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Sterically encumbered regioselective cycloaddition of a calixarene derived bis(spirodienone) with 1,2-benzoquinones

R. Luxmi Varma,[a,*] V. B. Ganga,[a] E. Suresh[c] and C. H. Suresh[b,*]

[a]*Organic Chemistry Section, Chemical Sciences Division, Regional Research Laboratory (CSIR), Trivandrum 695 019, India*
[b]*Computer Simulation and Modelling Section, Regional Research Laboratory (CSIR), Trivandrum 695 019, India*
[c]*Analytical Science Discipline, Central Salt and Marine Chemicals Research Institute, Bhavnagar 364 002, India*

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Abstract—A calix[4]arene derived bis(spirodienone) acts as the 2π component in a cycloaddition reaction with two molecules of 3,5-di-*tert*-butyl-1,2-benzoquinone in the [2+4] manner leading to macrocycles with a benzodioxin moiety. A theoretical rationalization of the results suggested a sterically encumbered regioselective pathway, which gives sterically crowded products.
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Calix[*n*]arenes[1] are versatile building blocks made up of '*n*' phenol and formaldehyde units. The literature is abundant with numerous examples of functionalized calixarenes with a myriad of applications ranging from molecule/ion recognition to supramolecular chemistry.[2] Many reactions have utilized upper/lower rim modification for the synthesis of new functionalized calixarenes.[3] Biali and co-workers[4] have discovered another interesting series of molecules namely 'bis(spirodienones)' **1a**, **1b** and **1c** prepared by the intramolecular oxidative cyclization through the phenolic hydroxyls of calix[4]arene (Fig. 1). The presence of two carbonyl groups and two ether oxygens in a 14-membered ring system makes these potential candidates as ionophores. However, the synthetic potential of these molecules for the design of new macrostructures based on their structural features viz. the presence of two cyclohexadienone rings attached to five-membered cyclic ether rings through a spirocentre remains mostly uninvestigated.

Our own investigations have shown that the bis(spirodienone) **1a** is an excellent 4π component in cycloaddition with acetylenes yielding bis-bicyclo[2.2.2]octenone derivatives in a highly regio- and stereo-selective manner.[5] As part of our continued interest in the design of calixarene-based novel structural frameworks, we undertook an investigation of the reaction of the bis(spirodienones) with 1,2-benzoquinones. 1,2-Benzoquinones are unique conjugated 1,2-diones that can elicit diverse modes of cycloaddition by acting as carbodienes, heterodienes, dienophiles, or heterodienophiles.[6] In this letter, we report the formation of new bis(spiroenone)

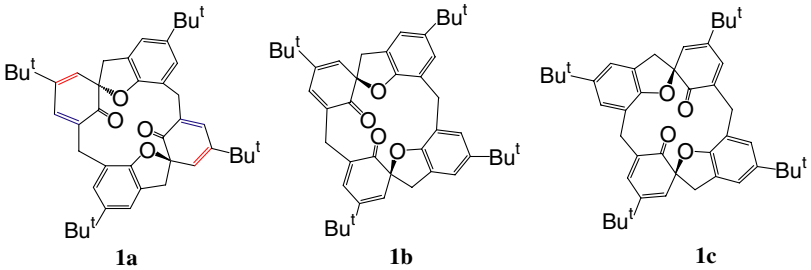

Figure 1. Three isomers of bis(spirodienones).

* Corresponding authors. Tel.: +91 4712515275; fax: +91 4712491712; e-mail: lux_varma@rediffmail.com

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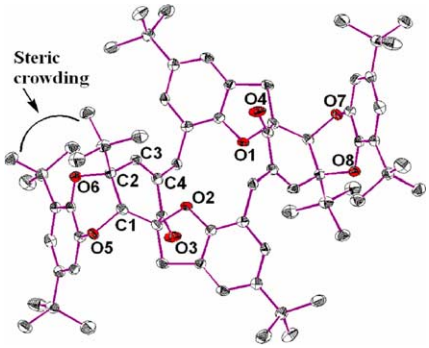


Figure 2. X-ray structure of compound **3a**. Hydrogen atoms are omitted for clarity. Steric crowding give a longer O6–C2 bond (1.478 Å) as compared to O5–C1 bond (1.435 Å).

macrocycles with benzodioxin moieties and a theoretical rationalization for the formation of the sterically crowded products.

