Stabilization of fulleropyrrolidine *N*-oxides through intrarotaxane hydrogen bonding†

Aurelio Mateo-Alonso,* Peter Brough and Maurizio Prato*

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The chemical stabilization of labile fulleropyrrolidine *N*-oxides is achieved by encapsulation through intrarotaxane hydrogen bonding.

Since the commercialization of fullerenes in 1990, several protocols for their functionalization have been developed.[1,2] One of the most versatile and popular procedures is the 1,3-dipolar cycloaddition of azomethine ylides,[3,4] which yields the highly stable fulleropyrrolidines. Recently, we have reported their oxidation to fulleropyrrolidine *N*-oxides as a novel family of fullerene derivatives.[5] Both fullerenes[6] and *N*-oxides[7] are well known for their ability to stabilize negatively charged species. In principle, the combination of both would potentially lead to groups with improved ability for stabilizing radicals.[7] This is particularly important in molecular photovoltaics, where the lifetime of a photogenerated radical-pair has a direct influence on solar photoconversion efficiency.[8,9] One of the disadvantages of fulleropyrrolidine *N*-oxides is their thermal instability, which complicates their study and characterization. In fact, the derivatives are only stable for days, even if stored at −20 °C. Their instability is patent from the facile reversibility of the oxidation reaction. Fulleropyrrolidine *N*-oxides can be cleanly deoxygenated to their parent fulleropyrrolidines by heating in the presence of protic solvents.[5]

A practical approach for the stabilization of labile species is based on their encapsulation by other molecules.[10] In this context, rotaxanes have shown to be very useful since they are comprised of a molecular axle encapsulated by a macrocycle. Encapsulation in rotaxanes has been applied not only in the enhancement of chemical[11] and photochemical[11–14] stability of other molecules but also as a way to modulate the physical properties[15–18] of the encapsulated parts. We have described the synthesis and properties of several fulleropyrrolidine stoppered rotaxanes[19–22] using the benzylic amide protocol of Leigh *et al.* In such rotaxanes, the macrocycle is clipped through hydrogen bond recognition between the precursors of the macrocycle and a template comprised of amides as binding sites. In this article, we report how the macrocycle can be translocated from a succinamide template to bind preferentially and encapsulate a fulleropyrrolidine *N*-oxide by hydrogen bonding. Remarkably, the encapsulation of the *N*-oxide by the macrocycle increases its chemical stability and inhibits its deoxygenation.

We began our research by studying thread **1**,[21] which consists of a fullerene stopper linked to a succinamide template that is connected to a diphenyl stopper through a long alkyl chain (Scheme 1). The known epoxidation reactions of fullerene itself are of some concern,[23] and, to minimize this undesired side reaction, we employed high dilution conditions. A dilute solution of *m*CPBA was added to a dilute solution of thread **1** over one hour. The reaction was monitored using thin layer chromatography and was never driven to completion in order to avoid the formation of mixed *N*-oxide–epoxide bisadducts. Purification by flash chromatography and reprecipitation yielded the desired thread *N*-oxide **2**. The solubility of thread *N*-oxide **2** in organic solvents is different to its unoxidized counterpart; for example, thread **1** dissolves well in chloroform, whereas thread *N*-oxide **2** is only sparingly soluble. This is a common theme spanning all of the molecules described in this work. However, the *N*-oxide molecules are more soluble in solvent systems of greater polarity.

