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Articles

Synthesis of Fluorous Fullerene Adducts: Reversible Solubilization of Fullerenes in Perfluorinated Solvents

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Fullerene (C_{60}) Diels–Alder adducts with perfluoroalkylated 1,3-cyclopentadiene **(1a**,**b)** were synthesized and studied. The perfluoroalkylated cyclopentadiene was found to be less reactive toward C_{60} than cyclopentadiene itself, possibly because of the electron-withdrawing effect of the side chain. Because of the same effect, the temperature of the retro-Diels–Alder reaction for the fluorinated adducts was lower (70 °C) than the reported value (95 °C) for the cyclopentadiene adducts of C_{60}. Higher adducts of the fluorous diene and C_{60} were found to be soluble in perfluorohexane and to show visible partitioning between organic (toluene) and fluorous phases. Also, the Diels–Alder addition of the fluorous diene was accompanied by extensive oxidation of the fullerene core, as revealed by MALDI-TOF data.

Introduction

Heavily fluorinated solvents are immiscible both in water and in most conventional organic solvents.[1] This fact provides several extremely interesting prospects for the field of organic chemistry. In the past few years, suggestions for taking advantage of this third liquid phase, the “fluorous phase”, have given rise to several promising applications in catalysis[2] and separation techniques in organic synthesis.[3]

The latter of these applications is of particular interest to us. The concept, in brief, is that derivatization of organic-soluble substrates with long perfluorinated groups, or Teflon ponytails, could render the substrates soluble in a perfluorocarbon phase, thereby allowing for easy and quick separation and purification using liquid–liquid extraction. Taking into account the latest developments in fullerene chemistry and the promising properties of fullerene derivatives in material science and biology,[4] we decided to examine how the fluorous-phase approach could facilitate the purification and separation of fullerene (C_{60}) derivatives for further studies and applications.

Results and Discussion

On the basis of the high Diels–Alder reactivity of cyclopentadiene[5] toward dienophiles such as C_{60} and the potential reversibility of the reaction, a fluorous reagent

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(1) Zhu, D.-W. *Synthesis* **1993**, 953–954.
(2) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72–75.
(3) Studer, A.; Hadida, S.; Ferrito, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826.
(4) (a) Da Ros, T.; Prato, M. *J. Chem. Soc., Chem. Commun.* **1999**, 663–669. (b) Wilson, S. R. Biological Application of Fullerenes. In *The Fullerene Handbook*; Kadish, K. M., Ruoff, R. S., Eds.; John Wiley & Sons: New York, in press.
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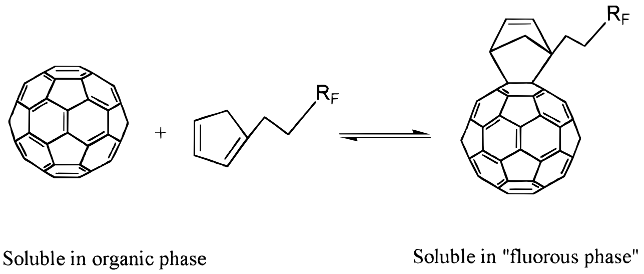
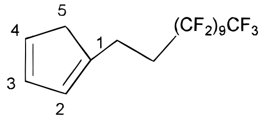
Scheme 1

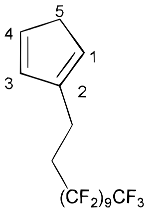


was selected that could reversibly introduce Teflon ponytails onto C_{60} (Scheme 1).

A 1,3-cyclopentadiene (CPD) derivative with a fluorinated side chain and an ethylene spacer to insulate the diene from the electron-withdrawing perfluorinated group was prepared in two steps from freshly prepared cyclopentadienylsodium and 1*H*,1*H*,2*H*,2*H*-perfluorododecyl iodide. As reported by Hughes et al.,[6] the product was found to be a mixture of the two isomers **1a** and **1b**. These isomers could easily be distinguished by ^{1}H NMR, because of the unique chemical shift of the CH_2 group of the cyclopentadienyl moiety, which, for **1a**, appears at 2.95 δ and, for **1b**, at 2.88 δ. NMR integration showed an approximately equal yield of the two isomers. Because no conditions could be found to separate **1a** and **1b**, the mixture was used for the subsequent experiments.



