A Solvolytic C−C Cleavage Reaction of 6-Acetoxycyclohexa-2,4-dienones: Mechanistic Implications for the Intradiol Catechol Dioxygenases

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6-Acetoxycyclohexa-2,4-dienones are found to undergo a rapid reaction in methanol/water under mildly basic conditions to give an acyclic ketoester as the major product for 6-phenyl and 6-methyl substrates. Reaction monitoring by UV spectroscopy indicates the formation of an unsaturated ketone reaction intermediate (λ_{max} 275 nm, R = Ph) and the transient appearance of a highly conjugated species. Reaction of the 6-phenyl substrate (4.95×10^{-6} s^{-1}) is 2-fold faster than the 6-methyl substrate (2.47×10^{-6} s^{-1}). The reaction rate is first order with respect to substrate concentration, and the final step in the reaction is pH-dependent. No cleavage was observed for a substrate lacking an acetyl substituent. A reaction mechanism for C−C cleavage is proposed involving a benzene oxide−oxepin interconversion. The possible relevance to the catalytic mechanism of the intradiol catechol dioxygenases is discussed.

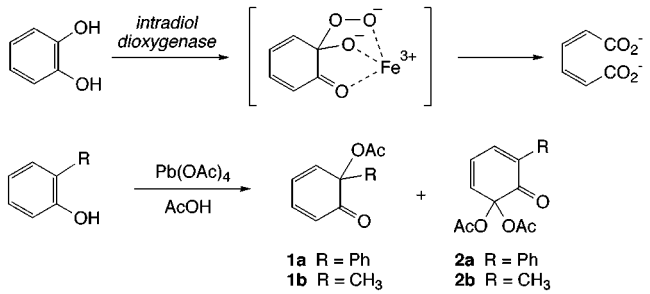
Introduction

The formation of 6-acetoxycyclohexa-2,4-dienones ("quinol acetates") from ortho-substituted phenols by lead(IV) acetate was discovered by Wessely, who synthesized a large range of such compounds.[1] These highly functionalized compounds have found synthetic utility in recent years due to their participation in intermolecular[2] and intramolecular[3] Diels−Alder reactions.

The structure of this family of compounds closely resembles the putative reaction intermediates that have been proposed for the catalytic mechanisms of the catechol dioxygenases, a family of nonheme iron-dependent enzymes that catalyze the oxidative cleavage of catechol and substituted catechols (see Scheme 1).[3,4] The intradiol dioxygenases catalyze the cleavage of the bond situated between the two catechol hydroxyl groups, utilizing nonheme iron(III) as cofactor, whereas the extradiol dioxygenases catalyze the cleavage of the bond adjacent to the two hydroxyl groups, utilizing nonheme iron(II) as cofactor.[4,5]

Mechanistic proposals for the catechol dioxygenases involve the formation of 6-hydroxy-6-peroxocyclohexa-2,4-dienone intermediates, which are proposed to undergo Criegee rearrangements to give either lactone (for extradiol cleavage) or anhydride (for intradiol cleavage) products.[4,5] Recent studies suggest that the reaction mechanisms of the extradiol and intradiol dioxygenases diverge from a common proximal hydroperoxide intermediate, the choice of reaction pathways depending on alkenyl vs acyl migration in the Criegee rearrangement step.[6,7] Although cyclohexadienone hydroperoxide intermediates have been invoked on many occasions, there are few studies that give insight into the chemical reactivity of functionalized 2,4-cyclohexadienones. This manuscript describes the observation of an unexpected and unusual C−C cleavage reaction of two 6-acetoxycyclohexa-2,4-dienones and studies to investigate the mechanism of C−C cleavage, which may relate to the mechanism of C−C cleavage in the intradiol catechol dioxygenases.

Scheme 1



Results

Base-Catalyzed Cleavage of 6-Acetoxy-cyclohexa-2,4-dienones. The method of Wessely,[1] namely treatment of a 2-substituted phenol with lead(IV) acetate in acetic acid, was used to synthesize 6-phenyl-6-acetoxycyclohexa-2,4-dienone (**1a**) and 6-methyl-6-acetoxycyclohexa-2,4-dienone (**1b**), shown in Scheme 1. The major byproduct of the reaction was the 2-substituted 6,6-

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(1) Wessely, F.; Sinwel, F. *Monatsch. Chem.* **1950**, *81*, 1055.
(2) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324 and references therein.
(3) Bichan, D. J.; Yates, P. *Can. J. Chem.* **1975**, *53*, 2057. Yates, P.; Auksi, H. *Can. J. Chem.* **1979**, *57*, 2853.
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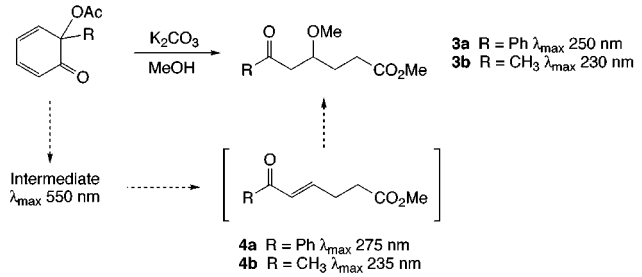
Scheme 2



diacetoxycyclohexa-2,4-dienone (**2a**,**b**) formed by consecutive oxidation in the unsubstituted ortho position. Treatment of of 2-*tert*-butylphenol and 2-trifluoromethylphenol under the same conditions failed to give the desired 6-substituted 6-acetoxycyclohexa-2,4-dienone products, in the first case yielding only 6,6-diacetoxy-2-*tert*-butylcyclohexadienone and in the second case giving a complex mixture of products.

