Steric Effects in the Cycloaddition Reactions of Electron-Deficient Unsymmetrically 8,8-Disbustituted 8-Cyano-8-(methoxycarbonyl)heptafulvene with Electron-Rich 6,6-Diphenyl- and 6,6-Dimethylfulvenes

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Introduction

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

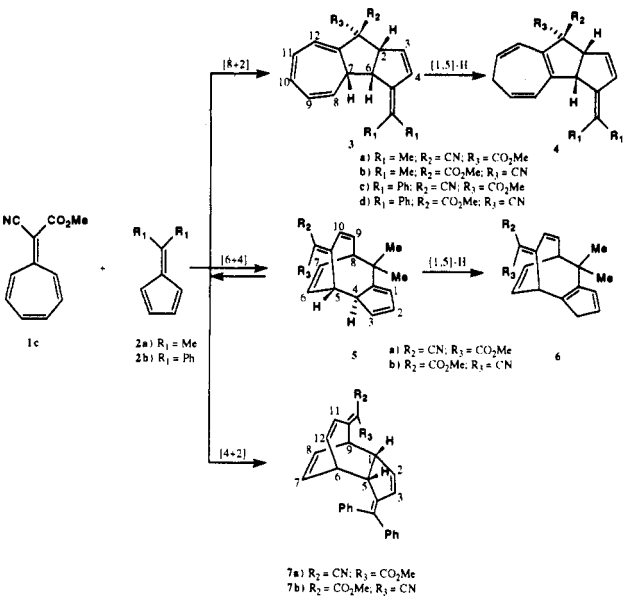
The competition among [4 + 2], [6 + 4], [8 + 2], and [8 + 6] cycloadditions, all symmetry-allowed thermal processes, has prompted much investigation. In a recent publication,[2] we reported that the cycloaddition reactions of electron-deficient 8,8-dicyanoheptafulvene (**1a**) and 8,8-bis(methoxycarbonyl)heptafulvene (**1b**) with electron-rich 6,6-dimethylfulvene (**2a**) and 6,6-diphenylfulvene (**2b**) give [4 + 2], [8 + 2], and/or [6 + 4] cycloadducts. We proposed that the sluggishness of the cycloadditions of **2b** cycloadducts and the preferred anti regioselectivity could be attributed to the steric repulsion between the exocyclic substituents on the heptafulvenes and fulvenes.

In order to get more information about the effects of the exocyclic substituent on the heptafulvene, we have now investigated the cycloaddition reactions of electron-deficient unsymmetrically 8,8-disubstituted 8-cyano-8-(methoxycarbonyl)heptafulvene (**1c**) with electron-rich 6,6-disubstituted fulvenes **2a,b** (Scheme I and Table I). The stereoselectivity and regioselectivity of the cycloadditions are discussed.

Results and Discussion

The reaction of 8-cyano-8-(methoxycarbonyl)heptafulvene (**1c**) with 6,6-dimethylfulvene (**2a**) in chloroform at room temperature for 7 days afforded the [8 + 2] adducts **3a** and **3b** and [6 + 4] adducts **6a,b** (1:1 mixture of inseparable regioisomers) in a 1:2.1:1.1 ratio (Scheme I and Table I). At a higher temperature (80 °C), HPLC monitoring of the reaction mixture revealed the initial formation of [6 + 4] adducts **6a,b** and the subsequent development of [8 + 2] adducts **3a** and **3b**. At 80 °C, the ratio of (**3a** + **3b**)/(**6a** + **6b**) increased steadily. At longer times (1 week) **3a** and **3b** (1:2.3 ratio) were the main reaction products. When the reaction was carried out in refluxing xylene for 1 day, [8 + 2] adducts **4a** and **4b** were formed in a ratio of 1:2.9. Because **3a** and **3b** were converted to **4a** and **4b**, respectively, when heated at 190 °C for 7 h, adducts **4** and **4b** were believed to come from

Scheme I



an [8 + 2] cycloaddition followed by a 1.5-sigmatropic hydrogen shift. We were unable to detect any [4 + 2] adduct.

