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ORIGINAL PAPER

Factors affecting the competitive reduction of 8,8-dimethylnaphthalene-1,4,5(8*H*)-trione in a Diels–Alder cycloaddition with hydroxysulfinyldienes

Iriux Almodovar · Wilson Cardona · Tomás Delgado-Castro · Gerald Zapata-Torres · Marcos Caroli Rezende · Ramiro Araya-Maturana

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Abstract Competing reduction and cycloaddition products were formed in the reaction of 8,8-dimethylnaphthalene-1,4,5(8*H*)-trione with a hydroxysulfinyldiene. The ratio of reduction to cycloaddition products depended on the stereochemistry of the diene and on the solvent employed, being higher in ethanol than in benzene. The ratio was also affected by the addition of Lewis acids, decreasing in the order $BF_3 = Al_2O_3 > MgCl_2 > ZnCl_2$. The results help to explain and predict the occurrence of these competing processes in Diels–Alder cycloadditions involving quinonedienophiles.

Keywords Diels–Alder · Cycloaddition · Reduction · Quinone · Sulfinyldienes

I. Almodovar (✉) · M. C. Rezende
Departamento de Ciencias del Ambiente, Facultad de Química y Biología, Universidad de Santiago de Chile, Avenida B. O'Higgins 3363, Estación Central, CP 9160000 Santiago, Chile
e-mail: iriux.almodovar@usach.cl

W. Cardona
Departamento de Ciencias Químicas, Universidad Andrés Bello, Autopista Concepción-Talcahuano 7100, Concepción, Chile

T. Delgado-Castro
Departamento de Ciencias Químicas, Universidad Andrés Bello, República 237, Santiago, Chile

G. Zapata-Torres
Departamento de Química Inorgánica y Analítica, Universidad de Chile, Casilla 233, Santiago 1, Chile

R. Araya-Maturana
Departamento de Química Orgánica y Físico-Química, Universidad de Chile, Casilla 233, Santiago 1, Chile
e-mail: raraya@ciq.uchile.cl

Introduction

Quinones are ubiquitous in nature, playing an important role in biological systems, where they act as electron-transfer agents in redox reactions [1–4]. They are found in most living organisms, in the oxidized (quinone) or reduced (hydroquinone) states.

Quinone derivatives have found a wide variety of applications as antineoplastics [5–9], antitumor agents [10–13], and antibiotics [14, 15], and are also effective against Alzheimer's disease [16–21]. They have also been employed in agriculture as antifungal agents [22–25]. Polycyclic quinones, such as naphthoquinones, are also important as environmental pollutants, with noxious effects on human health [26–28].

Quinones are important building blocks in organic synthesis [29–35]. As good electron-deficient dienophiles, they have been frequently used in Diels–Alder (D–A) cycloadditions [36–46]. Their electron deficiency also makes them good substrates for redox processes that may compete with the cycloaddition reaction. Fukuzumi et al. [47, 48] have reported the competing reduction of quinone dienophiles when performing D–A cycloadditions to these substrates.

Because these undesired reduction processes compete with D–A reactions, thereby diminishing the yields of the cycloaddition products, a good understanding of the factors that govern them is important when attempting to exploit D–A reactions with quinones.

In a recent report of a D–A cycloaddition of (2*S*, *SR*)-1-(*p*-tolylsulfinyl)-3,5-heptadien-2-ol (**1**) and of (2*R*, *SR*)-1-(*p*-tolylsulfinyl)-3,5-heptadien-2-ol (**2**) with quinone **3** we obtained high yields of adducts with good regio- and stereoselectivities [46]. A careful analysis of the reaction mixtures revealed the formation of hydroquinone **4**

