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Synthesis of novel heterocyclic calixarenes *via* the Diels-Alder reaction of calix[4]bis(spirodienones)

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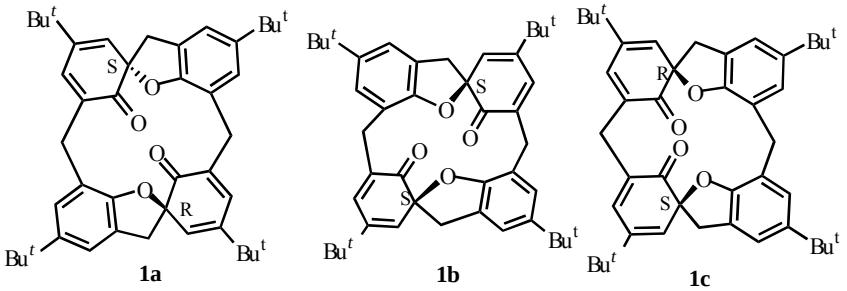
The reactivity of calix[4]bis(spirodienones) depends on the nature of the dienophile used. With 1,4-benzoquinones it acts as a 4π component whereas with 1,2-benzoquinones as a 2π system, yielding benzodioxin derived macrocycles in good yield. Bis(spirodienones) can thus perform as a diene as well as a dienophile in cycloaddition reactions.

Keywords: Calix[4]bis(spirodienone), benzodioxin derived macrocycle

Calix[n]arenes[1] are synthetic macrocycles obtained by the base catalysed condensation of *p*–substituted phenols and formaldehyde. These occupy an important position in the realm of host–guest chemistry, as they are amenable to modifications at the upper and lower rim by different routes making them highly versatile building blocks for the design of novel hosts for the recognition of metal ions, anions and neutral molecules[2,3]. Biali and coworkers[4-9] have shown that in the presence of tetraalkylammonium tribromide salt in a basic medium the hydroxyl groups bordering the lower rim of calix[4]arene can participate in an intramolecular oxidative cyclization reaction giving rise to an interesting series of multifunctional molecules namely bis(spirodienones) **1a**, **1b** and **1c** (**Figure 1**).

The calix[4]bis(spirodienone) derivatives are remarkable since in a single step the hydroxyl groups are transformed into carbonyl and ether functionalities, two phenolic rings are transformed to cyclohexadienone moieties and in the process, two spiro stereocentres are also introduced in the macrocycle. These functionalities provide a plethora of potential means for the modification of the calix skeleton. These spirodienone derivatives have been used as synthetic intermediates for achieving selective functionalisation of the calixarenes at the intra-annular, extra-annular and methylene positions[10].

The bis(spirodienones) appear attractive from the vantage point of their transformations to novel structural frameworks with potentially useful properties. Diels-Alder reactivity as the dienone



1a **1b** **1c**

Figure 1

moieties is of special interest in compounds **1a**, **1b** and **1c** and in principle these compounds can act as efficient 4π components. Some investigations have been carried out in this area and the preliminary results have been published. The results showed that the bis(spirodienone) **1a** can act as 4π component in cycloaddition reaction with activated acetylenes[11]. In continuation of studies in the cycloaddition chemistry of bis(spirodienones), an investigation on the cycloaddition reaction of **1a** with 1,2-benzoquinones has been undertaken and the preliminary results have been published[12]. This is the first report of the bis(spirodienone) acting as a 2π component. Detailed investigation of the cycloaddition reaction of **1a** with 1, 4-benzoquinones where **1a** participates as the 4π counterpart is also carried out. The detailed results of these investigations illustrating the dual reactivity profile of bis(spirodienone) towards 1,2- and 1,4-benzoquinones and are presented in the following section in detail. A theoretical rationalization of the cycloaddition reaction with the two substrates leading to different cycloadducts is also presented.

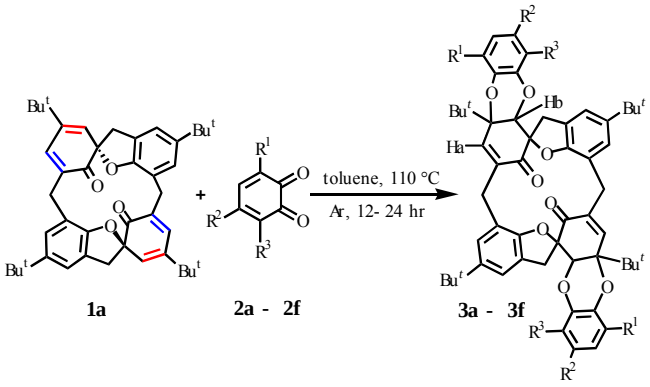
Results and Discussion

Cycloaddition reaction with 1, 2-benzoquinones

1,2-Benzoquinones are unique conjugated diones that can elicit diverse modes of cycloaddition by acting as carbodiene, heterodiene, dienophile or heterodienophile. Substituted 1,2-benzoquinones selected for these studies were synthesised from the corresponding catechol by standard procedure[13]. The bis(spirodienone) **1a** was synthesised following Biali's procedure[6].

