

Effect of Boron Trifluoride–Diethyl Ether ($\text{BF}_3 \cdot \text{OEt}_2$) in the Diels–Alder Reaction of Quinoline- and Isoquinoline-5,8-dione with Unsymmetrical Aliphatic Dienes: Theoretical Study on the Orientation of Cycloadditions

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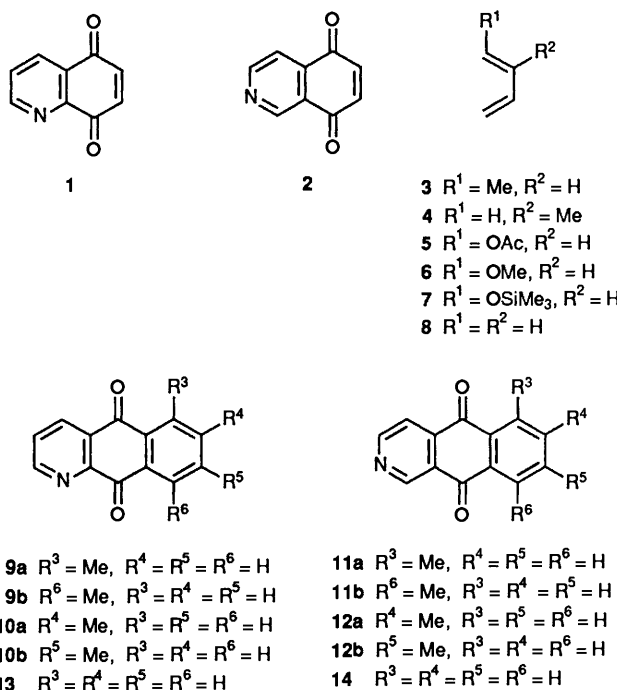
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The Diels–Alder reaction of quinoline- and isoquinoline-5,8-dione with piperlylene or isoprene gave regioisomers of the substituted azaanthraquinones, while the Lewis acid catalyst boron trifluoride–diethyl ether showed a drastic effect on regioselectivity in the reactions with piperlylene. The Frontier Molecular Orbital (FMO) theory (calculated by CNDO/2 method) was applied to explain the orientation of the catalysed regioselective cycloadditions, by considering secondary orbital interactions.

The Diels–Alder reaction of naphthoquinones¹ has received considerable attention, not only because the quinones are good dienophiles but also because their cycloadducts provide fundamental skeletons of many important biologically active compounds such as anthracyclines.² Theoretical studies of the regioselectivity in their cycloadditions is also well documented.³ However, their aza-analogues such as quinoline- and isoquinoline-5,8-dione also interest us in view of the regioselectivity of the Diels–Alder reaction,⁴ since these substrates have unsymmetrical electronic structures, as can be seen in the substituted naphthoquinones, due to the presence of nitrogen atoms in their rings. In a series of papers by Potts *et al.*,^{5–7} the position of the nitrogen atom was shown to provide control of the regiochemistry in their cycloaddition products with electron-rich dienes, such as 1-methoxycyclohexa-1,3-diene or Danishefsky's dienes, but, to our knowledge, the reactions with unsymmetrical aliphatic dienes have scarcely been studied. We now report the regioselectivity of the Diels–Alder reaction of both quinoline- and isoquinoline-5,8-dione with piperlylene and isoprene under boron trifluoride-catalysed conditions, and we also present a theoretical study to explain the drastic effect of the catalyst on the orientation of cycloaddition in terms of FMO theory calculated by the CNDO/2 method.

Results and Discussion

Diels–Alder Reaction of Quinoline- and Isoquinoline-5,8-dione with Aliphatic Dienes.—Piperlylene (penta-1,3-diene) **3** and quinoline-5,8-dione **1** were mixed in dichloromethane and allowed to react at room temperature to give a mixture of cycloadducts, which was treated with air in pyridine and nitrobenzene to form a mixture of 5-methyl- and 8-methyl-1-azaanthraquinone **9a** and **9b**. This mixture was successfully separated by column chromatography and the determination of the structure of each isomer was made by spectral data and elemental analysis. The ¹H NMR data of the isolated isomers revealed that the 5- and 8-methyl groups and the C-8 and C-5 protons of compounds **9a** and **9b** were not equivalent, due to different electron density between two carbonyl groups, so that the 8-methyl group and C-8 proton were adjacent to the more electron-deficient carbonyl group, therefore they had somewhat downfield chemical shifts (δ 2.89 for 8-methyl group; δ 8.36 for C-8 proton) compared with the 5-methyl group (δ 2.85) and C-5 proton (δ 8.13), respectively. As described by Potts,⁶ C-5 and C-8 protons of 6,7-dimethyl-1-azaanthraquinone are magnetically



