

## Ab initio and empirical computations of mechanism and stereoselectivity

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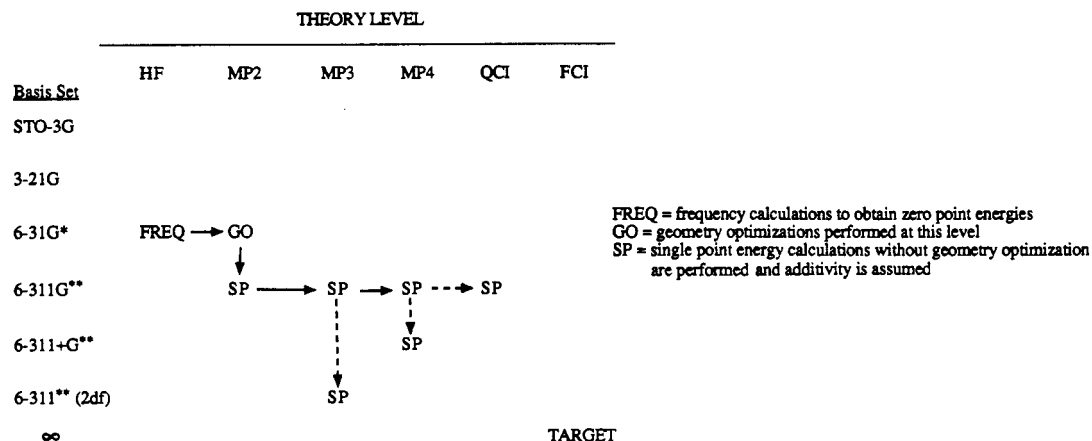
**Abstract** - Over the last few years, we have explored the use of theory to understand mechanisms of organic reactions and the various types of selectivities which they exhibit. Examples described in this lecture will include the Diels-Alder reaction, whose rates were studied quantitatively in 1964 by Sauer's group. *Ab initio* transition structures have been located for the reactions of butadiene with ethylene, acrylonitrile, maleonitrile, vinylidene cyanide, acrolein, and acrolein coordinated to a Lewis acid,  $BH_3$ . Further insights into conformation preferences of conformationally free dienophiles, the degree of asynchronicity induced by substituents, and the origin of *endo* stereoselectivity are discussed. The mechanism of the ketene-ethylene reaction and that of several substituted cases is discussed.

### INTRODUCTION

Computations have become an important mechanistic tool in organic chemistry. If complete and exact statistical mechanical treatments of reactions in solution could be performed, then the mechanism of a reaction could be predicted, and any detail desired could be extracted from the computations. Excellent solution simulations have now been performed in Jorgensen's group for several simple reactions, such as the reaction of chloride ion with methyl chloride.<sup>1</sup> In practice, much less thorough simulations than these are usually required because of the enormous computer size and time necessary to do such calculations. Nevertheless, a variety of computational techniques are available and are very useful in mechanistic studies. In this article I describe the techniques we use in such studies, and then demonstrate how they are used, and the power of these methods, by several examples. I have chosen to describe our calculations on substituent effects in the Diels-Alder reaction, in honor of the quantitative measurement of such effects measured approximately twenty-five years ago by Sauer's group, then at Munich. Second, I will briefly touch on our use of the results of such calculations to model stereoselectivity. Finally I will switch gears totally to describe a new result from our labs, of interest to many mechanistic chemists, the transition structure of the ketene cycloaddition.

### COMPUTATIONAL TECHNIQUES

There are three principle types of molecular computations used in our group. *Ab initio* quantum mechanical calculations can be carried out at many levels.<sup>2</sup> The drawing below is a diagram that John Pople has used to demonstrate the various levels of quantum mechanical calculations.<sup>3</sup> It is useful here to put into context the calculations we are doing. He has recently described a series of calculations to obtain bond energies to within  $\pm 2$  kcal/mol of the exact values. It involves geometry optimization (GO) at the MP2/6-31G\* level, single point (SP) calculations of correlation energies at MP2-MP4 levels, and additive correction at higher levels. Zero point energies are calculated at the RHF/6-31G\* level, and isogyric energy comparisons are used.



