Synthesis and characterization of the first trimetallic nitride templated pyrrolidino endohedral metallofullerenes†

Ting Cai, Zhongxin Ge, Erick B. Iezzi, Thomas E. Glass, Kim Harich, Harry W. Gibson* and Harry C. Dorn*

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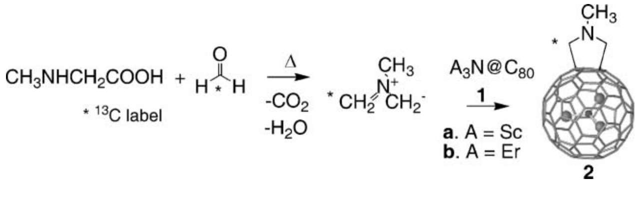
New pyrrolidino derivatives of both diamagnetic and paramagnetic trimetallic nitride templated endohedral metallofullerenes were synthesized by the Prato reaction, isolated and characterized by means of MALDI-TOF MS, NMR and UV–vis spectroscopies.

Trimetallic nitride templated (TNT) endohedral metallofullerenes,[1,2] the most abundantly formed endohedral metallofullerenes, are under current active investigation as powerful, next generation magnetic resonance imaging (MRI) agents and radiotracers,[3] as are other endohedral metallofullerenes.[4,5] In order to function as medical imaging and therapeutic agents these fullerenes need to be properly functionalized. Previously we have shown that these species undergo the Bingel–Hirsch cyclopropanation reaction.[6] We also demonstrated that these new fullerenes are capable of undergoing cycloaddition reactions with quinodimethanes.[7] Among the wide variety of functionalization methods of C_{60}, the 1,3-dipolar cycloaddition of azomethine ylides to fullerenes (the Prato reaction) is one of the most useful; it entails the formation of pyrrolidino fullerene derivatives by reactions with azomethine ylides formed *in situ* from aldehydes and N-substituted glycines.[8,9] Herein, we report functionalization of TNT endohedral metallofullerenes by the Prato reaction on both diamagnetic $Sc_3N@C_{80}$ (**1a**) and paramagnetic $Er_3N@C_{80}$ (**1b**), as a means of diversifying the chemistry of these valuable new species.

The synthesis of TNT endohedral pyrrolidinometallofullerenes **2** was carried out by heating *o*-dichlorobenzene solutions containing $A_3N@C_{80}$ (**1**, 1 equiv.), ^{13}C labeled formaldehyde (12 equiv.) and *N*-methylglycine (4 equiv.) at 110 °C for 10 h (Scheme 1). Monoadducts **2a** and **2b** were isolated in 30–40% yield after silica gel column chromatography using *o*-dichlorobenzene as eluent and subsequently purified by high pressure liquid chromatography (HPLC), using a PYE [2-(1′-pyrenyl)ethyl silica] column with CS_2 as eluent (Fig. 1). The monoadducts are well soluble in CS_2 and *o*-dichlorobenzene, but not in toluene, behavior similar to that of the monoadduct of $La@C_{82}$.[10] The dominant formation of the monoadducts of the TNT endohedral metallofullerenes is consistent with our previous observations[6,7] that trimetallic nitride endohedral metallofullerenes are less reactive than mono-metallofullerenes, *e. g.*, with $Gd@C_{82}$ up to octaadducts were observed in the Prato reaction.[11] The lower reactivity of the TNT endohedrals is due to the transfer of six electrons from the metal nitride cluster to the I_h symmetric C_{80} cage, resulting in a closed shell electronic structure[12] and higher chemical kinetic stability.[13,14]



Scheme 1 Cycloaddition of azomethine ylides to $Sc_3N@C_{80}$ (**1a**) and $Er_3N@C_{80}$ (**1b**).