Attempts to hydrolyze the acetate ester functional group of **1a** or **1b** under mildly basic conditions gave none of the corresponding alcohol. Treatment of **1a** with sodium carbonate in methanol/water (1:1) gave an immediate color change and a rapid reaction as observed by thin-layer chromatography. The major isolated product was an acyclic ester, methyl 4-methoxy-6-keto-6-phenylhexanoate (**3a**). The ^{1}H NMR spectrum of **3a** showed two 3H singlets at 3.60 and 3.26 ppm, a multiplet for H-4 at 3.85 ppm, diastereotopic H-5 signals at 3.25 and 2.87 ppm, and signals for H-2 and H-3 at 2.38 and 1.83 ppm. The ^{13}C NMR spectrum of **3a** showed evidence of two carbonyl carbons at 198.8 and 174.3 ppm, and the mass spectrum showed a molecular ion at *m*/*z* 250. Treatment of 6-methyl-6-acetoxycyclohexa-2,4-dienone (**1b**) under the same conditions gave the analogous acyclic ester methyl 4-methoxy-6-ketoheptanoate (**3b**) as the major isolated product (see Scheme 2).

The acyclic ester products **3a** and **3b** are at the same oxidation state as the starting materials but correspond to the addition of 2 equiv of methanol, and their formation requires a reaction mechanism involving cleavage of the C−C bond between the oxygenated carbons C-1 and C-6, analogous to intradiol catechol cleavage. The same reaction products were observed when the reaction was carried out in the dark, thus ruling out a photochemical reaction, which has been observed for other 2,4-cyclohexadienones.[8]

UV Spectroscopic Studies. The reaction of **1a** with sodium carbonate in methanol/water (1:1) was monitored by UV spectroscopy. Scanning from 200 to 600 nm at 10 s intervals revealed an immediate and rapid reaction, resulting in the gradual disappearance of **1a** at 317 nm,- and the appearance of a new species at 275 nm over the time period 0−2 min (Figure 1A). At longer reaction times, the species at 275 nm decreased, and a third species at 250 nm was formed (Figure 1B), which matches the UV spectrum of the final product **3a**. The UV spectrum of the reaction intermediate with λ_{max} 275 nm matches that expected for an α,β-unsaturated ketone **4a**,

