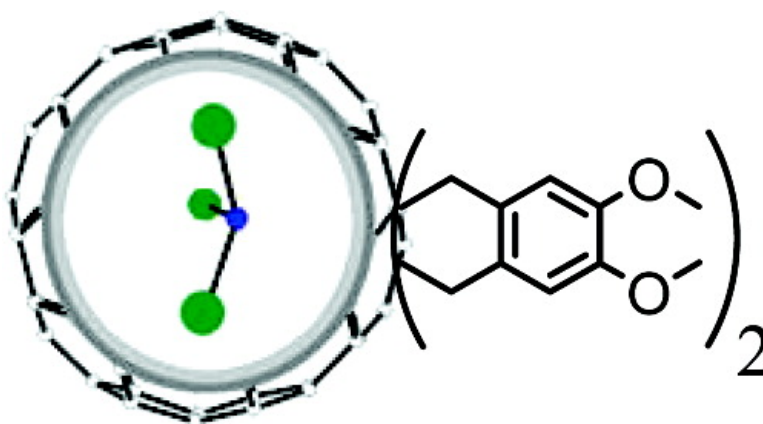Communication

Synthesis and Purification of a Metallic Nitride Fullerene BisAdduct: Exploring the Reactivity of GdN@C

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Synthesis and Purification of a Metallic Nitride Fullerene BisAdduct: Exploring the Reactivity of $Gd_3N@C_{80}$

Steven Stevenson,*,[†] Ryan R. Stephen,[†] Thomas M. Amos,[‡] Veronica R. Cadorette,[‡]
Jonathan E. Reid,[‡] and J. Paige Phillips[†]

*Contribution from the University of Southern Mississippi, Department of Chemistry and Biochemistry,
118 College Drive, #5043, Hattiesburg, Mississippi 39406, and Luna Innovations, 2851 Commerce Street,
Blacksburg, Virginia 24060*

Received May 30, 2005; E-mail: Steven.Stevenson@usm.edu

The encapsulation of atomic clusters inside fullerene[1] cages has created new structures for fundamental research and potential commercial applications. Recently discovered[2] metallic nitride fullerenes, MNFs (e.g., $M_3N@C_{80}$), have an entrapped trimetallic nitride nanocluster within a C_{80} fullerene cage, where M is a Group IIIB or 4f block element.[3,4] Biological applications (e.g., MRI contrast agents) often require water-soluble fullerene derivatives.[5–7] However, many monoadducts are only sparingly soluble in water, need cosolvents, or are suspensions.[8] Improved water solubility has been demonstrated by increasing the number of cage addition sites (i.e., monoadducts toward higher adducts).[8] Recent research discusses the importance of fullerene aggregation and water solubility.[9]

$Gd_3N@C_{80}$ MNFs[10,11] are especially of interest for medical applications. Efforts toward higher adducts of $Gd_3N@C_{80}$ MNF would permit hydrophilic functionalization at multiple cage surface sites. The motivation for synthesizing higher order MNF adducts is supported by literature describing the preparation of higher metallofullerene adducts for medical applications.[12]

Limited literature[13–17] addresses the chemical functionalization of MNF cage surfaces and derivatization[12,18–21] of related classical metallofullerenes (e.g., $Gd@C_{82}$, $Gd@C_{60}$). Carboxylations and hydroxylations of classical metallofullerenes for MRI contrast agents (e.g., $Gd@C_{60}$[9,12] and $Gd@C_{82}$[9,22]) and $Ho@C_{82}$[23] as radiopharmaceuticals have been reported with subsequent monitoring of their biodistribution. MRI interest is piqued based on $Gd_3N@C_{80}$ MNF having three times as many Gd atoms within its cage relative to the $Gd@C_{82}$ and $Gd@C_{60}$.

This work represents initial reactivity results for this new $Gd_3N@C_{80}$ MNF. Specifically, we report the reactivity of $Gd_3N@C_{80}$ in a cycloaddition reaction and introduce preliminary characterization for the first isolated MNF bisadduct. Monoadduct formation for other MNFs (e.g., $Sc_3N@C_{80}$, $Er_3N@C_{80}$, $Y_3N@C_{80}$) is now reported.[13–15]

It is known that *o*-quinodimethane diene intermediates and fullerene cage surfaces react in a [4 + 2] Diels–Alder type cycloaddition,[24,25] and a MNF monoadduct[16,17] has been isolated for $Sc_3N@C_{80}$. In this work, $Gd_3N@C_{80}$ is purified as previously described.[11] A 100-mL, round-bottom flask is charged with 5.0 mg of $Gd_3N@C_{80}$ MNF and a molar excess of 6,7-dimethoxy-3-isochromanone.[26] Using 1,2,4-trichlorobenzene (TCB) as the solvent, the dark brownish-red solution is refluxed for 1 h under a nitrogen blanket. The reaction scheme and corresponding HPLC traces are shown in Figure 1. Upon solvent removal under reduced pressure, the crude product mixture is separated by flash chromatography with chloroform. A first flash fraction (0–250 mL)
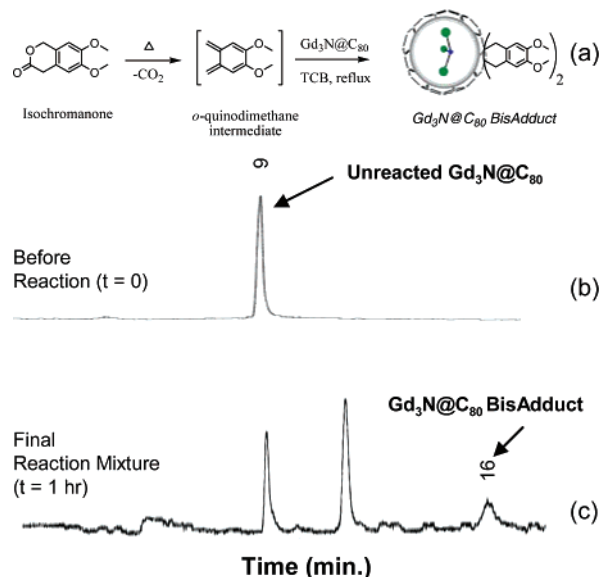
[†] University of Southern Mississippi.
[‡] Luna Innovations.

