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Tuning the Selectivity of Gd_3N Cluster Endohedral Metallofullerene Reactions with Lewis Acids

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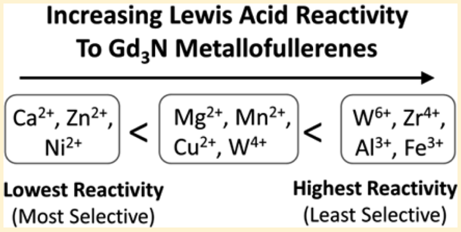
Supporting Information



ABSTRACT: We demonstrate the manipulation of the Lewis acid strength to selectively fractionate different types of Gd_3N metallofullerenes that are present in complex mixtures. Carbon disulfide is used for all Lewis acid studies. $CaCl_2$ exhibits the lowest reactivity but the highest selectivity by precipitating only those gadolinium metallofullerenes with the lowest first oxidation potentials. $ZnCl_2$ selectively complexes $Gd_3N@C_{88}$ during the first 4 h of reaction. Reaction with $ZnCl_2$ for an additional 7 days permits a selective precipitation of $Gd_3N@C_{84}$ as the dominant endohedral isolated. A third fraction is the filtrate, which possesses $Gd_3N@C_{86}$ and $Gd_3N@C_{80}$ as the two dominant metallofullerenes. The order of increasing reactivity and decreasing selectivity (left to right) is as follows: $CaCl_2 < ZnCl_2 < NiCl_2 < MgCl_2 < MnCl_2 < CuCl_2 < WCl_4 \ll WCl_6 < ZrCl_4 < AlCl_3 < FeCl_3$. As a group, $CaCl_2$, $ZnCl_2$, and $NiCl_2$ are the weakest Lewis acids and have the highest selectivity because of their very low precipitation onsets, which are below +0.19 V (i.e., endohedrals with first oxidation potentials below +0.19 V are precipitated). For $CaCl_2$, the precipitation threshold is estimated at a remarkably low value of +0.06 V. Because most endohedrals possess first oxidation potentials significantly higher than +0.06 V, $CaCl_2$ is especially useful in its ability to precipitate only a select group of gadolinium metallofullerenes. The Lewis acids of intermediate reactivity (i.e., precipitation onsets estimated between +0.19 and +0.4 V) are $MgCl_2$, $MnCl_2$, $CuCl_2$, and WCl_4. The strongest Lewis acids (WCl_6, $ZrCl_4$, $AlCl_3$, and $FeCl_3$) are the least selective and tend to precipitate the entire family of gadolinium metallofullerenes. Tuning the Lewis acid for a specific type of endohedral should be useful in a nonchromatographic purification method. The ability to control which metallofullerenes are permitted to precipitate and which endohedrals would remain in solution is a key outcome of this work.

■ INTRODUCTION

The emergence of endohedral gadolinium metallofullerenes for medical applications[1−11] has led to a desire for their isolation. Unfortunately, gadolinium soot extracts prepared under a typical dinitrogen/helium electric arc often produce complex mixtures that contain >50 types of empty-cage fullerenes (e.g., C_{60}, C_{70}, C_{76}, and C_{84}), metallofullerenes with different types of endohedral clusters (e.g., Gd, Gd_2, Gd_3, Gd_2C_2, and Gd_3N), and also their structural isomers.

High-performance liquid chromatography (HPLC) has been the conventional method for endohedral separations, but chromatography is impractical given their poor solubility, low throughput, expense of solvents and waste, and difficulty resolving coeluting[12] species.

To avoid HPLC purification, scientists have looked at nonchromatographic methods for fullerene separations. In 1994, Olah et al.[13] used $AlCl_3$ as a Lewis acid to purify C_{60} from soot extract that contained only empty-cage fullerenes. Soot extract becomes further complicated by the cosynthesis of metallofullerenes and fullerenes. In 2009, Stevenson et al.[14] investigated $AlCl_3$ for metallofullerene separations. The selectivity was sufficient to separate $Sc_3N@C_{68}$, $Sc_3N@C_{78}$, and $Sc_4O_2@C_{80}$ endohedrals from contaminant endohedrals ($Sc_3N@C_{80}$) and empty-cage fullerenes, whose presence dominated the fullerene distribution in the extract.[14]

In 2012, Shinohara et al.[15,16] used $TiCl_4$ to separate monometallic ($M@C_{2n}$), dimetallic ($M_2@C_{2n}$), and carbide ($M_2C_2@C_{2n}$) endohedrals. In 2013, Shinohara et al. extended their use of $TiCl_4$ as a precipitating agent toward CF_3-functionalized $Y@C_{2n}$ derivatives.[17] In 2013, further selectivity was achieved by Stevenson and Rottinger,[18] who discovered that $CuCl_2$ lowered the precipitation threshold to permit resolution among erbium endohedral isomers ($Er_2@C_{82}$) and selective precipitation of scandium nitrides ($Sc_3N@C_{78}$) and oxides ($Sc_4O_2@C_{80}$) from fellow endohedrals, such as $Sc_3N@C_{68}$ and $Sc_3N@C_{80}$.[18]

Non-Lewis acid approaches were also being developed. Other reactivity-based, nonchromatographic approaches for separating endohedrals include electrochemical reduction,[19,20] chemical redox recovery,[21,22] chemical oxidation,[23,24] host−guest complexation,[12,25−27] and reactive supports.[28−32]

Narrowing the focus to nonchromatographic methods specifically for $Gd_3N@C_{2n}$ endohedrals, there is a paucity of

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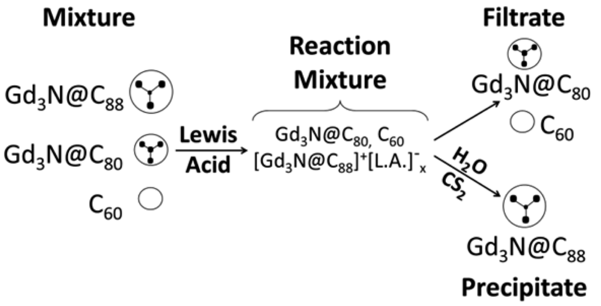
literature. The little work in this area has been the chemical-based separation of $Gd_3N@C_{80}$, which can be obtained by the reaction of gadolinium extract from cyclopentadiene-immobilized resin[33] or aminosilica.[28]

In contrast, this work represents initial research toward a nonchromatographic isolation of Gd_3N clusters entrapped within carbon cages beyond 82 atoms (i.e., $Gd_3N@C_{84-88}$). Manipulating the reactivity differences to fractionate these endohedrals minimizes the role of HPLC not just for $Gd_3N@C_{80}$ but also for gadolinium endohedrals with larger cages, such as $Gd_3N@C_{84}$ and $Gd_3N@C_{88}$.

