Catalysis and Regioselectivity of Quinone Diels–Alder Reactions

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In a series of six different cycloadditions of unsymmetrical quinones and alkyl-substituted butadienes, TiCl$_4$ afforded considerable catalysis (-78 °C) and gave regioselectivity *identical* with that of the thermal reaction (200 °C) and therefore complementary to that of BF$_3$ catalysis.

The prediction of regioselectivity[1-5] for cycloaddition of dienes to quinones is especially difficult since the directing effects of donating substituents are small on the otherwise symmetrical electron withdrawal of the parent quinone. We faced such a case in exploring the feasibility of a synthetic project involving cycloadditions to 6-methoxy-2-toluquinone (2). Several other methyl- and methoxy-quinones have been previously examined, and we have now studied the comparison cases of the 2,6-disubstituted quinones, (1) and (2) with and without catalysis, with three model alkyl-substituted dienes, (7), (8), and (9), shown in Figure 1 with their molecular orbital coefficients (LUMO for quinones; HOMO for dienes).[6]

The experimental results for the six possible disubstituted quinones (1)—(6) are summarized in Table 1. The quinones and dienes are oriented in Table 1 so that the lefthand column for each diene refers to the adduct orientation matching the structures as shown in Figure 1 (reacting at the right side of each quinone); the righthand column refers to the reversed regiochemistry. Traditional regioselectivity designations of *ortho*, *meta*, and *para* for substituents on the adduct ring are shown at the top of each column for the monosubstituted dienes. Results are tabulated for the simple thermal reaction (shown first, with temperature) and for catalysed reactions (TiCl$_4$, SnCl$_4$, BF$_3$) below 0 °C. The adducts obtained from (2) are (10)—(13).

The structures of the adducts were determined from their 500 MHz and/or 270 MHz ^{1}H n.m.r. spectra. The 3:1

mixture of (10) and (11) was separated chromatographically [SiO$_2$, 5% EtOAc–hexane: (10) m.p. 75—76 °C, (11) m.p. 87 °C]. The identities were essentially established by the double splitting of the methine proton in (10) (*J* 5 and 10 Hz) and single coupling in (11) (*J* 7.5 Hz), in accord with dihedral angles of the stable conformer from molecular mechanics calculations.† The spectra were fairly similar to those of the corresponding adducts from quinone (1).[7]

Whereas both isoprene adducts were formed about equally from quinone (1), (toluene solvent, 180 °C, sealed tube, 6 h, excess of isoprene) the isoprene adduct (12) (m.p. 94 °C) was the exclusive product (by h.p.l.c.) from the methoxyquinone,
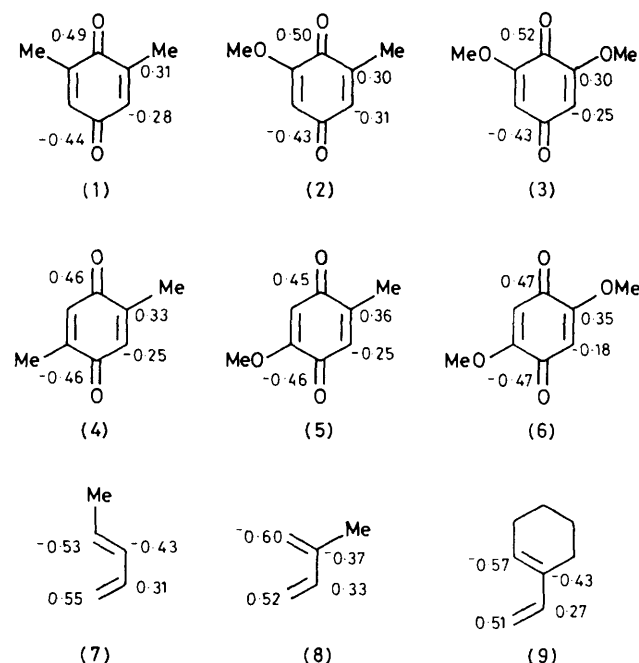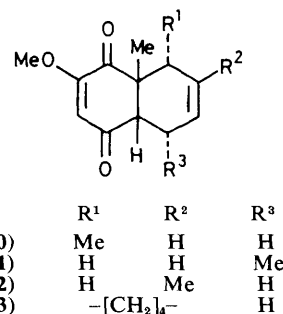

(1) (2) (3)

(4) (5) (6)

(7) (8) (9)

Figure 1

	R^1	R^2	R^3
(10)	Me	H	H
(11)	H	H	Me
(12)	H	Me	H
(13)	-[CH$_2$]$_4$-		H

Table 1. Quinone cycloadditions. Regioselectivity results and predictions from molecular orbital (MO) calculations.

