Tailor-Made Butadienes for the Site-Selective Cycloaddition with Quinizarinquinone and Other Unsymmetrically Substituted Quinones

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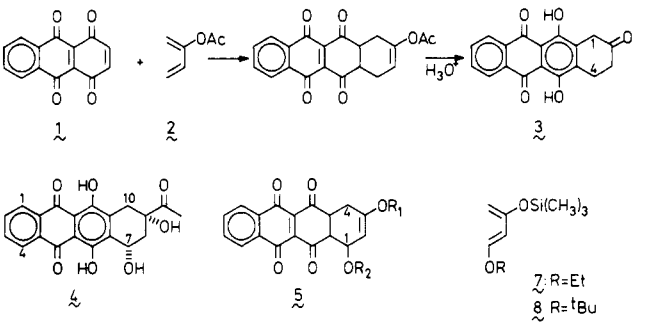
Two new electron-neutral 1,3-dioxybuta-1,3-dienes have been developed, namely, 1,3-diacetoxybuta-1,3-diene and 1-[(ethoxycarbonyl)oxy]-3-acetoxybuta-1,3-diene, which show other site selectivity toward unsymmetrically substituted quinones than the known 1-alkoxy-3-[(trimethylsilyl)oxy]buta-1,3-dienes and another new butadiene, viz., 1-acetoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene. Reaction of 1,3-diacetoxybutadiene with quinizarinquinone leads to a promising synthon for the preparation of demethoxydaunomycinone.

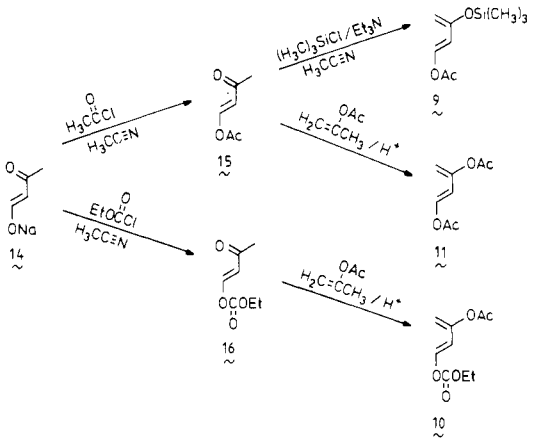
The great activity addressed to the preparation of anthracycline antitumor compounds such as daunomycine and adriamycine[1] has intensified the interest in cycloadditions to quinones. Many synthetic approaches[2-13] to the tetracyclic system occurring in anthracyclines are based on Diels–Alder reactions of suitably substituted naphtho- or anthraquinones. In the first Diels–Alder synthesis of daunomycinone by Kende et al.,[9] the cycloaddition of quinizarinquinone (**1**) with 2-acetoxybutadiene (**2**) followed by hydrolysis was used for the preparation of the tetracyclic compound **3** (Scheme I). Application of this product as a precursor for demethoxydaunomycinone (**4**) requires, however, the introduction of an oxygen substituent at C(4), what appeares to be a rather tedious task.[9a]

We envisaged that a better procedure for the preparation of **4** might be obtained when a diene containing two oxygen substituents at C(1) and C(3) is used in the cycloaddition. In the cycloadduct **5** a proper C(1) substituent would then already be present. 1-Alkoxy-3-[(trimethylsilyl)oxy]butadienes, which have shown broad synthetic scope for the generation of cyclic enones[14-16] and recently of β-hydroxycyclohexanones,[17] appeared unsuitable for this purpose; their cycloaddition with **1** proceeds exclusively at the internal double bond of the diquinone.

Scheme I



Scheme II. Preparations of Butadienes 9-11



Previous investigations have supplied a general insight into the site selectivity of cycloadditions between butadienes and a diquinone like **1**. Butadiene itself and other "electron-neutral" butadienes react preferentially at the external 2,3-double bond. Strongly nucleophilic butadienes containing electron-donating substituents add to the internal 4a,10a-double bond. This dependence of the re-

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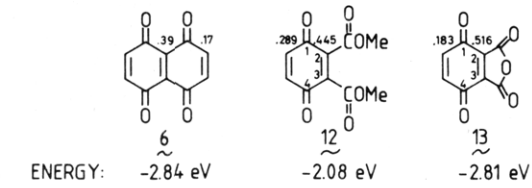


Figure 1. LUMO energies and coefficients of unsymetrically substituted benzoquinones.[18,21]

gioselectivity on the nature of substituents in the diene has been rationalized by a resonance theory model,[3] and more recently by a model[18] based on Fukui's frontier molecular orbital (FMO) theory.[19,20] Calculation of the LUMO energy and coefficients by Houk et al.[18] (STO-3G) of 1,4,5,8-naphthodiquinone (**6**, Figure 1) shows that the carbon atoms of the internal double bond have the higher LUMO coefficients.

