

REGIO- AND STEREOSELECTIVITY IN DIELS-ALDER REACTIONS.
THEORETICAL CONSIDERATIONS ¹

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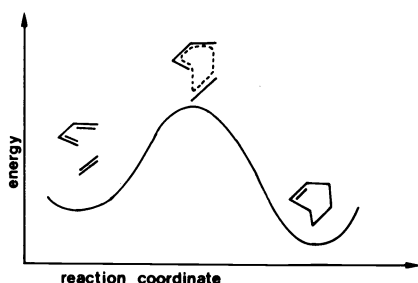
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Abstract - The regio- and stereoselectivity of Diels-Alder reactions is discussed in terms of second order orbital interactions, which may be subdivided into secondary orbital effects, substituent effects and polar group effects.

1) First Order Orbital Interactions

A large number of mechanistic investigations on Diels-Alder reactions² reveal³ that the new σ bonds are formed at the same time, i.e. we are dealing with a one-step-process as indicated in Fig. 1. In agreement with

Fig. 1 Energy profile of a Diels-Alder reaction



this interpretation are theoretical investigations using correlation techniques⁴ or by using frontier orbitals⁵.

In Fig. 2 both frontier orbital pairs (HOMO(diene)-LUMO(dienophile) and HOMO(dienophile)-LUMO(diene)) are shown for butadiene and ethylene. We find an *in phase relation* between the atomic orbital (AO) amplitudes at those centers where the new bonds are formed.

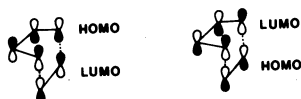


Fig. 2 Frontier orbitals for butadiene and ethylene.

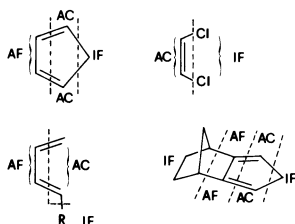
This *in phase relation* is crucial for the low activation energy of a synchronous process (Fig. 1) and it determines the stereospecificity. We will call the *in phase relation* a *first order orbital interaction*.

2) Second Order Orbital Interactions (Definition)

A still growing number of investigations in the field of cycloaddition reactions reveal regioselectivity or stereoselectivity³⁻⁵. In analogy to the first order orbital interactions we will call those electronic effects which determine the regio- and stereoselectivity *second order orbital interactions*.

To discriminate among the second order orbital interactions we divide the two reacting molecules (diene and dienophile) into different regions: the *active centers (AC)*, the *active frame (AF)* and the *inactive frame (IF)*.

The *active centers* are those centers between which the new bonds are formed. The *active frame* consists of those atoms that are involved in the σ/π reorganization during cycloaddition but which are not *active centers*. The *inactive frame* are those molecular fragments which are not involved in the reaction. To clarify this classification some examples are listed.



Using second order perturbation theory⁶ it can be shown¹ that the second order orbital interactions can be subdivided into *secondary orbital effects*, *substituent effects* and *polar group effects*. A definition is given in Fig. 3.

FIRST ORDER ORBITAL INTERACTIONS

in phase relation between AO's of
Active Centers in an unperturbed frame

SECOND ORDER ORBITAL INTERACTIONS

Secondary Orbital Effects	Substituent Effects	Polar Group Effects
in phase relation between AOs of Active Frames	a) polarization of π -systems b) σ/π mixing at Active Centers	interaction between Active Centers and Non-Active Centers and between Non-Active Centers

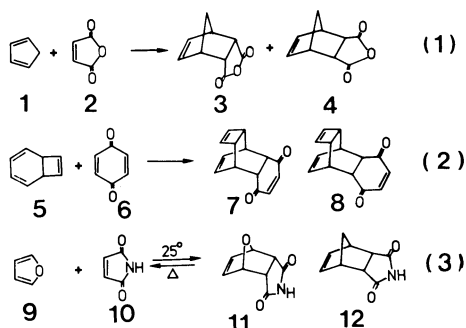
Fig. 3 Classification of nonpolar Diels-Alder reactions.

Discussion of Second Order Orbital Interactions

a) *Secondary Orbital Interactions*

According to Alder and Stein⁷ diene and dienophile add to each other in such a way that a maximum accumulation of double bonds is achieved.

Examples for the Alder-Stein rule are shown below:



Although the observed *endo-exo* ratio amounts mostly 99:1, it should be noted that the energy difference in the corresponding *endo* or *exo* transition state is only about 3 kcal/mol.

