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Sequential ene, Diels–Alder reactions of AF4-yne with 1,3,5-cycloheptatriene

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Abstract

(4,5-Dehydro)-1,1,2,2,9,9,10,10-octafluoro [2.2]paracyclophane (AF4-yne) undergoes an ene reaction with 1,3,5-cycloheptatriene, the adduct of which subsequently undergoes a further Diels–Alder reaction with a second equivalent of AF4-yne to give two stereoisomeric 2:1 adducts. A very small amount of the classic 1:1 Diels–Alder adduct also can be isolated from the reaction. Structure assignments of all products were determined by NMR through a series of H1–H1, H1–C13 one bond, and H1–C13 two and three bond correlation experiments as well as H1–H1 NOE experiments.

Keywords: AF4; [2.2]Paracyclophane; Ene reaction; Diels–Alder reaction; Cycloheptatriene; NMR

1. Introduction

In a series of recent papers, we have demonstrated that the aryne generated by either the facile base-catalyzed elimination of HI from AF4-iodide or via Cadogan's method of thermal decomposition of the *N*-nitrosoacetamide derivative of AF4, has extraordinary Diels–Alder reactivity, providing yields of 84 and 91%, respectively, in their reactions with benzene (Scheme 1) [1,2]. In our most recent report, it was also shown that the aryne generated via the Cadogan procedure (but not by the Cram method) exhibited excellent ene reactivity, reacting with 1-octene to provide a 91% yield of its ene adduct (Scheme 2).

In this short paper we would like to report the reaction of this diversely reactive aryne with 1,3,5-cycloheptatriene (CHT). CHT is a compound that classically undergoes Diels–Alder reactions via its norcaradiene valence isomer **5**, as shown below (Scheme 3) for its reaction with maleic anhydride, which was first studied in 1939 by Kohler et al. [3], with the correct structure of the norcaradiene-derived product first being proposed by Alder and Jacobs in 1953 [4]. Full stereochemical analysis of the Diels–Alder reactions of CHT in general [5], and more specifically of its reaction with maleic anhydride was accomplished by Goldstein and Gevirtz, and Ishitobi et al., respectively [6].

Although the vast majority of dienophiles, including the highly reactive tetracyanoethylene [7], and 4-phenyl-1,2,4-triazoline-3,5-dione [8], behaved similarly in their reactions with CHT, there are also some examples of CHT undergoing ene reactions in competition [9] or even in preference to the Diels–Alder reaction, such as in its reaction with diethyl azodicarboxylate (Scheme 4) [10].

The reaction of CHT with benzyne has also been examined, and no Diels–Alder product was observed. Instead 14% of a [2 + 2] adduct plus 10% of the ene product were obtained [11] Scheme 5.

2. Results

Considering the propensity of CHT to undergo ene reactions, it probably should not have been a surprise when aryne **1**, as generated under Cadogan conditions at 110 °C, gave four major products, *all* deriving from initial ene reaction, in a total *isolated* yield of 40% (Scheme 6). The actual primary ene product, **6**, was only isolated in 11% yield, along with 4% of its hydrogen-shift isomer, **7**. Under the temperature conditions of the reaction, it is not surprising that some 1,5-hydrogen shift product would be formed.

