

## TIME DEPENDENT INTERCONVERSION OF DIELS-ALDER ADDUCTS INTO MICHAEL ADDUCTS

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**Abstract-** Furans react with methyl 3-nitroacrylate to concurrently give Diels-Alder adducts and Michael adducts, and the former turns into the latter. The orbital energy difference between a HOMO<sub>diene</sub> and a LUMO<sub>dienophile</sub> seems to control the product distribution of the reaction.

Despite the aromatic nature of the furan ring, the Diels-Alder reactions of furan derivatives with electron deficient dienophiles take place to give Diels-Alder adducts. In some instances furans could add to the

electron deficient dienophiles to give addition products

of the formal Michael-type

reactions.<sup>1,2</sup> For example,

the reaction of 2-methylfuran

with 3,3,3-trichloro-1-nitro-

1-propene afforded Diels-Alder

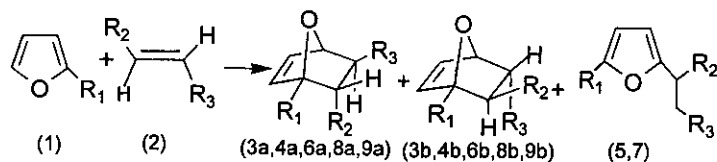
adducts, which were converted

into a Michael adduct with

extended reaction times.<sup>3</sup>

We found that the reactions of

furans (1) with some dieno-



|    | R <sub>1</sub> | R <sub>2</sub>      | R <sub>3</sub>     |                 | R <sub>1</sub> | R <sub>2</sub>      | R <sub>3</sub>      |
|----|----------------|---------------------|--------------------|-----------------|----------------|---------------------|---------------------|
| 1a | H              | NO <sub>2</sub>     | CO <sub>2</sub> Me | <i>endo</i> -3a | H,             | NO <sub>2</sub> ,   | CO <sub>2</sub> Me  |
| 1b | Me             | CN,                 | CN                 | <i>exo</i> -3b  | H,             | NO <sub>2</sub> ,   | CO <sub>2</sub> Me, |
| 1c | OMe            |                     |                    | <i>endo</i> -4a | Me,            | NO <sub>2</sub> ,   | CO <sub>2</sub> Me, |
|    |                |                     |                    | <i>exo</i> -4b  | Me,            | NO <sub>2</sub> ,   | CO <sub>2</sub> Me, |
|    |                |                     |                    | <i>endo</i> -4a | Me,            | CO <sub>2</sub> Me, | NO <sub>2</sub> ,   |
| 5a | Me,            | CO <sub>2</sub> Me, | NO <sub>2</sub>    | <i>exo</i> -4b  | Me,            | CO <sub>2</sub> Me, | NO <sub>2</sub>     |
| 5b | Me,            | NO <sub>2</sub> ,   | CO <sub>2</sub> Me | 6a              | Me,            | CN,                 | CN,                 |
| 7a | OMe,           | CO <sub>2</sub> Me, | NO <sub>2</sub>    | 6b              | Me,            | CN,                 | CN,                 |
| 7b | OMe,           | NO <sub>2</sub> ,   | CO <sub>2</sub> Me | <i>endo</i> -8a | OMe,           | NO <sub>2</sub> ,   | CO <sub>2</sub> Me, |
|    |                |                     |                    | <i>exo</i> -8b  | OMe,           | NO <sub>2</sub> ,   | CO <sub>2</sub> Me, |
|    |                |                     |                    | 9a              | OMe,           | CN,                 | CN,                 |
|    |                |                     |                    | 9b              | OMe,           | CN,                 | CN,                 |

philes (2) yielded both Diels-Alder adducts and Michael adducts.

