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Oxidative Deamination of Azafulleroids into C_{60} by Peracids

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Oxidation of azafulleroids with peracids regenerated C_{60} depending on the N-substituents. Alkyl-substituted azafulleroids preferred the oxidation of nitrogen to afford N-oxides as possible intermediates for C_{60} in moderate yields. Phenyl- and tosyl-substituted azafulleroids rather allowed the oxidation at cage carbon. The theoretical calculation predicted the reactivity order of azafulleroids as well as the relative N/C nucleophilicity.

Introduction

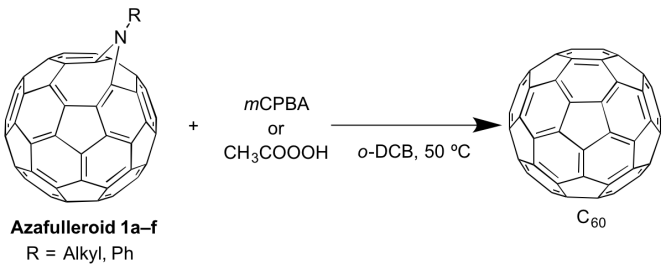
Azafulleroid, usually derived from the thermal denitrogenation of triazolinofullerene[1] or other sophisticated methods,[2] can behave as an ambident C/N-nucleophile at the bridged nitrogen atom and the adjacent two strained bridgehead double bonds. We recently reported the dual acid-catalyzed arylation of azafulleroids depending on the N-substituents; alkyl substituents preferred the N-protonation and the following nucleophilic arylation leading to monoarylated amino derivatives, while phenyl substituent induced the C-protonation and the consecutive stepwise arylation into pentakisaryl adducts via deamination of amino-bridge.[3] Such an intrinsic reactivity of azafulleroids would lead to the formation of various fullerene derivatives in the reaction with a number of other electrophilic reagents. In this context, we have attempted the oxidation of azafulleroids, because the relevant oxidation of fullerene and its derivatives gives various types of useful products for synthetic and material chemistry. For example, fullerene epoxide $C_{60}O$, derived from oxidation with peracids or other oxidants,[4] is a reactive intermediate for regioselective diarylfullerenes, acetalized fullerene, and indolinofullerene.[5] Moreover, further reaction or transformation of strained $C_{60}O$ or other oxidized fullerenes leads to fullerene dimer[6] and open-cage fullerenes.[7]

Here, we report that the oxidation of variously N-substituted azafulleroids with *m*-chloroperbenzoic acid (*m*CPBA) and peracetic acid (PAA) resulted in the regeneration of C_{60}. We will also discuss the mechanism of this oxidative deamination by evaluating the transition state energies on DFT calculations. Although the cycloreversion of fullerene adducts has been reported by the use of metal catalysts[8] or electrochemical condition,[9] the present deamination of fullerene core by easy-to-use peracids can be a useful synthetic method for obtaining regioselective and enantioselective fullerene derivatives via chiral auxiliary.[9]

Results and Discussion

Deamination reaction of azafulleroids

The oxidation with *m*CPBA was carried out for seven azafulleroids **1a–g** having alkyl/aryl/tosyl substituents (Scheme 1 and Table 1). This reaction yielded deaminated C_{60} for alkyl-substituted azafulleroids **1a–e** and phenyl-substituted azafulleroid **1f**, although the eliminated nitrogen fragments were not traced. The alkyl-substituted azafulleroids **1a–c** exhibited the higher reactivity with moderate yields,[10] while benzylazafulleroid **1e** provided relatively low yield probably due to the steric effects. Phenyl azafulleroid **1f** needed longer reaction time but gave the lower yield of C_{60} accompanying a considerable amount of insoluble oxidized byproducts. Tosyl azafulleroid **1g** did not produce C_{60} at all but only gave such byproducts. Low solubility of the byproducts even in *o*-DCB and DMSO inhibited purification and detailed characterization by NMR and IR (Fig. S1–S2, in ESI†). Moreover, the oxidation with PAA provided considerably lower yields than the oxidation with *m*CPBA (Table 2).



Azafulleroid 1a–f
R = Alkyl, Ph

Scheme 1

Table 1 Oxidative deamination of azafulleroids **1a**–**1g** with 5 equiv of *m*CPBA.

