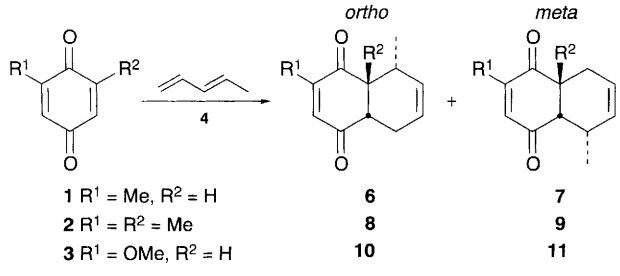
Control of Regioselectivity in the Diels–Alder Reactions of Alkyl-substituted 1,4-Benzoquinones by β-Cyclodextrin and its Derivatives

Wen-Sheng Chung* and Ju-Ying Wang

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan 30050, ROC

The Diels–Alder reactions of benzoquinones **1–3** with penta-1,3-diene **4** and isoprene **5** are studied in aqueous cyclodextrin solutions, where highly enhanced *ortho* (**6**, **8** and **10**) and *meta* (**13**, **15**) regioselectivities are achieved.

Quinones are widely employed as dienophiles in Diels–Alder reactions.[1] The diverse biological activity of quinones has led to the development of several new synthetic methods for quinones.[2,3] Much attention has been devoted to investigating the regio- and stereo-chemistry of Diels–Alder reactions by means of Lewis acid catalysis;[4] however, the acidic nature of the Lewis acid catalysts is not compatible with sensitive dienes or dienophiles prone to polymerization. The possibility of controlling the course of Diels–Alder reactions by the use of aqueous solvents[5,6] and by added cyclodextrins (CDs)[6,7] is also of considerable current interest. Although CDs have been known for several years to accelerate Diels–Alder reactions and enhance the *endo*/*exo* stereoselectivity,[6,7] surprisingly there have been few reports of their use in regio-selectivity control. As part of our continuing interest in using CDs to control diastereoselectivity in molecular reactions,[8] we report here a study in which aqueous CDs were applied to control the regioselectivity in Diels–Alder reactions of substituted 1,4-benzoquinones **1–3** with penta-1,3-diene **4** and isoprene **5**.



Scheme 1

The Diels–Alder reaction of methyl-1,4-benzoquinone **1** with **4** in the presence and absence of Lewis acids in an organic solvent has been reported previously by Valenta.[4c] The reaction of **1** (0.2 mol dm^{-3}) with **4** (0.2–0.35 mol dm^{-3}) in acetone at room temp. leads sluggishly to a 64:36 mixture of *ortho* and *meta* adducts, **6** and **7** (Scheme 1), in 52% yield; however, **7** was found to be the predominant product (**6**:**7** = 31:69) in BF_3·OEt_2 catalysed reactions (Table 1, entries 1, 5). The regioselectivity of **6**:**7** was found to increase from 66:34 in water to 83:17 in aqueous CD solution. Products were formed less selectively with modified β-CDs, which may be due to unfavoured geometry in inclusion complexes (Table 1, entries 3–4).[8] Table 1 summarizes some of our results in water and in β-CDs, where the plateau value is reported; *i.e.* the relative yield of *ortho* or *meta* products increased gradually with [β-CDs] until a constant value was reached (Fig. 1). Product yields were also improved in the presence of β-CDs compared with those in water alone.

Similar results were observed for the addition of 2,6-dimethylbenzoquinone **2** and 2-methoxy-benzoquinone **3** with **4** (Table 1, entries 6–12). When β-CD solution was used, excellent *ortho* selectivities (**8** and **10**) with very good yields were achieved. Notice that this *ortho* selectivity is reversed from that of the Lewis acid-catalysed reaction, where *meta* was the only product formed (Table 1, entry 8 *vs.* 9). β-CDs also have a profound effect on the rate of the Diels–Alder reactions of **2** and **3**; for example, less than 21% of adduct **10** was obtained in water compared to an 80% yield in β-CD for the same reaction time (Table 1, entries 10–12).