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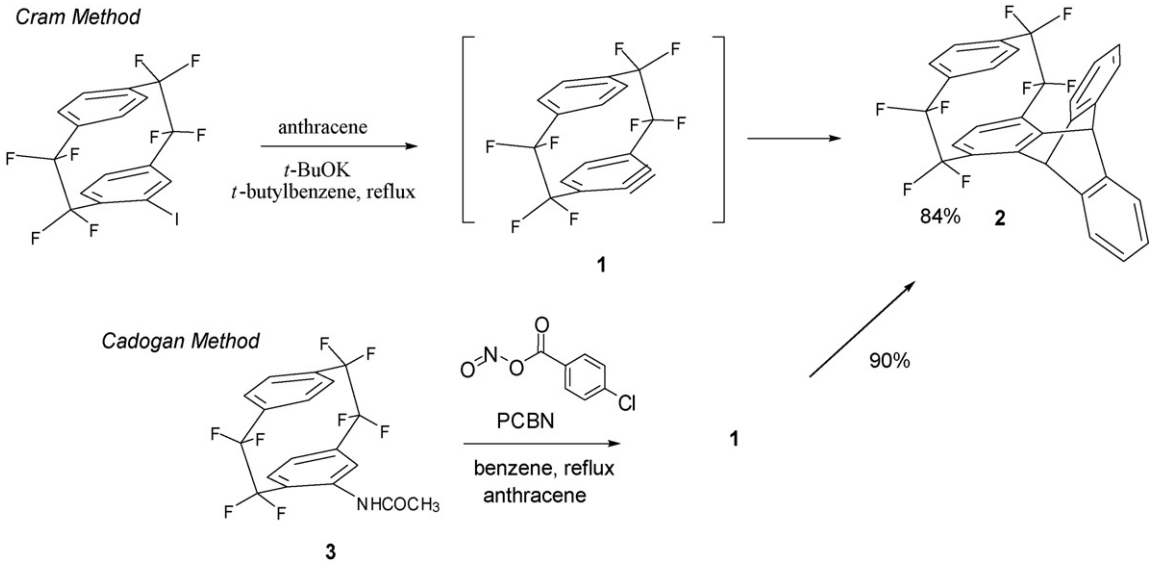
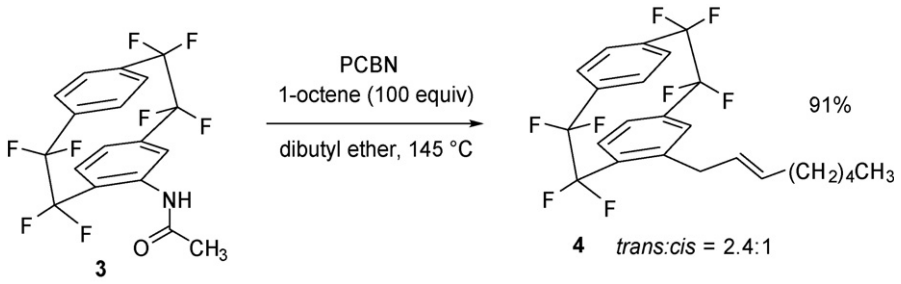
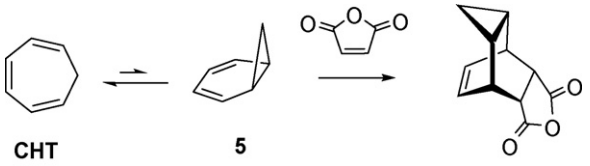


Scheme 1.



Scheme 2.



Scheme 3.

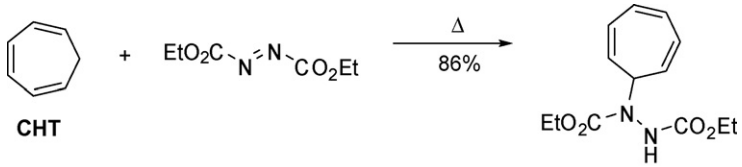
Two other significant products were formed resulting from subsequent Diels–Alder reaction of a second equivalent of aryne **1** with the primary ene product **6**, with **6** reacting via its norcaradiene tautomer, **8**. These two diastereomeric Diels–Alder products, **9** (syn) and **10** (anti), were formed in a total yield of 25% in an approximate ratio of 2:1.

Furthermore, when examining the fluorine NMR spectra of the various fractions from column chromatography of the reaction product mixture, a small amount of the prototypical CHT/AF4-yne adduct (**11**) (only the *exo*-isomer) could be detected and isolated in 2% yield (Scheme 7). No other adducts, such as the [2 + 2] adduct, were apparent in any of these fractions.

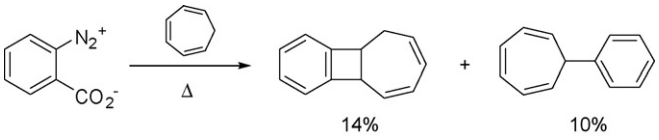
Perhaps the most remarkable aspect of this study is that it was possible to convincingly characterize all four products, the latter two involving relatively complex stereochemical aspects, without the need for X-ray, using available NMR techniques. The structures of the products are depicted below along with their respective proton and carbon chemical shifts (Schemes 8 and 9).

Products **6** and **7** were examined by NMR as an inseparable 2:1 mixture.

The sequence of the protons in the cycloheptatriene moiety was revealed by the DQCOSY spectrum. The carbons one bond away from these protons were identified in the GHMQC



Scheme 4.

