endo- and exo-Stereochemistry in the Diels–Alder Reaction: Kinetic versus Thermodynamic Control[1]

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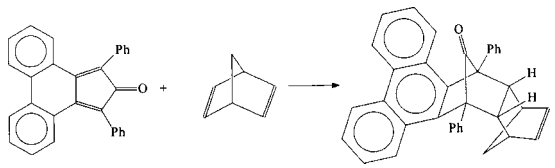
In these experiments, which were used in the problem-solving mode (*1*), the stereoselectivity of the Diels–Alder cycloaddition of *N*-phenylmaleimide to furan is deduced by the characteristic splitting patterns in the proton-NMR spectra. The relationship of coupling constants to dihedral angle, as described by the Karplus equation, is illustrated. The data can also be used to demonstrate the concept of kinetic versus thermodynamic control.

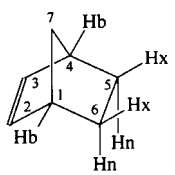
Two recent papers in this *Journal* reported laboratory experiments illustrating the stereochemistry of the Diels–Alder reaction (*2, 3*). Pickering (*2*) described the reaction of maleic anhydride with cyclohexadiene, α-phellandrene, and furan. Cyclohexadiene and α-phellandrene gave the endo stereoisomer, whereas furan gave the exo stereoisomer. These experiments were used in the problem-solving mode and students were asked to decide, by comparing their data with that in the literature, which stereoisomer was formed. In another experiment, Harrison (*3*) used NMR to study the Diels–Alder reaction between norbornadiene and phencyclone (reaction 1). The stereochemistry of this reaction was established from the fact that the methylene protons lie in the shielding cone of the aromatic system.



(1)

The majority of general organic chemistry texts present the Diels–Alder reaction as yielding endo products. In most cases the exo product is the thermodynamically more stable, but the endo adduct forms much more rapidly, and kinetic control is observed (*4*). The exceptional exo stereochemistry of the furan–maleic anhydride adduct was first demonstrated by Woodward and Baer (*5*) using classical methods and later confirmed by X-ray crystallography (*6*). More recently Lee and Herndon (*7*) demonstrated that the endo isomer forms more rapidly in a reversible reaction, resulting in the ultimate dominance of the thermodynamic (exo) product.

In the norbornene (bicyclo[2.2.1]heptene) system, **1** (which results from Diels–Alder additions to cyclopentadiene), endo and exo stereochemistry can be deduced experimentally from differences in the coupling constants of the bridgehead protons on C-1 and C-4 (Hb) to the exo (Hx) or endo (Hn) protons on C-5 and C-6 (see below) (*8*).The geometry of the 7-oxabicyclo[2.2.1]heptene system is very similar to that of the norbornenes; consequently, the corresponding coupling constants are very similar.



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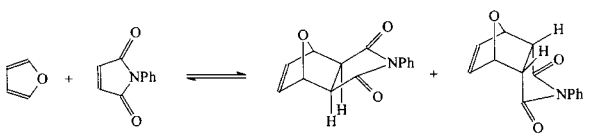
J (Hb,Hx) = 3.66 Hz
J (Hb,Hn) = 0.55 Hz

We felt that an ideal experiment would be one in which both endo and exo products are formed, with each product giving an NMR spectrum that students could use to assign stereochemistry. *N*-Phenylmaleimide (*9*) reacts with furan to produce a mixture containing the endo and exo isomers. These isomers may be separated by column chromatography as described below. As expected, the proton NMR of the endo isomer shows a coupled[2] signal for the C-5/C-6 protons (δ 3.8 ppm for the C-5/C-6 protons), while that for the exo isomer shows a singlet for the C-5/C-6 protons (δ 3.0 ppm). These spectra are shown in Figures 1 and 2. The splittings of the bridgehead protons are more complex (owing to additional coupling with the vinylic protons) and therefore less diagnostic. Thus reaction of *N*-phenylmaleimide with furan is an ideal system for teaching about the stereochemistry of the Diels–Alder cycloaddition.