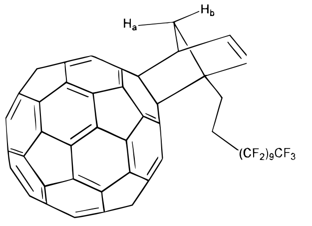
1a



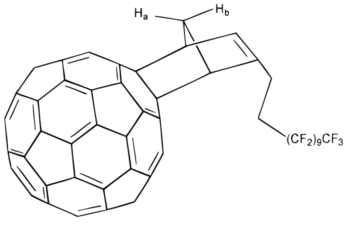
1b

The fluoroalkylated CPDs **1a**,**b** were found to be less reactive toward C_{60} than CPD itself. Whereas the latter rapidly reacts with equimolar amounts of C_{60},[7] HPLC studies of the Diels−Alder reaction of C_{60} with dienes **1a**,**b** revealed that, even when 2 equiv of the dienes was reacted with 1 equiv of C_{60} at room temperature overnight, some C_{60} always remained. The monoaddition product of C_{60} and Teflon-ponytailed CPD could be isolated, purified, and analyzed. As expected, the product was found to be a mixture of two isomers, which could be distinguished by ^{1}H NMR. Integration of peaks at δ-(H_a, **2a**) = 3.5 ppm and δ(H_a, **2b**) = 3.25 ppm showed that **2a** was formed in a higher yield than **2b**. The ratio of **2a** to **2b** was approximately 1.5:1.

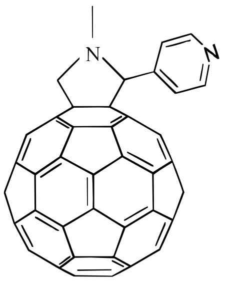
All attempts to obtain a molecular ion for adducts **2a** and **2b** by either FAB$^+$/FAB$^-$ or MALDI-TOF methods failed, because of the ease with which these adducts reverse to the starting components (see discussion below). On the other hand, the use of fullerene compounds “tagged” with groups that enhance signals in MS is successful in revealing the molecular ion. The mass spectrometry “tagging method” was pioneered in our group.[8] A new method has more recently been developed in our lab that uses tagged fullerene **3** in place of C_{60} itself to enhance the sensitivity of the MALDI and FAB experiment and to allow better observation of the molecular ions for adducts by mass spectroscopy.[9] The molecular ion for the Diels−Alder monoadduct from addition of **1a**,**b** to *N*-methyl-2-(4′-pyridyl)-3,4-fulleropyrrolidine (**3**)[10] could be observed by both FAB$^+$ (MH$^+$ = 1467) and MALDI (m/z = 1466) methods.



2a



2b



3

^{3}He NMR spectra of adducts of ^{3}He@C_{60} have been used by us and by others in studies of many types of fullerene reactions.[11] Thus, addition of **1a**,**b** to ^{3}He@C_{60} was carried out as above for further characterization of the Diels−Alder adducts. ^{3}He NMR analysis indicated the presence of two isomeric [6.6]-cycloadducts with peaks in the region characteristic of monoadducts to bonds between two six-membered rings on the fullerene sphere, at δ = −9.440 and −9.543 ppm, in a 1.5:1 ratio (Figure 1).

Using UV−vis spectroscopy (vida infra), the monoadducts **2a** and **2b** showed very low solubility in perfluorinated solvents such as perfluorohexane. However, the

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[6] Hughes, R. P.; Trujillo, H. A. *Organometallics* **1996**, *15* (1), 286−294.

[7] Meidine, M. F.; Roers, R.; Langley, G. J.; Avent, A. G.; Darwish, A. D.; Firth, S.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1993**, 1342−1344.

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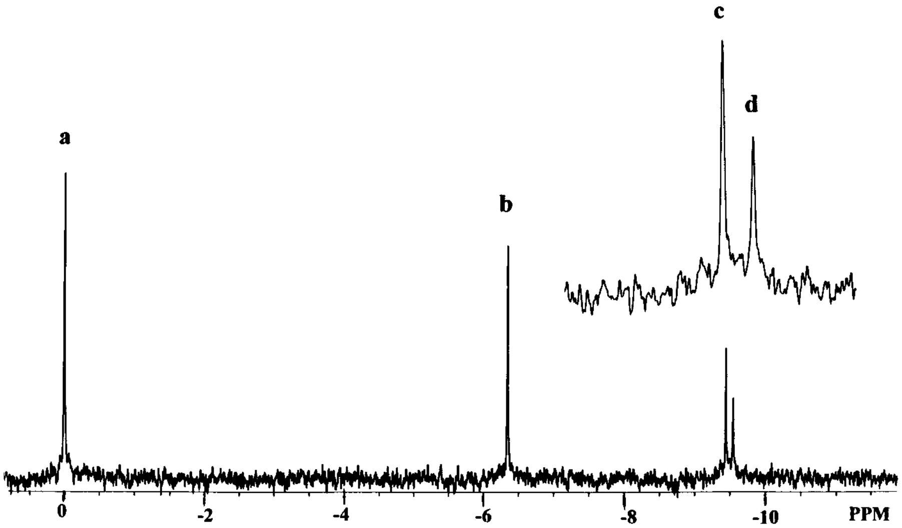

