

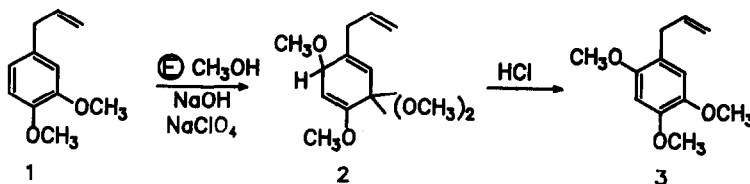
ANODIC 1,2- AND 1,4-ADDITION PRODUCTS FROM METHYL EUGENOL AS PREDICTED BY THE EEC_rC_p MECHANISM

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Summary: Anodic oxidation of 1,2-dimethoxy-4-allylbenzene (methyl eugenol) under a variety of constant current conditions in methanolic sodium hydroxide affords the 1,2- and 1,4-methanol addition products expected from the EEC_rC_p mechanism. These results differ markedly from those recently reported.¹

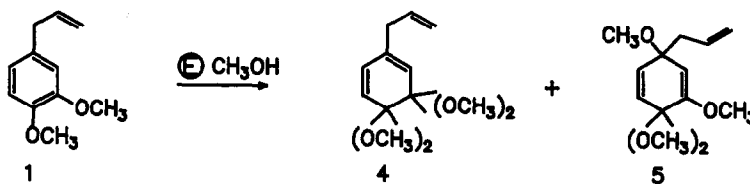
Recently, the anodic oxidation of 1,2-dimethoxy-4-allylbenzene, **1** (methyl eugenol), was reported to yield the 1,4-addition product **2**¹ which was then converted via elimination of methanol to 2,4,5-trimethoxyallylbenzene (γ -Asarone), **3**. The results of this anodic oxidation were particularly interesting since the anodic oxidation product **2** is not that predicted from the EEC_rC_p mechanism.^{2a,b} In addition, the allyl group would be exerting a pronounced effect on the reaction since 1,2-dimethoxyaromatic compounds usually form 1,2-addition products.^{2a,3,4} Although **2** conveniently rationalized the formation of **3**, no similar products have been obtained from anodic oxidation of benzenoid systems.^{2a,5,6} However, 1,4-addition products analogous to **2** have been isolated from anodic oxidations of methoxylated naphthalenes.^{2a,c}



When the anodic oxidation of **1** under a variety of conditions was monitored by glpc,⁸ two major products were observed. These compounds were partially separated by silica gel chromatography, and final purification was performed by preparative glpc. These same two products were detected in the ^1H NMR spectrum of the anodic oxidation mixture prior to chromatography; thus, they do not result from a rearrangement during the chromatography step. The structures assigned to these anodic oxidation products are **4** and **5**. The 1,2-addition product **4** showed the expected ^1H NMR spectrum⁹ (250 MHz) and ^{13}C NMR⁹ spectrum (62.9 MHz) as well as an acceptable exact mass measurement. Especially informative for the identification of **4** was the UV spectrum [$\lambda_{\text{max}} = 268 \text{ nm}$ (CH_3OH), $\epsilon = 2670$] which is very similar to 5,5,6,6-tetramethoxy-1,3-cyclohexadiene³, a compound lacking the allyl substituent [$\lambda_{\text{max}} = 265 \text{ nm}$ (no solvent given), $\epsilon = 2500$].

The 1,4-addition product is assigned as **5** rather than **2** on the basis of its NMR spectrum, proton-proton decoupling studies, and ^{13}C NMR spectrum.¹⁰ Especially informative in the ^1H NMR

**EFFECT OF ELECTROLYTE ON PRODUCT RATIO
FROM ANODIC OXIDATION OF 1***

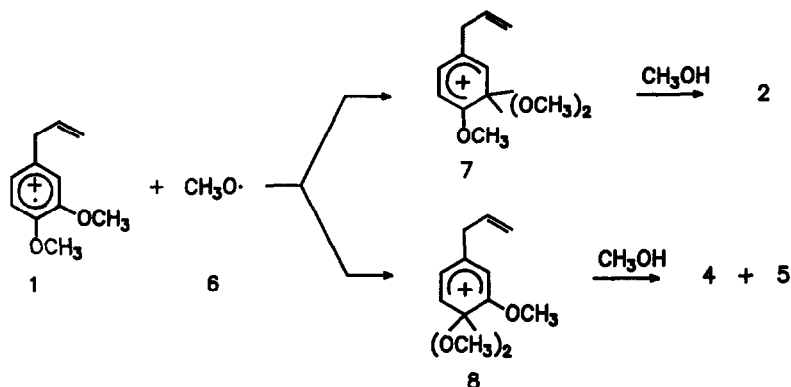


Current (amps)	Electrolyte/Additive	4 (%)	5 (%)
1.0	2% NaOH/ 1.3% NaClO ₄	41.3	44.6
0.05	2% NaOH/ 1.3% NaClO ₄	44.1	38.5
0.05	2% NaOH	41.5	36.1
0.5	2% KOH	39.5	41.7
0.2	2% K ₂ CO ₃	54.0	38.1

*All reactions were performed in methanol (60 mL) at 15 °C using 1 (0.55 g) and passing 3 F/mol of current. The progress of reaction was monitored by tlc and/or glpc and standard workup gave the product mixture in 80-85% yield.