Because empty-cage fullerenes lack an entrapped metal atom(s) to transfer the electron density to the carbon cage, their chemical reactivity is significantly different in comparison to gadolinium endohedrals. Because gadolinium and Gd_3N metallofullerenes do possess a charge transfer[34,35] from the encapsulated cluster to the cage, the electron-rich carbon surface should be prone to reactivity with Lewis acids.[14−16,18]

As we pursue nonchromatographic methods for isolating gadolinium endohedrals of various cage sizes (e.g., $Gd_3N@C_{80-92}$), we can now report our first step toward the ability to tune the Lewis acid strength to selectively fractionate Gd_3N metallofullerenes in mixtures. This strategic manipulation of the Lewis acid reactivity should open the door to future nonchromatographic methods to purify these valuable medical agent precursors (e.g., $Gd_3N@C_{80}$ and $Gd_3N@C_{88}$). Scheme 1 shows an overview of the Lewis acid approach to selectively separate higher cage $Gd_3N@C_{2n}$ species (e.g., $Gd_3N@C_{88}$) from the dominant $Gd_3N@C_{80}$ and empty-cage fullerenes.

Scheme 1. Reactivity of a Gadolinium Metallofullerene Mixture with Lewis Acids[a]



[a] L.A. = Lewis acid; *x* = number of Lewis acid groups on the cage surface.

The results reported herein also impact emerging separation method development for the nonchromatographic isolation of other M_3N endohedrals (e.g., $Er_3N@C_{80}$, $Lu_3N@C_{80}$, and $Sc_3N@C_{80}$). Increased sample availability will spur application development for these non-Gd_3N cluster endohedral metallofullerenes.

The ultimate goal would be an array of Lewis acids, each of which has a slightly higher precipitation onset, for use in a nonchromatographic separation method. Studies are currently underway for incorporating the results from this work into a new purification method. Complexation and decomplexation of endohedrals with Lewis acids are solvent-dependent, and carbon disulfide was selected for all Lewis acid experiments. Xylenes were used for the stir and filter approach (SAFA) with aminosilica.

EXPERIMENTAL SECTION

Synthesis of Soot Extract. Gadolinium soot extract was synthesized from an electric-arc generator. Carbon, Gd_2O_3, and copper metal were vaporized under a helium/dinitrogen atmosphere. The soot was extracted with an organic solvent (e.g., xylene), and gadolinium endohedral samples were readily obtained.[35,36]

SAFA. The monoaminosilica gel (MASG) was synthesized in accordance with our previous work.[31,32] The importance of using vacuum-dried aminosilica and avoiding "wet" solvents for SAFA experiments is described elsewhere.[29] In this research, a 150 g sample of aminosilica gel was vacuum-dried for a minimum of 6 h at 65 °C. Upon cooling to room temperature and repressurization of the vacuum oven with dinitrogen or argon, the aminosilica gel was quickly transferred from the oven to a stirring solution of 3000 mg of gadolinium extract in 3000 mL of freshly purchased xylenes, which was used directly from the manufacturer. The SAFA reaction time was 39 h.

Lewis Acid Reactions. The Lewis acids were freshly purchased in powder form and used directly from the manufacturer to minimize the use of chloride reagents with older shelf lives. Equimolar amounts of Lewis acids were used so direct comparisons of their reactivity differences could be made.

The amounts of added Lewis acids for round 1 and 2 precipitation experiments respectively were as follows: $CaCl_2$ (76 mg, 226 mg); $ZnCl_2$ (92 mg, 288 mg); $NiCl_2$ (88 mg, 264 mg); $MgCl_2$ (65 mg, 193 mg); $MnCl_2$ (100 mg, 300 mg); $CuCl_2$ (91 mg, 274 mg); WCl_4 (222 mg, 665 mg); WCl_6 (270 mg, 809 mg); $ZrCl_4$ (158 mg, 475 mg); $AlCl_3$ (91 mg, 270 mg); $FeCl_3$ (110 mg, 331 mg). Each Lewis acid experiment began (i.e., Round 1) with a solution containing 100 mL of newly purchased CS_2 to dissolve 100 mg of an enriched gadolinium metallofullerene mixture that was obtained via the SAFA precleanup method (Figure 1b).

Decomplexation of the precipitated endohedrals was performed with ice water and CS_2 as previously described.[14,18] After stirring for at least 1 h, the CS_2/H_2O mixture was poured into a separatory funnel. Upon decomplexation, the endohedrals are transferred and dissolved in CS_2, which is the bottom layer.

Because the focus of the work is reactivity comparisons, an emphasis on the quantitative recovery of endohedrals among the various precipitates was not in the scope of this study. The experiments with Lewis acids were reproducible and showed similar soluble and insoluble fullerene distributions.

Mass Spectrometry. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) in the positive-ion mode was performed with a Bruker Microflex LT mass spectrometer. Samples were spotted onto a stainless steel plate, and a matrix was not used. Care was taken to avoid the use of excessive laser power during analysis.

RESULTS AND DISCUSSION

Stage 1: Selective Immobilization of Contaminant Gadolinium Endohedrals onto Aminosilica. In the design of our experiments to probe the relative reactivity of $Gd_3N@C_{2n}$ endohedrals with Lewis acids, we prepared a more "simplified" mixture from the soot extract. The typical gadolinium metallofullerene extract is prepared under dinitrogen and helium and contains a highly complex mixture of empty-cage fullerenes (C_{2n}) and endohedrals of various cages sizes and cluster types (e.g., M, M_2, M_3, M_3C_2, and M_3N).

Because the focus of this paper is $M_3N@C_{2n}$ species, we desired to remove the majority of non-$M_3N@C_{2n}$ contaminant cluster types and larger empty-cage fullerenes beyond C_{70}. Their removal is accomplished with SAFA, which we previously reported[28,31,32] as a novel, nonchromatographic method to isolate $M_3N@C_{80}$ endohedrals from soot extract. However, the focus of that work was the immobilization of all fullerene and endohedral metallofullerenes onto diaminosilica gel (DASG), with the exception of the most inert compound, $M_3N@I_h\text{-}C_{80}$, where M = Er and Sc, which remained unreactive and purified from this SAFA process.[29,31,32]

Herein, we switch from DASG to the less reactive, MASG, which is sufficiently reactive[28] to remove most gadolinium contaminant species yet mild enough to permit the family of $Gd_3N@C_{2n}$ compounds to remain in solution during the SAFA reaction. Hence, these $Gd_3N@C_{2n}$ family members are found in the filtrate upon conclusion of SAFA.