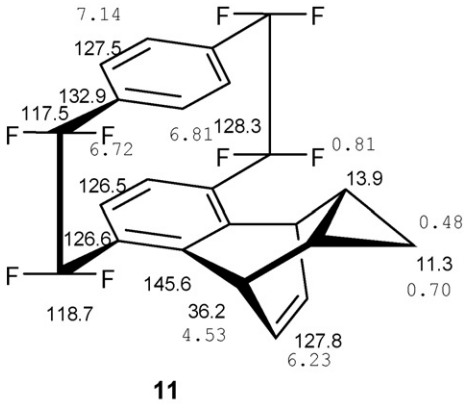


Scheme 5.

spectrum. The GHMBC spectrum displayed couplings for **6** between the protons at 5.50 and 4.58 ppm and the carbon at 142.9 ppm, and for **7** between the protons at 6.26 and 6.53 and the carbon at 142.6, which identified the carbon on the AF4 moiety to which the cycloheptatriene moiety is connected. Couplings between the protons and carbons of the methines at 39.1, 3.06 and at 126.8, 7.18 identified the methine *ortho* to 142.9 in **6**. A similar coupling between the proton at 7.09 and the carbon at 139.3 identified the proton *ortho* to 142.6 in **7**. Long-range couplings between the protons and carbons in a *meta* relationship were used to assign the chemical shifts on the AF4 moiety for **6**. In the case of the minor product **7**, these assignments could not be made because of severe overlap with the stronger peaks of **6**.

The assignment of the protons on the cycloheptatriene moiety in **6** assumed a geometry in which the proton at 3.06 is in the plane of the *para*-phenylene and is facing the nearest CF_2. This is the geometry found by a conformational search using MM2 in Hyperchem, and confirmed by the NOEs displayed by the products of the reaction of the AF4 arene with cyclopentene and with cyclohexene [2]. Two NOEs between 3.06 and 7.21 and between 5.50 and 7.11 allowed the assignment of the protons on the face of the other *para*-phenylene moiety of the AF4, as 7.21 being syn to 3.06. Proton 4.58 displays an NOE with 7.18 only. The conformation of the cycloheptatriene ring in **6** is with the double bond bearing the 6.62 and 6.70 protons folded toward 3.06, as demonstrated by NOEs between 3.06 and these other two protons.

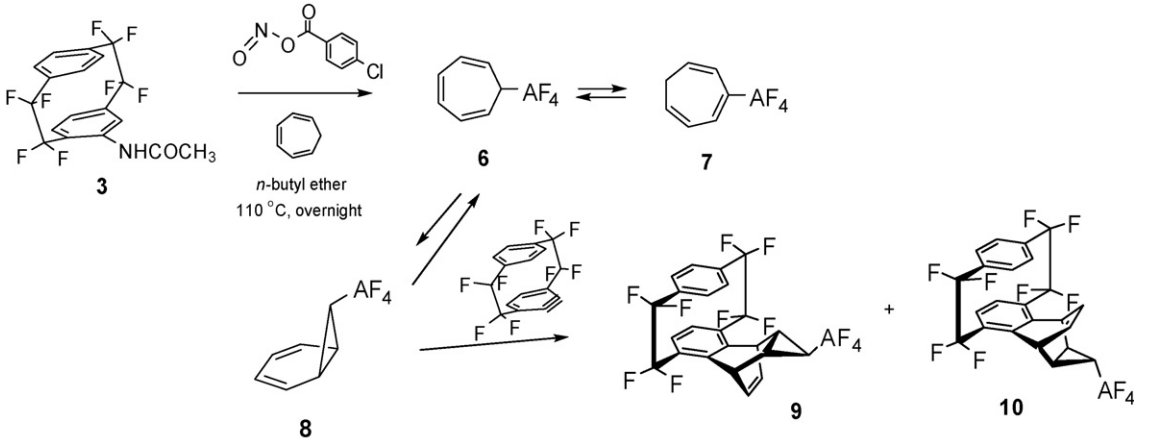
In the case of **7**, both 6.26 and 6.53 display NOEs with 7.27 and 7.09, as expected for little preference for one orientation or the other of the cycloheptatriene moiety. The most shielded proton at 7.27 was assigned as syn to the cycloheptatriene. The side *endo* to the AF4 displayed deshielding compared to the