By contrast, our results are usually carried out with geometry optimizations and frequency calculations at the 3-21G level, and single point energy evaluations at the MP2/6-31G\* level. Sometimes the geometries have been located at the MP2/6-31G\* level, and in a few test cases which I will describe today, energies have been evaluated at a higher level. Nevertheless, we must keep in mind throughout that our results are quite far from "chemically accurate". The evaluation of *ab initio* calculations comes either from experience on related systems, or in cases in which no calibration is available or possible, by increasing the quality of the calculation until no changes are observed.

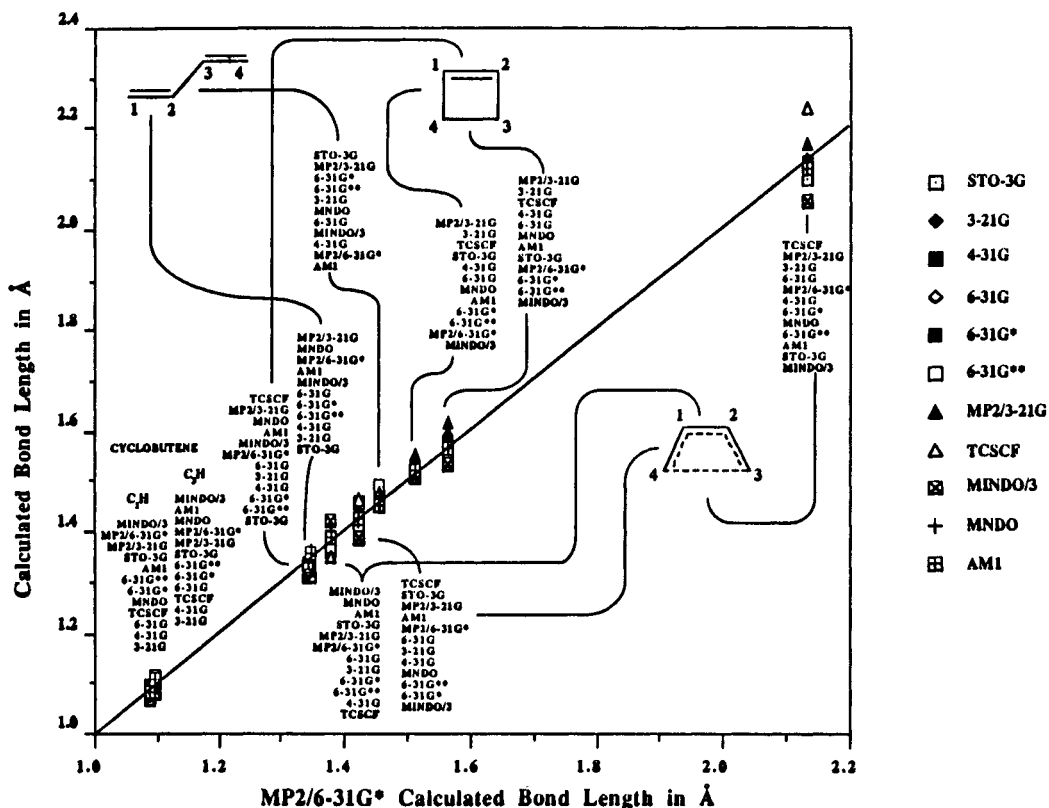
Semi-empirical calculations have been used frequently for the investigation of mechanisms. Such calculations involve various approximations to quantum mechanical calculations, along with parameterizations to fit experimental data. Michael Dewar's group has been quite active in this area. The MINDO/3, MNDO, and AM-1 methods of the Dewar group are approximations to the Hartree-Fock equations, but attempt also to include correlation energy and zero-point energy effects within the parameterization.<sup>4</sup> Semi-empirical methods are useful for studies of some reactions, but must be carefully tested by comparisons with experimental data.

