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Dramatic Mechanistic Change in Acid-Catalyzed Arylation of Azafulleroids Depending on their Ambident N/C Basicity: Formation of Cyclopentene Centered Pentakisadduct

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Abstract: Azafulleroid, amino-bridged [5,6]-open fullerene, has the ambident N/C basicity of the incorporated enamine moiety. Acid-catalyzed arylation of N-substituted azafulleroids proceeded via two types of initial N/C protonation to perform monoarylation or 1,4-bisarylation for the *N*-alkyl substituents and shuttlecock-type pentakisarylation for the *N*-phenyl substituent. The dramatic product change was explained by considering the possible mechanism as well as the DFT computational results.

Azafulleroid[1] is an attractive [5,6] open fullerene derivative because its amino-bridged highly twisted double bonds N−C=C (anti-Bredt olefins) seem to exhibit the enamine-like ambident reactivity depending on the steric and the electronic nature. For instance, acid-catalyzed hydrolysis of tricyclic enamine, 9-methyl-9-azabicyclo[3.3L]non-l-ene, proceeds through the dual N/C-acidification to give N-protonated intermediate and double bond protonated product, respectively.[2] However, the possible dual reactivity of azafulleroid has not been reported so far, although regioselective additions to the bridgehead double bonds have been found for azafulleroids,[3] and their analogues methano-bridged fulleroid[4] and azahomoazafullerene $C_{59}N(NH)R$.[5] Here, we report that the acid-induced arylation of *N*-substituted azafulleroids results in monoarylation or 1,4-bisarylation for *N*-alkyl substituents, while shuttlecock type pentakisarylation for *N*-phenyl substituent. We also explain this dramatic product change in terms of the substituent effects on the initial protonation at the N/C basic site of the N−C=C linkage.

First, we preliminary estimated the relevant N/C basicity of the representative *N*-methyl- and *N*-phenylazafulleroids based on the DFT-computational proton affinity (kcal mol^{-1})[6,7] as compared with C_{60}, pyridine, and *N*,*N*-dimethylenamine (Figure 1). It was noted that *N*-methylazafulleroid showed the most effective proton affinity at the N atom, while *N*-phenylazafulleroid at the adjacent C(α) atom of twisted C=C double bond. Their basicities were slightly lower than that of the weak base pyridine, but considerably higher than that of pristine C_{60}, indicating some possible reactivity with acids, in contrast to the lower acid-reactivity of C_{60}. The comparatively reduced N basicity of *N*-phenylazafulleroid is explained by the π-delocalization through the phenyl ring. Therefore, we can assume that *N*-alkylazafulleroids preferably cause the N-protonation, whereas *N*-arylazafulleroids the C(α)-protonation.

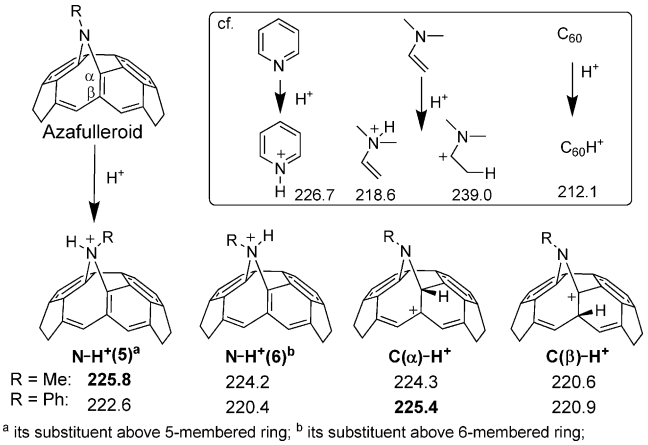

Figure 1. Proton affinities of azafulleroids, pyridine, *N*,*N*-dimethylenamine, and C_{60} (B3LYP6-31G** including zero point energy, in vacuum, kcal mol^{-1}). Bold value is the largest energy.

