transition state is apparently promoted by the greater structurally similarity of the ionic resonance structures (3 and 4) with the transition state (5) than with the unperturbed diene (6).



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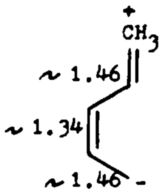

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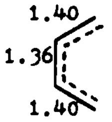

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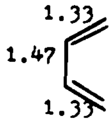
Salem's T.S.[12a]



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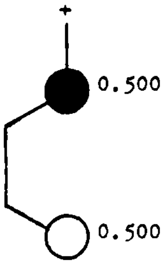
Salem's G.S.[12a]

The pentadienyl cation has primary HOMO coefficients (7) that are equal and has primary LUMO coefficients (8) that are very different.[10] Thus, greater pentadienyl cation character in the 1-(electron-withdrawing substituted)-1,3-butadiene cases is expected to increase the difference between the primary LUMO coefficients and slightly decrease the difference between the primary HOMO coefficients. The pentadienyl anion has primary HOMO coefficients (9) that are very different and primary LUMO coefficients (10) that are equal.[10] Thus, greater pentadienyl anion character in the 1-(electron-donating substituted)-1,3-butadiene cases is expected to increase the difference between the primary HOMO coefficients and slightly decrease the difference between the LUMO coefficients. These predictions agree with the changes that were observed in the primary FMO coefficients in the transition state (Table I). Furthermore, CNDO/2 calculations of the ionic resonance structures 3 and 4 support this explanation.



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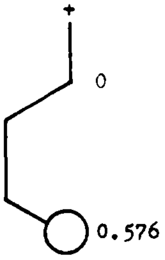
HOMO



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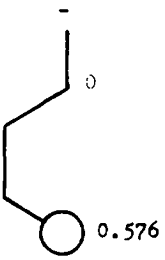
LUMO

Pentadienyl Cation



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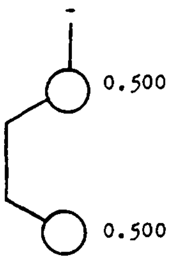
HOMO



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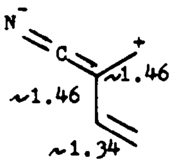
LUMO

Pentadienyl Anion

An increase in the ionic polarization of the 2-substituted-1,3-butadienes in the transition state is not expected because the structural similarity between the ionic resonance structures (11 and 12) and the transition state is not greater than the similarity between these structures and the unperturbed diene. In fact, a decrease in the importance of these resonances structures in the transition state is more likely because of the greater double bond character between the inner carbon atoms which enhances other ionic resonance. Thus, no change or a slight decrease



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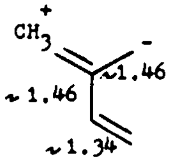

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in the differences between the primary HOMO/LUMO coefficients are predicted in these cases. Again the predictions agree with the changes that were observed in the primary FMO coefficients (Table I).

In conclusion, the agreement between the FMO predictions and experimental regioselectivities can be improved for 1-substituted-1,3-butadienes when the transition state FMO's of the reactants are considered. The better agreement results from the more realistic representation of the ionic polarization at the primary carbon sites.

References

[1] (a) Du Pont, (b) Virginia Commonwealth University.

[2] N. D. Epiotis, J. Am. Chem. Soc. 95, 5624(1973).

[3] (a) H. Guozheng, Z. Yala and C. Zhixing, J. Chem. Res. 1983, 205.
(b) C. Zhixing, Theort. Chim. Acta. 62, 293(1983).

[4] A. Oliva, J. I. Fernandez-Alonso and J. Bertran, Tetrahedron 34, 2029(1978).

[5] K. N. Houk, J. Am. Chem. Soc. 95, 4092(1973).

[6] P. V. Alston, R. M. Ottenbrite and D. D. Shillady, J. Org. Chem. 38, 4075(1973).

[7] O. Eisenstein, J. M. Lefour, N. T. Anh and R. F. Hudson, Tetrahedron 33, 1313 (1978).

[8] (a) I. Fleming, J. P. Michael, L. E. Overman and G. F. Taylor, Tetrahedron Letters 1978, 1313.
(b) L. E. Overman, G. F. Taylor, K. N. Houk and L. N. Domelsmith, J. Am. Chem. Soc. 100, 3182(1978).

[9] (a) P. Caramella, K. N. Houk and L. N. Domelsmith, J. Am. Chem. Soc. 99, 4511 (1977) and references cited therein.
(b) F. K. Brown and K. N. Houk, Tetrahedron Letters 1984, 4609.

[10] (a) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," Wiley, New York, 1976.
(b) W. C. Herndon, Chem. Rev. 72, 157(1972).

[11] P. V. Alston, M. D. Gordon, R. M. Ottenbrite and T. Cohen, J. Org. Chem. 48, 5051(1983) and references cited therein.

[12] (a) R. E. Townshend, G. Ramunni, G. Segal, W. J. Hehre and L. Salem, J. Am. Chem. Soc. 98, 2190(1976).
(b) L. A. Burke and G. Leory, Theoret. Chim. Acta. 44, 219(1977).

[13] J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, 1970.

[14] M. Kakushima, Can. J. Chem. 57, 2564(1979).

[15] W. C. Herndon, J. Chem. Ed. 58, 371(1981).

[16] H. R. Snyder and G. I. Poos, J. Am. Chem. Soc. 72, 4104(1950).

[17] T. Inukai and T. Kojima, J. Org. Chem. 36, 924(1971).

[18] Y. A. Titov, Russ. Chem. Rev. 31, 267(1961).