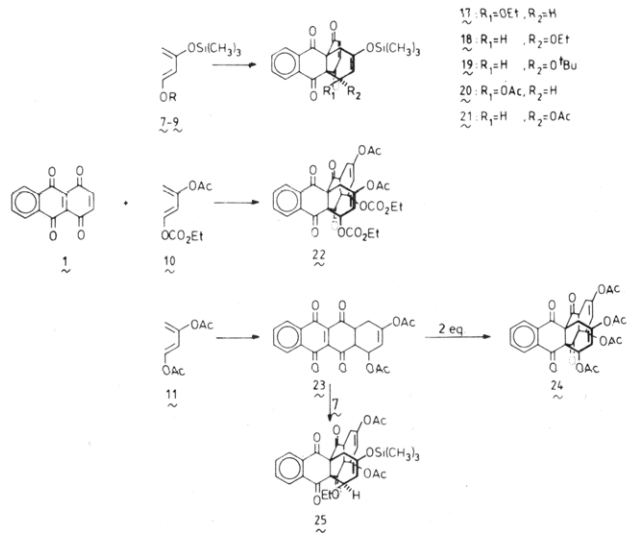
Therefore electron-rich butadienes (e.g., 1-alkoxy-3-[(trimethylsilyl)oxy]butadienes) having large HOMO coefficients at C(4) will add faster at the internal rather than at the external double bond. In cycloadditions of electron-neutral butadienes, having lower HOMO energies and coefficients, the electronic factor becomes less important. Because of the lower reactivity the transition state is reached at a later stage; the reaction is not completely controlled by FMO coefficients but also by steric factors. This leads to addition at the less hindered double bond.

Starting from this general insight we studied the regioselectivity of the cycloadditions of a series of butadienes, all having two oxygen substituents, with quinizarinquinone (**1**). The dienes used, arranged in order of decreasing HOMO energies, are 1-ethoxy-3-[(trimethylsilyl)oxy]butadiene (**7**), 1-*tert*-butoxy-3-[(trimethylsilyl)oxy]butadiene (**8**), 1-acetoxy-3-[(trimethylsilyl)oxy]butadiene (**9**), 1-[(ethoxycarbonyl)oxy]-3-acetoxybutadiene (**10**), and 1,3-diacetoxybutadiene (**11**). The compounds **7–11** were also used in cycloadditions with two unsymmetrically substituted benzoquinones, viz., **12** and **13** (Figure 1). The LUMO coefficients of these compounds were calculated by Kanematsu et al.[21] (MNDO), both benzoquinones have lower LUMO energies than benzoquinone (−1.51 eV), causing a higher reactivity. The steric relationships are comparable in **12** and **13**, and in both compounds the LUMO coefficients at C(2) and C(3) are larger than at C(5) and C(6). However, the difference between the LUMO coefficients in **12** is much smaller than in **13**; this might cause a higher site selectivity in reactions of the latter compound.

Preparation of the Butadienes 7–11. The preparation of the 1-alkoxy-3-[(trimethylsilyl)oxy]butadienes **7** and **8** has been described previously (ref 15a and 17, respectively). The newly synthesized butadienes **9–11** were obtained according to Scheme II. Sodium acetoacetaldehyde (**14**) was acylated in acetonitrile with acetyl chloride and with ethyl chloroformate, giving the products **15** and **16**, respectively. Treatment of **15** with chlorotrimethylsilane and triethylamine gave the butadiene **9**. The butadienes **10** and **11** were obtained by reaction of **16** and **15** with isopropenyl acetate and a catalytic amount of sulfuric acid.

Reactions with Quinizarinquinone (1). The cycloadditions were performed by mixing equimolar amounts

Scheme III. Reactions of Butadienes 7–11 with Quinizarinquinone (1)



of **1** and a butadiene in tetrahydrofuran as the solvent at room temperature. During the course of the reaction the insoluble quinone (**1**) went into solution and the reaction was terminated when **1** had disappeared completely. As expected the reactivity decreased in the order **7** ~ **8** > **9** > **10** > **11**. Two modes of cycloaddition are possible, addition at the internal double bond, leading to the products **17–21**, or addition at the external double bond, giving product **23** (Scheme III).

A third type of product might be a bis-adduct (**22**, **24**), formed by two subsequent cycloadditions at the external as well as the internal double bond. The nature of the product could easily be established by taking a sample of the reaction mixture, evaporating the solvent, dissolving the residue in $CDCl_3$, and tracing the NMR spectrum. Spectra of the products **17–21** contain three olefinic proton signals, two of them occurring as an AB pattern at relatively low field (ca. 7 ppm); product **23** contains only one olefinic proton (ca. 6 ppm). Cycloadditions to the internal double bond can lead to a mixture of diastereomers having RO endo toward the central quinone ring or toward the terminal quinone ring. The external cycloadducts may also occur in diastereomeric forms, but it is known that cycloadditions of a quinone lead generally to an endo adduct.

In the reaction with the butadiene **7** a diastereomeric mixture of the internal cycloadducts (**17** and **18**) appeared to be formed. In the minor product (37%) the triplet of the Me group in the EtO substituent is shifted to higher field ($\Delta\delta$ 0.48) in comparison with the corresponding signal of the major product, pointing to more shielding by the aromatic ring. Therefore, we assign **17** to the minor and **18** to the major product.

Butadiene **8** also gave an internal cycloaddition reaction, but product formation proceeded quite stereoselectively; only one product was found. Because steric crowding is less when the *t*-BuO group is endo toward the terminal quinone ring we assign the structure **19** to the product; the position of the *t*-Bu signal in the NMR spectrum (δ 1) points also to the absence of aromatic shielding.