The 7-oxabicyclo[2.2.1]heptene ring system is conformationally rigid. The difference in splitting patterns observed between the exo and endo adducts (**2** and **3**) results from the very different dihedral angles between the exo and endo protons (on C-5/C-6) and the bridgehead protons (on C-1/C-4). Examination of models of **2** and **3** indicates a dihedral angle (H–C_5–C_4–H) of almost 90° for the exo isomer **2** and a small dihedral angle for the endo isomer **3**. These dihedral angles are calculated to be 83° and 33.8° respectively using AM1 (*10*) as implemented in the HyperChem (*11*) software package. Using the Karplus equation (*12*), $J = 8.5 \cos^2\theta - 0.28$ where θ = the dihedral angle, the coupling constants for the exo isomer (**2**) and the endo isomer (**3**) are calculated to be 0.05 and 5.2 Hz, respectively.



2 **3**

At room temperature, the reaction of *N*-phenylmaleimide with furan may be run neat, in ether solution (a mixture of the two isomers precipitate), or in benzene solution (almost pure exo isomer **2** precipitates). Alternatively, in $CDCl_3$ solution the reaction may be followed by NMR with the following results (ratios obtained from integration [δ 6.8 for *N*-phenylmaleimide, 3.7 for endo, and 3.0 for exo]):

Time	Temp	exo (**2**) (%)	endo (**3**) (%)	*N*-phenyl-maleimide (%)
7 days	0 °C	36	49	14
7 days	ambient	48	41	11
20 days	ambient	68[a]	23[a]	9[a]
7 days then 5 h	0 °C 60 °C	43	21	36

[a]Equilibrium ratio.

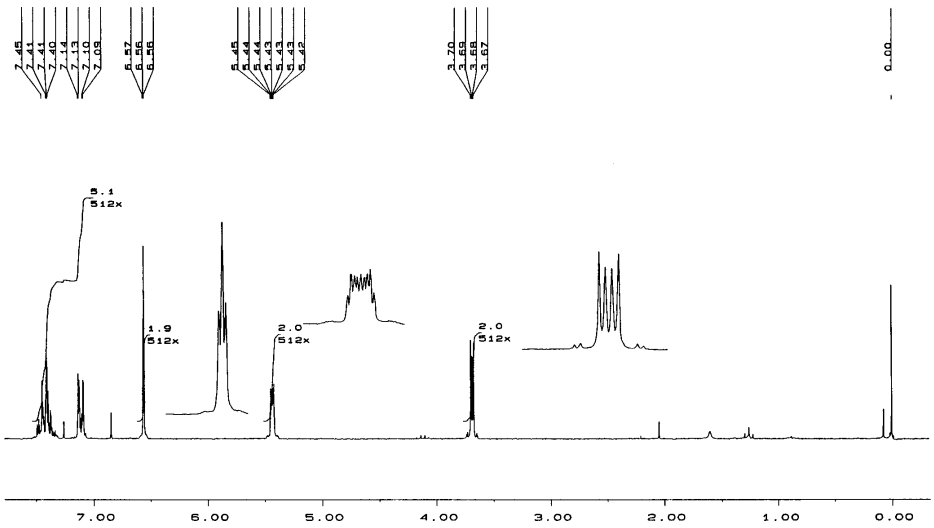


Figure 1. Proton-NMR spectrum of endo isomer in $CDCl_3$.

