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Endo- vs. Exo-Selectivity in Diels-Alder Reactions of Maleic Anhydride

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Abstract

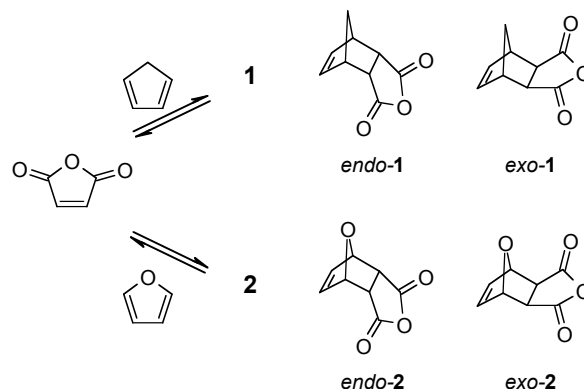
Qualitative and quantitative MO methods were used to test the assumption that the *endo*-product is the predicted kinetic product and the *exo*-adduct is the predicted thermodynamic product for the Diels-Alder reaction of maleic anhydride with cyclopentadiene and with furan. The reactions were then carried out and the products analyzed, and the results considered in terms of the relative energies of the reactants and products of each process and the Hammond postulate.

Introduction

The Diels-Alder reaction is a pericyclic [4+2] cycloaddition, in which a conjugated diene and an isolated alkene add together in a single step without intermediates by a cyclic redistribution of bonding electrons. This process is very useful in organic synthesis because it forms two carbon-carbon bonds in one step and is one of the few methods available for forming cyclic molecules. When both the diene and dienophile are cyclic, it is possible to form two products with different geometries, called *exo*- and *endo*-adducts.

A molecular orbital description of the Diels-Alder reaction is often used to account for the reactivity and the stereochemistry of the reaction. The highest occupied molecular orbital (HOMO) of the diene will donate electron density into the lowest unoccupied molecular orbital (LUMO) of the dienophile, resulting in the cyclic, nonpolar transition state and cyclic product. Secondary overlap can account for the preferred formation of, in the case of the reaction of two cyclic molecules, the transition state of the *endo*-reaction path. It is therefore the general case that the *endo*-adduct will form faster for these reactions.

In this report, we tested the hypothesis that the *endo*-adduct will be isolated from the reaction of maleic anhydride with two different dienes, cyclopentadiene and furan. The two possible products of the reaction of maleic anhydride with each diene are shown below. Cyclopentadiene and maleic anhydride can react to form either the *endo*- or *exo*-adduct bicyclo[2.2.1]hept-5-ene-*cis*-2,3-dicarboxylic anhydride, also called 5-norbornene-*cis*-2,3-dicarboxylic anhydride (**1**). Furan and maleic anhydride can react to form either adduct of 7-oxabicyclo[2.2.1]hept-5-ene-*cis*-2,3-dicarboxylic anhydride (**2**). Using *ab initio* calculations, the kinetic and thermodynamic product of each reaction was predicted. The two reactions were then carried out to test these predictions. The reaction with cyclopentadiene is known to be much faster, and much more exothermic, than the reaction with furan. The difference in reactivity, and the stereochemistry of the adducts formed from the two reactions, is considered in terms of the relative energies of the reactants, transition states and products.



Experimental

Maleic anhydride and the Diels-Alder adducts are intense skin irritants.

Molecular modelling

All calculations were performed using the program Spartan '02 for Windows, from Wavefunction. Cyclopentadiene, furan, and maleic anhydride were each built and their equilibrium geometry calculated using Hartree-Fock 3-21G* calculations. For each diene, a surface corresponding to the HOMO was generated. For maleic anhydride, a surface corresponding to the LUMO was generated. By visual observation of the overlap of the reactant HOMO and LUMO, a qualitative prediction of the kinetic product of each reaction could be made based on qualitative frontier molecular orbital theory. The ground state energy of each reactant was recorded.

The equilibrium ground state energies of the *endo*- and *exo*-forms of **1** and **2** were then calculated as described above for the reactants. This allowed prediction of the thermodynamic product of each reaction. Considering the energies of the reactants and product for each reaction, a qualitative prediction of the relative positions along the reaction coordinate of the transition states could be made based on the Hammond postulate.