Considering these computational results, we prepared three alkyl azafulleroids **1a–c** via thermal denitrogenation of triazolinofullerene[8] and phenylazafulleroid **1d** according to the previously reported methods.[1a,d] Acid-catalyzed reaction of butyrate-substituted **1a** in the presence of various aromatic compounds including thiophene and pyrene gave the corresponding 4-monoarylated products **2a–e**. This reaction involves acid-induced C–N bond cleavage followed by the nucleophilic arylation and the closure of [5,6] open ring (Table 1). The stronger protic acid CF_3SO_3H (TfOH) was practical for this arylation, similarly to the acidic arylation

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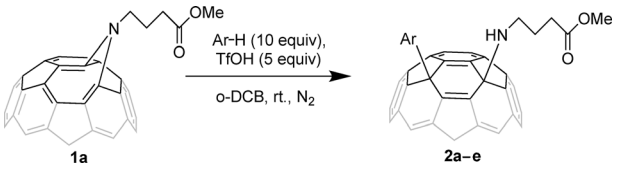
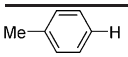
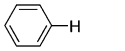
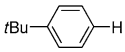
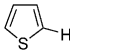
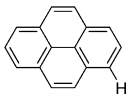
Table 1. Acid-catalyzed arylation of azafulleroid **1a** with various aromatic compounds (Ar-H) by several protic and Lewis acids.



1a **2a–e**

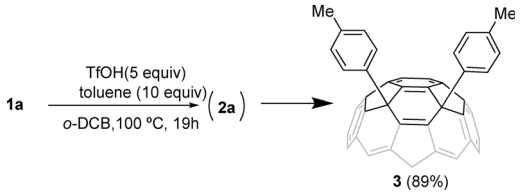
Various Ar-H (10 equiv) with TfOH (5 equiv)	*t* [h]	Yield of **2** [%][a]
	3.5	86 (**2a**)
	3	80 (**2b**)
	1.3	49 (**2c**)
	2.5	98 (**2d**)
	2	94 (**2e**)

Toluene (10 equiv) with various acids	*t* [h]	Yield of **2a** [%][a]
TfOH (1 equiv)	5	no reaction
TfOH (5 equiv)	3.5	86
MsOH (10 equiv)	20	no reaction
MsOH (50 equiv)	3	99
$BF_3{\cdot}Et_2O$ (5 equiv)	20	27
$AlCl_3$ (10 equiv)	29	74

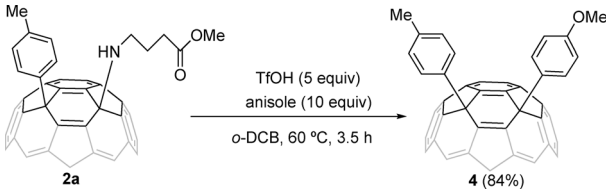
[a] Yield of isolated product.

of aziridinofullerene;[9] while the weaker CH_3SO_3H (MsOH) required far more excess amount of acid. The Lewis acid BF_3[10] provided relatively low yield of **2a** due to the formation of unidentified multiadducts. $AlCl_3$ under the anhydrous condition also gave a fair amount of **2a** rather than hydroarylated adducts, which were major products in the similar reaction of fullerene,[11] probably because of the absence of hydrolyzed $HAlCl_4$.

Interestingly, the reaction at 100 °C provided 1,4-bisarylladduct **3a** probably via the second arylation of monoarylfullerenyl cation arising from the acid-induced deamination of **2a** (Scheme 1). This elevated temperature reaction is useful for the cross arylation as represented in Scheme 2. Although the similar acid-catalyzed homobisarylation was also reported for the [6,6] closed tosyl aziridinofullerene[9,10] and fullerene epoxide,[12] these fullerenes cannot be applied for the stepwise cross arylation because of the lability of primary monoarylated products. So far, such cross arylation



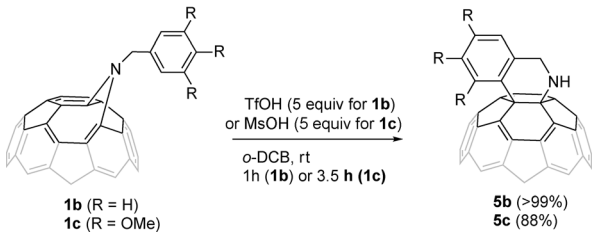
Scheme 1. 1,4-Diarylation of **1a** at elevated temperature. TfOH = CF_3SO_3H. *o*-DCB = o-dichlorobenzene.