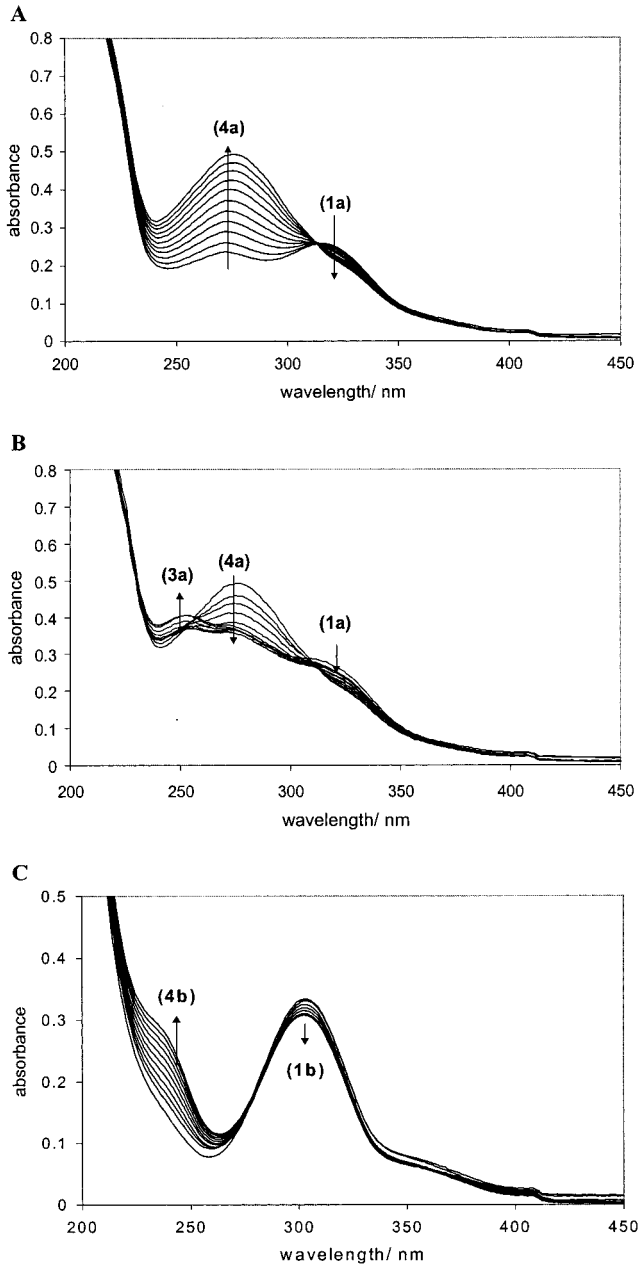


Figure 1. (A) UV spectra vs time for reaction of **1a**, showing the formation of intermediate **4a** (0−120 s). (B) UV spectra vs time for subsequent reaction of **1a**, showing the formation of final product **3a** (120−240 s). C. UV spectra vs time for reaction of **2a**, showing the formation of intermediate **4b** (0−120 s). Experiments were carried out in 50 mM Na_2CO_3 in methanol/water (1:1) at 20 °C; scans were recorded every 10 s.

which would be converted to the product **3a** by conjugate addition of methoxide (Scheme 2).

The reaction of **1a** was monitored by UV scanning over pH range 8.0−10.8, at 18 and 37 °C (Figure 2). At 18 °C, the predominant feature is the formation of intermediate **4a** at λ_{max} 275 nm. At pH 10.77, the formation of product **3a** at λ_{max} 250 nm is also apparent, indicating that the conversion of **4a** to **3a** is faster under basic conditions. At 37 °C, the formation of product **3a** at λ_{max} 250 nm is much faster, with little of the intermediate species observed at higher pH. Under these conditions, a linear decrease at 317 nm is visible, whose rate is independent of pH, although the rate is approximately 2-fold higher

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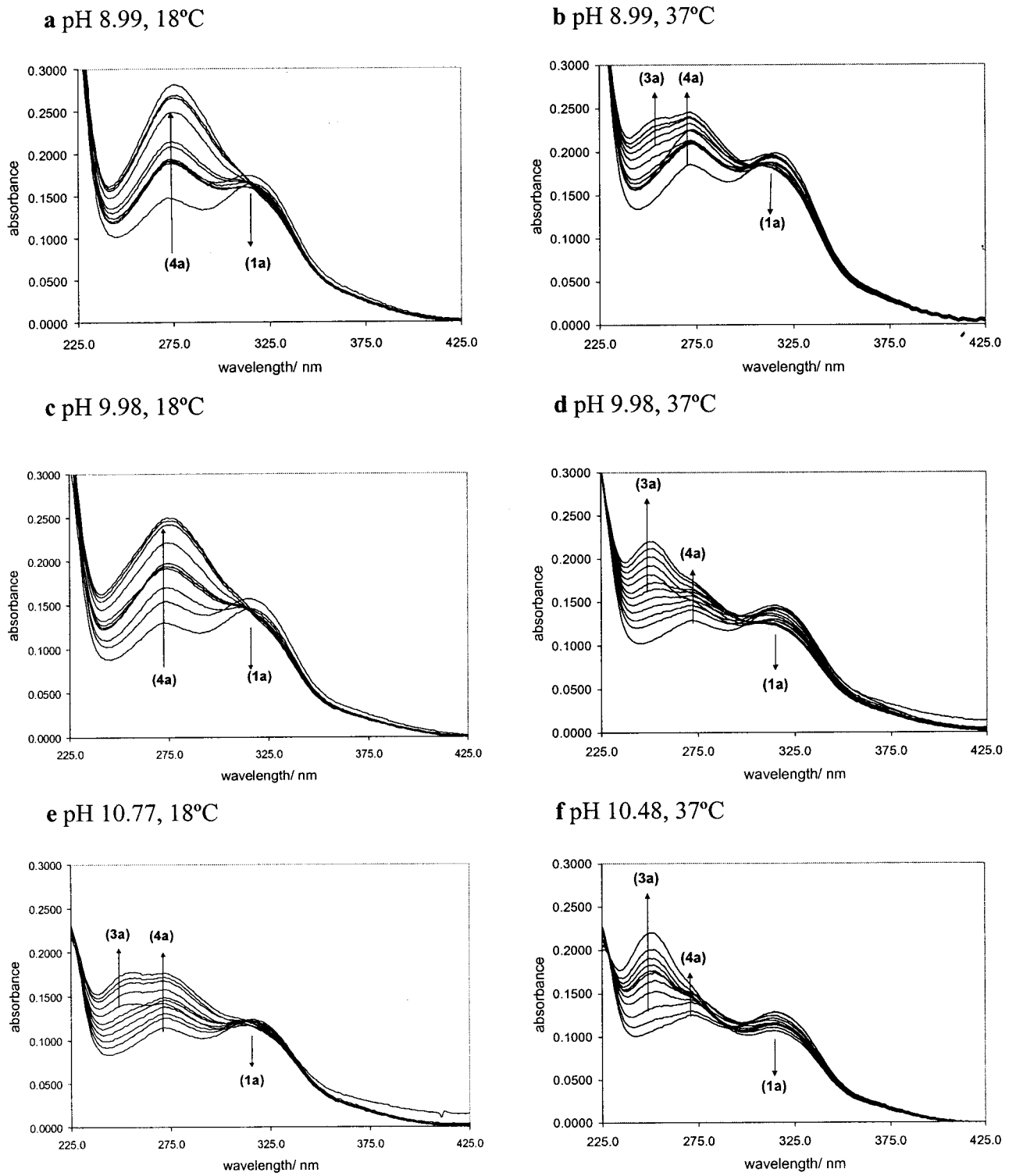