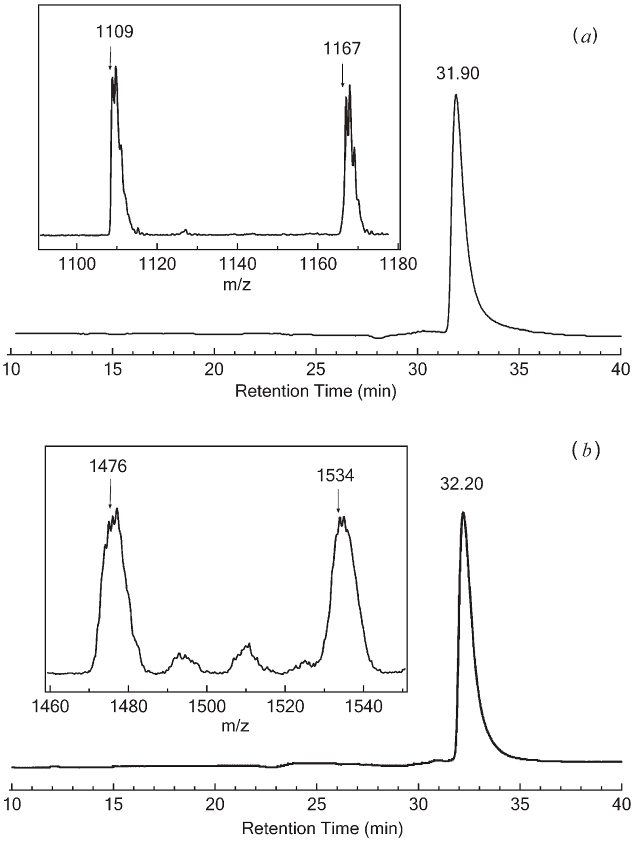


Fig. 1 HPLC chromatograms (1 × 25 cm PYE column at 0.5 ml min^{-1} flow rate with CS_2 eluent) and MALDI-TOF mass spectra (9-nitroanthracene as matrix and negative ionization) of pure monoadducts (*a*) **2a**; (*b*) **2b**.

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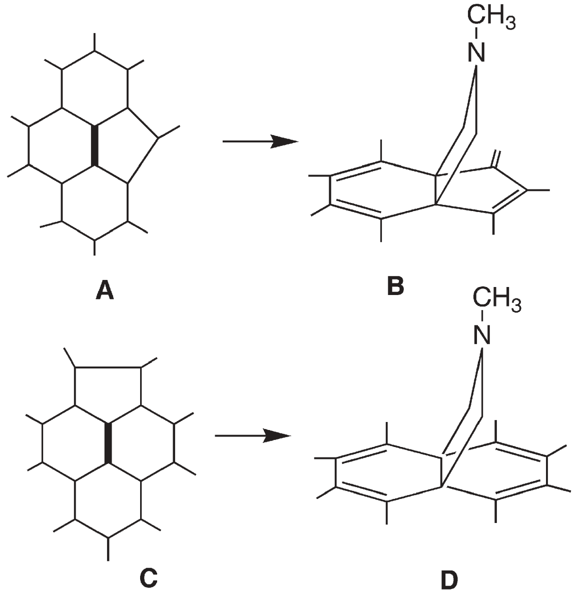
Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, USA 24061-0212. E-mail: hwgibson@vt.edu; hdorn@vt.edu; Fax: +1 540 231 3255; Tel: +1 540 231 5953
*hwgibson@vt.edu (Harry W. Gibson)

The matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra of the endohedral Prato monoadducts **2a** and **2b** were observed as strong M^- peaks at *m*/*z* 1167 and *m*/*z* 1534, respectively. The peaks at *m*/*z* 1109 and 1476 for M^- of **1a** and **1b** are due to loss of the exohedral functional groups $[(CH_2)_2NCH_3]$ from **2a** and **2b**, respectively, a common feature in mass spectra of fullerene derivatives.[6,7,15] The peak of monoadduct **2b** is about twice as broad as that of **2a** because of the isotopic distribution of Er, in good agreement with the calculated distributions.‡

In 1,3-dipolar cycloadditions of *N*-methylazomethine ylides the TNT endohedral metallofullerenes behave as 1,3 dipolarophiles and reactive 2π components. Therefore, the *N*-methylazomethine ylide can only react with a localized double bond at one of the two types of ring juncture available on the I_h symmetric C_{80} cage. These are the 5,6-ring juncture that is abutted by two six-membered rings (**A** in Scheme 2) and the 6,6-ring juncture abutted by one five- and one six-membered ring (**C** in Scheme 2). The 5,6-ring juncture proved to be the reaction site, as clearly demonstrated by the ^{13}C NMR spectrum of ^{13}C labeled adduct **2a**, which exhibits a single narrow signal at 71.6 ppm for the equivalent methylene carbon atoms of product **B**. Addition to the 6,6-juncture was thus ruled out because it would have led to an adduct (product **D**) with non-equivalent methylene carbon atoms. This result is consistent with our earlier report of Diels–Alder isochromanone-derived quinodimethane adduct formation with $Sc_3N@C_{80}$ (**1a**) at the same double bond site, as confirmed by X-ray structural analysis.[7]