Finally, empirical methods such as Allinger's MM2<sup>5</sup> and its successor MM3 involve parameterization of reasonable classical equations by comparisons with experimental data or quantities calculated by *ab initio* techniques. Such procedures are totally empirical and can only be used for systems closely related to those used for the parameterization.<sup>5</sup>

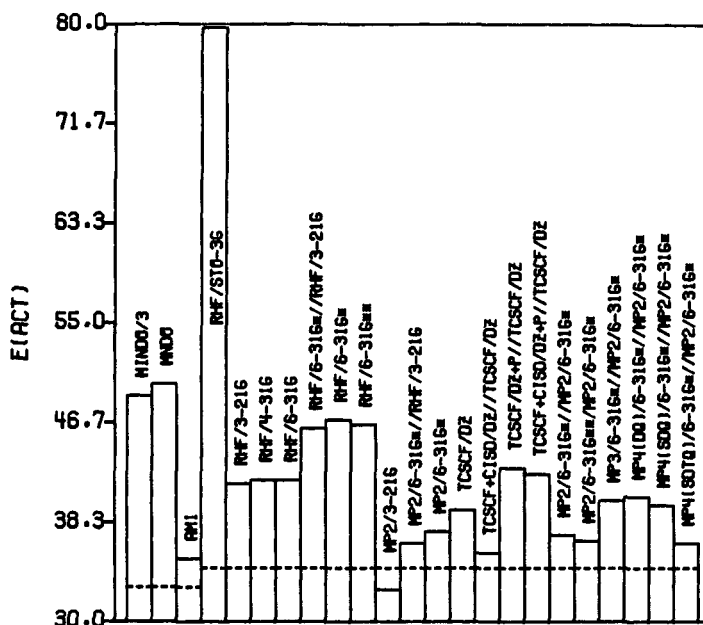
We have demonstrated the use of various methods by our investigation of the conrotatory cyclobutene electrocyclic ring-opening. The reaction has been studied by essentially all of the common computational methods.<sup>6</sup>



The figure below shows the values of geometrical parameters for cyclobutene, butadiene, and the conrotatory transition structure for their interconversion, plotted versus the best geometries that we have calculated, at the MP2/6-31G\* level. Although there are considerable variations in geometry, all computational methods do quite well on bond lengths and bond angles for this reaction.



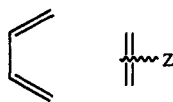
On the other hand, the energetics are much more dependent on the method of calculation. The semi-empirical AM-1 method does very well, while *ab initio* RHF techniques uniformly give the activation energies that are too high; these actually get even higher as the Hartree-Fock limit is approached. The application of correlation energy corrections brings the Hartree-Fock activation energies into reasonable agreement with experiment.<sup>6</sup>



We have carried out similar calculations at a variety of levels for the 1, 5-sigmatropic hydrogen shift, and have concluded in both cases that RHF/3-21G geometry optimizations followed by single point energy calculations at the MP2/6-31G\* level, give geometric and energetic results which are quite useful for descriptions of mechanisms and stereochemistries, at least for hydrocarbons and for molecules without exotic substituents.<sup>7</sup> Having established this, we turn to a study of reaction mechanisms for a type of reaction of special interest to this audience.

We will first describe the Diels-Alder reaction and the calculations we have carried out on substituted Diels-Alder reactions. We and others have calculated the transition structures of the parent reaction, and there is now good accord that the reaction of ethylene and 1,3-butadiene is concerted and synchronous.<sup>8,9</sup> Jorgensen and Blake have now obtained similar results for the cyclopentadiene-ethylene reaction, and these unpublished results are cited with their kind permission.<sup>10</sup>

We have undertaken a study of the reactions of a variety of substituted ethylenes with butadiene, and the figure below indicates the transition structures that we have obtained to date with RHF/3-21G calculations.