The compound **1a** was heated under reflux with 3,5-di-*tert*-butyl-1,2-benzoquinone **2a** in dry toluene for 12 hr. The reaction proceeded smoothly affording the (2 + 4) adduct **3a** in 88% yield (**Scheme I**).

The product **3a** was characterised on the basis of spectroscopic data. The IR spectrum showed characteristic absorption at 1698 cm^{-1} corresponding to the enone carbonyl. In the ^1H NMR spectrum, the aromatic protons of the bis(spirodienone) moiety appeared as singlets at δ 7.22 and 6.90. The aromatic protons of the benzodioxin part of the adduct also appeared as sharp singlets at δ 6.81 and 6.71. The olefinic proton H_a appeared as a singlet at δ 6.11 and the ring junction proton H_b appeared as a singlet at δ 4.68. In the ^{13}C NMR spectrum, the signal due to the enone carbonyl resonated at δ 188.7 and the spirocarbon at 89.5. Conclusive evidence for the



Scheme I

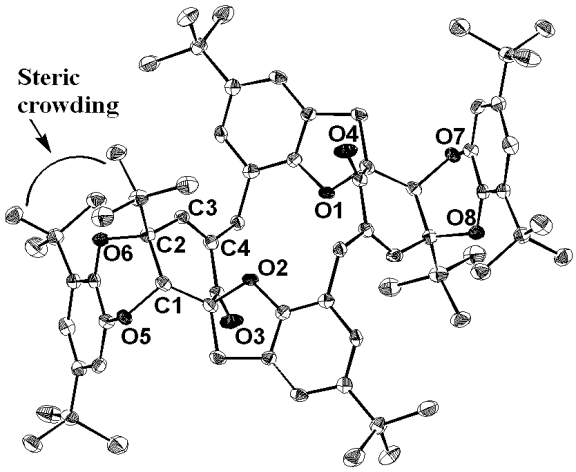


Figure 2 — ORTEP diagram of the compound **3a**. Hydrogen atoms are omitted for clarity.

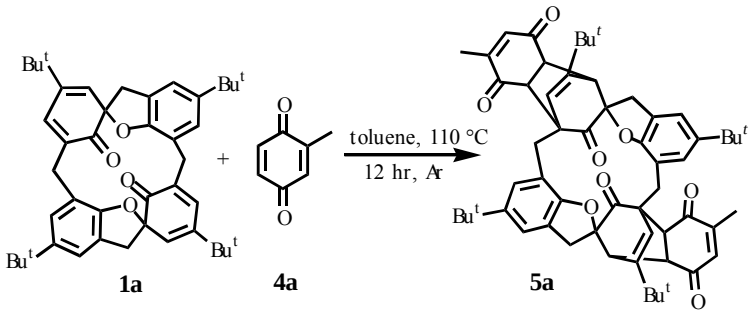
structure and stereochemistry was obtained by single crystal X-ray analysis (**Figure 2**).

Similar reactivity was observed with other 1,2-benzoquinones yielding the adducts in good yield. The results are summarised in **Table I**.

It is evident from **Table I** that the bis(spirodienone) **1a** can act as an efficient 2π component in its cycloaddition with 1,2-benzoquinones. The reaction afforded novel macrocycles with benzodioxin moieties. A sterically encumbered regioselective pathway which gives rise to a sterically crowded single product has been suggested for the reactions. A scrutiny of the X-ray structure of **3a** shows that the addition has occurred selectively at the longer, less reactive red double bond (**Scheme I**). It shows that even for a 1,2-benzoquinone with a bulky R^1 group, the cycloaddition product is formed in such a way that the R^1 and the *tert*-butyl group at C2 of the bis(spirodienone) moiety come closer. The steric crowding around O6 was reflected in the longer O6-

Table I– (2+4) Cycloaddition of bis(spirodienone) **1a** with 1, 2- benzoquinones

entry	*o*- quinones (**2a- 2f**)	time (hr)	product	yield (%)
1	$R^1 = R^2 = {}^tBu$, $R^3 = H$	12	**3a**	88
2	$R^1 = R^2 = {}^tBu$, $R^3 = OMe$	24	**3b**	62
3	R^1 = biphenyl methyl, $R^2 = {}^tBu$, $R^3 = H$	24	**3c**	40
4	$R^1 = R^2$ = biphenylmethyl, $R^3 = H$	24	**3d**	59
5	$R^1 = H$, $R^2 = {}^tBu$, $R^3 = OMe$	18	**3e**	63
6	$R^1 = R^3 = H$, $R^2 = {}^tBu$	18	**3f**	76



1a **4a** **5a**

Scheme II

C2 bond (1.478 Å) when compared to the shorter O5-C1 bond (1.435 Å) (**Figure 2**). If the product had been formed in the reverse way, *viz*. forming O5-C2 and O6-C1 bond, this steric crowding would have been avoided. The formation of only a single cycloadduct **3a** therefore suggests high steric control in this cycloaddition reaction. Hence, it is most appropriate to suggest a stepwise mechanism rather than a concerted one for the cycloaddition reaction. Therefore, the initial formation of the sterically favoured O5-C1 bond forces the formation of the O6-C2 bond in the sterically crowded region of the system. The theoretical calculations on the formation of the product also support this reaction pathway.

