The Reactions of Nitrile Oxides with Methoxy *p*-Benzoquinones

Tohru HAYAKAWA, Koji ARAKI, and Shinsaku SHIRAISHI*
Institute of Industrial Science, The University of Tokyo, Roppongi, Minato-ku, Tokyo 106
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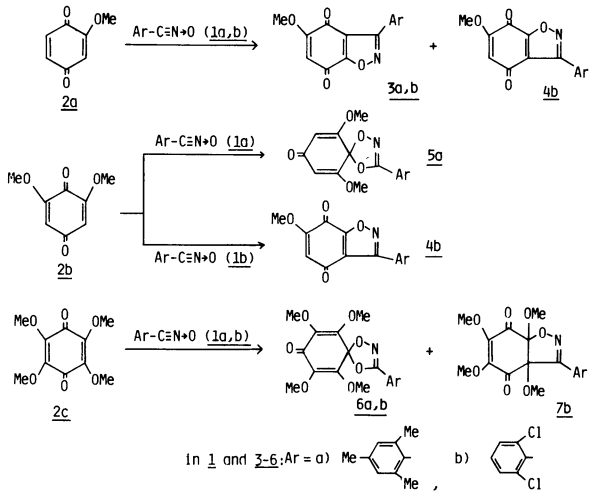
The 1,3-dipolar cycloaddition reactions of nitrile oxides with methoxy *p*-benzoquinones are discussed in terms of FMO theory. The unusual reaction pattern of methoxy *p*-benzoquinones with nitrile oxides is interpreted by considering both antibonding secondary orbital interaction and SHOMO(quinone)-LUMO (nitrile oxide) interaction.

In the previous paper[1] we reported the site- and regio-selective reactions of nitrile oxides with substituted *p*-benzoquinones by means of the FMO theory, showing the correlation between the reaction modes and two types of FMO interactions. The quinones were shown to be classified into two groups; one is a group giving C=O adducts, the reactions of which are chiefly governed by HOMO (nitrile oxide)-LUMO (quinone) interaction, and the other is that giving C=C adducts, the reactions of wihch are chiefly governed by LUMO (nitrile oxide)-HOMO (quinone) interaction. The critical energy difference of the two interactions determining the reaction mode of the quinones was roughly estimated to be about 4 eV. Steric effect was a minor factor but could not be disregarded. However, the reaction of 2,6-dichlorobenzonitrile oxide with tetramethoxy-*p*-benzoquinone, which gives both C=O and C=C adducts, could not be clearly understood even by considering the steric effect. In order to rationalize the reaction pattern, we studied the reactions of nitrile oxides with other methoxy *p*-benzoquinones and the effect of methoxyl groups is discussed in terms of FMO theory. The unusual reaction pattern of methoxy quinones was shown to be interpreted by considering both the antibonding secondary orbital interaction and MO interaction involving SHOMO's of the quinones.

Results and Discussion

The results of the reactions of nitrile oxides with methoxy *p*-benzoquinones, such as 2-methoxy-*p*-benzoquinone (**2a**) and 2,6-dimethoxy-*p*-benzoquinone (**2b**) are shown in Scheme 1 together with the result of those with tetramethoxy-*p*-benzoquinone (**2c**). As nitrile oxides, 2,4,6-trimethylbenzonitrile oxide (**1a**) and 2,6-dichlorobenzonitrile oxide (**1b**) were used. The characterization data of the reaction pruducts are described in experimental section.

The reaction of **1b** with **2a** gave two regio isomeric C=C adducts, **3b** and **4b**, which were formed by addition onto the same reaction site, unsubstituted side, but in different orientation. This is a notable contrast to the reaction with 2-methyl-*p*-benzoquinone which gave two 1:1-C=C adducts formed by addition onto different reaction site (2,3- and 5,6-position) each other.[1] The formation ratio of the regio isomers **3b** and **4b** was about 3:2 from the results of ^{1}H NMR spectrum of the reaction product. The olefinic proton of **3b** resonates as a singlet at about 0.1 ppm lower field than

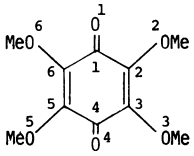


Scheme 1.

