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[60]Fullerene−Pyrrolidine-*N*-oxides

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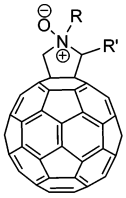

Synthesis and characterisation of [60]Fulleropyrrolidine-*N*-oxides

Eight members of a new family of fullerene derivatives, [60]fulleropyrrolidine-*N*-oxides, have been synthesized and characterized. Facile oxidation, by a peracid, of the parent [60]fulleropyrrolidine gave clean conversions into the product molecules, in which the tertiary amine is transformed into a quaternary amine bearing an oxygen atom. The reaction is very selective, favoring the nitrogen atom of the pyrrolidine ring in preference to epoxidation of the fullerene cage. The ^{1}H NMR shows an AB quartet splitting pattern, characteristic of nonequivalent hydrogens in the pyrrolidine ring and at a chemical shift displacement of 0.8 ppm downfield. Other methods of characterization are described, including MS, differential scanning calorimetry, thermogravimetric analysis, HPLC, UV/vis, and IR. Conclusive evidence for the formation of an *N*-oxide moiety is provided by the synthesis, oxidation, and NMR characterization of a novel [60]fulleropyrrolidine containing a ^{15}N isotope, showing an 85 ppm downfield heteroatom chemical shift. Preliminary details of the effects of substitution on the reactivity of the pyrrolidine ring are also reported.

Introduction

The fascinating chemistry surrounding the C_{60} cage has emerged since the development of its first synthesis in workable quantities.[1,2] Of the many ways to functionalize the sphere, the 1,3-dipolar cycloaddition of azomethine ylides provides a great deal of flexibility owing to the readily available starting materials.[3] As part of this reaction, a basic nitrogen atom is introduced onto the fullerene cage in the form of a pyrrolidine ring. Although the reactivity is much reduced in comparison to a normal amine, it still can be used as a point of further functionalization.[4] Alkylation using iodoalkanes gives the corresponding quaternary ammonium salt, which has been used in the study of fullerene aggregation and also possesses interesting electrochemical properties.[5,6] The pyrrolidine nitrogen atom may also be a source of some unwanted problems when applied to biological systems, in that tertiary amines are protonated under physiological conditions. DNA-interaction studies have shown

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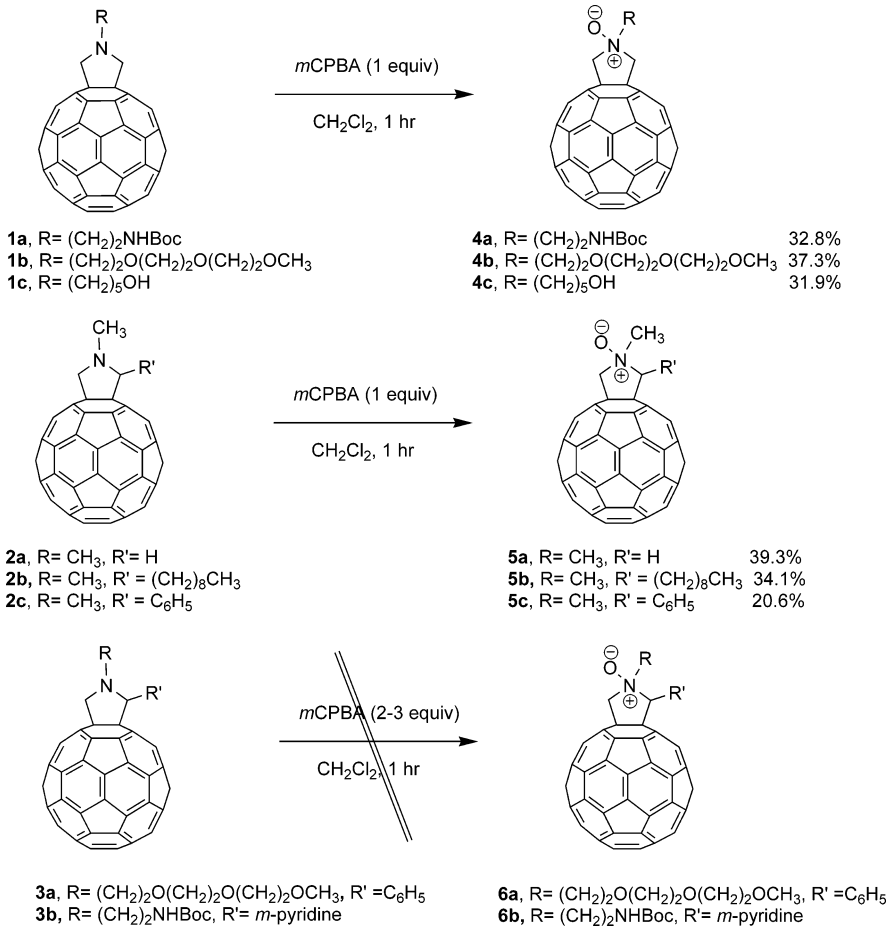
SCHEME 1. Oxidation of [60]Fulleropyrrolidines Using *m*CPBA



that protonated tertiary amines form an attractive electrostatic interaction with phosphates.[7] A method of masking this behavior is to convert the amine into an amine-*N*-oxide, which forms a repulsive electrostatic interaction with the DNA phosphates. In a more general sense, the amine-*N*-oxide is also known to be a useful protecting group in synthetic work.[8]