The IR spectrum of adduct **3a** showed characteristic cyano and ester absorptions at 2240 and 1740 cm^{-1}, respectively. The structure was eventually proved by a complete analysis of the NMR spectra and double-response experiments. The NMR spectrum showed sharp singlets at δ 1.72 and 1.89 for the two methyl groups on the unsaturated carbon, a broad doublet of doublets for H-7 at δ 2.42 ($J_{6,7}$ = 10.1 Hz, $J_{7,8}$ = 5.3 Hz), a doublet of doublets for H-6 at δ 3.89 ($J_{2,6}$ = 7.1 Hz, $J_{6,7}$ = 10.1 Hz), and a broad doublet for H-2 at δ 4.3 ($J_{2,3}$ = 2.1 Hz, $J_{2,4}$ = 2.5 Hz, $J_{2,6}$ = 7.1 Hz). The appropriate cycloheptatriene and cyclopentene resonances were also observed (Tables II-IV). The coupling constant of 10.1 Hz between H-6 and H-7 indicated an endo structure for the adduct.[3-5] Furthermore, H-2 was coupled to H-3, H-4, and H-6, and no coupling was observed for the rest of the cycloheptatriene ring system. These results are compatible only with an anti relationship between the cyano and dimethylmethylene groups. A series of NOE experiments further confirmed these structural assignments.

Upon irradiation at δ 1.72 (one of the methyl groups), a large enhancement at δ 3.89 (H-6) and small enhancements at both δ 2.42 (H-7) and 5.07 (H-8) were observed. No enhancements were observed at δ 4.30 (H-2), 5.62 (H-3), 6.51 (H-4) or for the rest of the cycloheptatriene ring system. Upon irradiation at δ 1.89 (the other methyl group), only a large enhancement at δ 6.51 (H-4) was observed. All these results are consistent with the regiochemistry of the fulvene and cycloheptatriene moieties shown in structure **3a**. Irradiation at δ 3.89 (H-6) produced large enhancements at δ 1.72, 2.42 (H-7), and 4.30 (H-2), confirming the results stated above. These NOES also confirmed the endo stereochemistry for this adduct.

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Table I. Cycloaddition Reactions of Heptafulvene 1c with Fulvenes 2a,b

reactants	solvent	temp	time, days	adduct (ratio)[a]	yield, %
1c + 2a	chloroform	rt	7	**3a + 3b + 6a,b**[c,d] (1:2.1:1.1)	55
	benzene	reflux[b]	7	**3a + 3b** (1:2.3)	72
	xylene	reflux[b]	1	**4a + 4b** (1:2.3)	82
1c + 2b	chloroform	rt	7	**3c,d**	5
	benzene	reflux	21	**3c,d**[c,e] + **7a,b**[c,d] (2.5:1)	65
	xylene	reflux	4	**4c,d**[c,f] + **7a,b**[c,d] (1.8:1)	75

[a] The adduct ratios were determined by HPLC. [b] Sealed-tube pyrolysis. [c] Ratio of adducts was estimated from the ^{1}H NMR of the inseparable mixture of adducts. [d] 1:1 ratio of inseparable regioisomers. [e] 1:1.9 ratio of inseparable regioisomers. [f] 1:1.8 ratio of inseparable regioisomers.

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

	chemical shifts, δ													
	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	$H_{10'}$	H_{11}	H_{12}	methyls
3a		4.30	5.62	6.51		3.89	2.42	5.07	6.09	6.65		6.70	6.40	1.72/1.89
3b		4.03	6.00	6.56		3.85	2.46	4.99	6.08	6.59		6.62	6.52	1.72/1.91
3c		4.29	5.82	6.56		3.87	2.22	5.24	6.16	6.64		6.69	6.38	
3d		4.12	6.22	6.59		3.76	2.36	5.27	6.20	6.61		6.70	6.55	
4a		4.01	5.36	6.36		4.37		6.12	5.40	2.21	2.37	5.40	6.18	1.75/1.89
4b		3.90	6.03	6.48		4.38		6.21	5.43	2.07	2.51	5.43	6.35	1.83/1.91
4c		4.19	5.65	6.43		5.02		5.42	5.18	1.95	2.64	5.45	6.15	
4d		4.05	6.23	6.50		4.95		5.62	5.18	2.13	2.36	5.45	6.30	
6a			3.09		5.74			3.12						1.25–1.31
6b			3.01		4.57			3.04						1.25–1.31
7a	3.30	6.00	6.36		3.95	2.97	6.28	5.94	5.22			6.41–6.54		
7b	3.38	6.00	6.36		3.95	2.97	6.28	5.93	4.08			6.41–6.54		

