Tetrahedron Letters, Vol. 33, No. 5, pp. 651-654, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

The "Cieplak Effect": Hyperconjugative Interactions in Diels Alder Reactions.

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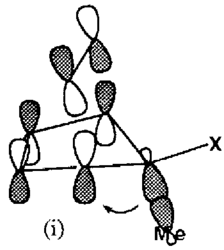
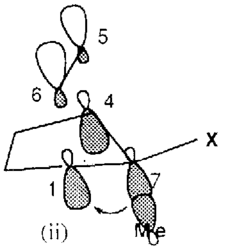
Abstract: *Molecular orbital calculations of the transition states for the reactions of the dienes* ***1a-e*** *with ethylene using the AM1 Hamiltonian show the diene C-X bond length for anti addition of the dienophile is longer than the comparable bond length when the X-substituent is syn to the approaching dienophile. The bond lengthening is consistent with hyperconjugative stabilization involving the donation of electron density from the σ-bond of the anti substituent to the forming σ*-orbital.*

Hyperconjugative stabilization in Diels-Alder reactions of 5-substituted cyclopentadienes by σ-bonds antiperiplanar to the bond forming centers has recently been proposed to account for the observed facial selectivity.[1] The explanation was first proposed by Cieplak[2] to account for the directing effects of remote substituents in addition reactions to substituted cyclohexanones. The basis of the "Cieplak effect" is that an incoming nucleophile will add to a carbonyl from the face that allows the greater anti-periplanar hyperconjugative stabilization from an adjacent σ-bond. By analogy Diels-Alder reactions of cyclopentadiene would be predicted to occur *anti* to the adjacent C7 σ-bond which is the better hyperconjugative donor,[3,4] as shown below for the diene HOMO and the developing incipent bonds with the LUMO of the dienophile (i). This C7 σ-bond will also best be able to stabilize the vacant σ*-orbitals of the incipient electron deficient σ-bonds forming at the transition state (ii and iii). This qualitative argument rationalises the experimental observations and the present study seeks to



(i)



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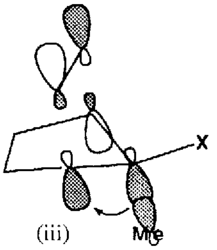
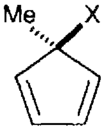


(iii)

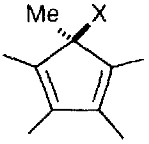
establish a more quantitative definition of the electronic interactions at the transition state for the Diels-Alder reaction of ethylene with substituted cyclopentadienes.

We report a series of RHF-AM1[5,6] calculations on each of the diastereotopic transition states for the Diels-Alder reactions of **1a-e** with ethylene as a model for the reactions of **2** which have been the subject of experimental studies with a number of substituted dieonphiles.[1] The RHF-AM1 method predicts a concerted reaction pathway, involving a symmetrical transition structure, for the reactions of ethylene with butadiene,[7,8] cyclopentadiene and cyclohexadiene[9] with activation energies consistent with the experimental evidence and high level calculations. The energies of the C_S stationary point for the reaction of butadiene and ethylene have been calculated at various levels of theory[10] and give activation energies which compare with the experimental value of 115.1 kJ mol^{-1}.[11] Using the published AM1 transition state geometry for ethylene and butadiene[6] as a starting point, gradient minimization procedures[5] were used to locate AM1 transition structures for the addition of ethylene to each face of **1a-e**.[12] Small variations from C_S symmetry were observed for the transition structures from **1c-e**. The most important geometrical parameters for the AM1 calculated transition states for reaction of ethylene and **1b** are shown and these geometries are representative of transition states for the reactions of **1a-e**.

1



a X = Me
b X = Cl
c X = OH
d X = OMe
e X = SMe



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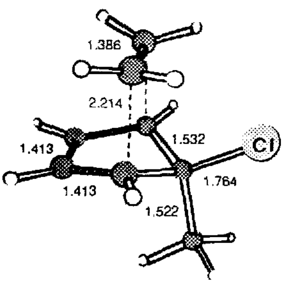

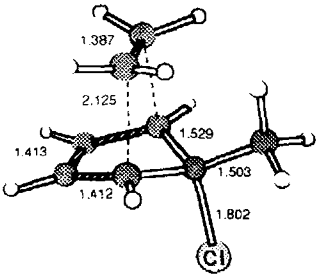

AM1 calculated bond lengths for the Diels-Alder transition structure for reaction of ethylene at each face of **1a-e**

	X	*Syn* C1C6 (Å)	*Syn* C4C5 (Å)	*Syn* C7X (Å)	*Syn* C7Me (Å)	*Anti* C1C6 (Å)	*Anti* C4C5 (Å)	*Anti* C7X (Å)	*Anti* C7Me (Å)	% bond extn *anti* vs *syn* to X	% bond extn *anti* vs *syn* to Me
1a	Me	2.112	2.112	1.509	1.531	2.122	2.122	1.531	1.509		1.5
1b	Cl	2.214	2.214	1.764	1.522	2.125	2.125	1.802	1.503	2.2	1.3
1c	OH	2.117	2.118	1.415	1.524	2.128	2.125	1.434	1.514	1.3	0.7
1d	OMe	2.118	2.117	1.423	1.523	2.130	2.123	1.443	1.513	1.4	0.7
1e	SMe	2.118	2.119	1.782	1.514	2.115	2.121	1.816	1.499	1.9	1.0

The most notable feature of the transition state geometry for the reaction of ethylene at each face of the diene is that the C-X or C-Me bond length for the *anti* addition of the dienophile is longer than the comparable bond length when the substituent is *syn* to the approaching dienophile. For example when the ethylene reacts *syn* to the chlorine in **1b** then the C7-chlorine bond length is calculated as 1.764Å, while for the reaction *anti* to the chlorine this distance lengthens to 1.802Å. Such a lengthening of the C-X bond is consistent with the donation of electron density from the σ-bond of the *anti* substituent to the forming σ^*-orbital. Similar bond lengthening from 1.503 to 1.522Å of the C-Me bond occurs for addition *anti* to the methyl .