To achieve this simplified SAFA sample of endohedrals for Lewis acid studies, the arc-produced gadolinium extract was dissolved in xylenes (see the Experimental Section). During stirring, 150 g of fresh, vacuum-dried MASG was added. Upon reaction for 39 h, the slurry was filtered and the solvent removed, and 2 g of a simplified extract was obtained. A mass spectral comparison of the samples before and after treatment of the extract with MASG is shown in Figure 1.

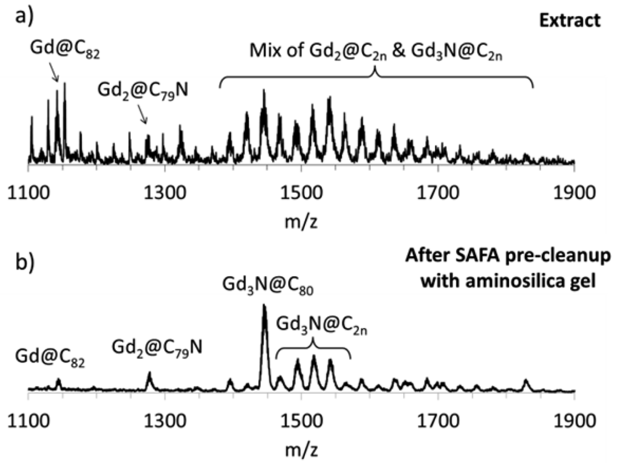


Figure 1. MALDI comparison of extract (a) before and (b) after the SAFA method.

Stage 2: Selective Reactivity of Gadolinium Endohedrals by Varying the Lewis Acid Strength. In 2009, Stevenson et al.[14] used $AlCl_3$ and $FeCl_3$ on scandium soot extracts to separate scandium endohedrals from empty-cage fullerenes. In 2012, Akiyama et al.[15,16] reported the use of $TiCl_4$ on gadolinium, lutetium, and thulium extracts, and a correlation was made between the first oxidation potential of a metallofullerene versus the precipitation onset inherent to the Lewis acid. For example, the precipitation threshold for $TiCl_4$ was reported as 0.62−0.72 V. Hence, a metallofullerene with a first oxidation potential below +0.62 V would complex with $TiCl_4$ and then precipitate from solution.

Selected first oxidation potentials of several key endohedrals are provided in Table 1. Note that $FeCl_3$, $AlCl_3$, and $TiCl_4$ possess precipitation thresholds above +0.6 V. The ability of these three "high strength" Lewis acids to precipitate the bulk of gadolinium metallofullerenes is consistent with our experimental findings as described below.

Table 1. Summary of First Oxidation Potentials for Selected Empty-Cage and Gadolinium Endohedral Metallofullerenes

fullerene	$E_{1/2}$, ox-I (V, Fc/Fc$^+$)	ref
C_{60}	+1.21	46
C_{70}	+1.19	46
C_{76}	+0.81	46
C_{82}-C_2	+0.72	46
$Gd_3N@I_h$-C_{80}	+0.58	45
$Gd_2@I_h$-$C_{79}N$	+0.51	47
$Gd_3N@C_2$-C_{78}	+0.47	48
$Gd_3N@C_s$-C_{82}	+0.37	43
$Gd_3N@D_3$-C_{86}	+0.35	43
$Gd_3N@C_s$-C_{84}	+0.32	45
$Gd@C_{2v}$-C_{82}	+0.09	46
$Gd_3N@D_2$-C_{88}	+0.06	45

Also of significance in Table 1 is the very low first oxidation potential for $Gd_3N@C_{88}$ (+0.06 V) in comparison to other $Gd_3N@C_{80-86}$ (+0.32−0.58 V) endohedrals. This much lower first oxidation potential for $Gd_3N@C_{88}$ was attributed to its two reversible oxidation processes, as reported by Echegoyen et al., who performed extensive electrochemical measurements for Gd_3N and other rare-earth M_3N endohedrals.[37−45] Their studies indicate that $Gd_3N@C_{80-88}$ metallofullerenes have similar reduction potentials.[38] However, for oxidation processes, which were mainly localized on the cage surface, $Gd_3N@C_{88}$ has two reversible oxidation potentials.[38] This feature makes $Gd_3N@C_{88}$ unique among the $Gd_3N@C_{2n}$ family members. It is this surprisingly low first oxidation potential for $Gd_3N@C_{88}$ that will be used to manipulate its separation from other fullerenes.

In 2013, Stevenson and Rottinger[18] discovered that $CuCl_2$ could strategically decrease the endohedral precipitation onset from +0.62 to +0.19 V. The benefit of decreasing the threshold was improved selectivity because the selective precipitation of endohedrals below +0.19 V served as a new separation approach for separating $Er_2@C_{82}$ structural isomers and fractionating metallic oxide, metallic carbide, and metallic nitride scandium endohedrals.[18] In contrast, metallofullerenes and empty-cage fullerenes having first oxidation potentials above +0.19 V would remain in solution. The ability of $CuCl_2$ to subdivide the metallofullerene family into multiple fractions represented a key advance in the pursuit of a nonchromatographic separation method. Because $CuCl_2$ also exhibited selectivity for scandium and erbium endohedrals,[18] this Lewis acid was chosen for this study to evaluate its reactivity with gadolinium metallofullerenes.

A goal of this work was to seek Lewis acids with a variety of precipitation thresholds. We hypothesized that other Lewis acids, such as those reported herein, would possess precipitation thresholds either below +0.19 ($CuCl_2$) or within the range of +0.19 to +0.6 V. For example, finding a Lewis acid with an onset <0.19 V would provide even better selectivity than $CuCl_2$ because fewer gadolinium endohedrals would be sufficiently reactive.

