Cycloadditions of Isobenzofuran to a Constrained Template Bearing Neighboring Dienophiles

Martin J. Stoermer,*[a] Douglas N. Butler,[b] Ronald N. Warrener,[b] K. D. V. Weerasuria,[a] and David P. Fairlie[a]

Abstract: A high yielding synthesis of the pentacyclic diene–dione **1** has enabled investigation of its reactivity as a double dienophile in Diels–Alder [4+2] cycloadditions with isobenzofuran, leading to novel and highly symmetrical three-sided cavitands **3** and **4**.

Keywords: cavitands · cycloaddition · NMR spectroscopy · semiempirical calculations · supramolecular chemistry

Introduction

Norbornenes, norbornadienes, and related analogues are frequently used as constrained U-turn templates in Diels–Alder and cycloaddition reactions,[1] creating rigid supramolecular structures for electron-transfer studies,[2] mimics of turn elements of protein structure,[3] and key intermediates with adjacent stereocenters in natural product syntheses.[4] Each alkene in the rigid scaffold **1** could similarly serve as a dieneophile for Diels–Alder reactions. The photo-assisted closure of **1** to a cage[5] suggests that these olefins are not isolated dienophiles, but rather approach each other closely enough to permit through-space $\pi-\pi$ interactions. Since Diels–Alder additions are strongly dependent on the separation distance between and electronic activation of dienophiles,[1b, 6] we decided to investigate the reactivity of **1** in Diels–Alder cycloadditions.

Template **1** is not formed from the Diels–Alder addition of two equivalents of cyclopentadiene to benzoquinone,[7] but has been synthesized in six steps from benzoquinone (Scheme 1) in 8% yield.[5] We now report a high yielding synthesis of **1**, its reaction with isobenzofuran to form cavitands **3** and **4** with eight and nine pairs of stereocenters, respectively, and extensive characterization by NMR spectroscopy and molecular modelling studies.

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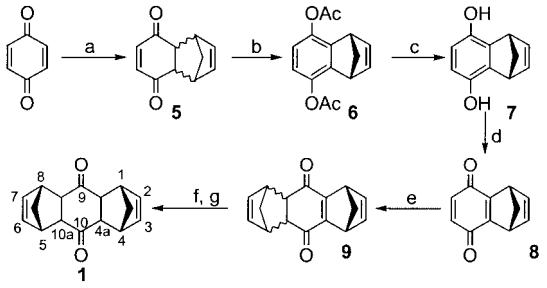

Scheme 1. Synthesis of bis-dienophilic template **1**. a) cyclopentadiene, ethanol 0 °C, 85%; b) Ac_2O, pyridine, 20 °C, 7 days, 75%; c) $LiAlH_4$/ether, <50%; d) Ag_2O, benzene 100%; e) cyclopentadiene, benzene, 100%; f) recrystallization from CH_2Cl_2/petroleum ether; g) $TiCl_3$, acetone,water 100%.

Results and Discussion

To facilitate the synthesis of cavitands like **3** and **4**, we sought to make **1** on a multigram scale through two modifications to the literature procedure.[5] First, the instability of quinol **7** to oxidation or polymerization, and our inability to increase its yield simply through ester hydrolysis of **6**, led us to optimize a one-pot conversion of **5**[8] to **8**. Treatment of **5** with base results in double-enolization[1d] to quinol **7**, which was inexpensively oxidized by anhydrous ferric chloride in ethanol or alternatively pyridinium chlorochromate in acetone. These simple modifications improved the yield of **8**[9] from **5** from 15% to 86%, contributing to an overall yield of 44% of **1** from benzoquinone.