Scheme 2. 1,4-Cross arylation of **2a** by stepwise treatment.

has been achieved via relatively stable 1,4-arylfullerenols.[13] Therefore, practical stability of monoarylated **2a–e** can be ascribed to the less facile leaving group of protonated butylamine than tosyl amine.

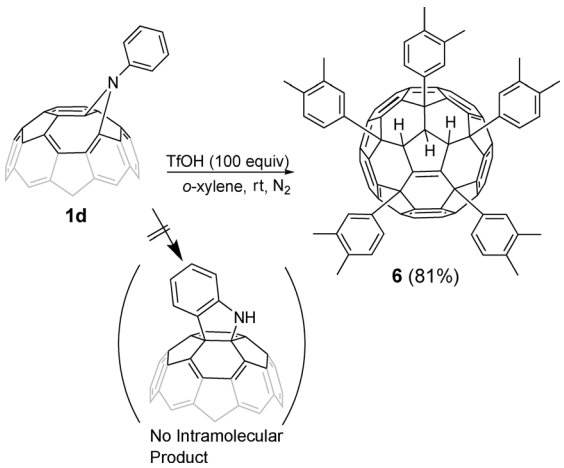
On the other hand, benzyl-substituted **1b,c** underwent the preferential acid-induced intramolecular Friedel–Crafts arylation of benzyl groups to afford tetrahydroisoquinolinofullerenes **5b,c** in excellent yields (Scheme 3). Particularly, tri-



Scheme 3. Intramolecular Friedel–Crafts reaction of benzyl-substituted azafulleroids **1b**,**c**. MsOH = CH_3SO_3H.

methoxybenzyl-substituted **1c** was activated even with weaker acid MsOH. Such acid-catalyzed intramolecular arylation of iminofullerenes[14] can be useful pathway for obtaining heterocyclic fullerenes.

In marked contrast to the alkyl- and benzylazafulleroids **1a–c**, phenylazafulleroids **1d** in *o*-xylene solvent under the excess TfOH demonstrated the elimination of phenylamino substituents and the formation of shuttlecock-type pentakisarylfullerene **6**[15] without forming dihydroindole product[9] by the intramolecular arylation (Scheme 4). The ^1H NMR of



Scheme 4. Acid-catalyzed pentakisarylation of phenylazafulleroids **1d**.

