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INFLUENCE OF THE POSITION OF *TERT*-BUTYL SUBSTITUENTS ON REACTIVITY OF QUINONE DIMERS YIELDING DIBENZOFURAN-1,4-DIONES

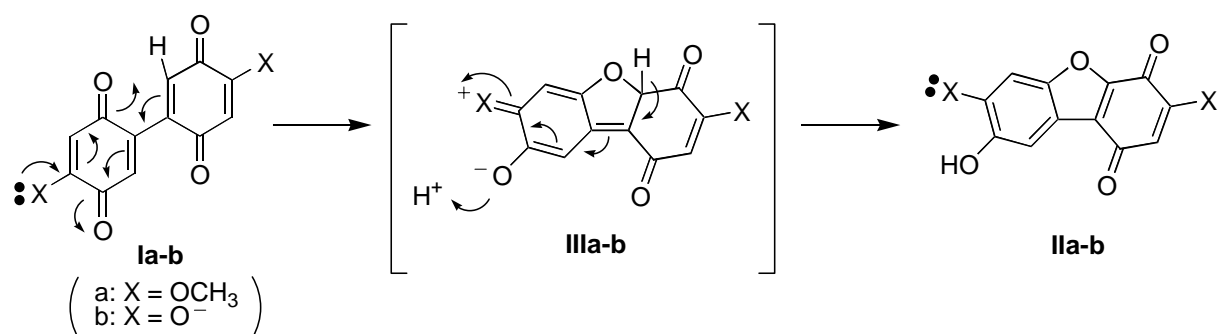
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Abstract – Reactivity of two isomeric quinone dimers, 5,5'-di-*tert*-butyl-2,2'-bisbenzoquinone (**2**) and 6,6'-di-*tert*-butyl-2,2'-bisbenzoquinone (**3**) have been compared. Both quinone dimers underwent thermal cyclization in ethanol to give dibenzofuran-1,4-diones exclusively, the reaction proceeding faster for **3** than for **2**. Molecular modeling analysis indicates that the different reactivity should be explained in terms of the steric hindrance of *tert*-butyl group in **2**, which prevents approaching of solvent molecules to C=O moiety so that the solvent-assisted proton transfer occurs more slowly.

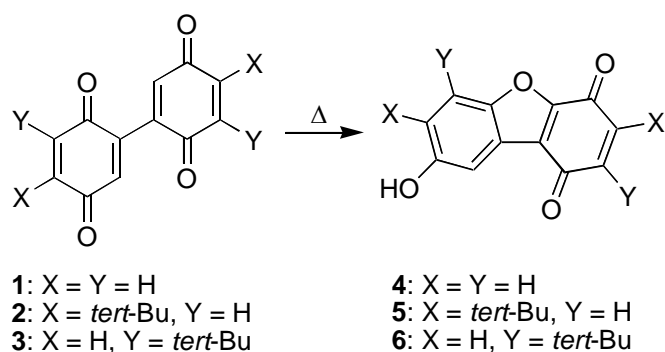
INTRODUCTION

Benzoquinone dimers (**I**) are known to undergo cyclization to give dibenzofuran-1,4-diones (**II**) either by thermally¹⁻⁴ or photochemically.^{5,6} Dibenzofuran-1,4-dione is an important structure, since it is a substructure of several natural compound including popolohuanone E, balsaminone A, and violet-quinone, which exhibit various biological and pharmaceutical activities.⁷ Comparing to other synthetic methods to obtain dibenzofuran-1,4-dione moieties,^{8,9} the cyclization of quinone dimer is advantageous because of its simplicity. This reaction was first reported by Erdtman¹: he found **Ia** gave **IIa** in a good yield, and proposed the reaction mechanism through a cation intermediate (**IIIa**) stabilized by a strong electron-donating methoxy group (Scheme 1). Recently, the essentially same explanation was adopted for the cyclization of **Ib**³ giving **IIb**.