Figure 1. (a) Reaction scheme and (b) HPLC chromatography profile of the initial reaction mixture prior to heating, $t = 0$, and (c) at $t = 1$ h. Chromatographic conditions are as follows: Buckyclutcher column, 2.0 mL/min chloroform, 335 nm UV detection, and 25 μL injection.

contains only 1.5% bisadduct by HPLC, and a second fraction (250–500 mL) yields 45.3% bisadduct. Subsequent fractions (500–750 mL, 750–1000 mL) contain bisadduct in 92.3% and 99.2% HPLC purity, respectively. Due to coeluting reaction byproducts, column chromatography does not completely separate $Gd_3N@C_{80}$ bisadduct. HPLC chromatography is used as a final cleanup step for collection of the bisadduct peak at 16 min, and multiple injections are performed until a single peak is obtained (Figure 2a). MALDI-TOF characterization data reveal the predicted m/z value (1774) expected for the bisadduct structure of $Gd_3N@C_{80}$ (Figure 2b). Mass spectral analysis of purified metallofullerene derivatives commonly reveals loss of functional groups from the carbon cage surface.[16] Fragmentation patterns relative to the parent ion provide information on the parent ion's molecular weight and the number of attached groups by monitoring the fragment's molecular weight.[13,16,21,27]

In this work, the bisadduct assignment to the purified $Gd_3N@C_{80}$ sample is supported by analysis of the mass spectral fragmentation data (Figure 2b). The presence of two attached functional groups on $Gd_3N@C_{80}$ (i.e., bisadduct) would result in a parent ion (M) of $m/z = 1774$, which is observed (Figure 2b). Each attached group represents 164 mass units, and the loss of one attached group (M − 164) is observed at $m/z = 1610$. Loss of the second attached functional group (M − 328) from the parent ion bisadduct gives

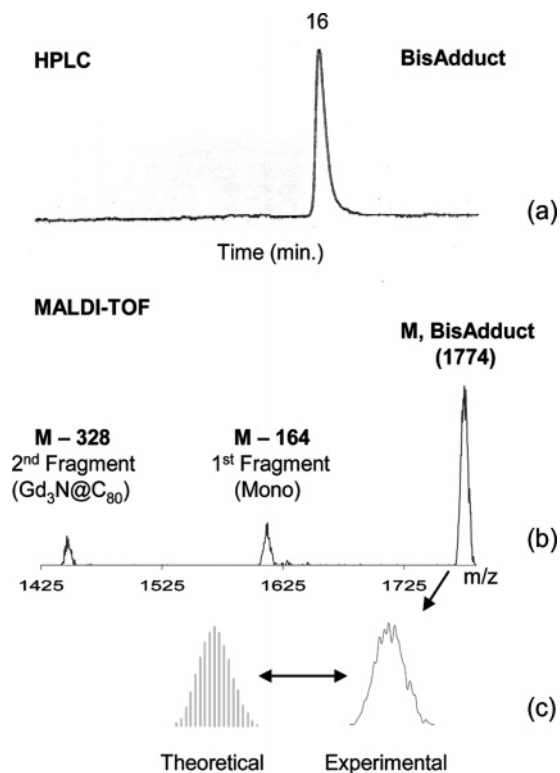**Figure 2.** (a) HPLC trace of purified $Gd_3N@C_{80}$ bisadduct on a Buckyclutcher column, (b) corresponding MALDI-TOF mass spectrum of purified $Gd_3N@C_{80}$ bisadduct with fragmentation species, and (c) mass spectral experimental versus theoretical isotope patterns.

an m/z value of 1446, the molecular weight of underivatized $Gd_3N@C_{80}$ MNF. The HPLC trace of purified bisadduct (Figure 2a) reveals neither monoadduct nor unfunctionalized $Gd_3N@C_{80}$, and we conclude that these fragment ions result from mass spectrometry (Figure 2b) and not as impurities in the isolated bisadduct sample. Additional support of the assigned bisadduct structure is substantiated by mass spectral isotope analysis which confirms the presence of three gadolinium atoms in the isolated bisadduct (Figure 2c). Further support of this $Gd_3N@C_{80}$ bisadduct assignment is obtained from recent MNF monoadduct literature where traces of $Y_3N@C_{80}$ bisadduct had been observed.[14]

The yield of bisadduct structure is modest as only 0.5 to 1 mg of bisadduct was isolated from 5 mg of $Gd_3N@C_{80}$ MNF starting material. The reaction was repeated twice, with isolated yields of $Gd_3N@C_{80}$ bisadduct being 10−20%. As other Gd MNF reactions are not in the literature, the closest yield comparison is $Sc_3N@C_{80}$ MNF, in which 30−40% yields of monoadducts were obtained in a pyrrolidino cycloaddition.[13]

Further characterization of the purified (99+%) $Gd_3N@C_{80}$ bisadduct by NMR and X-ray crystallography is not amenable to the sub-milligram quantities available. Future experiments include

NMR and crystallographic analysis to determine locations of the two isochromanone bonding attachment sites to the cage in relation to the entrapped Gd_3N nanocluster.

Supporting Information Available: Full Reference Information and HPLC data for collected flash chromatography fractions. This material is available free of charge via the Internet at http://pubs.acs.org.

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