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Orthoquinone Monoketal Chemistry. Experimental and Density Functional Theory Studies on Orthoquinol Acetate Rearrangements

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Abstract: The non-dimerizing orthoquinone monoketal, 6-acetoxy-6-methoxy-3-methoxycarbonylcyclohexa-2,4-dienone, conveniently prepared from oxidative acetoxylation of its parent phenol with $\text{PhI}(\text{OAc})_2$ in CH_2Cl_2 -AcOH (3:1), cleanly undergoes 1,3-acetoxy migrations in the presence of silica gel at room temperature to furnish a 60:40 product mixture conceivably derived from [3,5] and [3,3] sigmatropic rearrangements. Density functional theory calculations indicate that the [3,5] shift is pseudopericyclic, has a remarkably low activation energy of 20.1 kcal/mol, and is favored by 5.4 kcal/mol over the pericyclic [3,3] shift, in qualitative agreement with the experimental observations.

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Orthoquinone monoketals (i.e., 6,6-dioxocyclohexa-2,4-dien-1-one derivatives) constitute valuable electrophilic intermediates for the preparation of polyoxygenated carbo- and heterocycles. It is however often difficult to exploit the reactivity of their conjugated π -system in a controlled manner, mainly because of the propensity of their 2,4-dienone moiety to participate in Diels-Alder dimerization.^{1,2} These cyclohexadienones are also susceptible to rearrangements that often leads to aromatization events.³ Nevertheless, orthoquinone monoketals have found useful synthetic applications, in particular via $[4\pi + 2\pi]$ cycloadditions.⁴⁻⁶ Our own recent contribution to the study of these quinonoid synthons demonstrated their value in heterocyclizations for the construction of benzannulated oxygen ether rings.⁷

We report here experimental and density functional theory (DFT) results on the reactivity and mechanism of rearrangement of orthoquinone monoketals derived from 3-hydroxy-4-methoxybenzoate (**1**, Scheme 1). The monoketal **2** was presumably produced from oxidative methoxylation of **1** using $\text{PhI}(\text{O}_2\text{CCF}_3)_2$ (1.0 equiv.) and K_2CO_3 (2.0 equiv.) in $\text{MeOH}-\text{CH}_3\text{CN}$ (2:1) at -42°C , but this 6,6-dimethoxycyclohexa-2,4-dienone dimerized *in situ* to give the Diels-Alder product **3** in 55% isolated yield.⁸ Regiochemical assignment of *cis*-fused **3** is based on ^1H and ^{13}C NMR criteria (unassigned *endo/exo* orientation).⁹ In contrast to **2**, its 6-acetoxy-6-methoxy analogue **4** does not dimerize spontaneously. This orthoquinol acetate was initially prepared by Wessely oxidation of **1** with $\text{Pb}(\text{OAc})_4$ in CH_2Cl_2 .¹⁰ The lack of

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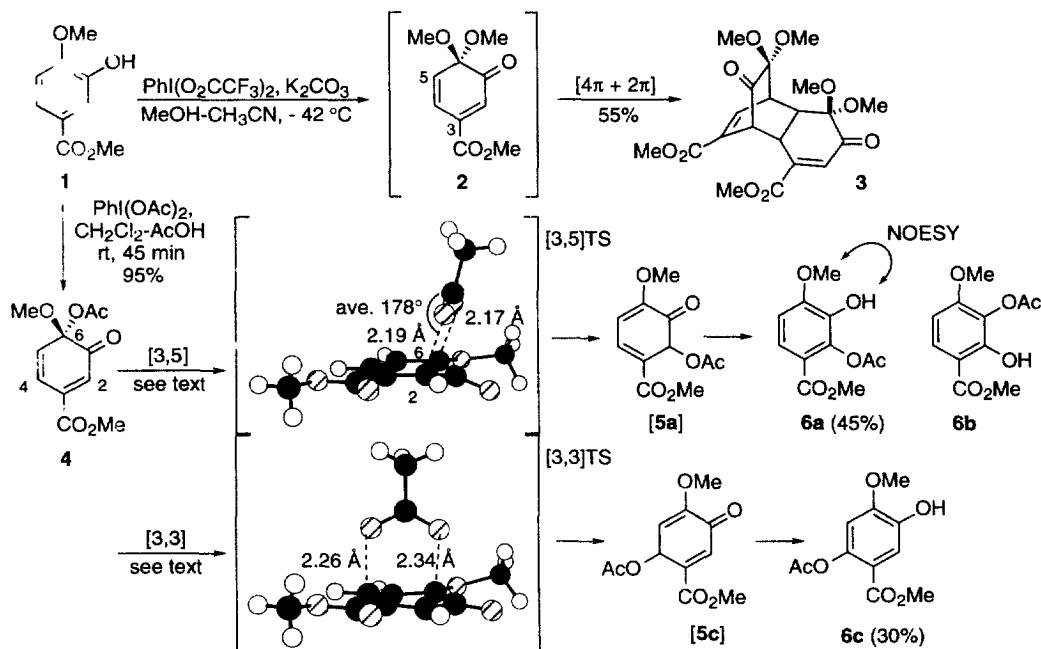
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reproducibility of this oxidative acetoxylation led us to look for a more convenient procedure. Thus, we found that oxidation of **1** with $\text{PhI}(\text{OAc})_2$ in CH_2Cl_2 -AcOH (3:1) at room temperature rapidly furnished **4** in excellent yield.¹¹