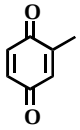
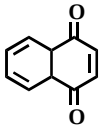
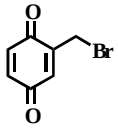
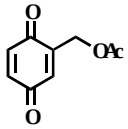
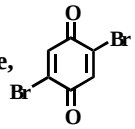
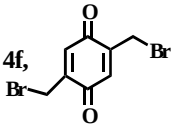
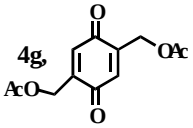
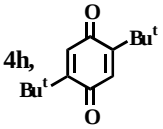
(4+2) Cycloaddition reactions of bis(spirodienone) 1a with 1,4-benzoquinones

Subsequent to the interesting results obtained with 1,2-benzoquinones, we turned our attention to another important class of diones namely the 1,4-benzoquinones. Substituted 1,4-benzoquinones[14-19] selected for this study were synthesised from the corresponding hydroquinones. In a prototype experiment, the reaction of **1a** with 2-methyl-1,4-benzoquinone in dry toluene under reflux condition yielding a novel macrocycle as a single product in 65% yield (**Scheme II**).

The structure of **5a** was established by spectroscopic techniques. In the IR spectrum, the absorption at 1734 cm^{-1} was assigned to the saturated carbonyl and the absorption at 1663 cm^{-1} to the α, β-unsaturated carbonyls of the quinone part. In the ^1H NMR spectrum, the resonance signals due to the olefinic proton and the ring junction proton of the bis(spirodienone) moiety appeared as singlets at δ 4.73 and 3.35 respectively. The olefinic proton of the quinone moiety appeared as a singlet at δ 6.46. The ring junction protons where the cycloaddition had taken place appeared as close doublets centred at δ 2.92 (J = 9.0 Hz) indicating a *syn* relationship. The methyl protons appeared as a singlet at δ 1.94. In the ^{13}C NMR spectrum, the three carbonyl carbons resonated at δ 202.9, 195.7 and 195.5 and the spiro carbon at 83.9.

In order to ascertain the generality of the reaction, **1a** was treated with a series of 1,4-benzoquinones and the results are summarised in **Table II**. The cycloadducts were obtained in good yields. For entries 3 and 4, the reactions were conducted in sealed tube using toluene as the solvent. The adducts **5a-d**

Table II- Cycloaddition reactions with 1, 4- benzoquinones

Entry	Substrate	1,4- benzoquinones	Reaction conditions	Yield (%)
1	**1a**	**4a**, 	110 °C, 12 hr	65.2, **5a**
2	"	**4b**, 	110 °C, 12 hr	93, **5b**
3	"	**4c**, 	110 °C, 24 hr (sealed tube)	56, **5c**
4	"	**4d**, 	110 °C, 48 hr (sealed tube)	45, **5d**
5	"	**4e**, 	110 °C, 48 hr	No reaction
6	"	**4f**, 	110 °C, 48 hr	No reaction
7	"	**4g**, 	110 °C, 48 hr	No reaction
8	"	**4h**, 	110 °C, 48 hr	No reaction

were obtained exclusively as single products. The addition had occurred selectively on the unsubstituted double bond of the 1,4-benzoquinone preferably due to steric reasons. In the case of 2,5-disubstituted-1,4-benzoquinones, all the substrates studied (entry 5-8) failed completely to react with the spirodienone **1a**. This suggests a large steric effect in these reactions mainly arising from the subtituents of both benzoquinone and spirodienone.

Theoretical Calculations

In order to understand the intriguing steric aspects and the mechanism of the reactions given in **Scheme I** and **Scheme II**, theoretical modelling[20] was carried out at the semi-empirical AM1 as well as B3LYP/6–31G* level of density functional theory (DFT)[21]. For the modelling studies, Gaussian 03 suite of programs have been used[22]. At first the [2+4] cycloaddition reaction between the unsubstituted bis(spirodienone) and unsubstituted 1,2-benzoquinone (Reaction I) as well as the [4+2] cycloaddition between unsubstituted bis(spirodienone) and unsubstituted 1,4-bezoquinone (Reaction II) have been modelled at B3LYP/6-31G* level of DFT (**Figure 3a** and **3b**). The *tert*-butyl-substituted spriodienone systems are quite big and theoretical studies on them are not viable at a