Butadiene **9** again gave a mixture of diastereomers in the ratio 3:2. In the NMR spectrum the singlet of the acetoxy group of the minor product is at higher field, indicating that **20** is the minor product. The reaction of **1** with **10** proceeded rather surprisingly. The reaction mixture contained only the bis-adduct **22** and an amount of unreacted **1**. Probably the product arises via an external cycloadduct because cycloadditions of **1** with an excess (2.5

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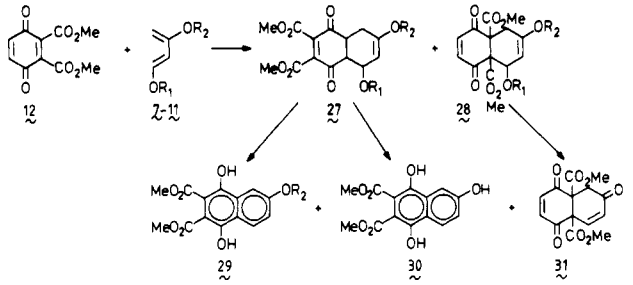
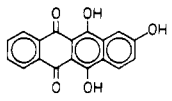
Scheme IV. Reactions of Butadienes 7, 9–11 with Quinone 12



equiv.) of 7, 8, or 9 did not yield bis-adducts indicating that butadienes do not add easily to the internal cycloadducts (17–21). The absence of an external monocycloadduct in the reaction mixture indicates that the reactivity of this compound in cycloadditions is increased in comparison with 1. As yet we have no good explanation for this establishment.[22]

The cycloaddition of 1 with the least reactive butadiene (11) gave at room temperature the external cycloaddition product 23 but in moderate yield. At higher temperature (40 °C) and using 11 in excess (2.5 equiv) the bis-adduct 24 was obtained. A "mixed" bis-adduct (25) could be obtained by the addition of 7 to 23. Only one isomer appeared to be formed. According to the position of the Me signal of the EtO group in the NMR spectrum, the EtO group was endo toward the naphthoquinone moiety.

The cycloadditions with 1 show that the weakly activated butadiene (11) adds quite selectively to the external double bond, giving a promising precursor for the preparation of anthracyclinones. Orientating experiments revealed that hydrolysis of 23 is accompanied by loss of the C(4) substituent through elimination. Under various conditions the aromatized product 26 was obtained. We are investigating whether the elimination can be suppressed when hydrolysis is preceded by hydrogenation of the central 5a,12a-double bond.



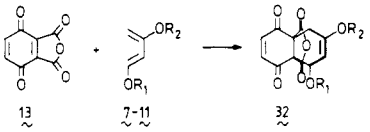
Reactions with the Substituted Benzoquinones 12 and 13. The reactions were performed similarly to the cycloadditions with 1 (equimolar amounts, THF as the solvent, room temperature, termination of the reaction when the insoluble quinone had disappeared). In the cycloadditions with 12 determination of the ratio of the two possible products (27 and 28, Scheme IV) from the NMR spectrum was slightly hampered by the instability of 27. In most experiments the elimination product 29 appeared to be present in the crude reaction mixture. Therefore, the product ratio was measured two times: (i) in the crude mixture, containing 27, 28, and 29 and (ii) in the mixture obtained after methanolysis and containing only stable compounds (29, 30, 31).

In both measurements the percentage of one of the products (28 or the corresponding 31) was evaluated from the intensity of the characteristic AB pattern for the quinone protons in 28 or 31 relative to the intensity of the combined signals of the COOMe groups in all compounds

Table I. Product Ratio of Cycloadditions of Butadienes 7, 9–11 with 12

	before methanolysis		after methanolysis	
butadiene	28	27 (+29)	31	29 + 30
7	100	0	100	0
9	90	10	80	20
10	36	64	25	75
11	28	72	20	80

Scheme V. Reactions of Butadienes 7, 9–11 with Quinone 13



present. The results (Table I) show that only the very nucleophilic butadiene 7 adds exclusively to the substituted double bond, giving 28 as the sole product, from which 31 can be obtained by methanolysis. On mild hydrolysis of 28 only the (trimethylsilyl)oxy group is transformed into a carbonyl group. The selectivity is lowered in the reaction of 12 with 9 and is reversed in the cycloaddition with 10. The reaction of 12 with 11 leads to a reaction mixture from which 29 (on methanolysis) or 30 (on mild hydrolysis with 0.01 N HCl in THF) can be obtained in good yield.

The reactions between 13 and the butadienes 7, 9–11 led always to addition at the substituted double bond (Scheme V), as could easily be established from the NMR spectra of the reaction mixtures. The high and general site selectivity in this case must be due to the larger difference between the LUMO coefficients on the carbon atoms of the external and internal double bond, in combination with the higher reactivity (lower LUMO energy) of 13 in comparison with 12.

Experimental Section

^{1}H NMR spectra were measured on a Bruker WH-90 spectrometer with Me_4Si as an internal standard. $CDCl_3$ was used as the solvent. IR spectra were measured with a Perkin-Elmer spectrophotometer, Model 997. Mass spectra were obtained with a double-focusing VG M-M7070E mass spectrometer (peak matching). Melting points were taken on a Kofler hot stage (Leitz-Weitzlar) and are uncorrected.