Molecular modeling calculations[10] suggest that **1** has $C_2\cdots C_7$ distances of 4.4 Å, and $H_{4a}\cdots H_{10a}$ distances of 2.9 A (Figure 1). Semiempirical calculations predicted significantly lower LUMO energies (0.73 eV) for **1** than for an isolated norbornene (1.28 eV), comparable to norbornenes activated by mild electron-withdrawing halogen substituents (Cl 0.85 eV; Br 0.71 eV).[10] Some $\pi-\pi$ interaction in **1** may

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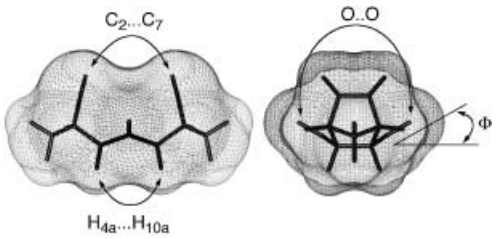
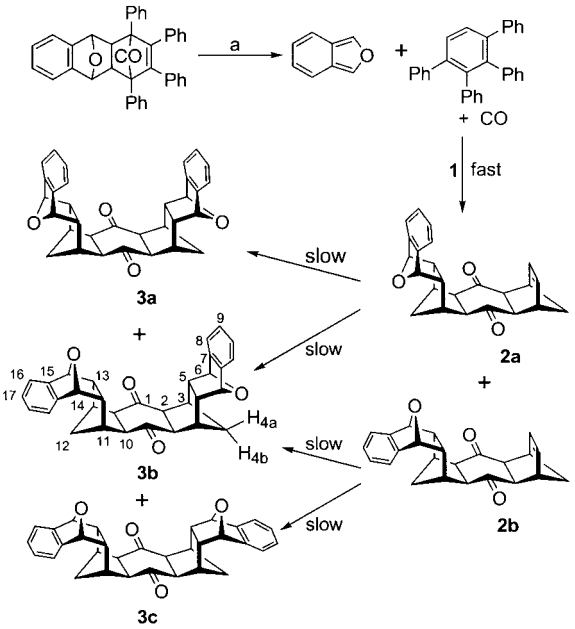


Figure 1. Representative distances and angles predicted for **1** by semi-empirical (Mopac AM1) calculations[10] ($C_2 \cdots C_7$ 4.37 Å; O···O 5.00 Å; $H_{4a} \cdots H_{10a}$ 2.92 Å, ϕ 20.8°) and the Connolly surface generated in InsightII.[11]

therefore possibly contribute to the lower LUMO, resulting in potentially more facile cycloaddition relative to norbornene.

We therefore investigated Diels–Alder reactions of **1** with dienes of varying reactivity. Compound **1** failed to undergo cycloaddition in $CHCl_3$ (80 °C) or DMSO (180 °C) with anthracene and it's derivatives (9,10-dimethyl-, 9-bromo-, 9-acetyl-, 9,10-dicyano-). Only decomposition of **1** was observed after prolonged heating above 180 °C. By contrast **1** did react rapidly with two equivalents of a more reactive diene (isobenzofuran,[12] IBF) in dyglyme, at the temperature (200 °C) necessary to generate IBF from its precursor,[13] to give three isomeric bis-adducts **3a–c** in the ratio 1:2:1 (Scheme 2). The cycloadditions are exclusively to the *exo*-face of **1**, but both *endo* and *exo* with respect to the diene IBF.



Scheme 2. Isobenzofuran cycloaddition of **1**. a) Diglyme 200 °C, **3a**:**3b**:**3c** = 1:2:1.

When the isobenzofuran cycloaddition is performed with one equivalent of the IBF precursor, a 1:1 mixture of the intermediates **2a** and **2b** is thus observed. Under those conditions the final products **3a–c** were only formed in trace amounts (<5% HPLC, NMR spectroscopy). This indicates that the rates for the second cycloaddition are significantly slower than for the first addition to **1** (Scheme 2). It is unlikely that there is any steric impediment to the second addition, so we suggest that the orbital interactions between neighboring dienophiles in **1** influence the faster rate of the first cycloaddition relative to the second cycloaddition.

Isomers **3a-c** (and **2a**,**b**) were readily distinguished by characteristic NMR (^1H, ^{13}C) spectra, particularly the diagnostic δ_H for methylene protons $H_{4a,b}$ and $H_{12a,b}$ (Figure 2).