	R	Time /h	Yield[a,b]/%
1a	Me	4	61 (61)
1b	$CH_2Si(CH_3)_3$	4	48 (48)
1c	$CH_2Si(CH_3)_2Ph$	5	43 (38)
1d	$(CH_2)_3COOMe$	24	35 (35)
1e	CH_2Ph	19	27 (23)
1f	Ph	96	18 (16)
1g	Ts[c]	96	0[d] (0)

[a] Yields based on consumed azafulleroids. [b] Values in parentheses are isolated yields. [c]10 equiv of *m*CPBA was employed. [d] 77% conversion.

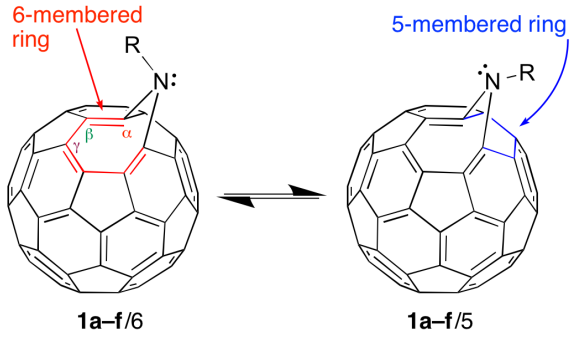
Table 2. Oxidative deamination of azafulleroids **1a**–**1g** with 10 equiv of PAA.

	R	Time /h	Yield[a,b]/%
1a	Me	23	20 (20)
1c	$CH_2Si(CH_3)_2Ph$	23	13 (13)
1d	$(CH_2)_3COOMe$	55	9 (8)
1e	CH_2Ph[c]	122	15 (12)
1f	Ph	168	7 (6)
1g	Ts	171	0[d] (0)

[a] Yields based on consumed azafulleroids. [b] Values in parentheses are isolated yields. [c] 3 equiv of PAA was employed. [d] 50% conversion.

Theoretical estimation for the initial attack site of peracids on azafulleroids

The formation of C_{60} is suggestive of initial oxidation of bridged nitrogen and the following elimination of N-oxide associated with the electron reorganization of fullerene cage, whereas the oxidation of bridgehead C=C double bond is responsible for the formation of insoluble unidentified products. In order to know the reaction pathway for azafulleroid oxidation, we theoretically deduce the reaction site and their transition states (TS) of oxidation of alkyl/aryl azafulleroid with peracids. In the calculations, we considered two azafulleroid conformers where their N-substituents were flipped above original 5- or 6-membered ring. In this paper, azafulleroid **1** with its substituent above 6-membered ring is denoted as **1**/6, while that above 5-membered ring as **1**/5, as shown in Scheme 2.



Scheme 2

Energy calculations with B3LYP/6-31G(d) showed that alkyl azafulleroids **1a,b,e**/6 were thermodynamically more stable than **1a,b,e**/5 whereas phenyl and tosyl substituents prefer **1f,g**/5 geometry (Table 3).[11] In these alkyl azafulleroids **1a,b,e**, electrophiles seem to preferably attack the 7-azepine framework due to the high distribution of HOMO orbital in both the 5/6 geometries (Fig. 1a–c and Fig. S3–S5). However, the HOMO of **1f** was mainly localized around the aniline moiety and on the Cα/β carbons (Fig. 1d and Fig. S6), but that of **1g** was only distributed on fullerene moiety, particularly on Cα and Cγ (Fig. 1e and Fig. S7). Thus, tosyl substituted **1g** has very low nucleophilicity at the nitrogen and seems to be preferably oxidized at its fullerene carbon cage. On the other hand, σ* orbital of O-O moiety of peracids resided in LUMO+2 for *m*CPBA (–0.19 eV, Fig. S8b), and in LUMO+1 for PAA (+0.03 eV, Fig. S8c), similarly to the previously reported calculations.[12] Its lower σ* orbital of *m*CPBA may be responsible for the higher reactivity with azafulleroids than that of PAA.