Note the similarity of first oxidation potentials for $Gd@C_{82}$ (+0.09 V) and $Gd_3N@C_{88}$ (+0.06 V). Both of these endohedrals readily precipitate with most Lewis acids so it would be difficult to find an effective Lewis acid approach that could be selective enough to separate these two species. To avoid this coprecipitation problem with Lewis acids, we first used SAFA on the extract to largely remove $Gd@C_{82}$ as a precleanup step. Indeed, Figure 1 demonstrates the successful immobilization and removal of $Gd@C_{82}$ from solution. It was this SAFA filtrate (i.e., unreactive to aminosilica) that was used for our Lewis acid study. Hence, there was only a trace of surviving $Gd@C_{82}$ available to interfere in subsequent experiments with our selected 11 Lewis acids. For this reason, our MALDI mass spectra in Figures 2−5 show only traces of $Gd@C_{82}$.

For those scientists interested in the monometallic endohedrals (e.g., $M@C_{82}$), recent studies have focused on their recovery from Lewis acid complexes.[15,16] Similar to $Gd@C_{82}$, the $La@C_{82}$ species also has a comparable low first oxidation potential (+0.07 V). Recent work with $La@C_{82}$ reactions with Lewis acids and solvents shows that the recovery of decomplexed $La@C_{82}$ was related to the reaction time, solvent, and Lewis acid.[15,16] The percent recovery of $La@C_{82}$ from its Lewis acid complex ranged from 10% to 100%, depending on these variables. They reported a high recovery of $La@C_{82}$ with $TiCl_4$, a Lewis acid that was not used in this study.[15,16] On the basis of inductively coupled plasma atomic emission spectrometry results from $Y@C_{82}$, $La@C_{82}$, and $Gd@C_{82}$, the number of $TiCl_4$ Lewis acid groups on the cage surface was estimated at 18−19.[15,16] The precipitation of endohedrals occurs when a sufficient number of Lewis acid groups attach onto the cage. Because the focus of this work was not $M@C_{82}$ but rather $M_3N@C_{2n}$, we investigated other Lewis acids that were targeted for finding the selectivity among various kinds of $M_3N@C_{2n}$ (i.e., trimetallic nitride) species.

Weakest Lewis Acids (Precipitation Thresholds < 0.19 V). In our experimental design, the choices of 4 h and 7 days were made as a compromise between the strongest and weakest Lewis acids. For the extremely weak Lewis acids, we needed 7 days to ensure sufficient opportunity to exhibit reactivity. The 4 h time frame was chosen to demonstrate the selectivity of Lewis acid−endohedral precipitation that is obtained in this relatively short reaction time.

Our initial efforts focused on finding a Lewis acid(s) with a lower strength (i.e., lower precipitation threshold) than $CuCl_2$. Of the compounds investigated, the two weakest Lewis acids were $CaCl_2$ and $ZnCl_2$, and these chlorides were the most selective of the 11 Lewis acids.

For example, 100 mg of a simplified metallofullerene extract (Figure 1b) was dissolved in 100 mL of carbon disulfide. During stirring, 76 mg of $CaCl_2$ was added, and the reaction was allowed to proceed for 4 h. After filtration, a decomplexation step for the recovery of metallofullerenes and fullerenes from the precipitate was performed.[14] Figure 2a shows the MALDI mass spectrum of the recovered endohedrals (round 1 precipitate). These data indicate the presence of primarily large-molecular-weight $Gd_2@C_{2n}$ endohedrals.

For a second round of reactions, an additional 226 mg of $CaCl_2$ was added to the filtrate, and the reaction proceeded for a much longer time (7 days) to permit sufficient time for a slow reaction. A MALDI mass spectrum corresponding to the precipitate that was decomplexed for 7 days is shown in Figure 2b. Analysis of this round 2 precipitate indicates the emergence and prominence of $Gd_3N@C_{88}$, along with a trace of residual $Gd_2@C_{2n}$ contaminants. This selective precipitation is consistent with the extremely low first oxidation potential for $Gd_3N@C_{88}$ (+0.06 V; Table 1) compared to other Gd_3N endohedrals and empty-cage fullerenes.

The filtrate, obtained after 7 days, represents "unreacted" fullerenes and resistant endohedrals that did not precipitate. Shown in Figure 2c is the filtrate's mass spectrum, which shows a small amount of residual $Gd_3N@C_{88}$, the bulk of empty-cage fullerenes, and the desired family of $Gd_3N@C_{80-88}$ species. Also present is $Gd_2@C_{79}N$ azametallofullerene, whose first oxidation potential is +0.51 V, a value that is rather large compared to most gadoliniun endohedrals and almost as high as that of $Gd_3N@C_{80}$ (+0.58 V). On the basis of these data, we can estimate a precipitation onset of approximately +0.06 V for $CaCl_2$.

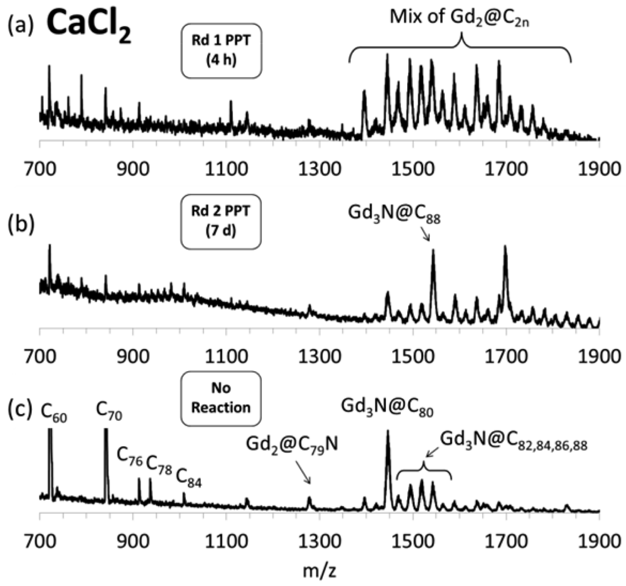


Figure 2. Endohedrals and fullerenes after reaction with $CaCl_2$ during the (a) round 1 precipitation, 4 h, (b) the round 2 precipitation, 7 days, and (c) species in the filtrate after 7 days.

When an equimolar amount of $ZnCl_2$ (92 mg) is substituted for $CaCl_2$, a slight increase in the precipitation onset is observed. When $ZnCl_2$ is compared to $CaCl_2$, the precipitate obtained after reaction with $ZnCl_2$ (Figure 3a) shows $Gd_3N@C_{88}$ as the dominant endohedral and requires only 4 h of reaction time (Figure 3a; round 1 precipitate) versus 7 days of reaction time with $CaCl_2$ (Figure 2b; round 2 precipitate). The selectivity of $ZnCl_2$ for $Gd_3N@C_{88}$ should be useful in developing a subsequent separation method for its nonchromatographic isolation.

