Stereochemical study on cyclic acetal formation during anodic oxidation of naphthalene derivatives by transformation of chiral alcohol to achiral acetal

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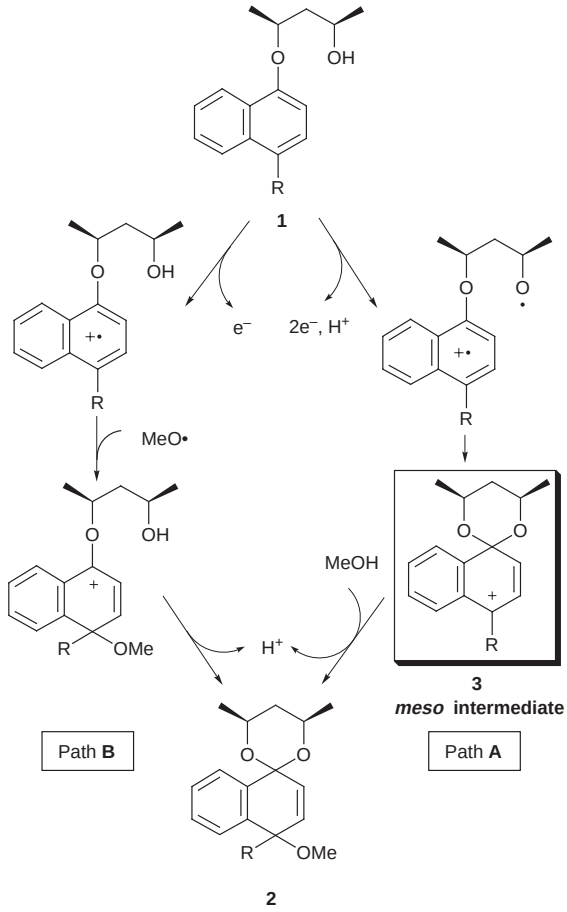
A novel stereochemical approach is employed in anodic oxidation of naphthalene derivatives to discriminate the intramolecular radical addition *vs*. intermolecular radical addition paths; the contribution of the latter is revealed to be important, judging from the stereodifferentiating addition of MeOH at C-4 during the anodic oxidation of (1′*S*,3′*R*)-1-(3′-hydroxy-1′-methylbutoxy)-4-methylnaphthalene.

The anodic oxidation of arenes in alkaline MeOH provides oxidative 1,4-addition of the aromatic ring to give acetals or *p*-quinol ethers.[1,2] Swenton *et al*. have revealed that the anodic oxidation proceeds *via* coupling of the arene radical cation with the methoxyl radical (MeO·) generated by the one-electron oxidation of the methoxide anion, followed by nucleophilic addition of a second molecule of MeOH.[3] Introduction of an intramolecular alcoholic function in the substrate through a proper length of linker increases the product yield resulting in cyclic acetal formation on the oxidative product.[3] In this case, there are two possible modes for the coupling of the arene radical cation, *i.e*. with the intramolecular alkoxy radical (Path **A**) or the intermolecular one (Path **B**). Swenton *et al*. proposed that the intramolecular radical coupling is an important path for the anodic oxidation, based on the increase in product yield due to the effective trap of the arene radical cation by the intramolecular alkoxyl radical.[3] However, it is difficult to distinguish between the intramolecular radical coupling path and the intermolecular one using the usual product analyses because these paths give the same product. To discriminate the reaction pathways, we introduce a novel stereochemical approach,‡ named 'chiral eclipse' methodology. The essentials of this stereochemical analysis are as follows (Scheme 1). The intramolecular radical coupling path (Path **A**) gives a *meso* intermediate **3** from the chiral substrate. Therefore, no optically active product is expected in Path **A** because the chirality of the side chain has already disappeared at the time of the addition at C-4. In contrast, the intermolecular coupling path (Path **B**) maintains the chirality of the side chain in the C-4 addition, which is expected to give an optically active product. Here the importance of the intermolecular coupling path (Path **B**) is revealed during the anodic oxidation of naphthalene derivatives having a (1′*S*,3′*R*)-3′-hydroxy-1′-methyl butoxy moiety **1** judging from the result that the optically active alcohol moiety can act as a chiral auxiliary to give a stereodifferentiating product.

Stereochemically pure substrates **1** were prepared in 90–59% *via* the Mitsunobu reaction[4] with the corresponding naphthol and (2*R*,4*R*)-pentane-2,4-diol. The anodic oxidation of **1a** in 1% methanolic KF solution at constant current at a platinum anode§ afforded **2a** in 75% yield at room temperature and 69% yield at −78 °C as a single diastereomer. The two possible products, **2-*si*** or **2-*re***, shown in Fig. 1 are produced by *si*- or *re*-face attack in the intramolecular acetal formation, respectively. The exclusive *si*-face attack of the intramolecular alcohol (**2** = **2-*si***) was proven by the NOE signal between the olefin proton and the methine protons. The diastereoface differentiation may be due to the steric repulsion between the *peri*-proton of the naphthalene core and the cyclic acetal moiety. The chirality of the alcohol moiety of **2** disappears due to the cyclic acetal forming.