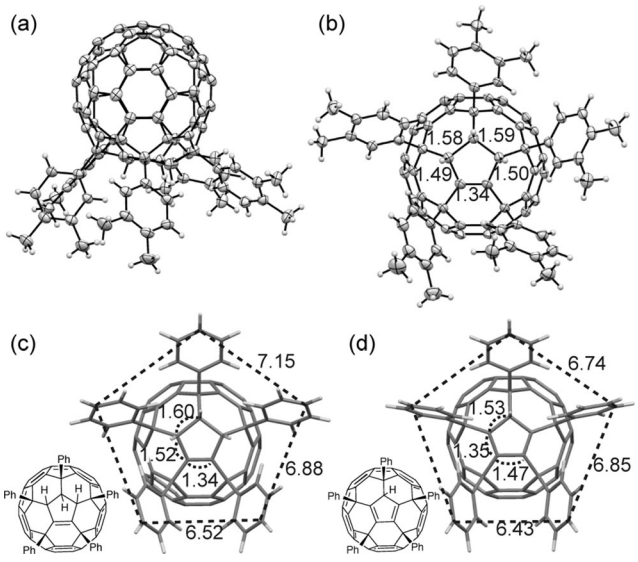


Figure 2. a,b) Crystal structure of **6** with thermal ellipsoids set at 50% probability; side view (a), top view (b). c,d) DFT-calculated (B3LYP/6-31G*) structures[6] of cyclopentenyl ($C_{60}H_3Ph_5$, C_S symmetry, (c)) and cyclopentadienyl ($C_{60}HPh_5$, C_S symmetry, (d)) pentakisphenylfullerenes. Solvent molecule (for (a,b)) and backside atoms (for (b–d)) are omitted for clarity. The values of the central pentagon (b–d) indicate their C–C bond lengths (Å) and values of outer pentagon (c,d) indicate distances (Å) between C4(para) carbon atoms of the five phenyl substituents.

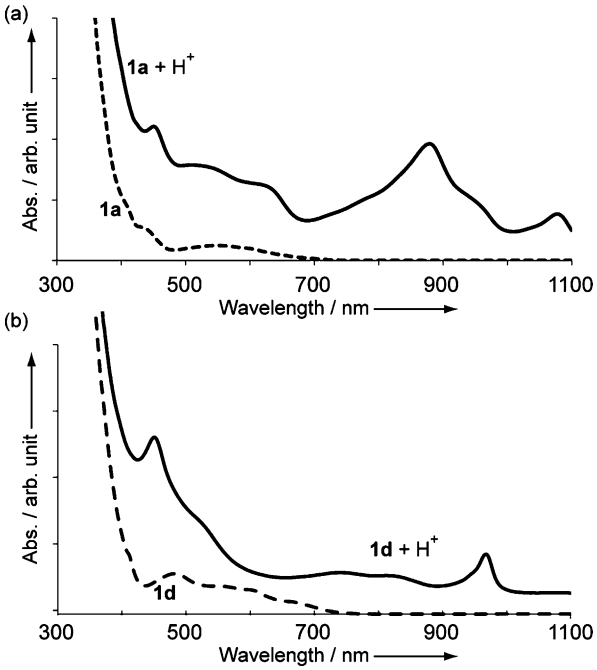
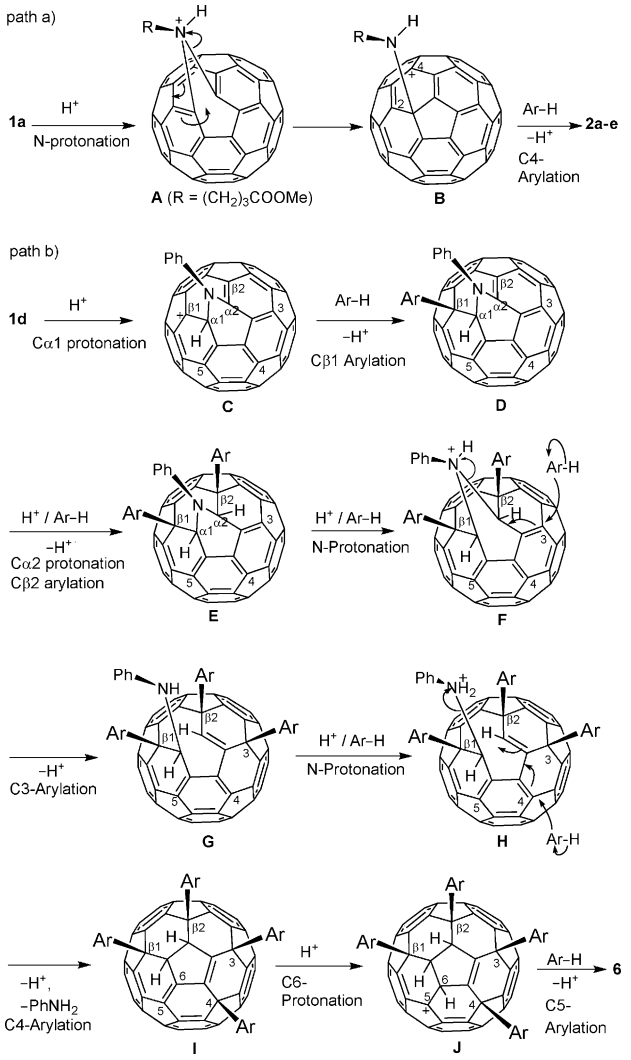


