



Hemicarceplex Formation Allows Ready Identification of the Isomers of the Metallofullerene Sc₃N@C₈₀ Using ¹H and ¹³C NMR Spectroscopy

Journal:	<i>ChemComm</i>
Manuscript ID:	CC-COM-06-2014-004695.R1
Article Type:	Communication
Date Submitted by the Author:	28-Jul-2014
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Hemicarceplex Formation Allows Ready Identification of the Isomers of the Metallofullerene $\text{Sc}_3\text{N}@C_{80}$ Using ^1H and ^{13}C NMR Spectroscopy

Cite this: DOI: 10.1039/x0xx000000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx000000x

www.rsc.org/

A cyclotrimeratrylene-based molecular cage forms hemicarceplexes that significantly increase the solubility of commercially available $\text{Sc}_3\text{N}@C_{80}$ in CDCl_3 . When incarcerated within the molecular cage, the two structural isomers of this metallofullerene, $\text{Sc}_3\text{N}@D_{5h}\text{-C}_{80}$ and $\text{Sc}_3\text{N}@I_h\text{-C}_{80}$, displayed characteristic signals in both ^1H and ^{13}C NMR spectra, allowing direct identification of each isomer without the need to enrich the sample with ^{13}C atoms.

A metallofullerene is a molecule in which one or more metal atoms or ions is encapsulated within a fullerene cage.¹ Because $\text{M}@C_{60}$ and $\text{M}@C_{70}$ species are generally insoluble in the common fullerene solvents (e.g., CS_2 , toluene),² the most accessible metallofullerenes are generally those based on higher fullerenes, especially those incorporating trimetallic nitride clusters.³ Nevertheless, these higher fullerenes, which generally exhibit structural isomerism, also possess limited solubility in common organic solvents, making the purification and identification of isomerically pure metallofullerenes a challenging task, especially for lowly abundant metallofullerene isomers. For example, the D_{5h} structural isomer of $\text{Sc}_3\text{N}@C_{80}$ was identified four years after the discovery of its more abundant and more symmetrical I_h isomer.⁴ Because of their lack of hydrogen atoms, the ^1H NMR spectra of metallofullerenes are generally featureless; accordingly, ^{13}C NMR spectroscopy, a less sensitive technique, has become the most powerful tool for identifying isomeric fullerene cages.⁵ Previously, we demonstrated that the cyclotrimeratrylene (CTV)-based molecular cage **1** can form hemicarceplexes with C_{70} .⁶ We suspected that if similar complexes could be generated from metallofullerenes, the external host might “sense” structural differences among the incarcerated isomers and report them through ^1H NMR spectroscopy. Because the formation of hemicarceplexes⁷ would also enhance the solubility of metallofullerenes significantly, the acquisition of ^{13}C NMR spectroscopic data should be much more efficient, possibly eliminating the need to synthesize ^{13}C -enriched metallofullerenes to identify their structural isomers. Herein, we report a CTV-based

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molecular cage **2** that forms hemicarceplexes with commercially available $\text{Sc}_3\text{N}@C_{80}$, allowing simple and direct identification of its two structural isomers through observation of the characteristic signals of $(\text{Sc}_3\text{N}@D_{5h}\text{-C}_{80})@2$ and $(\text{Sc}_3\text{N}@I_h\text{-C}_{80})@2$ in both ^1H and ^{13}C NMR spectra.

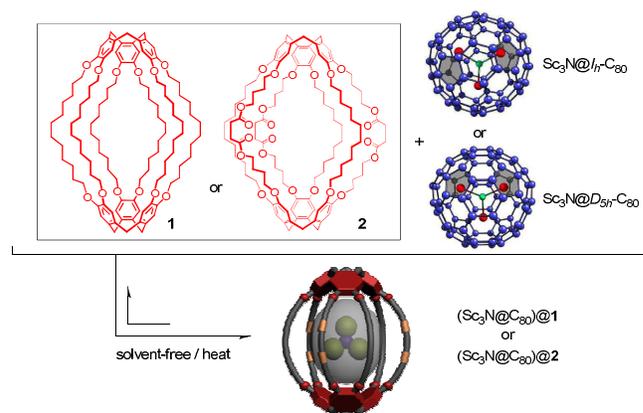


Figure 1. Formation of the hemicarceplexes $(\text{Sc}_3\text{N}@C_{80})@1$ and $(\text{Sc}_3\text{N}@C_{80})@2$ under solvent-free conditions.