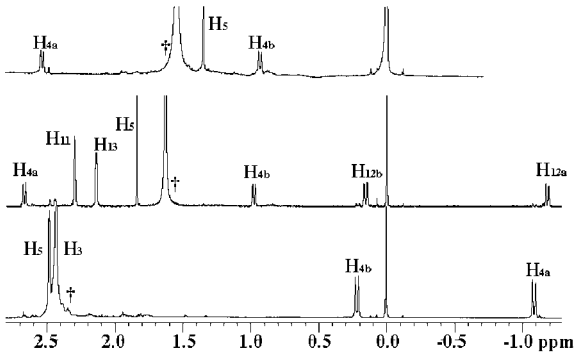


Figure 2. ^1H NMR spectra of **3a** (top), **3b** (middle), and **3c** (bottom) in $CDCl_3$ at 25 °C († water).

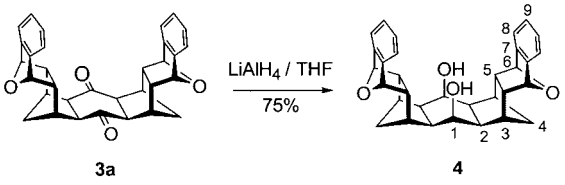
One equatorial methylene proton (H_{12a}) in **3b** and two (H_{4a}) in **3c** were shifted dramatically upfield[14] by the aromatic rings (−1.2 ppm from TMS, −2.6 ppm from **1**). Axial methylene protons (H_{12b}) in **3b** and (H_{4b}) in **3c** are less shielded ($\Delta \sim 1.2$ ppm). In contrast, the axial methylene protons (H_{4b}) in **3a** and **3b** were mildly shielded ($\Delta \sim 0.4$ ppm) by the ether oxygen atom, whereas the equatorial protons (H_{4a}) are strongly deshielded, appearing 1.3 ppm downfield of analogous protons of **1**.[15] Similar chemical shifts effects were seen for **2a** and **2b** and are also diagnostic of each isomer.

^1H and ^{13}C NMR assignments for **2a**, **2b**, **3a–c**, and **4** were made from ^1H, ^{13}C, DEPT, and two-dimensional NMR (HETCOR, HMBC, COSY, NOESY) spectra. Scalar H–H correlations were observed in COSY spectra for protons H_{4b}/H_5, H_{4a}/H_{4b}, H_3/H_{4a} in **3a**; H_3/H_{4a}, H_{4a}/H_{4b}, H_{4b}/H_5, H_{10}/H_{11}, H_{11}/H_{12a}, H_{11}/H_{12b}(weak), H_{12a}/H_{12b}, H_{12b}/H_{13}, H_{13}/H_{14} in **3b**; and H_2/H_3, H_3/H_{4a}, H_3/H_{4b}(weak), $H_{4a}/_{4b}$, H_{4b}/H_5, H_6/H_5 in **3c**. In particular, the ^4J W-couplings exemplified by H_{4b}/H_5 and H_{12b}/H_{13}, and the ^3J equatorial-bridgehead H_3/H_{4a} and H_{11}/H_{12a} correlations clearly establish the identities of the axial and equatorial methylene protons and the bridge protons in **3a–c**. From NOESY data, an axial–axial NOE correlation was observed for H_2/H_{4b} protons in **3a–c** and H_{10}/H_{12b} in **3b**. The ^4J W-couplings also established that Diels–Alder addition occurred exclusively on *exo* faces of **1**.

^{13}C NMR spectra for **3a–c** were very similar, with chemical shifts for the carbonyl resonances $\delta = 209.3$ (**3c**), 209.4 (**3b**), 209.9 ppm (**3a**). The carbon atoms of the bridgehead methine (C_3 and C_{11}) and methylene (C_4 and C_{12}) displayed the greatest chemical shift variability, the C_3 methine carbon atoms being ~4 ppm to lower field of C_{11}. The C_{12} methylene carbon atoms are shifted ~3 ppm to higher field due to shielding from aromatic rings. Similar chemical shifts effects were seen in **2a** and **2b**. The ion spray mass spectrum of **3a** in MeCN/(0.1% CF_3CO_2H in H_2O) exhibited a peak for the intact molecular

ion ($[M+H]^+$ $m/z = 477$), along with dehydration peaks (459, 441), and at high orifice potentials peaks for retro Diels–Alder products ($[M-H_2O+H]^+$, $[M-IBF-Cp]^+$, $[M-IBF-Cp-H_2O]^+$, $[IBF+Cp]^+$, $[IBF+Cp-H_20]^+$) were also observed.