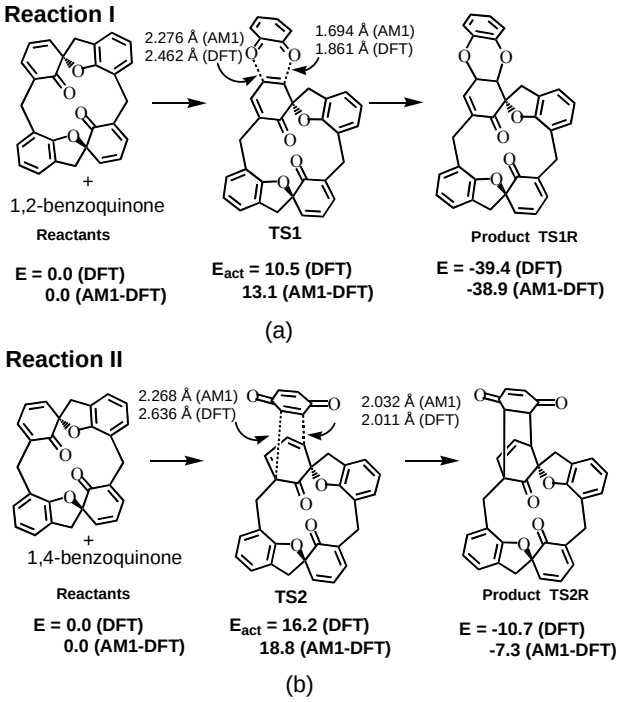


Figure 3 — Model reaction with unsubstituted systems. (a) [2+4] cycloaddition between spirodienone and 1,2-benzoquinone and (b) [4+2] cycloaddition between spirodienone and 1,4-benzoquinone. Relative energies in kcal/mol. DFT and AM1-DFT given in parenthesis represent the full DFT and the AM1-optimized DFT single point calculations, respectively. All bond lengths are in Å.

reasonable computational cost. Therefore, the fully substituted systems have been optimized at AM1 level of the semi-empirical theory[23]. However, for a better description of the energetics, the AM1 level optimized systems have been subjected to B3LYP/6-31G* level energy calculations (designated here as AM1-DFT procedure).

The activation barrier (E_{act}) obtained for reaction I using transition state **TS1** (**Figure 3a**) at the DFT level is only 10.5 kcal/mol. On the other hand, at the same level of theory, Reaction II shows a higher activation barrier of 16.2 kcal/mol. The energetics and the structural features of the systems obtained using the AM1-DFT procedure is in good agreement with the DFT level results (**Figure 3**). Therefore, we expect that AM1-DFT procedure is good enough for the description of the reactions involving *tert*-butyl substituted spirodienone systems.

Cycloaddition reaction with 1, 2-benzoquinones

At AM1-DFT level, the cycloaddition of **2a** across the double bond shown in red color in **1a** (**Scheme I**) is modeled (the red bond is the same as the C1-C2 bond given in **Figure 4**). Two transition states **TS3**

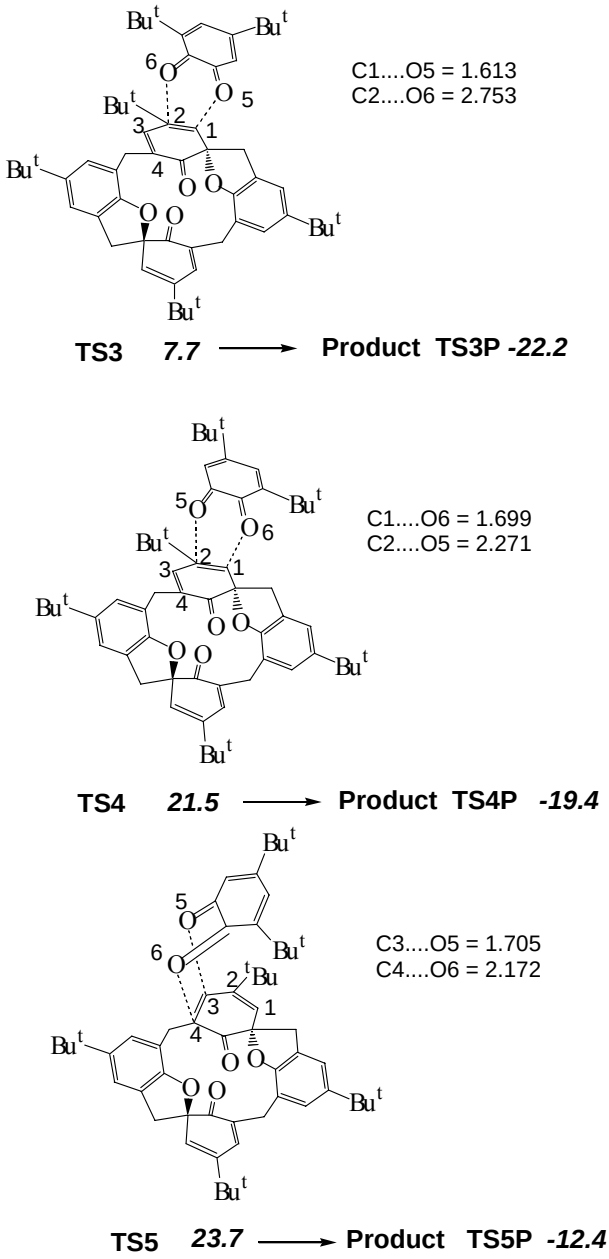


Figure 4 — Transition states for the different modes of [2+4] cycloaddition between bis(spirodienone) **1a** and 1,2-benzoquinone **2a**. Bond lengths are in Å and relative energy values (zero is for **1a**+**2a**) is given in kcal/mol.

