

The Reactivity and Stability Studies of Benzoquinone Methides by *Ab Initio* Calculations

Woonphil Baik,^{*} Shin Jong Kim, Eun-young Hurh, Sangho Koo, and Byeong Hyo Kim[†]

^{*}Department of Chemistry, Myong Ji University, Yong In, Kyung Ki Do 449-728, Korea

[†]Department of Chemistry, Kwangwoon University, Seoul 139-701, Korea

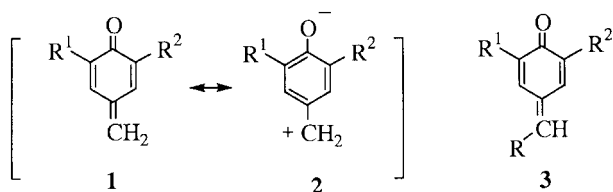
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The conformations of symmetrically hindered benzoquinone methides (=BMs), unsymmetrically hindered BMs, and simple BM have been optimized using density functional theories. It is shown that the optimized geometries of symmetrically hindered BMs are fully in accord with those expected for the planar conformations, in which the effective hyperconjugation of symmetrically substituted dialky groups with ring can occur. Relative stabilization energies calculated at the B3LYP/6-31G**//B3LYP/6-31G* level by means of isodesmic equation are 2.8-5.3 kcal/mol enhanced for symmetrically hindered BMs. This finding provides a rationalization for the previous experimental results that the BM formation is depend upon the substituents.

Keywords : Benzoquinone methide, *Ab initio*, B3LYP.

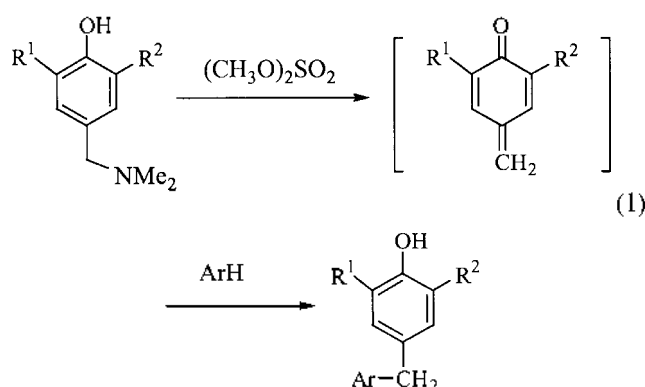
Introduction

A study of the reactive benzoquinone methides has been received a great attention since these intermediates were known to be involved in the oxidation of phenols¹ and in the biosynthesis of neolignans.² The benzoquinone methide **1** without a substituent on the methide part is highly reactive and only exists transiently in dilute solution. Therefore, it is usual that they can not be isolated, although they may be detectable by spectroscopy.³ The benzoquinone methide **1** can be explained by another resonance structure **2** with the dipolar character which shows the electrophilic property on the methine terminus. The application of these highly reactive intermediates for the reactions with a wide variety of nucleophiles is limited by the stability and the methods for its generation.⁴ The double bond and electrophilic characters of the exocyclic alkylidene carbon have been exploited both in the typical Diels-Alder reactions with dienes⁴ and in the 1,6-additions with nucleophiles,⁵ such as phosphites,^{5a} phosphines,^{5b} amines,^{5c} hydride, or phenoxides,^{5d} due to the additional driving force of aromatization after the conjugated addition. On the other hand, benzoquinone methides with substituents on the terminal methylene (structure **3**) are isolable and intramolecular electrophilic substitution reactions have been well studied by Angle and co-workers.⁶