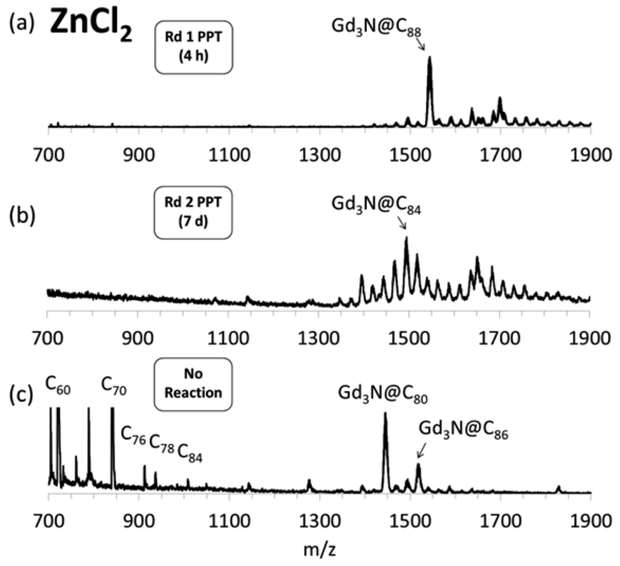


Figure 3. Endohedrals and fullerenes after reaction with $ZnCl_2$ during the (a) round 1 precipitation, 4 h, (b) round 2 precipitation, 7 days, and (c) species in the filtrate after 7 days.

Further selectivity for other Gd_3N cluster endohedrals can be achieved when 288 mg of additional $ZnCl_2$ is added to the filtrate and stirred for 7 days. The mass spectrum of the endohedrals obtained from the second round precipitate reveals that $Gd_3N@C_{84}$ emerges as the new dominant species (Figure 3b).

Characterization of the filtrate (Figure 3c) demonstrates that yet another M_3N metallofullerene (i.e., $Gd_3N@C_{80}$) is the dominant endohedral, followed by $Gd_3N@C_{86}$. Hence, the use of $ZnCl_2$ permits a nice fractionation of the $Gd_3N@C_{2n}$ family. Namely, $Gd_3N@C_{88}$ is obtained in the most reactive fraction (4 h), followed by $Gd_3N@C_{84}$ (7 days) in the intermediate fraction, with $Gd_3N@C_{86}$ and $Gd_3N@C_{80}$ remaining in the "inert" fraction (i.e., filtrate not precipitated after 7 days).

Comparison of Round 1 Precipitates (4 h). When equimolar amounts of the 11 Lewis acids are maintained and similar reaction times (4 h and 7 days) are used, a comparison can be made to assess their ability to precipitate gadolinium endohedrals (Table 1). The selectivity and control of the precipitation is clearly revealed by studying the mass spectral data shown in Figure 4, in which the endohedrals obtained from the 11 first round precipitates are compared.

A "tuning" of the selectivity and dominant species is observed in transitioning from $CaCl_2$ (i.e., primarily large-cage $Gd_2@C_{2n}$), as shown in Figure 4a, to the emergence of $Gd_3N@C_{88}$ as the dominant endohedral ($ZnCl_2$, $NiCl_2$, $MgCl_2$, $MnCl_2$, $CuCl_2$, and WCl_4), as shown in Figure 4b–g.

There is poor selectivity in gadolinium endohedral precipitation when the most reactive Lewis acids (WCl_6, $ZrCl_4$, $AlCl_3$, and $FeCl_3$) are used. The data in Figure 4h–k clearly indicate poor selectivity because the entire family of gadolinium metallofullerenes have precipitated.

The selectivity of the 11 Lewis acids in comparison to the dominant endohedral precipitated is summarized in Table 2.

Comparison of Round 2 Filtrates (7 days). Also of interest is a comparison of gadolinium endohedrals which are resistant to precipitation. Figure 5 shows a MALDI comparison of the 11 filtrates, which contain the endohedrals still remaining in solution after 7 days. As the weakest Lewis acid, $CaCl_2$ precipitated few endohedrals. The filtrate from the $CaCl_2$ experiment still contains the bulk of the original gadolinium endohedral content. With reactivities being slightly higher than those of $CaCl_2$, the $ZnCl_2$ and $NiCl_2$ filtrates also contain a variety of $Gd_3N@C_{82-86}$ family members, in addition to the more chemically inert $Gd_2@C_{79}N$ and $Gd_3N@C_{80}$ species.

Progressing in strength to the intermediate $MgCl_2$ and $MnCl_2$ Lewis acids, filtrates from these Lewis acids indicate primarily two endohedrals. The lack of reactivity for $Gd_2@C_{79}N$ and $Gd_3N@C_{80}$ is expected given their highest first oxidation potentials (Table 1). Also of intermediate Lewis acid strength is $CuCl_2$. Analysis of the $CuCl_2$ filtrate indicates the presence of just one dominant endohedral ($Gd_3N@C_{80}$) after 7 days of reaction.

For the most reactive Lewis acids, the 7 day filtrates obtained from WCl_4, WCl_6, $ZrCl_4$, $AlCl_3$, and $FeCl_3$ studies reveal an absence of gadolinium metallofullerenes because the endohedrals have previously been precipitated during the 4 h and/or subsequent 7 day experiments (see the SI).

Rankings of the Lewis Acid Strength. On the basis of the entirety of reactivity data, it is now possible to arrange the 11 Lewis acids in order of increasing Lewis acid strength toward the selected fullerenes and gadolinium metallofullerenes in carbon disulfide. Shown in Figure 6 is a comparison of their selectivity, strength, and reactivity. The benefit of ranking their reactivities is the ability to tune the selectivity such that one can control their precipitation for use in developing an appropriate separation scheme, such that more simplified and highly

