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Highly strained dihydroanthraquinones: oxidation versus elimination

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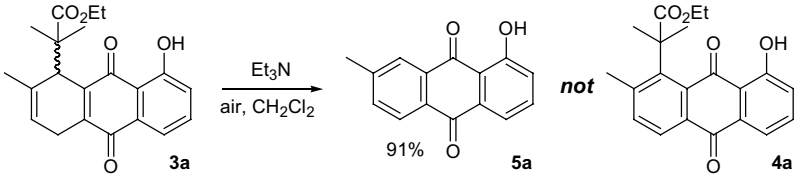
Abstract—The chemistry of strained dihydroanthraquinones was investigated for the purpose of developing syntheses for highly strained anthraquinones. The reaction of (1,4-dihydro-9,10-dioxo-anthracen-1-yl)-acetates with triethylamine under aerobic conditions was found to be dependent on the degree of substitution on the acetate. Dihydroanthraquinones bearing dimethylacetates underwent elimination of enolate exclusively, while those without acetate substitution dehydrogenated as expected. Furthermore, oxidation of the cyclohexadiene ring using iodine failed due to a competitive iodolactonization reaction. The desired strained anthraquinones could be prepared, in low yield, by treatment of the resulting lactones with acidic ethanol.

During the course of research involving the photochemistry of hydroxyanthraquinones, we required 1-hydroxyanthraquinones (see Scheme 1) with bulky substituents in either the 5- or 8- position.[1] Our synthetic strategy for these molecules started with a Diels–Alder reaction between dienes **1** and juglone (**2a**), to give tetrahydroanthraquinone adducts.[2] Our strategy then planned for oxidation of the cyclohexene and aromatization of the resulting cyclohexadiene.[3]

1,4-Dihydroanthraquinone acetates (e.g., **3a**) are constitutional isomers of the corresponding 9,10-dihydroxyanthracenes (hydroquinones), and they were expected to oxidize in a similar fashion. The oxidation of anthrahydroquinones to anthraquinones with oxygen is a well known and usually facile reaction.[4] Treatment with air under basic conditions is a common method of oxidizing hydroquinones.[5] The oxidation of Diels–Alder adducts to cyclohexadienes and then to anthraquinones was not anticipated to be difficult.[6]

However, **3a** displayed an unusual sensitivity to mild bases resulting in the loss of the acetate functionality (Scheme 1).[7] The expected oxidation product (**4a**) was not detected. Instead 1-hydroxy-7-methylanthraquinone (**5a**) was obtained in 91% yield. We suspected the elimination of an enolate, in a reaction similar to the elimination of methanol from 1-methoxy-1,4-dihydroanthraquinones.[8] The dimethylacetate moiety of **3a**, and the resulting steric congestion in the desired oxidation step, was suspected as the cause of this unexpected reactivity.

The result prompted our further investigation of this novel reaction. A series of 1,4-dihydroanthraquinone compounds (**3b–e**) was prepared to study the reaction



Scheme 1. Elimination of enolate from **3a**.

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	R_1	R_2	R_3	R_4	R_5	R_6
a	Me	Me	Me	H	Et	OH
b	Me	Me	H	Me	Me	H
c	Me	Me	H	H	Bn	H
d	Me	H	H	H	Bn	H
e	H	H	H	H	Bn	H

Scheme 2. Preparation of dihydroanthraquinones.

(Scheme 2).[9] These compounds were obtained using an $AlCl_3$ catalyzed Diels–Alder reaction of 1,4-naphthoquinone **2b** and 3,5-diene esters, **1b–e**. Silica gel chromatography of the initial cyclohexene adducts (not shown) resulted in partial conversion of the cyclohexene ring to a 1,4-cyclohexadiene. Therefore, the crude Diels–Alder adducts were stirred with silica gel to give 1,4-dihydroanthraquinones **3a–c**.

The behavior of **3a–e** under alkaline aerobic conditions was investigated (Scheme 3). Equal concentrations of substrates **3a–e** were treated with triethylamine at room temperature in oxygen saturated dichloromethane. In each case, either an anthraquinone acetate **4** or unfunctionalized anthraquinone **5** was the major product. Formation of oxidation product **4** was accompanied by the formation of varying amounts of dimer **6**;[10,11] elimination product **5** was accompanied by anthrone product **7** and ester products **8** and **9**. Isolated yields for products **4–7** are shown in Table 1.