In this work, we present the exploration of the oxidative transformation of [60]fullerene−pyrrolidines into their corresponding *N*-oxides, in which the tertiary amine is oxidized to a quaternary amine bearing an oxygen atom, $(R)_3N^+O^-$ (Scheme 1). We envisaged some useful properties stemming from the ability to unmask the *N*-oxide back into its parent amine by thermal treatment.[9] We have judiciously chosen the oxidant and conditions to prevent or minimize epoxidation reactions that are known, from the literature, to occur on C_{60}.[10]

Results and Discussion

Fulleropyrrolidine derivatives **1a**−**c**, **2a**−**c**, and **3a**,**b** were synthesized by the well-known 1,3-dipolar cycloaddition reaction (Scheme 1), using the appropriate amino acids and aldehydes.[3]

Many efficient oxidants are known for the conversion of amines into their oxides, such as dimethyldioxirane,[11] HOF·CH_3-CN,[12] bis(trimethylsilyl)peroxide,[13] and Mg−Al/H_2O_2.[14] In this work, we have used 3-chloroperoxybenzoic acid (*m*CPBA), a reagent introduced in the 1970s for oxidizing substituted amines and is commonly used in nitroxide chemistry, owing to its good solubility in organic solvents.[15,16] The former is an important consideration, because fullerene molecules are, generally, soluble in solvents such as dichloromethane or THF but much less soluble in alcoholic/aqueous media. The *m*CPBA used in this work was used as received to work with commercially available starting materials.

We have split the eight new *N*-oxides into three groups according to their functionalization, revealing valuable observations regarding their synthesis, stability, and physical properties.

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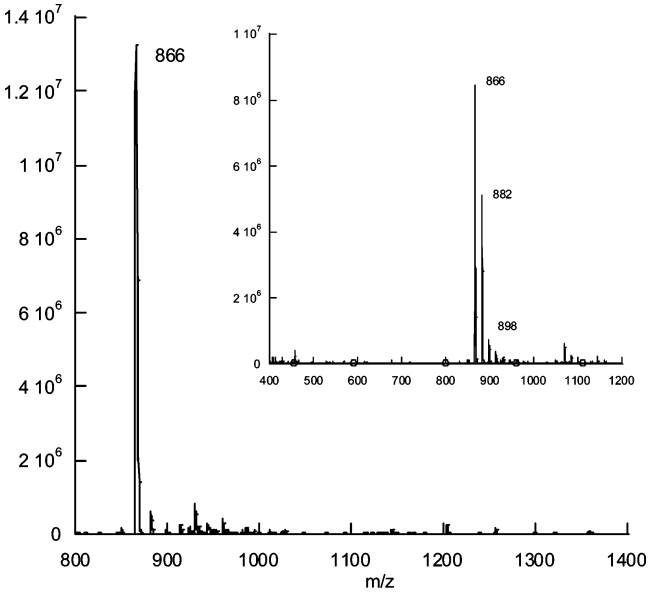

FIGURE 1. Oxidation of **4c** under dilute conditions and (inset) using concentrated conditions.

The first series, molecules **1a**−**c**, consists of fairly bulky groups occupying the tertiary position on the pyrrolidino nitrogen. Particular attention was made toward the incorporation of a substituent capable of hydrogen bonding to the *N*-oxide, such as the Boc-protected amine function. This is a useful tool that aids stabilization.[17] The second series of molecules (**2a**−**c**), bearing a small methyl substituent, were chosen to minimize steric crowding around the nitrogen atom while introducing some functionalization at the ortho position. Last, to provide insight into the effects of steric hindrance, we describe molecules **3a**,**b**, in which both the nitrogen of the pyrrolidine and its ortho position are substituted.

We began our research by oxidizing the molecules **1a**−**c**, in which the nitrogen of the pyrrolidine ring bears only one substituent, denoted R. The known epoxidation reactions of fullerene itself were initially of some concern, and to minimize this undesired side reaction, we employed dilute conditions, typically 0.05 mmol of fullerene molecule **1c** in 100 mL of $CHCl_3$. The addition of the *m*CPBA oxidant over a long period of time (1 h) and also using a dilute solution (0.05 mmol in 25 mL of $CHCl_3$) gave a product of mass corresponding to the addition of an oxygen atom (M + 16), **4c** (Figure 1). Its identity was confirmed by NMR and its purity was confirmed by HPLC (Figure 2). The yield of product was sufficient (30%), but higher conversions would be much more useful. With this in mind, we conducted the same reaction using more concentrated solutions. Oxidation using rapid addition times (5 min) furnished a mixture of products that result from the addition of one, two, and three oxygen atoms. An example is shown in Figure 1 (inset), in which compound **1c** was dissolved in $CHCl_3$ (8 mL) and was oxidized using a concentrated solution of *m*CPBA (1 equiv in 1 mL of $CHCl_3$). The mass spectrum shows that the product **4c** contains two major fractions, M + 16 and M + 32, and also a small amount of M + 48. We attribute these further addition products, M + 32 and M + 48, to the epoxidation of the fullerene cage. The chromatographic retention factors of