TABLE 1. ENERGY LEVELS AND COEFFICIENTS OF FMO OF METHOXY *p*-BENZOQUINONES

Quinone	FMO	ε(eV)	C_1	C_2	C_3	C_4	C_5	C_6	O_1	O_2	O_3	O_4	O_5	O_6
2a	LUMO	3.91	−0.33	−0.32	0.27	0.29	0.37	−0.35	0.51	0.16	—	−0.47	—	—
	HOMO	−7.49	0.10	−0.36	−0.55	0.15	−0.11	−0.13	0.29	0.48	—	0.40	—	—
	SHOMO	−8.92	−0.15	−0.12	−0.24	−0.13	0.52	0.52	−0.29	0.33	—	−0.22	—	—
2b	LUMO	4.25	−0.37	−0.33	0.28	0.28	0.28	−0.33	0.52	0.18	—	0.45	—	0.18
	HOMO	−6.86	0.07	−0.27	−0.36	0.22	−0.36	−0.27	0.27	0.30	—	0.53	—	0.30
	SHOMO	−7.65	0.00	−0.28	−0.48	0.00	0.48	0.28	0.00	0.41	—	0.00	—	−0.41
2c	LUMO	4.24	−0.36	−0.30	0.28	0.36	0.30	−0.28	0.48	0.16	−0.15	−0.48	−0.16	0.15
	HOMO	−6.08	0.05	−0.30	−0.32	0.05	−0.30	−0.32	0.32	0.33	0.34	0.32	0.33	0.34
	SHOMO	−6.15	−0.02	−0.34	−0.36	0.02	0.34	0.36	−0.03	0.39	0.36	0.03	−0.39	−0.36

a) The numbering of the atoms is following.



that of **4b**. The preparative separation of the two regio isomers was successfully effected by thin-layer chromatography. The reaction of **1a** with **2a** gave only one C=C adduct formed by addition onto 5,6-position in the orientation as shown in the Scheme 1.

The reaction of **2b** with **1a** has been known to give only C=O adduct,[2] while the reaction with **1b** gave exclusively the isoxazoloquinone **4b**, which was shown to be the same compound as the minor product in the reaction of **1b** with **2a**. In the reactions with **2c**, **1a** gave only C=O adduct, while **1b** gave both C=O and C=C adducts as reported before.[1,2] The difference in the modes of the reactions of **1a** and **1b** will be tried to be accounted in terms of FMO theory.

We list in Table 1 the energy values and FMO coefficients of methoxy *p*-benzoquinones calculated by *ab initio* method with STO-3G basis set[3] and in Table 2 those of nitrile oxides.[1] The geometry of quinone moiety of **2a** is that of *p*-benzoquinone[4] and that of substituent is standard one by Pople and Gordon.[5] The geometry of **2b** is that of X-ray result.[6] The substituent conformation was the most stable one by computation of the same manner described in the previous paper.[1]

The energy difference between LUMO (nitrile oxides)–HOMO (quinones) and HOMO (nitrile oxides)–LUMO (quinones) interaction is listed in Table 3. According to the energetical analysis described in the previous paper,[1] it may be predicted that the quinone **2b** will give a C=C adduct in either reaction of **1a** or **1b**. As mentioned above, however, the C=C adduct was obtained only in the reaction with **1b** and not with **1a** where C=O adduct was obtained. In addition, the high site-selectivity in the reactions is notable.

Considering the LUMO (nitrile oxide)–HOMO (quinone) interaction, one notes that the magnitude of the HOMO coefficients of the oxygen atoms of the methoxyl groups of methoxy *p*-benzoquinones is much larger than that of the carbon atoms of methyl groups of structurally similar methyl *p*-benzoquinones.[1] When nitrile oxides attack the methoxy-substituted C=C bond of the quinones, LUMO of nitrile oxides will experience an antibonding secondary orbital interaction with the oxygen orbital as shown in Fig 1. This antibonding secondary orbital interaction will decrease the net LUMO (nitrile oxide)-HOMO (quinone) overlapping to such an extent as the selectivity in the reactions may be significantly influenced. The importance of the antibonding secondary orbital interaction of methoxyl groups to the selectivity in the Diels-Alder reactions was pointed out by Tegmo-Larsson *et al.*[7] In this case, the interaction acts a role to reduce or diminish the primary orbital interaction. Gordon *et al.* rationalized the difference in the regio-selectivity between the 1,3-dipolar cycloaddition reactions of a nitrone with acrylonitrile and propiolonitrile by considering the secondary orbital interactions,[8] where the interaction acts to enhance or cooperate with the primary orbital interaction.

