Anal. Calcd for $C_{68}H_{80}N_2O_{10}$: C, 75.25; H, 7.43, N, 2.58. Found: C, 74.97; H, 7.66; N, 2.39.

**Diether Single-Spanned Double-Cavity Calix[4]arene 21 ($n$ = 3).** Following the general procedure described above, using glutaroyl chloride, the crude product was chromatographed, and the fractions that eluted with $CHCl_3$–EtOAc (90:10) were collected and recrystallized from $CHCl_3$–MeOH to give 138 mg (55%) of **21** ($n$ = 3): mp 318–319 °C; $^1$H NMR ($CDCl_3$) δ 8.87 (br s, 2, NH), 8.41 (br s, 2, OCNArH), 8.25 (br s, 2, OCNArH), 7.65 (br s, 2, OCNArH), 7.08 (s, 4, ArH), 6.70 (s, 4, ArH), 6.33 (s, 2, OH), 4.96 (s, 4, $ArCH_2O$), 4.23 (d, 2, $J$ = 13.2 Hz, $ArCH_2Ar$), 3.86 (s, 6, $OCH_3$), 3.22 (d, 4, $J$ = 12.9 Hz, $ArCH_2Ar$), 2.60 (t, 4, $COCH_2CH_2$), 2.19 (m, 2, $COCH_2CH_2$), 1.31 (s, 18, $ArC(CH_3)_3$), 0.90 (s, 18, $ArC(CH_3)_3$). Anal. Calcd for $C_{67}H_{78}N_2O_{10}$: C, 75.11; H, 7.34, N, 2.61. Found: C, 74.89; H, 7.11; N, 2.53.

**Determination of $K_{assoc}$ Values.** Commercially available materials were used without purification as guest compounds. In a typical determination 500 μL of a $10^{-2}$ M solution of **4** in $CDCl_3$ was treated with incremental amounts (5–10 μL) of a 1 M solution of the guest compound in $CDCl_3$. The $^1$H NMR spectrum was measured at 25 °C after each addition, and the chemical shift values for **4** and the guest compound were recorded for the various stoichiometries. A typical example is shown by the data in Figure 2. A plot of $\Delta\delta$ vs $\Delta\delta/[\text{guest}]_0$ at high guest concentrations gives a straight line, the slope of which allows the determination of the $K_{assoc}$ value by the application of the Benesi–Hildebrand expression.[14]

**Determination of Spin-Lattice Relaxation Times ($T_1$).** Using the inversion recovery method,[30] a series of spectra, each consisting of 8–20 scans, was obtained by using 180–$\tau$–90 pulse sequences. The equilibrium time ($D_1$) was chosen to be three to four times the longest $T_1$ of interest (20–24 s). For data acquisition for various recovery times ($D_2$) an array of $D_2$ values was created to cover a range of 0.1–3 times $T_1$, 8–12 values of $D_2$ being selected to ensure accurate results. All of the $T_1$ determinations were repeated three times, providing values accurate to ±5%.

**Molecular Modeling Studies.** Molecular mechanics calculations were carried out with the programs QUANTA/CHARMm (version 3.0, released June 1990 by Polygen Corp, Waltham, MA). A 2D representation of a double-cavity calixarene (e.g., **4**) was first drawn in CHEMNOTE, then transferred to QUANTA, the charges smoothed only on carbon atoms, and the structure minimized by Steepest Descents to improve the initial conformation, Adopted Basis Newton-Raphson for refinement, and Powell Conjugate Gradient for convergence to a root mean square value of 0.000 01 or less. Conformational searches were carried out in the quest of a global minimum. The more successful of these with **4** started with the ester carbonyl groups anti and involved 256 unique conformations, each of which were partially minimized. The lower energy conformers (ca. 20), covering a spread of 20 kcal/mol, were then fully minimized, leading to the structure shown in Figure 4. Calculations on complexes were carried out by first generating Connoly surfaces[31] which allows the docking of the two molecules to be carried out in a way that maximizes attractive dispersion forces, avoids steric repulsions, and optimizes electrostatic complementarity. With the use of this technique it became quickly apparent that productive complexation with **4** occurs only at the side of the lower cavity.

**Acknowledgment.** We are indebted to the National Institutes of Health (GM-23534) and the Robert A. Welch Foundation (P-1163) for providing generous financial support for this work and to Dr. P. Amruta Reddy for his help in addressing the problem of elemental analyses. Mass spectrometry data were obtained from the Washington University Mass Spectrometry Resource, supported by a grant from the National Institutes of Health (RR00954), through the generous assistance of Professor William Sherman.

**Supplementary Material Available:** Temperature-dependent $^1$H NMR spectrum of the diether double-cavity double-bridged calix[4]arene and the energies of guests and host–guest complexes generated by the CHARMm molecular mechanics program (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(30) Void, R. L.; Waugh, J. S.; Klein, M. P.; Phelps, D. E. *J. Chem. Phys.* **1968**, *48*, 3831.

(31) Connolly, M.; Program No. 427, Quantum Chemistry Program Exchange, Bloomington, IN, 1982.

# *Notes*

## Cycloadditions of Electron-Deficient 8,8-Disubstituted Heptafulvenes to Electron-Rich 6,6-Disubstituted Fulvenes

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### Introduction

Interest in the discovery of cycloadditions involving more than 6π electrons has continued for the 20 years since the discovery of the Woodward–Hoffmann selection rules for concerted cycloadditions.[1]

The competition among [4 + 2], [6 + 4], [8 + 2], and [8 + 6] cycloadditions, all symmetry allowed thermal processes, has prompted much investigation. Houk reported the periselective formation of 1:1 [6 + 4] adduct **3a**, in the reaction of tropone (**1a**) with 6,6-dimethylfulvene (**2a**), which immediately underwent a 1,5-sigmatropic hydrogen shift to yield the thermodynamically more stable cyclopentadiene **4a**, which subsequently underwent a second [6 + 4] cycloaddition with tropone to form 2:1 [6 + 4] adduct **5**. A trace of 1:1 [4 + 2] adduct **6a** was also observed (Scheme I).[2] In the reaction of 2-chlorotropone (**1b**) with **2a**, **4b** can be isolated as a major product because further reaction is kinetically slowed.[3] However, no cycloaddition was observed with 2,7-dichlorotropone (**1c**).[3] By contrast, Sasaki reported that 6,6-diphenylfulvene (**2b**) reacted with tropone to afford only 1:1 [4 + 2] adduct **6b** instead of the expected [6 + 4] adduct.[4] The differing

(1) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.