Butadiene	Ethylene
Cyclopentadiene	Acrylonitrile
	Maleonitrile
	Fumaronitrile
	Vinylidene Cyanide
	Acrolein
	Acrolein-BH <sub>3</sub>
	Acetylene
	Benzene
	Formaldehyde
	Formaldimine
	Singlet Oxygen
	Diimide

The most interesting series is that studied by Jürgen Sauer and his group<sup>11</sup>, then in Munich, who have served as the extraordinary hosts of our conference in Regensburg. In the figure below, I have reproduced the title section and the table of the classic paper which contains data which has been widely quoted and an extraordinary influence on the understanding and interpretation of Diels-Alder reactions.

JÜRGEN SAUER, HUBERT WIEST<sup>1)</sup> und ALBRECHT MIELERT

Eine Studie der DIELS-ALDER-Reaktion, I

Die Reaktivität von Dienophilen gegenüber Cyclopentadien  
und 9.10-Dimethyl-anthracen

Aus dem Institut für Organische Chemie der Universität München

(Eingegangen am 2. Juni 1964)

Die Additions-geschwindigkeiten verschiedener Dienophile an Cyclopentadien  
und 9.10-Dimethyl-anthracen werden in wasserfreiem Dioxan als Solvens durch  
kinetische Messungen ermittelt und in Hinsicht auf den Mechanismus der  
DIELS-ALDER-Reaktion diskutiert.

Tab. 4. Umsetzung von Cyanäthylenen in Dioxan bei 20° mit (1) 9.10-Dimethyl-anthracen  
(10<sup>6</sup>·k<sub>2</sub> [l/Mol·sec]) und (2) Cyclopentadien (10<sup>6</sup>·k<sub>2</sub> [l/Mol·sec])

Substituiertes Äthylen	(1)	(2)
Tetracyan-	~13 000 000 000	~43 000 000
Tricyan-	5 900 000	~480 000
1.1-Dicyan-	* 127 000	45 500
trans-2-Dicyan-	139	81 <sup>a)</sup>
cis-1.2-Dicyan-	131	91 <sup>a)</sup>
Monocyan-	0.89	1.04 <sup>a)</sup>

a) Aus den zwischen 100–130° erhaltenen Aktivierungsparametern errechnet.

Chem. Berichte, 97, 3183 (1964)