		(7) ortho	(7) meta	(8) meta	(8) para	(9)	(9)
(1)	180 °C[a,b]	1	0	1	1	1	0
	TiCl$_4$[a]	1	0	1	1	1	0
	BF$_3$[a,b]	0	1	—		0	1
	MO:[e] (P)	0.027	0.029	0.035	0.028	0.031	0.025
	(S–P)	*		*		*	
(2)	180 °C[a]	3	1	1	0	1	0
	TiCl$_4$[a]	3	1	1	0	1	0
	MO:[e] (P)	0.029	0.027	0.032	0.035	0.029	0.031
	(S–P)	*			*	*	
(3)	110 °C[c]	1	0	1	1		—
	MO:[e] (P)	0.025	0.027	0.032	0.024		
	(S–P)		*	*			
(4)	110 °C[c]	5	1	1	1		—
	MO:[e] (P)	0.031	0.033	0.039	0.029		
	(S–P)		*	*			
(5)	100 °C[d]	1	1	1	1	3	2
	SnCl$_4$[d]	1	20	20	1	0	1
	BF$_3$[d]	4	1	1	2.4	5	1
	MO:[e] (P)	0.036	0.039	0.047	0.035	0.042	0.034
	(S–P)		*	*		*	
(6)	150 °C[c]	1	0	1	1		—
	MO:[e] (P)	0.034	0.037	0.044	0.033		
	(S–P)		*	*			

[a] Studied in this work. [b] Ref. 7. [c] Ref. 9. [d] Ref. 8. [e] MO calculations: (P) primary sites, ref. 4, (S–P) secondary and primary sites, ref. 5. * Indicates calculated preference, Alston method, ref. 5.

† Performed by Mr. D. Pearson in our laboratory from an excellent program developed and kindly donated by Professor Clark Still (Columbia).

(2).‡ The ¹H n.m.r. spectrum shows two geminally split sharp doublets (δ 1.60 and 2.40, J 18 Hz) without further coupling for one methylene, while the two geminally split doublets (δ 2.12 and 2.57, J 20 Hz) from the other are multiplets further coupled to the methine proton (δ 2.68, dd, J 6, 6 Hz) as well as the isoprene vinyl proton (δ 5.3 br.), as shown by decoupling of each of the latter signals. Calculations showed two conformers differing by only 0.2 kcal/mol.§ The signals in the spectrum of the 1:1 mixture from quinone (1) and isoprene (8) showed more second-order overlap and the compounds were not chromatographically separable. Vinylcyclohexene (9) gave only a single adduct (13) from either quinone (1) (m.p. 106—107 °C) or (2) (m.p. 147—148 °C), with closely analogous spectra. The reversed adduct (m.p. 85—87 °C) from quinone (1) and (9), prepared by BF₃ catalysis, has a different spectrum.⁷

The predictions from MO theory are shown in Table 1; the squares of the products of the bonding coefficients for each regioisomer were computed and the larger one is shown for each isomer.⁴ The predictions are qualitatively correct in only 3 of the 15 examples, and the six cases of roughly equal mixtures of isomers tend to have the strongest numerical predictions. A correction involving secondary orbital overlap, advanced by Alston,⁵ is more complex and involves the subtraction of two very large values to obtain a small energy preference for one isomer. These preferences are very unlikely to be quantitatively meaningful and are shown only as qualitative predictions [(S–P) in Table 1]. In fact they alter only two of the primary-site predictions above, i.e., correct in 5 of the 15 examples. It may be noted that a simple steric prediction of regiochemistry based on bonding the less crowded sites on each component serves to indicate the correct product in 8 out of 9 cases with the 1-substituted dienes, (7) and (9). None of the six adducts with isoprene (8) shows any regioselectivity except for the surprising unique adduct from quinone (2), i.e. (12), and no basis for understanding this anomaly is apparent.

Unlike the xyloquinone (1) cases,⁷ catalysis of the cycloadditions with BF₃ or AlCl₃ yielded no adducts in the methoxyquinone (2) series. However, all six reactions were very markedly catalysed by TiCl₄. In general the thermal reactions required temperatures of 180—200 °C for several hours, but reaction was complete in less than half an hour at −78 °C

using TiCl₄ in CH₂Cl₂ solvent (1 mol. equiv.). Previously reported catalysis has generally been rationalized by complexation of Lewis acid with one carbonyl oxygen.⁷,⁸ This of course differentially affects the orbital coefficients as well as their energies and so tends to alter or even reverse the regiochemistry. Reusch's explanation⁸ that BF₃ complexes the more basic carbonyl while SnCl₄ complexes the one with an adjacent methoxy group is compelling for his examples with methoxyquinone (5) but it does not explain the preference for adduct (12) from methoxyquinone (2).¶ In all examples with quinone (1) and (2), while TiCl₄ catalysis strongly increased the rate, in no case did it alter the regioselectivity. Hence TiCl₄ offers here a complementary catalysis to other Lewis acids for synthetic purposes and it also suggests an alternate mechanistic mode of catalysis, i.e., one in which the TiCl₄ is centrally bound to the whole π-face of the quinone without especially altering the bonding coefficients which direct the regiochemistry.

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‡ The structure of (12) was further confirmed by a 2-dimensional n.m.r. spectrum (in C₆D₆) and nuclear Ovenhauser effect difference spectroscopy by Professor David G. Lynn and Nancy J. Phillips at the University of Virginia. We acknowledge gratefully their interest and assistance.

§ 1 kcal = 4.184 kJ.

¶ Catalysis of (2) + (8) by SnCl₄ at −78 °C gave the same single adduct, (12), as with TiCl₄, an experiment kindly performed by Mr. Ing-Lung Shih.