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Regioselective electrophilic addition vs epoxidation of *m*CPBA towards anti-Bredt olefin of fulleroid

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ABSTRACT

The *m*CPBA oxidation of methano-bridged [5,6] open fulleroid **1** anomalously resulted in the selective electrophilic addition at the bridgehead anti-Bredt double bond rather than the usual epoxidation. The mechanistic preference for the unprecedented stepwise addition of *m*CPBA vs the concerted epoxidation was explained in terms of the notable π -orbital misalignment ($>30^\circ$) based on the B3LYP/6-31G(d) level calculation.

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Although fullerenes are well known as electrophiles due to the low-lying LUMO orbitals,¹ they can also behave as nucleophiles in some chemical modifications such as epoxidation² with *m*-chloroperbenzoic acid (*m*CPBA). The fullerene epoxides are useful reactive intermediates in the synthesis of regioselective bis-adducts³ and fullerene dimer.⁴ However, the control of reaction conditions to selectively give monoepoxide has been a challenging task because of the presence of a number of reactive [6,6] bonds in spherical fullerenes. In fact, the reaction of C₆₀ with *m*CPBA gives a mixture of monoepoxide and various multiepoxides, from which it is difficult to separate each of them. We are interested in the reactivity of [5,6] open fulleroid^{5,6} **1** with highly-twisted bridgehead double bonds⁷ as a useful synthetic entity to develop a new regioselective synthetic methodology in fullerene chemistry. Fulleroids are known as homofullerenes still retaining 60 π -electron system and to exhibit the regioselective Zn(Cu) catalyzed hydrogenation⁸ and photooxygenation with singlet oxygen⁹ at the bridgehead olefin.

In our recent study on the comparative reactivity of the [5,6] open fulleroids vs C₆₀, we have found the noticeably enhanced reactivity of the fulleroids at the bridgehead double bonds in Diels–Alder reaction with some flexible 1,3-dienes.¹⁰ It was also expected that the higher π -orbital misalignment angle τ ¹¹ ($\sim 30^\circ$),^{8,10} as compared to the usual anti-Bredt olefins ($10\sim 20^\circ$, *vide infra*), would result in a dramatic change in the reactivity mode. These situations prompted us to investigate the *m*CPBA oxidation of fulleroids with the aim of bringing about the regioselective epoxidation. In this paper, we would like to report the unprecedented electrophilic addition of *m*CPBA to the anti-Bredt olefin of the fulleroid **1** as shown in Scheme 1 and discuss

the mechanistic feature on the basis of the B3LYP/6-31G(d) calculation.

Scheme 1 Electrophilic addition of *m*CPBA to fulleroid

Methano-bridged fulleroid **1** was prepared by the literature methods.^{10,12} The oxidation of **1** with *m*CPBA (10 equiv.) at 30 °C gave several oxidized products, as seen in the HPLC chart of the reaction mixture (Figure 1a). The APCI-LCMS measurement showed the sharp peak of the residual **1** along with the following broad peak consisting of a mixture of 1:1 adduct (**1**+*m*CPBA: m/z = 906) and its fragment (m/z = 751, **1**+OH⁺) (Figure 1b). The

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preceding shoulder fraction overlapped with **1** seems to be monoepoxide ($m/z = 922$) of the 1:1 adduct and its fragment ($m/z = 767$) (Figure 1c).

(a)

(b)

(c)

Figure 1. (a) HPLC chart for *m*CPBA oxidation of **1** (after 6h) and APCI-MS (positive) of (b) **2a+2b** and (c) byproduct.

The portion of 1:1 adduct was successfully fractionated by silica gel column chromatography (15.4 mg; 15% isolated yield).^{13,14} The purity was verified by HPLC (Figure S1). The isolated product showed the characteristic IR absorption at 1727 cm^{-1} assignable to the benzoate ester group. Unfortunately, this fraction was still the regioisomeric mixture (major/minor = 3) of 1:1 adducts **2a/2b** by ^1H NMR spectrum (Figure 2). Although an attempt to separate and assign these region-isomers was failed, we tentatively assign **2a** to the major isomer according to the calculation (*vide infra*). However, the 1,2-addition at the bridgehead double bond was undoubtedly evidenced by the following facts. (1) The significant down-field shift (1.6–2.3 ppm) of the methano-bridged H(b) was found for the major ($\delta =$

5.2 ppm, Figure S2) and for the minor (4.5), respectively, as compared to that of parent **1** (2.9).^{12d} These shifts were clearly explained by the reduction of the shielding effects of underlying hexagonal triene ring by 1,2-addition of *m*CPBA. (2) The 2D HMBC correlation is observed (Figure S3) between each of the bridged H(a)/H(b) and the OH or *m*-chlorobenzoate (*m*CB)-substituted remote sp^3 -carbon (C_β , red circle). (3) The existence of NOE interaction between the hydroxy proton H(g) and the magnetically isolated *o*-proton H(f) would support the formation of 1,2-adducts (Figure S4). However, there is no NOE enhancement between the bridged CH_2 and any proton of the *m*CB group, indicating the less congested outward orientation of *m*CB moiety.