Figure 2. pH and temperature dependence for the ring cleavage of **1a**. Experiments were carried out as described in the Experimental Section, at the pH and temperature indicated; scans were recorded every 10 s.

at 37 °C than 18 °C (the rate of appearance of **4a** shows no apparent change with temperature, due to the increased rate of conversion to **3a**). (Observed rate constants from Figures 2 and 3 are submitted as Supporting Information.) It therefore appears that the conversion of intermediate **4a** to **3a** is accelerated by higher pH and by temperature, as would be expected for the base-catalyzed addition of methanol to an α,β-unsaturated ketone. In contrast, the rate of conversion of **1a** to intermediate **4a** appears to be temperature-dependent but pH-independent.

The reaction of **1b** was monitored in the same way (Figure 1C). In this case, a linear disappearance of **1b** was also observed at 300 nm over 1−5 min. A new species was observed as a shoulder at 240 nm, which was assigned to intermediate **4b**.

Scans were carried at at short reaction times, to identify early reaction intermediates. At 10 and 20 s time

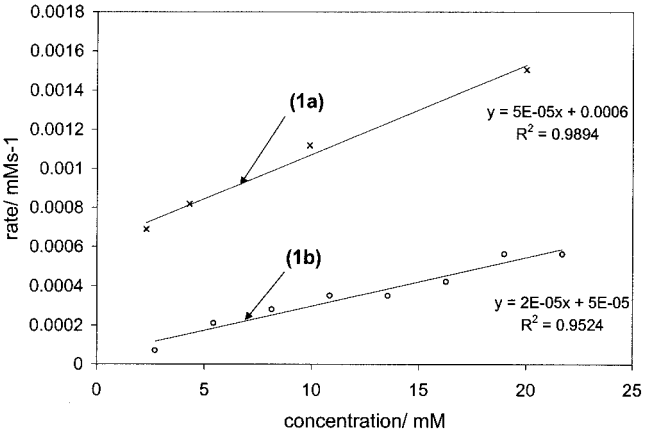
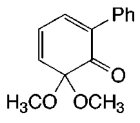


Figure 3. Rate dependence for ring cleavage of **1a** and **1b** vs reactant concentration. Reactions were carried out in 50 mM Na_2CO_3 in methanol/water (1:1), at 20 °C.

intervals in the reaction of **1a** a weak absorbance peak was detected at λ_{max} 550 nm, which disappeared at longer reaction times, suggesting the existence of a further short-lived reaction intermediate that has a highly conjugated structure.

Kinetic Studies. Monitoring of reaction rate for **1a** and **1b** was carried out in 50 mM sodium carbonate (pH 8.9) at 20 °C using methanol/water (1:1) as solvent. The rate of reaction, as monitored by the rate of disappearance of substrate, or the disappearance of the first product (at 275 or 236 nm, respectively) was found to be linear versus time. Comparison of the reaction rates for **1a** and **1b** versus concentration revealed that in both cases the reaction appears to be first order with respect to the concentration of the starting cyclohexa-2,4-dienone but that the first-order rate constant for reaction of **1a** (4.95×10^{-6} s^{-1}) is approximately 2-fold higher than the that of **1b** (2.47×10^{-6} s^{-1}) (Figure 3). (Observed rate constants from Figures 2 and 3 are submitted as Supporting Information.)

To investigate whether the presence of the acetyl ester was essential for C−C cleavage, a further cyclohexadienone was synthesized, which contained methoxy substituents rather than an acetoxy substituent. Treatment of 2-phenyl phenol with diacetoxy-iodosobenzene[9] (DAIB) in methanol gave 2-phenyl-6,6-dimethoxy-cyclohexa-2,4-dienone (**5**). Incubation of **5** in methanol/water (1:1) containing 50 mM sodium carbonate gave no reaction on a 5−10 min time scale as observed by UV spectroscopy or thin-layer chromatography.