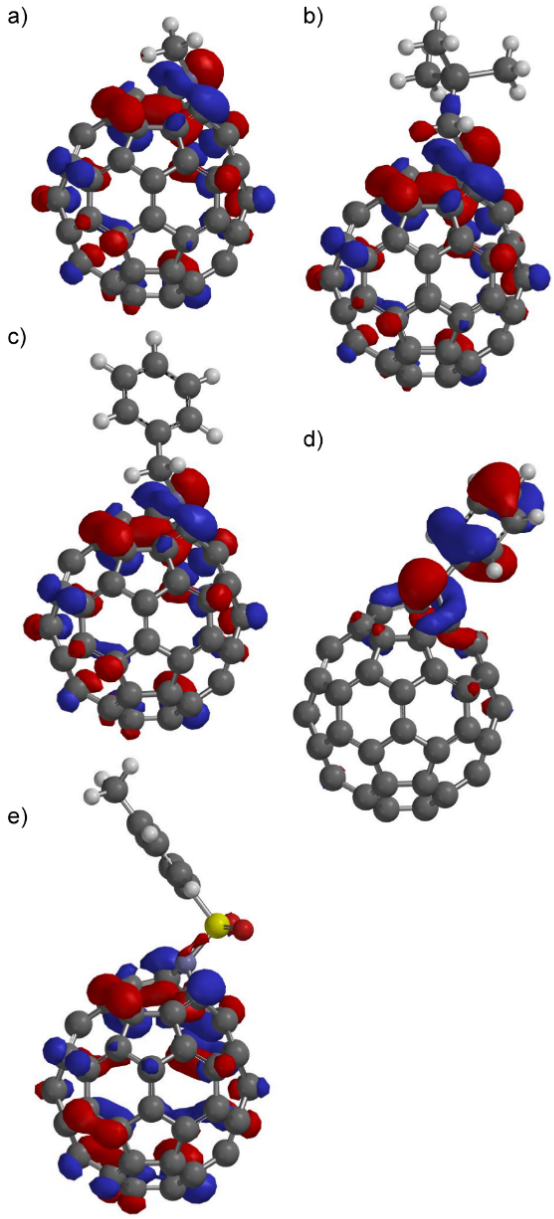


Fig. 1. HOMO orbitals of (a) **1a**/6, (b) **1b**/6-exo. (c) **1e**/6-exo, (d) **1f**/5, and (e) **1g**/5-exo with the most thermodynamically stable conformation, where the definition of exo is shown in Scheme S1.

Table 3 Relative energies and HOMO levels of azafulleroids with the 5/6 substituent direction.[a]

	R	E(**1**/6)–E(**1**/5) / kJ mol^{-1}	E_{HOMO}(6)/eV	E_{HOMO}(5)/eV
1a	Me	–5.9	–5.72	–5.85
1b	$CH_2Si(CH_3)_3$	–4.3[b]	–5.64	–5.80
1e	CH_2Ph	–3.9[b]	–5.72	–5.84
1f	Ph	+0.09	–5.54	–5.75
1g	Ts	+5.2[b]	–5.95	–5.85

[a] B3LYP/6-31G(d) (vacuum). [b] 6-exo and 5-exo are considered.

The TS calculations (B3LYP/6-31G(d) with IEFPCM(*o*-DCB)) of the interconversion between **1a**/5 and **1a**/6 via N-flipping (Fig. S9) and the *m*CPBA oxidation of **1a** are shown in Fig. 2. The lowest activation energy ($\Delta E^{\ddagger}$) of *m*CPBA addition was obtained for N-attack to **1a**/6 (44.5 kJ/mol), whereas Cα/Cβ/Cγ attacks had rather higher activation energies (51–65 kJ/mol), reflecting the higher yield of **1a** into C_{60}. Moreover, the TS geometries for C-attacks (Fig. 3) have an asymmetric triangular structure as reported in the oxidation of fulleroid[13] rather than the butterfly-like symmetrical oxirane type transition state of planar alkene epoxidation,[12,14] because of the highly twisted π-orbital of the 7-azepine framework. The Cγ addition also gave asymmetric TS structure, although the energy is higher than those of the bridgehead Cα=Cβ double bond with highly twisted π-orbital misalignment.