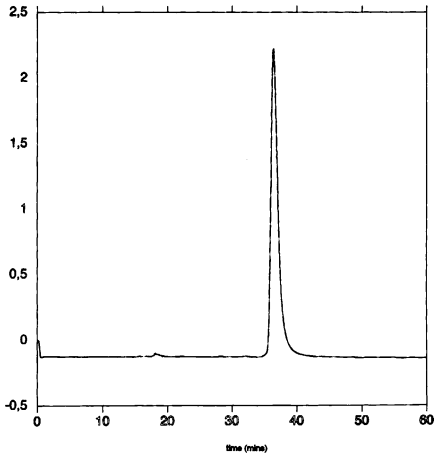

FIGURE 2. HPLC of *N*-oxide molecule **4a**.

these products were all of a similar value, hindering their separation, and we did not pursue characterization any further. Evidently, the known oxidation reaction of C_{60} was a significant side reaction.[10] Thus, control of reaction conditions and stoichiometry is essential for obtaining *N*-oxide products in good purity.

It is useful to note that the addition of a large excess of oxidant (10 equiv) results in the addition of multiple oxygen atoms along with partial decomposition of the fullerene molecule.

The solubility of fullerene-*N*-oxide molecules in organic solvents is different to their unoxidized counterparts, for example, compound **1b** dissolves well in toluene, whereas the *N*-oxide derivative **4b** is only sparingly soluble. This is a common theme spanning all of the molecules described in this work. The *N*-oxide molecules are much more soluble in solvent systems of greater polarity, for example, toluene/EtOH (8:2) and $CHCl_3$/EtOH (8:2). This proved to be very useful in this work, in which we were able to perform ^{13}C NMR analysis on compound **5a** owing to its good solubility in an 8:2 mixture of $CDCl_3/CD_3OD$.

The starting [60]fullerene−pyrrolidine molecules, in the cases of **1a**−**c** and **2a**−**c**, can be recuperated in their original states from the column chromatography (toluene/ethyl acetate (7:3) as eluent) in 45−55% yield. Mass spectra data corresponded to those of the starting materials. This is useful information but at the same time very curious. In the recovered compounds there is an absence of any oxidized materials, which ought to be present if the oxidation mechanism was indiscriminate with respect to the C_{60} cage and the pyrrolidino group. Indeed, careful monitoring of the reaction progress by TLC revealed that the *N*-oxide is the first product to arrive, and then during the latter stages a second product ensues, containing two or more oxygen atoms. These observations suggest that the reaction takes place preferentially on the nitrogen of the pyrrolidine, and the fullerene cage is only oxidized during the latter stages. This is consistent with an initial nucleophilic attack of the pyrrolidino nitrogen atom, which is known to resemble a tertiary amine, on a hydroxyl group of the peracid.[18]

From the unoxidized to the oxidized form there is a distinct change in the ^1H NMR chemical shift of the hydrogens belonging to the pyrrolidine group (Figure 3). The former shows as a singlet in the 4.4−4.6 ppm region, owing to rapid pyramidal

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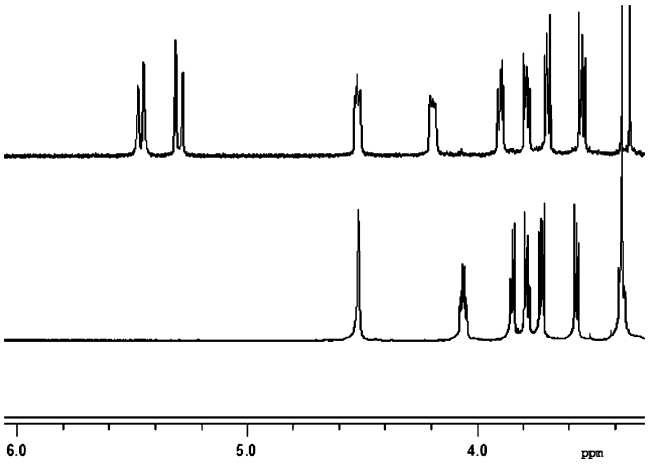

FIGURE 3. ^{1}H NMR of **4b** (top) vs **1b** (bottom) in $CDCl_3$.

inversion, whereas in the case of [60]pyrrolidino-*N*-oxides, they show as an AB quartet in the 5.2−5.5 ppm region. This splitting pattern was affected by different solvent systems in which well-separated AB quartets were observed for compound **4a** in $CDCl_3$, but the same molecule in $CDCl_3/CD_3OD$ (8:2) gave a singlet.