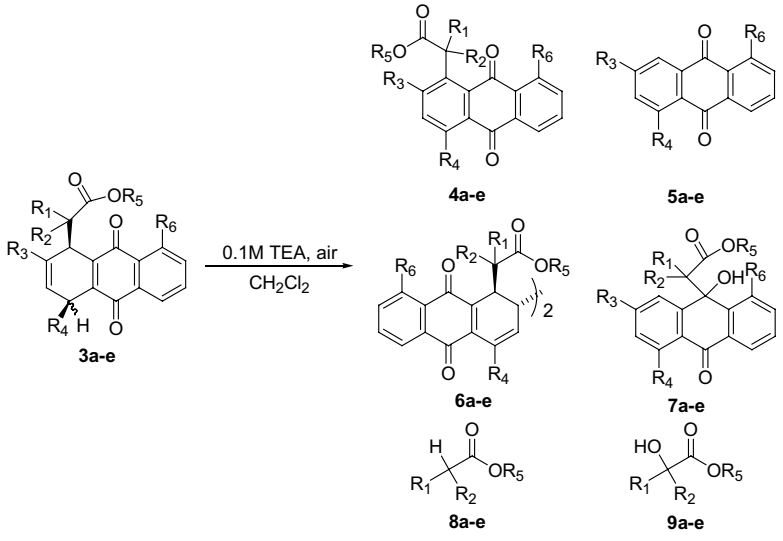
The difference in reactivity between dimethylacetates **3a–c**, which have some degree of methyl substitution at the α-position, and **3e**, which lacks methyl groups at the α-position, was distinct. The former compounds underwent elimination of enolate exclusively upon treatment with base to afford an anthraquinone and isobutyrate. The latter successfully oxidized to the substituted anthraquinone (as well as dimerization).

Table 1. Product distribution in oxidation/elimination of dihydroanthraquinone acetates

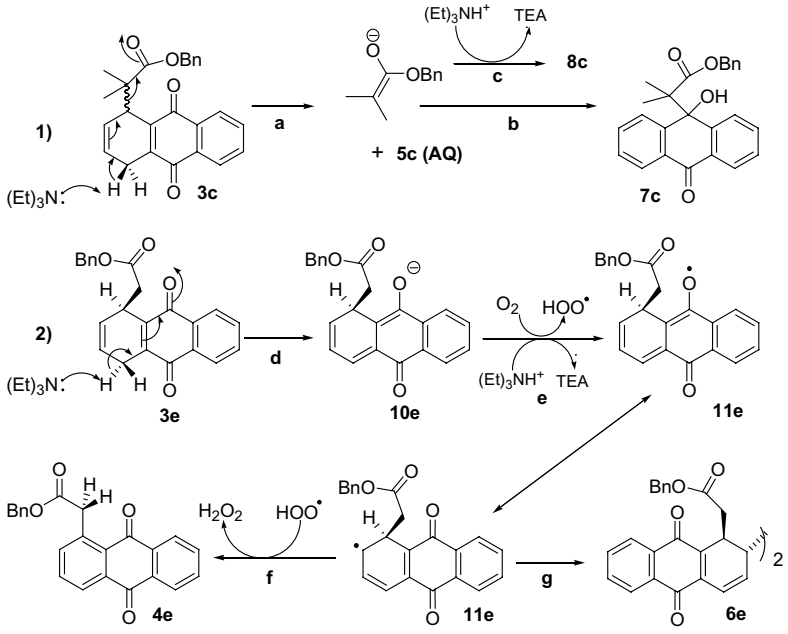
Entry	Substrate	**4**	**5**	**6**	**7**
1	**3a**	0	91	0	Trace
2	**3b**	0	85	0	0
3	**3c**	0	74	0	21
4	**3d**	45	8	44	0
5	**3e**	83	0	17	0

The dependence of the reaction pathway upon substitution at the α-position of the acetate group argues for a steric role in guiding the preferred pathway. Two possible mechanisms to account for the observed products are shown in Scheme 4. For the dimethylacetates, the only observed reaction pathway was enolate elimination (step a, mechanism 1). Attack by the enolate at the carbonyl of the newly formed anthraquinone led to hydroxyanthrone, **7c** (b). This step presumably must occur before solvent separation permits protonation of the enolate (c) to form ester **8c** (see below).

