Fullerene Chemistry

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Retro-Cycloaddition Reaction of Pyrrolidinofullerenes**

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Dedicated to Professor David Schuster
on the occasion of his 70th birthday

The 1,3-dipolar cycloaddition reaction of azomethine ylides to alkenes is one of the most important and elegant methods for the construction of nitrogen-containing five-membered ring compounds. This reaction has been successfully conducted with fullerenes and it is considered one of the most straightforward procedures for their functionalization.[1] The resulting C_{60}-fused pyrrolidines (pyrrolidino[3,4:1,2][60]fullerenes or simply pyrrolidinofullerenes) are easily prepared by reaction of the in situ generated azomethine ylides to [60]fullerene. Although azomethine ylides are reactive intermediates which can be generated in several ways by following efficient synthetic protocols, the decarboxylation of imminium salts, derived from condensation of α-amino acids with aldehydes or ketones, is the easiest and most general procedure commonly followed.[2] Other convenient methods for the synthesis of pyrrolidinofullerenes are based on the thermal ring opening of aziridines, acid-catalyzed or thermal desililation of trimethylsilylamino derivatives, or photochemical treatment of tertiary amines with C_{60}.[3] The isolation and characterization of all eight possible regioisomers of bisadducts of pyrrolidinofullerene derivatives have also been reported.[4]

Pyrrolidinofullerene cycloadducts have proven to be chemically stable species and, therefore, they typically do

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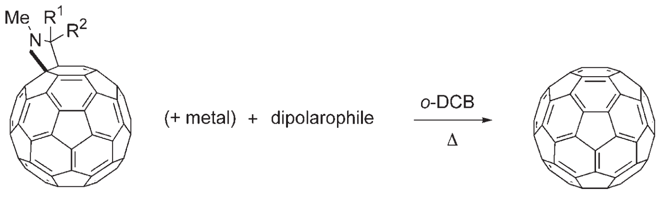
not undergo further chemical transformations. In contrast to other well-known fullerene derivatives, such as Diels–Alder cycloadducts[5] or Bingel's methanofullerenes,[6] which can undergo their corresponding retro-cycloaddition reactions, pyrrolidinofullerenes are considered to be very stable cycloadducts. Herein, we describe the first highly efficient retro-cycloaddition reactions of differently substituted pyrrolidinofullerenes which quantitatively afford the parent unsubstituted fullerene.

It was previously reported that pyrrolidines undergo a retro-cycloaddition reaction which leads to the alkene and the azomethine ylide.[7] Although it is well-known that pyrrolidinofullerenes exhibit a much lower basic and nucleophilic character than pyrrolidines owing to the electronegative character of the fullerene core,[8] we decided to investigate the retro-cycloaddition reaction of pyrrolidinofullerenes under thermal and catalytic conditions.

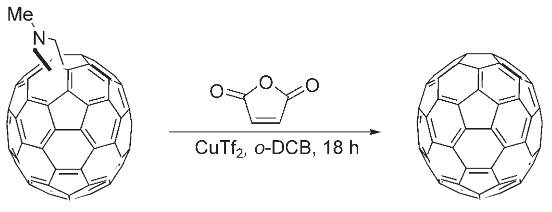
Following previously reported standard procedures,[9] pyrrolidinofullerenes **1a**–**e** were initially synthesized (Scheme 1). Compound **1a** ($R^1 = R^2 = H$) was heated at reflux in *o*-dicholorobenzene (*o*-DCB) for 24 h in the presence of an excess of a highly efficient dipolarophile, such as maleic anhydride, in order to trap the corresponding ylide that results from the thermal retro-cycloaddition reaction. However, under these conditions the reaction proceeded with a very low yield (Table 1, entry 1: 4.9 % of recovered C_{60} as determined by HPLC). When compounds **1b**–**d** were treated under similar reaction conditions, significantly better yields were obtained (entries 2–4). Surprisingly, when compound **1e** was heated at reflux in *o*-DCB for 12 h under the same experimental conditions (entry 6), C_{60} was recovered quantitatively. In fact, the initial brown solution of the pyrrolidinofullerene **1e** recovered the magenta color typical of solutions of [60]fullerene. Furthermore, **1e** led to pristine C_{60} in 96.5 % yield (determined by HPLC) after only 4 h at reflux in *o*-DCB (entry 5, Table 1). These results clearly indicate that the retro-cycloaddition reaction is strongly dependent on the nature of the substituents on the pyrrolidine ring which influence the stability of the thermally generated 1,3-dipole.



