Reactivity of an *o*-Indoloquinone to 1- and 2-Azadienes

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The cycloaddition reactions of *o*-indoloquinone 4 to azadienes are described. With 1-azadiene 2, quinone 4 works as a dienophile to give the directly aromatized cycloadduct 6. In contrast, when 2-azadiene 3 is used, the cycloaddition occurs with CO-4, indicating that this system functions as a heterodienophile.

Key words Diels-Alder; *o*-indoloquinone; 1-azadiene; 2-azadiene

Quinones are very interesting compounds with fascinating chemistry. Moreover, some of them are used as therapeutic agents or are recognized as enzyme cofactors or electron carriers in redox biological systems. Since the advent of the Diels-Alder reaction, *p*-quinones have been the subject of extensive investigations directed toward cycloadditions with numerous dienes.¹⁾ In contrast, *o*-quinones have received much less attention due to their instability. Most of the cycloaddition reactions concerning *o*-quinones were performed with carbodienes.^{2–5)} Recently, our group was the first to show the ability of benzofuran-4,5-diones as suitable dienophiles with 2-ethoxybut-2-enal *N,N*-dimethylhydrazone to give the directly aromatized furoquinoline-4,5-diones.⁶⁾ In order to obtain analogues of pyrroloquinolinequinone (PQQ),⁷⁾ a redox cofactor of quinoproteins known to participate in several physiological processes, we planned to investigate the hetero Diels-Alder reactions between 1-azadienes 1⁶⁾ or 2⁸⁾ and 2-azadiene 3⁹⁾ toward *o*-indoloquinone 4 (Chart 1).

The synthesis of 4 was achieved in two steps. Thus the

ester 5b¹⁰⁾ was readily prepared from the commercially available acid 5a and then oxidized with Frémy's salt to give *o*-quinone 4¹¹⁾ in 85% overall yield (Chart 2). Surprisingly, the cycloaddition reaction of 4 with the electron-rich azadiene 1 attempted in tetrahydrofuran (THF) at room temperature failed. The starting quinone was completely decomposed and no trace of a cycloadduct was evident. In contrast, the use of azadiene 2 in the same conditions afforded the directly aromatized cycloadduct 6¹²⁾ (42% yield) through a spontaneous elimination of dimethylamine. Neither a primary adduct nor a dihydro derivative was observed. The regiochemistry of 6 was assigned by analogy with the cycloadditions of electron-rich dienes and *o*-indoloquinones.⁵⁾ In order to explain this regiochemistry, we calculated the HOMO and LUMO frontier molecular orbital coefficients by the density functional theory (DFT) method with the hybrid B3LYP functional¹³⁾ using the GAUSSIAN 94 package¹⁴⁾ with basis set 6-31 G*. The results indicated that the larger HOMO coefficients of azadienes 1 and 2 are located at C-4, while those of the LUMO for quinone 4 are situated at C-7 (Table). Therefore, the assigned regiochemistry for compound 6 is in good agreement with calculations. In contrast, these latter cannot explain the difference in reactivity of azadienes 1 and 2 toward quinone 4, based on their similar 3p_z orbital coefficient values. The failure encountered with azadiene 1 remains inexplicable.

On the other hand, the behavior of quinone 4 toward 2-azadiene 3 was completely different (Chart 2). The reaction carried out in THF at room temperature for 40 min showed on thin-layer chromatography (TLC) the disappearance of the starting material and the formation of two diastereomers which were purified by column chromatography on silica gel. When maintained for 24 hours at room temperature, they were both spontaneously converted into a single, more polar compound 7. Structural assignment of the latter was made from its spectral data. Due to its poor solubility in CDCl₃, all NMR experiments were performed in dimethylsulfoxide (DMSO). The ¹H-NMR spectrum exhibited an AB system (6.58 and 6.26 ppm, *J*=9.9 Hz) and two signals at 11.08 ppm

Chart 1

Chart 2

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Table 1. Frontier Molecular Orbital Coefficients of Compounds **1** to **4** Calculated by the DFT Method

		2p _z	3p _z
Azadiene 1	N-1	0.186	0.133
(HOMO)	C-4	0.297	0.234
Azadiene 2	N-1	0.196	0.136
(HOMO)	C-4	0.282	0.233
Azadiene 3	C-1	0.077	0.101
(HOMO)	C-4	0.393	0.330
<i>o</i> -Indoloquinone 4	C-6	0.180	0.203
(LUMO)	C-7	0.250	0.247

