1,4-Selective Diels–Alder Reaction of 9,10-Diethynylanthracene with 3,6-Difluorobenzyne

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Diels–Alder reaction of 9,10-bis(3-hydroxy-3-methyl-1-butynyl)anthracene with 3,6-difluorobenzyne yields the naphthobarrelene derivative via 1,4-addition of difluorobenzyne in a higher yield than the 9,10-adduct having a triptycene core. The DFT calculations revealed that the intermediate for the former reaction is stabilized more significantly by attractive interaction between a fluorine atom at the benzyne ring and a hydrogen atom at the anthracene ring.

Diels–Alder reaction, a fundamental cycloaddition, forms a six-membered ring from a diene and a dienophile (i.e. alkene, alkyne). It has been applied to synthesis of wide variety of research fields including total synthesis of natural products,¹ bio-related compounds,² and supramolecular compounds.³ Since the transition state of the concerted reaction involves interaction between the HOMO of the diene and the LUMO of the dienophile,⁴ the Diels–Alder reaction of substrate with different diene groups in the molecule produces isomeric products and the regioselectivity is governed by the energy level of the frontier orbitals.

Two different diene groups of anthracenes, the central (9,10position) and terminal (1,4-position) six-membered rings, are able to undergo the reaction with dienophiles. Diels–Alder reaction between the anthracene and a typical dienophile, such as maleic anhydride and the diester of fumaric acid, provides the 9,10-addition product, because the orbital coefficients of the central diene is higher than that of terminal dienes.⁵ The reports of the reactions that provide 1,4-addition products are limited. Anthracenes with two phenyl or ferrocenyl substituents or with two CN substituents at 9- and 10-positions prefer the 1,4-addition of maleic anhydride.^{6,7} The reaction within a hollow coordination molecular cage allows the 1,4-addition to 9-(hydroxymethyl)anthracene.⁸ Recently, McKeown obtained the 1,4-adduct as the major product from the reaction of 1,2,3,4,8,9,10,11-octahydropentacene derivative with 4,5-di-



Scheme 1. Diels–Alder reaction of anthracene derivative with benzyne or 3,6-difluorobenzyne.

methoxybenzyne and attributed the selectivity to electronic effects of the substituents.⁹ Formation of the 1,4-adduct as a minor product was also reported.^{10,11} Herein we report the 1,4-favorable Diels–Alder reaction using 3,6-difluorobenzyne as the dienophile, which is enhanced by an attractive interaction between a fluorine atom at the benzyne ring and a hydrogen atom of the anthracene ring. Yamamoto and Heney also conducted the reaction of 9-substituted anthracene with 1,2,3,4-tetrafluorobenzyne and obtained the 1,4-adduct as a minor product.^{12,13}

Stirring a MeCN solution of anthracene or 9,10-bis(3-hydroxy-3-methyl-1-butynyl)anthracene and 2-(trimethylsilyl)phenyltriflate or 3,6-difluoro-2-(trimethylsilyl)phenyltriflate, in the presence of CsF yielded the cycloaddition products at 25 °C (Scheme 1).¹⁴ Table 1 summarizes the ratio of two isomeric products via 1,4-addition and 9,10-addition. Only the cycloaddition reaction between 9,10-bis(3-hydroxy-3-methyl-1butynyl)anthracene and 3,6-difluorobenzyne afforded the 1,4adducts (naphthobarrelene) as the major product (Table 1, Run 4). Other reactions (Table 1, Runs 1, 2, and 3) produced only 9,10-adducts (triptycene).

Figure 1 shows the ¹H NMR spectrum of the 1,4-adduct purified by silica gel column chromatography, which exhibited five major signals (A, B, C, D, E) in the same integration ratio. The signal at 6.69 ppm (A) is split by ¹H–¹⁹F coupling ($J_{H-F} =$ 5.8 Hz). ¹H–¹H COSY spectrum contains cross-peaks between the signals at 6.11 ppm (B) and 7.17 ppm (C), and those at 7.52 ppm (D) and 8.16 ppm (E), which indicates those paired peaks are assigned to the hydrogen atoms attached to the same ring. In the ¹⁹F{¹H} NMR spectrum appears a singlet peak at 129 ppm.

Although crystallography of the study was not feasible, X-ray measurement of the derivative after removal of the acetone

Table 1. Diels-Alder Reaction of Anthracenes with Arynes^{a)}

Run	\mathbb{R}^1	R ²	9,10-adduct		1,4-adduct		anthracenes
1	-H	-H	15 ^{b)}	:	>0.1 ^{b)}	:	85 ^{b)}
2	$-C \equiv CC(CH_3)_2OH$	–H	34 ^{b)}	:	>0.1 ^{b)}	:	66 ^{b)}
3	-H	–F	51 ^{b)}	:	>0.1 ^{b)}	:	49 ^{b)}
4	$-C \equiv CC(CH_3)_2OH$	–F	7 ^{b)}	:	13 ^{b)}	:	80 ^{b)}

a) Reaction condition; anthracene (1 equiv), benzyne precursor (1.5 equiv), CsF (1.5 equiv), MeCN, 25 °C, 24 h. b) Ratios were determined by ¹H NMR peak area of the reaction mixture.