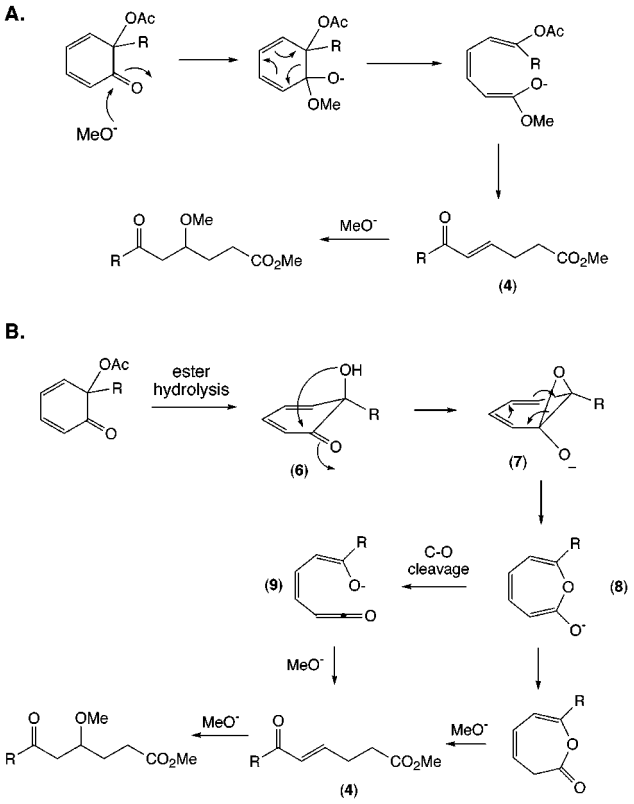


5

Discussion

An investigation of the solvolytic cleavage of 2-acetoxy-cyclohexa-2,4-dienes has not previously been reported, although in one report by Wessely a derivative of such a ring cleavage product was observed.[10] For this reaction,

Scheme 3. Proposed Mechanisms for Conversion of 1 to 3[a]



[a] Mechanism A proposed by Wessely;[10] mechanism B described in the text.

Wessely proposed a reaction mechanism involving nucleophilic attack of solvent on the ketone group, followed by an electrocyclic ring opening of the diene (Scheme 3, mechanism A).[10] Mechanism A does not fully account for the observed data in this paper, since nucleophilic attack at the C-1 ketone would be disfavored by increased steric bulk at the adjacent C-6 quaternary center. Hence, if mechanism A is followed, one would predict that the phenyl-substituted **1a** would react slower than the methyl-substituted analogue **1b**, whereas the opposite is found.

An alternative mechanism (B) is presented in Scheme 3. Since we have been unable to isolate any of the alcohol **6** resulting from acetyl ester hydrolysis, we propose that this alcohol is formed under basic conditions and undergoes a rapid rearrangement, involving attack onto the adjacent C-1 ketone, forming a benzene oxide intermediate (**7**), which undergoes rapid electrocyclic ring opening to the corresponding seven-membered oxepin (**8**). This oxepin might then be converted to a lactone, or might undergo internal C−O bond cleavage to give a ketene (**9**), either of which species could be attacked by methanol to give α,*β*-unsaturated ketone **4**. Conjugate addition of methanol then yields the final *β*-methoxy ketone product **3**.

Our experimental observations provide some support for mechanism B. The involvement of ester hydrolysis is supported by the observation that dimethoxy derivative **5** does not undergo reaction under the same reaction conditions. The observation that reaction of **1a** is twice as fast as reaction of **1b** implies that the phenyl substituent of **1a** provides some assistance to the rate-

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(10) Siegel, A.; Wessely, F.; Stockhammer, P.; Antony, F.; Klezl, P. *Tetrahedron* **1958**, *4*, 49.

determining step, which in mechanism B could come about either by lowering the pK_a of the neighboring hydroxyl group (which might, for example, accelerate **8** to **9**) or through some steric influence (for example, in promoting the formation of **7**).

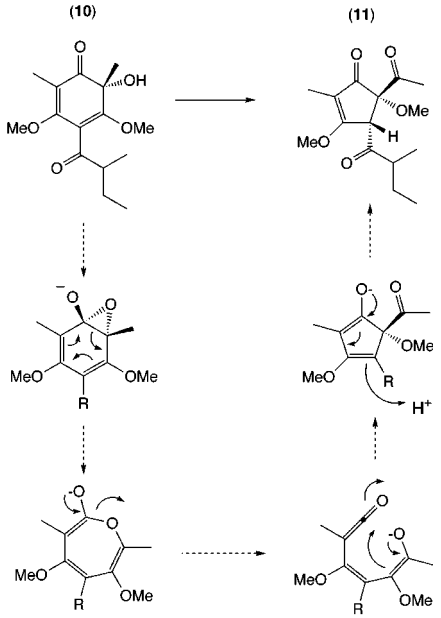
The effects of pH and temperature on the reaction (Figure 2) are also informative. The intermediate observed experimentally at λ_{max} 275 matches the expected UV spectrum for α,β-unsaturated ketone **4**, and its conversion to **3** is base-catalyzed and temperature-dependent, consistent with a bimolecular reaction of methoxide with **4**. The conversion of **1** to **4** shows no apparent pH dependence, but does show temperature dependence. The lack of pH dependence is contrary to expectations, since the ester hydrolysis step should be base-catalyzed. We suggest that the UV spectra of ester **1** and alcohol **6** will be very similar; hence, the conversion of **1** to **6** is not observable by UV spectroscopy. The observation that the disappearance of the initial peak at 317 nm is not strongly influenced by changes in pH would therefore imply that ester hydrolysis is faster than the subsequent reaction of **6** via this mechanism and, furthermore, that the rate-limiting step between **6** and **4** is not influenced by pH in the range 9−11.