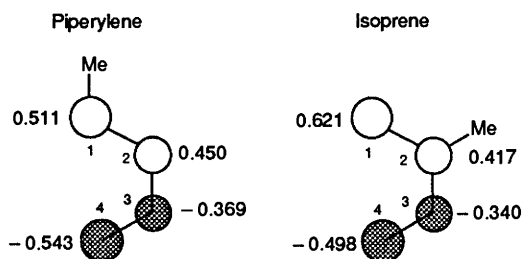
inequivalent and resonate at δ 8.08 and δ 8.19. Consequently, the isomers **9a** and **9b** were distinguished by ¹H NMR spectroscopy. According to these results, the ratio **9a**:**9b** initially formed as a mixture was determined by the integration of both methyl groups and was found to be 47:53 in the uncatalysed reaction (Table 1, entry 1).

On the other hand, addition of boron trifluoride–ether as a Lewis acid catalyst changed the ratio **9a**:**9b** drastically (entries 2–5). In the presence of an equimolar catalyst the ratio **9a**:**9b** was 1:99 when the reaction was performed at 0 °C (entry 2) but higher reaction temperature reduced the selectivity (entry 3). Interestingly, excess of catalyst also reduced the regioselectivity (entry 6), which would be caused by a multiple co-ordination of catalysts to compound **1** that might reduce electronic lean of reaction sites in compound **1**.

In contrast, when isoprene (2-methylbuta-1,3-diene) **4**

Table 1. Diels–Alder reactions of quinoline- and isoquinoline-5,8-dione with dienes.

Entry	Dienophile	Diene	BF ₃ ·OEt ₂ (mol equiv.) (T/°C)	Product ratio of regioisomers	Total yield (%)
1	1	3	0(room temp.)	9a:9b 47:53	51
2	1	3	1(0)	1:99	60
3	1	3	1(20)	16:84	52
4	1	3	2(0)	10:90	49
5	1	3	2(20)	7:93	44
6	1	3	6(0)	42:58	39
7	1	4	0(20)	10a:10b 46:54	28
8	1	4	1(0)	64:36	48
9	1	4	1(20)	56:44	55
10	1	4	2(0)	51:49	32
11	2	3	0(room temp.)	11a:11b 38:62	51
12	2	3	1(room temp.)	95:5	50
13	2	3	2(room temp.)	90:10	56
14	2	4	0(room temp.)	12a + 12b	63
15	1	5	0(20)	13	33
16	1	6	0(20)	13	69
17	1	7	0(20)	13	65
18	1	8	0(20)	13	40
19	2	6	0(20)	14	42
20	2	8	0(20)	14	32

**Fig. 1.** HOMO coefficients of piperylene and isoprene.¹⁰

was used as a diene, a mixture of 6- and 7-methyl-1-azaanthraquinone **10a** and **10b** were formed and the ratio was determined by ¹H NMR spectroscopy, where the C-5 proton and C-8 proton resonated at δ 8.03 and 8.24, respectively. In these reactions, the aforementioned remarkable regioselectivity was not found even in the presence of the catalysts as expected from the less polarized character of isoprene compared with that of piperylene (entries 7–11).

Use of isoquinoline-5,8-dione **2** as dienophile and piperylene **3** as diene led to high regioselectivity in the catalysed reactions (entries 12 and 13). Although our attempts to isolate the minor isomer were unsuccessful, the ratio of products could be determined from the mixture by ¹H NMR spectroscopy. On the other hand, unfortunately, neither the determination of the ratio nor the separation of isomers for cycloadducts from the quinone **2** and isoprene **4** could be made because of the very similar physical and chemical properties of 6- and 7-methyl-2-azaanthraquinone **12a** and **12b** (entry 14).

As an alternative, we used oxygen-functionalized dienes **5–7** for the synthesis of 1- and 2-azaanthraquinone without substituents. Aromatization accompanied by elimination of alkoxy, acetoxy and siloxy groups proceeded easily during the oxidation. All the results are summarized in Table 1.