Diketone **3a** was stereospecifically reduced to the diol **4** by the addition of hydride to the outside face by refluxing for 12 hours with $LiAlH_4$ in THF (Scheme 3). Rehybridization of



Scheme 3. Reduction of cavitand dione **3a** to diol **4**.

the carbonyl carbon from sp^2 to sp^3 was characterized by the shift in the C_1 ^{13}C chemical shift (209.9 to 70.9 ppm), and the appearance of H_1 and OH proton resonances at 4.28 and 3.18 ppm, respectively. Confirmation of the desired stereochemistry was established by the small vicinal coupling constants (< 0.5 Hz) of the C*H*OH protons.

Molecular models of cavitands **3a** and **4** are compared in Figure 3. The H_5 protons in **3a** and **4** are predicted to project

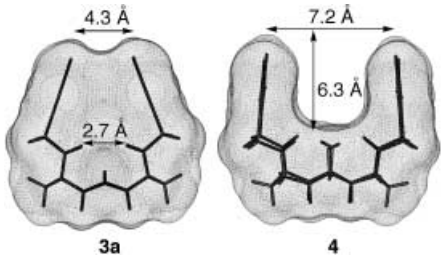


Figure 3. Mopac (AM1) minimized[10] structures of dione cavitand **3a** and diol cavitand **4** showing molecular dimensions and Connolly surfaces generated in InsightII.[11]

into the cavity, possibly impeding potential access of small guest ligands to the hydroxyl and carbonyl groups. Ligand docking studies support this proposition.[16] Rehybridization of the carbonyls from **3a** to **4** is predicted to dramatically change the dimensions of the cavity. Semiempirical calculations[10] predict that the cavity walls in **3a** (4.3 Å, top of benzene rings) widen to 7.2 Å in **4**. The resulting larger cavity of **4**, with hydroxyl substituents projecting axially into the interior of the cavity, would be expected to be more predisposed to guest capture than **3a**, though binding of small guests has not been detected by NMR spectroscopy.

In summary, we have developed a much higher yielding synthesis of the double dienophilic template **1**, facilitating an investigation of its reactivity in Diels–Alder cycloaddition chemistry. Addition of isobenzofuran proceeded in two steps at approximately tenfold different rates, the first cycloaddition evidently proceeding with electronic assistance from the neighbouring dienophile, while the slower second addition is unassisted. Neither cycloaddition step is stereoselective, resulting in three isomeric cavitands **3a–c**. Molecular modeling reveals that the cavity in the *exo*,*exo* addition product **3a** is very small, as shown by the merged Connolly surfaces for the aromatic walls in Figure 3. However, reduction of the unreactive ketones in **3a** under forcing conditions produced diol **4** with a larger cavity, which could, in principle, be capable of holding guest molecules.

Experimental Section

General methods: Materials obtained commercially were reagent grade unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on either a Varian Gemini 300 or Bruker ARX 500 spectrometers at 298 K. Proton and carbon assignments were determined by two-dimensional NMR experiments (TOCSY, NOESY, ROESY, HSQC, HMBC). Preparative-scale reverse-phase HPLC separations were performed on a 15 μM Phenomenex LunaC8(2) 250 × 21.2 mm column; analytical reverse phase HPLC was performed on a 5 μM Phenomenex Luna C8(2) 250 × 4.6 mm column with isocratic mixtures of water/0.1 % TFA (solvent system A) and water 10 %/acetonitrile 90 %/TFA 0.1 % (solvent system B). Mass spectra were obtained on a triple quadrupole mass spectrometer (PE SCIEX API III) equipped with an ionspray (pneumatically assisted electrospray) atmospheric pressure ionization source. Microanalytical data were obtained from the Commonwealth Microanalytical Service, Melbourne (Australia).

