The influence of cage size on the reactivity of trimetallic nitride metallofullerenes: a mono- and bis-methanoadduct of $Gd_3N@C_{80}$ and a monoadduct of $Gd_3N@C_{84}$†

Manuel N. Chaur,[a] Frederic Melin,[a] Andreas J. Athans,[a] Bevan Elliott,[a] Kenneth Walker,[b] Brian C. Holloway[b] and Luis Echegoyen*[a]

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A reactivity study of the higher TNT EMFs of gadolinium is reported here showing that the reactivity substantially decreases when the fullerene cage gets larger.

The trimetallic nitride templated endohedral metallofullerenes (TNT EMFs) have emerged as unique compounds with a wide range of potential applications. Specifically, gadolinium nitride cluster fullerenes have proven to be better contrast agents for magnetic resonance imaging (MRI) than the Gd^{3+}-based complexes currently in commercial use.[1,2] The functionalization of TNT EMFs is a key requirement in order to take full advantage of these compounds for MRI applications. To date many different reactions have been reported for TNT EMFs of general formula $M_3N@C_{80}$, and these have led to completely characterized monoadducts.[3–11] In the case of $Gd_3N@C_{80}$ derivatives the characterization has been limited to mass spectrometry and HPLC.[12] Nothing is currently known about the reactivity of TNT EMFs with cages larger than C_{80} due to the scarce amounts of the larger metallofullerenes obtained during the arc synthesis. There is therefore great interest to understand how the reactivity of TNT EMFs is influenced by the size of the cage.

The C_{80}-I_h cage has two possible sites for addition reactions, at [5,6] and [6,6] double bonds. Previous studies in our group have shown that with $Sc_3N@C_{80}$ [5,6]-adducts are exclusively obtained, whereas $Y_3N@C_{80}$ and $Er_3N@C_{80}$ lead mainly to [6,6]-adducts, which in some cases can be further converted to [5,6]-adducts by heating.[6,7] More recently, Wang and co-workers have shown that [6,6]-adducts are also favored in the case of $Gd_3N@C_{80}$.[12b] Our group has also reported that the [5,6] and [6,6] derivatives exhibit different electrochemical properties and therefore electrochemistry can be used as a characterization tool to distinguish between the two isomers.[7]

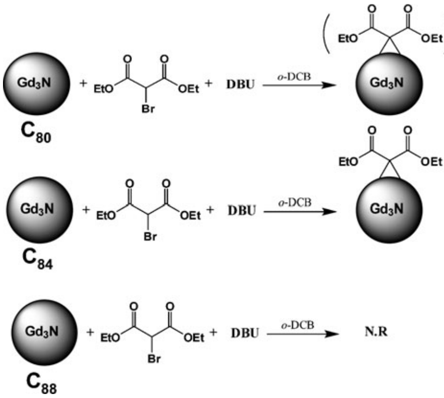
Here we report the first reactivity study of higher TNT EMFs. Specifically we compared the reactivity of $Gd_3N@C_{80}$, $Gd_3N@C_{84}$ and $Gd_3N@C_{88}$ in order to see how the cage-size affects the reactivity of the cyclopropanation reaction with bromomalonate (Bingel reaction).

The samples of $Gd_3N@C_{2n}$ ($2n$ = 80, 84, and 88) were synthesized, isolated, and purified as described before.[13] The [2 + 1] cycloaddition of bromodiethylmalonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature almost instantaneously afforded two highly stable products and several multiadducts of $Gd_3N@C_{80}$ (see Scheme 1). A monoadduct, $Gd_3N@C_{80}C(CO_2Et)_2$, and a bisadduct, $Gd_3N@C_{80}[C(CO_2Et)_2]_2$, were isolated and characterized by HPLC, mass spectrometry, UV-Vis-NIR, and cyclic voltammetry.

The malonate monoadduct was purified from the reaction mixture *via* silica gel column chromatography using CS_2–$CHCl_3$ (2 : 1) as eluent with further purification by HPLC (Buckyprep-M column, see Fig. 1). Finally the sample was analyzed by a Buckyclutcher column.