Figure 1. ^{3}He NMR spectrum of the monoadducts **2a**,**b**. Peak a, dissolved ^{3}He gas ($\delta = -0.001$ ppm); peak b, ^{3}He@C_{60} ($\delta = -6.343$ ppm); peak c, ^{3}He@monoadduct **2a** ($\delta = -9.442$ ppm); and peak d, ^{3}He@monoadduct **2b** ($\delta = -9.545$ ppm).

mixture was quite soluble in Freon 113 (1,1,2-trichlorotrifluoroethane). Because our aim was to extract fullerenes from toluene with fluorous solvents and because Freon 113 is miscible with toluene, it was decided to attempt the synthesis and characterization of multiple fullerene adducts with a higher fluorine content.

Bearing in mind the reduced reactivity of Teflon-ponytailed dienes **1a**,**b** toward C_{60}, we reacted an excess of **1a**,**b** (18 equiv) with C_{60} in toluene at room temperature overnight. The results were somewhat surprising. The orange-red product was indeed found to be soluble in perfluorohexane, showing visible partitioning between the organic (toluene) and fluorous (perfluorohexane) phases. The UV−vis absorption at 284 nm (a maximum for fullerene adducts) showed that up to 23% of the product mixture partitions from toluene to the perfluorohexane layer upon extraction. The solubilities of the product were found to be 0.46 mg/mL in perfluorohexane, 1.02 mg/mL in toluene, and 1.20 mg/mL in Freon 113. However, tremendous difficulties were encountered in attempting to separate and purify the products. It was anticipated that the product would consist of a complex mixture of isomers arising from (1) the isomeric nature of the starting diene reagent, (2) the formation of a mixture of bis, tris, and higher fullerene adducts in addition to monoadducts, and (3) the large number of isomers possible for each of the above. An unanticipated complication was also revealed, specifically, the oxidation of the adducts (see below). No HPLC conditions were found that allowed separation of this mixture. In addition, the adduct mixture behaved very strangely on the conventional HPLC columns used for fullerene separations, such as Buckyclutcher[12] or Cosmosil.[13] In both cases, the product peak appeared close to the solvent front, indicating little interaction with the solid support, and the elution time of the product was independent of the toluene:hexane ratio. Silica gel HPLC columns were also of little use because of the strong adhesion of the fluorous materials to the silica gel surface, presumably due to strong hydrogen bonding between the fluorous ponytails and hydroxyl groups on the silica gel.

Because all attempts to separate the mixture of the isomers failed, MS analysis was necessarily performed on the crude product. MALDI-TOF methods revealed that extensive oxidation of the fullerene core occurred during the Diels−Alder reaction. In some cases, up to 15 oxygen atoms could clearly be seen on the C_{60} core (Figure 2).

Fortuitously, this oxidation provided evidence for the presence of the multiple Diels−Alder adducts. Four clusters of peaks were distinguishable at m/z 720 (C_{60}) + 16n, m/z 1332 (monoadduct) + 16n, m/z 1944 (bisadduct) + 16n, and m/z 2556 (trisadduct) + 16n. Unfortunately, the ratio of the clusters may not represent the actual distribution of the products, as multiple adducts can revert to lower adducts and starting materials under the MS analysis conditions used. Elemental analysis indicated a mixture of products. From the carbon-to-fluorine ratio, the average formula of the product was found to be $C_{60}(\text{adduct})_{2.3}$. The analysis also indicates that a large amount of oxygen is present.

Two samples of the multiple Diels−Alder adducts were prepared using ^{3}He-doped C_{60} in the usual manner as well as with rigorous exclusion of air. The latter synthesis was performed in an attempt to avoid the complications arising from oxidation of the fullerene core (see above). However, in both cases, ^{3}He NMR spectra showed no product peaks and no peak for unreacted C_{60}. It appears that the individual product peaks are indistinguishable from noise because of the large number of products formed in the reaction. The IR spectrum of the adduct mixture was similar to that of the monoadduct, with the only obvious difference being the increase in the intensity of the peaks associated with C−F bonds (at 1215 and 1150 cm^{-1}) in the multiadducts mixture.

