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An unusual [4 + 4] cycloadduct from an *o*-quinodimethane: characterisation and computational studies

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An unusual [4 + 4] cycloadduct from an *o*-quinodimethane: characterisation and computational studies

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ABSTRACT

Trapping of a pyrimidinone-derived *o*-quinodimethane with tetraphenylcyclopentadienone gives a mixture of the [4 + 2] and formal [4 + 4] adducts. Computational studies show that the latter arises by a sequence of [4 + 2] cycloaddition, homolysis, radical recombination to a spiro-tetrahydrofuran and Claisen rearrangement under the thermolytic conditions.

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1. Introduction

The generation of *o*-quinodimethanes, for instance by thermal chelotropic elimination of SO₂, and their trapping by dienophiles in Diels-Alder reactions has been extensively studied.^{1,2} This chemistry, originally developed using benzenoid systems, has also been extended to a variety of heterocyclic systems. Judicious choice of the method of generation of the reactive intermediate and of the dienophile leads to good yields of the [4 + 2] cycloadducts. In the absence of efficient trapping, however, the *o*-quinodimethanes have often been found to dimerise to formal [4 + 4] products, as well as to polymerise (Scheme 1). The ratios of [4+2] and [4+4] dimers and polymers is dependent upon the aromaticity of the parent heterocycle (hence the inherent reactivity of the *ortho*-quinodimethane) and the steric bulk of substituents in the alpha positions.

Scheme 1. [4 + 2] and [4 + 4] cycloaddition pathways.

In general, head-to-head [4+4] dimers are favored in the case of furan³ pyrrole⁴, benzofuran⁵, oxazole⁶ and α -phenylthiazole⁷. α -Hindered thiophenes give both head to head and head to tail [4+4] dimers.⁸ [4+2] Dimers are favored with thiophene,⁹ benzothiophene,^{9a} α -hindered furan¹⁰ and indole¹¹ *ortho*-quinodimethanes. Mixtures of all the regioisomers of both [4+2] and [4+4] dimers were observed in the case of an oxazole *o*-quinodimethane¹² The [4+2] dimers have been determined to be the kinetic products whereas the [4+4] dimers are favored

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thermodynamically.¹⁰ It has been suggested that the conversion of [4 + 2] dimers to [4 + 4] dimers is by a radical process.^{3c}

2. Results and Discussion

It was previously shown that *o*-quinodimethanes could be generated from sulfone **1a** by thermolysis and trapped with *N*-phenylmaleimide, diethyl fumarate and methyl acrylate to give the expected Diels-Alder products.¹⁴ In all of these processes, the *o*-quinodimethane **2a** acts necessarily as the 4 π -component. If, on the other hand, a diene is added as the trapping reagent, the *o*-quinodimethane **2a** may act as either the 4 π - or the 2 π -component of the cycloaddition. Alternatively what could be called a formal [4 + 4] adduct (distinct from a dimer) might result. To the best of our knowledge, this question has not been addressed. To do so, tetraphenylcyclopentadienone **3** ("tetracyclone"), as a highly stable and readily available diene, was selected as the trapping reagent. Thermolysis of sulfone **1a** in the presence of tetraphenylcyclopentadienone **3** in either 1,2,4-trichlorobenzene at reflux or in toluene in a sealed tube at 200 °C yielded the expected [4 + 2] adducts **4a,a'** in which one double bond of the dienone acts as the 2 π -component (Scheme 2). These isomers were inseparable. Surprisingly, an additional isomer **5a** was also isolated which was confirmed to be the (formal) [4 + 4] cycloadduct of the *o*-quinodimethane **2a** and the dienone **3** by X-ray crystallography.¹⁵ **Notably, when the adducts, either the 4aa' mixture or 5a were resubmitted to the reaction conditions, no change was observed, i.e. the different cycloadducts do not interconvert at these temperatures.**

Curiously, although the related sulfone **1b** without the *N*-methyl substituent also gave a mixture of the [4 + 2] adducts **4b,b'** and the [4 + 4] adduct **5b**, yields were markedly lower. In addition some partially reduced tetraphenylcyclopentenone **6** was isolated. The mechanism of the reduction remains unknown. In contrast, both the methoxypyrimidinyl sulfone **1c** and the corresponding benzene analog **1d** gave only the expected [4 + 2] adducts **7a,b**, **8** and none of the corresponding [4 + 4] adducts.