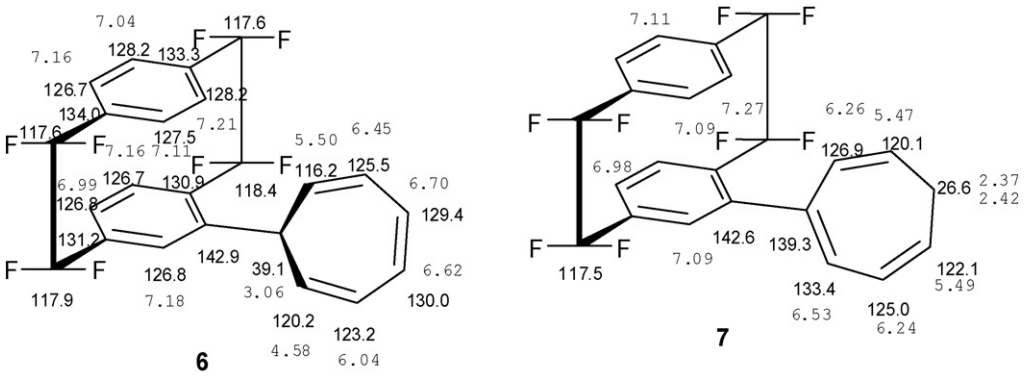
Scheme 7.

side *exo* in all of the compounds studied, therefore, one can assume that the preferred conformation has the CH_2 of cycloheptatriene on the *exo* side of the AF4.

Syn and anti-Diels–Alder products **9** and **10** (depicted below in a manner convenient for clear display of the various atomic sites and their proton and carbon chemical shifts) were also analyzed as an inseparable approximately 1:1 mixture. The sequence of protons in the contiguous coupling network of the [4.1.0]-bicycloheptene moiety was revealed by the DQCOSY experiment. The carbons to which these protons are bound were identified in the GHMQC spectrum. Proton–carbon couplings of ca. 165–175 Hz confirmed the methines of the cyclopropyl ring. The three carbons on the AF4 frames to which the [4.1.0]-bicyclohepta-3-ene moiety is attached (at ca. 140–145 ppm) have been identified by their cross-peaks in the GHMBC spectra to protons two or three bonds away. The carbons adjacent to them couple with the protons three bonds away, e.g., in the case of **9**, 2.54 couples with 126.5 and 131.4, 129.2 couples with 4.89 and 128.5 couples with 4.74. Three of these carbons, at 129.2, 128.5 and 131.4 are split as a triplet of ca. 30–35 Hz by the two fluorines two bonds away. The remaining protons and carbons on the *para*-phenylene moieties to which the [4.1.0]-bicyclohepta-3-ene moiety is attached were assigned on the basis of the couplings between protons and carbons three bonds away. The DQCOSY spectrum



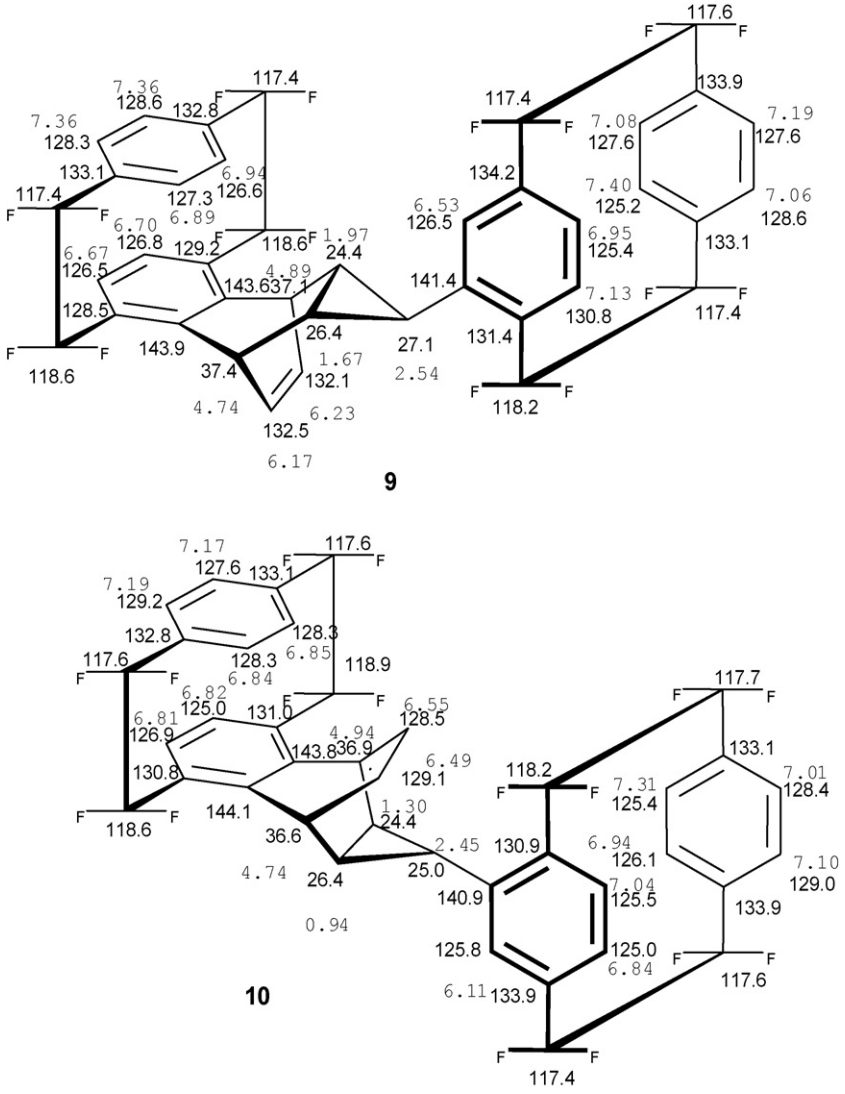
Scheme 6.