Due to the paramagnetic nature of the gadolinium metallofullerene we were unable to characterize the adducts by NMR spectroscopy. However, HPLC and mass spectroscopy reveal that a monoadduct was formed and cyclic voltammetry shows the same redox behavior as other [6,6] Bingel monoadducts reported previously (see Fig. 2).[7]

After purification through a one stage HPLC Buckyprep-M column, the bisadduct fraction of $Gd_3N@C_{80}$ was analyzed by Buckyclutcher and Buckyprep columns. Finally it was analyzed



Scheme 1 The [2 + 1] cycloaddition of bromodiethylmalonate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with $Gd_3N@C_{2n}$ (n = 40, 42 and 44) at room temperature.

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[a] *Department of Chemistry, Clemson University, Clemson, SC, USA. E-mail: luis@clemson.edu; Fax: +1 (864) 656 6613; Tel: +1 (864) 656 0778*
[b] *Luna Innovations, Inc. (nanoWorks division), 521 Bridge Street, Danville, Virginia, USA*

† Electronic supplementary information (ESI) available: MALDI-MS of malonate derivatives of $Gd_3N@C_{80}$ and $Gd_3N@C_{84}$, two-stage HPLC chromatogram of malonate bisadduct of $Gd_3N@C_{80}$, UV-Vis-NIR spectra of the functionalized derivatives of $Gd_3N@C_{80}$ and $Gd_3N@C_{84}$, and a table with their redox potentials. See DOI: 10.1039/b804847a

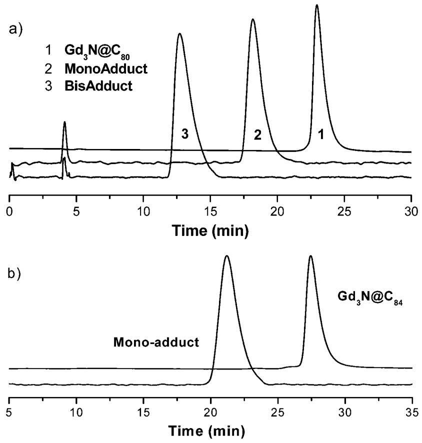

Fig. 1 HPLC chromatograms of (a) $Gd_3N@C_{80}$ before reaction and the isolated adducts (mono-adduct and bis-adduct) (b) $Gd_3N@C_{84}$ before and after reaction. Eluent: Toluene, flow rate: 4.0 mL min^{-1}, Buckyprep-M column. Detection: 372 nm.

by a linear combination of Buckyprep and Buckyprep-M columns, showing in every case a very narrow elution peak, indicating a surprising degree of isomeric purity (see Fig. 1 and supplementary information) which is in agreement with a very well defined CV obtained for this product (see Fig. 2). At the present time we are not able to establish specifically which regioisomer this compound corresponds to, but we feel confident that it is probably a single regioisomer and not a mixture.

We recently reported, in collaboration with Balch and Dorn, the X-ray crystal structure of $Gd_3N@C_{84}$, which possesses non-IPR symmetry with an egg-shape containing two adjacent pentagon rings at the pointed end.[14] It has been shown that the reactivity of fullerenes is determined by two factors. Bonds with high π orders are preferred as well as pyramidalized bonds. However, calculations suggest and X-ray data confirm that the pyramidalization is the most important factor in the determination of the most reactive sites for the additions.[8,15,16] For instance, C_{70} presents its most reactive bonds in the poles of the fullerene cage where the pyramidalization is higher.[17] In the case of $M_3N@C_{80}$ (M = Sc, Y and Er) it has been shown that the most pyramidalized C–C bonds are the most reactive ones.[8,15,16] For example, the D_{5h} isomer possesses greater reactivity than the I_h isomer due to its higher degree of pyramidalization.[8] The Gd_3N unit in $Gd_3N@C_{84}$ is oriented in such a way that one of its metallic ions is oriented toward the two fused pentagons.[14] This orientation makes the antiaromatic fused pentagon moiety more aromatic in character. Together with the already large degree of pyramidalization (compared with the other possible addition sites), this may make the [5,5] bond the most reactive double bond in the C_{84} cage.