Scheme 1



Several epoxidation attempts were performed on **4** with the aim of elaborating its carbocyclic moiety for further synthetic manipulations. Treatment of **4** with dimethyldioxirane in MeOH-acetone (4:1)¹² at 0 °C for 24 h did not give any epoxidized product, but furnished the Diels-Alder dimer **3**, via acetoxy-methoxy group exchange, and compound **6a**, in 40% and 12% isolated yields, respectively. Epoxidations with *m*-CPBA (1 to 4 equiv.) in CH_2Cl_2 at 0 °C for 3 to 5 days were also unsuccessful; **6a** was again produced in 10% isolated yield, together with unidentified degradation products. The reason for this apparent lack of reactivity of **4** toward epoxidation remains obscure, but the formation of **6a** under these mildly acidic conditions is an intriguing observation. Compound **6a** was also formed upon subjecting **4** to silica gel flash chromatography, which afforded a 9:1 mixture of **4**:**6a** in 45% yield. A stirred solution of **4** (44 mg) in CH_2Cl_2 (15 ml) was then exposed to silica gel (80 mg) at room temperature for 4 days. Under these conditions, **4** was cleanly converted into a 60:40 mixture of **6a**:**6c** (¹H NMR analysis), which was separated by silica gel chromatography in 75% yield.^{8,13} Compounds **6a** and **6c** result from 1,3-shifts of the acetoxy group from the 6- to the 2- and 4-position of **4** to give **5a** and **5c**, followed by aromatization (Scheme 1). These types of rearrangements have been previously observed with related quinol acetates and diacetates upon thermal induction or treatment with $\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$ or $\text{BF}_3\text{-Et}_2\text{O}$.^{3,14,15} In these related cases, migration of acetyl groups to adjacent phenolic positions can occur to furnish regioisomeric mixtures. Here, this isomerization did not take place; only **6a**, but not **6b**, was isolated.¹³ The regiochemistry of **6a** was confirmed by NOE spectroscopy (Scheme 1).

Several mechanisms involving either a concerted pathway, a radical process, or successive [1,2] shifts have been proposed to rationalize these 1,3-acetoxy migrations.³ The [3,5] concerted pathway was dismissed by consideration of the generally accepted rules of orbital symmetry conservation.¹⁶ However, our recent *ab initio* calculations on the analogous ester rearrangement of cyclohexa-2,4-dienyl formate have provided evidence for a concerted reaction involving a “pseudopericyclic” [3,5] sigmatropic shift; the calculated barrier for this remarkable rearrangement is 35.3 kcal/mol and is favored by 3 kcal/mol over the alternative pericyclic [3,3] boat transition state.¹⁷ The particularly mild conditions under which acetate rearrangements of **4** does occur led us to examine its mechanism as well. The aromatized rearrangement product **6a** can conceivably be derived from a similar possibly acid-catalyzed [3,5] pseudopericyclic sigmatropic shift, whereas **6c** would originate from the pericyclic [3,3] alternative.

The geometries of the reactant **4**, the [3,5] and [3,3] transition states and the products **5a** and **5c** were optimized at the B3LYP/6-31G* DFT level using Gaussian 94.¹⁸ Frequency calculations verified the transition states and provided free energies as well. The relative energies are reported in Table 1, and side views of the two transition states are shown in Scheme 1. Both transition states are concerted and fairly synchronous. The [3,5] transition state is clearly pseudopericyclic; the breaking and forming bonds are in the plane of the acetate and do not interact with the acetate π -system. The [3,3] transition state is a boat with the partial bonds at 159.6° and 147.0° to the acetate which is tipped away from the viewer in Scheme 1; in similar [3,3] ester rearrangements, the boat is lower in energy than the chair.^{17b}