The addition of isoprene **5** is usually regio non-selective in Diels–Alder reactions. For example, Houk[9a] and Chiba[9b] independently reported that the Diels–Alder reaction of iso-

Table 1 Diels–Alder reactions of isoprene **4** and penta-1,3-diene **5** with quinones **1–3** in different media

Entry	Diene	Dienophile	Conditions[a]	*t*/h[b]	Product ratio[c]	Yield(%)[c]	Ref.
1	**4**	**1**	Acetone	48	**6**:**7** = 64:36	52	4*c*
2	**4**	**1**	Water	6	66:34	73	
3	**4**	**1**	β-CD–Water	6	83:17	82	
4	**4**	**1**	7-β-CD–Water	6	70:30	70	
5	**4**	**1**	BF_3·OEt_2–Toluene	—	31:69	>75	4*c*
6	**4**	**2**	Benzene	47	**8**:**9** = 90:10	64[d]	4*d*
7	**4**	**2**	Water	9 d	>99:1	25[d]	
8	**4**	**2**	β-CD–Water	40	>99:1	74[d]	
9	**4**	**2**	BF_3·OEt_2–CH_2Cl_2	5	0:100	90[d]	4*c*, 4*d*
10	**4**	**3**	Benzene	48	**10**:**11** = 100:0	77[d]	4*e*, 10
11	**4**	**3**	Water	18	>99:1	21[d]	
12	**4**	**3**	β-CD–Water	18	>99:1	80[d]	
13	**5**	**1**	Acetone	11 d	**12**:**13** = 53:47	23	
14	**5**	**1**	Water	24	56:44	30	
15	**5**	**1**	β-CD–Water	12	14:86	86	
16	**5**	**1**	7-β-CD–Water	12	45:55	88	
17	**5**	**1**	BF_3·OEt_2–CH_2Cl_2	4.5	69:31	96	
18	**5**	**2**	Benzene	2.5 d	**14**:**15** = 55:45	6	4*d*
19	**5**	**2**	Water	8 d	65:35	4[e]	
20	**5**	**2**	β-CD–Water	48	12:88	76[e]	
21	**5**	**2**	7-β-CD–Water	48	65:35	21[e]	
22	**5**	**2**	BF_3·OEt_2–CH_2Cl_2	7	16:84	93[e]	

[a] Reactions were run at room temp. except for those of BF_3·OEt_2 at 0 °C and benzene at 110–115 °C. 7-β-CD is heptakis-(6-*O*-hydroxypropyl)-β-CD, [β-CDs] = 0.14–0.28 mol dm^{-3}. [b] Reaction time in hours unless stated otherwise. [c] Satisfactory spectral data and elemental analysis were obtained. Yields and ratios were determined by GC analysis (*ca.* ±2%) unless otherwise specified. [d] Isolated yields. [e] Yields and ratios were determined by ^1H NMR.

prene with 2,5-dimethyl benzoquinone shows a 1 : 1 ratio of *para* and *meta* adducts. Addition of isoprene to both **1** and **2** in the presence of 1–2 equiv. of β-CD resulted in a large increase in the amount of *meta* adducts (Scheme 2; Table 1, entries 13–15, 18–20). Note that the *meta*-selectivity in **1** with CDs is opposite to that with Lewis acid-catalysis[10] (Table 1, entry 15 *vs.* 17); also, it would be difficult to achieve such a synthesis by other methods.† In the reaction of **2** with **5**, both β-CD and $BF_3{\cdot}OEt_2$ reversed the normal *para* selectivity with excellent yield (Table 1, entries 19–22). Interestingly, such processes in CDs are often carried out in suspensions, and in these cases, the reaction proceeds *via* small amounts of dissolved reactants.