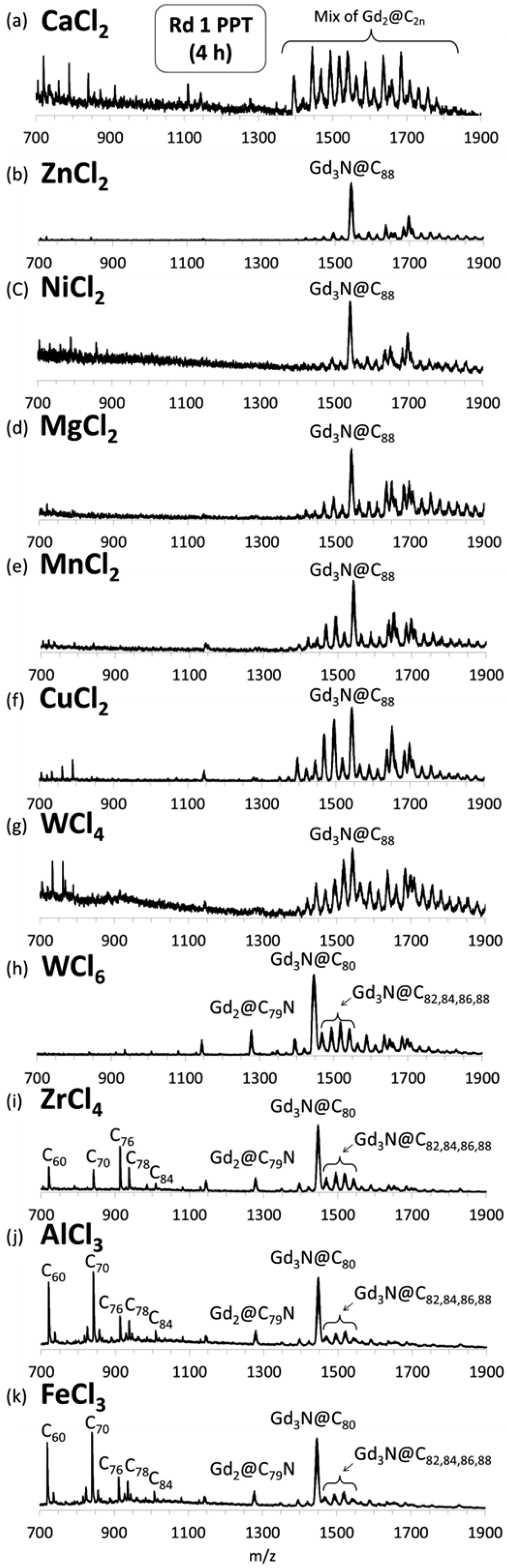


Figure 4. Endohedrals and fullerenes precipitated after 4 h of reaction with a given Lewis acid.

Table 2. Summary of the Dominant Endohedral Precipitated during the First 4 h of Reaction Time (Round 1 Precipitate)

Lewis acid	dominant endohedral precipitated
$CaCl_2$	$Gd_2@C_{2n}$
$ZnCl_2$, $NiCl_2$, $MgCl_2$, $MnCl_2$, $CuCl_2$, WCl_4	$Gd_3N@C_{88}$
WCl_6, $ZrCl_4$, $AlCl_3$, $FeCl_3$	$Gd_3N@C_{80}$

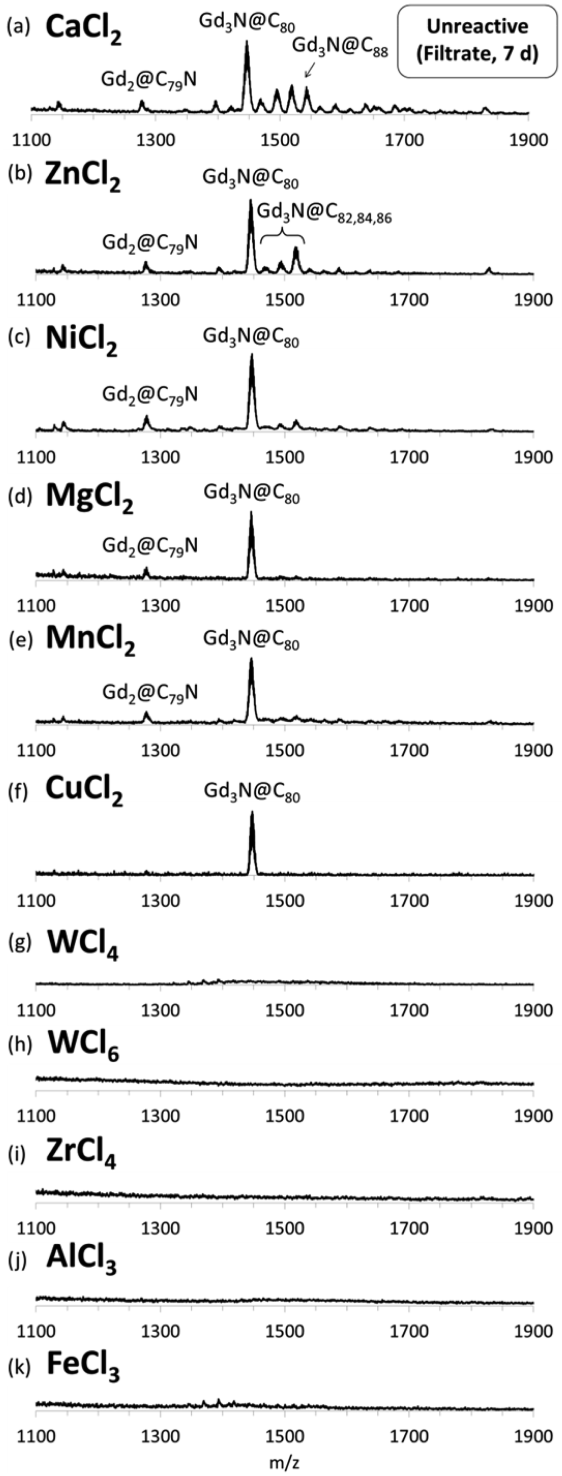


Figure 5. Endohedrals and fullerenes remaining in solution (filtrate) after 7 days.

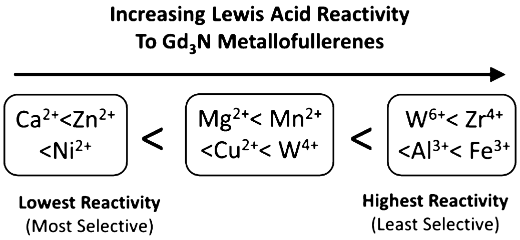


Figure 6. Comparison of the selectivities and reactivities of Lewis acids used in this study.

enriched samples can then be injected into HPLC for a quick and final pass for their purification.

We sought to compare the Lewis acid behavior toward gadolinium metallofullerenes with other Lewis acid studies from the literature. Because the endohedral cage surface possesses 5- and 6-membered carbon rings, a loose comparison can be made from the work of Olah et al.,[49] who also investigated the role of Lewis acids with carbon rings (i.e., benzene). In Olah's study, the relative reactivities of a large number of Lewis acids were ranked and placed in categories of very active, moderately active, and very weak/inactive. Serendipitously, 8 of the 11 Lewis acids described herein were used in both studies. The Lewis acids in common include $AlCl_3$, $ZrCl_4$, WCl_6, $FeCl_3$, $CuCl_2$, $MgCl_2$, $NiCl_2$, and $ZnCl_2$. Of note is the similarity in our findings of the reactivity and Lewis acid strength (Table 3).