Although the formation of the hemicarceplex $C_{70}@1$ can be achieved by heating a solution of C_{70} and the molecular cage **1** in $\text{CDCl}_2\text{CDCl}_2$ at 323 K for 12 h, the same conditions failed to give the desired hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@1$, presumably because $\text{Sc}_3\text{N}@C_{80}$ is more sizable than C_{70} and requires a higher activating energy to squeeze through the openings of the molecular cage **1**. Thus, we turned our attention to synthesizing the hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@1$ under solvent-free conditions.⁸ First, we ball-milled a solid mixture of $\text{Sc}_3\text{N}@C_{80}$ (5 mg) and the molecular cage **1** (20 mg) at a frequency of 20 Hz for 30 min and then we heated the mixture under Ar at 523 K for 12 h. Subsequent column chromatographic purification gave the desired hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@1$ in 34% yield. The ^1H NMR spectrum of this unique, Russian doll (*Matryoshka*)-like, multilayer, room temperature-isolable hemicarceplex features (Figure 2) two sets of signals at a ratio of approximately 4.6:1. Because slow rotation of the less-symmetrical $\text{Sc}_3\text{N}@C_{80}$ within the cavity of the highly symmetrical molecular cage **1** is very unlikely to result in such an integration ratio for the signals of the aromatic and benzylic protons of the CTV caps in ^1H NMR spectra recorded at room temperature at 800 MHz, we suspected that these two sets of signals represented

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† We thank the Ministry of Science and Technology (Taiwan) (NSC-102-2119-M-002-007) and National Taiwan University (NTU-102-R890913) for financial support.

two distinct hemicarceplexes: those in which the structural isomers of $\text{Sc}_3\text{N}@C_{80}$ ($\text{Sc}_3\text{N}@I_h\text{-}C_{80}$ and $\text{Sc}_3\text{N}@D_{5h}\text{-}C_{80}$) were each incarcerated within a unit of the molecular cage **1**. This assumption may, however, require further experimental support because the isomeric ratio of $\text{Sc}_3\text{N}@I_h\text{-}C_{80}$ and $\text{Sc}_3\text{N}@D_{5h}\text{-}C_{80}$ in an arced sample has been reported to be close to 9:1.^{4,9}

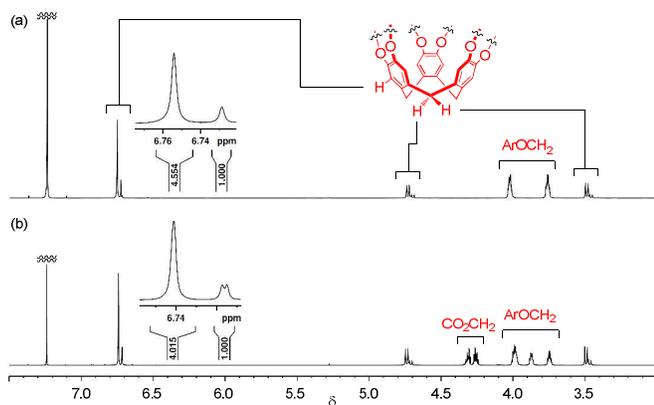


Figure 2. Partial ^1H NMR spectra (800 MHz, CDCl_3 , 298 K) of the hemicarceplexes (a) $(\text{Sc}_3\text{N}@C_{80})@1$ and (b) $(\text{Sc}_3\text{N}@C_{80})@2$.