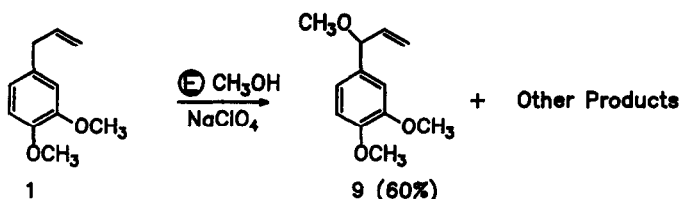
spectrum is the shielded vinyl ether proton at δ 4.8 which appears as a doublet ($J = 1.4$ Hz). Irradiation of the vinyl protons at δ 5.9 changed the δ 4.8 signal to a singlet. In addition, irradiation of the allyl methylene group at δ 2.4 did not change the appearance of any of the ring vinyl protons. The ¹H NMR spectrum of 2 should have two protons in the δ 5.0-4.0 region: the tertiary methine proton and the vinyl ether proton. The vinyl ether proton in 2 would be coupled to a methine hydrogen, and the other cyclohexene proton would show coupling to the allylic methylene group. The DEPT ¹³C NMR spectrum shows the sp³ carbon bearing the one methoxy group at δ 75.6 to be a singlet; this carbon would be a doublet in structure 2. The reported M-C₂H₆O fragment in the mass spectrum reported for 2¹ is a major peak (35% of base) found in that of 5.

In an effort to reproduce the formation of 2, the anodic oxidation of 1 was conducted with a series of supporting electrolytes (some of these conditions are given in the table). As long as a base is present, the two major products are 4 and 5. In addition, the product ratios show little temperature dependence between -15 °C and 40 °C. Only small amounts of the trimethoxy compound 3 were observed in the glpc of these reaction mixtures. These data rigorously establish 4 and 5 as the products from the anodic oxidation of 1 under a range of conditions. The EEC_rC_p mechanism involves two electrochemical oxidations (EE steps), a coupling of the anodically generated aromatic radical cation to methoxy radical (C_r step), and reaction of the resulting cation with methanol (C_p step). The products 4 and 5, as well as the product assigned as 2, could result from this mechanism. However, both the methoxy and alkyl groups would stabilize the intermediate leading to 8, thus favoring its formation over 7.



Interestingly, both the 1,2- and 1,4-addition products 4 and 5 are individually converted to γ -Asarone, 3, in methanol containing a catalytic amount of *p*-toluenesulfonic acid. When the crude electrolysis mixture was treated with *p*-toluenesulfonic acid, 3 was isolated in 80% yield. Obviously, the conversion of 4 and 5 to 3 is not so straightforward as the 2 \rightarrow 3 transformation. Under acidic conditions, 3 would be the lowest energy product in the system, presumably formed from aromatization of 2. However, all attempts to detect 2 in our studies have failed.

Previous studies^{2b} suggest that the EEC_rC_p mechanism would only operate when there is sufficient methoxide present to undergo facile oxidation to the methoxy radical. Indeed, anodic oxidation of 1 in methanol using sodium perchlorate as electrolyte, *but without added base*, gave the side-chain substitution product 9 as the major product (60% yield).¹¹



The results of these electrochemical studies differ markedly from those previously published.¹ Under a variety of experimental conditions¹² no evidence could be found for formation of the 1,4-addition product 2 in the anodic oxidation of 1. The 1,4-adduct 2 was a very convenient product for rationalizing the formation 3 in the chemistry presented earlier¹. However, these results indicate that 4 and 5 are the initial products from the anodic oxidations conducted here. Furthermore, both 4 and 5 can be converted to 3 under acid-catalysis. The 4/5 conversion into 3 must follow a circuitous route which may involve 2 as an intermediate.

Acknowledgment: We thank the National Science Foundation for support of this work.