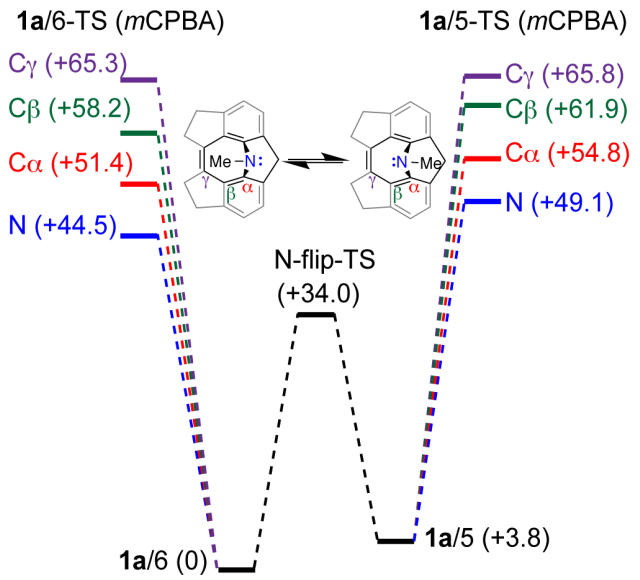


Fig. 2. Energy diagram of 5/6-transition and *m*CPBA (geom-1) addition to **1a** (kJ/mol, B3LYP/6-31G(d) with IEFPCM (*o*-DCB)).

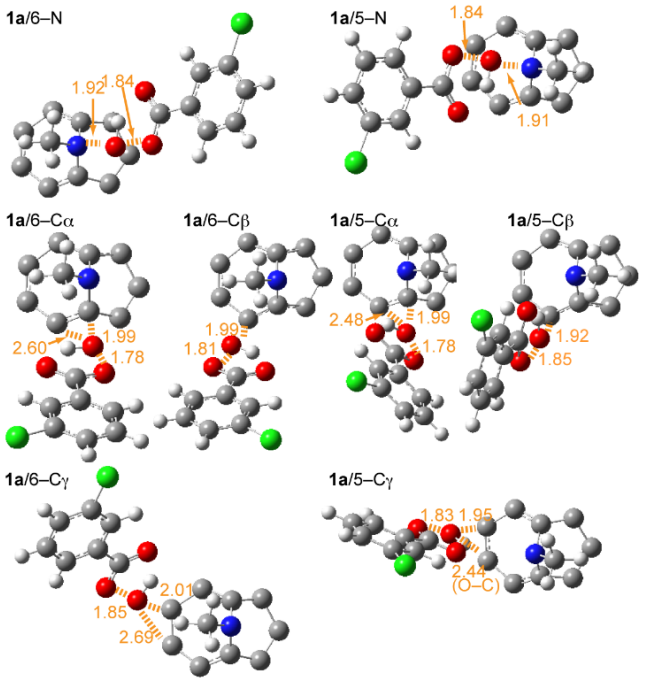


Fig. 3. Transition state geometries with atomic distances (Å) of N/Cα/Cβ/Cγ-attacks of *m*CPBA to **1a**/6 and **1a**/5. Backside atoms are omitted for clarity.

The TS calculations for the oxidation with PAA provided higher activation energies than those of *m*CPBA, as shown in Fig. 4 and Fig. S11. Moreover, the C/N attack-selectivity would be diminished by the smaller energy difference between N and C-attack (~2 kJ/mol) in consistent with the lower yield (20% in Table 2) of C_{60} than that with *m*CPBA.

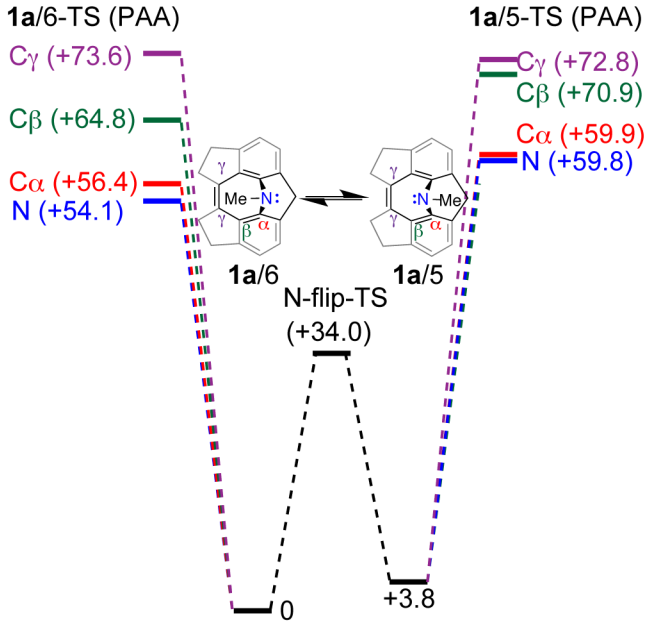


Fig. 4. Energy diagram of 5/6-transition and PAA addition to **1a** (kJ/mol, B3LYP/6-31G(d) with IEFPCM (*o*-DCB)).