The quinone **2a** has two different C=C bonds. The carbon atoms of 2- and 3-positions have larger HOMO coefficients than those of 5- and 6-positions. Nevertheless the most efficient orbitals overlapping expected to be obtained in the interaction with the C=C of 2,3-position, no adduct added on the 2,3-position was obtained. This experimental result can not be rationalized by considering only the steric effect referred in the reaction with 2-methyl-*p*-benzoquinone,[1] but can be rationalized well by considering the secondary antibonding orbital interaction with the oxygen HOMO orbital of the methoxyl group.

In the reaction of **1a** with **2b**, HOMO (**1a**)-LUMO (**2b**) interaction becomes more important than the LUMO (**1a**)–HOMO (**2b**) interaction due to the antibonding secondary interactions as described above, and C=O addition occured exclusively. The kinetic data support this interpretation. The reaction rate of **2b** with **1a** is 10—100 times slower than those of other C=O addition reactions.[9] This is rationalized by the larger energy gap between HOMO (**1a**) and LUMO (**2b**). The addition across to the C=O bond of methoxy-substituted side is well understood by considering the larger LUMO coefficient magnitude of the carbon and oxygen atoms of the carbonyl.

The SHOMO's of methoxy-substituted quinones, especially those of **2b** and **2c**, lies close to that of HOMO, the energy difference being far less than 1 eV, while that of the other quinones being more than 1 eV. Therefore, in the reaction of **1b** with **2b**, LUMO (**1b**)–SHOMO (**2b**) interaction becomes more important and effects to increase net orbital overlapping, though SHOHO has also large coefficient on oxygen of methoxyl group. SHOMO does not act a role in favor of C=O addition because the coefficient on carbonyl group is zero.

The reaction with **2c** is also rationslized in terms of the same interactions mentioned above. Because of the antibonding secondary orbital intersction with

Table 2. Energy levels and coefficients of FMO of nitrile oxides

Nitrile oxide	FMO	ε(eV)	C_α[a]	C	N	O
1a	LUMO	5.58	0.50	0.27	−0.42	0.28
	HOMO	−6.12	−0.32	0.41	0.21	−0.69
1b	LUMO	4.43	0.55	0.22	−0.40	0.29
	HOMO	−6.89	−0.24	0.46	0.18	−0.73

a) This carbon connects with the dipole moiety.

Table 3. Energy difference between LUMO(nitrile oxides)-HOMO(quinones) and HOMO(nitrile oxides)-LUMO(quinones) interaction

	2a	**2b**	**2c**
1a	3.04	2.07	1.30
1b	1.12	0.15	−0.62

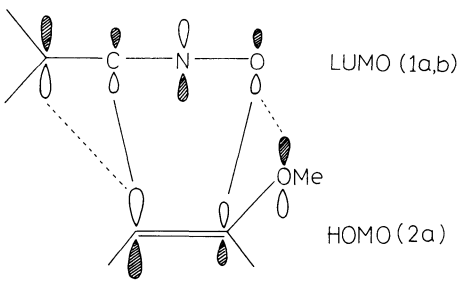


Fig. 1.

the oxygen atoms of methoxyl substituents acting to reduce the LUMO (**1a**)–HOMO (**2c**) overlapping, HOMO (**1a**)–LUMO (**2c**) interaction comes to be dominant to lead the C=O adduct formation in the reaction of **1a**. While in the reaction with **1b**, LUMO (**1b**)–SHOMO (**2c**) interaction favors C=C adduct formation due to the very small energy difference between SHOMO and HOMO of **2c** as shown in Table 1.

In the Diels-Alder reactions the role of the secondary orbtal interaction is widely recognized and applied, but in the 1,3-dipolar cycloaddition reactions not so much.[10] In this study it becomes clear that the antibonding secondary orbital interaction with oxygen atom of methoxyl substituent is the factor to control the site- and regio-selectivity in the cycloaddition reactions of nitrile oxides with methoxy *p*-benzoquinones. Moreover, it is shown that SHOMO becomes important in the interaction with the LUMO of the attacking reagent, when SHOMO lies close to HOMO.

