Reaction modes of oxidative dimerization of epoxycyclohexenols

Mitsuru Shoji, a Satoshi Kishida, a Yusuke Kodera, a Isamu Shiina, b Hideaki Kakeya, c
Hiroyuki Osada c and Yujiro Hayashi a,*

a Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
b Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
c Antibiotics Laboratory, Discovery Research Institute, RIKEN, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

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Abstract—Of the 16 possible modes of the oxidation-6π-electrocyclization-Diels–Alder reaction cascade for an epoxyquinone, and eight for a 2-alkenyl-3-hydroxymethyl-2-cyclohexen-1-one, only the endo-anti(epoxide)-anti(Me)-hetero and endo-anti(Me)-hetero are respectively observed, while both the endo-anti(epoxide)-anti(Me)-hetero and exo-anti(epoxide)-anti(Me)-homo reaction modes occur with epoxy-4-hydroxycyclohexenones owing to a hydrogen-bonding interaction.

Keywords: Diels–Alder reaction; 6π-electrocyclization; hydrogen-bonding; epoxyquinol.

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Recently we have reported the first asymmetric total synthesis of epoxyquinols A (1)1 and B (2), novel angiogenesis inhibitors with a highly-functionalized and complicated heptacyclic ring system containing 12 stereocenters, and determined their absolute stereochemistry.3 Key steps of the synthesis are the HfCl 4-mediated Diels–Alder reaction of furan 4 with the acrylate of Corey’s chiral auxiliary, and a biomimetic, oxidative Diels–Alder reaction of monomer 3. We have also established a practical synthetic route to both enantiomers of epoxyquinols A and B using the chromatography-free preparation of an iodolactone and a lipase-mediated kinetic resolution as key steps.5 Soon after our first synthesis, Porco et al. published an elegant synthesis of epoxyquinols A and B,6 and just recently Mehta et al. have also reported the synthesis of racemic epoxyquinols A and B.7 In our biomimetic oxidative dimerization (Scheme 1), oxidation of monomer 3 with MnO 2 afforded an aldehyde 4, which was converted to 2H-pyran derivatives 5a,b via 6π-electrocyclization. Hetero-dimerization of 5a and 5b, in which the reacting diene face in the Diels–Alder reaction is anti to the diene epoxide (anti(epoxide)) and anti to Me group (anti(Me)), afforded epoxyquinol A (1) via the orbitally-preferred endo-transition state (endo-anti(epoxide)-anti(Me)-hetero),8 while homo dimerization of 5a, also in which face of the diene anti to both the epoxide and Me group reacts, gave epoxyquinol B (2) via the exo-mode (exo-anti(epoxide)-anti(Me)-homo).8 Although there are 16 possible reaction modes of 5a, only the endo-anti(epoxide)-anti(Me)-hetero and exo-anti(epoxide)-anti(Me)-homo are respectively observed, while both the endo-anti(epoxide)-anti(Me)-hetero and exo-anti(epoxide)-anti(Me)-homo reaction modes occur with epoxy-4-hydroxycyclohexenones owing to a hydrogen-bonding interaction.

Scheme 1. Oxidative dimerization of the monomer 3.
modes, only the endo-anti(epoxide)-anti(Me)-hetero and exo-anti(epoxide)-anti(Me)-homo have been observed. In order to clarify the reaction course, we have investigated the oxidative dimerization with monomers possessing different substituents, with results disclosed in this paper.

In the course of our total synthesis of epoxyquinols A and B, we examined carefully the oxidation of monomer 3 and observed the following interesting phenomenon: When monomer 3 was treated with the Dess–Martin periodinane (DMP), both primary and secondary hydroxy groups were oxidized, affording cyclized 2H-pyran derivatives 7a/b, which gave endo-anti(epoxide)-anti(Me)-hetero mode-dimerized product 8 (epoxyquinol A-type) in 21% yield without formation of the exo-anti(epoxide)-anti(Me)-homo product (epoxyquinol B-type). The yield of 8 was increased to 70% when isolated epoxyquinone 6 was treated with DMP (Eq. (1)). Porco et al. also reported the same phenomenon in the syntheses of epoxyquinol A, torreyanic acid 12 and jesterone dimer (unnatural product). Epoxycyclohexenol 3 is oxidatively dimerized via both the endo-anti(epoxide)-anti(Me)-hetero and exo-anti(epoxide)-anti(Me)-homo modes, while only the endo-anti(epoxide)-anti(Me)-hetero dimer is formed in the dimerization of epoxyquinone 6.

As 3 has both epoxy and secondary hydroxy groups on the cyclohexene ring, the oxidative dimerization of a monomer 9 without these functional groups has been examined (Eq. (2)). Oxidation of 9 afforded the corresponding aldehyde quantitatively, and this was allowed to stand neat at room temperature, affording epoxyquinol A-type dimer 10 (endo-anti(Me)-hetero mode) in 70% yield after 10 h, while none of the epoxyquinol B-type dimer obtained. That is, of the eight possible reaction modes, only the endo-anti(Me)-hetero occurred.