The bis(spirodienone) **1a**, being the most stable isomer, was chosen as the substrate and we initiated our study by heating **1a** under reflux with 3,5-di-*tert*-butyl-1,2-benzoquinone (**2a**) in dry toluene. The yellow solution gradually turned colourless over a period of 12 h. A standard work-up and column chromatography over silica gel provided a single cycloadduct in 88% yield.[7]

A structural elucidation of the product by spectroscopic methods revealed it to be **3a**. The X-ray structure[8] of **3a** (Fig. 2) suggests that the benzoquinone **2a** has acted as the heterodiene (4π) and the double bond shown in red in **1a** as the dienophile (2π).

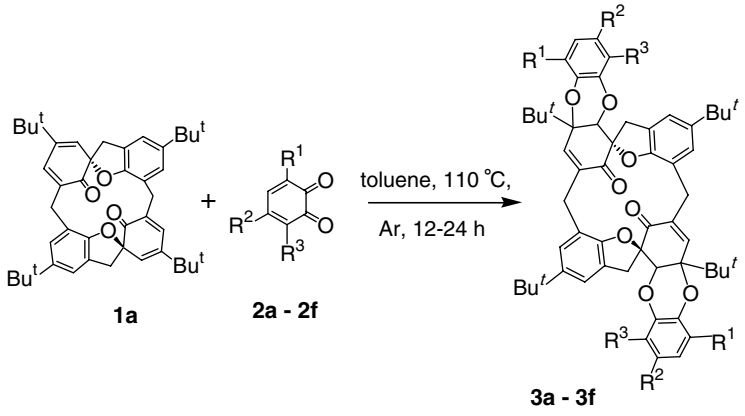
In order to prove the generality of the reaction, the cycloaddition of **1a** with a series of 1,2-benzoquinones was investigated (Scheme 1) and the results are summarized in Table 1. In all these cases, only one single cycloadduct was detected. It is evident from Table 1 that the bis(spirodienone) **1a** can act as an efficient 2π component in its cycloaddition reactions with 1,2-benzoquinones. The reaction afforded novel macrocycles with benzodioxin moieties. To the best of our knowledge, this is the first report on the synthesis of a macrocyclic system possessing benzodioxin moieties based on the calixarene framework.

Table 1. [2+4] Cycloaddition of bis(spirodienone) with 1,2-benzoquinones

Entry	1,2-Benzoquinones (**2a–f**)	Time (h)	Product	Yield (%)
1	$R^1 = R^2 = {}^t$Bu, $R^3 = H$	12	**3a**	88
2	$R^1 = R^2 = {}^t$Bu, $R^3 = OMe$	24	**3b**	62
3	$R^1 = CH(Ph)_2$, $R^2 = {}^t$Bu, $R^3 = H$	24	**3c**	40
4	$R^1 = R^2 = CH(Ph)_2$, $R^3 = H$	24	**3d**	59
5	$R^1 = H$, $R^2 = {}^t$Bu, $R^3 = OMe$	18	**3e**	63
6	$R^1 = R^3 = H$, $R^2 = {}^t$Bu	18	**3f**	76

According to the X-ray structure of **1a** reported by Biali et al.[4c] the double bond shown in blue is shorter (1.319 Å) than the red one (1.340 Å), and therefore the blue double bond is expected to be more electron rich than the red double bond (Fig. 1). The X-ray structure of **3a** suggests that the addition occurred selectively at the longer red double bond. This means that even for a 1,2-benzoquinone with bulky R^1 group, the cycloaddition product is formed in such a way that the position of R^1 comes close to the ^{t}Bu group of the bis(spirodienone) moiety (Fig. 2). The steric crowding around O6 was reflected in the O6–C2 and O5–C1 bonds where the former (1.478 Å) is 0.043 Å longer than the latter (1.435 Å). This steric crowding would have been avoided if O5 had added to C2 and O6 had added to C1. These observations suggest high steric control in the cycloaddition between **1a** and 1,2-benzoquinone **2a**.