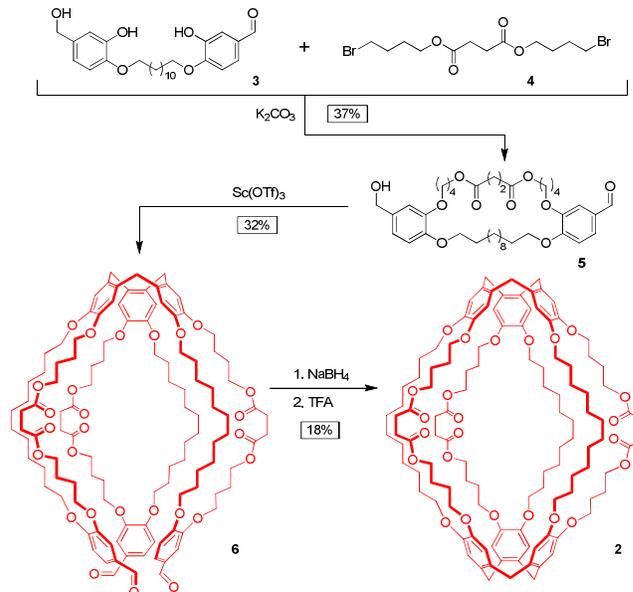
Because of their different molecular symmetries, $\text{Sc}_3\text{N}@I_h\text{-}C_{80}$ and $\text{Sc}_3\text{N}@D_{5h}\text{-}C_{80}$ can be differentiated simply by counting the number of signals in their respective ^{13}C NMR spectra.⁴ Thus, to correlate the two sets of ^1H NMR signals to the hemicarceplexes $(\text{Sc}_3\text{N}@D_{5h}\text{-}C_{80})@1$ and $(\text{Sc}_3\text{N}@I_h\text{-}C_{80})@1$, it was necessary for us to demonstrate the existence of two characteristic sets of signals belonging to $I_h\text{-}$ and $D_{5h}\text{-}C_{80}$ in the ^{13}C NMR spectrum of $(\text{Sc}_3\text{N}@C_{80})@1$; moreover, we would expect the integration ratio of these two sets of signals, when applying both inverse gated decoupling and a long relaxation delay during the acquisition to allow signal quantification,¹⁰ to be reasonably close to that in the ^1H NMR spectrum. Unfortunately, although the formation of $(\text{Sc}_3\text{N}@C_{80})@1$ did increase the solubility of $\text{Sc}_3\text{N}@C_{80}$ in CDCl_3 by approximately 50-fold (from 0.07 to 3.35 mg mL^{-1} ; Table 1), it remained insufficient to allow processing of a quantifiable ^{13}C NMR spectrum within a reasonable period of time. Therefore, to obtain even greater solubility in CDCl_3 , we prepared the hemicarceplex from $\text{Sc}_3\text{N}@C_{80}$ and the molecular cage **2**, which features succinic diester units within three of its six linkages.

Table 1. Solubility of $\text{Sc}_3\text{N}@C_{80}$ and its hemicarceplexes in CDCl_3 .

	MW	solubility ^a (hemicarceplex)	solubility ^b ($\text{Sc}_3\text{N}@C_{80}$)
$\text{Sc}_3\text{N}@C_{80}$	1110	–	0.07
$(\text{Sc}_3\text{N}@C_{80})@1$	2840	8.57	3.35
$(\text{Sc}_3\text{N}@C_{80})@2$	3020	43.06	15.82

^a Units: mg mL^{-1} . ^b Including both free and complexed forms of $\text{Sc}_3\text{N}@C_{80}$.

We synthesized the molecular cage **2** in four steps from the triol **3** (Scheme 1). Alkylation of the phenol groups of **3** with bis(4-bromobutyl)succinate (**4**) in the presence of a weak base (K_2CO_3) gave the macrocyclic alcohol **5**. A $\text{Sc}(\text{OTf})_3$ -catalyzed condensation joined together three units of the alcohol **5** into a CTV core, affording the trialdehyde **6**; subsequent reduction to the triol, followed by condensation under acidic conditions, afforded the molecular cage **2** (overall yield: 2.1%).



Scheme 1. Synthesis of the molecular cage **2**.