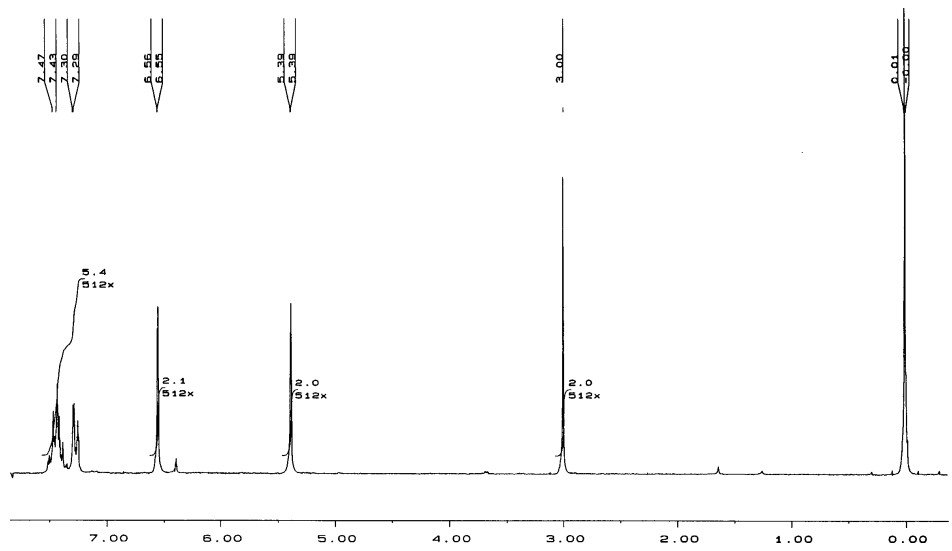


Figure 2. Proton-NMR spectrum of exo isomer.

For a student experiment, the first task is the preparation of *N*-phenylmaleimide, which is then reacted with furan (neat) for one week at room temperature. The products are analyzed by thin-layer chromatography and NMR and separated by column chromatography. Students are asked to determine the structures of all products (including the stereochemistry of the Diels–Alder adducts) and to provide a theoretical explanation for the changes in endo to exo ratio observed in the NMR experiment.

To do this students must understand the Karplus equation well enough to decide which of the isomeric products will show the observed splitting pattern in the NMR. In addition, NMR data similar to those described above are either collected by students or provided to them for interpretation and explanation of the changes.

Because the first product in the reaction series, maleanic acid, is not soluble in $CDCl_3$, the NMR spectrum in d-6 DMSO was provided for student interpretation. Using this and other IR and NMR spectral data, our students have had little trouble deciding on the correct structures for the maleanic acid and *N*-phenylmaleimide. Moreover, most of them concluded that two products were produced in the Diels–Alder reaction, and that these are adducts of the two reactants.

To give students a better chance to obtain the correct stereochemistry of the final products, we used a prelaboratory question asking them to deduce the structure of the product from the reaction of maleic anhydride with furan. IR and NMR spectra of the product were provided. The Karplus equation was introduced and we recommended that either molecular models be constructed or one of the molecular modeling programs be used to estimate the dihedral angles of adjacent protons. With such an introduction, several students assigned the stereochemistry correctly and all of them were oriented to work properly with the data they had. Even with these hints, however, a few students had difficulty in correctly assigning the structures. We find this problem to be a worthy challenge for the best of students. Even though students are introduced to the concept of thermodynamic and kinetic control in the lecture, very few are able to apply such theoretical concepts to make the correct explanation of the observed changes in the ratios of reactants and products. Technically the preparation and purification of the first two products presented little difficulty, but the final separation of the two isomeric Diels–Alder adducts was a challenge for the best of our student laboratory workers. We allowed three 3-hour laboratory periods for this experiment. The time students spent on this experiment outside of the laboratory obviously varied greatly. Most students reported spending between three and five hours in this fashion.

In all the problem-solving laboratory exercises in our program we ask students to decide for themselves what data to collect and interpret. Subsequently, the instructors meet with students to discuss their data and compare them with reference data obtained by the instructor. The correct interpretation of the data is also presented and discussed. Students generally comment favorably on these post-laboratory sessions as increasing their understanding of the experiment and providing insight into solving these types of problems.

Experimental Procedure

Safety precautions include the correct handling of flammable materials (ether, EtOAc, furan, and hexane), toxic