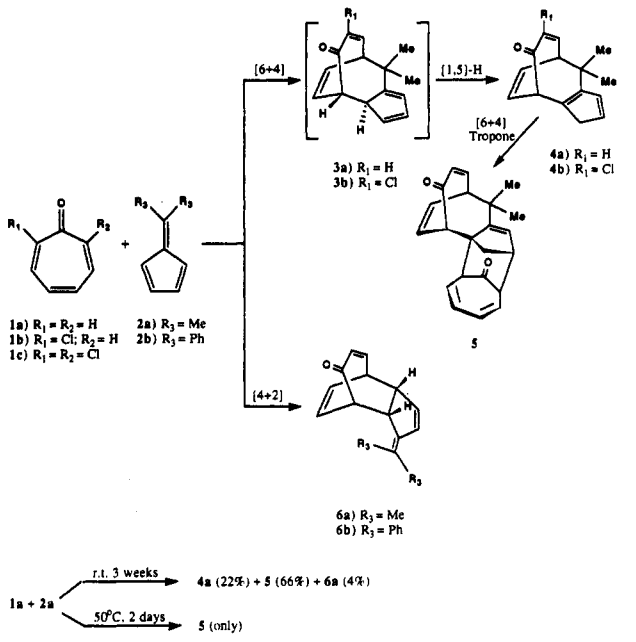
(2) Houk, K. N.; Luskus, L. J.; Bhacca, N. S. *J. Am. Chem. Soc.* **1970**, *92*, 6392.

(3) Pfaendler, H. R.; Tanida, H. *Helv. Chim. Acta* **1973**, *56*, 545.

(4) Sasaki, T.; Kanematsu, K.; Kataoka, T. *Chem. Lett.* **1973**, 1183.

0022-3263/92/1957-4539$03.00/0 

**Scheme I**




behaviors of these cycloaddition reactions seem to indicate sensitivity to steric requirements of substituents in either reaction partner, albeit, the structural, steric, and electronic factors that control the manner of these cycloadditions are not yet fully understood.

Heptafulvene (methylenecycloheptatriene) can be regarded as a methylene analog of tropone and its marked instability compared with tropone is considered to be due to the difference in the electron-withdrawing power of the carbonyl and methylene group, that is, the difference in the contribution of the aromatic tropylium structure. More stable heptafulvene derivatives were obtained by the introduction of electron-withdrawing groups such as cyano or alkoxycarbonyl into the 8-position of heptafulvene.[5,6]

In order to get more information about the effects of the substituent at both the fulvene and tropone moieties, we have investigated the cycloaddition reactions of electron-rich 6,6-disubstituted fulvenes (**2a,b**) with electron-deficient 8,8-disubstituted heptafulvenes (**7a,b**) (Schemes II and III and Table I). In addition, the reactivity, periselectivity, regioselectivity, and endo diastereoselectivity observed are briefly discussed.

## Results and Discussion

8,8-Dicyanoheptafulvene (**7a**) reacted sluggishly with 6,6-diphenylfulvene (**2b**) in chloroform at room temperature for 7 days to give mainly 1:1 [8 + 2] adduct **8b** in about 10% yield, along with traces of 1:1 [4 + 2] adduct **9b** (Scheme II and Table I). The adduct **8b** decomposed gradually when allowed to stand at room temperature, to form the adduct **9b**. At higher temperature (80 °C), thin layer chromatographic monitoring of the reaction mixture revealed first formation of a single adduct (**8b**) and subsequent development of a second adduct (**9b**) and another 1:1 [4 + 2] adduct (**10b**). The ratio of **8b**/(**9b** + **10b**) decreased steadily. Given more time (3 weeks), **9b** and **10b** were formed as the main reaction products. When the reaction was carried out in refluxing xylene for 4 days, only

(5) Nozoe, T.; Mukai, T.; Osaka, K.; Shishido, N. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1384.

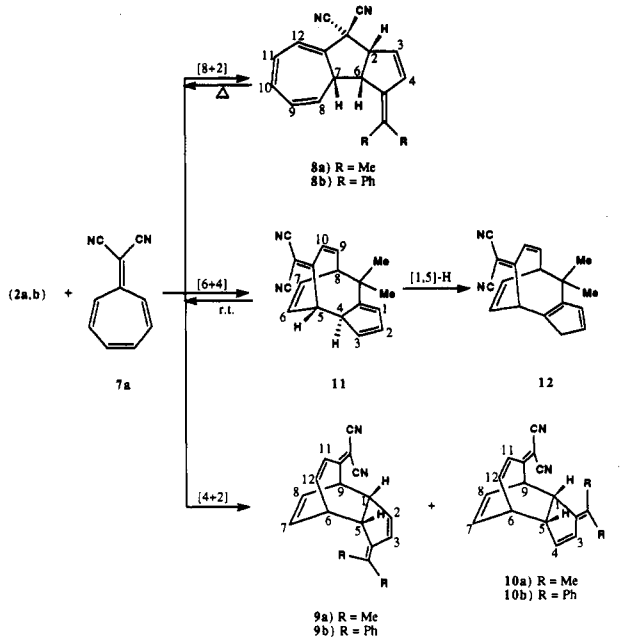
(6) Liu, C.-Y.; Mareda, J.; Houk, K. N. *J. Am. Chem. Soc.* **1983**, *105*, 6714 and references cited therein.