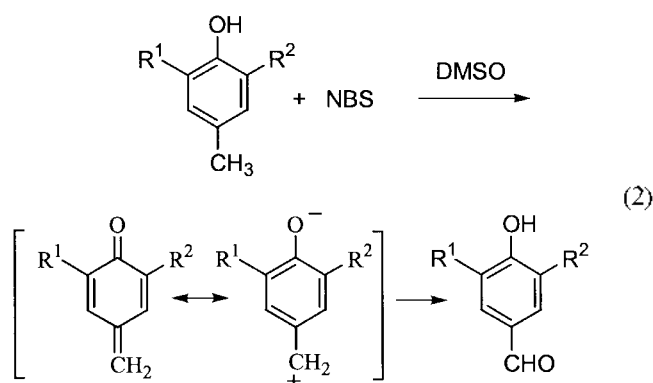


As we reported in a previous paper,⁷ the intermolecular electrophilic aromatic substitution with a symmetrical 2,6-di-*tert*-butylbenzoquinone methide generated *in situ* from the thermal decompose of Mannich base-(MeO)₂SO₂ is

smoothly occurred (eq. 1) and the formation of symmetrical benzoquinone methide is monitored with GC-MSD.⁷



However, the unsymmetrical benzoquinone methides under same reaction condition are not observed. In particular, supporting experimental evidence is the observation of the rate enhancements in the intermolecular electrophilic aromatic substitution with a symmetrical 2,6-dialkybenzoquinone methide in the order of di-*tert*-butyl, diisobutyl, and dimethyl. Our interest in the reactions of benzoquinone methides **1** has been promoted to examine various reactions for the *in situ* preparation and the electrophilic addition. In particular, we have been interested in the trapping of the conjugated methine part of **1** by the oxygen nucleophile of DMSO. It has been also known that only symmetrically hindered 2,6-dialky-4-methylphenols react smoothly with NBS to form symmetrically hindered dialkylbenzoquinone methides (BMs), which can be further processed to give hydroxybenzaldehydes in the presence of DMSO as shown in eq. 2.⁸ This reaction is initiated by the formation of phenoxy radical, followed by disproportionation to afford BMs. The application of the NBS-DMSO oxidation to other symmetrically hindered *p*-methylphenols provided their *p*-formylphenols in over 83% yields.



However, either unsymmetrically substituted or simple *p*-methylphenols underwent nuclear bromination on the ortho position of *p*-methylphenols. Only trace amounts of hydroxybenzaldehyde were observed.

Although our experimental results^{7,8} for the symmetrically hindered benzoquinone methides show the unusual stability, questions can be raised in terms of the nature of the conformation with symmetrically substituted dialkyl groups and their relative stabilization energies.

Results and Discussion

The *in situ* formation of benzoquinone methide was very sensitive to the electronic effect of the corresponding phenols, thus the conformational studies and stabilities of

benzoquinone methides, **1a** ($R^1, R^2 = t\text{-Bu}$), **1b** ($R^1, R^2 = \text{Me}$), **1c** ($R^1 = t\text{-Bu}, R^2 = \text{H}$), and **1d** ($R^1, R^2 = \text{H}$) were calculated using the density functional (DFT) geometry optimizations at the Becke 3-Lee-Yang-Parr (B3LYP) DFT levels.⁹ It is known that the density functional methods, and B3LYP in particular, can provide more reliable geometry optimizations and energies than the Hartree-Fock calculation.¹⁰ The structures of **1a**, **1b**, and **1c** are shown in Figure 1 and parameters are summarized in Table 1. It is clear from these data that the conformation of all benzoquinone methides examined are planar. Recent studies by NMR^{11a} and Raman^{11b} support a planar conformation of 1,4-cyclohexadiene as do *ab initio*.^{11c} Since benzoquinone methide has two additional exocyclic sp^2 bonds on the conjugate position of 1,4-cyclohexadiene part, it should have a greater tendency toward planarity. Two methyl groups in the *tert*-butyl substituent in **1a** have adapted a conformation close to the bisected geometry with both CC double bond and carbonyl group and the central C atom in *tert*-butyl groups lies in a coplanar, as shown the side-view of **1a** in Figure 1. The dihedral angles made between the plane defined by the ring and the plane defined by the central C atom in *tert*-butyl group to C atom in methyl group are $+60.6^\circ$ ($\varphi_{2,4,7,14}$) and -60.5° ($\varphi_{2,4,7,13}$). These two methyl groups clearly lean toward the carbonyl group.