The proposed oxepin intermediate (**8**) may correspond to the species observed transiently at λ_{max} 550 nm. There are no literature reports of stable 1-O-substituted oxepins; however, 1,6-dimethyl-oxepin is reported to absorb at 290-400 nm.[11] Studies of the benzene oxide interconversion have found that this electrocyclic ring opening occurs at room temperature.[11] It is known that pericyclic reactions such as the oxy-Cope rearrangement are greatly accelerated by the presence of an adjacent oxyanion;[12] thus, one would predict that the electrocyclic ring opening of **7** would be a rapid process. Two possible mechanisms are drawn in Scheme 3 for decomposition of oxepin **8**, via C-protonation to give a seven-membered lactone, or C−O cleavage to give a ketene **9**. Formation of ketenes from activated esters via C−O cleavage is known in the case of esters with acidic C_α-protons.[13]

Soga et al. have reported the conversion of cyclohexadienone natural product wasibidienone B_1 (**10**) to cyclopentenone **11**, effected by heating **10** in benzene at reflux overnight, as shown in Scheme 4.[14] Although no mechanism was proposed by Soga et al., the application of mechanism B, via a benzene−oxepin interconversion, could rationalize this transformation. Conversion of the oxepin intermediate to product (**11**) can be explained by C−O cleavage to give a ketene, followed by intermolecular reaction with an enolate anion to form the five-membered ring (see Scheme 4).

This reaction mechanism also provides a new, alternative reaction pathway for the later stages of the reaction catalyzed by the intradiol catechol dioxygenases. X-ray crystal structures have been solved for two members of this family, namely protocatechuate 3,4-dioxygenase from *Pseudomonas aeruginosa*[15] and catechol 1,2-dioxygenase from *Acinetobacter* sp. ADP1.[16] In both cases, the non-heme iron(III) cofactor is ligated by two tyrosine residues and two histidine residues. The proposed mechanism for this family of enzyme involves the rearrangement of a 6-hydroxy-6-peroxocyclohexa-2,4-dienone, via acyl migration, to give an anhydride, which is then hydrolyzed to give a muconic acid product.[4,5]

Scheme 4. Transformation of Wasabidenone B_1 Reported by Soga et al.,[14] with Mechanism Proceeding via Benzene Oxide−Oxepin Interconversion



To date, it has been assumed that the acyl migration step in this reaction mechanism occurs by direct Criegee rearrangement.[4,5] In support of this proposal is the observation that Baeyer−Villiger oxidation of 1,2-diketones gives anhydride products,[17] via acyl migration. However, studies on the Baeyer−Villiger oxidation of benzil using ^{17}O labeling have implicated a reaction mechanism involving intramolecular attack of an alkoxide ion on the adjacent ketone prior to O−O bond cleavage,[18] similar to our proposed mechanism. As shown in Scheme 5, a cyclohexadienone intermediate in which the alcohol substituent is positioned axially with respect to the ring could react via this mechanism to give an oxepin, which can undergo O−O cleavage to yield an anhydride and, hence, the muconic acid product. Thus, the studies in this paper provide a chemical basis for an alternative mechanism for intradiol cleavage, which remains to be investigated for the enzyme-catalyzed reaction.

Experimental Section

Reagents and solvents were purchased from Acros or Sigma-Aldrich and were used as received. Reactions were followed by the use of thin-layer chromatography (aluminum sheets precoated with Merck 60 F254 silica) and products were visualized using UV absorption (254 nm) and dinitrophenyl hydrazine. Silica flash chromatography columns were performed using Merck silica 60 (230−400 mesh). UV/visible