**Table I. Cycloaddition Reactions of Heptafulvenes 7a,b with Fulvenes 2a,b**

| reactants | solvent | temp, °C | time, days | adduct (ratio)[a] |
|---|---|---|---|---|
| **7a + 2b** | chloroform | rt | 7 | **8b + 9b** (99:1) |
| | benzene | reflux | 1[b] | **8b + 9b + 10b** (11.9:4.0:1)[b] |
| | xylene | reflux | 4 | **9b + 10b** (2.8:1) |
| **7a + 2a** | chloroform | rt | 1 | **8a + 11 + 12** (9.8:1:10.5) |
| | benzene | reflux[c] | 7 | **9a + 10a** (2.4:1) |
| | xylene | reflux[c] | 1 | **9a + 10a** (1.9:1) |
| **7b + 2b** | benzene | reflux | 7 | **9c + 15** (1:1)[d] |
| | xylene | reflux | 4 | **9c + 14** (1:1)[d] |
| **7b + 2a** | benzene | reflux | 7 | *e* |
| | xylene | reflux[c] | 1 | *e* |

[a] Adduct ratios were determined by HPLC. [b] See Table III for change in adduct ratios as a function of time. [c] Sealed-tube pyrolysis. [d] Ratio of adducts was estimated from $^1$H NMR data in the inseparable mixture of adducts. [e] Unidentified inseparable mixture.

**Scheme II**




**9b** and **10b** were formed in a ratio of 2.8:1. Furthermore, thermolysis of **8b** in refluxing xylene for 4 days also afforded **9b** and **10b** in the same ratio of about 2.8:1, along with trace amounts of **2b** and **7a**. The formation of **2b** and **7a** is apparently due to a retro-[8 + 2] reaction of **8b**. It appears that **8b** is the kinetic product, but its formation is reversible and **9b** and **10b** are the thermodynamically favored products that ultimately form.

Although adduct **8b** chould not be isolated in pure form because it underwent retro-[8 + 2] cycloaddition, samples suitable for spectral analysis were obtained by flash column chromatography. It has a characteristic $\alpha,\beta$-saturated cyano absorption in the IR spectrum (2245 cm$^{-1}$) and cycloheptatriene and cyclopentene resonances in the NMR spectrum (a broad doublet of doublets for H-7 at $\delta$ 2.40 ($J_{6,7}$ = 9.7 Hz, $J_{7,8}$ = 4.7 Hz), a doublet of doublets for H-6 at $\delta$ 3.80 ($J_{2,6}$ = 6.6 Hz, $J_{6,7}$ = 9.7 Hz), and a broad doublet of triplets for H-2 at $\delta$ 4.24 ($J_{2,3}$ = 2.3 Hz, $J_{2,4}$ = 2.5 Hz, $J_{2,6}$ = 6.6 Hz) (Table II)). The coupling constant of 9.7 Hz between H-6 and H-7 indicates an endo structure for the adduct.[6-8] Furthermore, H-2 was coupled to H-3, H-4,

(7) Liu, C.-Y.; Houk, K. N. *Tetrahedron Lett.* **1987**, *28*, 1371.

**Table II**

Proton Chemical Shifts of [8 + 2], [6 + 4], and [4 + 2] Cycloadducts

| | H-1 | H-2 | H-3 | H-4 | H-5 | H-6 | H-7 | H-8 | H-9 | H-10 | H-11 | H-12 | methyls |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **8b** | | 4.24 | 6.17 | 6.68 | | 3.80 | 2.40 | 5.26 | 6.18 | | 6.49–6.81 | | |
| **8a** | | 4.21 | 5.99 | 6.61 | | 3.92 | 2.51 | 5.03 | 6.10 | | 6.61–6.74 | | 1.73/1.92 |
| **15** | | 4.31 | 5.73 | 6.31 | | 3.62 | 2.16 | 5.16 | 6.16 | | 6.21–6.62 | | |
| **14** | | 4.26 | 5.70 | 6.38 | | 4.89 | | 5.46 | 5.16 | 1.94 | 5.36 | 6.41 | |
| **11** | 6.07 | 6.43 | 6.31 | 3.36 | 4.30 | 6.07 | 6.37 | 3.15 | 6.56 | 6.54 | | | 1.30/1.30 |
| **12** | 6.39 | 6.34 | 3.07 | | 4.43 | 6.08 | 6.25 | 3.17 | 6.71 | 6.68 | | | 1.30/1.25 |
| **13** | 6.62 | 3.79 | 1.78 | 2.26[a] | 4.45 | 5.91 | 6.28 | 3.07 | 6.79 | 6.73 | | | 1.34/1.11 |
| **9b** | 3.34 | 5.96 | 6.40 | | 3.95 | 3.07 | 6.30 | 5.97 | 3.98 | | 6.47 | 6.56 | |
| **10b** | 3.67 | | 5.77 | 6.40 | 3.88 | 3.41 | 6.31 | 6.09 | 3.88 | | 6.46 | 6.90 | |
| **9a** | 3.35 | 5.68 | 6.41 | | 3.35 | 3.55 | 6.35 | 5.89 | 4.06 | | 6.56 | 7.04 | 1.79/1.75 |
| **10a** | 3.09 | | 6.43 | 5.55 | 3.60 | 3.49 | 6.25 | 5.98 | 4.07 | | 5.56 | 6.99 | 1.87/1.78 |
| **9c** | 3.39 | 5.95 | 6.33 | | 3.97 | 2.79 | 6.25 | 5.93 | 4.12 | | 6.45 | 6.18 | |

Proton–Proton Coupling Constants for [8 + 2] Cycloadducts

| | 2,3 | 2,4 | 2,6 | 3,4 | 6,7 | 7,8 | 8,9 | 9,10 | $10_{gem}$ | 10,11 | 11,12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **8b** | 2.3 | 2.5 | 6.6 | | 9.7 | 4.7 | 9.6 | | | | |
| **8a** | 2.3 | 2.5 | 7.8 | 5.7 | 9.9 | 4.8 | 9.6 | | | | |
| **15** | 2.5 | 2.7 | 6.5 | 5.7 | 9.8 | 5.0 | 9.5 | | | | |
| **14** | 2.5 | 2.4 | 5.8 | 5.7 | | | 9.5 | 6.5 | 12.5 | 6.5 | 9.5 |