Scheme 1

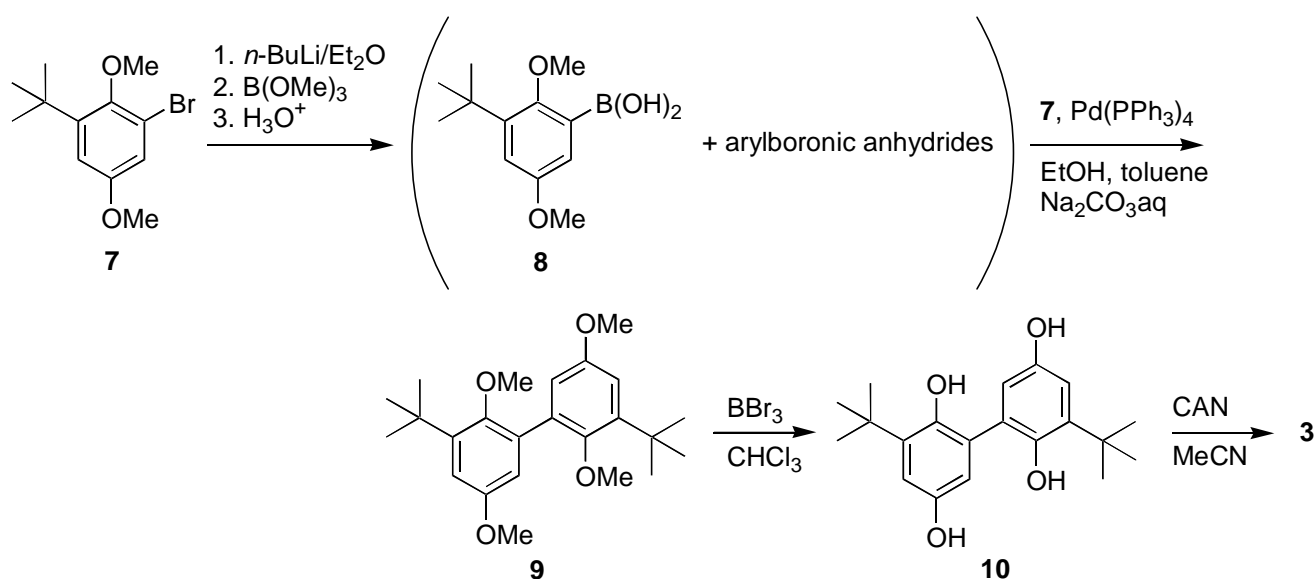
The presence of strong electron-donating group is not always essential in this type of reactions. In fact, non-substituted quinone dimer (**1**) is known to give dibenzofuran-1,4-dione (**4**). The reactivity was, however, so small that refluxing in nitrobenzene was required, probably because the reaction intermediate underwent no stabilization effect unlike **IIIa** and **IIIb**. Factors determining the reactivity in such cases have not yet been investigated. Therefore in the present study, the reactivity of 5,5'-di-*tert*-butyl-2,2'-bisbenzoquinone (**2**) and its structural isomer, 6,6'-di-*tert*-butyl-2,2'-bisbenzoquinone (**3**), which give dibenzofuran-1,4-diones **5** and **6**, respectively, were compared and influence of the position of *tert*-butyl substituents was investigated.



RESULTS AND DISCUSSION

2 was prepared according to the literature procedure.¹⁰ Although preparation of **3** by means of oxidative coupling was already known,⁸ **3** was synthesized in a similar manner to that of **2** in this study. 2-Bromo-6-*tert*-butyl-1,4-dimethoxybenzene (**7**) was converted to a mixture of boronic acid **8** and the arylboronic anhydrides. As the arylboronic anhydrides are known to serve as the boronic acid reagents, the unseparated boronic acid mixture was subjected to Suzuki-Miyaura coupling¹¹ with **7** to give **9**. **9** was demethylated by means of boron tribromide to give **10**, followed by oxidation using cerium (IV) ammonium nitrate (CAN) to yield **3** (Scheme 2).

When **2** was subjected to refluxing in ethanol, cyclization products **5** were obtained as a sole product (Table 1, entry 1). Under the same conditions, **3** gave **6** exclusively (entry 2). Considering that **1** gave a complex mixture by heating in ethanol,¹² *tert*-butyl groups of **2** and **3** can be regarded as protecting the



