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REGIOCHEMICAL CONTROL IN THE DIELS-ALDER REACTIONS OF SUBSTITUTED NAPHTHOQUINONES: ORIENTATION IN THE SYNTHESIS OF BENZ[A]ANTHRAQUINONES

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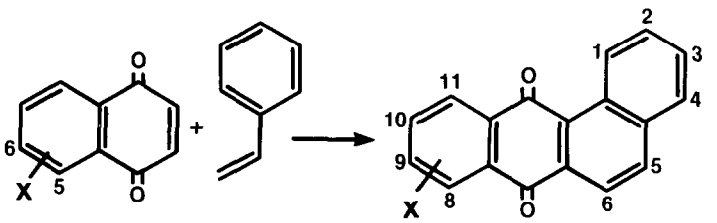
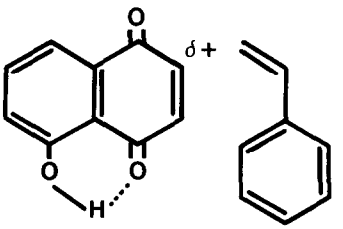
The regioselectivity in the Diels-Alder reactions of styrene with certain substituted 1,4-naphthoquinones was explored. The results were consistent with predictions based upon analysis of dione polarization.

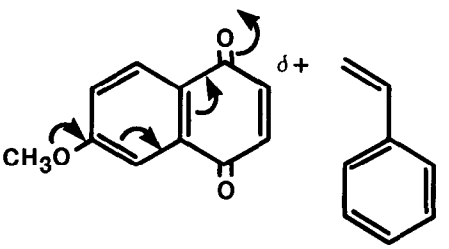
We have extended the general Diels-Alder reactions between styrenes and naphthoquinones that were used to prepare 1-,2-,3- and 4-halo[1] and methoxy[2] benz[a]anthracene-7,12-diones (BADs) by preparing BADs substituted in the D ring[3] (8-,9-,10- and 11-positions). Treatment of 5-hydroxy-1,4-naphthoquinone (1) with excess styrene and chloranil afforded a mixture of 8-hydroxybenz[a]anthracene-7,12-dione (2) and 11-hydroxybenz[a]anthracene-7,12-dione (3). A similar reaction between 6-methoxy-1,4-naphthoquinone[4] (4) and styrene gave a mixture of the 9-methoxy (5) and the 10-methoxy (6) isomers. The relative amounts of these products were consistent with predictions derived from a rationale put forth by Kelly[5] concerning the Diels-Alder reactions of substituted butadienes with naphthoquinones.



		1	4	7	8
1, X = 5-OH	2, X = 8-OH	16% 1		18% 1.5	
4, X = 6-OMe	3, X = 11-OH	33% 2		12% 1	
7, X = 5-OAc	5, X = 9-OMe		23% 1		
8, X = 5-OMe	6, X = 10-OMe		35% 1.5		
	9, X = 8-OMe				37% 3.5
	10, X = 11-OMe				11% 1



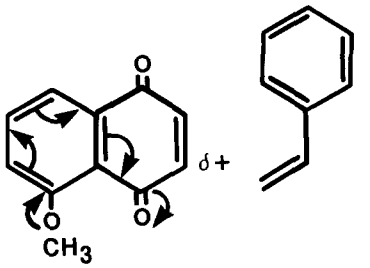
Accordingly, the activation of the C-2 position of 1 via hydrogen-bonding of the 5-hydroxy group with the C-4 carbonyl oxygen should favor addition of the β-carbon of styrene to this point to favor formation of 3. When a toluene solution of 1 was heated (100°, 7 days) with excess styrene, compounds 3 and 2 were produced in a 2:1 ratio in a 50% overall yield.



Similarly, the resonance donation of the 6-methoxy group shown above should deactivate the C-1 carbonyl and promote addition of the styrene such that the β-carbon of styrene adds to the C-2 carbon of 4 to form preferentially compound 6. When 4 was heated (100°, 10 days) with chloranil and excess styrene in toluene, 6 and 5 were formed in a 3:2 ratio in a 58% overall yield[3], consistent with prediction.

In an attempt to direct the Diels-Alder addition towards production of more of the 8-substituted BAD, 1 was acetylated to form 5-acetoxy-1,4-naphthoquinone (7) using Ac_2O/NaOAc and treated with a solution of excess styrene and chloranil in toluene (100-110°C). After 6 days little or no juglone acetate could be detected by TLC. Column chromatography of the solution on Silicar CC-7 using hexane then hexane-benzene afforded fractions of 2 and 3 in a 3:2 ratio in 30% overall yield. Little of the acetoxy-BADs were present and these materials were not isolated. Juglone itself was isolated but in low quantities. The isolation of hydroxy-substituted BADs in lieu of the acetoxy isomers revealed the deacetylation that occurred over the prolonged reaction times (most probably from attack of reduced quinones in the mixture). Even if some of the hydroxy BADs were formed from juglone produced by this deacetylation, the preponderance of the 8-substituted isomer dictated that the majority of the BADs formed resulted from styrene attack upon juglone acetate. This result is consonant with the redirecting effect found by Inhoffen, Muxfeldt and co-workers[6] in the reactions of juglone and juglone acetate with 1-acetoxybutadiene.

Analysis of 5-methoxy-1,4-naphthoquinone[7] (8) using the model suggested that resonance effects as shown below would furnish C-3 as the more electronegative reaction site. This



would promote formation of 8-methoxybenz[a]anthracene-7,12-dione (9) instead of the 11-methoxy isomer (10). When compound 7 was heated in toluene solution with chloranil and excess styrene at 110-120°C for 9 days 9, mp 189-190°C (lit[8] mp 184-185°C) and 10, mp 200.5-202°C (lit[8] mp 195°C) were isolated by column chromatography, as above, in about a 3.5:1 ratio in 48% yield. This, again, was consistent with prediction.

In an attempt to reduce reaction time, trichloroacetic acid (TCA) was added to the styrene-quinone mixtures. The catalytic effect of this acid upon Diels-Alder reactions was demonstrated by Wasserman[9] in his studies concerning the cycloadditions of cyclopentadiene to various quinones. In these studies the catalyst not only reduced reaction times 30 to 50%, but also affected isomer distribution and overall yield in the case of the formation of 2 and 3 from 1. Addition of TCA under the conditions stated earlier afforded 3 and 2 in a 3:1 ratio in 74% overall yield. An explanation of this effect should include the Wasserman observation from kinetic studies that the primary step in the catalysis is of the third order. This suggests association of the quinone with TCA at or near the transition state. The nature of the association remains speculative.

Compared with the butadienes used by Kelly, the poorer diene styrene did not affect the relative reactivity of the various naphthoquinones[5]. Juglone was by far the most reactive quinone, with compounds 7,8, and 4 following, in decreasing order. Although the formation of the BADs requires two oxidation subsequent to Diels-Alder adduct formation, our studies have shown that the adduct formation is rate-limiting.[10]

Recent work by Boeckman, et al[11] suggested that when various butadienes reacted with 1, 7, and 8, a large portion of the regioselectivity observed could be attributed to the particular polarization of the diene. Although styrene may confer a large portion of the regioselectivity when reacting with 1,7, and 8, this quality is not strong enough to effect similar isomer distribution when styrene reacts with 4.

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