The transition state energy of the predicted kinetic product was calculated for **1**. Starting with the product structure, the "Reaction" (blue curved arrow) module was used to draw arrows representing the retro-Diels-Alder reaction. The energy was then calculated by optimizing the transition state geometry using *ab initio* calculations at the 3-21G* level.

With the energies of the reactants, transition state and products for the formation of *endo*-**1** and *endo*-**2**, it was possible

to estimate the relative rates of these two reactions in the forward and the reverse directions $(k_1 / k_2)_f$ and $(k_1 / k_2)_r$. This requires the assumption that the entropy of activation (ΔS^\ddagger) of these processes is approximately equal:

$$\text{Thus} \quad \Delta H^\ddagger_1 - \Delta H^\ddagger_2 \approx \Delta G^\ddagger_1 - \Delta G^\ddagger_2 = \Delta \Delta G^\ddagger$$

$$\text{and} \quad k = (k_B T / h) \exp(-\Delta G^\ddagger / RT)$$

$$\therefore \quad k_1 / k_2 = \exp(-\Delta \Delta G^\ddagger / RT)$$

The reversibility of these two reactions was taken into account when rationalizing the stereochemistry of the isolated products of reactions **1** and **2**.

Bicyclo[2.2.1]hept-5-ene-cis-2,3-dicarboxylic anhydride (1).

In a 25-mL round bottom flask fitted with a drying tube, maleic anhydride (1.5 g) was added to dry ethyl acetate (5 mL), and the solid dissolved by gentle heating. Diethyl ether (5 mL) was added, and the solution swirled to mix the solvents. The solution was then cooled in an ice bath. Keeping the solution cold, freshly cracked cyclopentadiene (1.2 mL) was added, and the solution swirled (with cooling in an ice bath if necessary) until the exothermic reaction subsided, resulting in a white solid. The crude **1** was recrystallized *in situ* by gentle heating of the mixture until the solid dissolved, followed by slow cooling of the solution to room temperature to yield large crystals. The crystals were filtered and washed with a small amount of ice-cold ether, and the melting point compared to the known melting points of *endo*-**1**, 142-142 °C, and *exo*-**1**, 164-165 °C,

7-Oxabicyclo[2.2.1]hept-5-ene-cis-2,3-dicarboxylic anhydride (2).

In a conical centrifuge tube or small test tube, finely ground maleic anhydride (1.2 g) was dissolved in anhydrous diethyl ether (10 mL) by gentle heating in a water bath. The solution was then cooled in an ice bath, and the volume of ether restored to 10 mL. While the solution was still cool, furan (1.0 mL) was added, and the reaction swirled gently. The reaction flask was then stoppered, and the stopper wrapped tightly in parafilm to prevent evaporation of the ether. The reaction apparatus was secured and stood without stirring for 48 hours.

The resulting solid was collected on a Hirsch funnel, and washed with ice-cold hexane (~1 mL). Crude **2** was recrystallized from hexane-ethyl acetate by heating the solid in hexane (5 mL) until the mixture just reaches boiling, followed by addition of enough warm ethyl acetate (~1-3 mL) to dissolve the solid. The solution was allowed to cool to room temperature and, after crystals had appeared, cooled in an ice bath. The recrystallized **2** was filtered and washed with ice-cold hexane (2 x 1 mL), and dried. The melting point was compared to the known melting points of *endo*-**2**, 80-82 °C and *exo*-**2**, 125-126 °C.

Table 1. Calculated Energies for the Reaction of Cyclopentadiene and Maleic Anhydride

Reaction Component	3-21G* Energy/ Hartrees ^a	Normalized Energy/ (kJ mol ⁻¹)
Reactants	-566.8205	162.7
Endo-transition state	-566.7945	231.1
Endo-product (1)	-566.8803	5.798
Exo-product (1)	-566.8825	0

^aOne Hartree is equal to 2625.5 kJ/mol.

Table 2. Calculated Energies for the Reaction of Furan and Maleic Anhydride

Reaction Component	3-21G* Energy/ Hartrees ^a	Normalized Energy/ (kJ mol ⁻¹)
Reactants	-602.4536	92.40
Endo-transition state	-602.4179	186.1
Endo-product (2)	-602.4840	12.61
Exo-product (2)	-602.4887	0

^aOne Hartree is equal to 2625.5 kJ/mol.