Fullerenes, in which the carbon cage has been epoxidized, show distinct signals in the ^{13}C NMR, typically the sp^3 C−O bond appears at around 90 ppm.[10d] In most cases, this peak was absent, indicating that in these molecules the oxygen atoms are not present on the fullerene cage. However, a peak corresponding to the epoxidized fullerene was clearly observed in the *ortho*-phenyl molecule, **5c**. Even tuning the reaction conditions to favor one oxygen addition (using 0.5 equiv of *m*CPBA) failed to give a pure product. The reason for this is not clear at this time, but it could be attributed to an electronic effect, that is, the phenyl group deactivating the amine and making it a poorer nucleophile.

The ^{1}H NMR is a useful indication for the formation of *N*-oxide products; however, it is an indirect method of characterization, that is, the presence of an amine oxide is inferred by observing its effect on the hydrogens of the pyrrolidine. A more elegant method is to directly observe the spectroscopic change of the nitrogen atom from before to after oxidation. To conclusively show the presence of the nitrogen bearing an oxide moiety, we have synthesized the fullerene molecule **14** using a nitrogen-15 isotope in the pyrrolidine ring system.

The synthesis of the ^{15}N-labeled amino acid commenced from the commercially available ^{15}N glycine (Scheme 2). The first step was to protect the amine function using a *tert*-butyloxycarbonyl (Boc) group, giving molecule **7** (95% yield).[19] Protection of the carboxylic acid was then carried out by a reaction with benzyl bromide, furnishing **8** in 76% yield. To further functionalize the amine group, it was first necessary to remove the Boc (compound **9**) and replace it with another protecting group, 2-nitrobenzenesulfonyl chloride (nosyl chloride), obtaining compound **10**. This step was essential because the secondary amine retained sufficient reactivity for the subsequent Mitsunobu-type reaction with triethylene glycol monomethyl ether, giving molecule **11** in 45% yield.[20] Deprotection of the nosyl group in **11**, using 2-mercaptoethanol and a strong base, gave the ^{15}N amino acid derivative, **12**. Coupling to the C_{60} was then performed using paraformaldehyde and the standard conditions of the 1,3-dipolar cycloaddition, giving the ^{15}N-containing [60]-fulleropyrrolidine, **13**. Oxidation to the *N*-oxide **14** using *m*CPBA was carried out using the same method as that described for molecule **1b**.

Compound **14** contains a ^{15}N atom in the pyrrolidine group, and this was used as a direct NMR probe to observe the difference between the nitrogen atoms of **13** and those of its oxidized counterpart **14**. The ^{1}H−^{15}N correlation spectrum is shown in Figure 4, in which a large difference is observed in chemical shift. The nitrogen atom of **13** shows a signal at −340 ppm, whereas in the *N*-oxide **14** is it observed at −255 ppm. This exceptionally large downfield shift signifies a distinct change in the nitrogen atom and is firm evidence for the formation of an *N*-oxide moiety.

Both compounds **13** and **14** are present on the same NMR spectrum, owing to a partial deoxygenation of the latter into the former. It seems to occur in the solid state, but at present, the process is not fully understood.

The UV/vis profiles of molecules [60]fullerene−pyrrolidine-*N*-oxide, **4b**, and the nonoxidized precursor **1b**, at room temperature, are shown together in Figure 5. Both compounds share common absorption bands at 700, 325, and 430 nm, a characteristic of [6,6]-bridged monoadducts. These are consistent with previously reported mono-addition products of fullerenes.[21] Surprisingly, the presence of an *N*-oxide moiety on the pyrrolidine has little or no influence on the absorption maxima, in comparison to the precursor molecule. Other [60]fulleropyrrolidine molecules bearing formal cations exhibit a UV/vis blue shift from the normal 325−317 nm.[22] However, this is not the case in the amine oxides. We speculate that the special push−pull characteristics of this group, that is, it can act as an electron donor and/or electron acceptor, negate any observable changes in the π-electron system.

In summary of the analytical data, the mass spectra are consistent with the addition of one oxygen atom. In the ^{1}H NMR, the pyrrolidine hydrogens are split and moved further downfield toward the 5.0−5.5 ppm region, indicating that the nitrogen atom is much more deshielded and is not susceptible to pyramidal inversion. Signals corresponding to the epoxidation of the fullerene cage were absent in the ^{13}C NMR data. Upon oxidation, the nitrogen chemical shift of a ^{15}N-labeled molecule shifts 85 ppm downfield, owing to the different electronic environment. Thus, we can conclude that these molecules possess the *N*-oxide group.

Synthetically valuable molecules[23] can be prepared by rearrangement reactions of tertiary amine oxides, such as those of Meisenheimer[24] and Cope.[25] Deoxygenation is also a known occurrence under thermal activation.[9] The [60]fulleropyrrolidine-*N*-oxides belong to this class of molecules, and in this capacity, we have carried out some initial studies into their thermal behavior.