An MO based rationalization of the Alder-Stein rule has been suggested by Woodward and Hoffmann⁴. If we consider the important frontier orbitals of cyclopentadiene and maleic anhydride (Fig. 4) we find in addition to the first order orbital interaction (*in phase* relation between centers 1 and 4 of the diene and the centers 1' and 2' of the dienophile) a further *in phase* relation between the *active frames* of both molecules in the

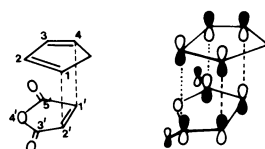
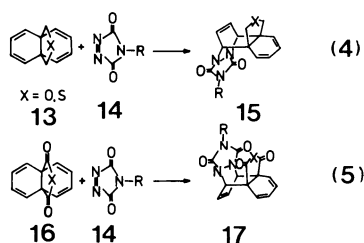


Fig. 4 HOMO of cyclopentadiene and LUMO of maleic anhydride.

endo transition state, *i.e.* the AO at the centers 2 and 3 of the diene and the centers 3' and 5' of the maleic anhydride (see Fig. 4).

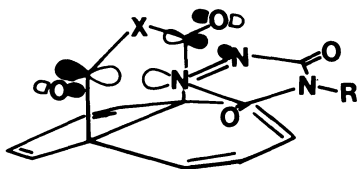
Other examples which demonstrate nicely the importance of secondary orbital effects for the stereoselectivity are reactions of propellanes investigated by D. Ginsburg and coworkers⁸⁻¹⁰.



Reaction between the propellanes of the type 13 with triazolinediones (14) yields the *anti* product 15 only. This can be rationalized by invoking the steric effects of the bridge. Replacing the CH₂-groups by CO to yield 16 one observes only the *syn* products 17. Although the steric effect of the bridging unit is reduced in 16 compared to that in 13 it is not clear why there should be exclusively *syn*-attack in 16 since the overall geometry is not all that different between 13 and 16.

A simple explanation is offered by *secondary orbital interactions*: The transition state for *syn* attack of 14 is stabilized by interactions

between the n -combination of the lone-pairs at the NN-bridge and the π^* orbital of the COXCO bridge of 16 as shown below in 18. This explanation



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is further supported by model calculations^{8,11}.

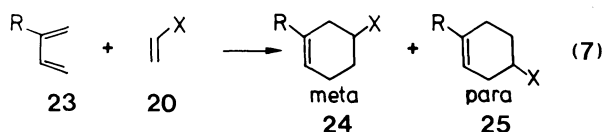
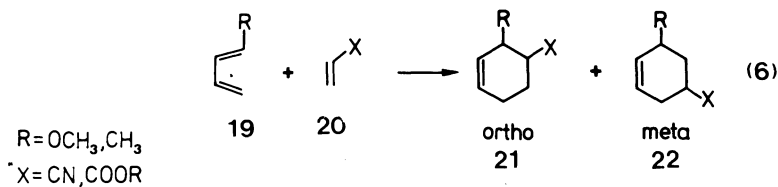
b) *Substituent Effects*

The substituent effects we can divide roughly into two groups (see Fig. 3):

- 1) substituents which cause a polarization of the frontier orbitals of π character in such a way that the size of the amplitudes are changed, but the $2p_\pi$ lobes stay parallel
- 2) substituents which cause a strong σ/π mixing, leading to rotation of the p_π lobes.

Polarization Effects

Examples for this effect are the cycloaddition reactions between substituted butadienes and acrylic acid derivatives as shown below:



Houk¹² and others¹³ have shown that these reactions can be rationalized by invoking second order orbital interactions. Since the energy difference between the HOMO(diene) and the LUMO(dienophile) is substantially smaller than the LUMO(diene) and HOMO(dienophile) we can simplify our discussion by only considering the HOMO of the diene and the LUMO of the dienophile. In Fig. 5 we have shown the frontier orbitals of some dienes substituted in 1 and 2 position and mono-substituted dienophiles¹². If one knows that the interaction between two large and two small AO coefficients (configuration A in Fig. 5) is more efficient than between two times a big and a small one (configuration B in Fig. 5) it follows that the ortho-arrangement in the case of a substituent at position 1 of the diene and that the para-product in case of a 2 substituent should result.