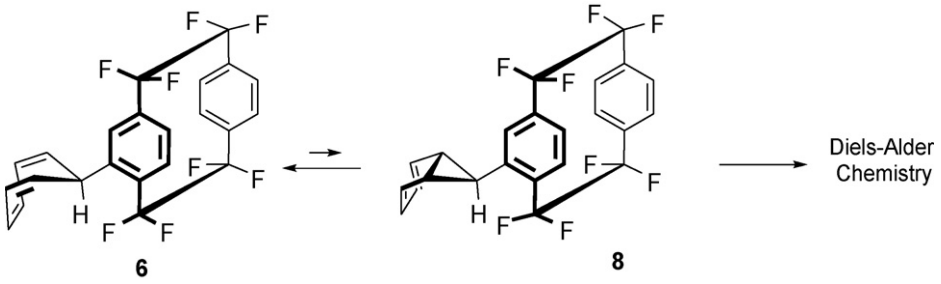
Scheme 8.

confirmed the large coupling between protons which are *ortho* and the small couplings between protons which are *meta*.

The relative configurations of compounds **9** and **10** were established by NOEs. In both **9** and **10**, the cyclopropyl protons adjacent to the AF4 display an NOE to the alkene protons (2.54 with 6.17 and 6.23; 2.45 with 6.49 and 6.55) while the other cyclopropyl protons do not, therefore, the configuration of the [4.1.0]-bicyclohepta-3-ene moiety is *endo* in both compounds. In **9**, the cyclopropyl protons at 1.67 and 1.97 display an NOE with two aromatic protons at 6.89 and 6.94, while in **10** the alkene protons at 6.49 and 6.55 display NOEs with the aromatic protons at 6.84 and 6.85, indicating that the addition of the



Scheme 9.



6 8

Scheme 10.

[4.1.0]-bicyclohepta-1,3-diene yielded the *endo* product for **9** and the *exo* product for **10**. The relative size of these NOEs allowed the assignment of the aromatic protons, i.e., the NOE of 1.67 with 6.89 was larger than the NOE of 1.67 with 6.94.

The use of NOEs in the assignment of the configuration of the AF4 unit bound to the cyclopropyl was based on the fact that the cyclopropyl proton α to the AF4 (2.54 in **9**) is approximately in the plane of the *para*-phenylene and is facing the nearest CF_2. This is the geometry found by a conformational search using MM2 in Hyperchem, and confirmed by the NOEs displayed by the products of the reaction of the AF4 arene with cyclopentene and with cyclohexene [2]. In compound **9**, 1.97 displays NOEs with two aromatic protons at 7.08 and 7.40, while 1.67 does not, therefore, the other *para*-phenylene ring of the AF4 moiety bound to the cyclopropyl ring is on the same side of this ring as 1.97. Of 7.40 and 7.08, only the former displays an NOE with 2.54, therefore, they are syn. Similar NOEs were used in the case of **10**, to assign the protons at 7.31 and 7.04.

Assignment of the protons and relative stereochemistry in minor Diels–Alder adduct **11** was accomplished as a result of NOEs between 7.14 and 6.72, 6.81 and 0.81, and 0.70 and 6.23 ppm.