The structure and behaviour of thread *N*-oxide **2** were confirmed from ^{1}H NMR and COSY experiments in different solvents. The NMR spectra show the typical signals of fulleropyrrolidine *N*-oxides.[5] From the unoxidized thread **1** to the oxidized thread **2** there is a distinct change in the ^{1}H NMR chemical shift of the protons D (the assignments correspond to the lettering shown in Scheme 1) belonging to the pyrrolidine group (Fig. 1a and 1c). For thread **1**, they show as a singlet at 4.5 ppm, owing to rapid pyramidal inversion, whereas in the case of thread *N*-oxide **2**, they split as an AB quartet at 5.1 ppm. The signals of protons J and G are shifted downfield due to the inductive effect of the partial positive charge on the nitrogen of the fulleropyrrolidine. Remarkably, the amidic proton A of thread *N*-oxide **2** is shifted downfield from 6.8 to 8.2 ppm, indicating that is hydrogen bonded. At a closer look, proton A and the fulleropyrrolidine *N*-oxide can establish an intramolecular hydrogen bond through a highly favoured chair-like complex. *N*-Oxides can form stronger hydrogen bonds than amides since they are more polarized and possess a higher hydrogen bond basicity.[24] Since no other interactions can be identified and the NMR experiments were carried out in very dilute solutions ($\ll 4 \times 10^{-3}$ M) due to the low solubility of thread *N*-oxide **2**, we must assume the intramolecular hydrogen bonded structure shown in Scheme 1. The NMR (^{1}H and COSY) experiments carried out in DMSO-d_6 confirm the structure of thread *N*-oxide **2**. In this case, the chemical shifts of the amidic protons (A, B and C) correspond with those of thread **1** in the same solvent, showing that there are no hydrogen bonds. In

Italian Interuniversity Consortium on Materials Science and Technology (INSTM), Unit of Trieste, Dipartimento di Scienze Farmaceutiche, Università degli Studi di Trieste, Piazzale Europa 1, 34127 Trieste, Italy. E-mail: amateo@units.it; prato@units.it; Fax: +39 040 52572; Tel: +39 040 5587883

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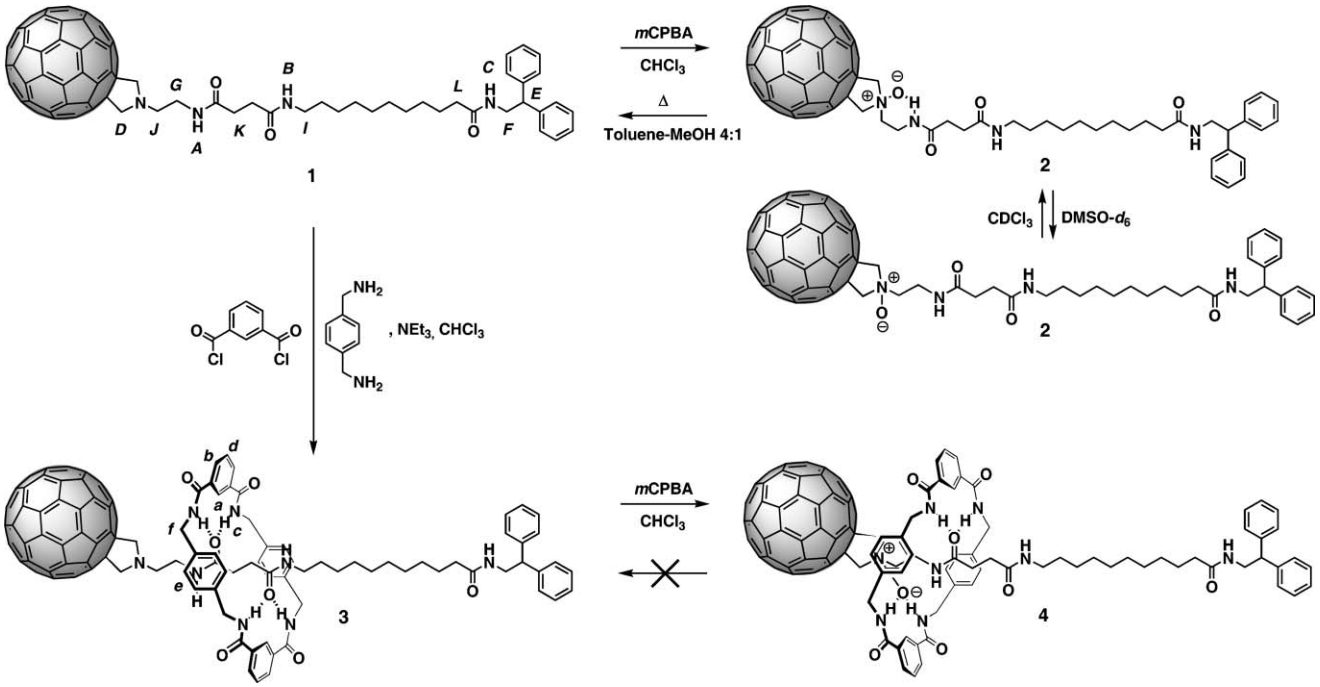