Preparation of 1-Alkoxy-3-[(trimethylsilyl)oxy]buta-1,3-dienes (7 and 8). These butadienes were prepared by methods described in the literature.[15c,17]

4-Acetoxy-3-buten-2-one (15). Acetyl chloride (17.2 g, 0.22 mol) was added dropwise at 0 °C to a suspension of sodium acetoacetaldehyde[23] (21.6 g, 0.20 mol) in 100 mL of acetonitrile. The mixture was stirred for 1 h after which it was filtered over hyflo. The filtrate was evaporated, and the residue was distilled through a Vigreux column (30 × 1.5 cm): yield 20.4 g (80%); bp 40 °C (0.5 torr) (lit.[24] bp 40 °C (0.5 torr); ^{1}H NMR δ 8.16 (1 H, d, J = 12 Hz, HC=C), 5.94 (1 H, d, J = 12 Hz, HC=C), 2.27 (3 H, s, OAc), 2.20 (3 H, s, CH_3); MS, m/e (EI) 128, 113, 100, 86, 85, 71, 43, 28, 15; M^+/e calcd 128.0473, found 128.0481.

1-Acetoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (9). Chlorotrimethylsilane (8.1 g, 75 mmol) was added to a solution of 4-acetoxybutenone (15) (6.4 g, 50 mmol) and triethylamine (2.4 g, 150 mmol) in 20 mL of acetonitrile. The reaction mixture was stirred overnight at 50 °C. The solvent was evaporated, and the residue was suspended in pentane. The precipitated salt was filtered and rinsed well with pentane. The pentane solutions were evaporated and the residue was purified by distillation through

(22) In a competition experiment 1 and 23 were brought in reaction with 1 equiv of the dienes 10 or 7. However, 1 appeared in every case more reactive than 23. So the enhanced reactivity must be a special property of the adduct of diene 10 and 1.

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a Vigreux column (30 × 1.5 mm): yield 7.6 g (76%); bp 56 °C (1.0 torr); ^{1}H NMR δ 7.50 (1 H, AB, J = 12 Hz, HC=C), 5.86 (1 H, AB, J = 12 Hz, HC=C), 4.24 (2 H, b s, H_2C=C), 2.13 (3 H, s, OAc), 0.23 (9 H, s, $Si(CH_3)_3$); MS, m/e (CI) 201 (M^+ + 1), 157, 129, 111, 87, 57, 43; (M^+ + 1)/e calcd 201.0944, found 201.0947.

1,3-Diacetoxybuta-1,3-diene (11). Chloroform (24 g, 0.20 mol) and isopropenyl acetate (50 g, 0.5 mol) were heated with 0.1 mL of concentrated sulfuric acid on an oil bath at 85 °C. 1-Acetoxybutenone (**15**) (6.4 g, 50 mmol) was added dropwise to the solution. The mixture was refluxed for 0.5 h after which a mixture of acetone and isopropenyl acetate was distilled from the solution (bp of the mixture, 55–64 °C). When the formation of acetone had stopped, the remaining isopropenyl acetate was evaporated. The residue was distilled through a Vigreux column (30 × 1.5 cm): yield 6.7 g (80%); bp 65 °C (0.5 torr); ^{1}H NMR δ 7.45 (1 H, AB, J = 12 Hz, HC=C), 5.97 (1 H, AB, J = 12 Hz, HC=C), 4.98 (1 H, AB, J = 2 Hz, H_2C=C), 4.89 (1 H, AB, J = 2 Hz, H_2C=C), 2.23 (3 H, s, OAc), 2.15 (3 H, s, OAc); MS, m/e (CI) 171 (M^+ + 1), 153, 129, 111, 87; (M^+ + 1)/e calcd 171.0657, found 171.0662.

4-[(Ethoxycarbonyl)oxy]-3-buten-2-one (16). Ethyl chloroformate (32.6 g, 0.30 mol) was added dropwise to an ice-cooled suspension of sodium acetoacetaldehyde (32.4 g, 0.30 mol) in 100 mL of acetonitrile. The mixture was stirred for 1.5 h at 0 °C and subsequently filtered. The filtrate was evaporated and the product distilled in vacuo through a Vigreux column (30 × 1.5 cm): yield 29.3 g (62%); bp 74 °C (0.7 torr); ^{1}H NMR δ 8.03 (1 H, d, J = 13 Hz, HC=C), 5.93 (1 H, d, J = 13 Hz, HC=C), 4.33 (2 H, q, J = 7 Hz, CH_2), 2.27 (3 H, s, CH_3), 1.38 (3 H, t, J = 7 Hz, CH_3); MS, m/e (EI) 158, 113, 99, 86, 71, 43, 29, 15; M^+/e calcd 158.0579, found 158.0579.