Proton–Proton Coupling Constants for [6 + 4] Cycloadducts

| | 1,2 | 1,3 | 2,3 | 2,4 | 3,4 | 4,5 | 5,6 | 6,7 | 7,8 | 8,9 | 9,10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **11** | 2.1 | 1.4 | 5.4 | 1.5 | 5.4 | 3.1 | 8.0 | 8.4 | 8.1 | 8.0 | 11.5 |
| **12** | 6.6 | 1.1 | 1.1 | | | | 8.2 | 8.1 | 7.9 | 7.9 | 11.5 |
| **13** | 3.5 | | 1.7 | | | | 8.2 | 8.0 | 7.8 | 7.5 | 11.9 |

Proton–Proton Coupling Constants for [4 + 2] Cycloadducts

| | 1,2 | 1,3 | 1,4 | 1,5 | 1,9 | 2,3 | 3,4 | 5,6 | 6,7 | 6,12 | 7,8 | 8,9 | 9,11 | 11,12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **9b** | 1.6 | 1.8 | | 7.5 | 1.9 | 5.7 | | 2.0 | 8.3 | 8.3 | 8.1 | 7.1 | 1.8 | 10.8 |
| **10b** | 2.4 | 2.0 | | 7.3 | <1 | 5.6 | | <1 | 7.7 | 8.6 | 7.7 | 7.3 | 1.8 | 10.7 |
| **9a** | 1.5 | 1.5 | | | <1 | 5.6 | | <1 | 7.9 | 8.7 | 7.9 | 7.4 | 1.9 | 10.7 |
| **10a** | | 2.1 | 1.9 | 7.6 | <1 | | 5.9 | <1 | 7.5 | 8.7 | 7.9 | 7.4 | 1.8 | 10.7 |
| **9c** | 2.4 | 1.8 | | 7.4 | 2.0 | 5.5 | | 2.0 | 8.6 | 8.6 | 8.7 | 7.3 | 1.8 | 11.1 |

[a] Chemical shift for another H-3.

and H-6, respectively, and no coupling was observed to the rest of the cycloheptatriene ring system. These results are compatible only with an anti regiochemistry for the cyano and diphenylmethylene groups. A series of NOE experiments further confirmed these structural assignments.

Upon irradiation at $\delta$ 2.40 (H-7), a large enhancement at both $\delta$ 3.80 (H-6) and 7.10 (one of the phenyls) and a small enhancement of $\delta$ 5.26 (H-8) was observed. No ehancement was observed at $\delta$ 4.24 (H-2), 6.17 (H-3), 6.68 (H-4), or for the rest of the cycloheptatriene ring system. Upon irradiation at $\delta$ 4.24 (H-2), a large enhancement at $\delta$ 3.80 (H-6) and a small enhancement at $\delta$ 6.17 (H-3) was observed. No enhancement was observed at $\delta$ 7.09–7.40 (phenyls), 6.68 (H-4), or for the rest of the cycloheptatriene ring system. All these results are consistent with the regiochemistry of the fulvene and cycloheptatriene moieties shown in structure **8b**. Irradiation at $\delta$ 3.80 (H-6) produced a large enhancement at both $\delta$ 2.40 (H-7) and 4.24 (H-2) and a small enhancement at $\delta$ 7.10, confirming the results stated above. This also established the endo stereochemistry for this adduct.

The IR spectra of adducts **9b** and **10b** showed a characteritic $\alpha,\beta$-unsaturated cyano absorption at 2215 $cm^{-1}$. The structures of these adducts were eventually proved by a complete analysis of the NMR spectra and double-resonance experiments. The NMR spectra showed four aliphatic protons, six olefinic protons, and ten aromatic protons (Table II). The small couplings between H-1 and H-9 and between H-5 and H-6 in **9b** and **10b** are compatible only with an endo stereochemistry for these adducts.[9] In adduct **9b**, H-1 was coupled to H-2, H-3, H-5, and H-9, respectively, indicating an anti regiochemistry of the cyano and diphenylmethylene groups, whereas in adduct **10b**, H-5 was coupled to H-4, H-3, H-1, and H-6, respectively, indicating a syn regiochemistry.

In contrast, the reaction of **7a** and the less hindered 6,6-dimethylfulvene (**2a**) in chloroform took place much more readily at room temperature. After 1 day of stirring, [8 + 2] adduct **8a** and [6 + 4] adducts **11** and **12** were obtained in a 9.8:10.5:1 ratio (Scheme II and Table I). The adduct **11** gradually underwent a 1,5-sigmatropic hydrogen shift when allowed to stand at room temperature, to yield the thermodynamically more stable cyclopentadiene **12**. Trace amounts of **7a**, **2a**, and the [8 + 2] adduct **8a** were also observed. The formation of starting materials **7a** and **2a** is apparently due to a retro-[6 + 4] reaction of **11**. At higher temperature (80 °C), HPLC monitoring of the reaction mixture revealed that the total amount of **8a**, **11**, and **12** initially increased and then decreased gradually while the total amount of 1:1 [4 + 2] adducts **9a** and **10a** increased. At longer times (1 week) **9a** and **10a** were the main reaction products. When the reaction was carried out in refluxing xylene for 1 day, only [4 + 2] adducts **9a** and **10a** were formed in a ratio of 1.9:1. As expected, the [8 + 2] adduct **8a**, although formed under milder conditions, reverted back to starting materials **7a** and **2a** at higher temperatures and in turn recombined to form the thermodynamically more stable [4 + 2] adducts **9a** and **10a**.

The adduct **8a** has a characteristic $\alpha,\beta$-saturated cyano absorption in the IR spectrum (2240 $cm^{-1}$) and cyclo-

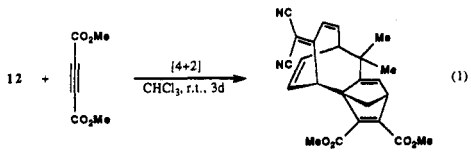
(8) Gandhi, R. P.; Ishar, M. P. S. *Chem. Lett.* **1989**, 101 and ref 5 cited therein.