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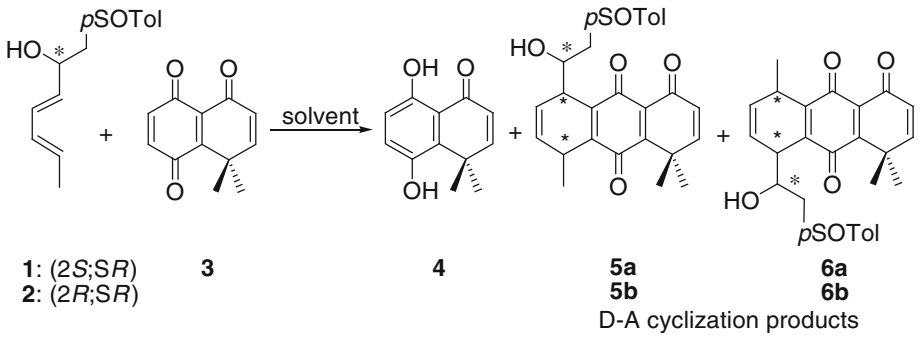
Scheme 1 Reaction of hydroxysulfinyldienes **1** or **2** with quinone **3**



together with the cycloadducts (Scheme 1). The formation of product **4** depended on the diene employed.

In the present paper, we describe the formation of **4** under various conditions. By analyzing in detail its dependence on the solvent and on the addition of Lewis acids, we have clarified some factors that govern this competing pathway.

Experimental

^{1}H NMR spectra were obtained in $CDCl_3$ with a Bruker Advance DRX-300 instrument. All chemical shifts are reported as ppm downfield from TMS; residual $CHCl_3$ (δ 7.26) was used as an internal reference.

Synthesis of the reacting compounds and characterization of all the products have been reported before [46, 49–52].

Toluene was dried over Na under N_2, using benzophenone as an indicator. CH_2Cl_2 was dried over P_2O_5 under N_2.

Reaction of sulfinyldienol 1 or 2 with dienophile 3

In the absence of Lewis acids

The sulfinyldienol **1** or **2** (0.128 mmol) and dienophile **3** (0.128 mmol) were dissolved in the appropriate solvent (benzene or EtOH, 5 mL). The solution was allowed to react at room temperature, in the absence of light, for 1 week. When EtOH was used as solvent it was evaporated and the residue redissolved in benzene. Silicagel (60 mg) was added, and the mixture was stirred overnight. The suspension was then filtered, and silicagel was washed repeatedly with a mixture of AcOEt:MeOH (1:1 v/v). The filtrates were concentrated to give a mixture of anthracenones which was analyzed by ^{1}H NMR. Characterization of products 5a, 5b, 6a, and 6b are given below.

(5S,8R)-9,10-dihydroxy-8-{(1S)-1-hydroxy-2-[(4-methylphenyl)-R-sulfinyl]ethyl}-4,4,5-trimethyl-5,8-dihydro-1(4H)-anthracenone (***5a***) Mp: 234–236 °C. IR (KBr) (cm^{-1}): 3,431, 2,925, 1,598, 1,423. ^{1}H NMR δ ($CDCl_3$, 300.13 MHz): 1.35 (d, 3H, $J = 7.0$ Hz), 1.58 (s, 3H), 1.64 (s, 3H), 2.42 (s, 3H), 2.86 (dd, 1H, $J = 2.0$ Hz, $J = 13.0$ Hz), 3.18 (dd, 1H, $J = 10.0$ Hz, $J = 13.0$ Hz), 3.42 (m, 2H), 3.82 (m, 1H), 4.52 (m, 1H), 4.61 (m, 1H), 5.94 (dd, 1H, $J = 5.0$ Hz, $J = 10.0$ Hz), 6.12 (dd, 1H, $J = 5.0$ Hz, $J = 10.0$ Hz), 6.23 (d, 1H, $J = 10.0$ Hz), 6.82 (d, 1H, $J = 10.0$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz), 7.51 (d, 2H, $J = 8.0$ Hz), 13.25 (s, 1H). ^{13}C NMR δ ($CDCl_3$, 75 MHz): 21.56, 25.06, 25.27. 30.45, 38.18, 40.56, 60.45, 68.36, 113.07, 121.60, 123.21, 123.94, 124.15, 129.97, 130.00, 132.95, 133.17, 137.69, 141.50, 142.80, 154.7, 161.14, 191.13. Anal. calcd. for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24; S, 7.08. Found C, 68.25; H, 6.41; S, 6.39.