An HPLC study of the retro-Diels−Alder reaction for both monoadducts and multiple adducts showed that the products begin to revert to the starting materials at 60−65 °C. At 70 °C, the reverse reaction is complete. Remarkably, when the multiple adducts were heated at 70 °C, no observable amounts of $C_{60}O$, $C_{60}O_2$, and other lower fullerene oxides were detected by HPLC analysis. However, a brownish-yellow precipitate was observed

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[12] Buckyclutcher I column, 250 × 4.6 mm, analytical, Regis Technologies, Inc., Morton Grove, IL.

[13] Cosmosil column, 250 × 4.6 mm, analytical, Buckyprep, SES Research Company, Houston, TX.

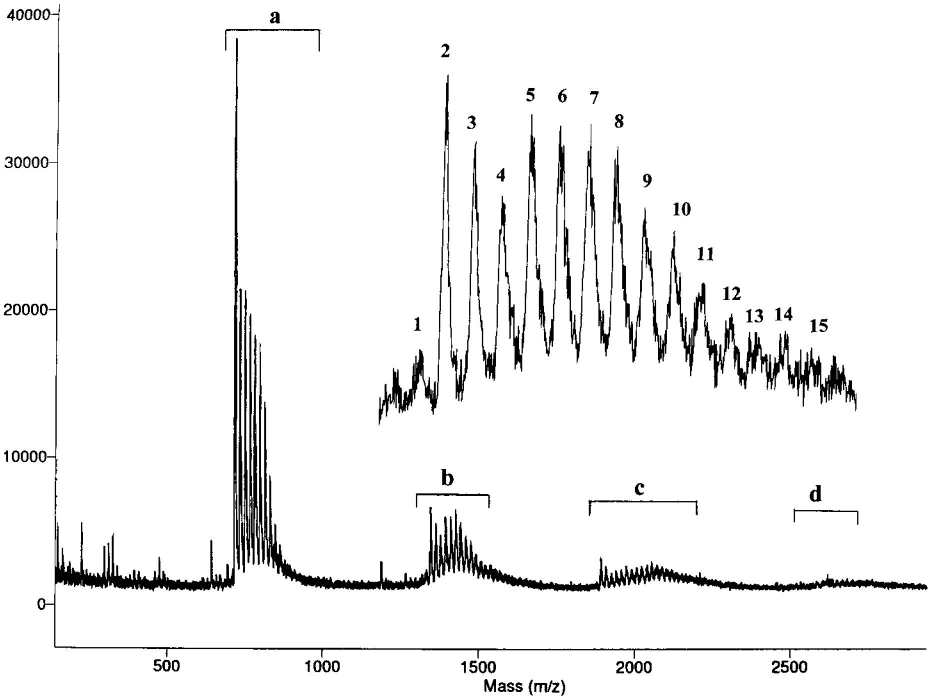

Figure 2. MALDI mass spectrum of the multiple adduct of C_{60} and fluorous diene **1a**,**b** (no matrix, negative mode). Cluster a, MO_n ($n = 0-9$); cluster b, MXO_n ($n = 0-14$); cluster c, MX_2O_n ($n = 0-15$); and cluster d, MX_3O_n ($n = 0-15$). M = C_{60} and X = **1a**,**b**. Expansion of cluster b (insert), MXO_{n-1} ($n = 1-15$): $n = 1$, 1331.64; $n = 2$, 1347.67; $n = 3$, 1364.34; $n = 4$, 1380.41; $n = 5$, 1396.47; $n = 6$, 1412.73; $n = 7$, 1428.94; $n = 8$, 1444.56; $n = 9$, 1461.32; $n = 10$, 1477.31; $n = 11$, 1493.12; $n = 12$, 1508.72; $n = 13$, 1524.28; $n = 14$, 1539.64; and $n = 15$, 1555.96.

during the retro reaction, which was insoluble in all conventional organic solvents, as well as in fluorous solvents. The precipitate is believed to be a mixture of higher fullerene oxide isomers and polymeric material.