Figure 1. ¹H NMR spectrum of 1,4-adducts after purification (500 MHz, CDCl₃, r.t.).



Figure 2. Crystal structure of 1,4-adduct after deprotection.

molecules indicated the naphthobarrelene skeleton (Figure 2). The angle of two aromatic rings was 117° . The distance between fluoride atom (F1) and closed hydrogen atoms (H7, H2) were 2.663 Å (F1–H7) and 2.545 Å (F1–H2), respectively.

We compared the reaction pathways of 9,10-diethynylanthracene with benzyne as the model reaction. Table 2 summarizes the activation energies of the Diels–Alder reaction obtained from DFT calculations at the BHHLYP/6-31G(d) level of theory, which involves the smaller delocalization error compared to the B3LYP density function.¹⁵ The activation energy of the reaction at the 9,10-position was lower than that at the 1,4-position in the reactions of 9,10-diethynylanthracene with benzyne (Table 2, Runs 1 and 2). The reaction of 9,10diethynylanthracene with 3,6-difluorobenzyne (Table 2, Runs 3 and 4) shows lower activation energies at 1,4-position ($\Delta G^{\ddagger} =$ 14.80 kcal mol⁻¹) than that of 9,10-position ($\Delta G^{\ddagger} =$ 16.25 kcal mol⁻¹). These results are consistent with the selectivity of the reactions.

The 1,4-favorable cycloaddition between 9,10-diethynylanthracene and 3,6-difluorobenzyne is related to the structures of the transition state.¹⁶ The transition states of 1,4-addition and 9,10-addition have a different structural relationship between the molecules. Parallel orientation was obtained for transition state of the 9,10-addition (Figure 3a). The transition state of the 9,10-addition has a C=C bond of the aryne and anthracene

Table 2. Activation Parameters $(\Delta G^{\ddagger}, \Delta H^{\ddagger})$ of the Diels– Alder Reaction between Anthracene and Benzyne Derivatives at 1,4- or 9,10-Positions by DFT Calculations (BHHLYP/6-31G(d))



Run	R ²	Product	ΔG^* /kcal mol ⁻¹	ΔH^* /kcal mol ⁻¹
1	Н	9,10-Adducts	18.49	6.21
2		1,4-Adducts	19.13	7.28
3	F	9,10-Adducts	16.25	3.64
4		1,4-Adducts	14.80	2.69



Figure 3. Calculated structures of the transition state of Diels–Alder reaction of 9,10-diethynylanthracene with 3,6-difluorobenzyne at (a) 9,10- or (b) 1,4-positions (BHHLYP/6-31G(d)).

plane at 22° (Figure 3b). The 1,4-addition of benzyne has a transition state with parallel orientation. The activation energy of the second reaction is lower than the others, and enhances the 1,4-addition of 3,6-difluorobenzyne. On the basis of the natural population analysis (NPA), the electric charges of fluorine atom at the benzyne ring and hydrogen atom at the 1-position of anthracene ring were simulated to be -0.35, +0.28, respectively. This result implies the electrostatic interaction between the fluorine and the hydrogen atoms induces decrease in the activation energy of 1,4-addition.¹⁷

In summary, we found the Diels–Alder reaction of anthracene with 1,4-selectivity in organic solvents. A fluorine atom of 3,6-difluorobenyne forms attractive H…F interaction with a CH group of the 9,10-diethynylanthracene at the intermediates and transition state, and renders the 1,4-addition smoother than the 9,10-addition.

Experimental

Synthesis and Characterization. See the Supporting Information for the experimental conditions and procedures, synthesis and compound characterization and ¹H, ¹³C{¹H} NMR spectroscopic data.

X-ray Crystallography. X-ray crystal structure analysis of 1,4-adduct was performed on a Bruker APEXII ULTRA/CCD diffractometer with graphite monochromated MoK α radiation. Single-crystal X-ray structure and supplementary crystallographic data (CCDC number: 1035011) for this paper can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

DFT Calculation. The computation of Diels–Alder reactions between anthracenes and benzynes were performed with Firefly 8.0.1.¹⁸ Minimum energy and transition state structures were optimized by BHHLYP functional in conjunction with the 6-31G(d) basis set. Frequency scale factor suitable for fundamental vibrations is set to be 0.9244.¹⁹ All optimized structures were verified to be local minima or transition states by Hessian calculations. The intrinsic reaction coordinates (IRC) followed the transition states corresponding to Diels–Alder reaction. The activation energy included thermal energy corrections based on scaled vibrational frequencies. Natural population analysis²⁰ was performed by NBO 5.G program.²¹

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Supporting Information

Detailed experimental procedures, NMR spectra, crystal structure and DFT data for the molecules. This material is available electronically on J-STAGE.

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