The RHF-AM1 calculated enthalpies of activation for the reaction of ethylene and **1b-e** are shown below together with the calculated *syn:anti* ratios. For dimethylcyclopentadiene **1a** the activation enthalpy is calculated as 136.8kJ mol^{-1}. For **1c,d** the AM1 calculations are in agreement with the experimental observations obtained for the additions of N-phenylmaleimide and maleic anhydride[1] to **2c,d** where addition occurs exclusively *syn* to the X-substituent. The calculated activation barrier for addition *syn* to the chloro or SMe group is increased over addition *syn* to the OH or OMe resulting in a lowering of the difference in activation barriers between the faces. For **1b** and **1e** RHF-AM1 calculations suggest reaction should occur from both faces. For **2e** additions of N-phenylmaleimide and maleic anhydride does occur from both faces, but not for **2b.** For **1e** calculation parallels experiment in that products of addition to both faces are observed. However, the AM1 method continues to predict that reaction will occur predominantly from the face of the diene *syn* to the sulphur-group whereas the experimental results[1] for **2e** show a reversal of selectivity with only 10% of the addition occurring *syn* to the sulphur substituent. The expectation that such calculations of activation barriers will be accurate to within 4kJ mol^{-1} is a demanding test for any theory. However the difference in AM1 calculated enthalpies of activation for reaction at each face is considerably less for the chloro and sulphur containing group than for **1c,d**. The activation barrier for *anti* addition to **1d** and **1e** increases by 5kJ mol^{-1}, and these differences are reflected in $\Delta\Delta H_{f\,(anti\text{-}syn)}$. While the AM1 method cannot qualitatively reproduce the experimental observations, the trend for reduced *syn* face reaction with sulphur containing substituents is reproduced by these calculations.

AM1 calculated enthalpies of activation (kJ mol^{-1}) for the Diels-Alder reactions of ethylene at each face of **1a-e** and calculated *syn* to *anti* ratios.

		Calc Enthalpy of Activation (kJ mol^{-1})		*Syn:Anti* Ratio		$\Delta\Delta H_{f\,(anti\text{-}syn)}$
	X	*Syn*	*Anti*	Calcd. for **1** @25°C	Expt. for **2**	
1b	Cl	131.9	134.6	75:25	100:0	2.7
1c	OH	116.9	135.9	100:0	100:0	19.0
1d	OMe	123.8	141.0	100:0	100:0	17.2
1e	SMe	139.1	141.2	70:30	10:90	2.1

Importantly, molecular orbital calculations of the transition states using the RHF-AM1 Hamiltonian for reactions of the dienes **1a-e** with ethylene show the diene C-X or C-Me bond length for the *anti* addition of the dienophile is longer than the comparable bond length when the X or methyl substituent is *syn* to the approaching dienophile. The method reproduces the strong preference for addition *syn* to the OH and OMe substituents and predicts a mixture of facial products for SMe. The lengthening of the C-X bond for *anti* addition is consistent with hyperconjugative stabilization involving the donation of electron density from the σ-bond of an *anti* substituent to the forming σ*-orbital, and with these interactions being important in determining facial selection for Diels-Alder reactions.

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3. The generally accepted order[1] of increasing σ-donor ability is $\sigma_{CO} < \sigma_{CN} < \sigma_{CCl} < \sigma_{CC} < \sigma_{CH} < \sigma_{CS} < \sigma_{CSi}$ such that oxygen, nitrogen or halogen substituents will favour *syn* addition when the other substituent at the 5-position is a C-C or a C-H bond. Sulphur and silicon containing substituents however, might be expected to stabilize an *anti* transition state better than an *anti*-periplanar C-C or C-H bond.
4.. For an alternative explanation involving the "orbital mixing rule" see Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, K. *J. Am. Chem. Soc.*, **1990**, *112*, 8981.
5. Dewar, M.J.S.; Zoebisch,E.G.; Healy, E.F.; Stewart, J.J.P., *J. Am. Chem. Soc.*, **1985**, *107*, 3902.
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7. The RHF AM1 method is the first semi-empirical method which favours the synchronous, concerted pathway for the reaction of butadiene and ethylene similar to those obtained by the high level *ab initio* calculations. Dewar believes a RHF procedure underestimates the stability of the biradical-like species in the unsymmetrical pathway and favours the synchronous pathway. Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P., *J. Am. Chem. Soc.*, **1986**, *108*, 5771 and Choi, J.Y.; Lee, I., *J. Chem. Soc. Faraday Trans.* 2, **1989**, *85*, 867.
8. For cyano substituted alkene addition the RHF AM1 method does not predict a synchronous pathway. *Ab initio* calculations of the reactions of cyano-substituted alkenes gave symmetrical or near symmetrical transition structures at the RHF 3-21G level of theory. The transition state geometries were similar to the RHF AM1 results, but the variation of calculated activation energy with increasing cyano substitution was more in line with the experimental observation. Houk, K.N.; Loncharich, R.J.; Blake, J.F.; Jorgensen, W.L., *J. Am. Chem. Soc.*, **1989**, *111*, 9172.
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12. Each transition structure was found to have a single imaginary vibrational frequency as required for a genuine transition state.

Acknowledgements: We thank the UGC and the New Zealand Lottery Board for support.

(Received in UK 19 November 1991)