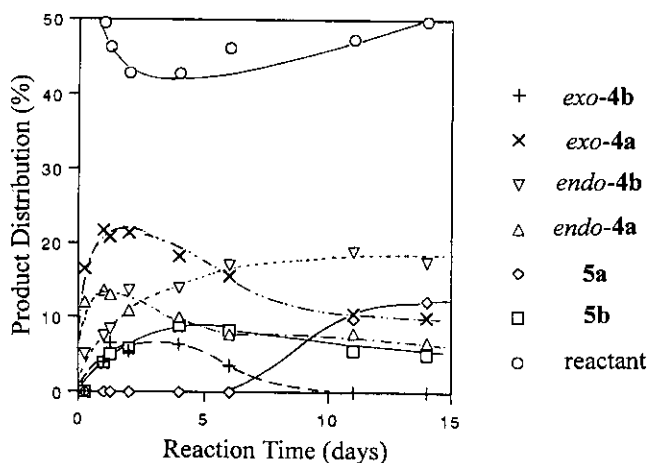
Furan (1a) reacted with methyl 3-nitroacrylate (2a) to give the known Diels-Alder adducts, *endo*-3a and *exo*-3b,<sup>4</sup> but the adduct ratios (3:2~1:1) and the yields (85~30%) depended upon the reaction conditions (the reactant concentrations, its ratios, and the reaction times).<sup>5</sup> The reaction of 1a with 2a in chloroform was followed by <sup>1</sup>H-NMR (90 MHz) for 2 months.<sup>6,7</sup> The results indicated that *endo*-3a was produced up to a 30% yield during the initial stage of the reaction (8 days), then this adduct was rapidly decomposed. In contrast, *exo*-3b slowly increased without decomposition, and after 19 days, an equilibrium composed of *endo*-3a (7%) and *exo*-3b (18%) was established.

The reaction of 2-methylfuran (1b) with 2a for 5 days yielded a product mixture containing a Diels-Alder adduct (*endo*-4a, 12% yield), a Michael adduct (5a, 40% yield),<sup>8</sup> and a few concomitant products. The reaction was carefully followed by <sup>1</sup>H NMR (250 MHz) at room temperature for 2 weeks.<sup>6,7</sup> The result given in Figure 1 indicated that the yields of three Diels-Alder adducts (*exo*-4a, *endo*-4b, *exo*-4b) reached their maximum values (22%, 13%, 6% yield, respectively) within 3 days. However, after 10 days these adducts significantly disappeared. In contrast, the yield of the fourth Diels-Alder adduct (*endo*-4a) steadily increased up to 18% after 2 weeks. One of the Michael adducts (5b) rather slowly increased during the early stage to reach a maximum yield of 8% at 4 days. Interestingly, the other Michael adduct (5a) was not detected during the early stage of the reaction, however, the increasing production of 5a and the reactant was observed after the three Diels-Alder adducts began to decompose.

2-Methoxyfuran (1c), one of the highly reactive dienes in the Diels-Alder reaction, actually reacted with 2a in benzene at room temperature to give the Michael adduct (7a, 72% yield).

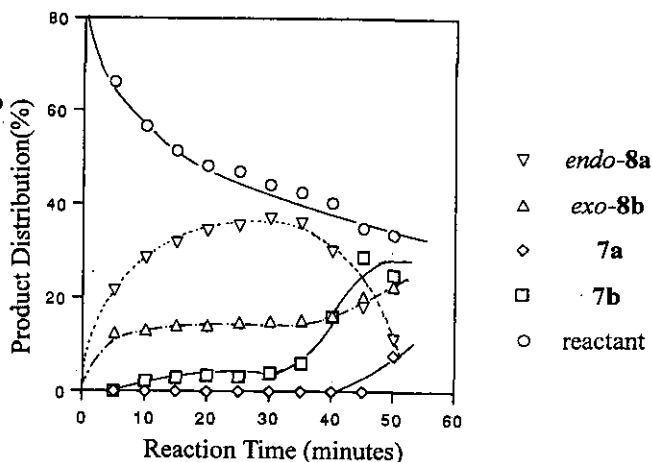
The reaction was also followed by temperature (-10°C) for 50 min.<sup>6,7</sup>

Figure 1 Time Dependent Product Distribution of the Reaction of 2-Methylfuran(1b) with Methyl 3-nitroacrylate(2a)