Figure 3. UV-Vis-NIR spectra (at rt) of a) **1a** and b) **1d** in TfOH (solid line) and in *o*-DCB (dotted line).

6 showed multiplet 3H peaks at 4.6–4.7 ppm, and ^{13}C NMR indicated *C*s symmetry of fullerene sphere with ca. 30 sp^2 peaks (along with 6 peaks of *o*-xylene) and five sp^3 peaks. The XRD structural analysis[16] apparently exhibited the pentakisarylation around the central cyclopentenyl ring (Figure 2b) characterized by one short sp^2 type C–C bond (1.34 Å) and the other longer sp^3 type C–C bonds (1.49–1.59), in consistent with the calculated lengths by B3LYP/6-31G(d) (Ar = Ph, Figure 2c)[7] and the analogous trihydroxy cyclopentene ring of $C_{60}(OH)_4(OiPr)_2(OOtBu)_2$.[17] Thus, the present cyclopentenyl pentakisarylated adduct **6** somewhat structurally differs from the previously reported cyclopentadienyl pentakisarylated adducts (Figure 2d) derived from the nucleophilic addition of Grignard reagents under copper catalysts.[18] By comparison of the DFT structures (Figure 2c and 2d), compound **6** is characterized by the appreciable opening of three aryl petals (7.15 vs 6.74 Å) due to the adjacent protonated sp^3 carbons. This flower opening will bring about the different packing features and the electric properties as compared to the more symmetric cyclopentadienyl adducts.

We ascribed the dramatic product change to the change of the initial protonation sites based on the above DFT calculation (Figure 1). To know the structural and electric difference between the protonated intermediates of alkyl/aryl azafulleroids, we have carried out the UV-Vis-NIR spectroscopic measurements of **1a**,**d** in neat TfOH vs in *o*-DCB. In TfOH, alkylazafulleroid **1a** showed three broad bands in the range of 500–650, 800–900, and 1050–1100 nm (Figure 3a). These absorption bands, though slightly red shifted, are similar in shape to those of chloromethylfullerenyl cation.[19] On the other hand, aryl azafulleroid **1d** provided a characteristic sharp peak at 960 nm in TfOH (Figure 3b). Although determination of the detailed cationic structures requires NMR measurements and/or some computational simulations for the exciting species, the spectra of **1d** indicated the unprecedented cationic intermediate derived from the initial protonation at the C(α) atom of twisted bridgehead double bond. Such C-protonated cation of aryl azafulleroid should be a key intermediacy for **6**. In fact, arylation of alkyl azafulleroid **1a** with *o*-xylene under the same reaction condition of **1d** gave a mixture of multiarylated products not containing **6** (Figure S1). In this condition, 1,4-bisadduct similar to **3** can be formed, but further arylation occurs not regioselectively, because of no specific basic site in the 1,4-bisadduct.

Finally, we describe a plausible mechanism for the acid-catalyzed arylation of azafulleroids as shown in Scheme 5. For alkylazafulleroid **1a** ($R = (CH_2)_3COOMe$, path a), the ammonium ion **A** by the protonation of nitrogen suffers the cleavage of one bridged enamine C–N bond and the [5,6] ring closure to generate fullerenyl cation **B**.[13,19] The nucleophilic attack of aromatic compounds preferably occurs at the less hindered *para*-position[9,10,12,13] to afford 1,4-monoarylated aminofullerenes **2a-e**. However, benzylazafulleroids **1b,c** ($R = CH_2Ar$) become tetrahydroisoquinolinofullerenes **5b,c** via an intramolecular nucleophilic cyclization of the corresponding fullerenyl cation **B** at the adjacent *ortho*-carbon. On the other hand, due to the reduced N-basicity by π-conjugation, arylazafulleroid **1d** (R = Ar, path b) would exhibit the acid-catalyzed arylation at the twisted bridgehead C(α)=C(β) double bonds by way of the favorable pro-