While [4 + 4] dimers of *o*-quinodimethanes have been frequently observed, a [4 + 4] adduct with the trapping agent is unusual. We were, therefore, interested to understand how this compound formed. Trahanovsky has shown that the [4 + 4] dimer of the 2,3-quinodimethane of furan most likely arises by initial formation of Diels-Alder adducts, followed by C-C bond homolysis and recombination.¹³ As a similar process might be suggested in the present case, we sought to explore the reaction pathway by computational methods (Scheme 3, Figure 1). Tetraphenylcyclopentadienone **3** may participate as a 2 π -component. This leads to the isolated [4 + 2] adducts **4a,a'**. It may be noted that the [4 + 2] adducts **4a,a'** are stable under the reaction conditions (refluxing 1,2,4-trichlorobenzene). Alternatively, the *o*-quinodimethane **2a** may act as a 2 π -component, with tetraphenylcyclopentadienone **3** as the diene. A complication is that *o*-quinodimethane **2a** may act as the 2 π -component through either its 5-methylene or 6-methylene groups. As the 5-methylene must be more electron rich, we anticipated the initial formation of a Diels-Alder adduct **9**. This is borne out by calculation as the intermediates along the corresponding pathway from **2a** to **5a** by initial Diels-Alder reaction at the 6-methylene group are all consistently higher in free-energy.¹⁶

Scheme 2. [4 + 2] and [4 + 4] cycloaddition pathways.

The Diels-Alder adduct between tetraphenylcyclopentadiene **3** and the 5-methylene group of the *o*-quinodimethane **2a**, then undergoes homolytic C-C bond fission, as proposed by Trahanovsky,¹³ to give diradical **10**. This is supported by KS-DFT calculations on model systems (Figure 1; three phenyl groups were omitted from the calculations for computational economy) which show that the triplet diradical is only 5.3 kcal/mol higher in energy than the Diels-Alder adduct. Thus, the highly resonance stabilized triplet diradical **10** is easily accessible under the reaction conditions. While we had initially suspected that the diradical **10** would directly recombine to give the [4 + 4] adduct **5a**, the calculations clearly showed that the diradical would, instead, recombine rapidly to give the spiro-tetrahydrofuran **11**. Further calculations showed that the resulting spiro-tetrahydrofuran **11** can easily undergo a [3,3]-sigmatropic rearrangement under the reaction conditions through a boat-like transition state to give the [4 + 4] adduct **5a** (Figure 2). The computed free-energy barrier for this process with the model system is 22.5 kcal/mol w.r.t the Diels-Alder adduct.

Figure 1. The calculated pathway. Y-axis is in terms of free-energies (kcal/mol). X-axis is the reaction co-ordinate. For the calculation of the pathway, only the phenyl group α to the radical is included.

Figure 2. The transition state calculated for the [3,3] sigmatropic rearrangement. The boat-like moiety is highlighted for clarity. Distances given in Ångstroms.