(a)

(b)

Figure 2. ^1H NMR chemical shifts (δ) of **2a/2b** (red: major, blue: minor) in (a) 7.5–8.5 ppm and (b) 4.4–5.7 ppm range.

This electrophilic esterification of fulleroid by *m*CPBA is unprecedented and markedly contrast to the usual epoxidation of C_{60} as well as the common olefins.¹⁵ It is likely that the highly twisted double bond of **1** plays a crucial role in the present 1,2-addition of *m*CPBA. Then, we calculated its transition state (TS) and intrinsic reaction coordinate (IRC) with B3LYP/6-31G(d) level (Figure 3) in order to gain a mechanistic insight into the *m*CPBA oxidation of **1**.¹⁶ The results showed the asymmetric transition state TS-1 (Figure 3a) in which the relevant OH group is located more closer to the bridgehead C_α than to the adjacent C_β carbon and then leads to the ionic intermediate **1aOH**⁺ (Figure 3b).¹⁷ On the other hand, the asymmetric approach of *m*CPBA to the C_β carbon would generate the energetically higher transition state TS-2 and provide the less stable intermediate **1bOH**⁺ (Figure 3c,d),¹⁷ in conformity with the minor **2b**. Although the energy difference (3.8 kcal/mol) between TS-1 and TS-2 is larger than the value deduced from the experimental product ratio (3:1), this may be ascribed to the several reasons.¹⁸ The appreciable difference in HOMO orbital coefficients of the *anti*-Bredt double

bond moiety is also likely responsible for such an asymmetric electrophilic attack (Figure S6). These two pathways can be terminologically categorized as bimolecular electrophilic addition (AdE₂).

Figure 3. Relative energy vs the reaction coordinate (translated to the distance between C_α (or C_β) and O_{CPBA} for TS-1 or TS-2, respectively, obtained from TS and IRC calculations. (a) Geometry of the TS-1 of **1** + *m*CPBA reaction (Imaginary freq. = -504 cm⁻¹, dipole moment (μ) = 3.6 D). (b) Geometry of the **1aOH**⁺ and *m*-chlorobenzoate (*m*CB⁻) obtained from the IRC calculation (not optimized structure).¹⁷ (c) Geometry of the TS-2 of **1** + *m*CPBA reaction (Imaginary freq. = -496 cm⁻¹, μ = 5.4 D). (d) Geometry of the **1bOH**⁺ and *m*-chlorobenzoate (*m*CB⁻) obtained from the IRC calculation (not optimized structure).¹⁷ These geometries and energies were calculated by B3LYP/6-31G(d) level without solvation parameter. The yellow balls denote the cycloheptatriene ring.

To verify whether the present calculations are reasonable, we have compared our results with those of the previously reported *m*CPBA oxidation of olefins.¹⁹⁻²¹ Though the reported studies have mainly concerned the simple and less twisted alkenes, two reaction pathways have been proposed; one is the generally accepted concerted process via a butterfly-like symmetrical transition state (route (a) in Scheme 2)¹⁹ and another is the stepwise process via asymmetric transition state and the ionic intermediate,²⁰ similar to the present calculation (route (b) in Scheme 2). While the higher level calculations^{19a} and the detailed investigation of isotope effect^{15a,21} supported the concerted mechanism, our results indicated that twisted olefin prefers the route (b),²² probably because the highly twisted π -orbital could not perform the symmetrical orbital interaction with *m*CPBA as

in route (a). The generated intermediate **1aOH**⁺ undergoes the addition of *m*-chlorobenzoate (*m*CB⁻), rather than the ring-closure to epoxide. Indeed, the intervention of such intermediate was proved by formation of the crossover *p*-methyl benzoate adduct (*m/z* = 886) when *p*-toluic acid coexists (route (c) in Scheme 2 and Figure S7).

Scheme 2 Comparative reaction pathways; (a) concerted epoxidation vs (b) stepwise electrophilic addition.