In contrast, in the case of unsubstituted **3e**, oxidation (mechanism 2) is the dominant pathway and elimination of enolate was not observed. Deprotonation of **3e** produced a semiquinone oxyanion, **10e** (d). Instead of elimination, single-electron transfer occurred between molecular oxygen and **10e** to give semiquinone radical **11e** and superoxide (e) as part of the usual mechanism of hydroquinone oxidation.[12] Protonation of superoxide affords hydroperoxyl radical and regenerates triethylamine. Abstraction of the methine hydrogen of **11e** by



Scheme 3. Products of the TEA elimination/oxidation of substituted dihydroanthraquinones.



Scheme 4. Proposed mechanism of elimination/oxidation.

hydroperoxyl radical aromatized the ring and gave anthraquinone acetate **4e** (f). In competition with this step, the semiquinone radical **11e** may dimerize to the bis-1,2-dihydroanthraquinone, **6e** (g), though this is a minor reaction for **3e**.

Though it is unclear why the elimination should proceed so much faster than the oxidation in **3c**, the results of our experiments are consistent with a steric role in the outcome of the reaction. Oxidation of dihydroanthraquinones **3a**–**e** requires the acetate group to move from a position above the quinone ring into the plane of the quinone (**11** → **4**). During this movement, the acetate group must pass close to the proximal quinone oxygen. In **3a**–**c**, the geminal dimethyl substitution requires that one methyl group make a close contact with this oxygen (data not shown). The steric interaction of the methyl and oxygen is enough to greatly retard the rate of oxidation. In **3e**, the methyl groups are absent and the protons on the acetate methylene have sufficient room to slide by the quinone oxygen.

Elimination of enolate, on the other hand, relieves unfavorable steric interactions in the dihydroanthraquinones. The X-ray crystal structure of **3c** is shown in Figure 1.[13] An examination of the structural parameters shows a lengthening of the C1–C15 sp^3–sp^3 bond to 1.574(4) Å and an opening of the tetrahedral angle at C13–C1–C15 to 112.6(2)°. This region of the molecule is sterically crowded with a number of short intramolecular nonbonded contacts. The contacts involve carbonyl carbon (C16) [C16···O28, 2.937(4) Å; C16···C9, 3.086(4) Å; C16···C13, 3.005(4) Å], oxygen O28 (O28···H21, 2.69 Å), and methyl carbons C17 (C17···H2, 2.81 Å) and C18 [C18···C14, 3.425(4) Å; C18···C3, 3.422 Å]. These close contacts likely create a barrier to the acetate group becoming coplanar with the quinone carbonyl, as would be required in going from **3c** to **4c**.

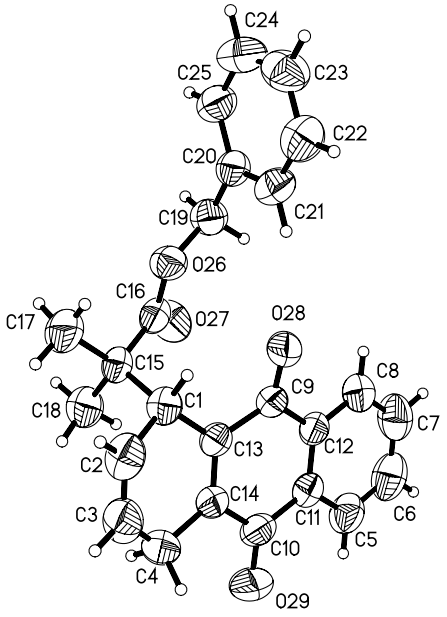
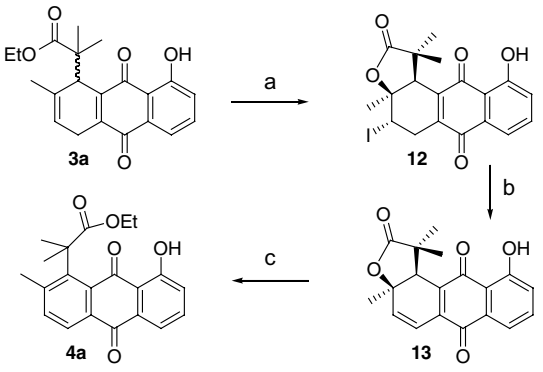


Figure 1. X-ray crystal structure of **3c**.