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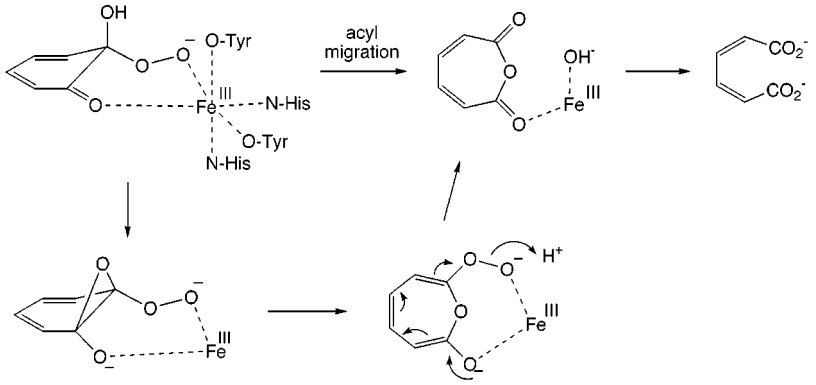
Scheme 5. Possible Mechanism for the Acyl Migration Step of the Intradiol Catechol Dioxygenase Reaction Mechanism, Involving the Conversion of a Cyclohexadienone Hydroperoxide to Muconic Anhydride via a Benzene Oxide−Oxepin Interconversion



spectra were recorded on a Beckman Coulter DU7400 spectrophotometer.

Preparation of 6-Acetoxy-6-phenylcyclohexa-2,4-dienone (1a). Glacial acetic acid (10 mL) was added to lead(IV) acetate (10.03 g, 20 mmol), and the slurry was stirred at room temperature under nitrogen. A solution of 2-hydroxybiphenyl (1.72, 10 mmol) in glacial acetic acid (10 mL) was added very slowly, over 20−30 min, and the dark red/brown mixture stirred for 2 h at room temperature and under nitrogen. The reaction was quenched with water (50 mL), and the mixture was extracted with ether, both phases being filtered to remove the lead oxide precipitate. The ether was washed first with $NaHCO_3$ (aqueous, saturated), to remove excess acetic acid, and then brine (2 × 20 mL) and dried over $MgSO_4$. The ether was removed in vacuo to give the crude product as a red oil and solid. The oil was dissolved in 20% ether in petroleum ether leaving the solid undissolved. This was then filtered and the solid washed in warmed 20% ether in petroleum ether, filtered again, and dried to give a yellow solid (0.649 g, 29% yield): δ_H (300 MHz, $CDCl_3$) 7.49−7.56 (2H, m), 7.31 (3H, dd, J = 5.5, 1.1 Hz), 7.05 (1H, ddd, J = 9.6, 5.8, 2.2 Hz, H-3), 6.50 (1H, ddd, J = 9.6, 6.0, 2.2 Hz, H-4), 6.36 (1H, dd, J = 9.6, 2.2 Hz, H-2), 6.15 (1H, d, J = 9.6, H-5), 2.24 (3H, s, $-COCH_3$) ppm; δ_C (75 MHz, $CDCl_3$) 196.88, 170.01, 141.34, 140.96, 134.16, 129.46, 129.32, 126.69, 125.93, 123.76, 82.45, 21.10 ppm; m/z (EI) 228 (M^+); HRMS 228.0786, $C_{14}H_{12}O_3$ requires 228.0779.

Preparation of 6-Acetoxy-6-methylcyclohexa-2,4-dienone (1b). Glacial acetic acid (10 mL) was added to lead-(IV) acetate (10.73 g, 21 mmol), and the slurry was stirred at room temperature under nitrogen. A solution of O-hydroxybiphenyl (1.12 g, 11 mmol) in glacial acetic acid (10 mL) was added very slowly, over 20−30 min, and the dark red/ brown mixture stirred for 2 h still at room temperature and under nitrogen. The reaction was quenched with water (50 mL) and filtered, and the mixture was extracted with ether. The ether was washed first with $NaHCO_3$ (aqueous, saturated), to remove excess acetic acid, and then brine (2 × 20 mL) and dried over $MgSO_4$. The ether was removed in vacuo to give the crude product as a brown/red oil. The product was purified by silica column chromatography (10% ether in petroleum ether) to give a yellow solid (0.386 g, 23% yield): δ_H (300 Hz, $CDCl_3$) 6.98 (1H, ddd, J = 9.8, 4.5, 3.0 Hz, H-3), 6.17 (2H, d, J = 2.9 Hz, H-4 + H-5), 6.11 (1H, d, J = 9.8 Hz, H-2), 2.02 (3H, s, $-COCH_3$), 1.35 (3H, s, $-CH_3$) ppm; δ_C (75 MHz, $CDCl_3$) 199.01, 164.08, 142.97, 140.99, 126.72, 122.10, 79.43, 23.85, 20.88 ppm; m/z (EI) 166 (M^+); HRMS 166.0629, $C_9H_{10}O_3$ requires 166.0630.