***endo*-1,4,4a,8a-Tetrahydro-1,4-methano-naphthalene-5,8-dione (5)**: Compound **5** was prepared in 85 % yield by the method of Albrecht,[8] as a pale yellow powder, m.p. 77 °C (lit. [8] 77–78 °C)

1,4-Dihydro-1,4-methano-naphthalene-5,8-dione (8): Degassed triethylamine (20 mL) was added to a rigorously degassed solution of **5** (80 g, 0.46 mol) in dichloromethane (800 mL). The mixture was stirred at room temperature overnight under a dry nitrogen atmosphere. The resulting quinol **7** was cooled (15 °C), treated with $FeCl_3$ (187 g, 1.13 mol) in degassed ethanol (1.5 L) at 30 °C, stirred for 2 h, diluted with water (1 L), extracted into benzene (2 × 1 L), washed (3 × 1 L H_2O, 2 × 1 L 10 % $NaHCO_3$, 3 × 1 L H_2O), and dried (anhyd. Na_2SO_4); the solvent was removed leaving **8** (73.8g, 93 %). Recrystallization from petroleum ether gave **8** as a yellow powder (68 g, 87 %); m.p. 66 °C lit.[9] 66–67 °C.

***endo-syn-endo*-1,4,4a,5,8,8a,9a,10a-Octahydro-(1,4),(5,8)-dimethano-9,10-anthraquinone (1)**: Quinone **8** in benzene (800 mL) was chilled in an ice/salt bath before adding freshly cracked cyclopentadiene (26.5 g, 0.4 mol) with stirring (ice/salt bath, 15 min; room temperature, 1 h). Solvent was removed in vacuo to yield a 60:40 mixture (by NMR spectroscopy) of *endo-syn* and *endo-anti* **9** (94.1 g, 100 %), m.p. 149–155 °C (lit.[5]155 °C). Recrystallization from CH_2Cl_2/petroleum ether gave 50 % of an 85:15 isomer mixture, m.p. 152–156 °C (lit.[5] 155 °C). Compound **9** (85:15 isomeric mixture, 53.6 g, 0.22 mol) in acetone (600 mL), and then water (10 mL) were added to a stirred suspension of $TiCl_3$ (79 g, 0.51 mol) in acetone (400 mL). The mixture was stirred at room temperature for 1 h, poured onto saturated $NaHCO_3$ solution (1 L), diluted with water (3 L), and extracted (2 × 400 mL CH_2Cl_2); the solvent was evaporated to give a near quantitative yield of **1** as a mixture of isomers (by NMR spectroscopy). Recystallization from CH_2Cl_2/pentane gave **1** (40.7 g, 77 %); m.p. 182–183 °C (lit.[5] 184 °C decomp); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.97$ (br dd, $J = 2.0$, 2.0 Hz, 4H), 3.39 (br s, 4H), 3.26 (br s, 4H), 1.38 (br d, $J = 9.80$ Hz, 2H), 1.23 ppm (br d, $J = 9.8$, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.5$, 136.7, 53.97, 46.99, 43.76 ppm; MS: *m/z*: 258 $[M+NH_4]^+$, 241 $[M+H]^+$.

Isobenzofuran (IBF) addition reaction of 1: Compound **1** (2.449 g, 10.2 mmol) was refluxed with Fieser's isobenzofuran precursor (13.42 g, 25.5 mmol) in diglyme (50 mL, 200 °C, 30 min). Solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel. Elution with 20 % dichloromethane/light petroleum removed 1,2,3,4-tetraphenylbenzene, followed by 20 % EtOAc/CH_2Cl_2 gave **3a–c**. Fractional recrystallization (CH_2Cl_2/cyclohexane) gave pure **3a** (135 mg, 3 %). A second crop and bulk of the material (2.70 g, 56 %) was a mixture of isomers **3a–c**. Extensive column chromatography (5 % EtOAc in CH_2Cl_2) followed by preperative HPLC (isocratic 70 % solvent B) gave pure **3b** and **3c**.

