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

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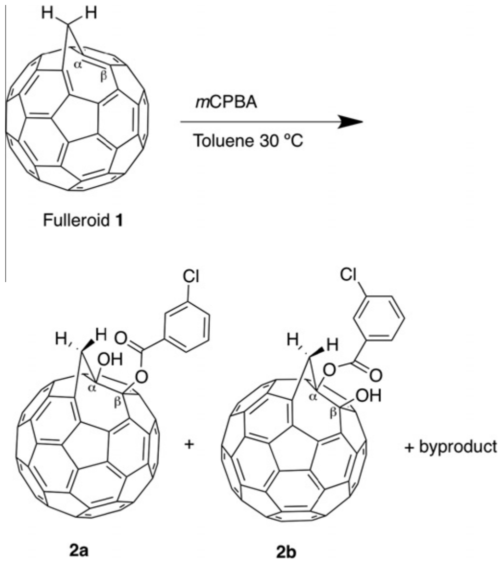
The *m*CPBA oxidation of methano-bridged [5,6] open fulleroid **1** anomalously resulted in the selective electrophilic addition at the bridgehead *anti*-Bredt double bond rather than the usual epoxidation. The mechanistic preference for the unprecedented stepwise addition of *m*CPBA vs the concerted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

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 epoxidation[2] with *m*-chloroperbenzoic acid (*m*CPBA). The fullerene epoxides are useful reactive intermediates in the synthesis of regioselective bis-adducts[3] 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 C_{60} 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 bonds[7] as a useful synthetic entity to develop a new regioselective synthetic methodology in fullerene chemistry. Fulleroids are known as homofullerenes still retaining 60π-electron system and to exhibit the regioselective Zn(Cu) catalyzed hydrogenation[8] and photooxygenation with singlet oxygen[9] at the bridgehead olefin.

In our recent study on the comparative reactivity of the [5,6] open fulleroids vs C_{60}, 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] (∼30°),[8,10] as compared to the usual *anti*-Bredt olefins (10∼20°, 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.

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

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 (Fig. 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 ^{1}H NMR spectrum (Fig. 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, Fig. 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 (Fig. S3) between each of the bridged H(a)/H(b) and the OH or *m*-chlorobenzoate (*m*CB)-substituted remote sp^3-carbon (C$_\beta$, 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 (Fig. 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.

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 (Fig. 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 (Fig. 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$^+$**(Fig. 3b).[17] On the other hand, the