and **TS4** are located for this reaction. Further, the cycloadduct formation of **2a** with the C3-C4 double bond of **1a** is also studied, and the corresponding transition state **TS5** is located. The product formed from **TS3** (**TS3P**) is characterized by the C1-O5 and C2-O6 bond formations. The product obtained in the experiment (**3a**) also contained the same bonds. As we can see from the relative energies given in **Figure 4**, **TS3** has much higher stability than **TS4** and **TS5**.

Therefore, **TS3** is the right choice for the formation of **3a** (ref.24). Analysis of the structure of the three transition states **TS3**, **TS4**, and **TS5** suggests that the C1…O5 and C2…O6 regions of **TS3** are the sterically the least and the most crowded regions, respectively. It means that the formation of C1-O5 bond is highly preferred and therefore the system is compelled to undergo the C2-O6 bond formation at the sterically the most crowded region. In other words, the reactions described in **Table I** can be considered as sterically encumbered cycloaddition reactions[12].

Cycloaddition reaction with 1, 4-benzoquinones

The reactivity of **1a** with **4a**, **4c**, and **4f** is modelled at the AM1-DFT level. The transition state **TS6** for the addition of **1a** with **4a** is given in **Figure 5**. In this TS, the C5 atom interacts strongly with spirodienone system at a C5-C distance of 2.048 Å than the C6 atom (C6-C distance is 2.272 Å). The interaction distances of C5-C and C6-C are nearly identical to the corresponding values obtained for **TS2,** the TS for the reaction of 1, 4-benzoquinone and **1a** at the AM1-DFT level (*cf.* **Figure 3**). Transition states **TS7** and **TS8** are also located for the [4+2] cycloaddition of (**1a** + **4c**) and (**1a** + **4f**), respectively. In **TS8**, the ordered pair of (C5-C, C6-C) distance is found to be (2.097 Å, 2.285 Å) while in **TS9**, it is (2.205 Å, 2.219 Å). The optimized geometry of product systems corresponding to **TS6**, **TS7**, and **TS8** are designated as **TS6P**, **TS7P**, and **TS8P**, respectively.

Table III—Energetics of the [4+2] substituted 1,4-benzoquinones at AM1-DFT level. All values in kcal/mol

Reactant	TS	Product
(1a + 4a) →	**TS6** →	**TS6P**
0.0	18.9	-11.1
(1a + 4c)	**TS7**	**TS7P**
0.0	25.7	-4.5
(1a + 4f)	**TS8**	**TS8P**
0.0	33.5	-1.4

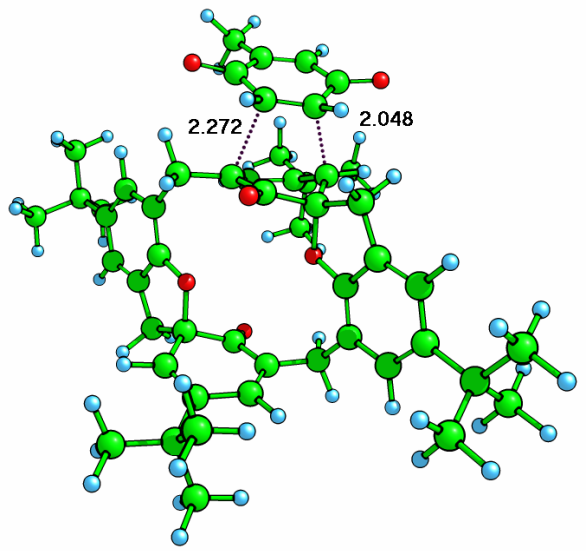


Figure 5 — Transition state **TS6** for the [4+2] cycloaddition between spirodienone **1a** and 1, 4-benzoquinone **4a**. All bond lengths are in Å.

The energetics obtained for the reactions of substituted 1,4-benzoquinones are summarised in **Table III**. All the reactions are exothermic which is normally the observed trend in all cycloaddition reactions, because a cycloaddition reaction produces two strong σ bonds at the expense of four π-electrons. In the present case, the exothermicity decreases with respect to the increase in the size of the substituent on the benzoquinone. An exothermicity of only 1.4 kcal/mol is observed when there is CH_2Br substitution at C2 and the C5 position of the 1,4-benzoquinone which may be attributed to the increased steric effect in the system. The steric effect is also reflected in the activation barrier. For instance, the activation barrier for the reactions of 1,4-benzoquinone, **4a**, **4c**, and **4f** at AM1-DFT level are 18.8, 18.9, 25.7, and 33.5 kcal/mol, respectively. It may be noted that **4f** showed no reaction with **1a** and the high activation barrier of 33.5 kcal/mol observed for this reaction is the main reason for its inert behaviour. Similarly, the steric effect and activation barriers are expected to be quite high in the [4+2] cycloaddition of **1a** with **4e**, **4g** and **4h** and therefore such reactions may not be feasible.