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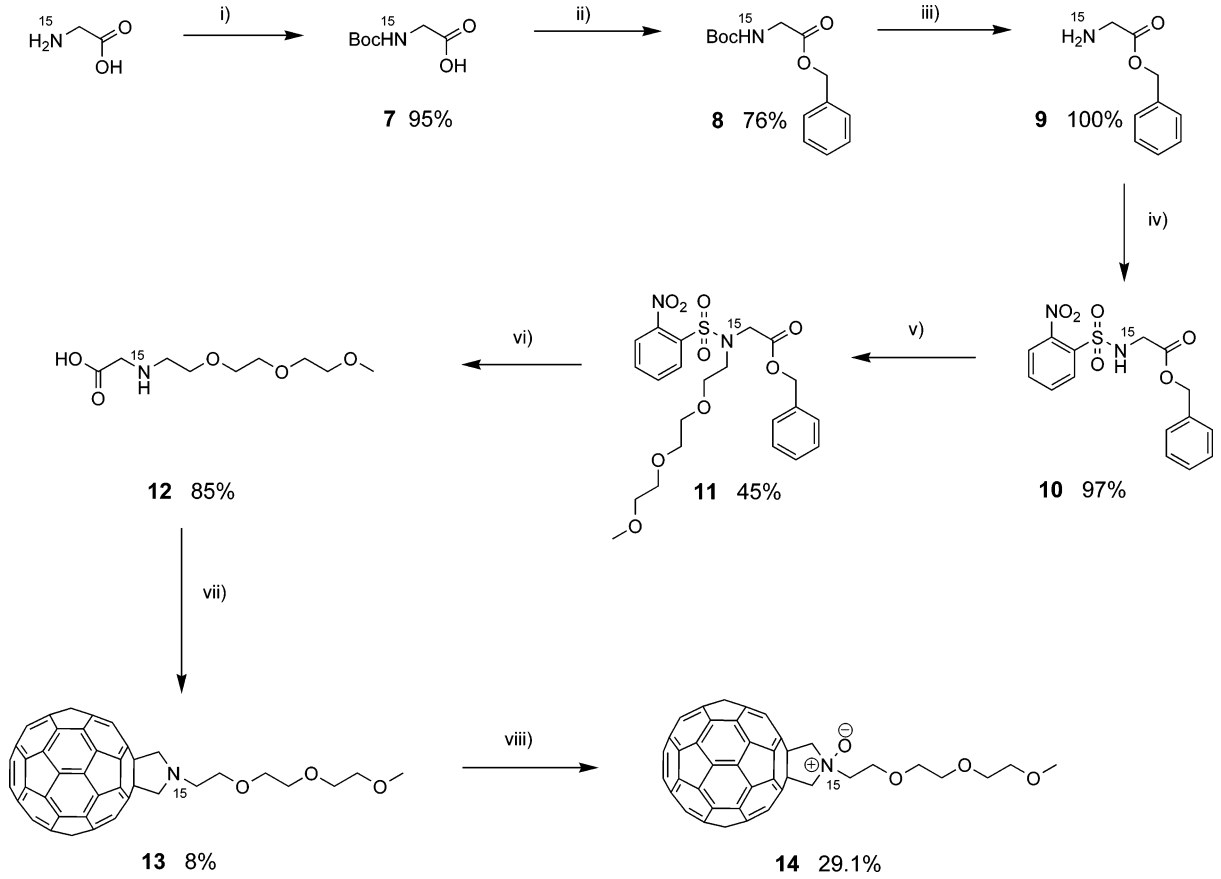
SCHEME 2. Synthesis of ^{15}N-Labeled [60]Fullerene−Pyrrolidine-*N*-oxide 14; (i) Boc_2O, NaOH; (ii) Benzyl Bromide, DBU; (iii) HCl; (iv) Nosyl Chloride, Et_3N; (v) Triethylene Glycol Monomethyl Ether, DEAD; (vi) 2-Mercaptoethanol, LiOH; (vii) C_{60}, Paraformaldehyde; (viii) *m*CPBA



When a three heat−cool cycle (50−200 °C) is used, differential scanning calorimetry (DSC) analysis of **5a** shows a broad exothermic peak at 134.8 °C during the first cycle (Figure 6). Notably, subsequent thermal profiles of the same molecule did not show this energy transition. All other *N*-oxide compounds studied gave similar traces, see Supporting Information for further information. ^{1}H NMR analysis of the heat-cycled solid showed peaks and splitting patterns corresponding to those of their precursor molecules. Thus, under thermal activation the *N*-oxide function had been lost and the compound had returned to its former [60]fullerene−pyrrolidine **2a**. Of course, this does not exclude the possibility that an oxygen atom was transferred to the fullerene cage. To elucidate the whereabouts of the