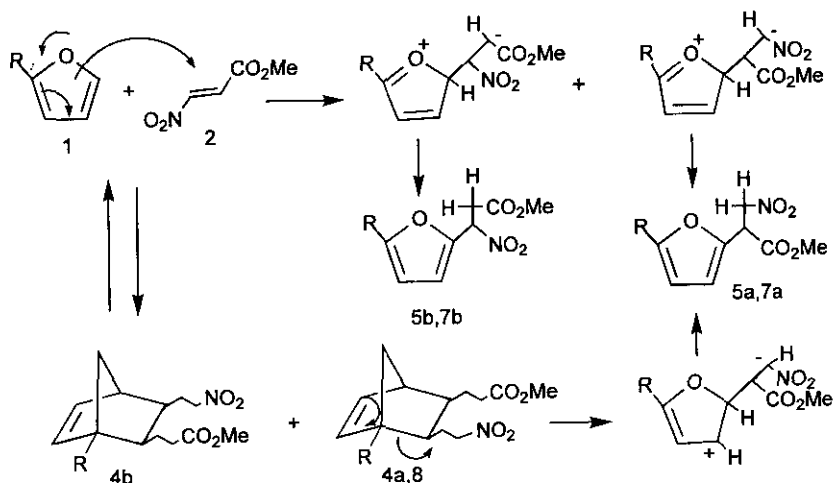
The result obtained was similar to that observed for the reaction of **1b** with **2a**. Only two Diels-Alder adducts (*endo*-**8a**, *exo*-**8b**) were observed, and no other isomer was detected.<sup>9</sup> (Figure 2) Thus, one of the Diels-Alder adducts (*endo*-**8a**, 37% yield at 30 min) was quickly produced but soon began to disappear, while the other one (*exo*-**8b**) steadily accumulated. One of the

Figure 2 Time Dependent Product Distribution of the Reaction of 2-Methoxyfuran(**1c**) with Methyl 3-nitroacrylate(**2a**)



Michael adducts (**7b**) was produced from the beginning, but production of the other one (**7a**) was significantly delayed; it appeared during the course of the reaction (45 min).

The Diels-Alder adducts are known as kinetic products accompanied by the retro-reaction while the Michael adducts are thermodynamic products.<sup>10</sup> Figures 1 and 2 clearly demonstrated the conversion of Diels-Alder adducts to Michael adducts. The formation process of these Michael adducts seems to be complex. We assumed that the Michael adducts were directly formed by a nucleophilic addition mode as depicted below. Furthermore, **5a** and **7a** were thought to be formed also by fission at the allylic carbon atom of the Diels-Alder adducts (*exo*-**4b**, *endo*-**8a**).



Fumaronitrile (**2b**) was also allowed to react with **1b** and **1c** in dichloromethane. The products were determined to be two Diels-Alder adducts (**6a**, **6b** and **9a**, **9b**, respectively),

but no Michael adduct was detected at all.

Thus, when a particular diene and dienophile were allowed to react, the reaction seemed to concurrently give Diels-Alder adducts and Michael adducts.<sup>11</sup> The present results are given in Table 1 together with those selected from the literature. An orbital energy difference between a HOMO<sub>diene</sub> and a LUMO<sub>dienophile</sub> (called the "HOMO-LUMO energy gap"<sup>12,13</sup> hereafter) for the respective reaction partners was calculated<sup>14</sup> and the values are also listed in this Table. These values apparently govern the division point controlling the course of the addition reactions to a Diels-Alder type or a Michael type, or both. It seems that the addition reactions having the HOMO-LUMO energy gap of 7.4-7.0 eV showed a Diels-Alder/Michael addition dichotomous nature. The reactions having the HOMO-LUMO energy gap above 7.5 eV exclusively yielded Diels-Alder adducts, while those having the gap below 6.9 eV afforded only the Michael adducts. Although we have not yet determine the reason for this controlling factor, the scope and limitation of the dichotomous nature of this reaction are now under examination.