Of the monomers examined, only 3 having the secondary hydroxy group afforded both epoxyquinol A and B dimers, while the other monomers 6 and 9 gave only epoxyquinol A-type dimer. To investigate the effect of this secondary hydroxy group, it was converted to its methyl ether. Oxidation and 6π-electrocyclization of 11 proceeded smoothly, affording a 4.5:1 diastereo-mixture of 2H-pyran derivative 12 (Eq. (3)). Although the diastereomer ratio of 12 had changed to 1.2:1 after 10 h, no Diels–Alder reaction occurred under various reaction conditions.

These results clearly indicate that the secondary hydroxy group is important not only for the formation of epoxyquinol B, but also to accelerate the Diels–Alder reaction. As illustrated in Figure 1, the secondary hydroxy group may be important in the dimerization because a hydrogen-bond is possible in the transition states leading to both epoxyquinols A and B.

In the endo-anti(epoxide)-anti(Me)-hetero Diels–Alder reaction a hydrogen-bond could activate the ketone function, while the two monomers may interact with each other by hydrogen-bonding in the exo-anti(epoxide)-anti(Me)-homo Diels–Alder reaction. This latter assumption is reasonable because a hydrogen-bond between these two OHs has in fact been observed in the crystal structure of epoxyquinol B. Moreover, if these hydrogen-bonds exist, the distribution of epoxyquinols A and B should be affected by solvent, which is found

![Figure 1. Hydrogen-bond in the transition states.](image-url)
to be the case although its precise mechanism is not clear. As shown in Table 1, epoxyquinol A (1) was formed predominantly in neat conditions or in benzene solution, while epoxyquinol B (2) was the major product in toluene and CH₂Cl₂. Lewis acids such as LiClO₄ favorably accelerate the reaction, affording epoxyquinol A predominantly. This is a piece of evidence that the orbitally-preferable mode is \textit{endo-anti}(epoxide)-anti(Me)-hetero even in the 4-hydroxycyclohexenone 3.

<table>
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<th>Time (h)</th>
<th>Yield (%)</th>
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<td></td>
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<tr>
<td>1</td>
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<tr>
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<td>CH₃CN</td>
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</table>

Table 1. Solvent effect on the oxidative dimerization of 3

Of the sixteen or eight possible reaction modes for the oxidative dimerization, only the \textit{endo-anti}(epoxide)-anti(Me)-hetero and \textit{endo-anti}(Me)-hetero modes were observed in the reactions of epoxyquinone 6 and cyclohexenone 9, respectively, while both the \textit{endo-anti}(epoxide)-anti(Me)-hetero and \textit{exo-anti}(epoxide)-anti(Me)-homo modes occurred in the reaction of epoxy-4-hydroxycyclohexenone 3. The \textit{anti}(epoxide)-anti(Me) mode is favorable because this face of the diene (anti to epoxide and anti to Me group) is sterically accessible. The \textit{endo}-mode is preferred according to the Frontier orbital theory (\textit{endo-rule}). Among \textit{anti}(epoxide)-anti(Me) modes, the \textit{endo}-homo and \textit{exo}-hetero modes are disfavored, because of the steric hindrance between the methyl groups of diene and dienophile. The \textit{endo}-hetero mode is orbitally and sterically favorable since the methyl groups of diene and dienophile orient themselves away from one another to avoid steric hindrance. The epoxy-4-hydroxycyclohexenone is a special case, in which both \textit{endo-anti}(epoxide)-anti(Me)-hetero and \textit{exo-anti}(epoxide)-anti(Me)-homo modes occur because of the hydrogen-bonding interactions shown in Figure 1.

In summary, in the oxidative dimerization of 2-alkenyl-3-hydroxymethyl-2-cyclohexen-1-ones, the preferred reaction mode is the \textit{endo-anti}(epoxide)-anti(Me)-hetero, affording the epoxyquinol A-type product, while both epoxyquinol A- and B-type products are formed via the \textit{endo-anti}(epoxide)-anti(Me)-hetero and \textit{exo-anti}(epoxide)-anti(Me)-homo modes in substrates with a 4-hydroxy group owing to intermolecular hydrogen-bonding.

Further studies, including the theoretical calculations, are under progress, and will be reported in due course.

Acknowledgements

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References

8. In this paper the designation of ‘endo’ and ‘exo’ follows that in the paper by Porco et al., and is different from that in our previous reference.
11. Syntheses of 6, 9 and 11 will be published in a full account.
14. Because of the lack of epoxy in 9, the number of possible reaction modes is reduced from sixteen in 3 to eight.