Table 3. Comparison of Activities of Lewis Acids Used in the Friedel–Crafts Benzylation of Benzene[49] versus Lewis Acids Used in Reactions with Carbon Cage Rings of Gadolinium Endohedrals

Lewis acid	benzylation reactions (Olah et al.)[49]	Gd_2 and Gd_3N endohedral reactions (this work)
$AlCl_3$	very active	very active
$ZrCl_4$	very active	very active
$FeCl_3$	moderately active	very active
WCl_6	moderately active	very active
$CuCl_2$	very weak	moderately active
$MgCl_2$	very weak	moderately active
$MnCl_2$	very weak	moderately active
$NiCl_2$	very weak	very weak
$ZnCl_2$	very weak	very weak

■ CONCLUSION

The extent of reactivity for 11 Lewis acids and their ability to form complexes with Gd_3N metallofullerenes was evaluated. The three weakest Lewis acids ($CaCl_2$, $ZnCl_2$, and $NiCl_2$) were the most selective because they targeted precipitation of endohedrals possessing the lowest first oxidation potentials. The precipitation thresholds for the reaction of gadolinium endohedrals with $CaCl_2$, $ZnCl_2$, and $NiCl_2$ are estimated at less than +0.1 V.

The precipitation threshold can be increased to a range of +0.1 to +0.5 V by using Lewis acids with intermediate strengths, i.e., $MgCl_2$, $MnCl_2$, $CuCl_2$, and WCl_4. These four Lewis acids, after reaction for 4 h, tend to leave in solution the more stable $Gd_2@C_{79}N$ and $Gd_3N@C_{80}$ endohedrals, which remain unreacted in the filtrate because of their very high first oxidation potentials (+0.51 and +0.58 V, respectively).

The most reactive Lewis acids are WCl_6, $ZrCl_4$, $AlCl_3$, and $FeCl_3$. The precipitation threshold is higher (greater than +0.6 V) for these four Lewis acids. The selectivity of these strong Lewis acids is poor because they tend to precipitate the entirety of the gadolinium endohedral family (i.e., Gd, Gd_2, Gd_3, and Gd_3N clusters). Thus, there is little to no fractionation among these metallofullerenes.

In summary, we can "tune" a separation within a family of gadolinium endohedrals by a judicious choice of which Lewis acid to use. We demonstrate the selective precipitation of gadolinium endohedrals below a desired precipitation threshold. The strategic use of Lewis acids described herein will aid the development of future nonchromatographic purification methods that are based on differences in the first oxidation potentials among endohedral mixtures. The ability to control which metallofullerenes are permitted to precipitate and which endohedrals remain in solution is a key outcome of this work.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

MALDI data for endohedrals recovered from round 2 precipitation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors contributed to the work described herein (e.g., separation science, reactivity of endohedrals with various Lewis acids, characterization of samples by HPLC and MALDI, and conclusions).

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ghiassi, K. B.; Olmstead, M. M.; Balch, A. L. *Dalton Trans.* **2014**, *43*, 7346.

(2) Fatouros, P. P.; Shultz, M. D. *Nanomedicine* **2013**, *8*, 1853.

(3) Zhang, J. Y.; Ye, Y. Q.; Chen, Y.; Pregot, C.; Li, T. H.; Balasubramaniam, S.; Hobart, D. B.; Zhang, Y. F.; Wi, S.; Davis, R. M.; Madsen, L. A.; Morris, J. R.; LaConte, S. M.; Yee, G. T.; Dorn, H. C. *J. Am. Chem. Soc.* **2014**, *136*, 2630.

(4) Zhang, J. F.; Fatouros, P. P.; Shu, C. Y.; Reid, J.; Owens, L. S.; Cai, T.; Gibson, H. W.; Long, G. L.; Corwin, F. D.; Chen, Z. J.; Dorn, H. C. *Bioconjugate Chem.* **2010**, *21*, 610.

(5) Shu, C. Y.; Gan, L. H.; Wang, C. R.; Pei, X. L.; Han, H. B. *Carbon* **2006**, *44*, 496.

(6) Toth, E.; Bolskar, R. D.; Borel, A.; Gonzalez, G.; Helm, L.; Merbach, A. E.; Sitharaman, B.; Wilson, L. J. *J. Am. Chem. Soc.* **2005**, *127*, 799.

(7) Sitharaman, B.; Bolskar, R. D.; Rusakova, I.; Wilson, L. J. *Nano Lett.* **2004**, *4*, 2373.

(8) Kato, H.; Kanazawa, Y.; Okumura, M.; Taninaka, A.; Yokawa, T.; Shinohara, H. *J. Am. Chem. Soc.* **2003**, *125*, 4391.

(9) Bolskar, R. D.; Benedetto, A. F.; Husebo, L. O.; Price, R. E.; Jackson, E. F.; Wallace, S.; Wilson, L. J.; Alford, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 5471.

(10) Okumura, M.; Mikawa, M.; Yokawa, T.; Kanazawa, Y.; Kato, H.; Shinohara, H. *Acad. Radiol.* **2002**, *9*, S495.

(11) Mikawa, M.; Kato, H.; Okumura, M.; Narazaki, M.; Kanazawa, Y.; Miwa, N.; Shinohara, H. *Bioconjugate Chem.* **2001**, *12*, 510.

(12) Chen, C. H.; Lin, D. Y.; Yeh, W. Y. *Chem.—Eur. J.* **2014**, *20*, 5768.

(13) Bucsi, I.; Aniszfeld, R.; Shamma, T.; Prakash, G. K. S.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 9019.

(14) Stevenson, S.; Mackey, M. A.; Pickens, J. E.; Stuart, M. A.; Confait, B. S.; Phillips, J. P. *Inorg. Chem.* **2009**, *48*, 11685.

(15) Wang, Z. Y.; Nakanishi, Y.; Noda, S.; Akiyama, K.; Shinohara, H. *J. Phys. Chem. C* **2012**, *116*, 25563.

(16) Akiyama, K.; Hamano, T.; Nakanishi, Y.; Takeuchi, E.; Noda, S.; Wang, Z. Y.; Kubuki, S.; Shinohara, H. *J. Am. Chem. Soc.* **2012**, *134*, 9762.