Because the three succinic diester linkages of the molecular cage **2** are longer than the alkyl linkages of **1**, the openings in the former are larger than those in the latter. This feature was manifested by our success at isolating $(\text{Sc}_3\text{N}@C_{80})@2$ (3 mg, 16% yield) from a mixture of $\text{Sc}_3\text{N}@C_{80}$ (12 mg) and the molecular cage **2** (12 mg) in $\text{CDCl}_2\text{CDCl}_2$ (2 mL) that had been heated at 323 K for 50 h. We were also able to obtain this hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@2$ in 28% yield (3.9 mg) after concentrating a suspension of $\text{Sc}_3\text{N}@C_{80}$ (5 mg) and **2** (20 mg) in CH_2Cl_2 (2 mL) and CS_2 (2 mL) and then heating the resulting solid under vacuum at 453 K for 12 h.¹¹

We grew single crystals suitable for X-ray crystallography through liquid diffusion of hexanes into a CH_2Cl_2 solution of the hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@2$. The solid state structure of $(\text{Sc}_3\text{N}@C_{80})@2$ reveals¹² the incarceration of Sc_3N within the closed C_{80} shell, which is itself incarcerated within the molecular cage **2**—a structure akin to the multilayer host/guest alignment in a Russian doll (Figure 3).¹³

Gratifyingly, the ^1H NMR spectrum of the hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@2$ also displayed two sets of signals with an integration ratio of approximately 4.0:1—reasonably close to the ratio we observed for the hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@1$. As revealed in Table 1, the solubility of the hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@2$ in CDCl_3 was approximately five times higher than that of $(\text{Sc}_3\text{N}@C_{80})@1$ in the same solvent. Indeed, the amount of $\text{Sc}_3\text{N}@C_{80}$ that could be taken up into CDCl_3 in the form of the hemicarceplex $(\text{Sc}_3\text{N}@C_{80})@2$ was approximately 200 times greater than that of the metallofullerene in its free state—a significant factor allowing us to obtain high-quality, quantifiable ^{13}C NMR spectra within a reasonable period of time.

As expected, the quantifiable ^{13}C NMR spectrum of $(\text{Sc}_3\text{N}@C_{80})@2$ featured two sets of signals that we could correlate to the hemicarceplexes of $\text{Sc}_3\text{N}@D_{5h}\text{-}C_{80}$ and $\text{Sc}_3\text{N}@I_h\text{-}C_{80}$ (Figure 4).¹⁴ The ratio of the integrated areas under the two intense signals at δ 136.1 and 143.3 and the six relatively weaker signals at δ 134.2, 137.4, 138.1, 142.7, 143.6, and 147.4, assigned to incarcerated $\text{Sc}_3\text{N}@I_h\text{-}C_{80}$ and $\text{Sc}_3\text{N}@D_{5h}\text{-}C_{80}$, respectively, was 4.04:1—a good match with the value determined from the ^1H NMR spectrum of the

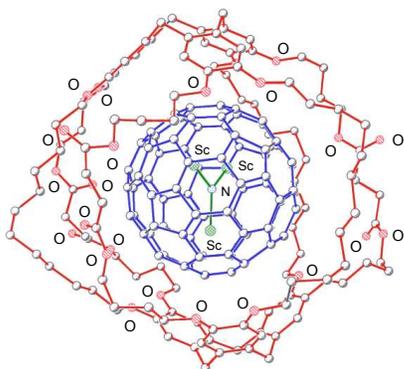


Figure 3. Ball-and-stick representation of the solid state structure of the hemicarceplex ($\text{Sc}_3\text{N}@C_{80}$)@2.

hemicarceplex ($\text{Sc}_3\text{N}@C_{80}$)@2. A closer look at the signals of the aromatic carbon nuclei of the CTV caps in the hemicarceplex ($\text{Sc}_3\text{N}@C_{80}$)@2 also revealed two sets of signals, each with an integration ratio of approximately 4:1 (insets to Figure 4), indicating that the host's two CTV units, which presumably underwent π -stacking with the metallofullerene units, could differentiate between the structural isomers of the guest in both the ^1H and ^{13}C NMR spectra.

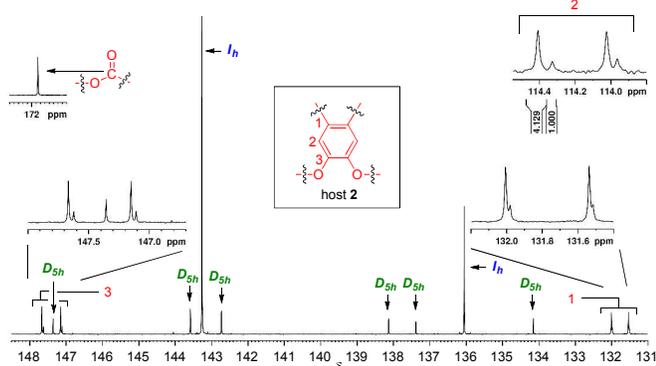


Figure 4. Partial ^{13}C NMR spectrum (200 MHz, CDCl_3 , 298 K) of the hemicarceplex ($\text{Sc}_3\text{N}@C_{80}$)@2.