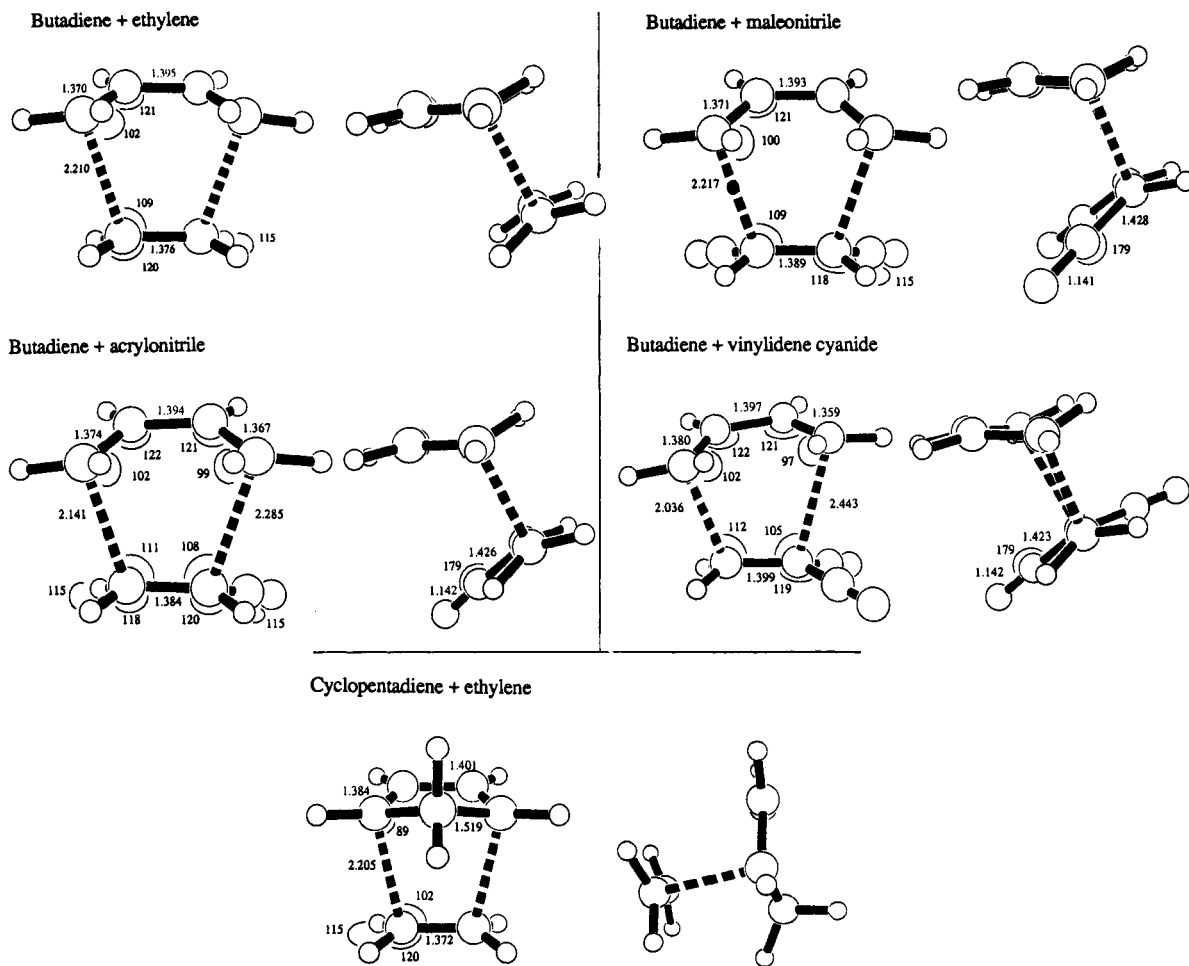
Most qualitative theoretical indices are capable of rationalizing these data very well. For example, we have shown that there is an excellent correspondence between the LUMO energies of the cyanoalkenes and their rates of reaction.<sup>12</sup> Curiously, AM-1 calculations by Dewar do not give the correct trends in substituent effects. Dewar proposed that there were significant solvation effects on rates of such reactions, which would be quite unprecedented for reactions of this type.<sup>13</sup> We undertook ab initio calculations of such reactions, whose relative rates and activation energies are shown below (left).

The results of our calculations and those of Jorgensen and Blake are shown in the figure below (right).

Cyanalkene	$k_{rel}(20^\circ C)$	$E_a$	Reaction	$E_a(3-21G-10)$	$E_a(exptl)$
	~0.000006	23.7 (Walsh and Wells, 1976)		20.1	23.7
	1.04	~15.2		16.0 endo 15.7 exo	~15.2 13.2
	81	12.6		25.9	27.5
	91	11.4		23.1 exo 23.7 endo	*25
	45,500	~8		21.2	*23
	~480,000	~6		21.8 exo 22.2 endo	*21
	~43,000,000	~4		18.5	*19

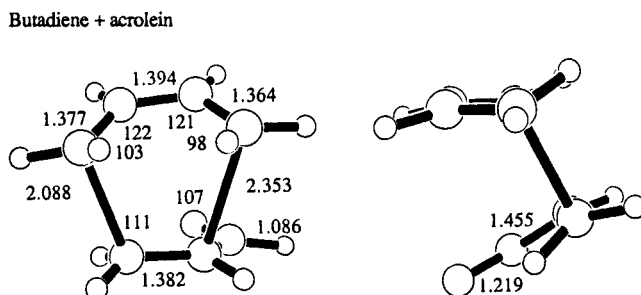
\* 10 kcal/mol has been added to Sauer's results for cyclopentadiene