The observed preference for the *ortho* (reactions with penta-1,3-diene **4**) or *meta* (reactions with isoprene **5**) regioselectivity in aqueous β-CDs may be interpreted in terms of a 'cavity control' in the transition state for adduct formation. The occurrence of deep binding of the reaction products, naphthohydroquinones, by CDs is supported by a report of Tabushi *et al.*[12] based on their study of the electronic and fluorescence spectra of complexes of CDs with substituted naphthohydroquinones or benzoquinones. Further support concerning the inclusion complexes comes from a ^{1}H NMR titration study, where the upfield shifts of H-3 and H-5 of β-CD in D_2O can be attributed to the diamagnetic anisotropic shielding effect of the benzoquinone ring of adduct **13** (Table 2). The results for modified β-CDs also support the notion that inclusion complexes are needed, otherwise no reversal in selectivity can be achieved (Table 1, entries 21 *vs.* 19).

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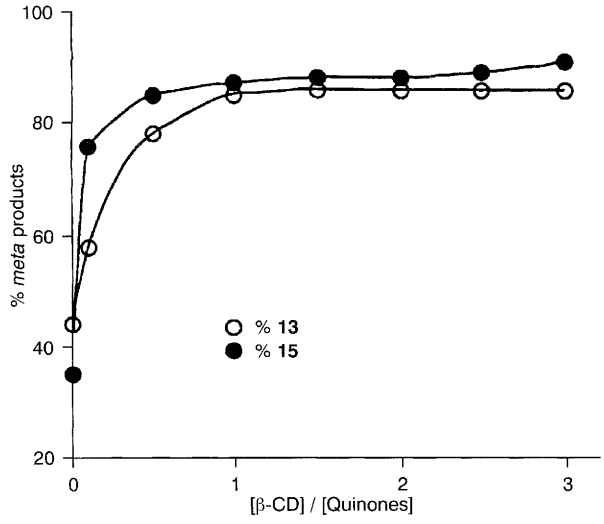
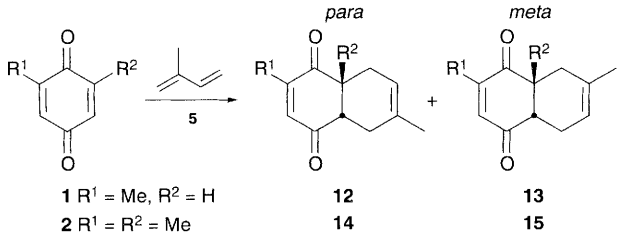


Fig. 1 % *meta*-Adducts (**13** and **15**) from the Diels–Alder reactions of isoprene with toluquinone **1** and 2,6-dimethyl-1,4-benzoquinone **2** as a function of the ratio [β-CD]: [Quinones].



Scheme 2

Table 2 ^{1}H NMR chemical shifts[a] for protons of β-CD and its complex with **13**

	δ					
	H-1	H-2	H-3	H-4	H-5	H-6
β-CD	1526.8	1095.1	1185.7	1074.3	1154.7	1163.2
β-CD + **13**	1525.1	1095.1	1176.4	1075.3	1130.3	1157.4
Δδ/Hz	−1.7	0	−9.3	+1.0	−24.4	−5.8

[a] Measured in a Varian Unity 300 MHz NMR at 24 ± 0.5 °C in D_2O with Me_4Si as an external standard.

Footnote

† Adducts **6**,[12] **7**[4d] and **10**[10] have been reported in the literature, our samples correspond in all respects with the reported properties. Compound **13** has been postulated but was not isolated before. Pure **13** (mp 76–77 °C) can be obtained by recrystallization from light petroleum (bp 35–60 °C) (Table 1, entry 15) ^{1}H NMR (300 MHz, $CDCl_3$)0 δ 1.66 (3 H, br s), 1.99 (3H, d, *J* 1.5 Hz), 1.99–2.22 (2 H, m); 2.32–2.47 (2 H, m), 3.11 (1 H, td, *J* 8.8, 5.9 Hz), 3.23 (1 H, td, *J* 8.8, 5.9 Hz), 5.33–5.40 (1 H, m) and 6.51 (1 H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 16.31, 23.36, 24.79, 28.80, 46.25, 46.77, 118.40, 131.64, 136.08, 148.96, 200.40 and 200.53; IR (KBr) ν/cm^{-1} 2894, 2914, 1670, 1637 and 1621.

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