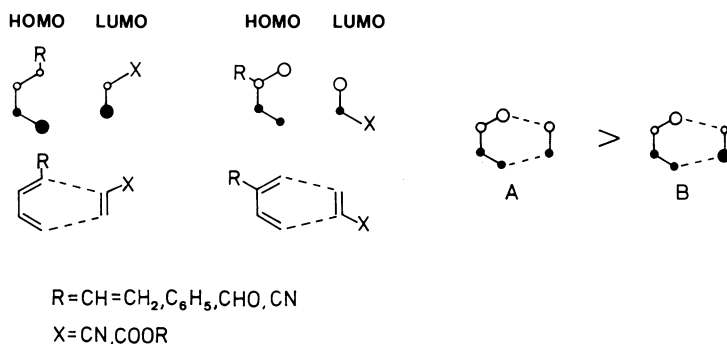
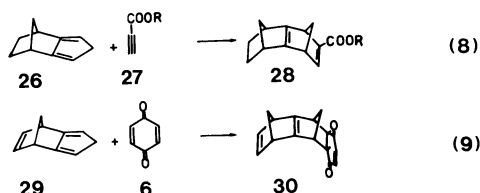


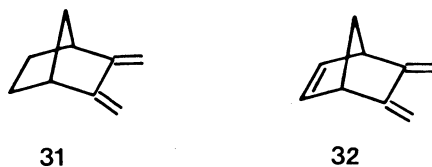
Fig. 5 Highest occupied MO's of substituted dienes and lowest unoccupied MO of dienophiles.

σ/π Interaction

Examples for the influence of σ/π interaction are shown below¹⁴⁻¹⁶. To ex-



plain the preference of the dienophile to attack *anti* to the methano group of the norbornane or norbornene fragment we can omit steric effects since the new bonds formed are three σ -bonds apart from the bridges. We also can exclude polar effects since we are dealing with simple hydrocarbons with a low dipole moment. Important for the understanding of the observed stereoselectivity indicated above are σ/π interactions. Model calculations on 31 and 32 predict¹⁵ a strong mixing between the lowest occupied π



orbital (π_s) of the diene moiety and high lying σ orbitals of proper symmetry. The resulting canonical molecular orbital is shown in Fig. 6 schematically. The rotation of the terminal p_π lobes for π_s of 32 is shown in the contour diagram of the same figure. It is seen that the rotation leads to significant differences in the frontier distribution on the *syn* and *anti* side. The rotation just described is due to σ/π mixing and not due to any rehybridization.

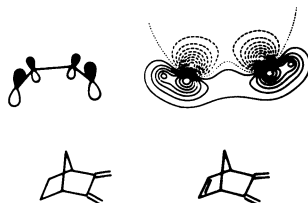


Fig. 6 Schematic representation of the π_s orbital of 31 and 32 (left) Contour diagram for 31 showing the deformation of the two terminal π lobes (right).

To understand the preferred addition of a dienophile *anti* to the methano bridge let us consider Fig. 7. If the dienophile adds from below the anti-bonding interaction between π_s of the butadiene moiety and the HOMO of the dienophile is smaller than in the case of a *syn* attack. This is due to the different overlap between the rotated $2p_\pi$ orbitals at the terminal carbon atoms of the butadiene fragment and the dienophile.

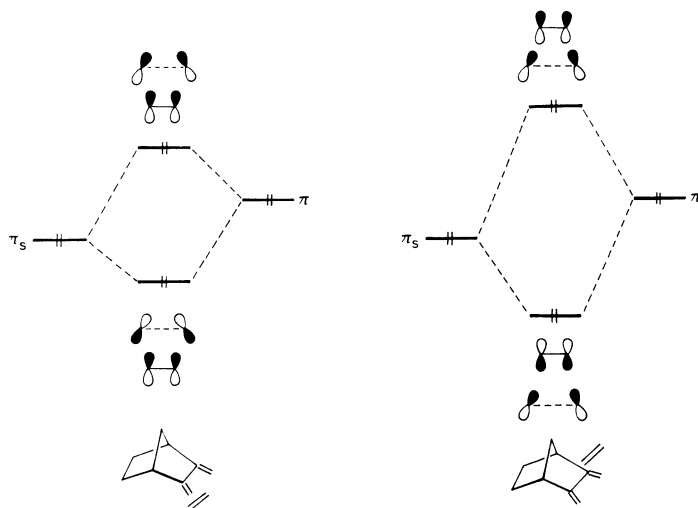
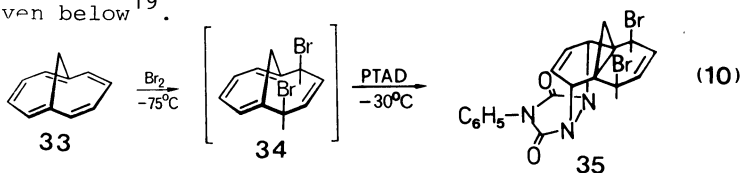
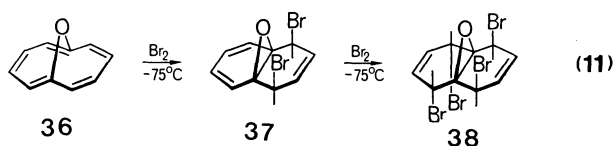