1-[(Ethoxycarbonyl)oxy]-3-acetoxybuta-1,3-diene (10). Isopropenyl acetate (50.0 g, 0.5 mol) was heated with 2 drops of concentrated sulfuric acid on an oil bath at 85 °C. 4-[(Ethoxycarbonyl)oxy]-3-buten-2-one (**16**) (15.8 g, 0.10 mol) was added dropwise. The acetone formed was distilled off as a mixture with isopropenyl acetate. The residue was extracted with pentane. The extract was filtered and evaporated. The residue was distilled at reduced pressure through a Vigreux column (30 × 1.5 cm): yield 10.3 g (49%); bp 82 °C (0.5 torr); ^{1}H NMR δ 7.22 (1 H, d, J = 12 Hz, HC=C), 5.98 (1 H, d, J = 12 Hz, HC=C), 4.98 (1 H, AB, J = 2 Hz, H_2C=C), 4.88 (1 H, d, J = 2 Hz, H_2C=C), 4.27 (2 H, q, J = 7 Hz, CH_2), 2.22 (3 H, s, OAc), 1.36 (3 H, t, J = 7 Hz, CH_3); MS, m/e (CI) 201 (M^+ + 1), 171, 159, 141, 129, 115, 111, 87, 69, 59, 43; (M^+ + 1)/e calcd 201.0770, found 201.0770.

Reaction of Butadiene 7 with Quinizarinquinone (1). To a suspension of quinizarinquinone (**1**)[13a] (1.19 g, 5 mmol) in 10 mL of THF was added butadiene **7** (0.93 g, 5 mmol). The mixture was stirred at room temperature for 3 h and subsequently evaporated. The residue was stirred with ether. Filtration of the suspension gave 0.25 g of the starting quinone. The ether was removed by evaporation. An NMR spectrum of the crude product showed only internal adducts (see text).

The product was purified by crystallization from ether/n-hexane, yielding 1.35 g (64%) of the internal monoadduct as a mixture of two isomers **17** and **18**, which were not separated: mp 105–107 °C; ^{1}H NMR δ 8.22–7.94 (2 H, m, ArH), 7.80–7.62 (2 H, m, ArH), 7.05 (0.63 H, A of AB, J = 10.5 Hz, HC=CH), 6.95 (0.37 H, A of AB, J = 10.5 Hz, HC=CH), 6.63 (0.63 H, B of AB, J = 10.5 Hz, HC=CH), 6.49 (0.37 H, B of AB, J = 10.5 Hz, HC=CH), 5.35–5.15 (1 H, m, HC=C), 4.84 (0.63 H, d, J = 12.6 Hz, HCO), 4.75 (0.37 H, d, J = 12.6 Hz, HCO), 3.71–2.80 (3 H, m, CH_2 and OCH_2), 2.13 (0.37 H, d, J = 18 Hz, CH_2), 2.03 (0.37 H, d, J = 18 Hz, CH_2), 0.99 (1.89 H, t, J = 7 Hz, CH_3), 0.53 (1.11 H, t, J = 7 Hz, CH_3), 0.25 (3 H, s, $Si(CH_3)_3$), 0.20 (6 H, s, $Si(CH_3)_3$); MS, m/e (CI) 425 (M + 1), 379, 353, 307, 297, 241, 179, 149, 115; (M^+ + 1)/e calcd 425.1420, found 425.1416. Elemental Anal. C, 64.99; H, 5.73. $C_{23}H_{24}O_6Si$ requires: C, 65.07; H, 5.70. IR (KBr) 1600 (s) (C=C), 1680, 1720 (C=O) cm^{-1}.

Reaction of Butadiene 8 with 1. To a suspension of **1** (1 g, 4.2 mmol) in 10 mL of THF was added butadiene **8** (1 g, 4.7 mmol). The mixture was stirred for 3 h at room temperature, after which the solvent was evaporated. An NMR spectrum was taken of the crude mixture which showed only internal addition. The oily product was crystallized from n-hexane, yielding 1.35 g (71%) of the internal monoadduct **19**: mp 98–99 °C; ^{1}H NMR δ 8.20–7.91 (2 H, m, ArH), 7.86–7.62 (2 H, m, ArH), 7.06 (1 H, A of AB, J = 10.2 Hz, HC=CH), 6.62 (1 H, B of AB, J = 10.2 Hz, HC=CH), 5.17 (1 H, dd, J = 1 Hz, J = 5.8 Hz, HC=C), 5.07 (1 H, d, J = 5.8 Hz, HCO), 3.21 (1 H, dd, J = 1 Hz, J = 18.3 Hz, CH_2), 1.99 (1 H, d, J = 18.3 Hz, CH_2), 1.04 (9 H, s, $C(CH_3)_3$), 0.18 (9 H, s, $Si(CH_3)_3$); MS, m/e (CI) 453 (M + 1), 397, 396, 379, 351, 299, 249, 241, 149; (M^+ + 1)/e calcd 453.1733, found 453.1725. Elemental Anal. C, 66.03; H, 6.22. $C_{25}H_{28}O_6Si$ requires: C, 66.35; H, 6.24. IR (KBr) 1600 (s) (C=C), 1680, 1710, 1725 (C=O) cm^{-1}.