9,10-dihydroxy-5-{(1S)-1-hydroxy-2-[(4-methylphenyl)-R-sulfinyl]ethyl}-4,4,5-trimethyl-5,8-dihydro-1(4H)-anthracenone (***5b***) Mp: 198–201 °C. IR (KBr) (cm^{-1}): 3,418, 2,924, 1,651, 1,601. ^{1}H NMR δ ($CDCl_3$, 300.13 MHz): 0.74 (d, 3H, $J = 7.0$ Hz), 1.58 (s, 3H), 1.65 (s, 3H), 2.40 (s, 1H), 2.80 (d, 1H, $J = 14.0$ Hz), 3.53 (d, 1H, $J = 14.0$ Hz), 3.65 (m, 1H), 3.87 (m, 2H), 5.70 (dd, 1H, $J = 5.0$, $J = 10.0$ Hz), 6.04 (dd, 1H, $J = 5.0$, $J = 10.0$ Hz), 6.15 (s, 1H), 6.23 (dd, 1H, $J = 1.0$, $J = 10.0$ Hz), 6.84 (dd, 1H, $J = 1.0$, $J = 10.0$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 7.40 (d, 2H, $J = 8.0$ Hz), 7.99 (s, 1H), 13.15 (s, 1H). ^{13}C NMR δ ($CDCl_3$, 75 MHz): 21.35, 21.43, 25.02, 25.45, 29.45, 38.44, 41.65, 55.06, 76.36, 113.53, 122.62, 124.01, 130.26, 134.36, 134.84, 136.20, 136.78, 142.04, 144.95, 153.98, 161.72, 191.57. Anal. calcd. for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24; S, 7.08. Found: C, 68.14; H, 6.61; S, 6.53.

(5R, 8S)-9,10-dihydroxy-8-{(1R)-1-hydroxy-2-[(4-methylphenyl)-R-sulfinyl] ethyl}-4,4,5-trimethyl-5,8-dihydro-1(4H)-anthracenone (***6a***) Mp: 144–147 °C. IR (KBr) (cm^{-1}) 3,416, 3,020, 2,959, 2,937, 1,651, 1,597, 1,029, 809. ^{1}H NMR δ ($CDCl_3$, 300.13 MHz): 1.43 (d, 3H, $J = 7.0$ Hz), 1.58 (s, 3H), 1.63 (s, 3H), 2.42 (s, 3H), 2.98(dd, 1H, $J = 12.9$, $J = 2.1$ Hz), 3.17 (dd, 1H, $J = 12.9$, $J = 10.4$ Hz), 3.45(m, 1H), 3.56 (d, 1H, $J = 4.1$ Hz), 3.82 (m, 1H), 4.59 (m, 1H), 4.73 (s, 1H), 5.81 (dd, 1H, $J = 9.9$, $J = 5.0$ Hz), 6.10 (dd, 1H, $J = 10.1$,

$J = 5$ Hz), 6.23 (d, 1H, $J = 10.0$ Hz), 6.82 (d, 1H, $J = 10.1$ Hz), 7.33 (d, 2H, $J = 8.2$ Hz), 7.56 (d, 2H, $J = 8.3$ Hz), 13.39 (s, 1H). ^{13}C NMR δ ($CDCl_3$, 75 MHz): 21.45, 21.51, 25.03, 25.28, 30.44, 38.19, 40.95, 62.00, 69.75, 113.08, 121.94, 122.92, 123.85, 124.26, 130.09, 133.35, 133.40, 137.10, 140.32, 140.02, 142.98, 154.14, 161.27, 191.22. HRMS (ESI–MS): Anal. clacd. for $C_{26}H_{29}O_5S$ $(M+H)^+$ 453.1711 found 453.1711.