Scheme 1 Synthesis and behaviour of fulleropyrrolidine *N*-oxides.

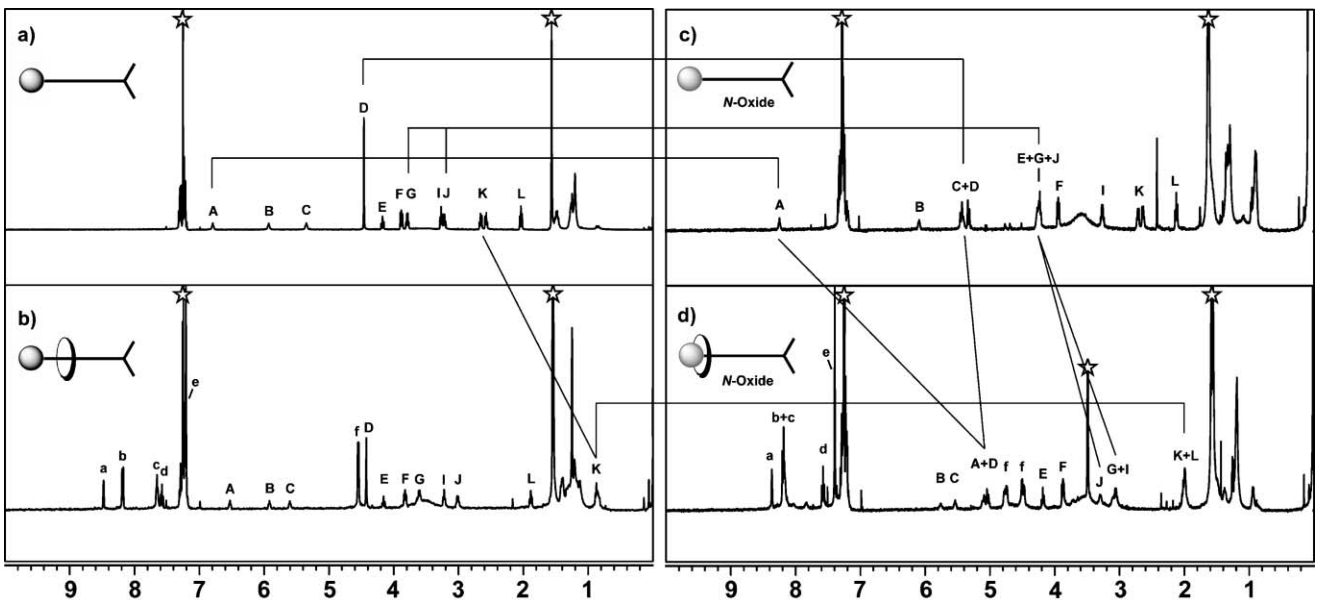

Fig. 1 400 MHz NMR spectra of (a) thread **1**; (b) rotaxane **3**; (c) thread *N*-oxide **2** in $CDCl_3$; (d) rotaxane **4** in $CDCl_3$–CD_3OD 99 : 1. Peaks highlighted with stars correspond to residual solvent signals.

fact, DMSO possesses similar hydrogen bond basicity to that of the *N*-oxide,[24] breaking the intramolecular hydrogen bonds by preferentially solvating the hydrogen bonding sites.