Experimental Section

All reactions were conducted in oven-dried glassware under an atmosphere of argon. Progress of the reactions was monitored by TLC and purification was effected using silica gel column chromatography. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX300 FTNMR spectrometer at 300 MHz and 75 MHz respectively. Chemical shifts are reported in δ (ppm) relative to Me_4Si (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal standards. Abbreviations for NMR multiplicities are as follows: s, singlet; d, doublet; m, multiplet; coupling constants *J* are reported in Hertz

(Hz). IR spectra were recorded on a Bomem MB Series FT-IR spectrometer and the absorbances are reported in cm^{-1}.

Typical procedure for the preparation of 3a

A solution of **1a** (50 mg, 0.078 mmole) and 3,5-di-*tert*-butyl 1, 2-benzoquinone **2a** (32.9 mg, 0.1629 mmole) in dry toluene (5 mL) was refluxed under an inert atmosphere of argon. The reaction-mixture was stirred at this temperature until the reaction was complete as indicated by TLC (12 hr). 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 crystallized from dichloromethane-acetonitrile.

Spectroscopic data for new compounds

Compound 3a

White crystalline solid, IR (KBr): 2961, 1698, 1593, 1488, 1416, 1364, 1292, 1239, 1191, 1077, 995, 852 cm^{-1}; ^{1}H NMR ($CDCl_3$): 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, *J* = 16.6 Hz, 2H), 3.67 (d, *J* = 16.2 Hz, 2H), 3.46 (d, *J* = 16 Hz, 2H), 2.72 (d, *J* = 15.4 Hz, 2H), 1.35 (s, 18H), 1.31 (s, 18H), 1.26 (s, 18H), 0.95 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 188.7, 152.3, 145.1, 145.0, 144.3, 141.3, 140.8, 140.0, 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; MS (FAB): *m/z* Calcd. for $C_{72}H_{92}O_8$ $[M+H]^+$: 1085.68. Found: 1085.33. Anal. Calcd. for $C_{72}H_{92}O_8$: C, 79.67; H, 8.54. Found: C, 79.42; H, 8.35%. CCDC file no: 277476.

Compound 3b

White crystalline solid, IR (KBr): 2965, 1701, 1483, 1416, 1365, 1199, 1068, 1001, 867, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.03 (s, 2H), 6.82 (s, 2H), 6.77 (s, 2H), 6.07 (s, 2H), 4.73 (s, 2H), 4.07 (d, *J* = 17.1 Hz, 2H), 3.87 (s, 6H), 3.65 (d, *J* = 17.1 Hz, 2H), 3.46 (d, *J* = 15.9 Hz, 2H), 2.74 (d, *J* = 15.9 Hz, 2H), 1.33 (s, 18H), 1.32 (s, 18H), 1.31 (s, 18H), 0.95 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 188.7, 152.3, 145.1, 145.0, 144.4, 140.8, 140.0, 138.7, 126.6, 125.8, 120.6, 119.6, 117.5, 112.8, 89.5, 82.2, 79.0, 55.9, 38.3, 34.6, 34.4, 34.3, 31.7, 31.4, 29.8, 24.8; MS (FAB): *m/z* Calcd. for $C_{74}H_{96}O_{10}$ $[M+H]^+$: 1145.70. Found: 1145.95.

Compound 3c

White crystalline solid, IR (KBr): 2962, 2870, 1702, 1598, 1484, 1363, 1202, 985, 854, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32- 7.17 (m, 14H), 7.05 (d, *J* = 7.5 Hz, 8H), 6.72 (s, 2H), 6.60 (s, 2H), 6.53 (s, 2H), 5.92 (s, 2H), 5.61 (s, 2H), 4.66 (s, 2H), 3.99 (d, *J* = 16.8 Hz, 2H), 3.55 (t, $J_1 = J_2$ = 15.3 Hz, 4H), 2.61 (d, *J* = 15.0 Hz, 2H), 1.25 (s, 18H), 1.15 (s, 18H), 0.83 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 188.8, 152.3, 145.3, 144.5, 143.1, 140.6, 140.2, 132.6, 129.1, 129.0, 128.2, 126.7, 126.3, 121.0, 120.3, 120.2, 112.2, 88.9, 82.0, 79.0, 48.9, 38.7, 34.3, 34.2, 31.3, 31.7, 31.3, 29.6, 28.6, 25.1; MS (FAB): *m/z* Calcd. for $C_{90}H_{96}O_8$ $[M+H]^+$: 1306.72. Found: 1306.78. Anal. Calcd. for $C_{90}H_{96}O_8$: C, 82.79: H, 7.41. Found: C, 82.34; H, 7.17%.