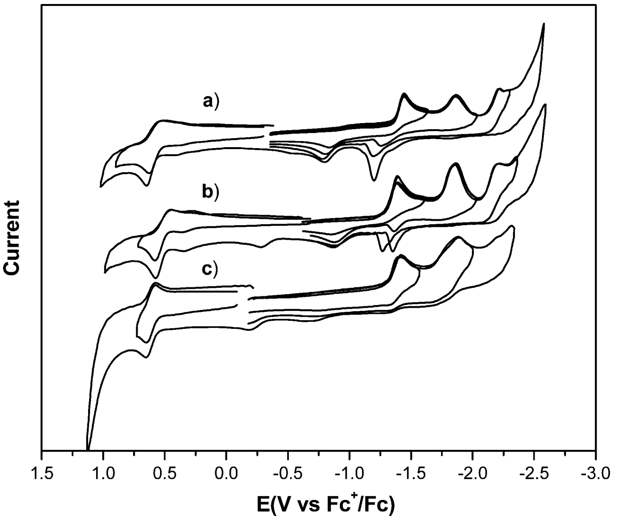

Fig. 2 Cyclic voltammograms of (a) $Gd_3N@C_{80}$, (b) [6,6] $Gd_3N@C_{80}C(CO_2Et)_2$ and (c) $Gd_3N@C_{80}[C(CO_2Et)_2]_2$ in NBu_4PF_6–*o*-DCB with ferrocene as internal standard, 100 mV s^{-1} scan rate.

The reaction of $Gd_3N@C_{84}$ under identical conditions as those described for $Gd_3N@C_{80}$ yielded only one product after 20 min of reaction at room temperature and no multiadducts were observed demonstrating its lower reactivity for the cyclopropanation reaction (see Scheme 1 and Fig. 1). Due to the paramagnetic character of the metallic cluster it was not possible to use NMR spectroscopy as a characterization technique to prove the site of addition. Interestingly, the cyclopropanation occurs at only one site on the cage, affording a single monoadduct. No further additions were found even after prolonged reaction times or elevated temperatures.

Perhaps the most surprising result was obtained when $Gd_3N@C_{88}$ was reacted. Despite its low HOMO–LUMO gap,[13] $Gd_3N@C_{88}$ showed no sign of reaction under the same conditions, even after a gradual increase of the temperature (up to 60 °C) and longer reaction time (5 h). This lower reactivity may be attributed to the lower degree of pyramidalization of this larger cage (see Scheme 1). According to these results $Gd_3N@C_{80}$ appears to be the most reactive metallofullerene in the family whereas $Gd_3N@C_{88}$ is completely unreactive under Bingel reaction conditions. Therefore there seems to be a gradual decrease in the reactivity of metallofullerenes as the size of the carbon cage increases.

Using DFT level calculations Dunsch and Popov[18] have shown that the most stable isomer for the $C_{88}{}^{6-}$ cage is the IPR D_2: 81 738, which is separated from other possible isomers by an energy gap of 70.6 kJ mol^{-1}, this isomer is the most stable for $Sc_3N@C_{88}$ and $Y_3N@C_{88}$. Therefore $M_3N@C_{88}$ metallofullerenes would have the same D_2 symmetry. By X-ray data Dorn, Balch and co-workers[19] showed that $Tb_3N@C_{88}$ possesses the D_2 symmetry. The C_{88} carbon cage appears to have a flattened shape and that could explain the lack of reactivity for $Gd_3N@C_{88}$ and the highly reactive behavior of the more curved shaped $Gd_3N@C_{80}$.

In addition to characterizing the adducts by HPLC and mass spectroscopy, UV-Vis-NIR spectra of the samples were taken in *o*-dichlorobenzene (*o*-DCB). The absorptions of the pristine samples did not seem to change after functionalization (see ESI†), even when two methano addends were present on the carbon cage, showing that the spherical chromophore is not significantly perturbed and that the derivatives are fulleroids.[10]

The electrochemistry of the $Gd_3N@C_{80}$ and $Gd_3N@C_{84}$ derivatives was carried out in *o*-DCB containing 0.05 M of NBu_4PF_6 as supporting electrolyte and using a 2 mm diameter glassy carbon disk as the working electrode. Ferrocene was added at the end of the experiments and used as a reference for measuring the potentials. The same conditions were used for the electrochemical studies of the non-derivatized $Gd_3N@C_{80}$ and $Gd_3N@C_{84}$ reported recently.[13]