As for phenyl-substituted **1f**, its reduced basicity of aniline moiety raised the activation energy for the N-attack of both the **1f**/5,6 conformers (Fig. 5 and Fig. S12). In addition, the steric hindrance of the bulky phenyl substituent seems to somewhat hinder the Cα/Cβ/Cγ attacks for **1f**/6 geometry. On the other hand, **1f**/5 geometry, with less steric effects on Cα/Cβ/Cγ addition, gave lower activation energies comparable with the N-attack. This energy degeneration of C/N-addition agrees with the experimental result of lower yield of C_{60} regeneration as well as the considerable amount of oxidized byproducts.

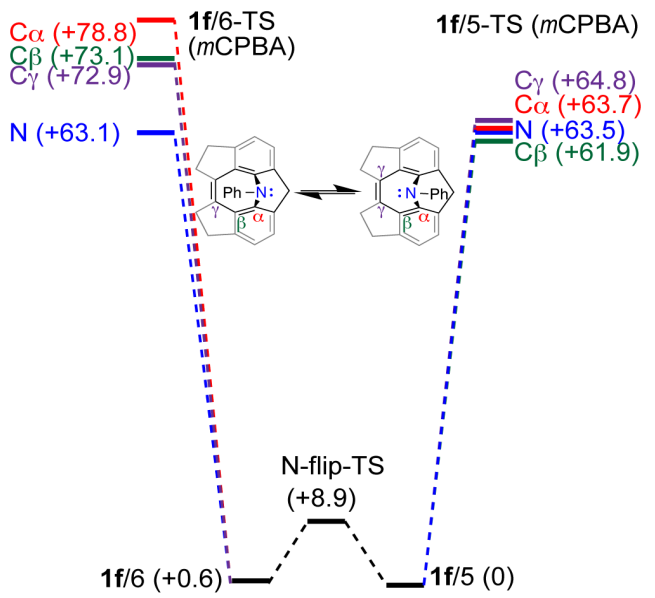
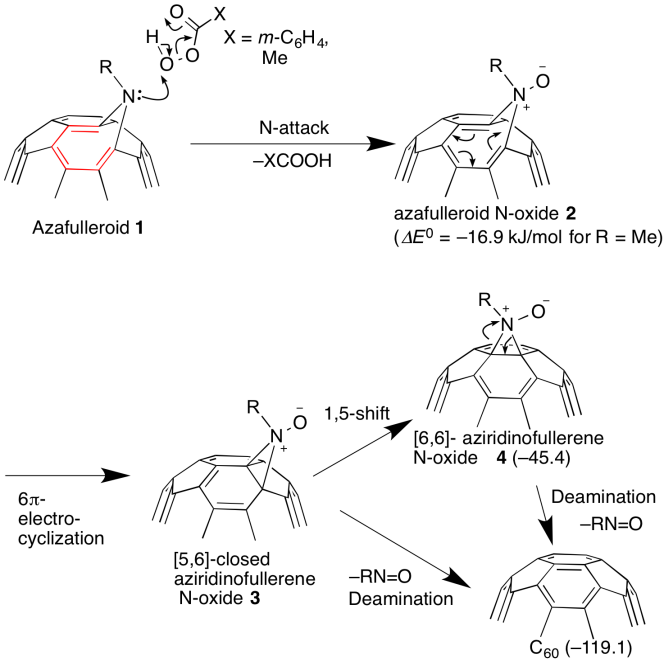


Fig. 5. Energy diagram of 5/6-transition and *m*CPBA addition to **1f** (kJ/mol, B3LYP/6-31G(d) with IEFPCM (*o*-DCB))