Further confirmation of this mode of addition came from ^1H NMR spectroscopy. Unlike the analogous C_{60} monoadduct (obtained in 41% yield) in which all the methylene hydrogens are equivalent,[8] the ^1H spectrum of derivative **2a** without the ^{13}C label (Fig. 2) exhibits signals for the diastereotopic geminal methylene hydrogens. These diastereotopic hydrogens differ in chemical shift by 1.2 ppm. One set (designated H_a) resonates at 2.87 ppm and the other (designated H_b) at 4.02 ppm. Interestingly these chemical shifts are nearly equally spaced from the diastereotopic methylene protons observed in the six-membered quinodimethane cycloadduct, 3.57 and 3.41 ppm.[7] This means that differential ring currents in the 5- and 6-membered rings adjacent to the reaction site cannot be the sole source of the large chemical shift difference. Both sets of signals are, however, shifted upfield from that of the corresponding C_{60} derivative, in which the methylene protons appear as a singlet at 4.38 ppm;[8] this overall ~0.9 ppm shielding increase is attributed to the increased ring current in the more electron rich TNT endohedral metallofullerene cage relative to C_{60}. If the nitrogen lone pair of electrons prefers to be away from the cage for electrostatic reasons, there are two potentially interconvertible diastereomeric adducts as shown in Fig. 3. It has long been known that *trans* lone pairs and *cis* N–C bonds in unsaturated heterocycles cause significant shielding of α-protons.[16] This effect, coupled with the inherent local asymmetry, leads to the large chemical shift differences of the intrinsically diastereotopic methylene protons in **2a**.



Scheme 2 Prato reaction at the 5,6-ring junction (**A** → **B**) and at the 6,6-ring junction (**C** → **D**). **A** and **B** have a horizontal plane of symmetry, while **C** and **D** have a vertical plane of symmetry. In **B** the methylene carbons are equivalent, while in **D** they are non-equivalent.

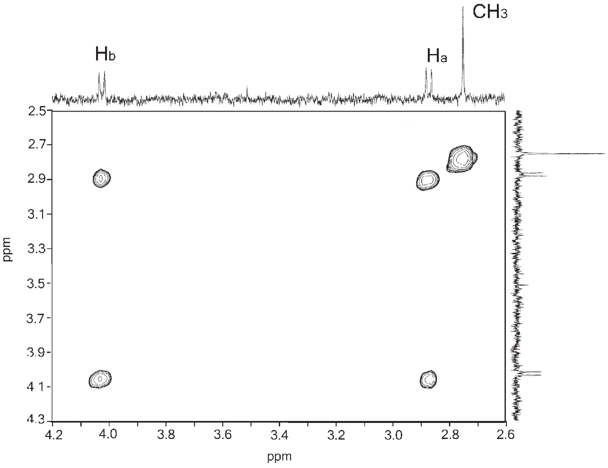


Fig. 2 The 500 MHz COSY spectrum of **2a** without the ^{13}C label in CS_2–$CDCl_3$. ^1H NMR: δ 4.02 (d, $^2J_{H–H}$ = 10 Hz, 2H), 2.87 (d, $^2J_{H–H}$ = 10 Hz, 2H), 2.74 (s, 3H).

The heteronuclear multiple quantum coherence (HMQC) spectrum (Fig. 4) verifies the proton assignments. The ^{13}C labeled methylene carbon is coupled to its diastereotopic, geminal methylene hydrogens, H_a* and H_b*, producing a doublet of doublets for both protons symmetrically disposed about the signals of the geminal methylene protons on the non-labeled carbon, H_a and H_b, that appear at 4.02 and 2.87 ppm, as in Fig. 2. That is, the

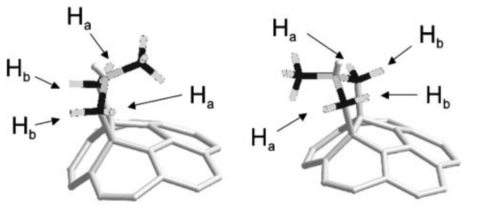


Fig. 3 Proposed diastereomeric partial structures of the Prato adducts **2a** and **2b** assuming the nitrogen lone pair of electrons is pseudoaxial for electrostatic reasons. (a) Left: CH_3 over 5-membered ring. (b) Right: CH_3 over 6-membered ring.

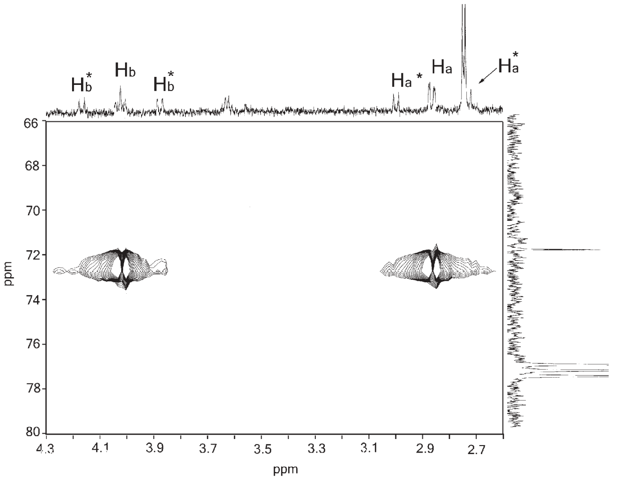


Fig. 4 The 500 MHz HMQC spectrum for purified ^{13}C-labeled **2a** in CS_2–$CDCl_3$. The impurity peak centered at ∼3.65 ppm does not exhibit any correlation and is not present in the natural abundance sample (Fig. 2).