Compound 3a: M.p. 235–240 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.90$ (m, 8H), 5.00 (br s, 4H), 3.00 (m, 4H), 2.87 (m, 4H), 2.53 (dt, $J =$ 10.0, 2.2 Hz, 2H), 1.36 (m, 4H), 0.94 ppm (br d, 2H, $J = 10.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) : $\delta = 209.9$, 145.2, 126.5, 118.2, 82.56, 53.67, 43.77, 42.03, 34.15 ppm; MS: m/z: 477 $[M+H]^+$, 459, 441, 293, 275, 183, 165; elemental analysis calcd (%) for $C_{32}H_{28}O_4$: C 80.7, H 5.9; found: C 80.5, H 5.8.

Compound 3b: M.p. 207–210 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.0$–7.40 (m, 8H), 5.17 (br s, 2H), 5.08 (dd, $J = 3.5$, 2.0 Hz, 2H), 3.03 (m, 2H), 2.91 (m, 2H), 2.87 (m, 2H), 2.68 (dt, $J = 10.3$, 2.1 Hz, 1H), 2.29 (m, 2H), 2.12 (m, 2H) 1.82 (m, 2H), 0.97 (dt, $J = 10.3$, 1.3 Hz, 1H), 0.16 (dt, $J =$ 11.7 Hz, 1.3 Hz, 1H), −1.18 pp, (dt, $J = 11.7$, 2.1 Hz, 1H); ^{13}C NMR. (75 MHz, $CDCl_3$): $\delta = 209.4$, 145.7, 144.4, 127.1, 126.6, 119.9, 118.9, 82.87, 81.16, 54.45, 53.73, 43.65, 41.99, 41.96, 37.98, 34.52, 31.93 ppm; MS: m/z: 494 $[M+NH_4]^+$, 477 $[M+H]^+$, 459, 441, 359; elemental analysis calcd (%) for $C_{32}H_{28}O_4$: C 80.7, H 5.9; found: C 80.7, H 6.0.

Compound 3c: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$ (m, 8H), 5.29 (m, 4H), 2.83 (m, 4H), 2.43 (m, 4H), 2.38 (m, 4H), 0.18 (br d, $J = 11.5$ Hz, 2H), −1.11 pp, (br d, $J = 11.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.4$, 144.3, 127.1, 119.8, 81.26, 54.40, 42.36, 38.14, 31.76 ppm; MS: m/z: 477 $[M+H]^+$, 459, 441.

Reduction of 3a: The diketone **3a** (101 mg, 0.21 mmol) was refluxed with LAH (100 mg, 2.5 mmol) in Na-dried tetrahydrofuran (5 mL) for 12 hours. The reaction mixture was quenched (50 mL MeOH, water 30 mL), the solvent was removed under reduced pressure, and the aqueous residue was carefully acidified with hydrochloric acid (3 M) to just below pH4 and extracted with CH_2Cl_2 (2×100 mL). The extracts were dried ($MgSO_4$), filtered, and evaporated, and the residue was recrystallized from CH_2Cl_2/pentane to yield **4** as colorless crystals (76 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.07$ (m, 8H), 4.97 (m, 4H), 4.28 (m, 2H), 3.18 (br s, 2H; OH), 2.75 (m, 4H), 2.61 (dt, $J = 9.5$, 2.2 Hz, 2H), 2.50 (m, 4H), 1.69 (m, 4H), 0.93 ppm (br d, $J = 9.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.5$, 126.0, 118.4, 83.08, 70.87, 46.06, 44.78, 43.05, 37.97 ppm; MS: m/z: 481 $[M+H]^+$; elemental analysis calcd (%) for $C_{32}H_{32}O_4$: C 80.0, H 6.7; found: C 79.7, H 6.6.

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