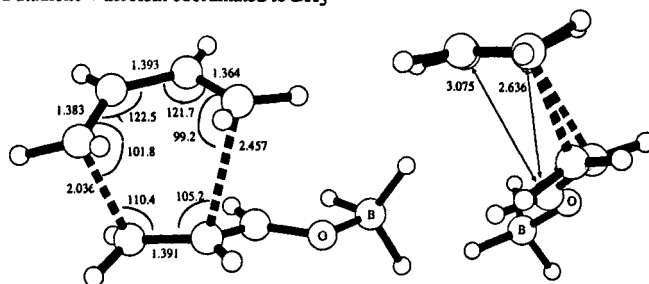
Because studies of the parent reaction have shown that correlation energy lowers the activation energy by approximately 10 kcal/mol, the calculated numbers from the 3-21G calculations are reduced by this amount. Also, since the activation energies for the cyclopentadiene reactions are significantly lower than those of butadiene, we have added 10 kcal/mol to Sauer's activation energies or estimated activation energies to approximate the activation energies for the reactions of butadiene. Although one might argue that these corrections represent a preordained agreement, it is nevertheless remarkable how well the RHF calculations reproduce the differences in activation energies. The series of figures that follow show the transition structures for many of these cases.



For symmetrical cases, bond formation remains synchronous, while unsymmetrical substitution cause shortening of one bond and lengthening of the other, as might be expected.<sup>14-16</sup> An extreme of asynchronicity results in a 0.4 Å difference in forming bond lengths in the vinylidene cyanide reaction.<sup>15</sup> Interestingly, the distortion of the diene is less unsymmetrical.

We have also studied the reactions of acrolein with butadiene and a model for a simple catalyzed process, involving coordination of  $\text{BH}_3$  to acrolein.<sup>16</sup> The results are shown below. There is good qualitative agreement of calculated activation energies with experiment here, and interesting geometrical changes in the transition structure as well as significant charge separation.<sup>16</sup>

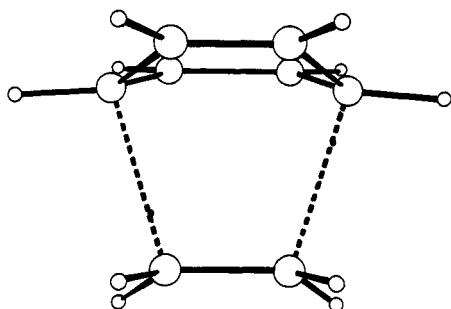


Butadiene + acrolein coordinated to BH<sub>3</sub>

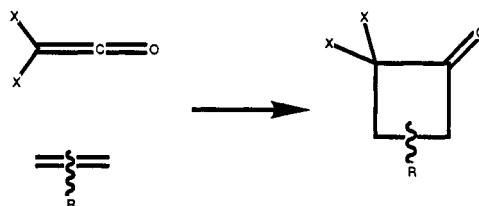
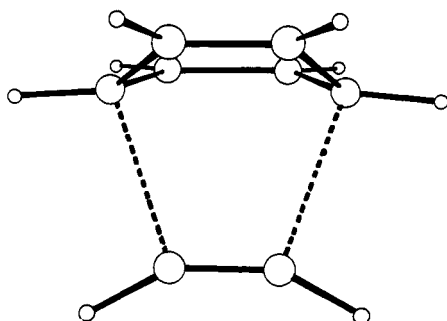
	$E_a$ (3-21G - 10kcal/mol)	$E_a$
	25.9	27.5
	20.5 endo-cis	19.7
	22.6 exo-cis	
	12.5 endo-trans	small

We have also studied the Diels-Alder reactions of benzene with ethylene and acetylene. These are shown below (left). The energy of concert of the benzene reaction is especially high<sup>18</sup>, which appears to be the result of maintenance of aromaticity in the transition state.