1a: $R^1 = R^2 = H$
1b: $R^1 = H$, $R^2 = Ph$
1c: $R^1 = H$, $R^2 = C_{16}H_{11}$
1d: $R^1 = R^2 = CH_3$
1e: $R^1 = H$, $R^2 = COOEt$

Scheme 1. Retro-cycloaddition reaction of pyrrolidinofullerenes **1a**–**e**.

To improve the efficiency of the removal of the pyrrolidine ring from the carbon sphere to yield pristine C_{60}, we carried out the thermal reaction in the presence of a metal Lewis acid to see if a possible coordination with the nitrogen atom could activate the retro-reaction. When compounds **1a**–**d** were heated at reflux in *o*-DCB for a variable time (8–18 h) in the presence of maleic anhydride (30 equiv) and copper(II) triflate (1 equiv), the reaction led in all cases (entries 7–10, Table 1) to the quantitative formation of the parent unsubstituted C_{60} (determined by HPLC), solutions of which were the typical magenta color. Interestingly, the reaction also proved to be highly efficient with the mono-adduct mixture of the three isomers of [70]pyrrolidinofullerene (**2**),[10] which afforded under these conditions pristine C_{70} in 95 % yield (by HPLC; see entry 11 in Table 1 and Scheme 2).



2

Scheme 2. Retro-cycloaddition reaction of C_{70} derivative **2** catalyzed by a metal Lewis acid. $Tf = CF_3SO_2$.

The 1,3-dipolar retro-cycloaddition reaction appears to be quite general in terms of substitution on the pyrrolidine ring (unsubstituted **1a**, monosubstituted **1b**,**c**,**e**, and disubstituted **1d**) as well as with higher fullerenes, such as C_{70} and C_{80}.

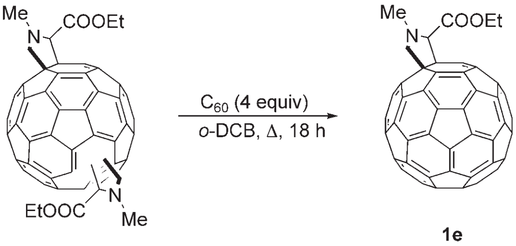
Table 1: Experimental conditions of the retro-cycloaddition reaction.[a]

Entry	Compound	Dipolarophile[b]	Catalyst	*t* [h]	Conv. [%][c]
1	**1a**	maleic anhydride	–	24	4.9
2	**1b**	maleic anhydride	–	24	43.5
3	**1c**	maleic anhydride	–	12	35.0
4	**1d**	maleic anhydride	–	24	15.3
5	**1e**	maleic anhydride	–	4	96.5
6	**1e**	maleic anhydride	–	12	100.0
7	**1a**	maleic anhydride	$CuTf_2$[d]	8	100.0
8	**1b**	maleic anhydride	$CuTf_2$[d]	8	99.3
9	**1c**	maleic anhydride	$CuTf_2$[d]	18	100.0
10	**1d**	maleic anhydride	$CuTf_2$[d]	8	100.0
11	**2**	maleic anhydride	$CuTf_2$[d]	18	95.0
12	**1e**	*N*-phenylmaleimide	$(Ph_3P)_3RhCl$[e]	18	100.0
13	**1e**	maleic anhydride	$(Ph_3P)_3RhCl$[e]	18	97.2
14	**1e**	1,4-benzoquinone	$(Ph_3P)_3RhCl$[e]	18	79.9
15	**1e**	diethyl maleate	$(Ph_3P)_3RhCl$[e]	18	60.9
16	**3**	C_{60} (4 equiv)	–	18	100.0

[a] All the reactions were carried out in *o*-DCB at reflux (4–24 h); [b] 30 equiv dipolarophile used unless otherwise stated. [c] Conversion determined by HPLC. [d] 1 equiv $CuTf_2$ (copper(II) trifluoromethylsulfonate) used. [e] 0.1 equiv Wilkinson's catalyst ($(Ph_3P)_3RhCl$) used.

To explore the use of other metals as well as the influence of the trapping dipolarophile on the reaction outcome, we carried out the thermal retro-cycloaddition reaction of **1e** in the presence of catalytic amounts of Wilkinson's catalyst (0.1 equiv) and using a variety of different efficient dipolarophiles (entries 12–15, Table 1). After heating at reflux in *o*-DCB for 18 h, the reaction gave good yields of C_{60} when *N*-phenylmaleimide (100 %) or maleic anhydride (97.2 %) was used as dipolarophiles. However, lower yields were observed when either 1,4-benzoquinone (79.9 %) or diethyl maleate (60.9 %) was used as the trapping dipolarophile (entries 14 and 15).