3. Discussion

Because cycloheptatriene exists in a tub-shaped conformation that does not have a planar diene entity, it does not undergo Diels–Alder reactions directly, but only via its norcaradiene tautomer. On the other hand, cycloheptatriene has been shown to be capable of undergoing ene reactions. Thus, in the presence of exceptionally reactive aryne intermediates such as benzyne itself or AF4-yne (**1**) which are known to exhibit good ene reactivity, the CHT apparently chooses to undergo an ene reaction, rather than wait around to form its norcaradiene tautomer to do Diels–Alder chemistry.

Our observation of the minor 2% product **11** deriving from reaction of AF4-yne (**1**) with CHTs norcaradiene tautomer **5** is the first example of such a product being reported for a reaction of an aryne with CHT. Although **11** is but a minor product, it is nevertheless interesting that its other (*endo*) stereoisomer (**11** with the paracyclophane bridges pointing downward) was not able to be detected in the reaction mixture.

Once the ene product is formed, it is probable that the large, electron deficient AF4 substituent at the 7-position will enhance the amount of norcaradiene tautomer present in equilibrium with its open, tub-shaped conformer, and hence facilitate the observed subsequent Diels–Alder reactions. Scheme 10 above shows the expected tautomeric equilibrium for the ene product **6**.

The two Diels–Alder products are formed via the two different possible (syn and anti) approaches of AF4-yne **1** to norcaradiene tautomer **8**, as depicted in Scheme 11 below.

A significant part of this work is the fact that using a combination of (a) H1–H1 correlation experiments to determine the molecular fragments having contiguous H1–H1 coupling, (b) H1–C13 one bond correlation experiments to determine the CH pairs, (c) H1–C13 two and three bond correlation experiments to ascertain the carbon skeleton connectivity, and (d) H1–H1 NOE experiments to determine the relative stereochemistries, it was possible to determine the structures of structurally complex Diels–Alder adducts **9** and **10** with excellent confidence.

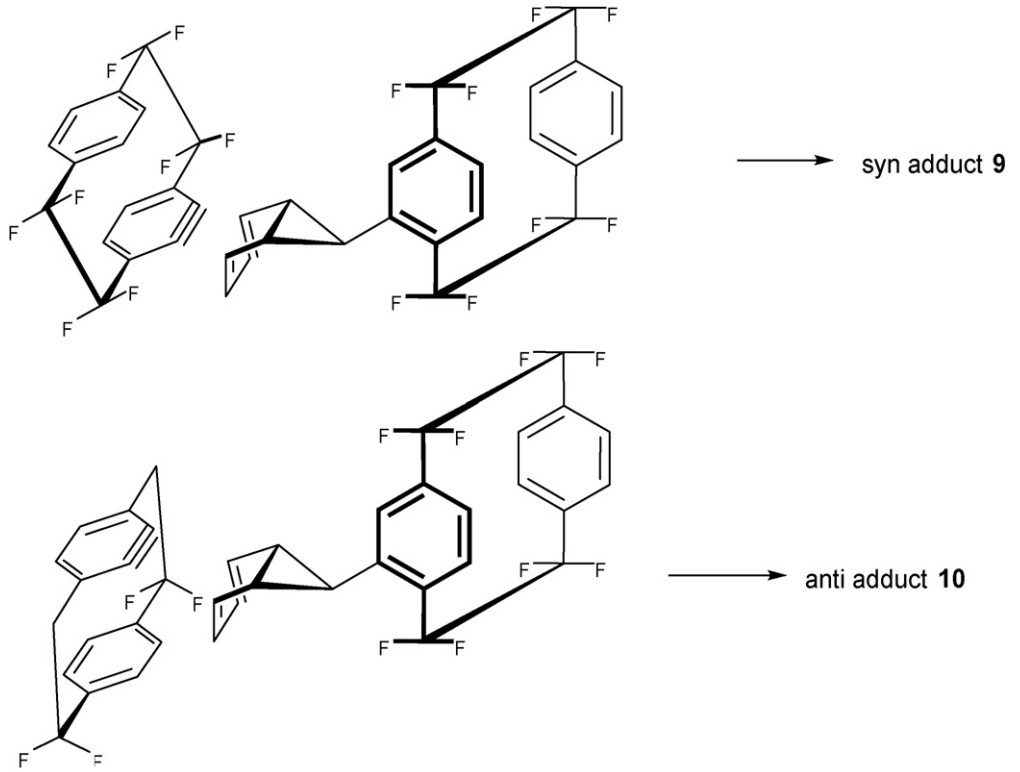
4. Experimental

4.1. General

All NMR spectra were obtained in $CDCl_3$ at 500 MHz for ^1H, at 126 MHz for ^{13}C and at 470 MHz for ^{19}F spectra. Coupling constants are reported in hertz (Hz). NMR reference standards were TMS for ^1H and ^{13}C NMR and $CFCl_3$ for ^{19}F NMR.