Conclusions

Because of the electron-withdrawing effect of the perfluoroalkyl group, cyclopentadienes with Teflon ponytails were not as reactive toward C_{60} as 1,3-cyclopentadiene itself. However, because of exactly the same electronic effect, the reverse Diels–Alder reaction of our C_{60} adducts occurred under milder conditions than those reported for cyclopentadiene adducts of C_{60}.[14] At this stage, the desired reversible phase transfer of fullerene (C_{60}) and its derivatives between organic and fluorous phases at moderate temperatures has not been achieved; however, we believe that such a process can be realized using more highly fluorinated ponytails and could prove useful for the purification of temperature-sensitive fullerene derivatives. One complication encountered in our experiments is the unexpected oxidation of the fullerene core, which accompanies the formation of Diels–Alder adducts of fluorous dienes with C_{60} in the presence of air, presumably because of the high solubility of O_2 in fluorous media.[15]

Experimental Section

General Procedures. All reagents and solvents were purchased from commercial sources and used as received. ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer. GC–MS experiments were performed using a DB5 capillary GC column. HPLC experiments were conducted on a Waters 600E system with a Waters 991 photodiode array detector. IR spectra were recorded as KBr pellets on a Matteson Instruments FTIR Galaxy System. ^{3}He NMR spectra were recorded at Yale University on a Brucker DRX-400 spectrometer. ^{3}He chemical shifts were measured relative to dissolved ^{3}He gas. All MALDI experiments were performed at the NIH Mass Spectrometry Facility at Michigan State University in East Lansing, MI, on a PerSeptive Biosystems (Framingham, MA) Voyager Elite delayed-extraction time-of-flight mass spectrometer equipped with a nitrogen laser (337 nm, 3-s pulse). MALDI experiments for the multiple adducts were carried out in negative ion mode, at a pressure of 7.74×10^{-8} mmHg, an accelerating voltage of 22 000, a grid voltage of 93.6%, and a guide wire voltage of 0.250%, and with no matrix (fullerenes were recently shown to serve as matrices themselves).[16]

Preparation of Fluorous Diene (1a,b). A modification of the procedure reported in ref 6 was employed. An 80% oil dispersion of NaH (0.22 g, 7.5 mmol) was washed with pentane and dissolved in 20 mL of freshly distilled anhydrous THF under argon. To that solution was added dropwise 0.62 mL (7.5 mmol) of freshly distilled 1,3-cyclopentadiene. After vigorous hydrogen evolution, the solution turned pink. The cyclopentadienylsodium solution was collected into a syringe and injected into a solution prepared by dissolving 1.0024 g (1.5 mmol) of 1*H*,1*H*,2*H*,2*H*-perfluorododecyl iodide (Oakwood Products, Inc.) in 20 mL of anhydrous THF. The solution was stirred overnight under argon in dry ice. After addition of 15 mL of water, the solution turned yellow-brown. The product was extracted three times with perfluorohexane. After solvent evaporation, a pale-yellow solid was isolated in 25% yield (0.23 g, 0.38 mmol). In some preparations, further purification was required because of the formation of diperfluoroalkylated cyclopentadienes, which were observed by GC–MS methods. In these cases, the desired product was separated from the

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[15] Yamanouchi, K.; Heldebrant, C. *Chemtech* **1992**, *6*, 354–359.

[16] Huang, J.-P.; Wang, L. Y.; Chiang, L. Y.; Shiea, J. *Fullerene Sci. Technol.* **1999**, *7*, 541–550.

impurities by liquid extraction as follows: the perfluorohexane solution of the crude product was washed with chloroform several times; the more fluorous impurities remained in the perfluorohexane layer, while the monoperfluoroalkylated diene was more soluble in the organic layer. Although some of the desired diene was lost in the perfluorous layer, this method nonetheless afforded a very clean sample of the dienes **1a**,**b**. GC−MS (*m*/*z*): 612 (M^+). FT-IR (cm^{-1}): 2967 (m), 1456 (w), 1212 (s), 1151 (s).^1H NMR (200 MHz, $CDCl_3$ + Freon 113) indicates that the product is a mixture of **1a** and **1b**. **1a** (δ): 6.09−6.46 (3H, m), 2.95 (2H, m), 2.67 (2H, m), 2.30 (2H, m). **1b** (δ): 6.09−6.46 (3H, m), 2.88 (2H, q), 2.67 (2H, m), 2.30 (2H, m).