It is well-known that [60]fullerene is a very efficient dipolarophile, and, therefore, we decided to evaluate its effectiveness in the present reaction. To test this, a mixture of bis-cycloadducts **3** was heated at reflux in *o*-DCB for 18 h in the presence of an excess (4 equiv) of pristine C_{60} (Scheme 3). The mono-adduct was recovered quantitatively (100 % by HPLC) together with unreacted C_{60} (entry 16). This finding confirms the general scope of this thermal retro-cycloaddition reaction and opens new avenues for improving the yields of mono-adduct formation from the usually undesired bis-cycloadducts in many 1,3-dipolar cycloaddition reactions of differently substituted azomethine ylides.



3
(mixture)

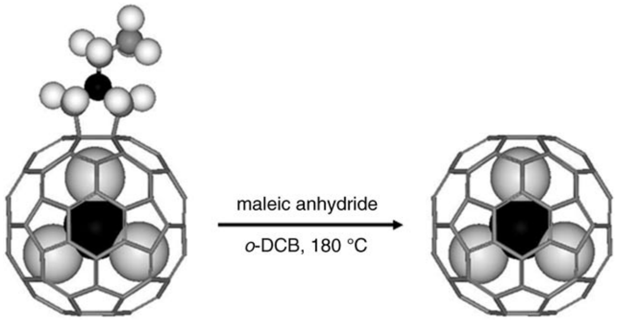
1e

Scheme 3. Reaction of a mixture of bis-adducts **3** in the presence of C_{60} as dipolarophile.

Depending on the substitution pattern on the pyrrolidinofullerene moiety, we can use different protocols to quantitatively remove the pyrrolidine ring from the carbon sphere to recover the parent fullerene. This new reaction significantly enhances the utility of one of the most important and successful reactions in the chemistry of fullerenes, as it can now be used as a highly efficient protection/deprotection protocol. This new strategy will enable the preparation of unusual addition patterns on different fullerenes. Just as the cyclopropanation/retro-cyclopropanation protocol has been successfully used in the purification of higher fullerenes and their enantiomers,[11] the pyrrolidine/retro-pyrrolidine strategy described here has the potential for similar applications. We thus decided to apply this thermal retro-cycloaddition reaction to the separation of pyrrolidine derivatives of trimetallic nitride endohedral metallofullerenes, whose constitutional isomers are difficult to separate.[12]

Recently, some of us reported the synthesis and characterization of a mono-adduct derivative of $Sc_3N@C_{80}$, an *N*-ethylpyrrolidinofullerene.[13] ^{1}H, ^{13}C, and 2D NMR experiments of this mono-adduct confirmed that the cycloaddition occurred selectively at a corannulene-type site (a double bond at a [5,6] ring junction abutted by two hexagons) of the icosahedral (I_h) C_{80} cage, in the same position as that described previously for a Diels–Alder mono-adduct of the same compound.[14] In our synthesis, the 1,3-dipolar cycloaddition reaction was very selective, and only one regioisomer product of the I_h constitutional isomer of $Sc_3N@C_{80}$ was isolated, even when the reaction was conducted in the presence of $Sc_3N@C_{78}$ (and presumably D_{5h} $Sc_3N@C_{80}$).[12] Therefore, the cycloaddition selectively extracts the I_h constitutional isomer from the product mixture, and the subsequent retro-cycloaddition constitutes an efficient purification method for I_h-symmetric $Sc_3N@C_{80}$ by its separation from other endohedral metallofullerenes and other constitutional isomers.

The 1,3-dipolar retro-cycloaddition reaction was successfully carried out with *N*-ethylpyrrolidino-$Sc_3N@C_{80}$ (with a ^{13}C label incorporated in the pyrrolidine ring) by heating at reflux in *o*-dichlorobenzene (20–24 h) in the presence of maleic anhydride (30 equiv) in sealed NMR tubes in the dark (Scheme 4). The retro-cycloaddition reaction of this endohedral metallofullerene was followed by TLC, HPLC, and NMR spectroscopy. The heteronuclear multiple quantum coherence (HMQC) NMR spectrum of the derivative (Figure 1) clearly shows that the starting compound is a pure pyrrolidine mono-adduct derivative of $Sc_3N@C_{80}$. The ^{13}C NMR spectrum exhibits a single signal at $\delta = 69.56$ ppm in [D$_4$]-*o*-dichlorobenzene, indicating that both the methylene carbon atoms of the five-membered ring are equivalent. The complete disappearance of the single ^{13}C signal after heating this derivative at 180 °C in the presence of maleic anhydride for 22 h indicates that retro-cycloaddition occurred in high yield as the pyrrolidine adduct is no longer present (Figure 1).