The CNDO/2 Calculations and an Explanation of the Orientation in Cycloadditions.—The regioselectivity in the Diels–Alder reaction has often been successfully explained in terms of Frontier Molecular Orbital theory (FMO).⁸ Although theoretical treatments of the Diels–Alder reaction of naphthoquinones are well documented, there has been little

work done on aza-analogues. However, a recent theoretical study on MO calculations of isoquinoline-5,8-dione by Dannenberg and Franck⁹ showed that from the results of their calculations using Frontier Orbital theory and a biradical model the choice of the diene and the acidity of the medium might provide regioselectivity in their reactions; thus, Lewis acid catalysts such as boron trifluoride should affect significantly the orientation of cycloadditions according to the co-ordination site of the acid catalyst with the dienophile. Although their work⁹ predicts the initial reaction sites of dienophiles, no mention of the contribution of secondary orbital interaction was made. Independently, we attempted to explain the regioselectivity shown by the experimental results, by employing MO calculations performed by the CNDO/2 method.

As generally treated in the Diels–Alder reaction, the eigenvectors of the HOMO (diene) and LUMO (dienophile) were selected to enable calculation of the orientation. In Fig. 1, the diene HOMO coefficients are described. Considering the magnitudes of the coefficients of piperylene **3**, where the difference between C-2 (0.450) and C-3 (0.369) is larger than that between C-1 (0.511) and C-4 (0.543), the importance of secondary orbital interaction in the Diels–Alder reaction can be readily identified when regioselectivity is discussed.^{10,11} In contrast, the coefficients of isoprene **4** showed a smaller difference between C-2 (0.417) and C-3 (0.340) than that between C-1 (0.621) and C-4 (0.498),¹⁰ from which the primary orbital interaction as well as the secondary orbital interaction may both play an important role in determining overall regioselectivity.

In Fig. 2, the neutral and boron trifluoride-co-ordinated forms **1a–1d**, **2a–2d** of quinones **1** and **2** are illustrated and their LUMO energy and coefficients are listed in Table 2. As shown in Table 2, the neutral forms of both dienophiles **1a** and **2a** have almost same magnitudes of coefficients in each pair C-6 and C-7, C-5 and C-8, from which one cannot expect regioselectivity in their cycloadditions. In contrast, the co-ordination of BF₃ at any side of quinone **1** increases the difference of magnitudes of either of the C-5 and C-8, C-6 and C-7 pairs in adducts **1b–d** and **2b–d**. It is well known that co-ordination of a Lewis acid to a dienophile increases the difference in the coefficients of the interacting FMOs and decreases the LUMO energies.¹² Of these co-ordinated forms, the nitrogen-boron complexes **1b** and **2b** give higher LUMO energy than do the oxygen-boron

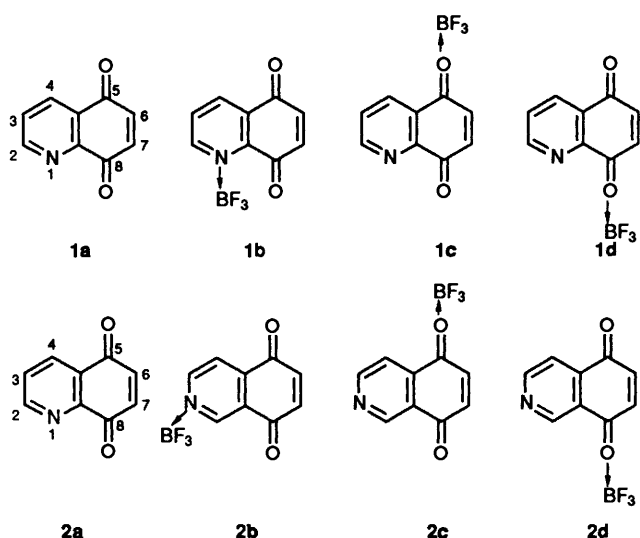


Fig. 2. Neutral and boron trifluoride-co-ordinated forms of quinoline- and isoquinoline-5,8-diones.