Scheme 2

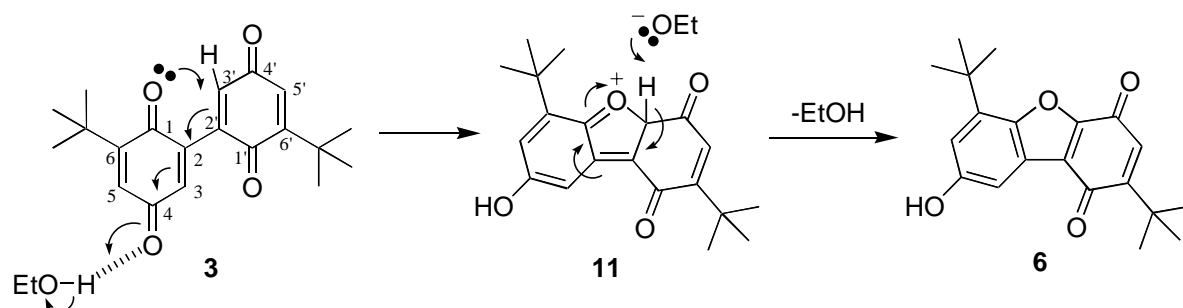
quinone moieties, probably, from nucleophilic attack of the solvent molecules. It is noted that, although the yields were comparable, the reaction time (which was defined as time until the substrate disappeared) of **2** (90 h) was about four times as long as that of **3** (27 h). The reactions in *tert*-butyl alcohol at the same temperature provided a striking contrast to those in ethanol. Whilst **3** yielded **6** similarly but more slowly and in lower yield, **2** gave only a trace amount of **5** as a sole distinguishable product after seven days refluxing (Table 1, entry 3 and 4).

Table 1. Results of thermal reactions of **2** and **3**.

entry	substrate	condition	additive	conversion	product (yield)
1	2	EtOH, reflux, 90 h	-	100%	5 (66%)
2	3	EtOH, reflux, 27 h	-	100%	6 (62%)
3	2	<i>t</i> -BuOH, reflux, 7 d	-	16%	5 (trace)
4	3	<i>t</i> -BuOH, reflux, 65 h	-	100%	6 (33%)
5	2	EtOH, reflux, 10 min	excess HCl	100%	complex mixture
6	3	EtOH, reflux, 10 min	excess HCl	100%	complex mixture
7	2	EtOH, 20 °C, 20 h	1 eq. <i>p</i> -TsOH	100%	complex mixture
8	3	EtOH, 20 °C, 20 h	1 eq. <i>p</i> -TsOH	100%	complex mixture

As depicted in Scheme 1, when the electron-donating group (X) is substituted on the quinone moiety, the reaction intermediate is stabilized, and the reaction will be accelerated. One might think that, as *tert*-butyl group is an electron-donating group, the similar electronic stabilization effect could be exerted in the reaction of **2** giving **5**. However, if it had been so, *tert*-butyl group at 5-position would accelerate the reaction more than that at 6-position would do; but actually **3** gave **6** more rapidly. This definitely indicates that influence of the *tert*-butyl group is not inductive but should be steric. It is considered that cyclization of **3** (and **2**, too) in alcoholic solution should proceed as depicted in Scheme 3: the oxygen

atom at 1-position attacks the 3'-position of the adjacent quinone moiety to give **6** through the intermediate **11**, during which the solvent molecule serves as a catalyst.



Scheme 3

The CPK models of **2** and **3** (Figure 1) clearly indicate that oxygen atom at 4-position is naked in **3**, thus the solvent-assisted cyclization can proceed efficiently. On the other hand, that of **2** is sterically hindered by the *tert*-butyl group at 5-position so that the solvent molecule would be difficult to participate in an cyclization. This explanation may be supported by the fact that **2** reacted much more slowly than **3** in *tert*-butyl alcohol. The larger difference in the reaction rate of **2** and **3** in *tert*-butyl alcohol should be ascribed to the more significant steric repulsion between the *tert*-butyl substituent and bulkier solvent molecules.

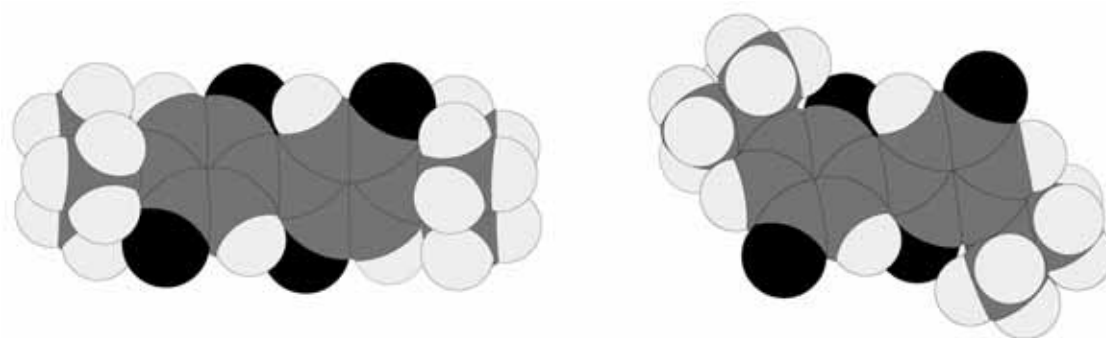
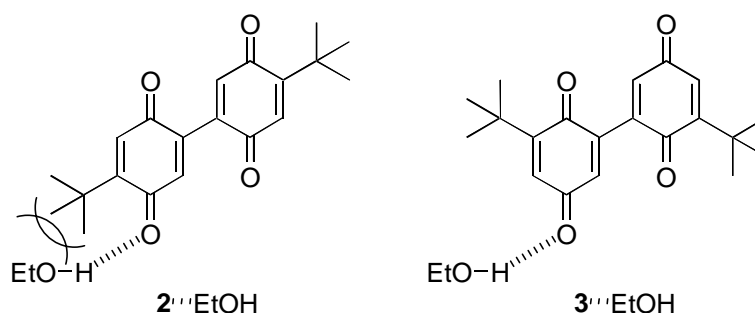