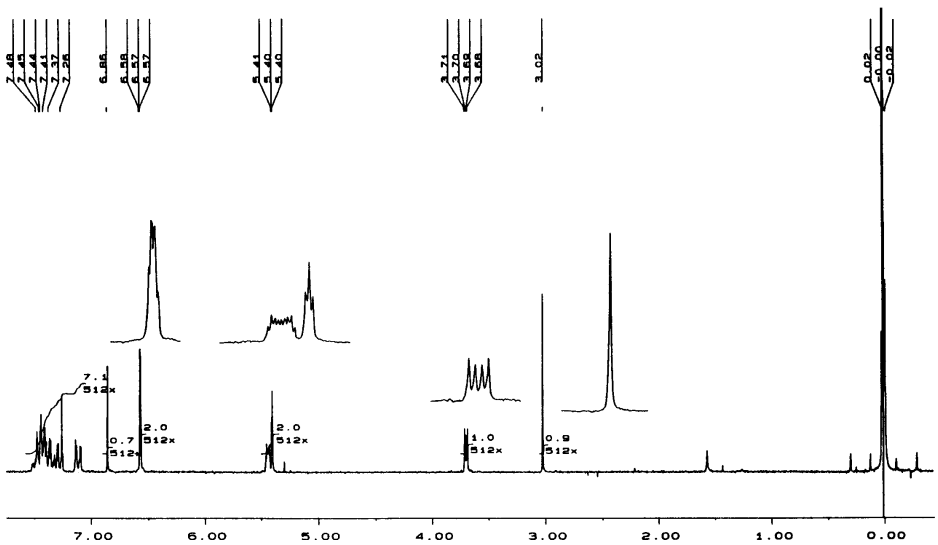


Figure 3. Proton-NMR spectrum of the reaction mixture.

compounds (aniline), and corrosive liquids (acetic anhydride, which is also a lachrymator). All compounds of interest absorb in the ultraviolet allowing TLC plates to be visualized using UV.

Maleanilic Acid

A scaled-down version of the preparation described in *Organic Synthesis* (*9*) was used, but another preparation described recently in this *Journal* (*13*) uses acetic acid as the solvent. Place 1.96 g (20 mmol) of maleic anhydride in a 50-mL Erlenmeyer flask containing a magnetic stirrer and 25 mL of ether. Stopper the flask and stir to form a solution. Remove the flask from the stirrer and chill in an ice-water bath for 10 min. In a separate flask prepare a solution of 1.82 mL (1.86 g, 20 mmol) of aniline in 10 mL of ether. Place the chilled solution of maleic anhydride back on the magnetic stirrer and using a dropper, add the aniline solution to the rapidly stirred solution of maleic anhydride. After addition is complete, stopper the flask and continue stirring for one hour. Collect the solid product using suction filtration and rinse it with 10 mL of ether. The product is pure enough for the next step. The filtrate is placed in a waste bottle provided for it. Collect the necessary data to identify the product. The NMR spectra are as follows: (d-6 DMSO) ^{1}H δ 6.32 (1H, d, J = 12Hz) 6.49 (1H, d, J = 12 Hz), 7.09–7.65 (5H, m), 10.41 (1H, s), 13.1 (1H, broad s); ^{13}C δ 119.5, 123.9, 128.8, 130.4, 131.6, 138.4, 163.2, 166.9.

N-*Phenylmaleimide*

Prepare a mixture of 0.33 g of anhydrous sodium acetate, 3.4 mL of acetic anhydride, and 1.50 g of the product from maleic anhydride with aniline in a 50-mL round-bottom flask. Attach a reflux condenser and heat the mixture on a steam bath for 40 min. Working in a hood pour the mixture into approximately 10 mL of ice water. Stir until the product is a solid, and collect by suction filtration. Dry by mashing the product on a piece of filter paper. Recrystallize from cyclohexane. The following data have been observed by us and reported by students: R_f, .65 – .70 (silica,[3] EtOAc:hexane 1:1); IR, (KBr) 1745, 1719, 1580, 1507; ^{1}H-NMR, ($CDCl_3$) δ 6.8 (2H, s), 7.34 (5H, m); ^{13}C-NMR, ($CDCl_3$) δ 126.0, 127.9, 129.1, 132.0, 134.2, 170.0 ppm.

endo *and* exo-*7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxy*-N-*phenylimide*

N-Phenylmaleimide 56 mg was dissolved in 0.5 mL of furan. The mixture was allowed to stand for at least 20 h.[4] The white, solid product was separated by filtration and washed with 2 mL of ether.[5] It weighed 69 mg (88%). TLC of the product using silica gel[3] and 1:1 EtOAc-hexane showed a trace of starting material at R_f .68, endo at R_f .47, and exo at R_f .33.