References and Notes

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3. Weinberg, N. L.; Belleau, B. *J. Am. Chem. Soc.* **1963**, *85*, 2525.
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5. Unpublished results from this laboratory.
6. A compound similar to the dihydro compound **2** had been considered as an intermediate in the anodic oxidation of 1,3-dimethoxybenzene⁷. However, this intermediate, **11**, was specifically excluded by an isotopic labeling experiment.⁷
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8. Preparative and analytical gas partition chromatography was performed using a 6' x 1/4" column of 5% Carbowax 20M on 80/100 mesh Chromosorb W HP (column at 150 °C and injector at 218 °C).
9. Spectroscopic data for **4**: IR (NaCl) 2970 (m), 2940 (s), 2910 (m), 2830 (m), 1465 (m), 1430 (m), 1400 (m), 1210 (m), 1180-1020 (br s), 1014 (m), 990 (m), 935 (s) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 5.92 (dd, *J* = 10, 1.5 Hz, 1 H), 5.88 (d, *J* = 10 Hz, 1 H), 5.86-5.70 (str m, 1 H), 5.60-5.58 (str m, 1 H), 5.12-5.08 (str m, 1 H), 5.05 (3-line m, 1 H), 3.38 (s, 6 H), 3.37 (s, 6 H), 2.85 (d of m, *J* = 6.5 Hz, 2 H); DEPT ¹³C NMR (62.9 MHz, CDCl₃) δ 136.0 (s, 1 C), 134.7 (d, 1 C), 129.5 (d, 1 C), 128.5 (d, 1 C), 124.6 (d, 1 C), 117.1 (t, 1 C), 100.3 (s, 1 C), 99.8 (s, 1 C), 50.9 (q, 2 C), 50.8 (q, 2 C), 38.9 (t, 1 C); mass spectrum, exact mass calcd for C₁₃H₂₀O₄ *m/e* 240.1361, obsd 240.1341.
10. Spectroscopic data for **5**: IR (NaCl) 2980 (m), 2940 (s), 2910 (m), 2830 (m), 1685 (m), 1650 (s), 1465 (m), 1455 (m), 1395 (m), 1370 (m), 1215 (s), 1170 (s), 1140 (s), 1085 (s, br), 1000 (m), 980 (s), 970 (m), 960 (m), 915 (m) cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 5.90 (pseudo d, 2 H), 5.88-5.71 (str m, 1 H), 5.08-4.99 (str m, 2 H), 4.84 (d, *J* = 1.4 Hz, 1 H), 3.67 (s, 3 H), 3.33 (s, 3 H), 3.23 (s, 3 H), 3.12 (s, 3 H), 2.41-2.36 (d of m, *J* = 6 Hz, 2 H); DEPT ¹³C NMR (62.9 MHz, CDCl₃) δ 154.2 (s, 1 C), 136.7 (d, 1 C), 133.1 (d, 1 C), 128.6 (d, 1 C), 118.1 (t, 1 C), 103.7 (d, 1 C), 94.6 (s, 1 C), 75.6 (s, 1 C), 54.7 (q, 1 C), 51.4 (q, 1 C), 51.3 (q, 2 C), 46.5 (t, 1 C); mass spectrum, exact mass calcd for C₁₃H₂₀O₄ *m/e* 240.1361, obsd 208.1153 (100% INT, M-CH₃OH), 194.0980 (34.78% INT, M-CH₃OCH₃), 193.0912 (52.60% INT, M-C₂H₇O).
11. Spectroscopic data for **9**: IR (NaCl) 2980 (m), 2940 (s), 2910 (m), 2830 (m), 1610 (m), 1595 (m), 1518 (s), 1468 (s), 1451 (sh), 1445 (sh), 1445 (sh), 1415 (m), 1260 (s), 1235 (s), 1160 (s), 1140 (s), 1085 (s), 1030 (s) cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ 6.85 (br s, 3 H), 6.2-5.75 (m, 1 H), 5.35-5.16 (str m, 2 H), 4.55 (br d, *J* = 6 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.32 (s, 3 H); mass spectrum, exact mass calcd for C₁₂H₁₆O₃ *m/e* 208.1099, obsd 208.1110.
12. *Experimental.* A solution of **1** (0.5 g, 2.81 mmol), NaOH (1.2 g, 30 mmol), and NaClO₄ (0.75 g, 6.1 mmol) in CH₃OH (60 mL) was maintained at 15 °C and electrolyzed in a single cell at a constant current of 50 mA for 4.5 h (3 Faradays passed). A circular platinum mesh anode (2.7" diameter x 2.7" high) and a tungsten wire (0.021" diameter, 24 gauge) cathode were employed. The reaction mixture was concentrated in vacuo at < 30 °C, the residue was diluted with H₂O (60 mL), and the aqueous phase was extracted with Et₂O (3 x 50 mL). Standard workup gave a mixture of **4** and **5** as determined by ¹H NMR spectroscopy and vpc⁸. This material was dissolved in anhydrous methanol (50 mL), *p*-toluenesulfonic acid was added (10 mg), and the solution was stirred at room temperature for 10 min. After addition of saturated NaHCO₃ (10 mL), standard extractive workup and chromatography on silica gel (5% Et₂O/hexane as eluant) gave γ -Asarone, **3** (0.47 g, 80%).