Scheme 5. A plausible mechanism for a) monoarylation of alkylazafulleroid **1a** and b) pentakisarylation of phenylazafulleroid **1d**. Although an S_N2' type process is shown for ArH attack and C–N bond cleavage in **F** and **H**, an S_N1 mechanism cannot be ruled out.

tonation at the C(α) and the following arylation at the C(β). The protonated cation **C** seems to be responsible for the sharp absorption over 960 nm (Figure 3b). The second protonation/arylation will occur at the other bridgehead double bond, giving rise to bisarylated product **E**. The bisadduct **E** would be protonated at the N atom because the two introduced hydrogens and aromatic rings inhibit the π-conjugation between the nitrogen and substituent Ph ring to enhance the N basicity (the dihedral angle between Ph and [5,6]-bridge is 45° by DFT, Figure S2). Then it undergoes the S_N2' (or S_N1) displacement by the third aromatic nucleophile leading to the bridge-opened trisarylated adduct **G**. The fourth arylation (in **H**) will be accompanied by the acid-catalyzed deamination, nucleophilic arylation at the conjugated C(4) atom, and electron reorganized transannular [5,6] ring-closure to afford tetrakisarylated adduct **I**. The final protonation at the torsionally strained C(6) atom is essential for the final arylation at the adjacent carbocation center C(5). As a result, pentakisarylation was performed in a clockwise/counterclockwise direction around the central pentagon ring depending on which bridge (C–N bond) of **F** is first cleaved by the S_N2' reaction.

In conclusion, we have found that the acid-catalyzed arylation of variously N-substituted [5,6] open azafulleroids much depended on the nature of the substituents R (=alkyl, benzyl, and phenyl group), because the initial protonation of the incorporated bridged enamine framework varies with the substituents. Alkylazafulleroid brought about the monoarylation via the [5,6] ring closure and the protonated aminobridge opening. However, benzylazafulleroid gave rise to tetrahydroisoquinolinofullerene via the preferential intramolecular cyclization. On the other hand, phenylazafulleroid exhibited the protonation at the most strained Cα carbon and underwent the multi S_N2' type reactions to perform the metal-free pentakisarylation around the central cyclopentene ring.

Acknowledgements

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Keywords: arylation · homogeneous catalysis · fullerenes · nucleophilic substitution · protonation

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[16] Crystal data for $C_{100}H_{48}$ (**6**)·C_7H_8 (along with one disordered solvent molecule, omitted by SQUEEZE calculation): F.W. = 1341.62; red block crystals grown by slow vapor diffusion of hexane into toluene solution of **6** at room temperature; $0.30\times0.20\times0.20$ mm^3; triclinic, space group $P\bar{1}$ (#2), $a=14.8043(3)$, $b=14.8372(3)$, $c=18.2953(3)$, $\alpha=99.7765(10)$, $\beta=95.1935(10)$, $\gamma=109.9613(10)$, $V=3674.22(12)^3$; $\lambda=1.54187$; $2\theta_{max}=136.5°$, $Z=2$; $\rho_{calc}=1.213$ mg m^{-3}; $\mu=5.259$ cm^{-1}; $T=93$ K; Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu $K\alpha$ radiation. Of the 64637 reflections that were collected, 13250 were unique ($R_{int}=0.081$); All calculations were performed using the CrystalStructure crystallographic software package[20] except for refinement with SHELXL-97[21] and for SQUEEZE calculation with PLATON;[22] $R_1=0.0681$, $wR_2=0.2119$. CCDC 999159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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