(9) (a) Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1969**, 775. (b) Ito, S.; Takeshita, H.; Shoji, Y. *Ibid.* **1969**, 1815. (c) Ito, S.; Sakan, K.; Fujise, Y. *Ibid.* **1970**, 2873.

heptatriene and cyclopentene resonances in the NMR spectrum (a sharp singlet for two methyls on unsaturated carbon at both $\delta$ 1.73 and 1.92, a broad doublet of doublets for H-7 at $\delta$ 2.51 ($J_{6,7}$ = 9.9 Hz, $J_{7,8}$ = 4.8 Hz), a broad triplet for H-6 at $\delta$ 3.92 ($J_{2,6}$ = 7.8 Hz, $J_{6,7}$ = 9.9 Hz), and a broad doublet for H-2 at $\delta$ 4.21 ($J_{2,3}$ = 2.3 Hz, $J_{2,4}$ = 2.5 Hz, $J_{2,6}$ = 7.8 Hz)). The coupling constant of 9.9 Hz between H-6 and H-7 indicates and endo structure for the adduct.[6-8] Furthermore, H-2 was coupled to H-3, H-4, and H-6, respectively, and no coupling was observed to the rest of the cycloheptatriene ring system. These results are compatible only with an anti regiochemistry for the cyano and dimethylmethylene groups. A series of NOE experiments further confirmed these structural assignments.

Upon irradiation at $\delta$ 1.73 (one of the methyls), a large enhancement at $\delta$ 3.92 (H-6) and a small enhancement at both $\delta$ 2.51 (H-7) and 5.03 (H-8) was observed. No enhancement was observed at $\delta$ 4.21 (H-2), 5.99 (H-3), 6.61 (H-4), or for the rest of the cycloheptatriene ring system. Upon irradiation at $\delta$ 1.92 (the other methyl), only a large enhancement at $\delta$ 6.61 (H-4) was observed. All these results are consistent with the regiochemistry of the fulvene and cycloheptatriene moieties shown in structure **8a**. Irradiation at $\delta$ 3.92 (H-6) produced a large enhancement at $\delta$ 1.73, 2.51 (H-7), and 4.21 (H-2), confirming the results stated above. This also established the endo stereochemistry for this adduct.

Although adduct **11** could not be isolated in pure form and underwent slow isomerization to **12** and retro-[6 + 4] cycloaddition, samples suitable for spectral analysis were obtained by flash column chromatography. The IR spectra of adducts **11** and **12** showed a characteristic $\alpha,\beta$-unsaturated cyano absorption at 2220 cm$^{-1}$. The stereochemistry and regiochemistry of these adducts were assigned on the basis of a careful analysis of their NMR spectra (Table II), double-resonance experiments, and by comparing their spectra with those of related compounds.[2,3] Additional structural evidence for **12** is the [4 + 2] cycloaddition of **12** with DMAD, which gave **13** (eq 1). In particular, the




(1)

13

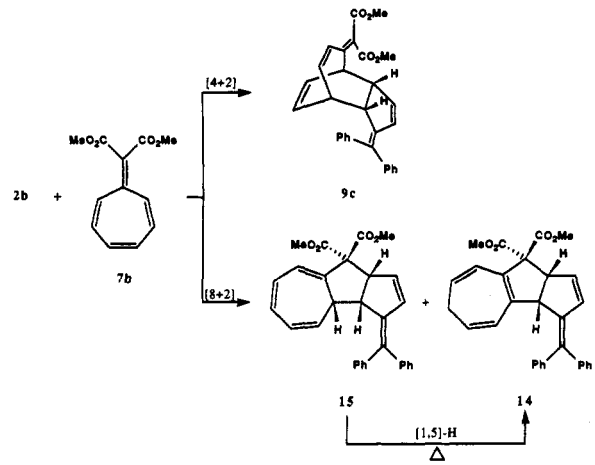
presence of a methylene group was clearly shown by the resonances at $\delta$ 1.78 and 2.26 ($J_{gem}$ = 6.5 Hz) in the NMR spectrum (Table II).

The IR spectra of adducts **9a** and **10a** showed a characteristic $\alpha,\beta$-unsaturated cyano absorption at 2215 cm$^{-1}$. The stereochemistry and regiochemistry of these adducts were assigned on the basis of a careful analysis of their NMR spectra, double-resonance experiments, and by comparing their spectra with those of related adducts **9b** and **10b**. A series of NOE experiments further confirmed these structural assignments.

Upon irradiation of one of the methyl protons in **9a** at $\delta$ 1.79, a large enahncement at $\delta$ 3.55 (H-6) and a small enhancement at $\delta$ 3.35 (H-5) were observed. No enhancement was observed at $\delta$ 4.06 (H-9), 5.68 (H-2), or 6.41 (H-3). Upon irradiation at $\delta$ 1.75 (the other methyl) only a large enhancement at $\delta$ 6.41 (H-3) was observed. All these results are consistent with the anti regiochemistry for the cyano and dimethylmethylene groups shown in structure **9a**.

In adduct **10a**, irradiation at $\delta$ 1.87 (one of the methyls) produced a large enhancement at $\delta$ 4.07 (H-9) and a small

**Scheme III**




enhancement at $\delta$ 3.09 (H-1). No enhancement was observed at $\delta$ 3.60 (H-5), 3.49 (H-6), 5.55 (H-4), or 6.43 (H-3). Upon irradiation at $\delta$ 1.78 (the other methyl) only a large enhancement at $\delta$ 6.43 (H-3) was observed. All these results are consistent with the syn regiochemistry for the cyano and dimethylmethylene groups shown in structure **10a**.

When the more weakly electron-deficient 8,8-bis(methoxycarbonyl)heptafulvene (**7b**) was reacted with 6,6-diphenylfulvene (**2b**) in refluxing xylene for 4 days, the [4 + 2] adduct **9c** and the [8 + 2] adduct **14** were obtained as an inseparable mixture in a ratio of about 1:1 (Scheme III). At 90 °C, both **9c** and another [8 + 2] adduct (**15**) were formed, also as an inseparable mixture in the same ratio of 1:1. After 1:1 mixtures of **9c** and **15** were heated at 190 °C for 7 h, 1:1 mixtures of **9c** and **14** were observed. Thus, **15** is the initial product of [8 + 2] cycloaddition of **7b** and **2b**, while **14** is formed by a subsequent 1,5-sigmatropic hydrogen shift. The IR spectra of the mixtures showed characteristic $\alpha,\beta$-unsaturated and $\alpha,\beta$-saturated ester frequencies at 1725 and 1740 cm$^{-1}$, respectively. The structures of these adducts were assigned by a complete analysis of the NMR spectra, double-resonance experiments, and by comparing their spectra with those of related adducts **8b** and **9b**. We were unable to detect the existence of any syn [4 + 2] adduct.