3. Conclusion

When the *o*-quinodimethane is generated in the presence of a tetraphenylcyclopentadienone **3**, several possible [4 + 2] cycloaddition reactions occur in which the added diene may act as either the 2π or 4π component. In the latter case, the final product is a formal [4 + 4] cycloaddition product, formed from the corresponding [4 + 2] cycloaddition product by a combination of homolysis-radical recombination and a hitherto unsuspected Claisen rearrangement of a spiro-tetrahydrofuran intermediate.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were carried out under an inert atmosphere (nitrogen or argon) using oven-dried glassware (150 °C). Unless otherwise specified, all starting materials, reagents, anhydrous solvents and solvents were obtained from commercial vendors and used as received. Reactions were monitored by crude NMR or analytical thin-layer chromatography (TLC) using Merck silica gel 60, F254 precoated glass plates. Column chromatography was performed with either silica gel 60 (230 - 400 mesh) or RediSep® normal-phase silica flash columns on Teledyne Isco CombiFlash® system. Microwave reactions were carried out using a Biotage® Initiator microwave synthesiser. ^1H and ^{13}C NMR spectra were recorded on Bruker AV400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with TMS or CHCl_3 as the internal standard (For ^1H NMR, TMS: 0.00 ppm, CHCl_3 : 7.26 ppm. For ^{13}C NMR, TMS: 0.00 ppm, CHCl_3 : 77.0 ppm). Coupling constants, J , are recorded in Hz and data are reported as follow: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration. ^{13}C NMR spectra are obtained with complete proton decoupling. Mass spectra were recorded on Finnigan LCQ DECA XP MAX Ultra instrument with ESI mode, Finnigan Polaris Q GCMS XP instrument with EI mode, ABSciex API 3200 instrument with ESI mode or Waters Acquity UPLC ZQ2000 instrument with ESI mode. High resolution mass spectra were recorded on Waters Q-ToF Premier instrument or LTQ Orbitrap XL mass spectrometer. Infrared (FTIR) spectra were recorded on Bruker Alpha-E FT-IR or IR Jasco FT-IR 4100 instruments either as a thin film or solid. Melting points were determined on Büchi melting point B-540 instrument and are uncorrected. Optical rotations were recorded on Jasco P-1030 polarimeter at wavelength of 589 nm. Chiral purity were determined either using Agilent 1100 LC system or Thar SFC X5-250 instrument. Sulfones **1a**, **1b** and **1c** were prepared by the method reported previously.¹⁴

Reaction of 2,3-dimethyl-5,6-dimethylenepyrimidin-4-one **1a with tetraphenylcyclopentadienone **3**.** 2,3-Dimethyl-3*H*-5,7-dihydrothieno[3,4-*d*]pyrimidin-4-one 6,6-dioxide **1a** (0.28 g, 1.31 mmol) and tetraphenylcyclopentadienone **3** (0.6 g, 1.57 mmol) were added to 1,2,4-trichlorobenzene (3 mL) and the resulting solution was heated at reflux for 3 hours. The reaction mixture was then allowed to cool and the crude mixture was purified first by gravity column chromatography (silica gel, 50% dichloromethane in petroleum ether as eluant) to remove the solvent and the excess of tetraphenylcyclopentadienone and then the polarity of the eluant was increased in increments to 50% ethyl acetate in petroleum ether and the products isolated by flash column chromatography. The major product, identified as an inseparable pair of Diels-Alder adducts **4aa'** in a 2:1 ratio, was

isolated as a white crystalline solid (0.34 g, 49% yield), m.p. 119–145 °C. $\nu_{\max}$ (nujol) 1695, 1661 cm^{-1} ; δ_{H} (CDCl_3) major: 2.35 (s, 3H), 3.06 (d, 1H, $J = 14.7$ Hz), 3.25 (d, 1H, $J = 16.2$ Hz), 3.50 (s, 3H), 3.59 (d, 1H, $J = 14.7$ Hz), 3.76 (d, 1H, $J = 16.2$ Hz), 6.47–6.54 (m, 2H), 6.89–7.25 (m, 18H, Ph); minor: 2.49 (s, 3H), 3.17 (d, 1H, $J = 15$ Hz), 3.33 (d, 1H, $J = 15.9$ Hz), 3.36 (s, 3H), 3.45 (d, 1H, $J = 15$ Hz), 3.53 (d, 1H, $J = 15.9$ Hz), 6.47–6.54 (m, 2H), 6.89–7.25 (m, 18H, Ph); δ_{C} major: 23.3, 29.6, 31.4, 35.6, 62.1, 64.0, 117.1, 126.1, 126.8, 127.5, 127.9, 128.1, 128.1, 128.6, 128.7, 128.8, 129.1, 129.3, 129.5, 130.1, 131.3, 134.2, 140.7, 141.9, 142.5, 157.3, 159.4, 160.9, 171.2, 207.3; minor: 22.7, 29.4, 31.3, 37.3, 62.3, 64.7, 117.0, 126.2, 126.8, 127.5, 127.9, 128.1, 128.1, 128.6, 128.7, 128.8, 129.1, 129.3, 129.5, 130.1, 131.0, 131.5, 134.0, 140.9, 141.6, 157.9, 159.4, 160.7, 172.5, 207.6; m/z M^+ 534 (68%), 508 (4), 466 (6), 457 (17), 438 (7), 425 (5), 384 (62), 356 (27), 327 (9), 307 (4), 289 (5), 278 (8), 265 (7), 252 (5), 214 (7), 178 (100), 176 (10), 152 (8), 105 (11), 91 (6), 77 (7), 56 (46), 43 (7); HRMS: 534.23133, $\text{C}_{37}\text{H}_{30}\text{N}_2\text{O}_2$ requires 534.23071.

