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

Stéphane Quideau,* Matthew A. Looney, and Laurent Pouységuy
Sihyun Ham, and David M. Birney

Department of Chemistry, Texas Tech University, Box 41061, Lubbock, Texas 79409, USA

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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 PhI(OAc)2 in CH2Cl2-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.

Keywords: dimerization; oxidation; quinonoid compounds; rearrangements

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 [4π + 2π] 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 PhI(O2CCF3)2 (1.0 equiv.) and K2CO3 (2.0 equiv.) in MeOH-CH3CN (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 13C 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 Pb(OAc)4 in CH2Cl2.10 The lack of

1 E-mail: SQuideau@ttu.edu.
2 Current address: Laboratoire de Chimie des Substances Végétales, Institut du Pin, Université Bordeaux I, 351, cours de la Libération, 33405 Talence Cédex, FRANCE.
3 Current address: Department of Chemistry, University of Washington, Box 351700, Seattle, WA 98195-1700, USA.
4 E-mail: vddmb@ttacs.ttu.edu.

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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 PhI(OAc)_2 in CH_2Cl_2–AcOH (3:1) at room temperature rapidly furnished 4 in excellent yield.\textsuperscript{11}

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)\textsuperscript{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 (\textit{1H} NMR analysis), which was separated by silica gel chromatography in 75% yield. 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 Ac_2O/H_2SO_4 or BF_3–Et_2O.\textsuperscript{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 no 6b, was isolated.\textsuperscript{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-aeetoxy migrations.\textsuperscript{3} The [3,5] concerted pathway was dismissed by consideration of the generally accepted rules of orbital symmetry conservation.\textsuperscript{16} However, our recent \textit{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.\textsuperscript{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 6\textsubscript{a} can conceivably be derived from a similar possibly acid-catalyzed [3,5] pseudopericyclic sigmatropic shift, whereas 6\textsubscript{c} 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 5\textsubscript{a} and 5\textsubscript{c} were optimized at the B3LYP/6-31G* DFT level using Gaussian 94.\textsuperscript{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.\textsuperscript{17b}

<table>
<thead>
<tr>
<th></th>
<th>4 [3,5]TS</th>
<th>5\textsubscript{a}</th>
<th>5\textsubscript{c}</th>
</tr>
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<tr>
<td>(E_{\text{rel}}) B3LYP/6-31G*</td>
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<td>21.1</td>
<td>26.8</td>
</tr>
<tr>
<td>(\Delta G), B3LYP/6-31G*</td>
<td>0.0</td>
<td>20.1</td>
<td>25.5</td>
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</table>

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 6\textsubscript{a} 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 6\textsubscript{c} 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).\textsuperscript{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 6\textsubscript{a}.

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REFERENCES AND NOTES


8. Isolation/purification of compounds were performed by silica gel chromatography, eluting with hexanes-EtOAc (4:1 → 1:1).

9. 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, 1.3 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), 3.86 (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; EI MS 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.


11. Typical oxidative acetoxylation procedure: a solution of I (0.9 mmol) in dry CH2Cl2 (15 ml) was added dropwise to a stirring solution of PhI(OAc)2 (0.9 retool) in CH2Cl2-AcOH (3:1, 13 ml) at rt. The reaction mixture became yellow. After 45 min, the mixture was poured over 1M H3PO4, extracted twice with CH2Cl2, washed with brine, dried over Na2SO4, filtered and evaporated to dryness to give 4 in 95% yield as a bright yellow oil: IR (NaCl) 1732, 1693 cm-1; 1H NMR (200 MHz, CDCl3) δ 2.08 (s, 3 H), 3.44 (s, 3 H), 3.85 (s, 3 H), 6.28 (dd, J = 10.1, 1.0 Hz, 1 H), 6.79-6.86 (m, 2 H); 13C NMR (75 MHz, CDCl3) δ 192.1, 169.7, 164.9, 138.9, 134.6, 128.2, 124.2, 92.4, 52.9, 51.4, 20.3; EI MS m/z (relative intensity) 240 (M+, 6), 198 (71), 166 (100); Anal. Calcd for C11H12O6: C, 54.99; H, 5.04. Found: C, 54.77; H, 4.99. This material was used without further purification.


13. 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 181.0, 168.4, 157.0, 154.8, 128.1, 127.4, 107.0, 102.9, 56.2, 52.2, 20.3; EI MS m/z (relative intensity) 240 (M+, 4), 166 (83), 138 (5); Anal. Caled 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), 5.53 (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, 150.4, 144.9, 142.9, 116.5, 115.1, 106.2, 56.2, 52.0, 20.9; EI MS m/z (relative intensity) 240 (M+, 32), 209 (25), 166 (100). HRMS (CI) calcd for C11H12O6 (MH+) 241.0712, found 241.0708.