Table 1. Relative Energies (B3LYP/6-31G*//B3LYP/6-31G*, kcal/mol)

	4	[3,5]TS	[3,3]TS	5a	5c
E_{rel} , B3LYP/6-31G*	0.0	21.1	26.8	-2.3	1.1
ΔG , B3LYP/6-31G*	0.0	20.1	25.5	-2.4	0.2

The free energy of activation at 25 °C is calculated to be 20.1 kcal/mol for the [3,5] rearrangement. Although there is admittedly some uncertainty in this calculated barrier, it is clearly surmountable at room temperature. Furthermore, this uncatalyzed TS is lower (5.4 kcal/mol) than for the [3,3], in qualitative agreement with the experimental observation that **6a** is the major rearrangement product which could arise from a mild acid catalysis in the presence of silica gel. It is also worth noting that the formation of **6c** was obvious only upon prolonged exposure to silica gel. Although a direct comparison is not appropriate because the calculations were at different levels of theory, the barrier for the [3,5] rearrangement of **4** (20.1 kcal/mol) is lower than that calculated for the [3,5] rearrangement of cyclohexa-2,4-dienyl formate (35.3 kcal/mol).¹⁷ This is not unexpected; ester rearrangements have long been understood as being polarized, with a negative charge on the ester and positive charge on the carbon fragment. In the case of **4**, the acetate is better at stabilizing a negative charge than a formate and the methoxy group at C-6 will stabilize the ring positive charge. In addition, the forming bond involves nucleophilic addition of an ester carbonyl to a carbon. The carbomethoxy group at C-3 would be expected to activate the C-2 center towards such attack, as would protonation of the C-1 carbonyl. Together these factors permit to rationalize the remarkably low activation energy for the pseudopericyclic [3,5] rearrangement of **4** into **6a**.

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- Isolation/purification of compounds were performed by silica gel chromatography, eluting with hexanes-EtOAc (4:1 → 1:1).
- 3** (amber needles from CH₂Cl₂-light petroleum): mp 166-168 °C; IR (KBr) 1720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.94 (s, 3 H), 3.10 (s, 3 H), 3.19 (bd, *J* = 6.9 Hz, 1 H), 3.25 (dd, *J* = 8.3, 1.2 Hz, 1 H), 3.30 (s, 3 H), 3.36 (s, 3 H), 3.56 (s, 3 H), 3.73 (ddd, *J* = 8.3, 2.8, 1.3 Hz, 1 H), 3.75 (s, 3 H), 3.86 (dd, *J* = 2.8, 1.9 Hz, 1 H), 6.64 (d, *J* = 1.2 Hz, 1 H), 6.96 (dd, *J* = 6.9, 1.8 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 200.1, 193.6, 164.7, 163.2, 144.2, 140.5, 132.6, 132.2, 98.4, 94.2, 52.7, 51.9, 51.5, 50.4, 50.1, 49.8, 49.0, 40.9, 38.2, 38.1; EIMS *m/z* (relative intensity) 424 (M⁺, 8), 396 (64), 381 (14), 336 (17); Anal. Calcd for C₂₀H₂₄O₁₀: C, 56.59; H, 5.70. Found: C, 56.39; H, 5.83.
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- 6a** (off-white solid, 20 mg, 45%): mp 117-119 °C; IR (KBr) 3448, 1762, 1664, 1629 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.35 (s, 3 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 6.50 (d, *J* = 9.0 Hz, 1 H), 7.70 (d, *J* = 9.0 Hz, 1 H), 10.94 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 170.1, 168.4, 157.0, 154.8, 128.1, 127.4, 107.0, 102.9, 56.2, 52.2, 20.3; EIMS *m/z* (relative intensity) 240 (M⁺, 4), 166 (83), 138 (5); Anal. Calcd for C₁₁H₁₂O₆: C, 54.99; H, 5.04. Found: C, 55.37; H, 5.14. **6c** (amber oil, 13 mg, 30%): IR (NaCl) 3418, 1766, 1715 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.54 (s, 1 H), 6.56 (s, 1 H), 5.55 (s, 1 ArOH), 3.90 (s, 3 H), 3.81 (s, 3 H), 2.32 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 164.5, 150.44, 144.9, 142.9, 116.5, 115.1, 106.2, 56.2, 52.0, 20.9; EIMS *m/z* (relative intensity) 240 (M⁺, 32), 209 (25), 166 (100). HRMS (CI) calcd for C₁₁H₁₃O₆ (MH⁺) 241.0712, found 241.0708.
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