Reaction of Butadiene 9 with 1. Butadiene **9** (1.0 g, 5 mmol) was added to a suspension of **1** (1.19 g, 5 mmol) in 5 mL of dry THF. The mixture was stirred overnight at room temperature. Evaporation of the solvent led to an oily residue from which an NMR spectrum was taken, showing the formation of only the internal adducts. The product was crystallized from diisopropyl ether/n-hexane, yielding 1.60 g (73%) of a mixture of **20** and **21**: mp 80–90 °C dec; ^{1}H NMR δ 8.16–7.93 (2 H, m, ArH), 7.90–7.62 (2 H, m, ArH), 7.14 (0.6 H, A of AB, J = 10 Hz, HC=CH), 6.93 (0.4 H, A of AB, J = 10 Hz, HC=CH), 6.69 (0.6 H, B of AB, J = 10 Hz, HC=CH), 6.57 (0.4 H, B of AB, J = 10 Hz, HC=CH), 6.13 (0.6 H, d, J = 5.6 Hz, HC=C), 6.02 (0.4 H, d, J = 5.6 Hz, HC=C), 5.35–5.02 (1 H, m, HCO), 3.48–3.04 (1 H, m, CH_2), 2.36–2.13 (1 H, m, CH_2), 1.85 (1.8 H, s, OAc), 1.25 (1.2 H, s, OAc), 0.22 (3.6 H, s, $Si(CH_3)_3$), 0.18 (5.4 H, s, $Si(CH_3)_3$); MS, m/e (CI) 438 (M), 379, 307, 241, 205, 133, 91, 75; IR (KBr) 1595 (w) (C=C), 1680, 1710, 1750 (C=O) cm^{-1}. Elemental Anal. C, 63.37; H, 4.72. $C_{23}H_{22}O_7Si$ requires: C, 62.99; H, 5.06.

Reaction of Butadiene 11 with Quinone 1. (a) To a suspension of **1** (1.19 g, 5 mmol) in 10 mL of THF was added butadiene **11** (0.85 g, 5 mmol). The reaction mixture was stirred at room temperature for 5 days. Evaporation of the reaction mixture left the crude product. The ^{1}H NMR spectrum showed only external addition. The crude product was dissolved in ether, and the precipitated starting quinone (0.1 g) was filtered off. The product crystallized on addition of n-hexane. The product was recrystallized from n-hexane yielding 0.85 g (43%) of 1,4,4a,12a-tetrahydro-1,3-diacetoxynaphthacene-5,6,11,12-tetrone (**23**): mp 170–180 °C dec; the residue sublimes at 240 °C; ^{1}H NMR δ 8.22–7.98 (2 H, m, ArH), 7.85–7.66 (2 H, m, ArH), 5.82 (1 H, d, J = 5.8 Hz, HC=C), 5.55 (1 H, dd, J = 5.8 Hz, J = 7.0 Hz, HCO), 3.75 (1 H, dd, J = 4 Hz, J = 7 Hz, CH), 3.58 (1 H, dd, J = 4 Hz, J = 7 Hz, CH), 3.10 (1 H, d, J = 18.25 Hz, CH_2), 2.53 (1 H, dd, J = 18.25 Hz, J = 4 Hz, CH_2), 2.20 (3 H, s, OAc), 1.70 (3 H, s, OAc); MS, m/e (CI) 349 (M + 1 - HOAc), 307, 241, 103, 61 (HOAc); (M^+ + 1 - HOAc)/e calcd 348.0634, found 348.0631; IR (KBr) 1595 (w) (C=C), 1715, 1750 (C=O) cm^{-1}.

(b) Butadiene **11** (2.55 g, 12.5 mmol) was added to a suspension of **1** (1.19 g, 5 mmol) in 10 mL of THF. The reaction mixture was stirred at 40 °C for 24 h. Evaporation of the solvent led to an oily residue, which crystallized after three precipitations with $CHCl_3$/n-hexane, yielding 1.90 g (65%) of the bis-adduct **24**: mp 151–154 °C dec; ^{1}H NMR δ 8.29–8.0 (2 H, m, ArH), 7.95–7.71 (2 H, m, ArH), 6.13 (1 H, d, J = 5.8 Hz, HC=C), 5.86–5.68 (3 H, m), 3.90–2.25 (6 H, m), 2.13 (3 H, s, OAc), 2.10 (3 H, s, OAc), 1.92 (3 H, s, OAc), 1.29 (3 H, s, OAc); IR (KBr) 1595 (s) (C=C), 1695, 1750 (C=O) cm^{-1}.

Reaction of Butadiene 10 with Quinone 1. Butadiene **10** (1 g, 5 mmol) was added to a suspension of quinone **1** (1.19 g, 5 mmol) in 10 mL of dry THF. The resulting mixture was stirred for 3 days at room temperature. The solvent was evaporated. An NMR spectrum taken of the residue showed a mixture of bis-adduct **22** and starting material in a ratio 1:1. The residue was suspended in ether and the precipitate of the starting material was filtered off. The ether was evaporated and the residue was crystallized from n-hexane, yielding 0.90 g (55%) of **22**: mp 197–199 °C; ^{1}H NMR δ 8.27–7.98 (2 H, m, ArH), 7.92–7.66 (2 H, m, ArH), 6.13–5.60 (4 H, m), 4.38–2.18 (10 H, m), 2.13 (3 H, s, OAc), 2.00 (3 H, s, OAc), 1.24 (3 H, t, J = 7 Hz, CH_3), 0.96 (3 H, t, J = 7 Hz, CH_3). Elemental Anal.: IR (KBr) 1595 (s) (C=C), 1695, 1750 (C=O) cm^{-1}.