*9,10-dihydroxy-5-{(1R)-1-hydroxy-2-[(4-methylphenyl)-R-sulfinyl] ethyl}-4,4,5-trimethyl-5,8-dihydro-1(4H)-anthracenone (**6b**)* Mp: 248 °C. IR (KBr) (cm^{-1}): 3,377, 3,020, 2,925, 2,854, 1,655, 1,599, 1,077, 804.^{1}H NMR δ ($CDCl_3$, 300.13 MHz): 1.37 (d, 3H, $J = 7$ Hz), 1.57 (s, 3H), 1.65 (s, 3H), 2.45 (s, 3H), 3.09 (dd, 1H $J = 13.1$ Hz, $J = 9.5$ Hz), 3.14 (dd, 1H, $J = 12.9$ Hz, $J = 2.0$ Hz), 3.80 (m, 2H), 4.32 (ddd, 1H, $J = 9.6$ Hz, $J = 9.6$ Hz, $J = 1.9$ Hz), 5.67 (dd, 1H, $J = 9.7$ Hz, $J = 5.5$ Hz), 6.02 (s, 1H), 6.22 (d, 1H, $J = 10.1$ Hz), 6.24 (dd, 1H, $J = 9.6$ Hz, $J = 5.5$ Hz), 6.82 (d, 1H, $J = 10.0$ Hz), 7.39 (d, 2H, $J = 8.2$ Hz), 7.60 (d, 2H, $J = 8.2$ Hz), 8.01 (s, 1H), 13.18 (s, 1H). ^{13}C NMR δ ($CDCl_3$, 75 MHz): 21.51, 22.37, 25.04, 25.47, 29.82, 38.42, 42.12, 59.14, 78.34, 113.61, 122.62, 123.90, 123.93, 127.68, 130.46, 134.32, 134.42, 136.83, 139.90, 142.81, 145.00, 154.13, 161.61, 191.52. HRMS (ESI–MS): Anal. calcd. for $C_{26}H_{28}O_5NaS$ $(M+Na)^+$ 475.1549, found 475.1547.

In the presence of Lewis acids

A mixture of diene **1** or **2** (0.128 mmol) and the appropriate Lewis acid (0.128 mmol) dissolved in dry toluene (3 mL) was stirred under N_2 at 0 °C for 30 min. Then, a solution of **3** (0.128 mmol) in dry toluene (3 mL) was added. The reaction was allowed to warm up to room temperature, and course of the reaction was followed by TLC.

When the reaction was complete, a saturated aqueous solution of NH_4Cl was added, the mixture was stirred for 15 min, and was then extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4 and filtered, the filtrate was concentrated and the residue redissolved in benzene. Silicagel (60 mg) was added, and the mixture was stirred overnight. The suspension was then filtered. Silicagel was washed several times (as described above), and the filtrates were concentrated to give a mixture of anthracenones which was analyzed by ^{1}H NMR.

Results and discussion

The reaction of sulfinyldienes **1** or **2** with quinone **3** was carried out in benzene and ethanol. The different yields of reduction product **4**, determined from the ^{1}H NMR spectra of the reaction mixtures, showed that the medium played an important role in this reaction. This led us to compare the effect of different Lewis acids added to the reaction in toluene, to gain a more detailed picture of the medium effects that govern the reduction process.

Table 1 Yields of hydroquinone **4** and of regioisomers **5** and **6** from the reactions of quinone **3** with dienes **1** or **2** in benzene or ethanol

Product	Product yield (%)			
	Benzene		Ethanol	
	Diene **1**	Diene **2**	Diene **1**	Diene **2**
4	15	30	50	65
5	70	60	30	10
6	15	10	20	25

Effect of the solvent and of the sulfinyldienol on the reduction of **3**

When the reaction of **1** or **2** with quinone **3** was carried out in benzene, the major products were in both cases D–A adducts [46]. Besides, non-negligible amounts of hydroquinone **4** were also formed, in yields that depended on the diene. However, the same reaction in ethanol led to a very different product distribution with a strong preference for the reduction product over the D–A adducts **5** and **6**: quinone **3** was reduced in 50–65 % yield when compared with 15–30 % observed when the reaction was run in benzene. Relevant variations in the ratio of the obtained regioisomers in the D–A cycloaddition were also observed in ethanol.