A 52-mg portion of the product was dissolved in 1 mL of hot EtOAc[6] and chromatographed on 5.5 g of silica gel[7] using a 10-mm i.d. chromatographic column and 1:1 EtOAc–hexane. The eluate was monitored by TLC. The following volumes of eluate collected are typical.

Fraction Vol. (mL)	Material Present
16	*N*-phenylmaleimide, Tr
14	endo product, 30 mg
16	exo product, 18 mg

The IR spectra are, endo: 1713, 1696; exo: 1712 cm^{-1}. For ^{13}C-NMR, ($CDCl_3$), endo: δ 173.9, 134.6, 131.4, 129.2, 128.8, 126.3, 79.8, 45.9; exo: δ 175.3, 136.7, 131.5, 129.1, 128.8, 126.5, 81.4, 47.5.

NMR Experiment

Prepare a mixture of 60 mg of *N*-phenylmaleimide, 40 mg of furan, and 1 mL of $CDCl_3$ in an NMR tube.[8] Determine the spectrum immediately after mixing and at appropriate intervals.[9]

Acknowledgment

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Notes

1. Presented at the Thirteenth Biennial Conference of Chemical Education, 1994.

2. Unfortunately this signal is complicated by second-order effects. A first-order analysis of this spin system leads to the anticipation of observing a doublet for these protons. However, the coupling pattern is more complicated (resembling a doublet of doublets). More advanced NMR experiments (COSY and double resonance) clearly demonstrate that the only significant couplings for these C-5/C-6 protons are to the bridgehead protons (on C-1 and C-4).

3. TLC aluminum sheets precoated with a 0.2-mm-thick layer of 60 F_{254} silica gel from EM Separations, 480 Democrat Road, Gibbstown, NJ 08027, were used. These were cut to size with a paper cutter.

4. Generally the solid product begins to precipitate after three hours. If it does not, a small amount of the solution may be evaporated on a stirring rod and reintroduced to seed the reaction mixture and cause the product to precipitate. In the experiment reported here the reaction mixture was worked up after 20 hours. The solid product separated by filtration 10 days after the mixture was prepared contained 64% endo isomer and 36% exo isomer.

5. The starting *N*-phenylmaleimide is very soluble in ether (and is easily removed by ether washing), whereas the products are not.

6. The products are soluble in dichloromethane, but, when a sample was transferred to the column in this solvent, the chromatographic separation was unsuccessful.

7. We used "Baker" silica gel for flash chromatography.

8. For this work an IBM NR/200 FT NMR instrument was used. The quantities of reagents may have to be increased for a 60-MHz instrument.

9. We have experienced no difficulty in heating closed NMR tubes containing this reaction mixture to 60 °C.

Literature Cited

1. Cooley, J. H. *J. Chem. Educ.* **1991,** *68*, 503.
2. Pickering, M. *J. Chem. Educ.* **1990,** *67*, 524–525.
3. Harrison, E. A., Jr. *J. Chem. Educ.* **1991,** *68*, 426–427.
4. Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany 1970.
5. Woodward, R. B.; Baer, R. *J. Am. Chem. Soc.* **1948,** *70*, 1161–1166.
6. Baggio, S.; Barriola, A.; de Perazzo, P. K. *J. Chem. Soc. Perkin Trans. 2,* **1972,** 934.
7. Lee, M. W.; Herndon, W. C. *J. Org. Chem*. **1978,** *43*, 518.
8. Abraham, R. J.; Fisher, J. *Magn. Reson. Chem*. **1985,** *23*, 856.
9. Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Org. Synth. Coll. Vol. 5*; **1973,** 944–946.
10. Stewart, J. J. P. *J. Comp. Aided Mol. Design* **1990**, *4*, 1.
11. HyperChem for Windows; Hypercube, 1994.
12. Silverstein, R. M.; Bassler, G. C.; Morrill, T. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991; p 197.
13. Ram, R. N.; Varsha, K. *J. Chem. Educ.* **1990,** *67*, 985–986.