A plausible mechanism for deamination

These calculations infer that electrophilic *m*CPBA preferably attacks at the nitrogen for methyl substituent **1a**, while non-regioselectively add to N/C for phenyl substituent **1f**. Although an attempt to calculate the transition states of deamination or the oxygenated intermediates has not been achieved, a possible pathway to C_{60} can be shown in Scheme 3 according to the previous examples of oxidative deamination of 1,4-imines[15] and aziridine.[16] For **1a**, peracids prefer the N-attack of relatively stable **1a**/6 geometry, leading to azafulleroid N-oxide **2**. The 5,6-open structure of **2** was transformed into 5,6-closed aziridinofullerene N-oxide **3** via 6π-electrocyclization. Similar to the deamination of aziridine N-oxide, **3** would undergo the cheletropic elimination of nitroso-bridge to give C_{60}. However, the unstable **3** can transfer to the [6,6]-bridged aziridinofullerene N-oxide **4** (~28 kJ/mol stable, vs. **2**) via 1,5-shift because such N-oxidized aza-bridge has the same electronic structure to that of [5,6]-methano bridge of fulleroid which easily isomerizes to [6,6]-closed methanofullerene.[17] Nevertheless, **4** also undergoes the deamination of its [6,6]-aziridino framework to give C_{60}. On the other hand, oxidation of **1f** would also give various C-oxidized (Cα, Cβ, Cγ or maybe the other sites in C_{60} sphere) products in addition to C_{60} from N-oxidized intermediate. As shown in Scheme S2, both Cα/ Cβ-adduct seems to be unstable due to the hemiaminal N-C-OH framework and iminium-like cationic structure, respectively. These very labile cationic intermediates are probably responsible for the unidentified insoluble products, in marked contrast to the stable ester adducts for fulleroid.[13] For tosyl azafulleroid **1g**, lower basicity of nitrogen would inhibit the N-attack and then only provide labile C-oxidized product, similarly to **1f**.



Scheme 3. A plausible mechanism of regeneration of fullerene. ΔE^0 values of **2, 4** and C_{60} are calculated with B3LYP/6-31G(d) with IFEPCM (*o*-DCB).

Conclusions

Unlike fulleroids, oxidation of azafulleroids **1a–f** with peracids regenerated the component C_{60} by the oxidative elimination of the relevant amino bridge. The yields depend on the nucleophilicity of the bridged nitrogen and the steric nature of azafulleroid along with the electrophilicity of peracids. Experimental evidence has not fully exhibited the ambident C/N-reactivity of azafulleroids yet, because of the lower solubility of byproducts. Nevertheless, the DFT calculations for phenyl substituted azafulleroid **1f** supported the preferential oxidation of bridgehead C=C bonds rather than N-oxidation, being consistent with the lower yield of deamination and the large amount of byproducts.

Experimental Section

Synthesis of N−Methylazafulleroid 1a

N-methyl triazolinofullerene[18] was dissolved in toluene, and heated 1 hour at 100 ºC. After cooled to the room temperature, the solution was concentrated in vacuo. The residue was purified with silicagel column chromatography (CS_2:hexane = 1:1) to give azafulleroid **1a** with 20% yield. ^{1}H NMR (400

MHz, $CS_2/CDCl_3$): δ 3.58 (s, 3H) ppm; ^{13}C NMR(100 MHz, $CS_2/CDCl_3$) δ 38.18, 133.44, 135.12, 136.95, 136.60, 136.87 , 137.68, 137.79, 138.28, 139.02, 140.51, 141.12, 142.50, 142.60, 142.71, 142.91, 143.20, 143.29, 143.43, 143.65, 143.78, 143.98, 144.06, 144.16, 144.29, 144.41, 144.53, 144.53, 144.85, 147.34, 147.63 ppm. HRMS (MALDI-TOF MS, negative): *m/z* calced for $C_{61}H_3N^-[M^-]$: 749.0271, found 749.0260.

Synthesis of azafulleroids 1b–f

Other azafulleroids **1b–c**,[1d] **1d**,[3] **1e**,[1a,3] **1f**,[1c] and **1g**[2a] were prepared by the previously reported methods.

Oxidation of azafulleroid with peracids

m-Chloroperbenzoic acid (*m*CPBA, 27 mg, 0.14 mmol) or peracetic acid (6% solution in AcOH, corresponding to 0.14 mmol) was added to the solution of azafulleroids (27 μmol) in *o*-DCB (20 mL). The mixture was stirred at 50 ºC with monitoring reaction by HPLC. After almost disappearing azafulleroid peak, the reaction was quenched by $NaHSO_3$ solution. Organic layer was separated, dried over MgSO4, filtrated and concentrated in vacuo. The residue was submitted for column chromatography (silicagel, CS_2:hexane = 1:1), to obtain C_{60}.