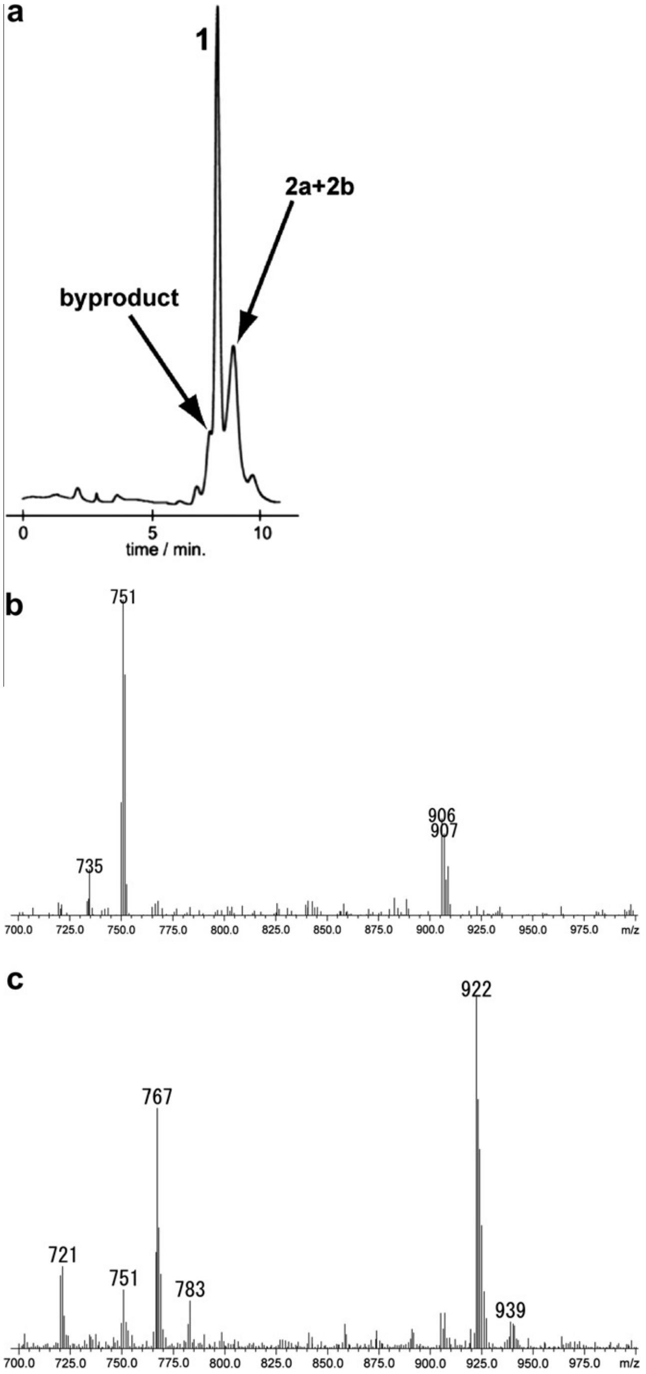


Figure 1. (a) HPLC chart for *m*CPBA oxidation of **1** (after 6 h) and APCI-MS (positive) of (b) **2a** + **2b** and (c) byproduct.

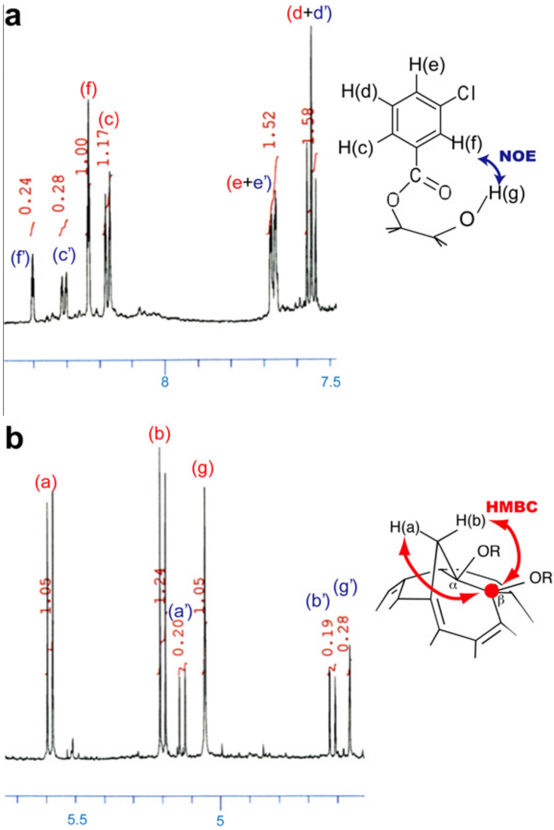


Figure 2. ^{1}H NMR chemical shifts (δ of **2a**/**2b** (red: major, blue: minor) in (a) 7.5–8.5 ppm and (b) 4.4–5.7 ppm range.