Compound 3d

White crystalline solid, IR (KBr): 2965, 2950, 1694, 1602, 1489, 1280, 1196, 1024, 984, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.41- 7.08 (m, 34H), 6.69 (dd, *J* = 6.9 Hz, 8H), 6.53 (s, 2H), 6.26 (s, 2H), 6.16 (s, 2H), 5.68 (s, 2H), 5.46 (d, *J* = 7.2 Hz, 4H), 4.63 (s, 2H), 3.90 (d, *J* = 16.7 Hz, 2H), 3.46 (uneven t, J_1 = 15.9 & J_2 = 16.5 Hz, 4H), 2.42 (d, *J* = 15.9 Hz, 2H), 1.27 (s, 18H), 0.90 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 188.6, 152.3, 144.4, 143.7, 142.4, 138.4, 137.8, 129.5, 129.4, 129.4, 128.6, 128.1, 126.5, 126.2, 126.2, 125.6, 119.9, 89, 83.6, 79.8, 76.4, 52, 51.8, 38.0, 34.3, 31.8, 31.3, 29.7, 25.0; MS (FAB): *m/z* Calcd. for $C_{108}H_{100}O_8$ $[M+H]^+$: 1526.94. Found: 1527.19.

Compound 3e

White crystalline solid, IR (KBr): 2965, 1706, 1618, 1512, 1481, 1436, 1284, 1253, 1196, 1101, 854 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 2H), 6.81 (s, 4H), 6.42 (d, *J* = 8.7 Hz, 2H), 6.11 (s, 2H), 4.73 (s, 2H), 4.01 (d, *J* = 17.1 Hz, 2H), 3.85 (s, 6H), 3.77 (d, *J* = 17.4 Hz, 2H), 3.45 (d, *J* = 15.9 Hz, 2H), 2.69 (d, *J* = 16.8 Hz, 2H), 1.33 (s, 18H), 1.31 (s, 18H), 0.96 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 189.4, 152.2, 147.9, 145.3, 144.3, 141.2, 139.7, 132.2, 126.6, 126.3, 120.8, 119.7, 119.3, 105.0, 89.7, 82.7, 79.2, 55.8, 38.2, 34.3, 33.9, 31.8, 30.9, 30.0, 24.8; MS (FAB): *m/z* Calcd. for $C_{66}H_{89}0_{10}$ $[M+H]^+$: 1033.34. Found: 1032.36. Anal. Calcd. for $C_{66}H_{89}0_{10}$: C, 76.71; H, 7.80. Found: C, 76.79; H, 8.69%.

Compound 3f

White crystalline solid, IR (KBr): 2959, 1701, 1598, 1508, 1486, 1283, 1196, 1035, 984, 868 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22 (s, 2H), 6.93- 6.67 (m, 8H), 6.02 (s, 2H), 4.66 (d, *J* = 8.0 Hz, 2H), 4.03 (d, *J* =

16.2 Hz, 2H), 3.66 (d, *J* = 15.6 Hz, 2H), 3.57 (d, *J* = 16.5 Hz, 2H), 2.71 (d, *J* = 15.9 Hz, 2H), 1.36 (s, 18H), 1.27 (s, 18H), 0.91 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 188.3, 152.4, 144.4, 142.2, 141.3, 140.3, 126.6, 125.8, 120.0, 119.5, 118.8, 117.2, 116.1, 115.0, 114.0, 88.6, 88.6, 81.5, 81.5, 79.0, 39.0, 38.9, 34.2, 32.6, 31.8, 31.5, 31.4, 29.6, 28.4, 25.7, 25.5; MS (FAB): *m/z* Calcd. for $C_{64}H_{76}O_8$ $[M+Na]^+$: 995.55. Found: 995.00.

Typical procedure for the synthesis of 5a-d

A solution of **1a** (50 mg, 0.078 mmole) and 2-methyl-1,4-benzoquinone, **4a** (19.87 mg, 0.1629 mmole) in dry toluene (5 mL) was refluxed under inert atmosphere. The reaction-mixture was stirred at this temperature for 12 hr, until the reaction was complete as indicated by TLC. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane-ethylacetate (95:5) as the eluent to yield **5a** (45 mg, 65%).

Compound 5a

White crystalline solid, IR (KBr): 2961, 1734, 1663, 1480, 1425, 1361, 1263, 1208, 1103, 893, 846 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.08 (d, *J* = 5.1 Hz, 4H), 6.46 (s, 2H), 4.73 (s, 2H), 3.96 (d, *J* = 13.8 Hz, 2H), 3.51 (d, *J* = 15.6 Hz, 2H), 3.33 (d, *J* = 14.4 Hz, 4H), 3.18 (d, *J* = 14.4 Hz, 2H), 2.93 (d, *J* = 10.8 Hz, 4H), 1.94 (s, 6H), 1.33 (s, 18H), 0.83 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 202.9, 195.6, 195.5, 154.6, 154.1, 149.4, 144.1, 138.5, 127.8, 124.0, 120.5, 120.1, 119.5, 115.7, 115.4, 112.2, 83.9, 53.1, 52.6, 48.8, 46.5, 37.4, 34.2, 33.9, 31.7, 29.6, 27.8, 27.3, 16.7, 16.2; MS (FAB): *m/z* Calcd. for $C_{58}H_{64}O_8$ $[M+H]^+$: 889.46. Found: 888.65.