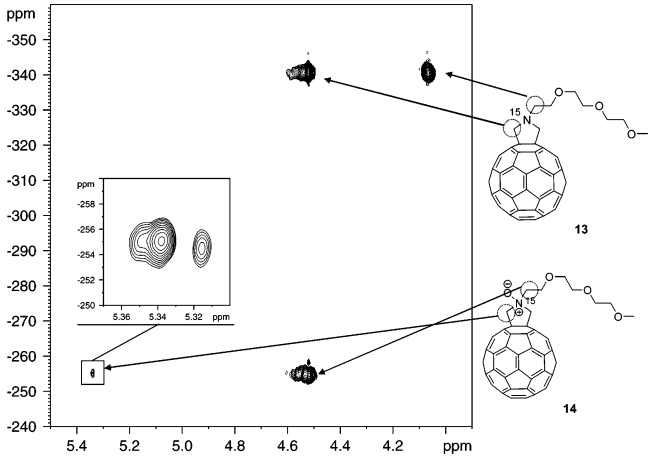


FIGURE 4. ^{1}H−^{15}N correlation spectrum of molecules **13** and **14**. Inset: zoom of the peak at ~5.35 ppm. The intensity of this correlation peak was weak because the J_{NH} coupling constant of the heteronuclear multiple-bond correlation pulse sequence was not optimized.

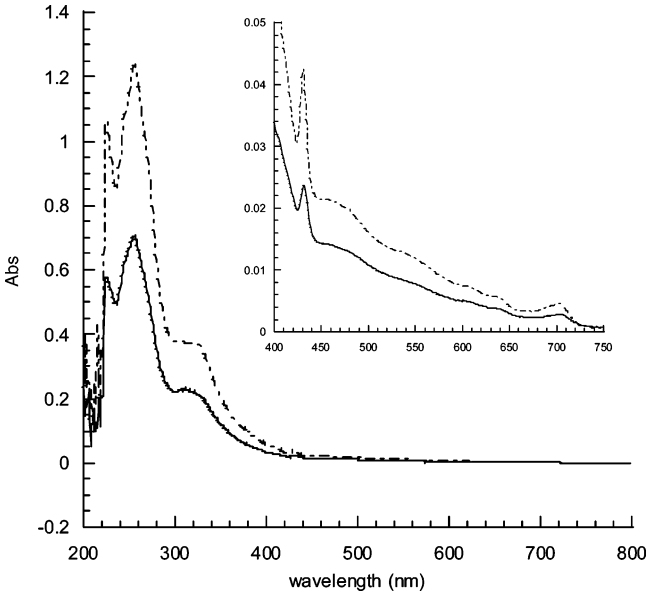


FIGURE 5. UV of *N*-oxide **4b** (—) vs normal **1b** (— · —); the inset is zoomed between 400 and 750 nm.

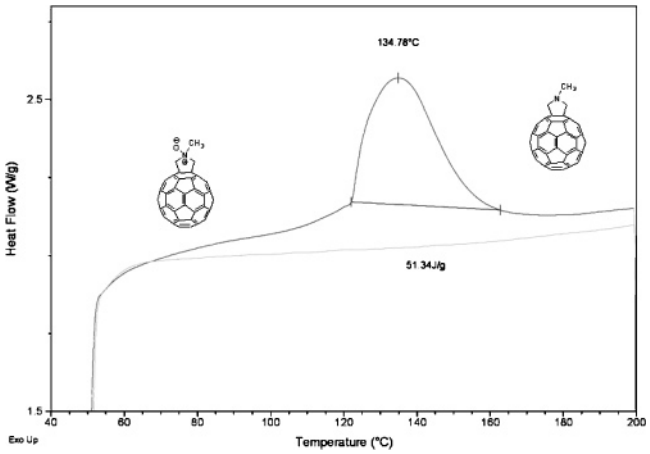


FIGURE 6. DSC profile of **5a**.

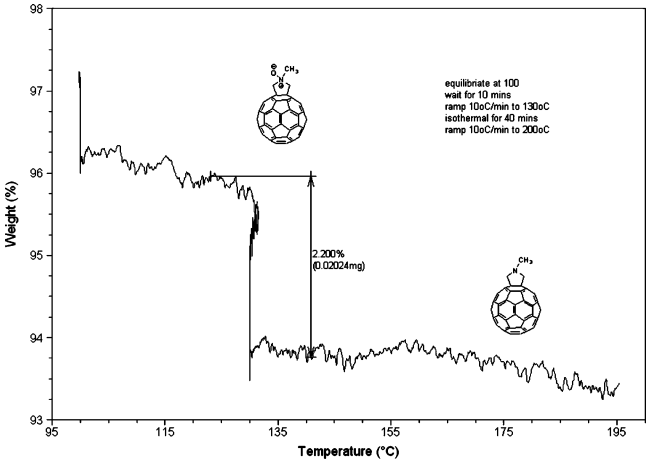


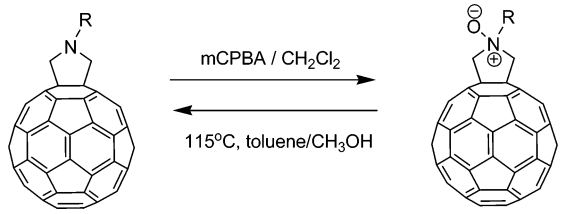
FIGURE 7. Close-up view of the TGA of **5a** decomposition in the range of 50−200 °C.

oxygen, we performed mass spectrometry on some thermally treated molecules, revealing that the oxygen atom had been lost and the mass of the major product corresponded to that of the parent molecule. Some degradation was also present, as seen in signals below 720 mass units.