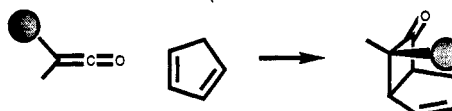
## Benzene + ethylene



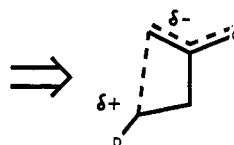
## Benzene + acetylene



1. Stereospecific (cis form cis, trans form trans)
2. Stereoselective (to form more crowded adduct)



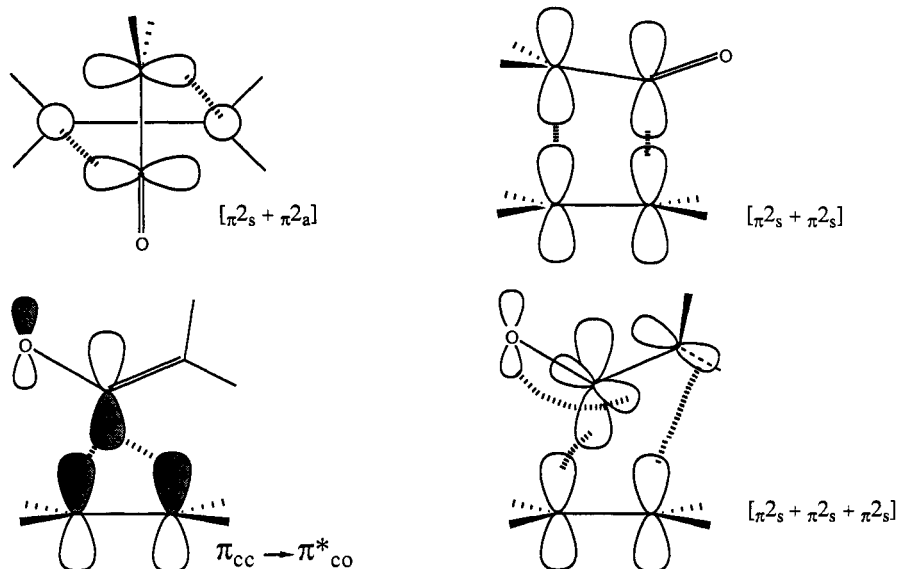
3. Regioselectivity, isotope effects, solvent effects imply partial zwitterionic character



4. 1,2- not 1,4- additions to dienes

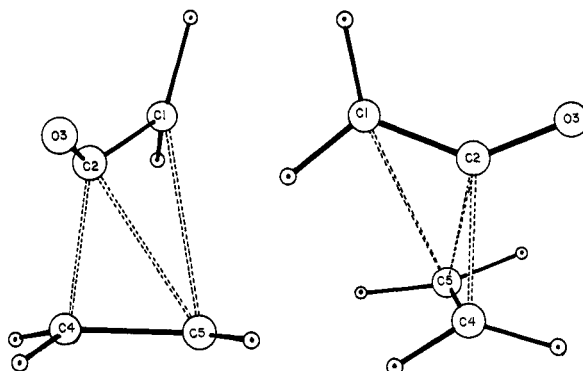
Finally, we turn to a classic reaction of considerable interest for some time, but particularly since the Woodward-Hoffmann rates in 1970.<sup>19</sup> The principle characteristics of the reaction are summarized above (right).<sup>19-22</sup>

Woodward and Hoffmann speculated about a variety of electronic interactions.<sup>19</sup> They considered the possibility that the reaction was concerted  $\pi^2_s + \pi^2_a$  cycloaddition, *antarafacial* on the ketene because of the low steric hindrance offered to the necessary "sideways" approach. They also emphasized that the carbonyl group LUMO is the "spearhead of reactivity".<sup>2</sup> Thus, the additional interaction shown at the lower left could occur, to give a [2+2+2] reaction as implied by the dashed lines in the picture at the lower right.



Burke carried out a study of this reaction with *ab initio* minimal basis set calculations including a small configuration interaction correction for correlation energy contributions.<sup>23</sup> This extensive study was performed before gradient optimizations were available, so that a saddle-point was not located accurately.