One question is raised why *m*CPBA oxidation of several anti-Bredt olefins²³ exclusively gave the epoxides. The π -orbital misalignment angle τ (15.7° for bicyclo[3.3.1]non-1-ene, calculated by B3LYP/6-31G*) is considerably smaller than those of the fullerenes (>30°).^{8,10} The calculation for the bicyclic compound provided rather symmetrical TS (Figure S8) in accord with the actual epoxidation, implying that even anti-Bredt olefins allow the symmetrical TS via route (a), when τ is not so large.

In conclusion, we have found that the methano-bridged [5,6] open fulleroid **1** underwent the stepwise bimolecular electrophilic addition (AdE₂) of *m*CPBA at the twisted bridgehead double bond to afford the regioisomeric mixture of α -hydroxyfullerenyl *m*-chlorobenzoates. This unusual addition was rationalized by the larger torsional angle of double bond ($\tau \sim 30^\circ$), which would inhibit the symmetrical TS (so-called butterfly TS) generally argued for the concerted epoxidation of olefins.

Supporting Information Available Experimental procedure, NMR of **2a+2b**, DFT calculation for **2a** and **2b**, crossover experiment with *p*-toluic acid, transition state calculation of bicyclo[3.3.1]non-1-ene, and full citation of Gaussian 09.

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13. **Reaction procedure and spectral data of the regioisomeric mixture of 2a and 2b.** mCPBA (386 mg, 2.23 mmol) and **1** (82.1 mg, 0.112 mmol) were dissolved in toluene. The solution was stirred overnight at 30 °C, and the progress of reaction was traced by HPLC (buckyprep). The reaction mixture was concentrated and submitted to silica gel column chromatography (toluene/hexane) to give 15.4 mg of **2a+2b** mixture (0.017 mmol, conversion yield is 24%, and isolated yield is 15%) and recovered **1** (29.4mg) and byproduct (8 mg). ¹H NMR (600 MHz, CS₂: CDCl₃ = 3:1), **Major isomer**: δ 5.06 (s, 1H), 5.20 (d, *J* = 11.4 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 7.56 (t, *J* = 8.4, 7.8 Hz, 1H, overlapped with minor), 7.67 (d, *J* = 7.8 Hz, 1H, overlapped with minor), 8.18 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H); **Minor isomer**: δ 4.56 (s, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 5.13 (d, *J* = 11.4 Hz, 1H), 7.56 (t, *J* = 8.4, 7.8 Hz, 1H, overlapped with major), 7.67 (d, *J* = 7.8 Hz, 1H, overlapped with major), 8.31 (d, *J* = 8.4 Hz, 1H), 8.40 (s, 1H). ¹³C NMR (150 MHz, CS₂: CDCl₃ = 3:1) δ 32.7(s, CH₂), 85.7(s, C), 94.6(s, C), 127.8(s, CH), 130.0(s, CH), 130.3(s, CH), 134.0(s, CH), 163.3(s, C=O), except for the signals assigned to the fulleroid sp² carbons (125–155 ppm, See Figure S2). IR (KBr) 3438, 2929, 1727, 1282, 1251, 1086 cm⁻¹. HRMS (FAB-MS): Calcd for C₆₈H₇O₃Cl 906.0084. Found 906.0112.
14. The low isolated yield (15%) of the 1:1 adducts **2a/2b** is mainly due to the incompleteness of the reaction (to avoid further epoxidation) as well as the column chromatographic isolation.
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16. DFT calculations were carried out with Gaussian 09 program. Its full citation is shown in Supporting Information.
17. Both these cationic intermediates **1aOH⁺** and **1bOH⁺** were not calculated their optimized geometries, because of the absence of solvent parameter on the calculation to stabilize such zwitterionic state.
18. No isomerization reaction was observed between **2a** and **2b** on 2 days standing at 25 °C in CDCl₃ as confirmed by the NMR measurement. Incidentally, compound **2a** was 3.4 kcal/mol more stable than **2b** by DFT calculation (Figure S5). One reason for the inconsistency between the differential TS energy and the isomer ratio may be the absence of entropy term ($\Delta S^\ddagger$) on the present calculation in addition to the lack of solvation parameter. One can also conceive that the solvent toluene (μ = 0.375 D, from *CRC Handbook of Chemistry and Physics 91st Ed.*) will more stabilize the polar TS-2 (μ = 5.4 D) than TS-1 (μ = 3.6 D), thus reducing the differential isomer ratio of **2a/2b**.
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