Scheme 4. 1,3-Dipolar retro-cycloaddition of *N*-ethylpyrrolidino-$Sc_3N@C_{80}$.

The reaction proved to be quantitative upon analysis by TLC (93 % recovered after column chromatography on SiO_2), and only $Sc_3N@C_{80}$ was isolated and characterized by HPLC (Figure 2, peak at 6.16 min) and MALDI mass spectrometry. We believe that the product must be the I_h isomer, as this was the only isomer of the pyrrolidine derivative present initially.

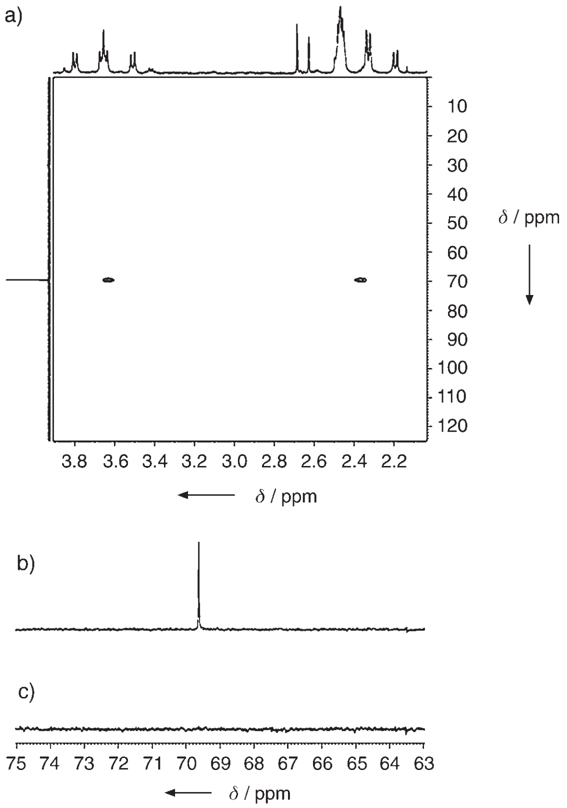


Figure 1. a) HMQC NMR spectrum of ^{13}C-labeled I_h-symmetric *N*-ethylpyrrolidino-$Sc_3N@C_{80}$ mono-adduct in [D$_4$]-*o*-dichlorobenzene, and b, c) ^{13}C NMR spectra recorded before (a) and after (b) heating the adduct at reflux in the presence of maleic anhydride in *o*-dichlorobenzene.

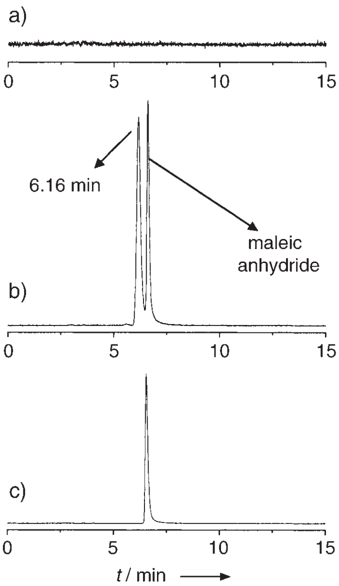


Figure 2. HPLC traces of a) the initial reaction mixture, b) the mixture after completion of the reaction, and c) maleic anhydride under identical conditions (Buckyclutcher column: 25 cm × 10 mm (Regis Chemical Company); toluene, flow rate: 4 mL min^{-1}; detection at $\lambda = 310$ nm).