Scheme 1

In this case, the enantiomer ratio of the oxidative product shown in Table 1 directly gives the stereodifferentiation at the C-4 position.

During the anodic oxidation of **1a** at −78 °C, definite π-facial differentiation (67:33) at C-4 was observed, whereas the enantiomer ratio dropped to 53:47 at room temperature. The cyclic acetal **1a** was readily hydrolysed to give the corresponding dienone **4a** in 97% under acidic conditions. The enantiomer ratio of **4a** (67:33) is in good agreement with that of **2a** (67:33),

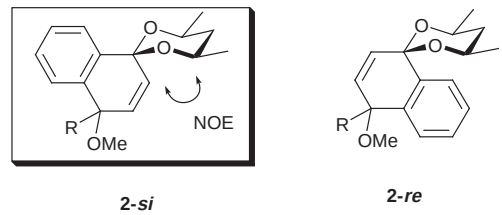
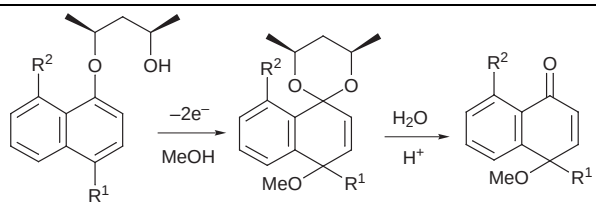


Fig. 1

Table 1 Anodic Oxidation of **1** at −78 °C[a]



1 **2** **4**

a R^1 = Me, R^2 = H **b** R^1 = Me, R^2 = Me

c R^1 = Et, R^2 = H **d** R^1 = Pr^i, R^2 = H

	Yield[b] (%)	Enatiomer ratio[c]
a	67 (73)	67:33 (53:47)
b	26 (56)	72:28 (53:47)
c	74[d]	57:43[e]
d	59[d]	54:46[e]

[a] The values in parentheses are those obtained at room temperature. [b] Two step yield from **1** to **4**. [c] The values were determined by GC analysis of **4** using a CHROMPACK-Chirasil-DEX CB (i.d. 0.25 mm × 25 m) column. [d] Yield from **1** to **2**. [e] Enantiomer ratio of **2**.

indicating that the hydrolysis proceeds without epimerisation. The stereodifferentiation indicates the significant participation of Path **B** during the anodic oxidation of **1** because in Path **A** the chirality of the linker is eclipsed before the methanolic addition at C-4 resulting in a racemic product. A decrease in the stereodifferentiation was observed when bulky alkyl groups (Et, Pr^i) were introduced at C-4 (**1c**, **d**). The poor stereodifferentiation may be caused by a decrease in the contribution for path **B** due to steric hindrance for the intermolecular MeO· addition at C-4. In contrast, the enantiomer ratio slightly increased to 72:28 in the anodic oxidation of 1,8-dimethyl substituted naphthalene **1b** at −78 °C. The *peri* strain may partially inhibit the intramolecular alkoxyl radical coupling (Path **A**). Thus, the stereodifferentiating addition at C-4 is a general phenomenon during anodic oxidation of **1**, and reflects the contributions of Path **A** and Path **B** to the anodic oxidation mechanism.

As already mentioned, radical addition to the radical cation of the naphthalene derivatives is a key step for the stereodifferentiation during the anodic oxidation as well as the anodic oxidation itself. The regioselectivity for the radical attack at the arene radical cation is strongly influenced by the spin density of the arene radical cation. A high spin density (0.14) is observed at C-4 rather than at C-1 (0.04) in the 4-methylanisole radical cation by EPR measurements.[5,6a] This indicates that radical attack on C-4 is more favorable than on C-1 during the anodic oxidation and supports the importance of the intermolecular radical addition (Path **B**). The intramolecular solvation for arene radical cations has been reported using transient absorption spectra in low polarity media.[6b] The intramolecular alcohol solvates the arene radical cation without attacking it nucleophilically.[6b,7] Such intramolecular association by the chiral alcohol to the arene radical cation may contribute to the stereodifferentiating radical addition at C-4.

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Notes and References

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‡ Recent examples of mechanistic probes using the stereochemical approach are shown in ref. 8. In these cases, the contribution of achiral intermediates was tested using a stereochemical approach.

§ All anodic oxidations were conducted in a single cell at constant current, employing a bulk electrolysis cell set with a circular platinum gauze anode and a platinum wire as the cathode (Bioanalytical System Inc.). Typically, a methanolic solution (40 ml) containing **1** (40 mg) and KF (0.4 g) was deaerated by argon bubbling and electrolysed at 45 mA and 10 V at −78 °C for 135 min.

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