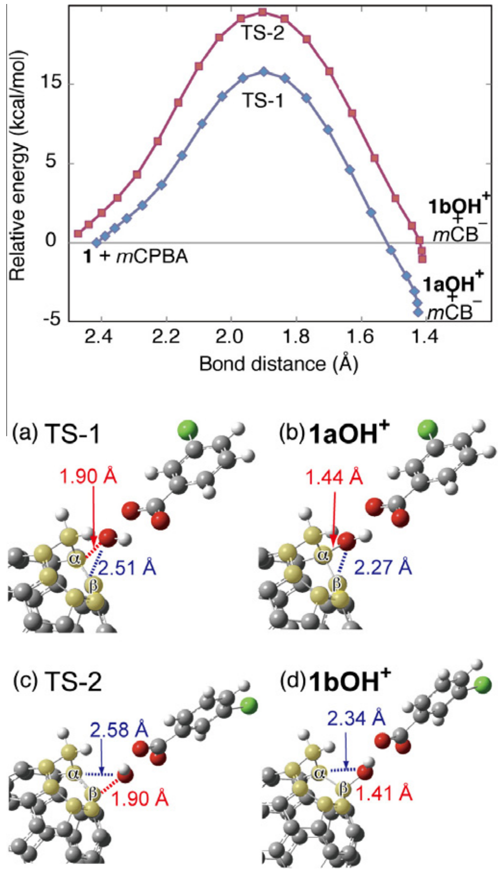
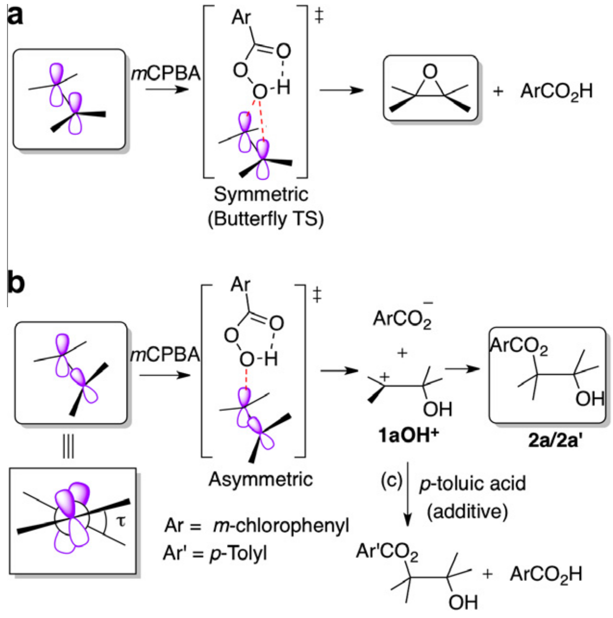


Figure 3. Relative energy versus the reaction coordinate (translated to the distance between C_α or C_β) and O_{CPBA} for TS-1 or TS-2, respectively, obtained from TS and IRC calculations. (a) Geometry of the TS-1 of **1** + *m*CPBA reaction (imaginary freq. = $-504\ cm^{-1}$, dipole moment (μ) = 3.6 D). (b) Geometry of the $\mathbf{1aOH^+}$ and *m*-chlorobenzoate (mCB^-) 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 $\mathbf{1bOH^+}$ and *m*-chlorobenzoate (mCB^-) 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.



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

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 $\mathbf{1bOH^+}$ (Fig. 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 (Fig. S6). These two pathways can be terminologically categorized as bimolecular electrophilic addition (AdE_2).

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 $\mathbf{1aOH^+}$ undergoes the addition of *m*-chlorobenzoate (mCB^-), 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 Fig. S7).

One question is raised why *m*CPBA oxidation of several *anti*-Bredt olefins[23] exclusively gave the epoxides. The π-orbital misalignment angle τ (15.7° for bicyclo[3.3.l]non-l-ene, calculated by B3LYP/6-31G(d)) is considerably smaller than those of the fulleroids (>30°).[8,10] The calculation for the bicyclic compound provided rather symmetrical TS (Fig. S8) in accord with the actual epoxidation, implying that even *anti*-Bredt olefins allow the symmetric 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 (AdE_2) 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 (τ ~30°), which would inhibit the symmetric TS (so-called butterfly TS) generally argued for the concerted epoxidation of olefins.

