## Transition State Structure and Frontier Orbital Influence on the Cycloaddition Reactions of 2,5-Dimethyl-3,4-Dimethylenethiophene With Styrenes and Benzaldehydes

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**Abstract:** The biradical 2,5-dimethyl-3,4-dimethylenethiophene reacts with styrenes and benzaldehydes to give fused cycloadducts. The effect of substituents on the efficiency of the benzaldehyde trapping reaction resembles that of normal electron-demand Diels-Alder reactions and is linear with the Hammett  $\sigma$ -constant With the styrenes, the Hammett plot is non-linear. Frontier orbital theory provides a rationalization of these effects in terms of the uniquely small HOMO-LUMO gap charactenstic of biradicals

The reactivity pattern and strict stereospecificity shown by the heterocyclic tetramethyleneethane (TME) derivatives 3,4-dimethylenefuran and 3,4-dimethylenethiophene<sup>1, 2</sup> in their cycloadditions with some electron-deficient alkenes are reminiscent of those of the Diels-Alder reaction.<sup>3</sup> In fact, the relative reactivities of such alkenes toward these diyls are linear with those toward cyclopentadiene.<sup>1, 2</sup> The present research probes the theoretical bases of such structural effects on reactivity in a study of cycloadditions of *p*-substituted styrenes and benzaldehydes with the related biradical 2,5-dimethyl-3,4-dimethylenethiophene 1.<sup>4</sup>

Thermal decomposition of solutions of diazene  $2^5$  in deaerated CH<sub>2</sub>Cl<sub>2</sub> were strictly first order. Consistent with the mechanism of Scheme I involving a reactive intermediate, the pseudo-first-order rate constant of 6.3 x 10<sup>-4</sup> s<sup>-1</sup> at 24 °C was invariant to the concentration of trapping agent in the range 0.25-2.5 *M*. Products of type **3** and **4**, respectively, were formed in high yields from the styrenes and the benzaldehydes.<sup>5</sup>

Scheme I.



Table I shows the relative rate constants<sup>6</sup> for trapping of the biradical by a series of substituted styrenes as determined from competition experiments. For a frontier molecular orbital (FMO)<sup>7</sup> interpretation of the data, we have calculated by AM1/Cl<sup>8</sup> the energies of the frontier orbitals of the biradical **1** (HOMO -4.57 eV and LUMO -3.96 eV, respectively) and of the styrenes.

Substituent	Product	k rel	HOMO (eV)	LUMO (eV)
o-NHo	2.0	0.59	-5.80	-2.17
p-CH3	3e	0.68	-6.29	-2 4
p-OCH3	3f	0.70	-6.16	-2.37
<i>p</i> -F	3g	0.98	-6.53	-2.72
Н	3 d	1.00	-6.39	-2.56
p-Cl	3 h	1.9	-6.54	-2.74
p-acetyl	3 b	6.4	-6.58	-3 65
m - NÓ2	3c	8.5		

**Table I.** Relative Rate Constants<sup>a</sup> for Reaction of Styrenes<sup>6</sup> with 2,5-Dimethy-3,4dimethylenethiophene Diyl **1** and the HOMO and LUMO Energies of the Substituted Styrenes<sup>b</sup>

a Determined by integration of the peak area of capillary GC traces performed on solutions of the diazene 2 that had been allowed to decompose thermally in the presence of a known concentration of two substituted styrenes b Orbital energies obtained from AM1 calculations including 4x4 configuration interaction with geometry optimization. For details of the calculation please see reference 1b and references cited therein

These results show that for the cycloaddition of the parent styrene with the 2,5-dimethyl-3,4dimethylenethiophene diyl 1, the HOMO<sub>diyl</sub> - LUMO<sub>styrene</sub> energy gap (2.0 eV) is nearly the same as the the HOMO<sub>styrene</sub> - LUMO<sub>diyl</sub> gap (2.4 eV). One might have expected, therefore, that the reactivity profile of the substituted styrenes would resemble that of "neutral" Diels-Alder dienophiles<sup>9</sup> and alkenic carbenophiles of "ambiphilic" carbenes <sup>10</sup> In each of those cases, the Hammett plot is V-shaped, because the reactivity of the trapping agent increases when the substituent is <u>either</u> electron-withdrawing or electron-releasing