Unfortunately, the attempted reaction of **7b** with **2a** in chloroform at room temperature or in refluxing xylene gave complex reaction mixtures. No products of these reactions have been identified.

**Stereoselectivity.** The endo diastereoselectivity observed in the above cycloaddition reactions can be rationalized satisfactorily in terms of interplay of stabilizing secondary orbital interactions in the endo transition state.

**Reactivity of Electron-Deficient 8,8-Disubstituted Heptafulvenes.** From the results presented in Table I it is clear that heptafulvene **7a** is more reactive than heptafulvene **7b** toward fulvenes. This higher reactivity can be related to the lower LUMO energy caused by the stronger electron-withdrawing group, CN, thus favoring the interaction with the HOMO of the fulvene.

**Reactivity of Electron-Rich 6,6-Disubstituted Fulvenes.** Table I shows that, in the case of the electron-rich 6,6-disubstituted fulvenes evaluated, fulvene **2a** is more reactive than fulvene **2b** toward heptafulvenes. The apparent lower tendency of **2b** to give cycloadducts may presumably be attributed to the greater steric repulsions of its exocyclic substituents (i.e., Ph > Me).

**Regioselectivity.** The above cycloaddition reactions gave predominantly, or exclusively, the anti regioisomers

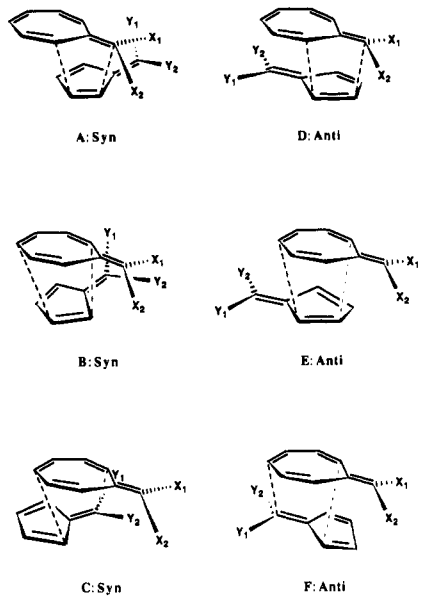



**Figure 1.** Endo transition states of the [8 + 2] (A, D), [4 + 2] (B, E), and [6 + 4] (C, F) cycloadditions.

(Table I). All these results can be explained by comparing the various transition states involved in the cycloadditions. The possible transition-state geometries for these cycloadditions are sketched in Figure 1. Examination of these transition states indicates that the steric repulsion between the exocyclic substituents on the heptafulvene and fulvene destabilizes the syn transition states A, B, and C relative to the anti transition states D, E, and F. Indeed, increasing steric bulk of the exocyclic substituents on the fulvenes and heptafulvenes causes an increased formation of [4 + 2] anti regioisomers (e.g., **9b** and **9a**, **9c** and **9b**). In the case of [8 + 2] and [6 + 4] cycloaddition reactions, only anti regioisomers were observed (e.g., **8a**, **8b**, **11**, **12**, **14**, and **15**).

## Experimental Section

**General Methods.** Infrared spectra were determined on a JASCO IR Report-100 infrared spectrometer. $^1H$ and $^{13}C$ NMR spectra were determined on Varian Jemini-200L and Bruker AM-300WB spectrometers with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. Mass spectra were determined on a JEOL JMS-D-100 mass spectrometer. High resolution mass spectra (HRMS) were determined on a JEOL JMS-HX-110 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. All reagents were of reagent grade and were purified prior to use. All reactions were performed under an inert atmosphere of nitrogen. The preparations of 8,8-dicyanoheptafulvene (**3a**),[5] 8,8-bis(methoxycarbonyl)heptafulvene (**3b**),[5] 6,6-dimethylfulvene (**2a**),[10,12] and 6,6-diphenylfulvene (**2b**)[11,12] were by literature procedures.

**General Procedure for Cycloaddition Reactions of Heptafulvenes 7a,b with Fulvenes 2a,b.** A solution containing heptafulvene **7a** or **7b** and fulvene **2a** or **2b** was stirred for a certain period of time (the solvents and the reaction conditions are all indicated in Table I). After removal of the excess solvent under reduced pressure, the crude mixture was subjected to silica gel flash column chromatography using 5–10% EtOAc in *n*-hexane as the eluant to give the pure products. NMR data for all new compounds are summarized in Table II.

Other data for **8b**: IR ($CHCl_3$) 2245 (CN) $cm^{-1}$; MS *m/z* 384 ($M^+$); exact mass calcd for $C_{28}H_{20}N_2$ 384.1628, found 384.1632. Anal. Calcd for $C_{22}H_{20}N_2$: C, 87.46; H, 5.24; N, 7.29. Found: C, 87.1; H, 5.15; N, 7.0.

Other data for **9b**: IR ($CHCl_3$) 2215 (CN) $cm^{-1}$; MS *m/z* 384 ($M^+$); exact mass calcd for $C_{28}H_{20}N_2$ 384.1628, found 384.1631. Anal. Calcd for $C_{22}H_{20}N_2$: C, 87.46; H, 5.24; N, 7.29. Found: C, 87.5; H, 5.19; N, 7.15.

Other data for **10b**: IR ($CHCl_3$) 2215 (CN) $cm^{-1}$; MS *m/z* 384 ($M^+$); exact mass calcd for $C_{28}H_{20}N_2$ 384.1628, found 384.1633. Anal. Calcd for $C_{22}H_{20}N_2$: C, 87.46; H, 5.24; N, 7.29. Found: C, 87.8; H, 5.20; N, 7.10.