In order to understand these intriguing steric aspects and the mechanism of the reaction, theoretical modelling[9] was carried out and we chose the formation of **3a** as the example for the modelling study. For this, semi-empirical AM1 and B3LYP/6-31G* level[10] density functional theory (DFT) methods have been used as implemented in the Gaussian03 suite of programs.[11] At first, the [2+4] cycloaddition reaction shown in Figure 3 was modelled at the B3LYP/6-31G* level, where the systems are the unsubstituted bis(spirodienone) acting as the dienophile and the 1,2-benzoquinone acting as



Scheme 1. Reaction of bis(spirodienone) **1a** and 1,2-benzoquinones.

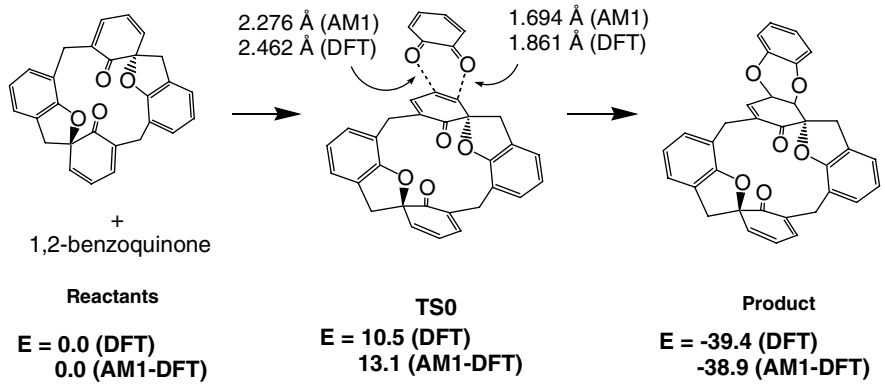


Figure 3. The model reaction with unsubstituted systems. Relative energies in kcal/mol. DFT and AM1-DFT represent the full DFT and the AM1-optimized DFT single point calculations, respectively.

a diene. The activation barrier (E) using transition state (TS) **TS0** (Fig. 3) at the DFT level is only 10.5 kcal/mol. The original systems with several bulky ^{t}Bu groups are too big to optimize at the DFT level. Therefore, the larger systems were optimized by the AM1 method and the energetics were calculated at the B3LYP/6-31G* level