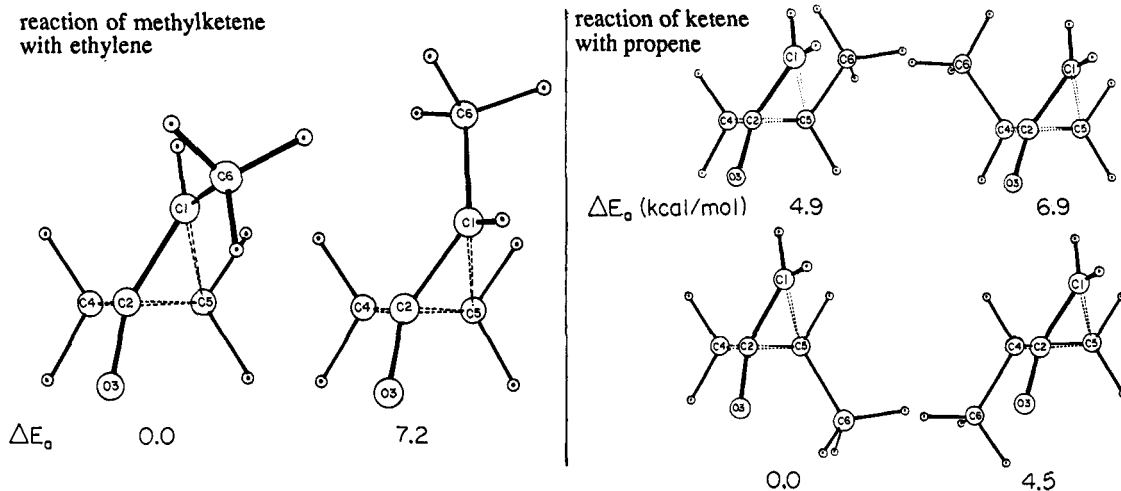
Calculations performed at various levels of theory gave rise to transition structures of similar geometry. While the MP2/6-31G\* calculations are presumably closest to reality, the same qualitative conclusions can be made from any of these calculations.



As shown, the single bond between the central ketene carbon and one carbon of ethylene is almost fully formed (1.78 Å). The other incipient carbon-carbon bond, between the methylene carbon of ketene and the remaining ethylene carbon, is much longer (2.43 Å). This latter carbon is in fact much closer to the central ketene carbon in the transition state (2.08 Å) than to the carbon to which it will be bonded in the product. The ketene molecule remains almost planar, which is another indication of the small degree of bonding at CH<sub>2</sub> of the ketene. The transition structure is similar to those of carbene cycloadditions to alkenes and of hydroborations where the vacant p orbital of carbon or boron accepts electrons from alkene, and the carbene lone-pair or borane BH bond donates electrons to the alkene.<sup>25</sup> These comparisons emphasize the importance of the orthogonal donor and acceptor orbitals in transition structures of reactions of this type.

We have also located two transition states for the reaction of methylketene with ethylene and four transition structures for the reaction of ketene with propene.

For the reaction of methylketene with ethylene, the difference in activation energy between the two modes of addition is calculated to be 7.2 kcal/mol. The preferred transition state has smaller steric interactions between the methyl group and the terminal ethylene CH<sub>2</sub> group. It may also be stabilized slightly by the electrostatic attraction between the methyl group and the oxygen atom. As a result of both of these factors, the <CCC angle in **1** (120°) remains like that in methylketene, while in **2** it is distorted to 129°. The observed preferential formation of the more crowded product in reaction with *cis*-alkenes is nicely accounted for by these results.



For the reaction of ketene with propene, four transition structures are possible: two regioisomers, each of which can exist as either of two stereoisomers. The most stable transition state places the methyl on the ethylene carbon which bears substantial positive charge, and in the sterically least crowded and electrostatically favored position. If we assume that the energetic effects of methyl substitution pictured above are additive, the activation energy for the reactions of ketene with *trans*-butene can be estimated to be 2.4 kcal/mol greater than the corresponding reaction with *cis*-butene. Therefore, our calculation not only reproduces the experimentally observed regiochemistry, but also explains the enhanced reactivity of *cis*-alkenes over *trans*-alkenes.

#### Acknowledgements

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