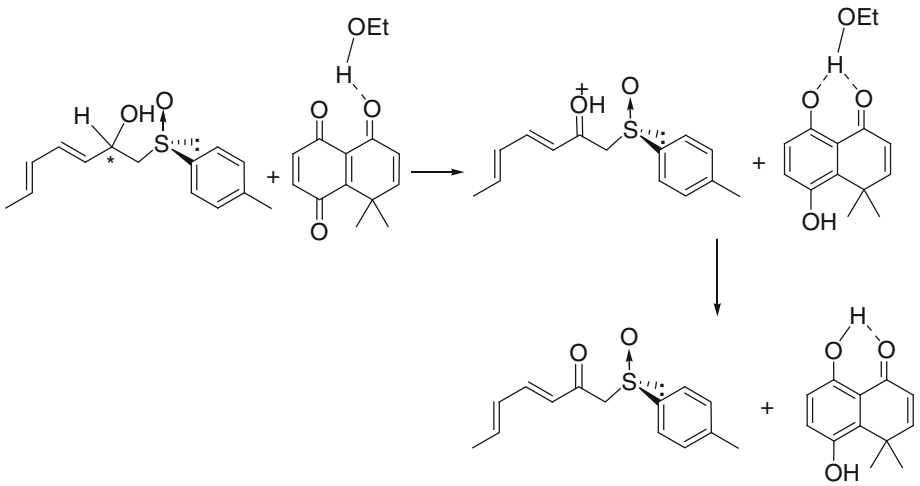
Table 1 summarizes the results described above.

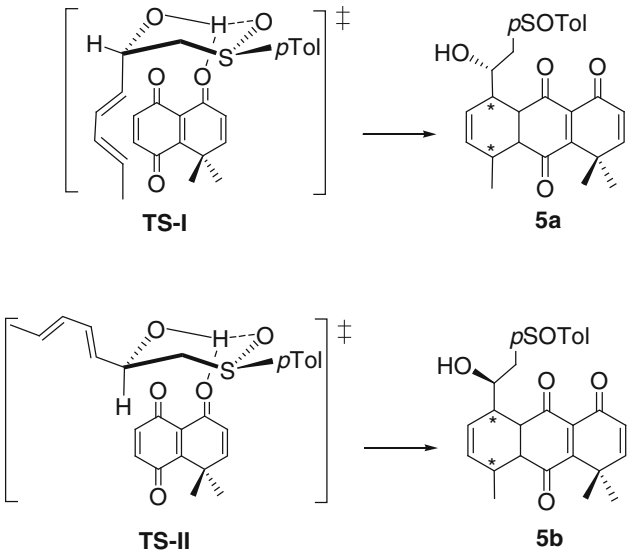
The data of Table 1 show that the formation of hydroquinone **4** depends not only on the employed solvent, but also on the stereochemistry of the dienol (**1** or **2**).

The drastic differences observed when the reaction solvent was changed from nonpolar aprotic benzene to polar protic ethanol most likely reflect the importance of hydrogen bonds between the solvent and the quinone **3** [53], favoring reduction of the latter. In fact, reports of catalysis by hydrogen bond donors in the reduction of quinones are found in the literature [54, 55]. Hydride transfer to these substrates is assisted by partial protonation of the carbonyl oxygen; thus, increasing the electrophilicity of the quinone. The hydride source in these reductions is doubtless the dienol **1** or **2**. Hydride transfer from these compounds should be made easier by the presence of the neighboring sulfoxide group, and by the formation of a conjugated dienone system (Scheme 2).

A comparison of the two dienols also shows that, in both solvents, reactions with dienol **2** led to higher yields of the

Scheme 2 Hydride transfer from dienol **1** or **2** to quinone **3** in ethanol





Scheme 3 Possible transition-state geometries for reactions of **1** (TS-I) or **2** (TS-II) with **3**

reduction product **4**, and to lower regioselectivities in the D–A cycloaddition (Table 1). Both effects may be rationalized by invoking the cyclic complexes depicted below for these reactions (Scheme 3) [46].

As discussed previously [46], such postulated complexes should account for the preferential formation of regioisomers **5a** and **5b** in the D–A cycloadditions, because of the role played by the hydroxyl proton of the dienol in bringing together dienes and quinone **3** in the appropriate conformations. This role is more important in benzene than in ethanol, due to competition with the hydroxyl proton of the latter solvent, which should partly disrupt the intermolecular interaction between diene and quinone. The result of this is the lower regioselectivity observed in ethanol in the formation of the D–A adducts **5** and **6** (Table 1).