(17) Wang, Z. Y.; Nakanishi, Y.; Noda, S.; Niwa, H.; Zhang, J. Y.; Kitaura, R.; Shinohara, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 11770.

(18) Stevenson, S.; Rottinger, K. A. *Inorg. Chem.* **2013**, *52*, 9606.

(19) Tsuchiya, T.; Wakahara, T.; Shirakura, S.; Maeda, Y.; Akasaka, T.; Kobayashi, K.; Nagase, S.; Kato, T.; Kadish, K. M. *Chem. Mater.* **2004**, *16*, 4343.

(20) Lu, X.; Li, H. J.; Sun, B. Y.; Shi, Z. J.; Gu, Z. N. *Carbon* **2005**, *43*, 1546.

(21) Raebiger, J. W.; Alford, J. M.; Bolskar, R. D.; Diener, M. D. *Carbon* **2011**, *49*, 37.

(22) Raebiger, J. W.; Bolskar, R. D. *J. Phys. Chem. C* **2008**, *112*, 6605.

(23) Ceron, M. R.; Li, F. F.; Echegoyen, L. *Chem.—Eur. J.* **2013**, *19*, 7410.

(24) Elliott, B.; Yu, L.; Echegoyen, L. *J. Am. Chem. Soc.* **2005**, *127*, 10885.

(25) Maeda, Y.; Tsuchiya, T.; Lu, X.; Takano, Y.; Akasaka, T.; Nagase, S. *Nanoscale* **2011**, *3*, 2421.

(26) Tsuchiya, T.; Sato, K.; Kurihara, H.; Wakahara, T.; Nakahodo, T.; Maeda, Y.; Akasaka, T.; Ohkubo, K.; Fukuzumi, S.; Kato, T.; Mizorogi, N.; Kobayashi, K.; Nagase, S. *J. Am. Chem. Soc.* **2006**, *128*, 6699.

(27) Ku, M.-Y.; Huang, S.-J.; Huang, S.-L.; Liu, Y.-H.; Lai, C.-C.; Peng, S.-M.; Chiu, S.-H. *Chem. Commun.* **2014**, *50*, 11709.

(28) Stevenson, S.; Rottinger, K. A.; Field, J. S. *Dalton Trans.* **2014**, *43*, 7435.

(29) Stevenson, S.; Rose, C. B.; Robson, A. A.; Heaps, D. T.; Buchanan, J. P. *Fullerenes, Nanotubes, Carbon Nanostruct.* **2014**, *22*, 182.

(30) Stevenson, S.; Rose, C. B.; Maslenikova, J. S.; Villarreal, J. R.; Mackey, M. A.; Mercado, B. Q.; Chen, K.; Olmstead, M. M.; Balch, A. L. *Inorg. Chem.* **2012**, *51*, 13096.

(31) Stevenson, S.; Mackey, M. A.; Coumbe, C. E.; Phillips, J. P.; Elliott, B.; Echegoyen, L. *J. Am. Chem. Soc.* **2007**, *129*, 6072.

(32) Stevenson, S.; Harich, K.; Yu, H.; Stephen, R. R.; Heaps, D.; Coumbe, C.; Phillips, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 8829.

(33) Ge, Z. X.; Duchamp, J. C.; Cai, T.; Gibson, H. W.; Dorn, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 16292.

(34) Kobayashi, K.; Sano, Y.; Nagase, S. *J. Comput. Chem.* **2001**, *22*, 1353.

(35) Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M. R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M. M.; Maitra, K.; Fisher, A. J.; Balch, A. L.; Dorn, H. C. *Nature* **1999**, *401*, 55.

(36) Stevenson, S.; Mackey, M. A.; Thompson, M. C.; Coumbe, H. L.; Madasu, P. K.; Coumbe, C. E.; Phillips, J. P. *Chem. Commun.* **2007**, 4263.

(37) Ceron, M. R.; Li, F. F.; Echegoyen, L. A. *J. Phys. Org. Chem.* **2014**, *27*, 258.

(38) Rivera-Nazario, D. M.; Pinzon, J. R.; Stevenson, S.; Echegoyen, L. A. *J. Phys. Org. Chem.* **2013**, *26*, 194.

(39) Chaur, M. N.; Aparicio-Angles, X.; Mercado, B. Q.; Elliott, B.; Rodriguez-Fortea, A.; Clotet, A.; Olmstead, M. M.; Balch, A. L.; Poblet, J. M.; Echegoyen, L. *J. Phys. Chem. C* **2010**, *114*, 13003.

(40) Valencia, R.; Rodriguez-Fortea, A.; Clotet, A.; de Graaf, C.; Chaur, M. N.; Echegoyen, L.; Poblet, J. M. *Chem.—Eur. J.* **2009**, *15*, 10997.

(41) Chaur, M. N.; Melin, F.; Ortiz, A. L.; Echegoyen, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7514.

(42) Chaur, M. N.; Melin, F.; Elliott, B.; Kumbhar, A.; Athans, A. J.; Echegoyen, L. *Chem.—Eur. J.* **2008**, *14*, 4594.

(43) Chaur, M. N.; Athans, A. J.; Echegoyen, L. *Tetrahedron* **2008**, *64*, 11387.

(44) Melin, F.; Chaur, M. N.; Engmann, S.; Elliott, B.; Kumbhar, A.; Athans, A. J.; Echegoyen, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 9032.

(45) Chaur, M. N.; Melin, F.; Elliott, B.; Athans, A. J.; Walker, K.; Holloway, B. C.; Echegoyen, L. *J. Am. Chem. Soc.* **2007**, *129*, 14826.

(46) Suzuki, T.; Kikuchi, K.; Oguri, F.; Nakao, Y.; Suzuki, S.; Achiba, Y.; Yamamoto, K.; Funasaka, H.; Takahashi, T. *Tetrahedron* **1996**, *52*, 4973.

(47) Fu, W. J.; Zhang, J. Y.; Fuhrer, T.; Champion, H.; Furukawa, K.; Kato, T.; Mahaney, J. E.; Burke, B. G.; Williams, K. A.; Walker, K.; Dixon, C.; Ge, J. C.; Shu, C. Y.; Harich, K.; Dorn, H. C. *J. Am. Chem. Soc.* **2011**, *133*, 9741.

(48) Beavers, C. M.; Chaur, M. N.; Olmstead, M. M.; Echegoyen, L.; Balch, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 11519.

(49) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448.