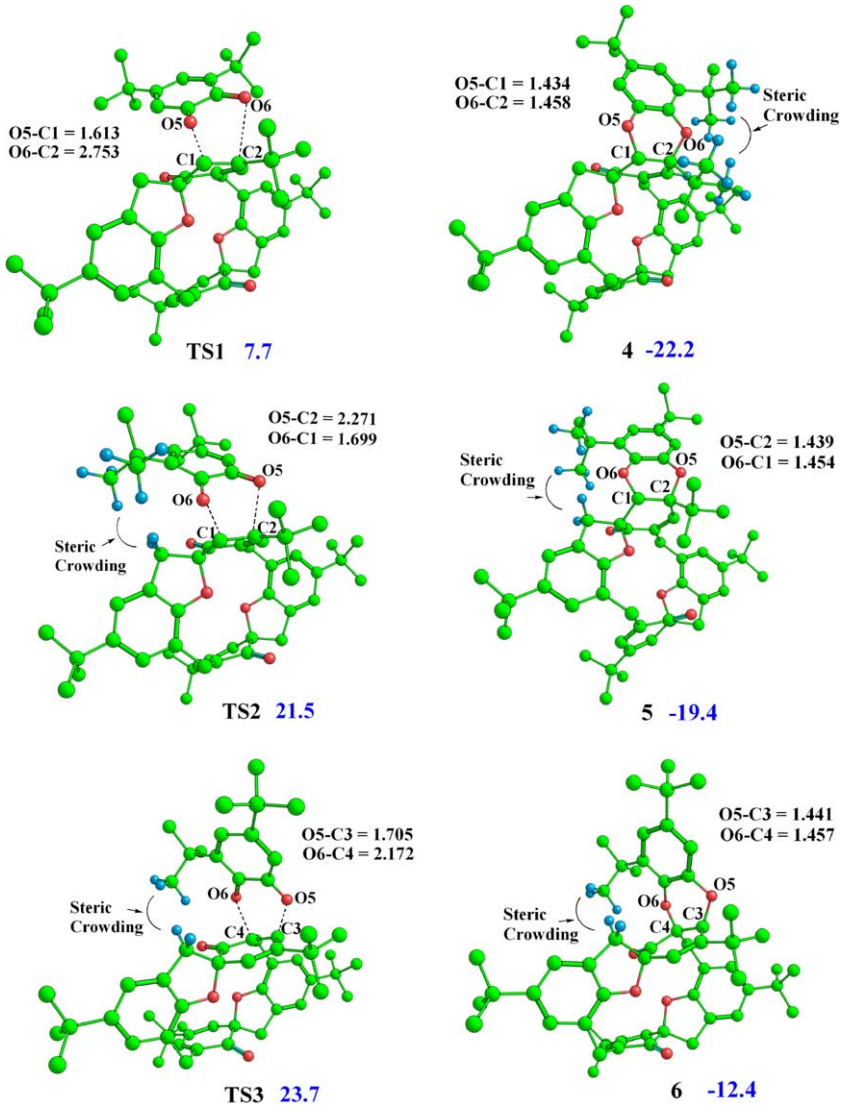


Figure 4. Various modes of cycloaddition of the bis(spirodienone) and 1,2-benzoquinone obtained at the AM1 level. The energetics are based on B3LYP/6-31G* single point energies and relative with respect to (**1a**+**2a**). Some hydrogen atoms are omitted for clarity.

using AM1 level geometries. This AM1-DFT approach to energetics is found to be reasonable because the reaction in Figure 3 modelled in this manner showed good agreement with the full DFT level calculations.

In Figure 4, **TS1** corresponds to the transition state for the cycloaddition of **2a** across the double bond shown in red in **1a**. This TS gives the product **4** in which the O5–C1 and O6–C2 bonds are formed. On the other hand, **TS2** gives the second possible cycloaddition product **5** in which the O5–C2 and O6–C1 bonds are formed. A transition state **TS3** is also located, which corresponds to the cycloaddition of **2a** across the double bond shown in blue in **1a**. The corresponding product is **6**.

Among the transition states **TS1**, **TS2** and **TS3**, **TS1** is the most stable. In this transition state, the O5–C1 distance of 1.613 Å suggests a strong interaction, while the O6–C2 distance of 2.753 Å suggests only a negligible interaction between the corresponding atoms. However, in both **TS2** and **TS3**, the O5 and O6 atoms show significant interaction with the carbon atoms. In **TS1**, the O5–C1 interaction is highly favoured because it has sterically the least crowded region around O5 meaning that the sterically less crowded O5 prefers to attack the sterically less crowded C1. Although, the O5–C1 interaction is highly favoured, the O6–C2 interaction is very weak in **TS1** because of the presence of the bulky ^{t}Bu group on the *ortho* position of O6–C and another ^{t}Bu group on C2. Therefore, we can conclude that the formation of the O5–C1 bond forces the formation of the O6–C2 bond in the sterically crowded region of the system. This is an interesting scenario because the steric control of the reaction yields a sterically crowded product.