Also isolated was a white crystalline solid, (0.23 g, 33% yield), m.p. 220 °C (dec.) which was identified as the formal [4+4] cycloadduct **5a**. $\nu_{\max}$ (nujol) 1741, 1645, 1459 cm^{-1} ; δ_{H} (CDCl_3) 2.46 (s, 3H), 3.08 (d, 1H, $J = 16.5$ Hz), 3.51 (s, 3H, CMe), 3.58 (d, 1H, $J = 16.5$ Hz), 3.78 (d, 1H, $J = 16.5$ Hz), 4.53 (d, 1H, $J = 16.5$ Hz), 6.62–6.71 (m, 4H), 6.88–7.02 (m, 6H), 7.20–7.45 (m, 10H); δ_{C} 22.8, 31.7, 33.9, 45.6, 63.8, 64.4, 119.5, 127.1, 127.2, 127.4, 127.5, 127.7, 127.8, 128.3, 128.4, 128.4, 128.5, 129.5, 129.8, 134.9, 135.0, 138.5, 138.7, 142.4, 142.8, 155.5, 158.4, 163.48, 219.8; m/z M^+ 534 (36%), 506 (8), 384 (63), 356 (25), 307 (4), 276 (7), 254 (8), 214 (7), 178 (100), 149 (14), 56 (71). HRMS: 534.23027; $\text{C}_{37}\text{H}_{30}\text{N}_2\text{O}_2$ requires 534.23071.

Reaction of 2-methyl-3H-5,7-dihydrothieno[3,4-d]pyrimidin-4-one 6,6-dioxide **1b with tetraphenylcyclopentadienone **3**.**

2-Methyl-3H-5,7-dihydrothieno[3,4-d]pyrimidin-4-one 6,6-dioxide **1b** (0.1 g, 0.51 mmol) and tetraphenylcyclopentadienone **3** (0.24 g, 0.62 mmol) were added to 1,2,4-trichlorobenzene (2 mL) and the resulting solution was heated at reflux for 5 hours. The reaction mixture was then allowed to cool and the crude mixture was purified first by gravity column chromatography (silica gel, 50% dichloromethane in petroleum ether as eluant) The product **5b** was isolated as a white crystalline solid (0.05 g, 19% yield) m.p. 180 °C (dec. with gas evolution); $\nu_{\max}$ (film) 3130, 1698, 1652; δ_{H} (CDCl_3) 2.40 (s, 3H), 3.05 (d, 1H, $J = 16.2$ Hz), 3.65 (d, 1H, $J = 16.2$ Hz), 3.88 (d, 1H, $J = 16.2$ Hz), 4.50 (d, 1H, $J = 16.2$ Hz), 6.62–6.70 (m, 4H, Ph), 6.85–7.08 (m, 6H, Ph), 7.22–7.44 (m, 10H, Ph); δ_{C} 21.4, 32.6, 46.0, 64.6, 119.9, 127.3, 127.5, 127.6, 127.8, 128.3, 128.4, 128.6, 129.6, 129.8, 130.4, 131.9, 133.7, 134.8, 138.3, 138.5, 142.4, 143.0, 155.0, 163.0, 166.1, 169.9, 219.4; m/z M^+ 520 (20%), 384 (36), 356 (16), 278 (6), 265 (5), 207 (7), 178 (100), 136 (8), 91 (8), 77 (13), 42 (33). HRMS: 520.21518, $\text{C}_{36}\text{H}_{28}\text{N}_2\text{O}_2$ requires 520.21503.