Table 1. Reaction of Furans with Electron Deficient Dienophiles

| Furan     | Dienophile                           | Products                         | HOMO-LUMO<br>Energy gap (ev) <sup>a</sup> | Reference |
|-----------|--------------------------------------|----------------------------------|-------------------------------------------|-----------|
| 1a        | Diethyl maleate                      | DA adducts <sup>b</sup>          | 8.39                                      | 16        |
| 1b        | "                                    | "                                | 8.08                                      | 17        |
| 1b        | 2b                                   | "                                | 7.84                                      |           |
| 1a        | 2a                                   | "                                | 7.63                                      |           |
| 1c        | 2b                                   | "                                | 7.54                                      |           |
| 1b        | O <sub>2</sub> NCH=CHCl <sub>3</sub> | DA adducts and<br>Michael adduct | 7.41                                      | 4         |
| 1b        | 2a                                   | "                                | 7.35                                      |           |
| 3-Boc-NH- | 2a                                   | "                                | 7.32                                      | 18        |
| 1c        | 2a                                   | "                                | 7.05                                      |           |
| 1c        | 2a                                   | Michael adduct                   | 6.89                                      | 19        |
| 2-TMSO-   | 2a                                   | "                                | 6.51                                      | 20        |

a: HOMO<sub>diene</sub> - LUMO<sub>dienophile</sub> energy gap calculated by SPARTAN<sup>14</sup> ver. 4.1 with the PM3 Hamiltonian. b: Diels-Alder Adducts.

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  - 6 The reactant concentration was the measurable dilution by means of  $^1\text{H}$  NMR (0.30 mmol in 5 mL  $\text{CDCl}_3$ ), and its ratio was equivalent.
  - 7 The yield of byproducts was not below 10%, and was not taken into account in the calculation of the yield given in Figures 1 and 2.
  - 8 Part of the Diels-Alder adducts was converted into the Michael adducts during the isolation procedure.
  - 9 In this case, the calculated activation energies<sup>14</sup> of *endo*-8a and *exo*-8b are lower by 2 Kcal/mol or more than those of the undetected isomers (*exo*-8a;  $\text{R}_2 = \text{CO}_2\text{Me}$ ,  $\text{R}_3 = \text{NO}_2$  and *endo*-8b;  $\text{R}_2 = \text{CO}_2\text{Me}$ ,  $\text{R}_3 = \text{NO}_2$ ). However, in the reaction of 1b with 2b, there are no such differences in the activation energy between *exo*-, *endo*-4a and *exo*-, *endo*-4b.
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  - 15 Representative data:  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): 7a: 3.75 (3H, s), 3.84 (3H, s), 4.47 (1H, dd,  $J=5.0, 9.0$  Hz), 4.65 (1H, dd,  $J=5.0, 14.5$  Hz), 5.03 (1H, dd,  $J=9.0, 14.5$  Hz), 5.09 (1H, d,  $J=3.3$  Hz), 6.18 (1H, d,  $J=3.3$  Hz): 7b: 3.73 (3H, s), 3.78 (3H, s), 4.61(1H,dd,  $J=5.2, 7.4$  Hz) 4.83 (1H, dd,  $J=5.2, 7.4$  Hz), 5.11 (1H, d,  $J=3.3$  Hz), 6.23 (1H, d= $3.3$  Hz), 6.69 (1H, d,  $J=7.4$  Hz): *endo*-8a: 3.42 (1H, d,  $J=3.3$  Hz), 3.65 (3H, s), 3.84 (3H, s), 5.20 (1H, d,  $J=2.1$  Hz),

- 5.39 (1H, d,  $J=3.3$  Hz), 6.39 (1H, d,  $J=5.5$  Hz), 6.85 (1H, dd,  $J=2.1, 5.5$  Hz): *exo*-8b: 3.61 (3H, s), 3.73 (3H, s), 4.17(1H, dd,  $J=3.3, 5.0$  Hz), 5.02 (1H, d,  $J=3.3$  Hz), 5.27 (1H, dd,  $J=1.8, 5.0$  Hz), 6.45 (1H, d,  $J=5.7$  Hz), 6.74 (1H, dd,  $J=1.8, 5.7$  Hz).
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