Compound 5b

White crystalline solid, IR (KBr): 2966, 1732, 1678, 1593, 1482, 1361, 1295, 1202, 1099, 988 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94 (t, *J* = 7.5Hz, 4H), 7.73-7.63 (m, 4H), 7.27 (s, 2H), 7.10 (s, 2H), 4.84 (s, 2H), 4.04 (d, *J* = 14.1 Hz, 2H), 3.59 (d, *J* = 15.3 Hz, 2H), 3.47(d, *J* = 13.5 Hz, 4H), 3.37(d, *J* = 14.4 Hz, 2H), 3.17 (s, 4H), 1.37 (s, 18H), 0.61 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 203.6, 195.0, 194.0, 154.7, 148.7, 144.0, 137.5, 134.7, 134.5, 133.6, 128.1, 126.9, 126.6, 123.9, 121.5, 120.7, 119.5, 84.2, 54.1, 53.2, 48.8, 46.9, 37.5, 34.3, 33.7, 31.8, 28.0, 27.7; MS (FAB): *m/z* Calcd. for $C_{64}H_{64}O_8$ $[M+H]^+$: 961.46. Found: 960.90.

Compound 5c

Pale yellow solid, IR (KBr): 2955, 1733, 1667, 1484, 1358, 1263, 1196, 1102, 940, 891, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.06 (d, *J* = 9.3 Hz, 4H), 6.57 (s, 2H), δ 4.85 (s, 2H), 4.39 (d, *J* = 10.5 Hz, 2H), 3.97 (d, *J* = 14.7 Hz, 2H), 3.85 (d, *J* = 10.2 Hz, 2H), 3.52 (d, *J* = 15.3 Hz, 2H), 3.32 (d, *J* = 15.9 Hz, 4H), 3.17 (d, *J* = 15.0 Hz, 2H), 3.07 (d, *J* = 9.0 Hz, 2H), 2.88 (d, *J* = 9.0 Hz, 2H), 0.87 (s, 18 H), 1.31 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 202.3, 196.0, 193.5, 154.5, 151.2, 149.2, 144.2, 138.4, 128.0, 123.9, 120.1, 119.9, 119.7, 83.4, 53.7, 52.5, 49.5, 46.9, 37.6, 34.3, 34.2, 31.8, 29.6, 27.8, 27.7, 27.1, 25.5; MS (FAB): *m/z* Calcd. for $C_{58}H_{62}Br_2O_8$ $[M+H]^+$: 1045.28. Found: 1046.25.

Compound 5d

Pale orange solid, IR (KBr): 2950, 1744, 1670, 1486, 1259, 1215, 1102, 1039, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.13 (s, 2H), 7.08 (s, 2H), 6.50 (s, 2H), 4.74 – 4.91 (m, 6H), 3.98 (d, *J* = 14.4 Hz, 2H), 3.53 (d, *J* = 15.3 Hz, 2H), 3.33 (d, *J* = 16.8 Hz, 4H), 3.19 (d, *J* = 14.4 Hz, 2H), 2.97 (s, 4H), 2.09 (s, 6H), 0.81(s, 18H), 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 203.0, 195.7, 194.4, 169.6, 154.6, 151.1, 149.4, 144.4, 136.3, 128.0, 123.9, 120.7, 120.5, 119.8, 84.0, 59.7, 53.2, 53.1, 48.8, 46.4, 37.5, 34.4, 34.1, 31.9, 29.8, 27.9, 27.7, 20.6; MS(FAB): *m/z* Calcd. for $C_{62}H_{68}O_{12}$ $[M+Na]^+$: 1028.19. Found: 1028.72.

Conclusion

In conclusion, a dual reactivity profile of the calix[4]arene derived bis(spirodienone) towards 1,2- and 1,4-benzoquinones has been unravelled. While the bis(spirodienone) acted as a 2π component with 1,2-benzoquinones as the 4π counterpart yielding benzodioxin derived macrocycles, it reacted as a 4π component in its cycloaddition with 1,4-benzoquinones. The highly reactive unhindered olefinic double bond of the 1, 4-benzoquinone acted as the dienophile and the reaction yielded bisadducts in good yield. However, when the 1- and 4- positions were sterically hindered by substitutions at the C2 and C5 carbon atoms, the reaction did not occur. The presence of reactive α,β-unsaturated carbonyls in the [2+4] and [4+2] cycloadducts makes them amenable to further modifications. Further work towards modifications of the macrocycles for more favourable structures are in progress and will be reported in due course.

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24 In order to make **3a** system, one more molecule of **2a** has to be added to the **TS3R** system. The transition state for this step is expected to be very similar to **TS3**.