4.2. The reaction of 1,3,5-cycloheptatriene with 4-acetamido-1,1,2,2,9,9,10,10,-octafluoro[2.2]paracyclophane (3)

A 50 mL three-necked round bottom flask was charged with AF4-4-acetamide (1.53 g, 3.74 mmol), 10 mL *n*-butyl ether and cycloheptatriene (0.82 mL, 7.92 mmol, 2.12 equivalents). This mixture was heated to 110 °C and the *p*-chlorobenzoyl nitrite (1.20 g, 6.47 mmol, 1.73 equivalents) in 10 mL butyl ether was added over a period of 30 min. This reaction mixture was maintained at this temperature overnight. Then the mixture was cooled and solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography, eluting initially with neat hexanes. The products were then eluted incrementally using increasingly polar mixtures of hexanes/dichloromethane, finishing with a ratio of 5:1, respectively. Upon evaporation and combination of the like fractions the products were obtained. Crystals of the minor Diels–Alder adduct, **11**, were observed to be translucent and needle like in appearance, and they were obtained in the amount of 32.1 mg



Scheme 11.

(2%). The crystals of ene adducts **6** and **7** were white and snowflake in appearance, and were obtained in a combined weight of 0.25 g (16%), with a ratio of isomers of 72:28. Crystals of **9** and **10** were also white and snowflake in appearance, and they were obtained in a combined weight of 0.37 g (25%), with the ratio of isomers being 66:34. All products were fully characterized spectroscopically, **6** and **7** as a mixture of isomers, and **9** and **10** as a mixture of isomers, with isomeric ratios being obtained by fluorine NMR.

6: ^{1}H NMR, δ 7.18 (s, 1H), 7.16 (d, J = 8.8, 2H), 7.04 (d, J = 8.4, 1H), 6.99 (d, J = 7.8, 1H), 6.70 (dd, J = 10.6, 5.7, 1H), 6.62 (dd, J = 10.6, 5.9, 1H), 6.45 (dd, J = 9.5, 6.1, 1H), 6.04 (dd, J = 9.2, 6.1, 1H), 5.50 (dd, J = 9.3, 5.8, 1H), 4.58 (dd, J = 8.6, 6.2, 1H), 3.06 (t, J = 5.9, 1H); ^{13}C NMR, δ 142.9, 130.9, 134.0, 133.3, 131.2, 130.0, 129.4, 128.2, 128.2, 127.5, 126.7, 126.7, 126.8, 126.8, 125.5, 123.2, 120.2, 118.4, 117.9, 117.6, 117.6, 116.2, 39.1; ^{19}F NMR (all equal intensity), δ −110.0 (d, J = 244), −113.3 (d, J = 244), −117.0 (d, J = 245), −117.4 (d, J = 241), −117.4 (d, J = 243), −117.7 (d, J = 241), −119.4 (d, J = 240), −119.6 (d, J = 240).

7: ^{1}H NMR, δ 7.27 (d, J = 9.8, 1H), 7.11 (d, J = 9.8, 2H), 7.09 (s, 2H), 6.98 (s, 2H), 6.53 (d, J = 5.8, 1H), 6.26 (dd, J = 9.0, 2.2, 1H), 6.24 (s, 1H), 5.49 (m, 1H), 5.47 (m, 1H), 2.42 (m, 1H), 2.37 (m, 1H); ^{13}C NMR, δ 142.6, 139.3, 133.4, 134.0, 133.3, 131.2, 130.9, 128.2, 128.2, 127.5, 126.9,126.7, 126.7,126.8, 126.8, 125.0, 122.1, 120.1, 117.6, 117.9, 117.6, 118.4, 26.6; ^{19}F NMR (all equal intensity), δ −104.4 (d, J = 242), −112.3 (d, J = 240), −115.7 (d, J = 240), −117.1 (d, J = 239), −117.5 (d, J = 242), −118.2 (d, J = 241), −119.6 (d, J = 240), −119.8 (d, J = 240); MS (EI) m/z 442(M^{+})(29), 352(9), 265(70), 177(17), 176(100); HRMS Calc. for $C_{23}H_{14}F_{8}$ 442.0968, found 442.0977.