The different outcome of the reaction with dienols **1** and **2** can also be explained resorting to the postulated transition states. The interaction between diene and dienophile is facilitated by their proximity in complex TS-I, which originates from dienol **1**. In the corresponding complex TS-II for dienol **2**, diene and dienophile are widely separated and it must dissociate for the D–A transition state to arise. Instead, in this complex, a hydride transfer from the dienol to the quinone becomes an important competing process with the D–A cycloaddition, leading, in all cases, to a greater proportion of the reduced hydroquinone product **4** (Table 1).

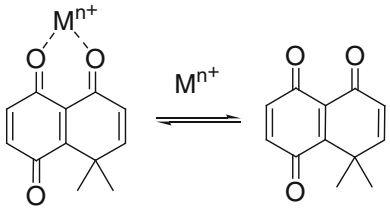
Table 2 Yields of hydroquinone **4** in the reaction of dienols **1** or **2** with quinone **3** in toluene, in the presence of various Lewis acids

Dienols	Lewis acid	% of 4
1	BF_3 Et_2O	100
1	Al_2O_3	100
2	Al_2O_3	100
1	$MgCl_2$	75
2	$MgCl_2$	89
1	$ZnBr_2$	2
2	$ZnBr_2$	6

Effect of Lewis acids on the reduction of **3**

Lewis acids have been extensively used in D–A cycloadditions, to increase selectivities or reaction rates [56–58]. The reactions of dienols **1** or **2** with quinone **3** was, therefore, investigated in toluene, in the presence of various Lewis acids. Interestingly, the competing reduction of **3** was strongly dependent on the nature of the acid, as can be seen from the data of Table 2.

The data of Table 2 allow a distinction to be made between three types of acid: those which elicited a complete reduction of **3** to the hydroquinone **4** (BF_3, Al_2O_3), those that strongly favored this process ($MgCl_2$), or that



Scheme 4 Activated complex formed by interaction between quinone **3** and Lewis acid M^{n+} in toluene

suppressed it almost completely ($ZnBr_2$). This order may be related to the hardness of the studied cations. According to Klopman [59], hardness decreases in the order $B^{+3} = Al^{+3} > Mg^{+2} > Zn^{+2}$, and the same order is followed for the corresponding Lewis acidity. Thus, the data of Table 2 suggest that the ease of reduction of quinone **3** increases with the hardness and/or the acidity of the added Lewis acid.

In general, metal cations will interact with donor groups of the dienol and the quinone in benzene. Thus, the role of a relatively soft Lewis acid like $ZnBr_2$ in catalyzing the D–A cycloaddition in benzene may be rationalized by invoking transition states, where the metal cation replaces the hydroxyl proton.

Interaction of the metal cation with the sulfinyl group of the dienol will not significantly affect the frontier orbitals of the diene. The situation is rather different for the quinone **3**. Metal chelation by the neighboring carbonyl groups will lead to a harder and more electrophilic species (Scheme 4).

Thus, the harder the Lewis acid M^{n+}, the harder and more electrophilic the quinone complex becomes. As the metal cation becomes harder and more acidic, the reaction of the quinone with the dienol gradually shifts from a process governed by frontier molecular orbitals to an electrostatic process, where the reduction potential of the quinone complex becomes increasingly important. This interpretation is in line with the results of Table 2. In the presence of very hard acids, such as BF_3, or Al_2O_3, the frontier molecular orbital-controlled D–A cycloaddition is completely suppressed, while it is the major pathway in the presence of the softer Zn^{2+}. This interpretation also agrees with the previous observations in the literature on the effect of Lewis acids on the reduction potential of quinones [47].

Conclusions

Hydroquinone **4** was always a side product in the reaction of dienols **1** or **2** with quinone **3**, as recently described by us [46]. In the present communication, we show that the formation of **4** is ultimately determined by interactions between the quinone C-1 carbonyl and a hydrogen bond donor solvent-like ethanol, or an added Lewis acid. In the latter case, the harder the metal cation, the greater the yield of reduced quinone. Quinones are frequently used in D–A cycloadditions that are often modified or accelerated by the addition of Lewis acids. Thus, the present results and interpretations may prove useful in defining the reaction conditions or optimizing these reactions in synthesis.

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