The redox behavior of the mono methanofullerene derivatives of $Gd_3N@C_{80}$ (Fig. 2) is very similar to that of the [6,6]-methanofullerene derivatives of $Y_3N@C_{80}$ and $Er_3N@C_{80}$[7] with irreversible monoelectronic reductive steps and a reversible monoelectronic oxidative step. Previous studies with functionalized $Sc_3N@C_{80}$, $Y_3N@C_{80}$, and $Er_3N@C_{80}$ have invariably shown that the electrochemical behavior is highly dependent on the addition site, with [5,6] addends always exhibiting reversible reductive processes and [6,6] addends exhibiting irreversible reductions. Given that the observed electrochemical behavior for the monoadduct of $Gd_3N@C_{80}$ in the present case is essentially identical to that observed for all [6,6] monoadducts of trimetallic nitride endohedrals studied thus far, it seems reasonable to conclude that it is also a [6,6] adduct. In the case of a methano monoadduct on $Y_3N@C_{80}$, it was recently shown to be 'open' at the [6,6] ring junction,[10] a likely possibility for the present example based on the observed similarities.

The bisadduct of $Gd_3N@C_{80}$ exhibits a remarkably simple electrochemical response with well defined peaks (see Fig. 2); two clearly identified irreversible reductive steps and one reversible oxidative step. Based on previous work with bisadduct regioisomers of C_{60}, which exhibit very different electrochemical behavior,[20] the observed electrochemical response for this bisadduct indicates a high degree of regioisomeric purity, in agreement with the HPLC observations. Interestingly the addition of one and two methano addends to $Gd_3N@C_{80}$ (Table 1 of supporting information) does not systematically shift the reduction potentials cathodically, as observed for C_{60} derivatives.[20]

The CV of the methano derivative of $Gd_3N@C_{84}$ displays irreversible reduction steps and one reversible oxidation step, as in the unfunctionalized parent fullerene (see Fig. 3). Since there are no relevant electrochemical data reported, it is not possible to assign with confidence the site of addition based on the electrochemical results.

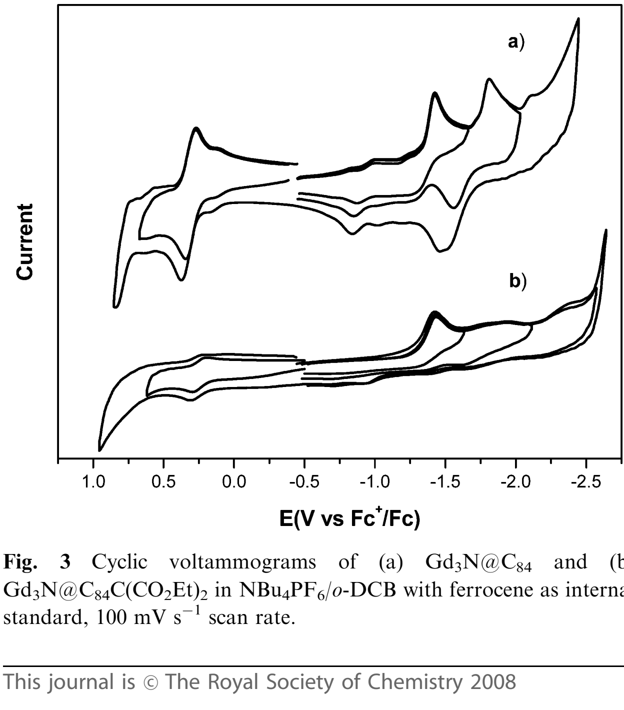

Fig. 3 Cyclic voltammograms of (a) $Gd_3N@C_{84}$ and (b) $Gd_3N@C_{84}C(CO_2Et)_2$ in NBu_4PF_6/*o*-DCB with ferrocene as internal standard, 100 mV s^{-1} scan rate.

Since, as mentioned before, the highly paramagnetic nature of the cluster prevented us from obtaining NMR spectra of these derivatives, the regiochemistry of the second group added to $Gd_3N@C_{80}$ and the addition site on $Gd_3N@C_{84}$ still need to be determined. Further characterization of the monoadducts of $Gd_3N@C_{80}$ and $Gd_3N@C_{84}$ and bisadduct of $Gd_3N@C_{80}$ including X-ray crystallography, is currently underway.

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