signal for proton H_b* at 4.02 ppm is a doublet of doublets with $^{2}J_{\mathrm{H–H}} = 10$ Hz and $^{1}J_{\mathrm{C–H}} = 145$ Hz and the signal for proton H_a* at 2.87 ppm is a doublet of doublets with $^{2}J_{\mathrm{H–H}} = 10$ Hz and $^{1}J_{\mathrm{C–H}} = 133$ Hz; note that one of the ^{13}C-split doublets for H_a* lies under the methyl signal at 2.74 ppm. Additionally other ^{13}C-splittings are observed. The methyl protons now appear as a doublet with $^{3}J_{\mathrm{C–H}} = 8$ Hz. The signal for H_b on the non-labeled carbon is also split with a small $J_{\mathrm{C–H}}$, yielding a multiplet that is part of a complex pattern. There is also long range ^{13}C coupling to its geminal partner H_a with $J_{\mathrm{C–H}} = 3$ Hz, yielding a doublet of doublets for H_a at 2.87 ppm.

We were unable to obtain high-resolution ^{1}H and ^{13}C NMR spectra for the ^{13}C labeled erbium adduct **2b**. This observation, coupled with significant line broadening (factor of 2) of the ^{1}H solvent line (chloroform), strongly suggests that the pyrrolidino-metallofullerene **2b** is paramagnetic, as expected. In addition, the T_2 spin–spin relaxation time for the ^{1}H chloroform signal in the presence of adduct **2b** (∼0.2 mM) is 1.2 s *versus* 2.4 s (9.4 T) for the chloroform–CS_2 solvent without adduct **2b**.

UV–vis absorption spectra of the TNT endohedral metallofullerenes **1a–b** are similar to those of their monoadducts **2a–b** (Fig. 5), indicating that the pyrrolidine derivatives retain the main aromatic cage features of the parent metallofullerenes.[1,3]

In summary, we have successfully synthesized and characterized the first TNT endohedral pyrrolidinometallofullerenes *via* 1,3-dipolar cycloaddition of azomethine ylides to both diamagnetic and paramagnetic TNT endohedral metallofullerenes. The development of the Prato reaction on TNT endohedral metallofullerenes is noteworthy because it affords access to various derivatives that have great potential for applications in medical and materials science. We are currently trying to obtain single crystals of these compounds for X-ray structural analysis to verify their structures; we are also examining the magnetic (*e. g.*, low temperature ESR on **2b**) and MRI relaxation properties of these and related lanthanide TNT pyrrolidinometallofullerenes.

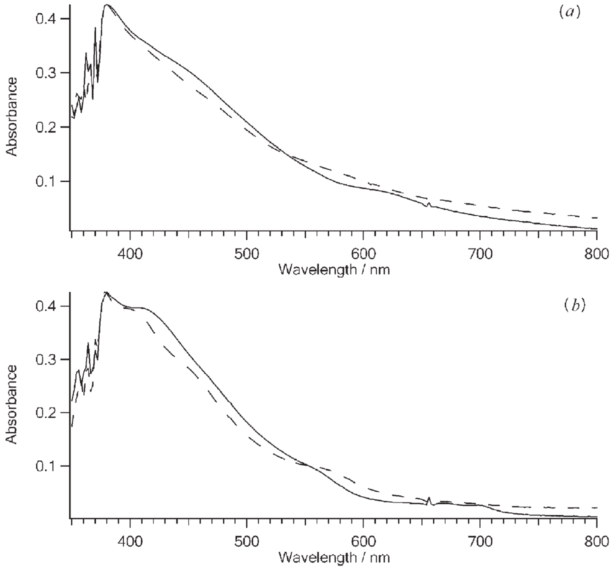


Fig. 5 UV–vis spectra (solvent: CS_2): (*a*) **1a** (solid line) and **2a** (dotted line); (*b*) **1b** (solid line) and **2b** (dotted line).

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Notes and references

‡ Er exists as isotopes ^{164}Er, ^{166}Er, ^{167}Er, ^{168}Er and ^{170}Er in natural abundances of 1.6, 33.4, 22.9, 27.1 and 14.9%, respectively. For details of computer simulations of the isotopic distribution see ESI.†

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