The formation of anthrone product **7c** suggests that the leaving group in the elimination reaction is an enolate.[14] Once free, this enolate adds to the quinone carbonyl before separation and protonation occurs. In a control reaction, triethylamine failed to promote the addition of benzyl isobutyrate to anthraquinone under the conditions of the oxidation. This suggests that the production of anthrone occurs from a caged pair. However, benzyl hydroxyisobutyrate **9c** was observed when benzyl isobutyrate was treated with TEA in the presence of



Scheme 5. Conversion of **3a** to **4a** via an iodolactone. Reagents and conditions: (a) I_2, H_2O/CH_3OH; (b) TEA, CH_2Cl_2, 88% from **3a**; (c) H_2SO_4, EtOH, Δ, 120 h, 31%.

oxygen, demonstrating that **9c** is a secondary product formed after elimination.

Substrate **3d** provides an interesting midpoint between the dimethyl substrates **3a–c** and unsubstituted **3e**. Anthraquinone (elimination product) was produced in small (8%) yield. Enolate elimination for **3d** is expected to be slower than enolate elimination for **3a–c** due to reduced steric strain in the dihydroanthraquinone. Surprisingly, the quantity of dimer **6d** produced was nearly equal to the amount of oxidation product **4d**. This suggests that the dynamic concentration of radical **11d** must increase relative to that found in the oxidation of **3e** in order for dimerization (g) to compete with aromatization. Hydrogen abstraction (f) thus appears to be rate limiting for the oxidation of substrates **3d–e**; abstraction must be markedly slower for **3d**. If the oxidation reaction of **3d** is quenched with aqueous acid within a few minutes of amine addition, a significant amount of a 1,2-dihydroanthraquinone acetate product is observed in addition to the usual products. Furthermore, when **3d** is treated with triethylamine under anaerobic conditions, no oxidation is observed while the amount of elimination (**5c**) is unchanged.

Finally, we attempted to oxidize the cyclohexadiene ring of **3a** with iodine (Scheme 5). Again, oxidation to the anthraquinone was not observed. Instead, iodolactonization occurred.[15] The iodolactone, **12**, converted slowly to **13** under ambient conditions and, therefore, was immediately treated with triethylamine to produce **13** in 88% yield from **3a**.[16–18] This compound could be converted, in low yield, to the desired anthraquinone **4a** by heating **13** in 0.5 M H_2SO_4 in ethanol for 120 h.

In summary, we have found that sterically congested dihydroanthraquinones exhibit unusual reactivity patterns when exposed to base or oxidants. Oxidation to the corresponding anthraquinone is not observed. Alternative reaction pathways, such as elimination of enolate or iodolactonization involving esters are competitive with the desired oxidation. We continue to investigate the interesting chemistry of strained anthraquinones and will report on additional syntheses of these molecules and their chemistry in the future.

Acknowledgements

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7. A dihydroanthraquinone was isolated in low yield (<10%) that had a 1,5,6-substitution pattern as opposed to the 1,7,8 pattern in **3a**. Although this minor regioisomer was obtained in too little quantity for thorough investigation, it appeared to behave similarly when treated with base.
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9. Data for **3b**: mp 118–119 °C. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.25 (s, 3H), 1.39–1.42 (d, $J = 7.2$), 3.60–3.69 (s, 1H), 3.65 (s, 3H), 4.16–4.19 (t, $J = 4.5$, 1H), 5.75–5.80 (dd, $J = 5.5$, 4.5, 1H), 5.98–6.03 (dd, $J = 5.5$, 4.3, 1H), 7.70–7.74 (m, 2H), 7.93–8.01 (m, 1H), 8.05–8.10 (m, 1H). ^{13}C NMR ($CDCl_3$) 184.2, 182.9, 177.1, 146.9, 143.4, 132.5, 132.4, 131.6, 131.5, 131.3, 125.3, 125.2, 122.0, 51.0, 45.1, 40.3, 30.0, 22.8, 21.7, 19.9. HRMS calcd for ($C_{20}H_{20}O_4$+Na^+): 347.125378. Found: 347.12513. Anal. Calcd for $C_{24}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.92; H, 6.20.
10. Data for **4d**: mp 123–124 °C; ^{1}H NMR ($CDCl_3$): 1.66 (d, $J = 7.2$ Hz, 3H), 5.01 (q, $J = 7.2$ Hz, 1H), 5.12 (d, $J = 12.4$ Hz, 1H), 5.17 (d, $J = 12.4$ Hz, 1H), 7.22–7.26 (br s, 5H), 7.66 (dd, $J = 7.7$, 1.7 Hz, 1H), 7.70 (t, $J = 7.7$ Hz, 1H), 7.75–7.78 (m, 2H), 8.18–8.21 (m, 1H), 8.23–8.26 (m, 1H), 8.33 (dd, $J = 7.7$, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): 185.3, 183.5, 174.1, 143.5, 136.2, 135.4, 134.9, 134.4, 134.0, 133.9, 132.8, 130.9, 128.6, 128.3, 128.2, 127.7, 127.3, 126.9, 66.7, 43.6, 29.9. Anal. Calcd: C, 77.82; H, 4.90. Found: C, 77.52; H, 4.87.
11. Data for **6d**: mp 171 °C (dec); ^{1}H NMR ($CDCl_3$): δ 0.90 (d, $J = 7.2$ Hz, 6H), 2.46 (dq, $J = 7.2$, 4.5 Hz, 2H), 2.79 (d,