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Supplementary data

Supplementary data (NMR of **2a** + **2b**, DFT calculation for **2a** and **2b**, crossover experiment with *p*-toluic acid, transition state calculation of bicyclo[3.3.l]non-l-ene, and full citation of Gaussian 09) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.007. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Hirsch, A. *Chemistry of the Fullerenes*; Thieme: Stuttgart, 1994; (b) Diederich, F.; Thilgen, C. *Science* **1996**, *271*, 317–323; (c) Hirsch, A.; Brettreich, M. *Fullerenes Chemistry and Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005.
2. (a) Balch, A. L.; Costa, D. A.; Noll, B. C.; Olmstead, M. M. *J. Am. Chem. Soc.* **1995**, *117*, 8926–8932; (b) Tajima, Y.; Takeuchi, K. *J. Org. Chem.* **2002**, *67*, 1696–1698.
3. Tajima, Y.; Hara, T.; Honma, T.; Matsumoto, S.; Takeuchi, K. *Org. Lett.* **2006**, *8*, 3203–3205.
4. (a) Smith, A. B.; Tokuyama, H.; Strongin, R. M.; Furst, G. T.; Romanow, W. J.; Chait, B. T.; Mirza, U. A.; Haller, I. *J. Am. Chem. Soc.* **1995**, *117*, 9359–9360; (b) Tsyboulski, D.; Heymann, D.; Bachilo, S. M.; Alemany, L. B.; Weisman, R. B. *J. Am. Chem. Soc.* **2004**, *126*, 7350–7358.
5. (a) Suzuki, T.; Khemani, K. C.; Almarsson, O. *Science* **1991**, *254*, 1186–1188; (b) Suzuki, T.; Li, Q.; Khemani, K. C.; Wudl, F. *J. Am. Chem. Soc.* **1992**, *114*, 7301–7302; (c) Smith, A. B.; Strongin, R. M.; Brard, L.; Furst, G. T.; Romanow, W. J.; Owens, K. G.; King, R. C. *J. Am. Chem. Soc.* **1993**, *115*, 5829–5830; (d) Hall, M. H.; Shevlin, P.; Lu, H.; Gichuhi, A.; Shannon, C. *J. Org. Chem.* **2006**, *71*, 3357–3363.
6. Photolysis of $C_{60}O_3$ lead to [5,6]-open fullerene oxide bearing high regioselectivity at the bridgehead, similar to the fulleroid. See: (a) Weisman, R. B.; Heymann, D.; Bachilo, S. M. *J. Am. Chem. Soc.* **2001**, *123*, 9720–9721; (b) Escobedo, J. O.; Frey, A. E.; Strongin, R. M. *Tetrahedron Lett.* **2002**, *43*, 6117–6119; (c) Tsyboulski, D.; Heymann, D.; Bachilo, S. M.; Alemany, L. B.; Weisman, R. B. *J. Am. Chem. Soc.* **2004**, *126*, 7350–7358; (d) Yao, J. Y.; Yang, D. Z.; Xiao, Z.; Gan, L. B.; Wang, Z. M. *J. Org. Chem.* **2009**, 3528–3531.
7. (a) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683–1715; (b) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067–1093.
8. Weedon, B. R.; Haddon, R. C.; Spielmann, H. P.; Meier, M. S. *J. Am. Chem. Soc.* **1999**, *121*, 335–340.
9. (a) Kabe, Y.; Hachiya, H.; Saito, T.; Shimizu, D.; Ishiwata, M.; Suzuki, K.; Yakushigawa, Y.; Ando, W. *J. Organomet. Chem.* **2009**, *694*, 1988–1997; Such selective photooxygenation was also reported for azafulleroid. See: (b) Hummelen, J. C.; Prato, M.; Wudl, F. *J. Am. Chem. Soc* **1995**, *117*, 7003–7004; (c) Hachiya, H.; Kabe, Y. *Chem. Lett.* **2009**, *38*, 372–373.
10. (a) Ikuma, N.; Susami, Y.; Oshima, T. *Org. Biomol. Chem.* **2010**, *8*, 1394–1398; (b) Ikuma, N.; Susami, Y.; Oshima, T. *Eur. J. Org. Chem.* **2011**, 6452–6458.
11. Wijsman, G. W.; De Wolf, W. H.; Bickelhaupt, F.; Kooijman, H.; Spek, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 9191–9192.