DFT Calculation

Relative thermodynamic stabilities of **1**/5 or **1**/6 and their HOMOs were calculated with B3LYP/6-31G* of SPARTAN '08 software (full citation is in ESI). The azafulleroids **1b**, **1e** and **1g** have more conformers where the substituents have exo/endo configurations, as shown in Scheme S1. By the calculations, only the thermodynamically most stable conformers, **1a**/6, **1b**/6-exo, **1e**/6-exo, **1f**/5 and **1g**/5-exo are shown in Fig. 1 and Table 3, while the other metastable conformers are shown in Fig. S3–S7. For *m*CPBA, three conformers are calculated as shown in Fig. S8a. The thermodynamically most stable geometry of *m*CPBA was geom-1 although geom-3 has almost similar energy (+0.03 kJ/mol). All orbital contours of HOMO/LUMO in this paper are defined as isovalue of 0.032.

For the estimation of the reaction site of alkyl/phenyl azafulleroids, TS calculations were carried out for the oxidation of **1a** (R = Me) and **1f** (R = Ph) with *m*CPBA and PAA. In this calculation we applied B3LYP/6-31G(d) level of Gaussian 09 software (full citation is in ESI) with the polarizable continuum model using the integral equation formalism variant (IEFPCM) of *o*-DCB. To simplify calculations, we only considered four reaction sites, the bridged nitrogen, the ring carbons Cα, Cβ and Cγ of azafulleroids. After the transition state calculation, IR calculation was carried out to confirm only one imaginary frequency, as shown in ESI†. While only geom-1 of *m*CPBA were considered in Fig. 2–5, some representative TS calculations with geom-2 and geom-3 *m*CPBA are shown in Fig. S10. Geom-3 of *m*CPBA had similar TS structure and energy to that of geom-1. TS of geom-2 *m*CPBA showed higher activation energy than that of geom-1, although geom-2 (*s*-trans) geometry of peracids sometimes has competitive TS energies in some alcoholic alkenes.[19] In our case, no hydrogen bonding between OH of *m*CPBA and the bridged nitrogen was observed.

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Notes and references

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† Electronic Supplementary Information (ESI) available: NMR charts, calculational results (supplemental results and energy list), estimated intermediates of C-adducts, and full citation of calculation software. See DOI: 10.1039/b000000x/.

1 (a) M. Prato, Q. C. Li, F. Wudl, and V. Lucchini, *J. Am. Chem. Soc.,* 1993, **115**, 1148; (b) C. J. Hawker, P. M. Saville and J. W. White, *J. Org. Chem.,* 1994, **59**, 3503; (c) J. Averdung and J. Mattay, *Tetrahedron,* 1996, **52**, 5407; (d) H. Hachiya, T. Kakuta, M. Takami, and Y. Kabe, *J. Organomet. Chem.,* 2009, **694**, 630.

2 (a) T. Nagamachi, Y. Takeda, K. Nakayama and S. Minakata, *Chem. Eur. J.,* 2012, **18**, 12035; (b) C. B. Miao, X. W. Lu, P. Wu, J. Li, W. Ren, M. Xing, X. Sun and H. Yang, *J. Org. Chem.,* 2013, **78**, 12257.

3 N. Ikuma, Y. Doi, K. Fujioka, T. Mikie, K. Kokubo and T. Oshima, *Chem. Asian J.*, 2014, **9**, 3084.

4 (a) K. M. Creegan, J. L. Robbins, W. K. Robbins, J. M. Millar, R. D. Sherwood, P. J. Tindall, D. M. Cox, J. P. McCauley and D. R. Jones, *J. Am. Chem. Soc.*, 1992, **114**, 1103; (b) Y. Elemes, S. K. Silverman, C. Sheu, M. Kao, C. S. Foote, M. M. Alvarez and R. L. Whetten, *Angew. Chem. Int. Ed. Engl.* 1992, **31**, 351; (c) A. L. Balch, D. A. Costa, B. C. Noll, and M. M. Olmstead, *J. Am. Chem. Soc.*, 1995, **117**, 8926.

5 (a) Y. Tajima, T. Hara, T. Honma, S. Matsumoto and K. Takeuchi, *Org. Lett.,* 2006, **8**, 3203; (b) Y. Shigemitsu, M. Kaneko, Y. Tajima, and K. Takeuchi, *Chem. Lett.*, 2004, **33**, 1604; (c) Y. Numata, J. Kawashima, T. Hara, and Y. Tajima, *Chem. Lett.*, 2008, **37**, 1018; (d) Y. Tajima, K. Takeshi, Y. Shigemitsu, and Y. Numata, *Molecules*, 2012, **17**, 6395.