Table III. Proton–Proton Coupling Constants for [8 + 2] Cycloadducts

	coupling const, Hz										
	2,3	2,4	2,6	3,4	6,7	7,8	8,9	9,10	10_{gem}	10,11	11,12
3a	2.1	2.5	7.1	5.8	10.1	5.3	9.5	4.2		10.1	4.9
3b			7.7		9.8	4.7	9.8	4.9		9.5	5.1
3c	2.5	2.6	7.1	5.8	9.8	5.1	9.5	5.5		10.7	5.2
3d	2.5	2.7	6.5	5.9	9.8	4.8	9.8	5.5		10.3	5.5
4a		2.2	6.2	5.8			9.5	6.9	13.1	6.9	9.9
4b	2.1	2.3	5.9	5.8			9.6	7.2	12.9	7.2	9.5
4c	2.5	2.0	6.1	5.7			10.1	7.5	12.9	7.5	9.8
4d	2.8	2.1	5.9	5.8			9.7	7.3	12.9	7.3	10.8

Table IV. Proton–Proton Coupling Constants for [4 + 2] Cycloadducts

	coupling const, Hz									
	1,2	1,5	1,9	2,3	5,6	6,7	6,12	7,8	8,9	11,12
7a	2.0	7.5	<2	5.6	<2	7.8	7.5	7.8	7.3	10.9
7b	2.0	7.5	1.7	5.6	1.8	7.8	7.8	7.8	7.3	10.9

There are similarities in the ^{1}H NMR spectra of **3b** and **3a**, **4a** and **3a**, and **3b** and **4b**. 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 NOE experiments.

Adducts **6a,b** must arise from an initial [6 + 4] cycloaddition that forms **5a,b** followed by a 1,5-sigmatropic hydrogen shift in the cyclopentadiene moiety. Although adducts **6a,b** could not be isolated in pure form because they underwent retro-[6 + 4] cycloadditions, samples suitable for spectral analysis was obtained by flash column chromatography. Their structures were assigned on the basis of a careful analysis of their NMR spectra, double-resonance experiments, and comparison of their spectra with those of related compounds.[2,6,7]

In contrast to the reaction of **1c** and **2a**, the reaction of **1c** with more hindered 6,6-diphenylfulvene (**2b**) in chloroform at room temperature for 7 days was sluggish and afforded mainly [8 + 2] adducts **3c,d** in about 5% yield (Scheme I). At 80 °C for 3 weeks, [8 + 2] adducts **3c,d** (1:1.9 mixture of inseparable regioisomers) and [4 + 2] adducts **7a,b** (1:1 mixture of inseparable regioisomers) were obtained in a ratio of about 2.5:1 (Scheme I and Table I). When the reaction was carried out in refluxing xylene for 4 days, both **7a,b** and [8 + 2] adducts **4c,d** (1:1.8 mixture of inseparable regioisomers) were obtained in a ratio of about 1:1.6. After mixtures of **3c,d** were heated at 190 °C for 7 h, mixtures of **4c,d** were obtained. Thus, **3c,d** are the initial products of [8 + 2] cycloaddition of **1c** and **2b**, and **4c,d** are formed by a subsequent 1,5-sigmatropic hydrogen shift. We were unable to detect of any [6 + 4] adduct.

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, NOE experiments, and comparison of their spectra with those of related compounds.[2,6,7]

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

From the results presented in Table I, it is clear that fulvene **2a** is more reactive than fulvene **2b** toward hep-

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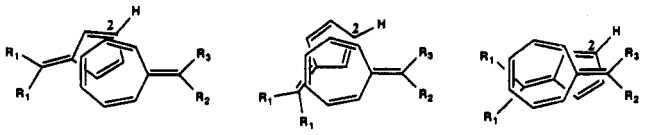

A B C

1) R_2 = CN; R_3 = CO_2Me
2) R_2 = CO_2Me; R_3 = CN

Figure 1. Anti-endo transition states of the [4 + 2] (**A**), [6 + 4] (**B**), and [8 + 2] (**C**) cycloadditions.

tafulvene **1c**. The sluggishness of the cycloadditions of **2b** may presumably be attributed to the greater steric repulsion between its exocyclic substituents (i.e., Ph > Me) and those of **1c**.