Reaction of Monoadduct 23 with Butadiene 7. Butadiene **7** (250 mg, 1.34 mmol) was added to a solution of monoadduct **23** (100 mg, 0.25 mmol) in 10 mL of dry THF. The mixture was stirred at room temperature for 16 h. Evaporation of the solvent led to an oily residue, which crystallized from n-hexane, yielding 90 mg (61%) of the mixed bis-adduct **25**: mp 87–90 °C dec; ^{1}H NMR δ 8.20–7.90 (2 H, m, ArH), 7.84–7.63 (2 H, m, ArH), 5.89–5.62

(2 H, m), 5.16 (1 H, d, J = 5.6 Hz, HC=C), 4.65 (1 H, d, J = 5.6 Hz, HCO), 3.77–2.0 (8 H, m), 2.10 (3 H, s, OAc), 1.91 (3 H, s, OAc), 0.51 (3 H, t, J = 7.0 Hz, CH_3), 1.23 (9 H, s, $Si(CH_3)_3$); IR (KBr) 1600 (m) (C=C), 1680, 1750 (C=O) cm^{-1}.

4a,8a-Dicarbomethoxynaphthalene-1,4,6(5*H*)-trione (31). 2,3-Dicarbomethoxy-1,4-benzoquinone (**12**) (448 mg, 2 mmol) was suspended in 5 mL of dry THF. Butadiene **7** (390 mg, 2.1 mmol) was added. The mixture was stirred for 0.75 h, after which the solvent was evaporated. The NMR spectrum showed the formation of only **28** (R_1 = Et, R_2 = $SiMe_3$).

The crude product was dissolved in 10 mL of THF and stirred for 15 min after the addition of 1 mL of 0.1 N HCl. The product crystallized upon addition of *n*-hexane. Recrystallization from $CHCl_3$/*n*-hexane led to 440 mg (65%) 4a,8a-dicarbomethoxy-8-ethoxy-4a,7,8,8a-tetrahydronaphthalene-1,4,6(5*H*)-trione: 4a,8a-dicarbomethoxy-8-ethoxy-4a,7,8,8a-tetrahydronaphthalene-1-(2*H*),4(3*H*),6(5*H*)-trione: mp 143–145 °C; ^1H NMR δ 6.90 (1 H, A of AB, J = 10 Hz, HC=C), 6.75 (1 H, B of AB, J = 10 Hz, HC=C), 4.45 (1 H, t, J = 2.6 Hz, H(8)), 3.91 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.72 (1 H, dd, J = 16 Hz, J = 2 Hz, H(5a)), 3.72–2.98 (2 H, m, CH_2), 2.82 (1 H, d, J = 16 Hz, H(5e)), 2.72 (1 H, ddd, J = 15 Hz, J = 2 Hz, J = 2.6 Hz, H(7a)), 2.28 (1 H, dd, J = 15 Hz, J = 2.6 Hz, H(7e)), 0.98 (3 H, t, J = 7 Hz, CH_3). Elemental Anal. Found: C, 56.63; H, 5.32. $C_{16}H_{18}O_8$ requires: C, 56.80; H, 5.36. MS, m/e 338 (M), 306, 279, 274, 247, 234, 207, 190, 179, 175, 151, 113, 99, 82, 59, 54.

This product (250 mg, 0.74 mmol) was dissolved in 10 mL of methanol and 0.5 mL of concentrated hydrochloric acid. The mixture was refluxed for 3 h, after which the methanol was evaporated. The residue was dissolved in ethyl acetate and washed with brine. After drying over Na_2SO_4, the solvent was evaporated and the residue crystallized from ether/*n*-hexane leaving 200 mg (93%) of **31**: mp 127–129 °C; ^1H NMR δ 6.90 (1 H, A of AB, J = 10 Hz, HC=CH), 6.87 (1 H, d, J = 10 Hz, H(7)), 6.75 (1 H, B of AB, J = 10 Hz, HC=C), 6.12 (1 H, d, J = 10 Hz, H(8)), 3.85 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 3.49 (1 H, d, J = 17.5 Hz, H(5)), 2.81 (1 H, d, J = 17.5 Hz, H(5)). Elemental Anal. Found: C, 57.03; H, 4.32. $C_{14}H_{12}O_7$ requires: C, 57.54; H, 4.14. MS, m/e 292 (M), 261, 233, 205, 179, 151, 113, 82, 59, 54.