The Hammett plot of the relative rate data for the styrene cycloadditions of Table I (Figure Ia) is curious. As expected, positive  $\sigma$  (electron-withdrawing) substituents cause a roughly linear enhancement of the rate. However, negative  $\sigma$  substituents do not produce the expected inversion of slope. Instead, the rate merely flattens out and becomes essentially unresponsive, even to the most strongly electron-releasing substituents.



a The curve is merely a smooth connection of the data of Table I

b. Linear least-squares treatment of the of Table II

Figure I. Log of the relative rate constants for reaction of styrenes (1a) and benzaldehydes (1b) with 2,5dimethyl-3,4-dimethylenethiophene (1) vs the Hammett σ parameter

The observed relative reactivities in the benzaldehyde series are quite different from those of the styrenes. The reasons for this emerge from the FMO relationships. Our calculations, as well as experimental ionization potential and electron affinity data,<sup>11</sup> suggest that the HOMO and LUMO of benzaldehyde should lie at least 1 eV lower in energy than the corresponding FMO's for styrene. Thus, in contrast to the styrene cycloadditions, only the interaction corresponding to the HOMOdiyl - LUMO benzaldehyde term should be significant for the benzaldehydes. This situation corresponds to the Diels Alder reaction with "normal" electron-demand, for which linear Hammett plot behavior has been observed in several cases.<sup>3,12</sup> The relative rate constants for cycloaddition of substituted benzaldehydes with 2,5-dimethyl-3,4-dimethylenethiophene are shown in Table II and plotted against the  $\sigma$  values of the substituents in Figure 1b.

Table II.	Relative	Rate Co	onstan	ts <sup>a</sup> for	Reaction	of Ber	nzaldehydes
with 2,5-D	)imethy-3	,4-dimet	hylene	thioph	ene Diyl	1	•
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<u>Substituent</u>	Product	<u> </u>
<i>р</i> -ОСН3	4f	0.09
<i>р</i> -СНз	4 e	0 29
Н	4 d	10
<i>p</i> -F	4 g	11
p-Cl	4 h	2.9
p-CF <sub>3</sub>	4 i	21
<u>p-CN</u>	<u>4j</u>	64

a Determined by integration of the peak area of capillary GC traces performed on solutions of the diazene 2 that had been allowed to decompose thermally (R T) in the presence of a known concentration of two substituted benzaldehydes

Consistent with the predictions based on FMO theory, the Hammett plot of Figure 1b is linear ( $r^2 = 0.99$ ). Furthermore, variation of the substituent on the benzaldehyde now causes a dramatically increased reactivity spread (a factor of 700,  $\rho = +2.9$ ) on the cycloaddition efficiency compared with the styrene series, where the spread is only 15-fold. This again is consistent with FMO expectation, since substituent-induced perturbations on the HOMO or LUMO energy of the trapping agent should exert a larger relative effect on cycloaddition efficiency as the magnitude of the HOMO-LUMO energy difference decreases.<sup>13</sup>

Why then is the rate profile in the styrene series (Figure I) not V-shaped? We suggest that this results from an increase in the destabilizing filled-filled interaction of the diyl and styrene HOMO's, which increases in magnitude as the HOMO energy of the styrene increases. Effectively, this term partially cancels the stabilization of the transition state which results from decreasing the HOMOstyrene-LUMOdiyl energy gap. The filled-filled interaction, which usually is neglected in the conventional FMO analysis,<sup>7</sup> emerges to significance here because of the small HOMO-LUMO gap (0 61 eV) of the diyl. It is noteworthy that this effect does not appear to influence carbene-olefin cycloadditions, where the carbene HOMO-LUMO gap is much larger<sup>10f</sup> and ambiphilic behavior clearly has been observed 1<sup>0a-e</sup>

We conclude that although near-equality of the two inter-reactant FMO gaps is generally conducive to an ambiphilic substituent effect, the uniquely small intra-reactant FMO gap

characteristic of a biradical can produce an important filled-filled interaction and damp the bimodal response.

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REFERENCES

(1)(a) Stone, K. J.; Greenberg, M. M.; Blackstock, S. C. and Berson, J. A., J. Am. Chem. Soc., 1989, 111, 3659.