6 (a) A. B. Smith III, H. Tokuyama, R. M. Strongin, G. T. Furst, W. J. Romanow, B. T. Chait, U. Mirza and I. Haller, *J. Am. Chem. Soc.*, 1995, **117**, 9359. (b) S. Lebedkin, S. Ballenweg, J. Gross, R. Taylor, and W. Krätschmer, *Tetrahedron Lett.*, 1995, **36**, 4971. (c) D. Tsyboulski, D. Heymann, S. M. Bachilo, L. B. Alemany and R. B. Weisman, *J. Am. Chem. Soc.*, 2004, **126**, 7350.

7 (a) J. C. Hummelen, M. Prato, F. Wudl, *J. Am. Chem. Soc.*, 1995, **117**, 7003; (b) G. C. Vougioukalakis, M. M. Roubelakis, and M. Orfanopoulos, *Chem. Soc. Rev.*, 2010, **39**, 817; (c) L. Gan, *Chem. Rec.*, 2015, **15**, 189.

8 (a) N. Martín, M. Altable, S. Filippone, A. Martín-Domenech, L. Echegoyen, and C. M. Cardona, *Angew. Chem. Int. Ed.,* 2006, **45**, 110; (b) J. L. Delgado, F. Oswald, F. Cardinal, F. Langa and N. Martín, *J. Org. Chem.*, 2008, **73**, 3184; (c) M. Nambo and K. Itami, *Chem. Eur. J.*, 2009, **15**, 4760.

9 M. A. Herranz, F. Diederich and L. Echegoyen, *Eur. J. Org. Chem.,* 2004, 2299.
10 Oxidation of alkylazafulleroids at a longer reaction time (~ overnight) lead to fullerene epoxides due to the reaction of derived C_{60} with the remaining *m*CPBA as indicated in ref. 4c.
11 Although the B3LYP calculational energy difference of **1f** was inconsistent with the previous PBE/TZ2P results in which **1f**/6 is 0.64 kcal/mol (2.7 kJ/mol) stable than **1f**/5, both isomers would interconvert in solvent as indicated transition state calculation ($\Delta E^{\ddagger}$ = 8.9 kJ/mol, Fig. S9). *See:* V. Zverev, V. I. Kovalenko, I. P. Romanova and O. G. Sinyashin, *Int. J. Quantum Chem.,* 2007, **107**, 2442.
12 H. Shi, Z. Zhang and Y. Wang, *J. Mol. Catal. A,,* 2005, **238**, 13.
13 N. Ikuma, S. Sumioka, H. Asahara and T. Oshima, *Tetrahedron Lett.,* 2012, **53**, 3581.
14 (a) P. D. Bartlett, *Rec. Chem. Progr*. 1950, **11**, 47; (b) R. D. Bach, M. N. Glukhovtsev, C. Gonzalez, M. Marquez, C. M. Estévez, A. G. Baboul, and H. B. Schlegel, *J. Phys. Chem. A*, 1997, **101**, 6092; (c) R. D. Bach and O. Dmitrenko, *J. Phys. Chem. A,* 2003, **107**, 4300.
15 G. W. Gribble, R. W. Allen, P. S. Anderson, M. E. Christy, and C. D. Colton, *Tetrahedron Lett.*, 1976, **17**, 3673.
16 H. W. Heine, J. D. Myers, and E. T. Peltzer III, *Angew. Chem. Int. Ed. Engl.*, 1970, **9**, 374.
17 (a) J. C. Hummelen, B. W. Knight, F. LePeq, F. Wudl, J. Yao and C. L. Wilkins, *J. Org. Chem.,* 1995, **60**, 532; (b) M. H. Hall, H. Lu and P. B. Shevlin, *J. Am. Chem. Soc.,* 2001, **123**, 1349; (c) H. Kitamura and T. Oshima, *Org. Lett.,* 2008, **10**, 293.
18 N. Ikuma, T. Mikie, Y. Doi, K. Nakagawa, K. Kokubo, and T. Oshima, *Org. Lett.,* 2012, **14**, 6040.
19 M. Freccero, R. Gandolfi, M. Sarzi-Amadè, A. Rastelli, *J. Org. Chem*., 2005, **70**, 9573.