Preparation of the Monoadduct of C_{60} and Fluorous Diene. C_{60} (15 mg, 0.02 mmol) was dissolved in 20 mL of toluene. The fluorous dienes **1a**,**b** (25.6 mg, 0.04 mmol) in 10 mL of Freon 113 were added to that solution dropwise. The color of the solution eventually turned chestnut brown. The reaction mixture was stirred for 6 h. The progress was monitored by HPLC (Cosmosil column, toluene solvent, 1 mL/min, 340 nm UV−vis detector). The monoadduct was separated by preparative TLC (silica gel, CS_2) to give 64% yield. FT-IR (cm^{-1}): 2966 (m), 1640 (w), 1462 (w), 1414 (w), 1261 (s), 1217 (m), 1151 (m), 1097 (s), 1020 (s), 800 (s). ^1H NMR (200 MHz, $CDCl_3$) revealed the presence of two isomers **2a** and **2b**. **2a** (δ): 6.7−6.85 (2H, m), 4.36 (1H, m), 3.5 (1H, d). **2b** (δ): 7.15 (1H, d), 4.47−4.58 (2H, m), 3.25 (1H, d), 2.96 (2H, t). The remaining protons for both **2a** and **2b** appeared as a complex set of resonances between 2.8 and 2.3 ppm. The ^3He adducts **2a**,**b** were prepared in the same manner as above by addition of 25.6 mg of **1a**,**b** to15 mg of $^3He@C_{60}$ at room temperature in toluene. ^3He NMR (methylnaphthalene:CD_2Cl_2, 3:1; δ): −9.440 **(2a)**, −9.543 **(2b).**

Preparation of the Monoadduct of Dienes 1a,b and *N*-Methyl-2-(4′-pyridyl)-3,4-fulleropyrrolidine (3). *N*-Methyl-2-(4′-pyridyl)-3,4-fulleropyrrolidine (10 mg) was dissolved in 20 mL of toluene, and to this solution was added 14.3 mg of dienes **1a**,**b**. The mixture was stirred for 3 h, after which the solvent was removed under vacuum. FAB^+: 1467 (MH^+). MALDI (*m*/*z*): 1466.

Preparation of Multiple Adducts to C_{60} of Dienes 1a,b. C_{60} (20 mg, 0.027 mmol) was dissolved in 30 mL of toluene. To that solution was added dropwise a solution of 0.31 g (0.5 mmol) of the fluorous dienes **1a**,**b** in 10 mL of Freon 113. The mixture was stirred overnight at room temperature. Upon completion of the reaction, no C_{60} could be detected by HPLC (Cosmosil column, toluene solvent, 1 mL/min, 340 nm UV−vis detector). The solvent was evaporated, and the excess of fluorous diene was trapped with maleic anhydride and removed by several extractions with water and an aqueous solution of potassium carbonate, leaving an oily red-orange product. MALDI-TOF (*m*/*z*): $720 + 16n$ ($9 \leq n \leq 15$), $1332 + 16n$, $1944 + 16n$, $2555 + 16n$, and sometimes even higher mass clusters. Anal. Calcd for $C_{77}H_9F_{21}$ (bis adduct): C, 69.39; H, 0.68; F, 29.93. Calcd for $C_{94}H_{18}F_{42}$ (tris adduct): C, 58.05; H, 0.93; F, 41.01. Found: C, 40.45; H, 5.97; F, 19.85; O, 33.76. In the ^3He NMR spectrum, no peaks were observed for adducts or for unreacted $^3He@C_{60}$. The same FT-IR spectrum was observed as for the monoadduct, except for an increase in intensity of the peaks at 1217 and 1151 cm^{-1}.

Preparation of Multiple Adducts from $^3He@C_{60}$ in the Absence of Air. Argon was bubbled for 2 h through a solution of 20 mg (0.027 mmol) of ^3He-doped C_{60} dissolved in 30 mL of toluene. At the same time, a 20 mL solution of 0.31 g (0.5 mmol) of the fluorous dienes **1a**,**b** in Freon 113 was subjected to five freeze−pump−thaw cycles, after which argon was admitted. The Freon solution of the diene was collected into a syringe and injected into the C_{60} solution under argon. ^3He NMR analysis yielded the same result as above, namely, no observable peaks for products or for $^3He@C_{60}$.

Retro-Diels−Alder Reactions. All retro-Diels−Alder reactions were carried out in toluene in an oil bath using a slight excess of maleic anhydride to trap the generated dienes **1a**,**b**. Aliquots of the solution were removed and analyzed by HPLC, on either Cosmosil or Buckyclutcher columns, using toluene as the eluent at a flow rate of 1 mL/min and with UV−vis detection at 340 nm. In all instances, the gradual disappearance of the peaks for the adducts and appearance of the C_{60} peak were observed.

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