Thread *N*-oxide **2** presents enhanced stability when compared with other fulleropyrrolidine *N*-oxides and is stable for months at −20 °C. This might be due to the stabilization of the *N*-oxide by intramolecular hydrogen bonding. Nevertheless, thread *N*-oxide **2** behaves as the previous fulleropyrrolidine *N*-oxides and can be converted to the initial thread **1** by thermal deoxygenation in a solution of toluene–MeOH (4 : 1).

Rotaxane **3** was assembled by simultaneous addition of isophthaloyl chloride and *p*-xylylenediamine to a solution of thread **1** in the presence of triethylamine.[21] Purification by flash chromatography to separate unreacted thread **1**, followed by reprecipitation–centrifugation, yielded rotaxane **3**. NMR spectroscopy is the best tool to locate precisely the location of the macrocycle along the thread. The encapsulated thread protons are shielded by the anisotropy effect of the aromatic rings of the macrocycle, revealing its position. In $CDCl_3$, protons K were shielded by nearly 1.4 ppm relative to the thread, showing that the

macrocycle is located over the succinamide template (Scheme 1, Fig. 1a and 1b).

Rotaxane **3** was allowed to react with *m*CPBA using the high dilution conditions for the preparation of thread *N*-oxide **2**. Rotaxane **4** was purified from unreacted rotaxane **3** by flash chromatography, followed by reprecipitation–centrifugation. As expected, rotaxane **4** presents the lowest solubility of the whole set of molecules studied, being almost insoluble in $CDCl_3$. However, the compound was sparingly soluble in $CDCl_3$–CD_3OD 99 : 1. In the NMR spectrum of rotaxane **4** (Scheme 1, Fig. 1d), shielding of protons D, J and G (0.4, 0.9 and 1.2 ppm respectively) is observed when compared with thread *N*-oxide **2** (Fig. 1c), while protons K undergo negligible shielding in comparison with thread *N*-oxide **2** (Fig. 1c) and are deshielded by 1.1 ppm in comparison with rotaxane **3** (Fig. 1b). Therefore the macrocycle was displaced from the succinamide template to bind preferentially the *N*-oxide and the adjacent amide. This is consistent with the fact that *N*-oxides are better hydrogen bond acceptors than amides.[24] The macrocycle is located over the mixed *N*-oxide–amide binding site even in DMSO-d_6, where signals D, J and G were shielded by 0.6, 0.9 and 0.9 ppm respectively. This is in contrast with what has been observed previously for hydrogen bonding sites in which internal rotation and intramolecular hydrogen bonds can take place,[25] where shuttling is a consequence of solvation of the binding sites.[19,21] It can be argued that the shielding of protons D, J and G in DMSO-d_6 could be due to the reverse shuttling[21] observed in the unoxidized rotaxane **3**. However, if interactions between the macrocycle and the fullerene were responsible for its position, protons D would be more shielded than J and G because of the closer proximity of the macrocycle to the fullerene as observed in rotaxane **3**, while in this case protons J and G are by far more shielded than those of D.

Rotaxane **4** and thread *N*-oxide **2** show enhanced stability when compared with other fulleropyrrolidine *N*-oxides and are stable for months at −20 °C. Additionally, rotaxane **4** did not undergo deoxygenation under the typical thermal activation conditions, 12 h reflux in toluene–methanol (4 : 1). These results indicate that the enhanced stability of the rotaxane *N*-oxide is a function of both intramolecular hydrogen bonding and encapsulation of the *N*-oxide.

We have demonstrated that the labile fulleropyrrolidine *N*-oxides can be stabilized by intramolecular and intrarotaxane hydrogen bonding. The stabilizing effect is especially strong in the case of intrarotaxane hydrogen bonding, in which *N*-oxidation could not be reversed due to encapsulation of the *N*-oxide by the macrocycle.

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