Also isolated as a white crystalline solid, m.p. 315–322 °C (dec., charring above 200 °C) which was an inseparable pair of Diels-Alder adducts **4b,b'** (0.4 g, 13% yield) corresponding to the two expected regioisomers in a 1:1 ratio. $\nu_{\max}$ (film) 3130, 1698, 1652; δ_{H} (CDCl_3) 2.39–2.65 (m, 2H), 2.45 (s, 3H), 2.56 (s, 3H), 3.37–4.11 (m, 2H), 6.87–7.36 (m, 20H); m/z M^+ 520 (8%), 493 (14), 492 (41), 385 (18), 384 (55), 356 (27), 276 (10), 267 (23), 225 (91), 178 (100), 152 (7), 105 (21), 77 (22), 42(12). HRMS: 520.21518, $\text{C}_{36}\text{H}_{28}\text{N}_2\text{O}_2$ requires 520.21503.

Also isolated was a white crystalline solid (35 mg, 18%) of comparable polarity to tetraphenylcyclopentadienone and this

was identified as tetraphenylcyclopentenone (dihydrotricyclone)²¹ **6**: $\nu_{\max}$ 1690 cm^{-1} ; δ_{H} (CDCl_3) 3.75 (d, 1H, $J = 2.5$ Hz) 4.56 (d, 1H, $J = 2.5$ Hz), 7.07–7.44 (m, 20H); δ_{C} 57.7, 63.2, 127.1, 127.3, 127.7, 127.9, 128.2, 128.3, 128.5, 128.6, 128.7, 129.0, 129.1, 129.5, 129.9, 131.8, 134.9, 139.3, 141.5, 168.8, 206.0; m/z M^+ 386 (65%), 309 (20), 267 (21), 252 (6), 203 (11), 191 (12), 178 (31), 167 (16), 111 (11), 105 (23), 69 (26), 57 (35), 45 (100).

Reaction of 2-phenyl-4-methoxy-5,7-dihydrothieno[3,4-d]pyrimidine-6,6-dioxide **1c with tetraphenylcyclopentadienone **3**.**

2-Phenyl-4-methoxy-5,7-dihydrothieno[3,4-d]pyrimidine-6,6-dioxide **1c** (90 mg, 0.33 mmol) and tetraphenylcyclopentadienone **3** (0.15 g, 0.39 mmol) were dissolved in 1,2,4-trichlorobenzene (3 mL) and the solution was heated at reflux for 3 hours. The entire reaction mixture was then purified by column chromatography (silica gel, 10% DCM in hexane to remove the solvent and tetraphenylcyclopentadienone, then 50% DCM in hexane) to give the product **7a,b** as two inseparable diastereoisomers (0.16 g, 81% yield), m.p. 148–155 °C. $\nu_{\max}$ (film) 3062, 1755, 1703 cm^{-1} ; δ_{H} (CDCl_3) 3.16 (dd, 1H, $J = 15.9$, 1 Hz), 3.26 (d, 1H, $J = 15.3$ Hz), 3.40 (d, 1H, $J = 14$ Hz), 3.47 (d, 1H, $J = 14$ Hz), 5.78 (d, 1H, $J = 15.6$ Hz), 3.86 (d, 1H, $J = 15.3$ Hz), 4.03 (s, 3H), 4.12 (s, 3H), 4.24 (d, 1H, $J = 15.6$ Hz), 4.34 (d, 1H, $J = 15.9$ Hz), 6.30–6.34 (m, 2H), 6.44–4.48 (m, 1H), 6.62–6.70 (m, 1H), 6.83–7.01 (m, 10H), 7.04–7.23 (m, 16H), 7.26–7.48 (m, 16H), 8.23–8.26 (m, 2H), 8.44–8.50 (m, 2H); m/z M^+ 596 (16%), 567 (3), 389 (4), 384 (17), 356 (12), 278 (6), 245 (10), 178 (100), 176 (12), 152 (10), 118 (39), 104 (25), 91 (12), 77 (26), 55 (13), 43 (14).