12. (a) Oshima, T.; Kitamura, H.; Higashi, T.; Kokubo, K.; Seike, N. *J. Org. Chem.* **2006**, *71*, 2995–3000; (b) Kitamura, H.; Kokubo, K.; Oshima, T. *Org. Lett.* **2007**, *9*, 4045–4048; (c) Kitamura, H.; Oshima, T. *Org. Lett.* **2008**, *10*, 293–296; (d) Nakamura, Y.; Inamura, K.; Oomuro, R.; Laurenco, R.; Tidwell, T. T.; Nishimura, J. *Org. Biomol. Chem.* **2005**, *3*, 3032–3038.
13. Reaction procedure and spectral data of the regioisomeric mixture of **2a** and **2b**. *m*CPBA (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** (29.4 mg) and byproduct (8 mg). ^{1}H NMR (600 MHz, CS_2:$CDCl_3$ = 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). ^{13}C NMR(150 MHz, CS_2:$CDCl_3$ = 3:1) δ 32.7(s, CH_2), 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 sp^2 carbons (125–155 ppm, See Fig. S2). IR (KBr) 3438, 2929, 1727, 1282, 1251, 1086 cm^{-1}. HRMS (FAB-MS): Calcd for $C_{68}H_7O_3Cl$ 906.0084. Found 906.0112.
14. The low isolated yield (15%) of the 1:1 adducts **2a**/**2b** is mainly due to the incompletion of the reaction (to avoid further epoxidation) as well as the column chromatographic isolation.
15. A literature survey showed the reactions of some sterically strained olefins with mCPBA produce α-hydroxyl esters, although the mechanism was not discussed or featured to involve an epoxidation/acidic ring-opening sequence. See: (a) Koerner, T.; Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1999**, *64*, 196–201; (b) Zehnder, L. R.; Wei, L. L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *3*, 2141–2144; (c) Toselli, N.; Martin, D.; Achard, M.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **2009**, *74*, 3783–3791.
16. DFT calculations were carried out with Gaussian 09 program. Its full citation is shown in Supplementary data.
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 $CDCl_3$ as confirmed by the NMR measurement. Incidentally, compound **2a** was 3.4 kcal/mol more stable than **2b** by DFT calculation (Fig. 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**.
19. (a) Bach, R. D.; Glukhovtsev, M. N.; Gonzalez, C.; Marquez, M.; Estevez, C. M.; Baboul, A. G.; Schlegel, H. B. *J. Phys. Chem. A* **1997**, *101*, 6092–6100; (b) Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron Lett.* **2002**, *43*, 4215–4219.
20. Yamabe, S.; Kondou, C.; Minato, T. *J. Org. Chem.* **1996**, *61*, 616–620.
21. Angelis, Y. S.; Orfanopoulos, M. *J. Org. Chem.* **1997**, *62*, 6083–6085.
22. Although our calculational method (DFT/B3LYP) is relatively rough as compared to the previous theoretical calculations (such as QCISD in Ref. 19a), these higher calculations cannot be straight forwardly applied to fulleroid with too many atoms and electrons. Multi-layered method such as ONIOM will enable such higher level calculation to fulleroid, as the following recent ONIOM application to the Diels–Alder reaction of fullerene. See: Osuna, S.; Morera, J.; Cases, M.; Morokuma, K.; Solà, M. *J. Phys. Chem. A* **2009**, *113*, 9721–9726.
23. Shea, K. J.; Kim, J. *J. Am. Chem. Soc.* **1992**, *114*, 3044–3051.