Fig. 7 Qualitative diagram of the interaction between π_s of the butadiene unit of 31 and 32 with a π bond. On the left the situation of the approach of the ethylene *anti* to the methylene group, on the right the corresponding *syn* approach is shown.

To estimate the energy difference for exo and endo attack in the case of the dienes 28 and 30 we have calculated the four electron destabilization energies¹⁵ between π_s of 28 and 30 and π of ethylene assuming a distance of 2.18 Å. The energy difference for the endo *vs.* exo addition amounts to 3 (30) and 4.6 kcal/mol (28).

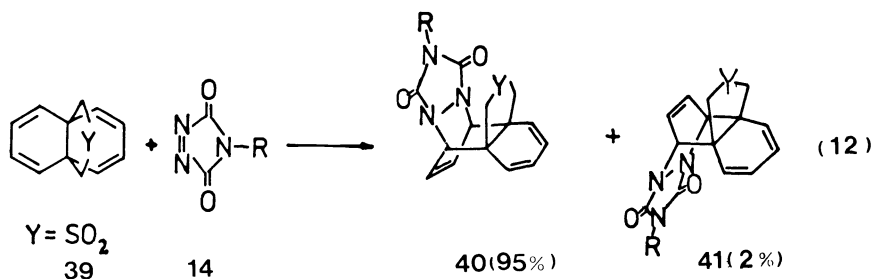
Further reactions showing the importance of π/σ interaction have been published by several groups¹⁷⁻¹⁹. Two examples in which steric effects are overruled are given below¹⁹.





Polar Group Effects

A good example for the influence of polar groups on the regioselectivity of Diels-Alder reactions is seen by comparing reaction (4) with (12). Replacing X=S by SO₂ in 13 changes the regioselectivity considerably^{8,20}. To explain



the effect of the polar SO₂-group we have plotted in Fig. 8 the electrostatic potential of 39 and 13 using wave functions derived from an Extended Hückel calculation¹¹. Inspection of Fig. 8 shows that the preferred syn

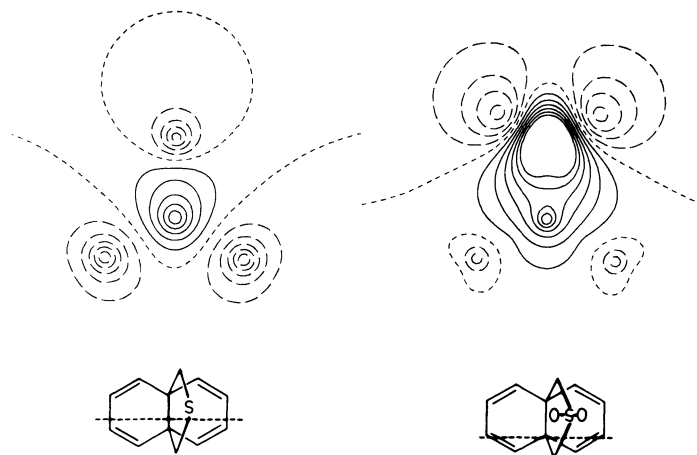


Fig. 8 Contour diagrams of the calculated electrostatic potentials of 13 (X=S) and 39. The maps are drawn in the plane parallel to the *x,z*-plane indicated by the dashed line in the formulae. The interval between the contours is 15 kcal/mol in the case of 13 (X=S) and 30 kcal/mol in the case of 39. Positive potentials are indicated with full lines, negative potentials with broken lines.

attack in case of 39 can be rationalized due to a stabilizing Coulomb attraction between the strongly electron deficient S atom in the SO₂ group and the electron rich NN group in the triazolinedione.

References and Notes

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