Table 2. FMO energies and coefficients of quinoline- and isoquinoline-5,8-dione and their boron trifluoride complexes.^a

	LUMO (eV)	LUMO coefficients			
		C-5	C-6	C-7	C-8
1a	-0.055	0.309	0.311	-0.310	-0.312
1b	-0.868	-0.299	-0.268	0.286	0.270
1c	-2.192	0.441	0.245	-0.360	-0.253
1d	-2.228	0.251	0.358	-0.242	-0.442
2a	-0.213	-0.306	-0.322	0.330	0.295
2b	-1.452	-0.292	-0.268	0.290	0.258
2c	-2.260	0.428	0.255	-0.378	-0.244
2d	-2.222	-0.254	-0.374	0.266	0.419

^a Fixed parameters: bond length between: boron and nitrogen, 1.85 Å for 1b and 2b; boron and oxygen, 1.65 Å for 1c and 1d; 1.70 Å for 2c and 2d.

complexes and show not so large difference in magnitudes of coefficients in both interacting pairs, as shown by Dannenberg,⁹ while the oxygen-boron complexes give a significant difference in magnitude and lower LUMO energies. Thus, co-ordination of the catalyst at either oxygen probably gives rise to the regioselectivity. On comparison of adducts 1c and 1d, 2c and 2d, both pairs of which have reversed magnitudes, the LUMO energies of adducts 1d and 2c are a little lower than those of 1c and 2d, respectively. FMO theory predicts that the smaller energy difference of the interacting FMOs gives the greater contribution to the stabilization of the transition state and also greater reactivity.⁸ Therefore, we can explain the remarkable regioselectivity in the catalysed cycloaddition of quinones 1 and 2 with piperylene 3 or isoprene 4 by considering that the selectivity control is provided mainly by the secondary orbital interaction of piperylene's HOMO with the LUMOs of the adducts 1d and 2c. In spite of our uncertainty as to which is the predominant form in a reaction mixture of these postulated complexes, we assume that complexes 1d and 2c react with dienes faster than do their competitors. On the other hand, primary or secondary orbital interactions of isoprene HOMO with the LUMOs of complexes 1d and 2c gives the reversed orientation in their cycloadditions, which would provide less selectivity because of dual interaction due to primary and secondary orbital interaction as mentioned above.

Experimental

M.p.s were determined with a Yanagimoto hot-stage apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer Model 240 elemental analyser. IR spectra were recorded on a JASCO IRA-1 spectrometer (KBr disk), ¹H NMR spectra on a JEOL PMX 60 (60 MHz) and JNM-FX 90 (90 MHz) spectrometer for solutions in deuteriochloroform (tetramethylsilane as the standard), and mass spectra on a JEOL JMS-01SG-2 spectrometer (at 75 eV). Column chromatography was carried out with Wakogel C-200. Purity of products was checked by TLC (Merck, silicagel 60F₂₅₄, precoated plastic sheet, 0.2 mm).

Quinoline- and isoquinoline-5,8-dione 1¹³ and 2,¹⁴ 1-acetoxybuta-1,3-diene 5,¹⁵ 1-methoxybuta-1,3-diene 6¹⁶ and 1-trimethylsilyloxybuta-1,3-diene 7¹⁷ were prepared according to previously known procedures.

General Procedure of the Diels-Alder Reaction of Quinoline- and Isoquinoline-5,8-dione 1 and 2 with Dienes 3-8.—A ten-fold excess of piperylene 3 or isoprene 4 was added to a solution of quinoline- or isoquinoline-5,8-dione 1 or 2 (0.48 g, 3 mmol) in dichloromethane (200 cm³). After being allowed to react under nitrogen for five days, the solvent and unchanged dienes were removed under reduced pressure. The residue was dissolved in a mixture of pyridine (3 cm³) and nitrobenzene (12 cm³) and heated under reflux for five hours. After removal of the solvent by steam distillation, the precipitate was filtered off and washed with water. The crude products were chromatographed on silica gel (chloroform as eluant), and isolated adducts were recrystallized from chloroform. The catalysed reaction of substrates 1 and 3 was similarly performed by addition of boron trifluoride-diethyl ether to a reaction mixture. Thus were prepared the following compounds.

5-Methyl-1-azaanthraquinone 9a. Yellow microcrystals, m.p. 190–192 °C (Found: C, 75.1; H, 3.9; N, 6.1%; M⁺, 223. C₁₄H₉NO₂ requires C, 75.3; H, 4.1; N, 6.3%; M, 223); ν_{\max} 1680 and 1660 cm⁻¹; δ_{H} (90 MHz) 2.85 (3 H, s, Me), 7.5–7.9 (3 H, m, 3-, 6- and 7-H), 8.36 (1 H, dd, *J* 3.6 and 6.0 Hz, 8-H), 8.61 (1 H, dd, *J* 1.5, 8.0 Hz, 4-H) and 9.09 (1 H, dd, *J* 1.5 and 4.6 Hz, 2-H).