In addition, the *tert*-butyl group bond distances in **1a** (C3-C8=C4-C7=1.538 Å) is 0.011 shorter than that found in 2,6-di-*tert*-butyl-4-methylphenol, meanwhile the bond distances of the bisected two methyl groups (C8-C15=1.550 Å) are

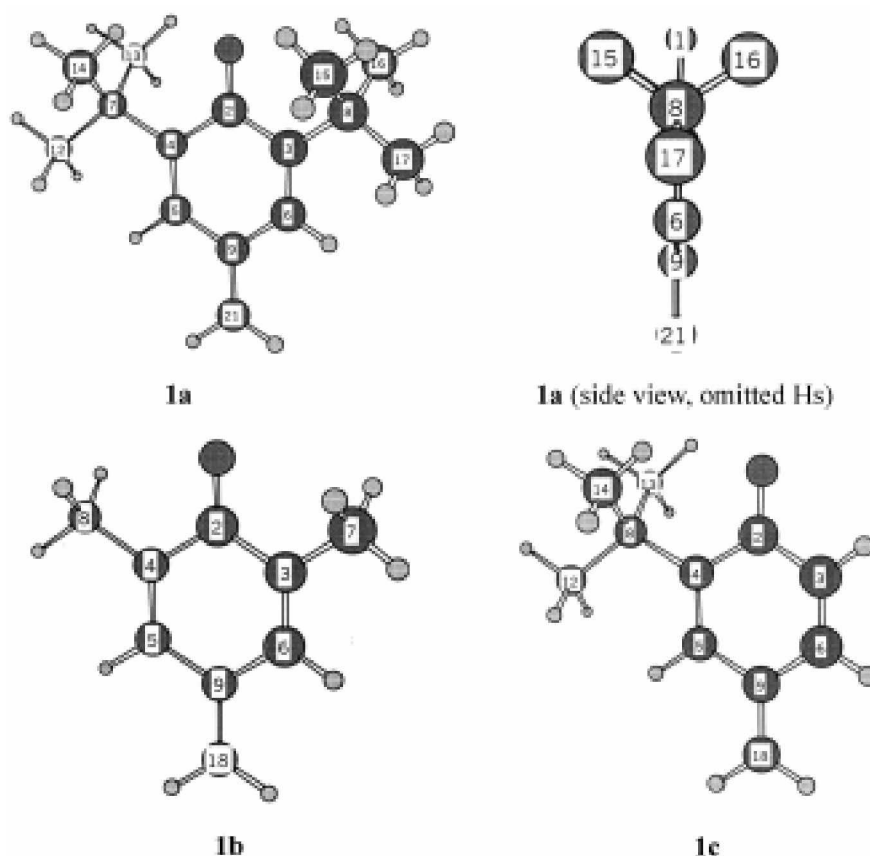


Figure 1. Calculated geometries of **1a**, **1b** and **1c** at the B3LYP/6-31G* level.

Table 1. Dipole moments and selected Bond Lengths and Angles for **1a**, **1b**, **1c**, and **1d**^a

BQ	Dipole Moment	Length (Å)						Angle (deg)
1a	3.21 D	C2=O	1.235	C4=C5	1.353	C9=C21	1.354	C3,C2,C4=119.22
		C2-C4	1.500	C4-C7	1.538			C2,C4,C5=118.36
1b	3.43 D	C2=O	1.233	C4=C5	1.352	C9=C18	1.353	C3,C2,C4=118.31
		C2-C4	1.486	C4-C8	1.520			C2,C4,C5=119.66
1c	3.79 D	C2=O	1.233	C4=C5	1.356	C9=C18	1.352	C3,C2,C4=117.60
		C2-C3	1.479	C3=C6	1.346			C2,C4,C5=117.73
		C2-C4	1.498	C4-C8	1.536			C2,C3,C6=122.54
1d	4.44 D	C2=O	1.230	C4=C5	1.348	C9=C18	1.352	C3,C2,C4=116.15
		C2-C4	1.479					C2,C4,C5=121.63

^aOptimized geometries of the individual species calculated at the B3LYP/6-31G**/B3LYP/6-31G* level.