Experimental

Melting points were measured using a micro-melting-point measuring apparatus (Yazawa Co., Ltd.) and are uncorrected. Column chromatography was conducted on silica gel (Wako gel C-200) with benzene as an eluent. IR spectra were recorded with a JASCO IRA-1 spectrophotometer. ^{1}H NMR spectra were measured in $CDCl_3$ with a JEOL JNM MH-100 spectrometer, and chemical shifts were reported in ppm from internal tetramethylsilane. Mass spectra were recorded with a Hitachi RMU-7L high resolution mass spectrometer.

Materials. 2,4,6-Trimethylbenzonitrile oxide (**1a**) and 2,6-dichlorobenzonitrile oxide (**1b**) were prepared by the method of Grundmann.[11] 2-Methoxy-*p*-benzoquinone (**2a**) was prepared by the method of Jeffreys.[12] 2,6-Dimethoxy-*p*-benzoquinone (**2b**) was prepared by the method of Will.[13]

*Reaction of 2,4,6-Trimethylbenzonitrile Oxide (1a) with 2-Methoxy-*p*-benzoquinone (2a).* A solution of 0.484 g (3 mmol) of **1a** and 0.829 g (6 mmol) of **2a** in 100 ml benzene was stirred for about 5 d at room temperature. Solvent was then evaporated under reduced pressure, and the residue was subjected to column chromatography. The first fraction gave 3-mesityl-5-methoxy-1,2-benzisoxazole-4,7-dione, **3a**, (0.62 g 69%), which was recrystallized from benzene–hexane. Mp 196—197 °C. IR (KBr) 1660 and 1690 cm^{-1} ($\nu_{C=O}$). ^{1}H NMR ($CDCl_3$) δ=2.09 (s, 6H, mesityl *o*-methyl), 2.36 (s, 3H, mesityl *p*-methyl), 3.89 (s, 3H, methoxyl methyl), 6.02 (s, 1H, olefinic), and 6.96 (s, 2H, aromatic)

Found: C, 68.78; H, 5.09; N, 4.88%. Calcd for $C_{17}H_{13}N_1O_4$: C, 68.68; H, 5.09; N, 4.71%.

*Reaction of 2,6-Dichlorobenzonitrile Oxide (1b) with 2-Methoxy-*p*-benzoquinone (2a).* The reaction was conducted and worked up in the same manner as the above. The second fraction gave a mixture of the regio-isomer, **3b** and **4b**, (0.41 g 44%). The NMR spectrum of the product revealed this to be a mixture of two C=C adducts. The signals at 6.05 and 5.94 due to the olefinic proton of the two adducts was in the ratio of 3:2. The product was separated by thin-layer chromatography with benzene–hexane 1:1 mixture as an eluent. 3-(2,6-Dichlorophenyl)-6-methoxy-1,2-benzisoxazole-4,7-dione, **4b**, was obtained from the first fraction zone, and recrystallized from benzene–hexane. Mp 190—193 °C. IR (KBr) 1660 and 1720 cm^{-1} ($\nu_{C=O}$). ^{1}H NMR ($CDCl_3$) δ=3.90 (s, 3H, methoxyl methyl), 5.94 (s, 1H, olefinic), and 7.43 (s, 3H, aromatic).

Found: C, 51.98; H, 2.14; N, 4.46%. Calcd for $C_{14}H_7N_1O_4Cl_2$: C, 51.88; H, 2.18; N, 4.32%.

The second fraction gave 3-(2,6-dichlorophenyl)-5-methoxy-1,2-benzisoxazole-4,7-dione, **3b**, which was recrystallized from benzene–hexane. Mp 181—182 °C. IR (KBr) 1670 and 1710 cm^{-1} ($\nu_{C=O}$). ^{1}H NMR ($CDCl_3$) δ=3.94 (s, 3H, methoxyl methyl), 6.05 (s, 1H, olefinic), and 7.47 (s, 3H, aromatic).

Found: C, 51.95; H. 2.10; N, 4.40%. Calcd for $C_{14}H_7N_1O_4Cl_2$: C, 51.88; H, 2.18; N, 4.32%.

*Reaction of 2,6-Dichlorobenzonitrile Oxide (1b) with 2,6-Dimethoxy-*p*-benzoquinone (2b).* A solutuion of 0.49 g (2.5 mmol) of **1b** and 0.42 g (2.5 mmol) of **2b** in 50 ml benzene was stirred for several days at room temperature and the solvent was evaporated under reduced pressure. The residue was worked up with column chromatography to give **4b**, (0.58 g 71%). The recrystallization was carried out from benzene–hexane.

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