Fig. 1. 1D ¹H NOE DIFF and 2D ¹H-¹³C COSY Correlations in **7b** Fig. 2. Electron Densities of **4** Calculated by the DFT Method

(d, 1H, $J=9.6$ Hz) and 8.84 ppm (d, 1H, $J=9.6$ Hz). The ¹H-NMR spectrum with D₂O indicated the presence of three exchangeable protons at 12.54 (NH), 11.08 (N=C-OH), and 5.85 ppm (4-OH). ¹³C-NMR distortionless enhancement by polarization transfer (DEPT) showed four CH, one CH₃, and one CH₂. We propose the structure **7b**¹⁵ for compound **7**, since we are aware that an equilibrium exists with the imide form **7a**. It was previously reported for analogous structural products that such an equilibrium is solvent dependent.¹⁶ Therefore, in a polar solvent like DMSO, the equilibrium would be totally displaced to the enolic form **7b** which may be stabilized through an intramolecular hydrogen bonding. Then, both the 1D ¹H nuclear Overhauser effects difference (NOE DIFF) and 2D ¹H-¹³C correlation spectroscopy (COSY) experiments are in agreement with this structure (Fig. 1). In order to confirm this, we calculated the optimized molecular geometry of compound **7** by the semiempirical PM3 method. The calculated distances were found to be compatible with the NOE DIFF results and with the presence of the hydrogen bonding ($d_{O...H}=1.81$ Å). A probable mechanism to explain the formation of **7** is that *o*-quinone **4** does not function as a carbodienophile but as a heterodienophile. Thus the activated 2-azadiene **3** adds to CO-4 of quinone **4** to give diastereomeric spiro intermediates that are not stable and open to yield compound **7**. Similar [4+2] cycloadditions on the carbonyl of a quinone were previously reported to occur between electron-rich carbodienes and *o*-benzoquinones¹⁷ or a 2-azadiene and a naphthoquinone.¹⁸ Calculations by the DFT method¹³ of electron densities of C-4 (−0.332) and C-5 (−0.397) (Fig. 2) agree with the preferred nucleophilic attack of C-4 of azadiene **3** on C-4 of quinone **4**.

This work describes the first example of cycloaddition reactions of an *o*-indoloquinone with heterodiene systems. *o*-Quinone **4** can react either as a carbodienophile or as a heterodienophile. Moreover, its cycloaddition reaction with 1-azadiene **2** illustrates a new synthetic approach to a PQQ analogue.

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- The bright orange *o*-quinone **4** was very unstable over silica gel or alumina. It was used in the Diels-Alder step without purification. ¹H-NMR (300 MHz, DMSO-*d*₆) δ : 13.0 (1H, broad s), 7.32 (1H, d, $J=10.0$ Hz), 7.07 (1H, s), 6.2 (1H, d, $J=10.0$ Hz), 3.79 (3H, s). IR (KBr) cm^{-1} : 3250, 1690, 1660.
- ¹H-NMR (300 MHz, DMSO-*d*₆) δ : 12.90 (1H, s), 8.55 (1H, s), 8.50 (1H, s), 7.16 (1H, s), 3.91 (3H, s), 2.40 (3H, s). IR (KBr) cm^{-1} : 3240, 2960, 1725, 1670, 1650.
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- Compound **7** was obtained in 70% yield. mp 190 °C (dec.). ¹H-NMR (300 MHz, DMSO-*d*₆) δ : 12.54 (1H, s), 11.08 (1H, d, $J=9.6$ Hz), 8.84 (1H, d, $J=9.6$ Hz), 7.02 (1H, s), 6.58 (1H, d, $J=9.9$ Hz), 6.26 (1H, d, $J=9.9$ Hz), 5.85 (1H, s), 3.81 (3H, s), 2.99 (1H, d, $J=15.4$ Hz), 2.79 (1H, d, $J=15.4$ Hz). ¹³C-NMR (75 MHz, DMSO-*d*₆) δ : 193.4 (C), 170.6 (C), 162.9 (CH), 160.6 (C), 141.7 (C), 140.1 (CH), 123.8 (C), 118.1 (C), 115.8 (CH), 112.2 (CH), 71.7 (C), 51.6 (CH₃), 45.7 (CH₂). IR (KBr) cm^{-1} : 3450, 3250, 3200, 2960, 1740, 1690, 1660. HRMS m/z : 292.0672 (Calcd for C₁₃H₁₂O₆N₂: 292.0695).
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