Figure 1. CPK models of **2** (left) and **3** (right). White, gray, and black spheres represent hydrogen, carbon, and oxygen atoms, respectively.

As it seemed likely that the reaction could be accelerated by acid catalyst according to the above mechanism (Scheme 3), the reactivity of **2** and **3** in the presence of either HCl (excess) or TsOH (1 eq) was examined. Contrary to the expectation, neither **5** nor **6** but complex mixtures were given in all cases (Table 1, entry 5-8). This may be due to replacement of the *tert*-butyl substituents, because the *tert*-butyl group on aromatic ring is facily replaced by acid catalyst, and quinone dimers bearing no substituents thus obtained (**1**) were reported to be considerably unstable in hot ethanol solution.^{10,12}

In conclusion, different reactivity of isomeric quinone dimers bearing *tert*-butyl groups (**2** and **3**) to afford dibenzofuran-1,4-diones (**5** and **6**, respectively) was described. The reaction rate of **3** was larger than that of **2** both in ethanol and *tert*-butyl alcohol, the results being explained in terms of steric effects of the



Scheme 4

tert-butyl group. Namely, the reaction is considered to proceed by a mechanism including solvent-assisted proton transfer, which is depressed by *tert*-butyl substituents to more extent in **2** than in **3**. The reaction, however, could not be accelerated by addition of acid catalyst, probably due to replacement of the *tert*-butyl substituents. The present results may provide a simple method to synthesize dibenzofuran-1,4-dione bearing no strong electron-donating groups and a useful information to understand the reaction mechanism.

EXPERIMENTAL

General. All commercially available chemicals were used without further purification except ether, which was dried over sodium. All reactions were performed in standard glassware under an inert argon atmosphere. Melting points were determined on microscopic thermometer without correction. ^1H and ^{13}C NMR spectra were recorded on a JEOL ECX-300/TRH (300 MHz for ^1H and 76 MHz for ^{13}C) with tetramethylsilane as internal reference. Mass spectra were conducted on a JEOL MStation JMS-700 (EI) and a JEOL JMS-SX102A (HRMS/EI). Infrared spectra were measured on a JASCO FT/IR-6100.

Synthesis of 3,3'-di-*tert*-butyl-2,2',5,5'-tetramethoxybiphenyl (9). To a solution of 2-bromo-6-*tert*-butyl-1,4-dimethoxybenzene (**7**) (4.08 g, 15 mmol) in dry Et_2O (120 mL) was dropwisely added *n*-butyllithium (1.6 M in *n*-hexane, 14.9 mL, 24 mmol) at -78°C . After stirring for 1 h at -78°C , trimethyl borate (3.35 mL, 30 mmol) was slowly added. The resulting mixture was stirred for additional 1 h, while the temperature was held at -78°C , then the reaction mixture was allowed to warm to ambient temperature. The reaction was quenched by dilute hydrochloric acid and extracted with Et_2O . Combined organic extracts were washed with brine, dried over MgSO_4 , and evaporated to dryness. The crude product was washed with hexane to give a mixture of **8** and the arylboronic anhydrides as a white solid (3.26 g).

A bi-layer solution of **7** (2.02 g, 7.4 mmol) and the above mixture (2.19 g) in toluene (60 mL), EtOH (20 mL) and 1 mol L^{-1} aqueous Na_2CO_3 (40 mL) was degassed with argon. After tetrakis-(triphenylphosphine)palladium (0.44 g, 0.38 mmol) was added, the reaction mixture was refluxed for

overnight. After cooling, organic layer was separated, and aqueous layer was extracted with CHCl_3 . Combined organic phase was washed with brine, dried over MgSO_4 , and evaporated to dryness. From the crude product, **9** (2.23 g, 78%) was isolated by preparative chromatography (SiO_2 , *n*-hexane/EtOAc 8:2) as a colorless oil.