2,3-Dicarbomethoxy-1,4,6-trihydroxynaphthalene (30). 2,3-Dicarbomethoxy-1,4-benzoquinone (**12**) (440 mg, 2 mmol) was suspended in 5 mL of dry THF. Butadiene **11** (357 mg, 2.1 mmol) was added and the mixture was stirred at room temperature for 16 h, after which the solvent was evaporated. The residue was dissolved in 10 mL of concentrated HCl and refluxed for 1.5 h. The solvent was evaporated. The residue was dissolved in $CHCl_3$ and crystallized upon addition of *n*-hexane, yielding 280 mg (48%) of **30**: mp 174–177 °C (from ether); ^1H NMR δ 10.51 (1 H, s, ArOH), 10.20 (1 H, s, ArOH), 8.46 (1 H, d, J = 9.0 Hz, H(8)), 8.20 (1 H, d, J = 2.3 Hz, H(5)), 7.73 (1 H, dd, J = 9.0 Hz, J = 2.3 Hz, H(7)), 4.04 (6 H, s, OCH_3), 2.91 (1 H, bs, OH(6)). Elemental Anal.: C, 57.52; H, 4.28. $C_{14}H_{12}O_7$ requires: C, 57.54; H, 4.14. MS, m/e 292 (M), 260, 228, 200, 174, 144, 120, 89.

2,3-Dicarbomethoxy-6-acetoxy-1,4-dihydroxynaphthalene (29, R_2 = Ac). 2,3-Dicarbomethoxy-1,4-benzoquinone (**12**) (448 mg, 2 mmol) was mixed with butadiene **10** (357 mg, 2.1 mmol) in 5 mL of dry THF. The mixture was stirred for 16 h at room temperature, after which 5 mL of THF and 1 mL of 0.1 N HCl was added. The mixture was stirred for 15 min and evaporated. The residue was crystallized from $CHCl_3$/*n*-hexane, yielding 300 mg (45%) of the pure product: mp 96–98 °C; ^1H NMR δ 10.41 (1 H, s, ArOH), 10.22 (1 H, s, ArOH), 8.37 (1 H, d, J = 8.8 Hz, H(8)), 8.05 (1 H, d, J = 2.4 Hz, H(5)), 7.75 (1 H, dd, J = 2.4 Hz, J = 8.8 Hz, H(7)), 3.92 (6 H, s, OCH_3), 2.37 (3 H, s, OAc). Elemental Anal.: C 57.31; H, 4.24. $C_{16}H_{14}O_8$ requires: C, 57.49; H, 4.22. MS, m/e 334 (M), 302, 260, 228, 200, 174, 173, 119, 89.

Site Selectivity in Reactions of Butadienes with Benzoquinone 12, a Standard Procedure. The butadiene (2.0 mmol) was added to a suspension of dicarbomethoxy-1,4-benzoquinone **12** (448 mg, 2.0 mmol) in 5 mL of THF. The mixture was stirred at room temperature for 16 h. The solvent was evaporated and an NMR spectrum was taken from the residue. The percentage of **28** was evaluated as indicated in the text.

The residue was dissolved in 10 mL of methanol and 0.5 mL of concentrated hydrochloric acid and refluxed for 3 h. The solvent was evaporated leaving a mixture of products **29**, **30**, and **31**. The percentage of **31** was determined from the NMR spectrum as indicated in the text.

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Registry No. 1, 1709-63-3; 4, 95725-17-0; 7, 84302-38-5; 8, 83352-53-8; 9, 83352-55-0; 10, 95725-18-1; 11, 95725-19-2; 12, 77220-15-6; 13, 63401-20-7; 15, 13945-19-2; 16, 95725-20-5; 17, 95725-21-6; 18, 95783-37-2; 19, 95725-22-7; 20, 95725-23-8; 21, 95783-38-3; 22, 95725-24-9; 23, 95725-25-0; 24, 95725-26-1; 25, 95725-27-2; 26, 66314-42-9; 28 (R_1 = Et, R_2 = TMS), 95725-28-3; 29 (R_2 = Ac), 95725-29-4; 30, 95725-30-7; 31, 95725-31-8; 4a,8a-dicarbomethoxy-8-ethoxy-4a,7,8,8a-tetrahydronaphthalene-1,4,6(5*H*)-trione, 95725-32-9; sodium acetoacetaldehyde, 926-59-0; isopropenyl acetate, 108-22-5.

Syntheses and Inclusion Behavior of 5,8,14,17,23,26,32,35-Octamethoxy[3.3.3.3]paracyclophane and [3.3.3.3](2,5)-*p*-Benzoquinonophane

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Syntheses of 5,8,14,17,23,26,32,35-octamethoxy[3.3.3.3]paracyclophane (**1**)[1] having a π-electron-rich cavity and [3.3.3.3](2,5)-*p*-benzoquinonophane (**2**) having a π-electron-poor cavity are described, and the inclusion behaviors of these hosts are discussed. In principle, a host molecule having a π-electron-rich cavity may include π-electron-poor molecules and vice versa. Unexpectedly, neither π-electron-poor *p*-benzoquinone nor organic solvents were included in the π-electron-rich cavity of **1**. Although the π-electron-poor host **2** did not include π-electron-rich molecules such as hydroquinone and hydroquinone dimethyl ether, **2** was found to retain dioxane or CH_2Cl_2 in a 1:1 (host–guest) ratio, respectively. These results indicate that charge-transfer interaction does not play an important role in the formation of intracavity inclusion complexes between [3.3.3.3]cyclophane host molecules and neutral organic molecules.

Since Stetter's proposal[2] of the concept that cyclophane host molecules and uncharged organic molecules could form "intracavity inclusion complexes",[3] a few examples of the intracavity inclusion in the crystalline state have

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