Table 2. The stabilization energies of benzoquinone methides calculated at the B3LYP/6-31G**/B3LYP/6-31G* level^a

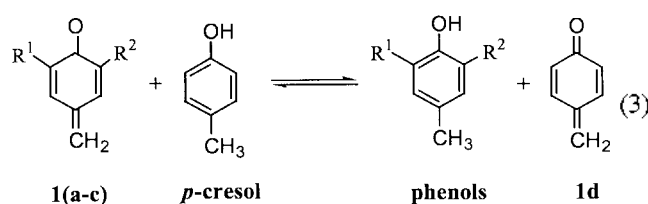
1 (R ¹ , R ²)	BM	<i>p</i> -cresol	phenol	1d	SE ^b (kcal/mol)
1a , (<i>t</i> -Bu, <i>t</i> -Bu)	-660.052585	-346.776027	-661.279322	-345.539585	+6.09
1b , (Me, Me)	-424.182408	-346.776027	-425.413180	-345.539585	+3.56
1c , (<i>t</i> -Bu, H)	-502.796942	-346.776027	-504.032136	-345.539585	+0.78
1d , (H, H)	-345.539585	-346.776027	-346.776027	-345.539585	0

^aEnergies in hartrees were uncorrected for zero-point energy. ^bThe stabilization energy SE=E_{phenol} + E_{1d} - E_{BM} - E_{cresol} in kcal/mol.

elongated by 0.002 Å. This optimized geometry gives a demonstration of the stable conformation for the effective conjugation of *tert*-butyl group with adjacent CC double bond and carbonyl group.

While mono *tert*-butyl substituted benzoquinone methide **1c** does have a conjugation effect, however, the cyclohexadiene ring is not symmetrical. It can be seen that the two central CC double bonds (C3-C6 and C4-C5) of the symmetrical benzoquinone methides have the same bond lengths, 1.354 Å for **1a**, 1.352 Å for **1b**, and 1.348 Å for **1d**, however, in the case of unsymmetrically hindered benzoquinone methide **1c**, the one double bond substituted by *t*-Bu group (C4-C5=1.356 Å) is elongated by 0.010 Å comparing to the other double bond (C3-C6=1.346 Å). The similar trend for the C-C single bonds of ring in **1c** is displayed, C2-C4=1.498 Å and C2-C3=1.479 Å. Thus, overall the ring is not symmetrical. It is of importance to compare the optimized geometry found for the 1,4-cyclohexadiene at the same B3LYP/6-31G* level: the two double bonds have the same distance 1.334 Å and the four single bonds are 1.507 Å each. Comparisons with the analogous bond lengths for **1a**, **1b**, **1c**, **1d** and cyclohexadiene demonstrate that the bond distance of CC double bond is elongated by additional exocyclic double bonds and alkyl substituents. These changes are resulted from the effective conjugation of the additional exocyclic double bonds and the bisected alkyl substituents.

In order to obtain more reliable estimates for the enhanced stabilities of the symmetrically hindered benzoquinone methides, we compared the relative stabilities at the B3LYP/6-31G* levels by means of isodesmic equations¹⁰ such as that illustrated in eq 3 and parameters are summarized in Table 2.



The stabilization energies for **1a**, **1b**, **1c** and **1d** are +6.09, +3.56, +0.78, and 0 kcal/mol, respectively. Even though one *tert*-butyl group in **1c** has the conjugation effect, the energy of **1c** is 2.78 kcal/mol lower than that of dimethylbenzoquinone methide **1b**. The higher stabilization energies for symmetrically hindered benzoquinone methides, **1a** and **1b**, comparing to **1c** and **1d** are capable of explaining the conjugation effects: in particular, in the case of di-*tert*-butylbenzoquinone methide **1a** displays the symmetrically bisected geometry without distortion, thus it gives unusual higher stabilization energy. The relatively low stabilization energies for **1c** and **1d** are consistent with the experimental results that the halogenation reaction with NBS is predominant over the formation of benzoquinone methide.

Summary

In addition, the *ab initio* calculations show that the relative stabilization energies and optimized conformations of the symmetrically hindered benzoquinone methides account for the stability. The major effect of stability is the conjugation of substituents with double bonds located in the bisected conformation. The reasonable agreement between the theoretical calculation and experimental results indicates that the symmetrically hindered benzoquinone methide could be a

good intermediate as an electrophile or a dienophile.

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