^1H NMR (CDCl_3): δ = 6.89 (2H, d, J = 3.0 Hz, Ar), 6.83 (2H, d, J = 3.0 Hz, Ar), 3.77 (6H, s, OCH_3), 3.30 (6H, s, OCH_3), 1.41 (18H, s, *tert*-Bu). ^{13}C NMR (CDCl_3): δ = 154.35, 151.24, 144.14, 133.10, 113.29, 113.13, 59.86, 55.56, 35.31, 30.57. MS: m/z = 387 ($[\text{M}+1]^+$). HRMS (m/z): 386.2457 (M^+ , calcd. 386.2455 for $\text{C}_{24}\text{H}_{34}\text{O}_4$).

Synthesis of 3,3'-di-*tert*-butyl-2,2',5,5'-tetrahydroxybiphenyl (10). To a solution of **9** (0.20 g, 0.53 mmol) in CHCl_3 (25 mL) was dropwised boron tribromide (0.20 mL, 2.1 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was quenched with MeOH then water, and organic was extracted into Et_2O . The solution was washed with water and brine, dried, and the solvent was removed under vacuum leaving **10** (0.16 g, 91%) as a white solid

Mp 83-84 °C (lit.,¹³ 240-241 °C from benzene-light petroleum). ^1H NMR (CDCl_3): δ = 6.87 (2H, d, J = 3.1 Hz, Ar), 6.56 (2H, d, J = 3.1 Hz, Ar), 5.01 (2H, s, OH), 4.48 (2H, s, OH), 1.41 (18H, s, *tert*-Bu). ^{13}C NMR (CDCl_3): δ = 148.93, 145.84, 139.10, 123.35, 115.39, 114.27, 35.10, 29.49. IR (Nujol): ν (cm^{-1}) 3539 (OH), 3308 (OH). MS: m/z = 330 (M^+). HRMS (m/z): 330.1831 (M^+ , calcd. 330.1828 for $\text{C}_{20}\text{H}_{26}\text{O}_4$).

Synthesis of 6,6'-di-*tert*-butyl-2,2'-bis-*p*-benzoquinone (3). To a solution of **10** (1.20 g, 3.6 mmol) in MeCN (110 mL) was added a solution of cerium ammonium nitrite (CAN, 7.99 g, 15 mmol) in minimum amount of water at ambient temperature. After stirring for 3 h, the reaction mixture was quenched with water (100 mL). The precipitate was separated by suction filtration, washed with acetone-water, and evaporated to yield **3** (0.95 g, 80%) as brownish orange crystals.

Mp 156-157 °C (lit.,¹³ 160-161 °C).

A typical procedure of quinone dimer to give dibenzofuran-1,4-dione. A solution of **2** (20 mg, 0.061 mmol) in EtOH (10 mL) was refluxed for 90 h, at which disappearance of **2** was confirmed by TLC. After cooling, the solvent was evaporated. The reaction mixture was chromatographed (SiO_2 , *n*-hexane/EtOAc 9:1) to isolate 3,7-di-*tert*-butyl-8-hydroxydibenzofuran-1,4-dione **5** (13 mg, 66%) as a white solid.

5: Mp 252-254 °C. ^1H NMR (CDCl_3): δ = 8.93 (1H, s, OH), 7.61 (1H, s, Ar), 7.47 (1H, s, Ar), 6.65 (1H, s, C=CH), 1.49 (9H, s, *tert*-Bu), 1.38 (9H, s, *tert*-Bu). ^{13}C NMR (CDCl_3): δ = 184.62, 177.81, 170.80, 155.97, 155.62, 154.04, 151.99, 141.27, 132.75, 121.07, 111.20, 107.65, 36.30, 36.03, 29.24, 28.93. IR

(KBr): ν (cm^{-1}) 3370 (OH), 1650 (C=O). MS: $m/z = 326$ (M^+). HRMS (m/z): 326.1516 (M^+ , calcd. 326.1519 for $\text{C}_{20}\text{H}_{22}\text{O}_4$).

The cyclization product from **3** was identified as 2,6-di-*tert*-butyl-8-hydroxydibenzofuran-1,4-dione **6** by comparison of ^1H NMR (CDCl_3) and IR (KBr) data to those in ref 5a. **6**: ^{13}C NMR (CDCl_3): $\delta = 185.05, 177.09, 171.01, 157.20, 156.73, 152.05, 149.91, 138.10, 125.12, 123.60, 116.41, 104.89, 36.06, 35.00, 29.98, 29.03$

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