Preparation of Methyl 6-Keto-6-phenyl-4-methoxyhexanoate (3a). Potassium carbonate (0.143 g, 1 mmol) was dissolved in water (10 mL) and methanol (10 mL). 6-Acetyl-6-phenylcyclohexa-2,4-dienone (97 mg, 0.43 mmol) was then dissolved in methanol (10 mL) and added to the aqueous solution with stirring. The brown/red solution was stirred overnight. The solvents were removed in vacuo, and the products were purified by silica column chromatography (1:1 diethyl ether/petroleum ether) to give a yellow oil (67 mg, 63% yield): δ_H (300 MHz, $CDCl_3$) 7.89 (2H, d, J = 9.2 Hz), 7.50 (1H, tt, J = 7.7, 1.7 Hz), 7.39 (2H, t, J = 7.7 Hz), 3.85 (1H, qn, J = 6.1 Hz, $-CH(OMe)-$), 3.60 (3H, s, $-COOCH_3$), 3.26 (3H, s, $-OCH_3$), 3.25 (1H, dd, J = 18.0, 6.1 Hz, H-5), 2.87 (1H, dd, J = 18.0, 6.1 Hz, H-5′), 2.38 (2H, td, J = 7.7, 3.1 Hz, H-2), 1.93−1.73 (2H, m, H-3) ppm; δ_C (75 MHz, $CDCl_3$) 198.86, 174.33, 137.50, 133.63, 129.23, 128.55, 76.93, 57.80, 52.03, 43.32, 30.31, 29.90 ppm; m/z (CI) 251 (MH^+); HRMS 251.1287, $C_{14}H_{19}O_4$ requires 251.1283.

Preparation of Methyl 6-Keto-4-methoxyheptanoate (3b). Potassium carbonate (0.35 g, 2.1 mmol) was dissolved in water (10 mL) and methanol (10 mL). 6-Acetyl-6-methylcyclohexa-2,4-dienone (66 mg, 0.29 mmol) was then dissolved in methanol (10 mL) and added to the aqueous solution with stirring. The brown/red solution was stirred overnight. The solvents were removed in vacuo, and the products were purified silica column chromatography (1:1 diethyl ether/ petroleum ether) to give a yellow oil (35 mg, 46% yield): δ_H (300 MHz, $CDCl_3$) 3.59−3.72 (1H, m, $-CH(OMe)-$), 3.67 (3H, s, $-COOCH_3$), 3.63 (3H, s, $-OCH_3$), 2.65 (1H, dd, J = 15.5, 7.7 Hz), 2.52−2.45 (2H, m), 2.41−2.33 (2H, m), 2.24 (3H, s, CH_3CO-), 1.98−1.70 (2H, m) ppm; δ_C (75 MHz, $CDCl_3$) 207.71, 174.33, 76.38, 57.49, 52.06, 48.15, 31.42, 29.16, 27.88 ppm; m/z (CI) 189 (MH^+); HRMS 189.1128, $C_9H_{17}O_4$ requires 189.1127.

Preparation of 6,6-Dimethoxy-2-phenylcyclohexa-2,4-dienone (5). To a stirred solution of diacetoxyiodobenzene (1.14 g, 3.3 mmol) in dry methanol (25 mL) was added dropwise a solution of 2-hydroxybiphenyl (0.51 g, 3.0 mmol) in dry methanol (25 mL) and the reaction stirred overnight at room temperature. The solvent was then removed in vacuo, and the products were re-suspended in diethyl ether. The white solid produced was filtered off and the ether removed in vacuo. The crude product was then purified using silica column chromatography (3:1 → 1:1 petroleum ether/diethyl ether) to give a yellow oil (20 mg, 4% yield): δ_H (300 MHz, $CDCl_3$) 7.38 (5H, m), 6.88 (2H, dd, J = 8.0, 3.7 Hz), 6.38 (1H, dd, J = 11.0, 1.5 Hz), 3.38 (6H, s, OCH_3) ppm; m/z (CI) 231 (MH^+).

UV Scanning of C−C Cleavage Reactions. To a 1:1 mixture of methanol/water (960 μL) in a quartz cuvette was added 100 mM aqueous Na_2CO_3 solution (20 μL) and a methanol solution (20 μL) of either compound **1a** (49 mM) or compound **1b** (63 mM), and the UV/visible spectrum was scanned between 200 and 700 nm every 10 s. Reaction rates were measured by recording absorbance at 305 nm (for **1a**) or 274 nm (for **1b**) versus time.

Dependence of reaction rate upon substrate concentration was determined by measurement of reaction rates at a final concentrations of 20−200 μM **1a** or **1b** in 50 mM sodium carbonate (pH 8.9) in 1:1 methanol/water at 20 °C. Extinction coefficients of 4160 and 2215 $M^{-1}cm^{-1}$ were measured for **1a** and **1b**, respectively, under these conditions, which were used to calculate reaction rates in μM/s.

pH and Temperature Dependence in the UV Scanning of C−C Cleavage Reactions. Aqueous solutions (100 mM) of Na_2CO_3 and $NaHCO_3$ were mixed to prepare 100 mM carbonate buffers of pH 8.9−10.8. To a mixture of methanol (480μL) and buffer (500μL) in a quartz cuvette was added a 20 μL aliquot of **1a** in methanol (2 mM stock), and the UV/visible spectrum was scanned between 200 and 700 nm every 10 s. Assays and reagents were maintained at either 18 or 37 °C.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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