To eliminate degradation effects from addends we examined the thermal profiles of precursor molecules, **1b**−**c**, **2a**−**c**, and **3a**,**b**, and no exothermic or endothermic peaks were observed. Temperatures significantly higher than those corresponding to deoxygenation resulted in the breakdown of the *tert*-butylcarbonyl group in molecule **1a**, under thermal gravimetric analysis (TGA).

Using a conventional ramp-heating profile, TGA would normally show the loss of mass corresponding to an oxygen atom. However, the DSC data already showed that deoxygenation in the *N*-oxide molecules **4a**−**c** and **5a**−**c** is a slow progressive process, occurring through a wide temperature range. Additionally, the percentage weight loss of one oxygen atom would be very small (1−2%) and difficult to observe. In fact, we found there was a gradual weight loss in the TGA analyses, but accurate measurement was difficult owing to the shallowness of the gradient. A much better method was to quickly ramp the temperature to a point in the middle of the deoxygenation temperature range and to measure the weight loss as a function of time. Figure 7 shows an example in the case of *N*-oxide molecule **5a** in which the observed weight loss (2.20%) is a

SCHEME 3. Oxidation and Thermal Deoxygenation of [60]Fulleropyrrolidine-*N*-oxides



direct match for the theoretical (2.02%), within experimental error. It is worthy to note that at higher temperatures other reactions may take place, for example, the fascinating retrocycloaddition reaction of pyrrolidinofullerenes in which the pyrrolidine ring is deconstructed, reforming the parent C_{60}.[26]

In the solid state, the deoxygenation reaction did not occur cleanly, and the product contained a significant amount of degraded molecules. To improve on the quality of the final materials, we explored solution and suspension deoxygenation. The first solvent we examined was $CHCl_3$, a solvent able to dissolve **4b**, yet not able to participate in hydrogen bonding. Under reflux conditions, there was no discernible deoxygenation after 12 h. Protic solvents are known to assist in the oxygen removal of *N*-oxide molecules, so we examined refluxing compound **4c** in toluene/methanol (4:1), Scheme 3.[27] After 12 h, mass spectrometry and NMR showed that complete conversion to **1c** had occurred, with a small amount of impurities. It is also possible to gently convert **4c** into **1c** by suspending the solid in water and warming at 40 °C. Using this method, we could see a clean but slow conversion (approximately 50% after 24 h).

To explore further the generality of the oxidation, we introduced a bulky group at the ortho position to the pyrrolidino nitrogen (Scheme 1). Fullerene molecules **3a**,**b** were easily prepared by employing benzaldehyde and 3-pyridine carboxaldehyde, in the place of formaldehyde, in the cycloaddition reaction. Oxidation did not proceed smoothly, as was the case for **1a**−**c**. After the addition of 1 equiv of *m*CPBA, a quantity that previously generated reasonable product yields, only traces of oxidized material could be observed by TLC. Further oxidation, using another 1 equiv of oxidant, gave sufficient quantities of product, which were isolated using conventional chromatography. HPLC analysis of the products revealed that they contained a mixture of several different products, all having similar retention times. This was verified by mass spectra, which showed multiple oxygen additions, and also by NMR that were characterized by many broad peaks. With conventional chromatography, separation of these molecules proved to be futile, and we did not continue the study of this complicated mixture.

We speculate that steric crowding around the pyrrolidine group tends to inhibit oxidation of the nitrogen atom. In this case, the fullerene cage may be preferentially epoxidized at many different positions. Electronic effects may also be of significance, in which electron-withdrawing substituents may partially deactivate the pyrrolidine nitrogen toward nucleophilic attack. An example of this is the oxidation of **2b** and **2c**, in which the former, bearing an *ortho*-alkyl group, proceeds

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(27) Hans-Rene, B.; Gambarotti, C.; Jensen, V. R.; Gonzalez, R. R. *J. Org. Chem.* **2005**, *70*, 3218−3224.

smoothly, while the latter, bearing an *ortho*-phenyl group, gives reduced yields of *N*-oxide and significant quantities of epoxidized products.