(b) Greenberg, M. M.; Blackstock, S. C.; Stone, K. J. and Berson, J. A. J. Am. Chem. Soc., 1989, 111, 3671

(c) Greenberg, M. M.; Blackstock, S. C., Berson, J. A. Tetrahedron Lett. 1987, 28, 4263. (d) Zilm, K. W.; Merrill, R. A.; Greenberg, M. M and Berson, J. A.; J. Am. Chem. Soc., 1987, 109. 1567

(2) (a) Scalano, J. C.; Wintgens, V.; Bedell, A. and Berson, J. A.; J. Am. Chem. Soc., 1988, 110, 4050.

(b) Scalano, J. C; Wintgens, V.; Haider, K. and Berson, J. A.; J. Am. Chem. Soc., 1989. 111, 8732.

- (3)(a) Sauer, J; Wiest, H.; Mielert, A. Chem. Ber. 1964, 97, 3183. (b) Sauer, J.; Sustmann, R , Angew. Chem. Int. Ed. Eng., 1980, 19, 779.
- (4) (a) Spectroscopic evidence for 1,  $\lambda_{max}$  = 640 nm, immobilized in glassy matrices, has been obtained by photolysis of three different precursors: Blackstock, S. C., Porter, T. A, Berson, J. A unpublished work.
- (5) The bis-carbamate precursor of diazene 2 and the adducts of the 3 and 4 series were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and by elemental composition determined by high-resolution mass spectroscometry.
- (6) Competition experiments were carried out with a known concentration of two benzaldehydes or styrenes from ca 0.1-4.0 M. All of the benzaldehydes were commercially available and were purified by washing with bicarbonate solution immediately prior to use. The styrenes were all commercially available except 4-acetylstyrene which was synthesized by addition of methyl lithium (2 3 eq) to 4-vinylbenzoic acid in THF at -78 C. Each styrene was purified by distillation at reduced pressure prior to use. Relative rates were cross-checked by alternative pairwise competitions.
- (7) Fleming, I., "Frontier Orbitals and Organic Chemical Reactions" John Wiley & Sons, 1976, pp. 23-29, and references cited therein.
- (8) Dewar, M J. S.; Zoebisch, E. G.; Healey, E. F.; Stewart, J. J. P. J. Am. Chem. Soc. 1985, 107, 3902.
- Yasuda, M.; Harano, K. and Kanematsu, K ; J. Org. Chem., 1980, 45, 659. (9)
- (10) (a) Moss, R A. Acc. Chem. Res., 1989, 22, 15. (b) Moss, R A.; Acc. Chem. Res., 1980, 13, 58 (c) Soundararajan, N.; Platz, M. S.; Jackson, J. E.; Doyle, M. P.; Oon, S., Liu, M. T H, Anand, S. M; J. Am. Chem. Soc., 1988, 110, 7143. (d) Moss, R A.; Guo, W.; Krogh-Jespersen, K.; Tetrahedron. Lett., 1982, 23, 15. (e) Moss, R. A; Perez, L.; Tetrahedron Lett., 1983, 24, 2719. (f) For the ambiphilic methoxychlorocarbene in the trans conformation a HOMO-LUMO gap of 13 3 eV at the 4-31G level is calculated in ref. 10a
- (11) (a) Electron affinity (EA ) of styrene = -0.55eV cited in Miller, J R , J. Phys. Chem., 1978, 82, 767. (b) EA of benzaldehyde = 0.42eV: Chen, E C. M.; Wentworth, W. F.; J. Chem. Phys., 1975, 63, 3183. (c) Ionization potential (IP)of styrene = 8.40eV) Herndon, W. C; J. Am. Chem. Soc., 1976, 98, 887 (d) IP of benzaldehyde = 9.71eV Gal, J. F.; Gerıbaldi, S, Guillouzo, G P.; Morris, D. G.; J. Chem. Soc. Perkin Trans. II, 1985, 103
- (12) (a) Benghiat, I; Becker, E. I.; J. Org. Chem., 1958, 23, 885. (b) Brueckner, R., Huisgen, R; Tetrahedron Lett., 1990, 31, 7133.
- (13) (a) Ruecker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R; Chem. Ber., 1980, 113. 1663. (b) Mielert, A.; Braig, C.; Sauer, J.; Martelli, J.; Sustmann, R., Justus Liebig Ann. Chem., 1980, 954. (c) Kiselev, V. D.; Konovalov, A. I.; Veisman, E. A; Ustyugov, A N, J. Org Chem. USSR, 1978, 14, 118

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