Other data for **8a**: IR ($CHCl_3$) 2240 (CN) $cm^{-1}$; MS *m/z* 260 ($M^+$); exact mass calcd for $C_{18}H_{16}N_2$ 260.1314, found 260.1313. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.03; H, 6.19; N, 10.76. Found: C, 83.15; H, 6.31; N, 10.59.

Other data for **11**: IR ($CHCl_3$) 2220 (CN) $cm^{-1}$; MS *m/z* 260 ($M^+$); exact mass calcd for $C_{18}H_{16}N_2$ 260.1314, found 260.1305. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.03; H, 6.19; N, 10.76. Found: C, 83.17; H, 6.35; N, 10.63.

Other data for **12**: IR ($CHCl_3$) 2220 (CN) $cm^{-1}$; MS *m/z* 260 ($M^+$); eact mass calcd for $C_{18}H_{16}N_2$ 260.1314, found 260.1305. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.03; H, 6.19; N, 10.76. Found: C, 82.74; H, 5.95; N, 11.53.

Other data for **9a**: IR ($CHCl_3$) 2215 (CN) $cm^{-1}$; MS *m/z* 260 ($M^+$); exact mass calcd for $C_{18}H_{16}N_2$ 260.1314, found 260.1317. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.03; H, 6.19; N, 10.76. Found: C, 83.16; H, 6.24; N, 9.99.

Other data for **10a**: IR ($CHCl_3$) 2215 (CN) $cm^{-1}$; MS *m/z* 260 ($M^+$); exact mass calcd for $C_{18}H_{16}N_2$ 260.1314, found 260.1325. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.03; H, 6.19; N, 10.76. Found: C, 82.91; H, 6.31; N, 10.43.

Other data for **9c/15**: IR ($CHCl_3$) 1740 (C=O), 1725 (C=O) $cm^{-1}$; MS *m/z* 450 ($M^+$); exact mass calcd for $C_{30}H_{26}O_4$ 450.1832, found 450.1831. Anal. Calcd for $C_{30}H_{26}O_4$: C, 79.97; H, 5.82. Found: C, 80.07; H, 5.95.

Other data for **9c/14**: IR ($CHCl_3$) 1740 (C=O), 1725 (C=O) $cm^{-1}$; MS *m/z* 450 ($M^+$); exact mass calcd for $C_{30}H_{26}O_4$ 450.1832, found 450.1830. Anal. Calcd for $C_{30}H_{26}O_4$: C, 79.97; H, 5.82. Found: C, 79.67; H, 5.70.

**Thermolysis of [8 + 2] Adduct 8b.** Thermolysis of **8b** (20 mg) in refluxing xylene (30 mL) for 4 days afforded a reddish yellow oil. Column chromatography, using 5% EtOAc in *n*-hexane as eluant, gave **9b** and **10b** in 87% yield in a 2.8:1 ratio and trace amounts of retro-[8 + 2] cycloadducts **2b** and **7a** were also observed.

**Thermolysis of [8 + 2] Adduct 8a.** Thermolysis of **8a** (20 mg) in 30 mL of xylene at 150 °C for 1 day in a sealed tube afforded a reddish yellow oil. Column chromatography, using 5% EtOAc in *n*-hexane as eluant, gave **9a** and **10a** in 85% yield in a 1.9:1 ratio. Trace amounts of retro-[8 + 2] cycloadduct **2a** and **7a** were also observed.

**Isomerization of [8 + 2] Adduct 11 to 12.** Thermal isomerization of **11** (15 mg) in 10 mL of chloroform at room temperature for 1 week afforded a reddish yellow oil. Column chromatography, using 5% EtOAc in *n*-hexane as eluant, gave **12** in 90% yield. Trace amounts of retro-[6 + 4] cycloadducts **2a** and **7a** and the [8 + 2] adduct **8a** were also observed.

**Diels–Alder Reaction of 12 with DMAD.** A solution of **12** (20 mg, 0.05 mmol) and DMAD (10 mg, 0.07 mmol) in chloroform (5 mL) was stirred at room temperature for 3 days, affording a yellowish oil. Column chromatography, using 10% EtOAc in *n*-hexane as eluant, gave **13** in 94% yield.

For the NMR spectra of **13**, see Table II.

Other data for **13**: IR ($CHCl_3$) 2215 (CN), 1720 (C=O) $cm^{-1}$; MS *m/z* 402 ($M^+$); exact mass calcd for $C_{24}H_{22}N_2O_4$ 402.1581, found 402.1575. Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.61; H, 5.51; N, 6.96. Found: C, 71.35; H, 5.68; N, 6.81.

**Isomerization of [8 + 2] Adduct 15 to 14.** Thermal isomerization of **15** (20 mg, 1:1 mixture inseparable from **9c**) in 30 mL of xylene at 190 °C for 7 h in a sealed tube in the presence of BHT afforded a yellow oil. Column chromatography, using 10% EtOAc in *n*-hexane as eluant, gave **14** (1:1 mixture inseparable from **9c**) in about 90% yield.

**Acknowledgment.** We are grateful to the National Science Council of the Republic of China for financial support of this research. We thank Professor Kendall N.

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(12) Fulvenes **2a** and **2b** can be purchased from Aldrich Chemical Co.

Houk and Dr. Tahsin Chow for helpful discussions.

**Registry No.** **2a**, 2175-91-9; **2b**, 2175-90-8; **7a**, 2860-54-0; **7b**, 141665-68-1; **8a**, 141684-30-2; **8b**, 141665-69-2; **9a**, 141684-31-3; **9b**, 141665-70-5; **9c**, 141665-72-7; **10a**, 141665-62-5; **10b**, 141665-71-6; **11**, 141665-63-6; **12**, 141665-64-7; **13**, 141665-65-8; **14**, 141665-66-9; **15**, 141665-67-0; dimethyl acetylenedicarboxylate, 762-42-5.