8-Methyl-1-azaanthraquinone 9b. Yellow microcrystals, m.p. 185–187 °C (Found: C, 75.6; H, 3.9; N, 6.5%; M⁺, 223); ν_{\max} 1675 and 1660 cm⁻¹; δ_{H} (90 MHz) 2.89 (3 H, s, Me), 7.4–7.85 (3 H, m, 3-, 6- and 7-H), 8.13 (1 H, dd, *J* 3.8 and 4.5 Hz, 5-H), 8.51 (1 H, dd, *J* 1.5 and 9.8 Hz, 4-H) and 9.55 (1 H, dd, *J* 1.5, 6.0 Hz, 2-H).

6-Methyl-1-azaanthraquinone 10a. Yellow microcrystals, m.p. 201–204 °C (Found: C, 75.1; H, 4.0; N, 6.1%; M⁺, 223); ν_{\max} 1680 and 1660 cm⁻¹; δ_{H} (90 MHz) 2.53 (3 H, s, Me), 7.5–7.84 (2 H, m, 3- and 7-H), 8.04 (1 H, s, 5-H), 8.24 (1 H, d, *J* 8 Hz, 8-H), 8.6 (1 H, dd, *J* 1.5 and 8.4 Hz, 4-H) and 9.08 (1 H, dd, *J* 1.5, 4.8 Hz, 2-H).

7-Methyl-1-azaanthraquinone 10b. Yellow microcrystals, m.p. 185–190 °C (Found: C, 75.5; H, 4.2; N, 6.4%; M⁺, 223); ν_{\max} 1680 and 1665 cm⁻¹; δ_{H} (90 MHz) 2.56 (3 H, s, Me), 7.5–7.84 (2 H, m, 3- and 6-H), 8.21 (1 H, d, *J* 8 Hz, 5-H), 8.22 (1 H, s, 8-H), 8.67 (1 H, dd, *J* 1.5 and 7.8 Hz, 4-H) and 9.10 (1 H, dd, *J* 1.5 and 4.8 Hz, 2-H).

5-Methyl-2-azaanthraquinone 11a. Yellow microcrystals, m.p. 161–163 °C (Found: C, 75.1; H, 4.0; N, 6.1%; M⁺, 223); ν_{\max} 1680 cm⁻¹; δ_{H} (60 MHz) 2.89 (3 H, s, Me), 7.64–7.71 (2 H, m, 6- and 7-H), 8.02 (1 H, d, *J* 5.3 Hz, 4-H), 8.27 (1 H, dd, *J* 1.8 and 6.7 Hz, 8-H), 9.08 (1 H, d, *J* 5.3 Hz, 3-H) and 9.51 (1 H, s, 1-H).

The isomer 11b could not be isolated.

6- and 7-Methyl-2-azaanthraquinone 12a and 12b. Attempts to isolate both adducts were unsuccessful. The ¹H NMR spectrum of the mixture showed δ_{H} (60 MHz) 2.52 (3 H, s, Me), 7.43–7.70 (1 H, m, 7- or 6-H), 7.90–8.25 (3 H, m, 4-, 5- and 8-H), 9.05 (1 H, d, *J* 5.0 Hz, 3-H) and 9.47 (1 H, s, 1-H). This mixture gave no correct analytical data.

1-Azaanthraquinone 13. Yellow microcrystals, m.p. 271 °C (sublime) (lit.,¹³ 280 °C) (Found: C, 74.4; H, 3.5; N, 6.6%; M⁺,

209. Calc. for $C_{13}H_7NO_2$: C, 74.6; H, 3.4; N, 6.7%; M, 209; ν_{\max} 1700 cm^{-1} ; δ_H (60 MHz) 7.56–7.98 (3 H, m, 3-, 6- and 7-H), 8.09–8.49 (2 H, m, 5- and 8-H), 8.58 (1 H, dd, J 1.5 and 7.5 Hz, 4-H) and 9.07 (1 H, dd, J 1.5 and 4.5 Hz, 2-H).

2-Azaanthraquinone 14. Yellow needles, m.p. 179 °C (sublime) (lit.,¹⁴ 179 °C) (Found: C, 74.4; H, 3.3; N, 6.6%; M⁺, 209); ν_{\max} 1690 cm^{-1} ; δ_H 7.76–7.93 (2 H, m, 6- and 7-H), 8.05–8.4 (3 H, m, 4-, 5- and 8-H), 9.13 (1 H, d, 3-H) and 9.56 (1 H, s, 1-H).

CNDO/2 Calculations.—The molecular calculations were made using the library program of the Calculation Centre of the University of Tokyo.

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