Conclusion

[60]Fullerene−pyrrolidine-*N*-oxides have been prepared in moderate yields (20−40%) using the *m*CPBA oxidation of [60]-fullerene−pyrrolidines. Selective oxidation of the nitrogen atom was favored under dilute conditions, whereas concentrated solutions furnished mixtures of products. Molecules in which the pyrrolidine is sterically crowded tend to shift oxidation away from the pyrrolidino-nitrogen atom and onto the fullerene moiety, giving a multitude of products.

A novel ^{15}N-labeled [60]fullerene−pyrrolidine molecule was synthesized and oxidized to the corresponding *N*-oxide. The presence of a ^{15}*N*-oxide moiety was confirmed using ^{15}N NMR, in which the chemical shift of the nitrogen atom was displaced 85 ppm further downfield in comparison to the unoxidized precursor.

Thermal profiling showed that when heated (80−180 °C) in both solid state and solution, deoxygenation occurs such that the oxygen atom from the *N*-oxide is irreversibly lost.

We have prepared a number of molecules that should be attractive compounds for the study of coordination complexes and biological applications.

Experimental Section

General Procedure for 1,3-Dipolar Cycloaddition. A toluene solution (200 mL) of C_{60} (200.0 mg, 0.28 mmol) and the appropriate aldehyde (0.28 mmol) and amino acid (0.28 mmol) was heated to reflux for 3 h. After cooling to room temperature, the product was purified by column chromatography (toluene or toluene/ethyl acetate, 7:3). The brown solids **1a**−**c**, **2a**−**c**, and **3a**,**b** were dissolved in CH_2Cl_2 and precipitated by the addition of CH_3OH or Et_2O. This precipitation procedure was repeated another two times.

Compound 1a.[28] $C_{69}H_{18}N_2O_2$ (MW, 906.89), 30.7% yield (78.8 mg, 0.086 mmol). MS ($CHCl_3$/MeOH, 1:1) *m*/*z* 907 M^+. UV (CH_2Cl_2) λ_{max}, nm: 255, 322, 430, 703. ^{1}H NMR: δ 4.47 (s, 4H, pyrrolidine), 3.71−3.65 (m, 2H, CH_2), 3.29−3.23 (m, 2H, CH_2), 1.51 (br s, 9H, CH_3).^{13}C NMR: δ 154.73, 146.19, 146.01, 145.94, 145.37, 145.23, 144.49, 143.05, 142.58, 142.14, 142.01, 141.83, 140.11, 136.15, 70.66, 67.75, 54.20, 28.54. IR-DRIFT (KBr): 2980, 2790, 1705, 1510, 1120, 770, 525.

General Procedure B—Oxidation of Compounds 1a−c, 2a−c, 3a,b, and 13. To a solution of compounds **1a**−**c**, **2a**−**c**, **3a**,**b**, and **13** (0.0497 mmol in 100 mL $CHCl_3$) was added, dropwise, *m*CPBA (1 equiv, 0.0497 mmol, in 25 mL $CHCl_3$) over a period of 1 h. Progress was monitored by TLC. The solution was stirred for an additional 30 min and then filtered through a short column of SiO_2, first washing with toluene to remove organic compounds and then with eluent solution to take the product mixture. A concentration on a rotavap to a small amount of liquid (approximately 3 mL) and flash chromatography on SiO_2 (toluene/EtOH or $CHCl_3$/EtOH mixtures as eluent) gave the product (**4a**−**c**, **5a**−**c**, **6a**,**b**, and **14**) as a brown solid.

Compound 4a. $C_{69}H_{18}N_2O_3$ (MW, 922.89), 32.8% yield (15.5 mg, 0.016 mmol). The eluent used was $CHCl_3$/EtOH (9:1). UV (CH_2Cl_2) λ_{max}, nm: 255, 322, 430, 703. MS ($CHCl_3$/CH_3OH, 1:1) *m*/*z* 924 M^+. Purity was checked on HPLC and estimated at 97%. ^{1}H NMR ($CDCl_3$): δ 5.42−5.22 (AB quartet, 4H, J = 10.27 Hz, pyrrolidino Hs), 4.15 (br s, 4H, $-CH_2CH_2$), 1.50 (s, 9H, *tert*-butylcarbonyl). ^{13}C NMR ($CDCl_3$/CD_3OD, 8:2): δ 153.92, 151.51, 147.11, 146.05, 145.59, 145.72, 145.59, 145.44, 145.08, 145.00, 144.68, 144.47, 144.06, 142.39, 141.81, 141.61, 141.46, 141.24, 139.75, 137.78, 135.34, 79.89, 68.86, 35.63, 28.12. IR-DRIFT (KBr): 2973, 1710, 1518, 1373, 1288, 1266, 1174, 767, 545 cm^{-1}.

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Supporting Information Available: Experimental procedure, ^{1}H and ^{13}C or ES-MS spectra for compounds **1c**, **2b**,**c**, **4a**−**c**, **5a**−**c**, and **7**−**14**. TGA analysis for **5a**, DSC analyses for **4c** and **5b**,**c**, and HPLC analysis of **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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