## Kinetics of a Heterogeneous Enzymatic Hydrolysis of a Prochiral Diester

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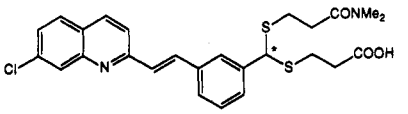
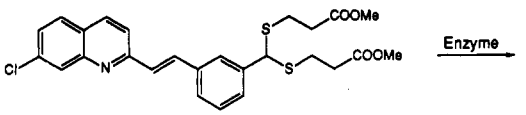
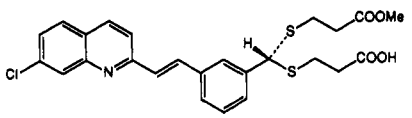
**Kinetics of a Heterogeneous Enzymatic Hydrolysis of a Prochiral Diester.** An enantioselective enzymatic hydrolysis of a prochiral diester was devised in our laboratories as the key step in short, efficient syntheses of both enantiomers of leukotriene $D_4$ antagonist MK-0571 **1**, being investigated as a therapeutic agent for bronchial disease.[1]




**1**




**2**




**3**

Lipase from *Pseudomonas* species cleanly hydrolyzed diester **2** to (*S*)-ester–acid **3** in >98% enantiomeric excess and 95% yield, with overreaction of only 2% to the corresponding diacid. The chemically and optically pure **3** was readily converted into either enantiomer of **1**. These studies have been described in detail along with further examples of successful enzymatic hydrolyses of similar esters having remote chiral/prochiral centers up to five bonds away from the ester carbonyl group.[2] We present here a quantitative analysis of the kinetics of enzymatic hydrolysis of **2** wherein enzyme inhibition by the hydrolysis product plays an important role.

In the key hydrolysis step, solid **2** is slurried in a solution of the lipase and surfactant Triton X-100 (used to speed the reaction) in 0.1 M pH 7.5 aqueous phosphate buffer at 40 °C. Analyses revealed that both **2** and **3** became supersaturated and then precipitated during the reaction, and the hydrolysis rate was quite an unusual function of the reaction time. Kinetic studies of the simpler homogeneous hydrolysis, carried out at low initial **2** concentration, allowed us to explain the kinetic data of the heterogeneous reaction mixtures.

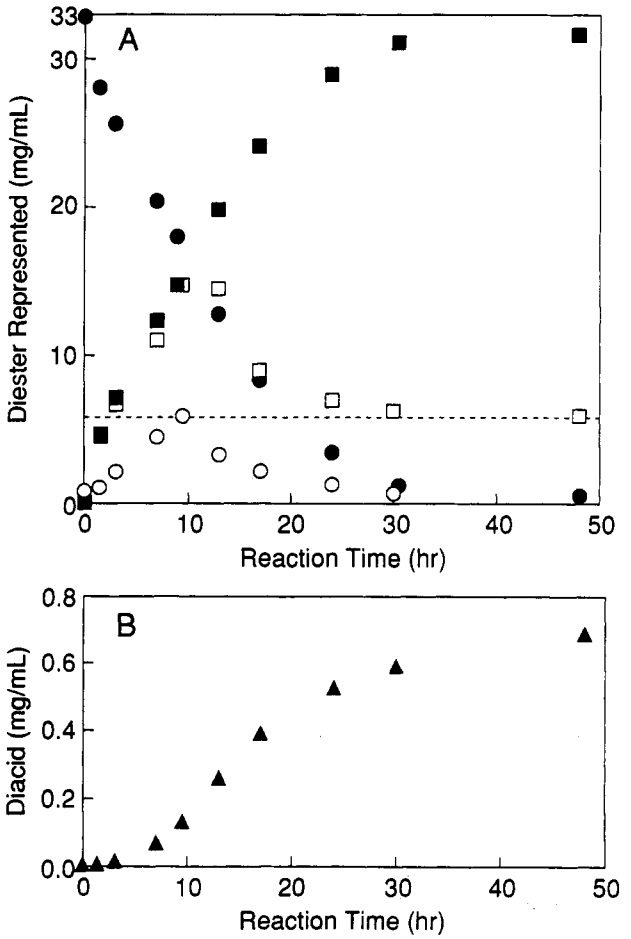



**Figure 1.** (A) Heterogeneous hydrolysis of diester **2** (1 g) in 0.1 M pH 7.5 phosphate buffer (30 mL) containing Triton X-100 (18 mg/mL) and the lipase (1.33 mg/mL) at 40 °C. Key: (●) total **2**; (○) **2** in filtrate; (■) total **3**; (□) **3** in filtrate; (---) solubility of **3**. (B) Expanded presentation of the diacid data.

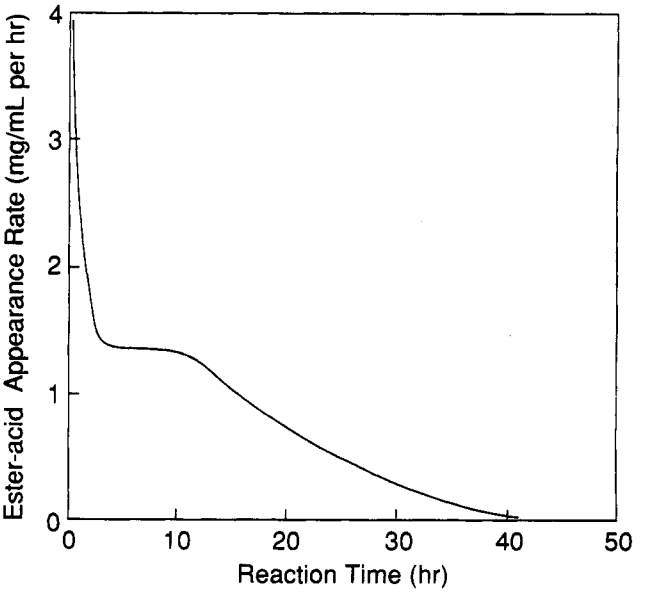



**Figure 2.** Appearance rate of **3** in heterogeneous hydrolysis of **2** (1 g) in 0.1 M pH 7.5 phosphate buffer (30 mL) containing Triton X-100 (18 mg/mL) and the lipase (1.33 mg/mL) at 40 °C.

### Results and Discussion

Kinetic data for **2** and **3**, both the total amounts present and concentrations in filtrates, are shown in Figure 1A for

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