9: ^{1}H NMR, δ 7.40 (s, 1H), 7.36 (s, 2H), 7.19 (s, 1H), 7.13 (s, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 6.95 (s, 1H), 6.94 (d, J = 7.6, 1H), 6.89 (s, 1H), 6.70 (d, J = 8.4, 1H), 6.67 (d, J = 9.3, 1H), 6.53 (s, 1H), 6.23 (t, J = 7.1, 1H), 6.17 (t, J = 6.9, 1H), 4.89 (t, J = 5.4, 1H), 4.74 (s, 1H), 2.54 (s, 1H), 1.97 (dt, J = 8.6, 4.3, 1H), 1.67 (dt, J = 8.0, 4.0, 1H); ^{13}C NMR, δ 143.9, 143.6, 141.4, 134.2, 133.9, 133.1, 133.1, 132.8, 132.5, 132.1, 131.4, 130.8, 129.2, 128.6, 128.6, 128.5, 128.3, 127.6, 127.6, 127.3, 126.8, 126.6, 126.5, 126.5, 125.4, 125.2, 118.6, 118.6, 118.2, 117.4, 117.4, 117.4, 117.6, 117.4, 37.4, 37.1, 27.1, 26.4, 24.4; ^{19}F NMR (all equal intensity), δ −112.0 (d, J = 244), −112.1 (d, J = 244), −112.3 (d, J = 247), −114.4 (d, J = 246), −115.1 (d, J = 245), −115.3 (d, J = 244), −115.9 (d, J = 244), −116.1 (d, J = 224), −117.8 (d, J = 240), −117.9 (d, J = 245), −118.0 (d, J = 241), −119.0 (d, J = 242), −119.1 (d, J = 239), −119.3 (d, J = 240), −119.4 (d, J = 242), −119.9 (d, J = 244).

10: ^{1}HNMR, δ 7.31 (d, J = 8.8, 1H), 7.19 (s, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 6.94 (d, J = 7.6, 1H), 6.85 (d, J = 8.9, 1H), 6.84 (d, J = 9.3, 1H), 6.84 (s, 1H), 6.82 (s, 1H), 6.81 (s, 1H), 6.55 (t, J = 7.1, 1H), 6.49 (td, J = 6.8, 1.5, 1H), 6.11 (s, 1H), 4.94 (t, J = 5.0, 1H), 4.74 (m, 1H), 2.45 (s, 1H), 1.30 (dt, J = 8.7, 4.2, 1H), 0.94 (dt, J = 8.3, 4.2, 1H); ^{13}C NMR, δ 143.9, 144.1, 140.9, 133.9, 133.9, 133.1, 133.1, 131.0, 132.8, 130.9, 129.0, 129.2, 129.1, 128.5, 128.4, 128.3, 128.3, 127.6, 126.9, 126.1, 125.8, 125.5, 125.4, 125.0, 125.0, 118.9, 118.6, 118.2, 117.4, 117.7, 117.6, 117.6, 117.6, 36.9, 36.6, 26.4, 24.4, 25.0; ^{19}F NMR (all equal intensity), δ −110.9 (d, J = 249), −111.7 (d, J = 246), −112.8 (d, J = 243), −114.3

(d, J = 245), −116.1 (d, J = 223), −116.2 (d, J = 244), −116.8 (d, J = 246), −117.4 (d, J = 249), −117.78 (d, J = 241), −117.84 (d, J = 241), −118.1 (d, J = 241), −119.34 (d, J = 243), −119.34 (d, J = 242), −119.45 (d, J = 239), −119.6 (d, J = 242), −120.6 (d, J = 242); MS (EI) *m/z* 792(M^+)(14), 442(2), 352(8), 177(19), 176(100); HRMS (EI), Calcd. for $C_{39}H_{20}F_{16}$ 792.1309, found 792.1331.

11: mp 160 °C; ^{1}H NMR, δ 7.14 (d, J = 1.1, 2H), 6.81 (d, J = 1.1, 2H), 6.72 (s, 2H), 6.23 (m, 2H), 4.53 (m, 2H), 0.81 (m, 2H), 0.70 (dt, J = 5.7, 3.5, 1H), 0.48 (dt, J = 5.8, 7.2, 1H); ^{13}C NMR, δ 145.6, 132.9, 128.3, 127.8, 127.5, 126.6, 126.5, 118.7, 117.5, 36.2, 13.9, 11.3; ^{19}F NMR (all equal intensity), δ −112.0 (d, J = 243), −115.1 (d, J = 243), −117.8 (d, J = 241), −119.4 (d, J = 240).

Acknowledgements

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