We have demonstrated that, by generating corresponding hemicarceplexes, the existence of two structural isomers of $\text{Sc}_3\text{N}@C_{80}$ can be readily identified through ^1H NMR spectroscopy. Because the solubilities of the metallofullerene isomers in CDCl_3 are significantly greater in their hemicarceplexes than in their free states, we could identify both the I_h and D_{5h} forms using common ^{13}C NMR spectroscopy. We believe that this method will be useful in future for discovering and identifying less-abundant metallofullerene isomers as well as highly insoluble “missing” metallofullerenes.

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- M. R. Cerón, F.-F. Li and L. Echegoyen, *Chem. Eur. J.* 2013, **19**, 7410. To determine the isomeric ratio of the commercial $\text{Sc}_3\text{N}@C_{80}$ sample (SES Research), we used a Cosmosil-packed 5PPB analytical column (4.6×250 mm; mobile phase, toluene; UV detection, 285 nm; elution rate, 0.3 mL min^{-1}). Although integration of the HPLC signals of $\text{Sc}_3\text{N}@C_{80-I_h}$ and $\text{Sc}_3\text{N}@C_{80-D_{5h}}$ gave an isomeric ratio of approximately 2.8:1, there was great overlap of the two signals; that is, this ratio should be considered as only a very rough estimation. Therefore, it is too early for us to draw any conclusions regarding whether the host 1 exhibits any selectivity toward the incarceration of either of the two isomers of $\text{Sc}_3\text{N}@C_{80}$.
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- Our efforts at separating ($\text{Sc}_3\text{N}@C_{80-I_h}$)@2 and ($\text{Sc}_3\text{N}@C_{80-D_{5h}}$)@2 through HPLC using Cosmosil 5-PPB (eluent: toluene) and SunFire Silica [eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99.6:0.4), $\text{CHCl}_3/\text{MeOH}$ (99.7:0.3), and hexanes/EtOAc (8:2)] columns were unsuccessful, presumably because the interactions of the external CTV cages with the column-packing materials were influenced only weakly, or not at all, by the small structural differences of the metallofullerene isomers.
- Crystal data for ($\text{Sc}_3\text{N}@C_{80}$)@2: [$\text{C}_{194}\text{H}_{156}\text{O}_{24}\text{Sc}_3\text{N}$]; $M_r = 3020.08$; triclinic; space group $P-1$; $a = 17.8883(3)$; $b = 18.2158(3)$; $c = 28.6383(3)$ Å; $V = 7875.6(2)$ Å³; $\rho_{\text{calc}} = 1.274 \text{ g cm}^{-3}$; $\mu(\text{MoK}\alpha) = 0.198 \text{ mm}^{-1}$; $T = 120(2)$ K; brown plates; 34,755 independent measured reflections; F_2 refinement; $R_1 = 0.1337$; $wR_2 = 0.3244$. The program PLATON/SQUEEZE was applied to account for the residual electron density. CCDC-978461 contains the supplementary crystallographic data for this study.
- We suspect that the crystal selected for X-ray analysis very unlikely contained solely the major hemicarceplex ($\text{Sc}_3\text{N}@C_{80-I_h}$)@2. The minor isomer ($\text{Sc}_3\text{N}@C_{80-D_{5h}}$)@2 would, however, contribute significantly weaker electron density compared to the major isomer in the X-ray scattering. In some regions the electron density of the two isomers may overlap, thereby complicating the data resolving process. To simplify data analysis, we resolved the incarcerated $\text{Sc}_3\text{N}@C_{80}$ solely based on the I_h -symmetry; such a simplification was, in part, responsible for the relatively high values of R_1 and wR_2 in the crystal data.
- We collected 932 scans for the spectrum using an inverse gated decoupling pulse sequence at 30° with a relaxation delay of 30 s to ensure that we could obtain quantitative information. Exponential multiplication of $\text{LB} = 1$ was applied prior to Fourier transformation.