$J = 5.3$ Hz, 2H), 3.25 (d, $J = 4.5$ Hz, 2H), 4.97 (d, $J = 12.8$ Hz, 2H), 5.01 (d, $J = 12.8$ Hz, 2H), 5.89 (dd, $J = 9.7$, 5.3 Hz, 2H), 6.98 (d, $J = 9.7$ Hz, 2H), 7.11 (dd, $J = 7.7$, 0.9 Hz, 2H), 7.29–7.41 (m, 12H), 7.60 (dt, $J = 7.7$, 1.5 Hz, 2H), 8.07 (dd, $J = 7.7$, 0.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 184.0, 182.5, 173.90, 137.12, 137.05, 135.9, 134.6, 133.4, 133.3, 132.0, 131.9, 128.8, 128.7, 128.5, 126.4, 125.6, 122.9, 66.8, 43.3, 37.5, 30.7, 12.9. HRMS calcd for ($C_{48}H_{38}O_8$+Na^+): 765.24588. Found: 765.24474.

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13. Crystallographic data for **3c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 229187. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
14. **7c** was prepared, in low yield, by treating benzyl isobutyrate with LDA and quenching the enolate with anthraquinone.
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16. The *cis* stereochemistry for **12** has not been established. However, an analog of **12** lacking the C-7 methyl was prepared and did possess a *cis* ring fusion (data not shown).
17. Data for **13**: mp 170–172 °C. ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.51 (s, 3H), 1.56 (s, 3H), 3.63 (s, 1H), 6.32 (d, $J = 9.8$ Hz, 1H), 6.85 (d, $J = 9.8$ Hz, 1H), 7.32 (dd, $J = 8.2$, 1.4 Hz, 1H), 7.66 (t, $J = 8.2$ Hz, 1H), 7.69 (dd, $J = 8.2$, 1.4 Hz, 1H), 12.11 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 189.3, 181.5, 180.3, 161.7, 138.3, 138.0, 137.2, 136.8, 131.5, 125.0, 119.7, 118.7, 115.1, 81.8, 48.2, 45.2, 28.1, 27.4, 21.1. HRMS calcd for ($C_{19}H_{16}O_5$+Na^+): 347.088993. Found: 347.08774.
18. Data for **4a**: mp 163–165 °C. ^{1}H NMR ($CDCl_3$) δ 1.06 (t, $J = 7.2$ Hz, 3H), 1.86 (br s, 6H), 2.65 (s, 3H), 4.02 (q, $J = 7.2$ Hz, 2H), 7.26 (dd, $J = 8.3$, 1.1 Hz, 1H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.62 (t, $J = 8.3$ Hz, 1H), 7.74 (dd, $J = 8.3$, 1.1 Hz, 1H), 8.13 (d, $J = 7.9$ Hz, 1H), 11.88 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 192.6, 182.7, 178.2, 161.6, 146.2, 145.1, 138.2, 136.3, 135.8, 132.9, 132.9, 125.8, 124.3, 118.9, 117.4, 60.5, 49.3, 24.6, 14.2, 1.2. HRMS calcd for ($C_{21}H_{20}O_5$+Na^+): 375.120293. Found: 375.12098.