The retro-cycloaddition proceeded in the presence of maleic anhydride as the dipolarophile in both dark aerobic and anaerobic conditions. ^{12}C- and ^{13}C-enriched formaldehyde was a noticeable by-product of the retro-cycloaddition reaction under oxygenated conditions when ^{13}C-labeled *N*-ethylpyrrolidinofullerene was employed, as shown by the ^{1}H NMR spectra (Figure 3) recorded before and after retro-cycloaddition. Such a strategy also worked successfully and quantitatively for the isolation of I_h-symmetric $Y_3N@C_{80}$ when *N*-ethylpyrrolidino-[5,6]-$Y_3N@C_{80}$[15] was subjected to the retro-cycloaddition conditions described above. We are currently analyzing the other by-products of the reaction and investigating the roles of oxygen and light in the reaction in order to elucidate the mechanism and compare it to the retro-cycloaddition of fullerene derivatives with empty cages. Our interest also lies in the isolation of other constitutional isomers such as D_{5h}-symmetric $Sc_3N@C_{80}$, which has eluded isolation thus far.

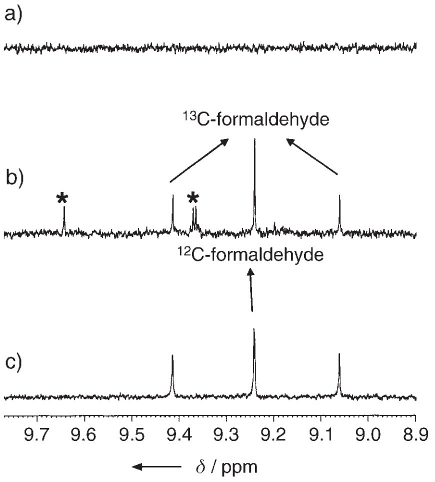
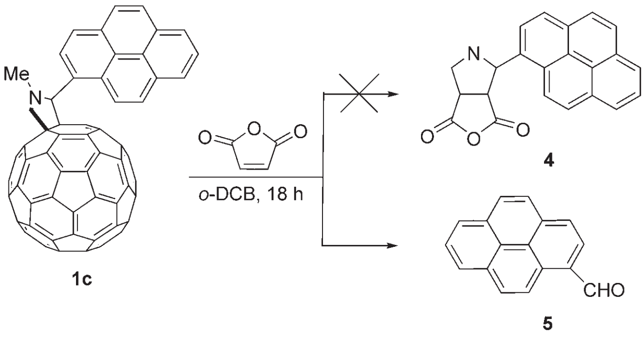


Figure 3. ^{1}H NMR spectrum of ^{13}C-enriched I_h-symmetric *N*-ethylpyrrolidino-$Sc_3N@C_{80}$ a) before the reaction and b) after 22 h at 180 °C in the presence of maleic anhydride, showing signals for the azomethine ylide product after retro-cycloaddition. c) ^{1}H NMR spectrum of a (control) solution of maleic anhydride and paraformaldehyde (both ^{12}C- and ^{13}C-enriched) in [D$_4$]-*o*-dichlorobenzene after 22 h at 180 °C. The asterisk (*) denotes unknown products.

Although the reaction mechanism of the retro-cycloaddition reaction is not yet clear, the above experiments suggest that thermal treatment leads to the formation of the azomethine ylide, which is efficiently trapped by the dipolarophile that is present in the reaction medium. When pyrrolidinofullerene **1c**, which bears a fluorescent pyrene unit as substituent at C2 of the pyrrolidine ring, was heated at reflux in *o*-DCB under standard conditions (maleic anhydride (30 equiv), 18 h), formation of the corresponding pyrene-substituted pyrrolidine **4** was not observed. However, aldehyde **5** was isolated as the only characterizable compound instead (Scheme 5) which thus suggests that oxygen could play a role in the evolution of the 1,3-dipole, although the influence of the trace amounts of water present in the solvent cannot be ruled out. More studies are therefore required to



Scheme 5. Retro-cycloaddition reaction of pyrene-substituted pyrrolidinofullerene **1c**.

determine if this is a simple thermal cycloreversion or a more-complex oxidative process. In this regard, preliminary investigations using oxidative controlled-potential electrolysis indicate that retro-cycloaddition is also efficiently obtained under these conditions. These experiments are ongoing and may shed additional information about the nature of the mechanism.

Experimental Section

In a typical experiment, pyrrolidinofullerene (0.02 mmol), dipolarophile (0.06 mmol), and metal catalyst (0.002 mmol) were heated at reflux in *o*-DCB (6 mL). The reaction was monitored by HPLC (Cosmosil Buckyprep column, 4.6 mm (i.d.) × 250 mm; toluene, flow rate: 1 mL min^{-1}). Retention times: 5.8–6.2 min for the pyrrolidinofullerenes; 8.0 min for C_{60}.

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