The formation of **5** and **6** can be excluded because **TS2** and **TS3** need a higher *E* than **TS1**. In the case of **TS2**, the steric crowding around O6 is the main reason for its high energy. As mentioned earlier, product **6** is the result of the cycloaddition of 1,2-benzoquinone on to the double bond shown in blue in **1a**. Such an addition would leave an isolated C=O bond and another isolated C=C bond (C1–C2 bond) in **6**. This situation is thermodynamically less favoured than that of **4** or **5** where the C–O and C1–C2 double bonds are in conjugation. Therefore, this electronic factor can be attributed as the main reason for the high energy for both **TS3** and **6**. To some extent the steric factor as shown in **TS3** also disfavours this reaction.

The theoretical calculation thus supports the cycloaddition pattern of (**1a**+**2a**)→**TS1**→**4**. This can be called a sterically encumbered cycloaddition because in the TS, we see the preferential attack of O5–C1. In other words, the reaction is more like a stepwise reaction rather than a typical concerted cycloaddition reaction. At first, the sterically less crowded O5 and C1 react and that forces the subsequent reaction at the sterically crowded O6 and C2.

Once **4** is formed, a similar reaction of another molecule of **2a** on the second cyclohexadienone moiety of **4** would give the product **3a** (Fig. 2). In terms of the steric influence, the benzoquinones **2c** and **2d** (Table 1) are very similar to **2a**, and therefore we expect that **3c** and **3d** will follow the same regiochemistry as that of **3a**. In the examples given in Table 1, **2b** is the most substituted benzoquinone, and even though OMe is sterically less bulky than ^{t}Bu, steric control of the reaction is expected to give a sterically crowded ^{t}Bu region in **3b** (cf. Fig. 2 and compound **4** in Fig. 4). Since the substituents R^1 and R^3 are not bulky, no significant steric effect is present in the reactions 5 and 6 depicted in Table 1. However, these reactions also supported the heterodiene character of benzoquinone **2a**.

In summary, we have unraveled the unique scenario of the sterically controlled regioselective cycloaddition profile of bis(spirodienone) **1a** with 1,2-benzoquinone giving rise to sterically crowded macrocyclic products. Moreover this is the first report of a bis(spirodienone) acting as a 2π component in cycloaddition reactions. Further functionalizations of these products are underway.

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7. Typical experimental procedure: A solution of **1a** (50 mg, 0.078 mmol) and 3,5-di-*tert*-butyl 1,2-benzoquinone (32.9 mg, 0.1629 mmol) in dry toluene (5 ml) was refluxed under an inert atmosphere. The reaction mixture was stirred at this temperature until the reaction was complete as indicated by TLC (12 h). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–ethyl acetate (99:1) as the eluent to yield **3a** (70 mg, 88%). The product was recrystallized from dichloromethane–acetonitrile mixture. IR (KBr) ν_{max}: 2961, 1698, 1593, 1488, 1416, 1364, 1292, 1239, 1191, 1077, 995, 852 cm^{-1}. ^1H NMR: δ 7.22 (s, 2H), 6.90 (s, 2H), 6.81 (s, 2H), 6.71 (s, 2H), 6.11 (s, 2H), 4.68 (s, 2H), 4.02 (d, 2H, $J = 16.6$ Hz), 3.67 (d, 2H, $J = 16.2$ Hz), 3.46 (d, 2H, $J = 16.0$ Hz), 2.72 (d, 2H, $J = 15.4$ Hz), 1.35 (s, 18H), 1.31 (s, 18H), 1.26 (s, 18H), 0.95 (s, 18H). ^{13}C NMR: δ 188.7, 152.3, 145.0, 144.9, 141.3, 140.8, 139.9, 138.7, 126.6, 125.8, 117.5, 112.8, 89.5, 82.2, 79.0, 77.1, 38.2, 34.4, 34.3, 31.7, 31.4, 30.7, 29.8, 24.8. Mass spectrometric analysis (FAB) calculated for $C_{72}H_{92}O_8$+H: 1085.68. Found: 1085.33.
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11. All calculations were carried out using the Gaussian 03 program (Frisch, M. J. et al. Gaussian 03, Revision C.02, Gaussian, Wallingford, CT, 2004).