The regioselectivity observed in these reactions in quite dramatic. Only the anti regioisomers are formed. The selectivity can be attributed to the steric repulsion between the exocyclic substituents on the heptafulvenes and fulvenes.[2]

Interestingly, the cycloaddition reactions gave [4 + 2] adducts **7a,b** and [6 + 4] adducts **6a,b** both in 1:1 ratios. However, in the [8 + 2] cycloaddition reactions, the adducts (**3b/3a, 3d/3c, 4b/4a,** and **4d/4c**) were formed in an unexpected ratio of approximately 2:1 (Table I). All these results can be explained by comparing the various transition states involved in the cyloadditions. The possible transition-state geometries (anti-endo) for these cycloadditions are sketched in Figure 1. Examination of these transition states indicates that steric repulsion results from the proximity of the R_3 group of the heptafulvene to the C-2 methine group of the fulvene in transition state C. Thus, transition state C, with the smaller R_3 substituent (CN < CO_2Me) is more favorable and leads to the formation of adducts **3b,d** and **4b,d**.

Experimental Section

General Methods. ^1H NMR specra were determined with tetramethylsilane as the internal standard and $CDCl_3$ as the solvent. 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-cyano-8-(methoxycarbonyl)heptafulvene (**1c**),[8] 6,6-dimethylfulvene (**2a**),[9,11] and 6,6-diphenylfulvene (**2b**)[10,11] were by literature procedures.

General Procedure for Cycloaddition Reactions of Heptafulvenes 1c with Fulvenes 2a,b. A solution containing heptafulvene **1c** (94 mg, 0.5 mmol) and either fulvene **2a** (64 mg, 0.6 mmol) or **2b** (115 mg, 0.5 mmol) in 6 mL of solvent was stirred for the time period indicated in Table I (the solvents and the reaction conditions are all indicated in Table I). After evaporation of the excess solvent under reduced presure, the crude mixture was subjected to silica gel flash column chromatography with 5–10% EtOAc in *n*-hexane as the eluant to give the pure products. NMR data of all new compounds are summarized in Tables II–IV.

Other data for **3a**: IR ($CHCl_3$) 1740 (C=O), 2245 (CN) cm^{-1}; MS *m/z* 293 (M^+); exact mass calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1426.

Other data for **3b**: IR ($CHCl_3$) 1740 (C=O), 2245 (CN) cm^{-1}; MS *m/z* 293 (M^+); exact mass calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1419.

Other data for **6a/6b**: IR ($CHCl_3$) 1725 (C=O), 2220 (CN) cm^{-1}; MS *m/z* 293 (M^+); exact mass calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1405.

Other data for **4a**: IR ($CHCl_3$) 1740 (C=O), 2245 (CN) cm^{-1}; MS *m/z* 293 (M^+); exact mass calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1413.

Other data for **4b**: IR ($CHCl_3$) 1740 (C=O), 2245 (CN) cm^{-1}; MS *m/z* 293 (M^+); exact mass calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1409.

Other data for **3c/3d**: IR ($CHCl_3$) 1740 (C=O), 2245 (CN) cm^{-1}; MS *m/z* 417 (M^+); exact mass calcd for $C_{29}H_{23}NO_2$ 417.1729, found 417.1736.

Other data for **4c/4d**: IR ($CHCl_3$) 1740 (C=O), 2245 (CN) cm^{-1}; MS *m/z* 417 (M^+); exact mass calcd for $C_{29}H_{23}NO_2$ 417.1729, found 417.1729.

Other data for **7a/7b**: IR ($CHCl_3$) 1720 (C=O), 2215 (CN) cm^{-1}; MS *m/z* 417 (M^+); exact mass calcd for $C_{29}H_{23}NO_2$ 417.1729, found 417.1728.

Isomerization of [8 + 2] Adducts 3a–d to 4a–d. Thermal isomerization of **3a** (20 mg) or **3b** (20 mg) or **3c,d** (30 mg) 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 with 10% EtOAc in *n*-hexane as eluant gave **4a**, **4b**, and **4c,d**, respectively, in about 80–85% yield.

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Supplementary Material Available: ^1H NMR spectra for adducts **3a–d, 4a–d, 6a,b,** and **7a,b** (10 pages). This material is contained in 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.

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