5,7-Dihydrothieno[3,4-d]-benzene-6,6-dioxide **1d.**

m-CPBA (3.5 g, 16.2 mmol) was slowly added to a solution of 5,7-dihydrothieno[3,4-d]-benzene (**1** g, 7.4 mmol) in dichloromethane (25 mL) at room temperature. The solution stirred overnight. The reaction mixture was washed with aq. sodium thiosulfate solution and the product extracted into dichloromethane. The organic extracts were dried over MgSO_4 and concentrated *in vacuo* to yield a white crystalline solid (1 g, 80%), m.p. 152–153 °C, lit.²² 150–151 °C. δ_{H} (CDCl_3): 4.37 (s, 4H), 7.27–7.39 (m, 4H); δ_{C} 56.9, 126.0, 128.8, 131.3.

Reaction of sulfone **1d with tetraphenylcyclopentadienone **3** to give compound **8**.**

5,7-Dihydrothieno[3,4-d]-benzene-6,6-dioxide **1d** (0.25 g, 1.5 mmol) and tetraphenylcyclopentadienone **3** (0.69 g, 1.8 mmol) were dissolved in 1,2,4-trichlorobenzene (2 mL) and the solution heated at reflux for 4 hours. On cooling, the entire reaction mixture was purified by flash column chromatography (silica gel, 20% dichloromethane in petroleum ether as eluant), to give adduct **8** as a white crystalline solid (0.29 g, 40%), m.p. 261–263 °C. $\nu_{\max}$ (nujol) 1693, 1615 cm^{-1} ; δ_{H} (CDCl_3) 3.09 (d, 1H, $J = 13.6$ Hz), 3.47 (d, 1H, $J = 13.9$ Hz), 3.56 (d, 1H, $J = 13.9$ Hz), 3.74 (d, 1H, $J = 13.6$ Hz), 6.20–6.28 (m, 2H), 6.54–6.60 (m, 1H), 6.87–7.32 (m, 21H); δ_{C} 29.7, 36.1, 44.4, 61.6, 64.7, 125.8, 126.3, 126.5, 126.8, 127.2, 127.4, 127.5, 127.7, 127.9, 128.0, 128.4, 128.7, 128.8, 129.6, 129.8, 131.5, 134.2, 135.8, 136.3, 141.1, 142.4, 143.3, 172.9, 208.6; m/z M^+ 488 (100%), 411 (5), 397 (9), 384 (19), 356 (13), 291 (7), 279 (5), 267 (6), 205 (5), 191 (5), 178 (43), 165 (5), 152 (5), 97 (3), 85 (3), 71 (4), 57 (5), 43 (5), 28 (15). HRMS: 488.2101 $\text{C}_{37}\text{H}_{28}\text{O}$ requires 488.2140.

4.2 Computational Details

All the calculations were performed using the *Gaussian 09* suite of programs.¹⁷ The geometries were optimized with the dispersion corrected ω B97XD¹⁸ density functional in conjunction with 6-31+G(d,p) basis-sets. Harmonic frequencies computed at the same level of theory revealed the nature of the saddle-point obtained (no imaginary frequency for a minimum energy structure, and one imaginary frequency for a transition-structure). Thermal corrections to the free-energies/energies and zero-point energies were also included. A combination of IRC calculations¹⁹ and steep-optimizations were carried out to ensure that the transition structure connected with the desired minima on both the sides. Single point energies were subsequently procured at the ω B97XD/6-311++G(3df,2p) level of theory with the implicit SMD²⁰ solvation model (solvent – toluene).

To expedite the calculations, model system 1 (Figure 1) containing one phenyl group was employed. Since the inclusion of the other phenyl groups is only expected to further enhance the resonance stabilization of the proposed diradical **10**, the choice of the model system is not anticipated to alter the insights obtained via computations. Broken-symmetry DFT calculations were performed to get the singlet spin-state of the diradical which is confirmed to be considerably higher in energy than the triplet state. Lastly, the $\langle S^2 \rangle$ values for the triplet-state are 2.091 and 2.002 (before and after the annihilation of the first spin-contaminant, respectively), thus indicating insignificant spin-contamination.

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Supplementary Material

¹H and ¹³C NMR spectra for compounds **4aa'** and **5a**; X-Ray crystallographic data for compound **5a**. The co-ordinates for all the structures shown in Figure 1, and a comparison between Diels-Alder additions at the 5-methylene and 6-methylene positions of **2a**.