Tetrahedron xxx (2015) 1–9

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Synthesis and properties of bis(pyrrolidino)fullerenes bridged by a flexible alkyl-tether

Tatjana Kop [a], Mira Bjelaković [a], Dragana Milić [b,*]

[a] ICTM-Center for Chemistry, University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia
[b] Faculty of Chemistry University of Belgrade, Studentski trg 12-16, 11158 Belgrade, Serbia

ARTICLE INFO

*Article history:*
Received 24 February 2015
Received in revised form 29 April 2015
Accepted 11 May 2015
Available online xxx

*Keywords:*
Fullerene
Biscycloaddition regioselectivity
SEM
FOX method

## ABSTRACT

The one-pot biscycloaddition of alkyl-tethered diglycines to $C_{60}$ provided five series of bridged bis(pyrrolidino)fullerenes with good regioselectivity, giving mainly *cis*-2 and *cis*-3 products. An influence of the bridge length and addition pattern on spectroscopic properties, as well as on the shape of hierarchically organized supramolecular structures was observed. Additional investigation of all synthesized compounds confirmed their strong in vitro antioxidant activity 4–10-fold better than the standard antioxidant vitamin C.

## 1. Introduction

Due to pronounced antioxidant capacity and rigid well-defined 3D-structure $C_{60}$ fullerene is an attractive building block in material and bioorganic chemistry, but its usage is limited by low solubility in both polar and nonpolar media. Two main approaches to overcome this problem are non-covalent encapsulation in a variety of carriers (calixarenes,[1] cyclodextrins,[2,3] micelles,[4] liposomes[5]) and covalent functionalization. Among the many possible reactions,[6] cycloadditions such as Bingel, Diels–Alder or Prato reaction, are the most common way to improve the solubility by covalent modification. Fulleropyrrolidines obtained in 1,3-dipolar cycloaddition of azomethine ylides to $C_{60}$ (Prato reaction) are stable compounds with well-defined structure and tunable electrochemical and morphological properties. Nanometre size of molecules and particular 3D-structure are crucial in their possibility to participate in some biomimetic processes. Unique electrochemical properties, emerged from the low energy gap between HOMO and LUMO levels, providing widespread utilization of fulleropyrrolidines in materials chemistry and electrochemistry. Although mono-adducts of fulleropyrrolidines easily undergo further addition to yield higher, mainly bis- and trisadducts, low selectivity of this reaction and large number of possible isomers[7] aggravates its wider synthetic application. On the other hand, bisadducts have proved to be more applicable then parent monoadducts in many research domains. For example, bis-dendritic fulleropyrrolidine possessed better liquid-crystalline properties than related monoadduct.[8] Also, some cationic bisadducts exerted significantly higher anti-HIV activity than the parent monoadduct.[9] As such, there was a need to improve the selectivity of multiaddition reactions in aim to get pure bisadducts in higher yields. Significant breakthroughs in selectivity were made with rigid tether templated bisaddition[10–14]—from selective synthesis of the *equatorial* mixed Bingel–Diels–Alder bisadduct in 50% yield,[15] over targeted preparation of a single or major isomer of bis(methano)fullerenes bridged with different poorly flexible spacers (xylenes,[16] Tröger bases,[17] porphyrins,[18,19] crown ethers[20]) to Prato's bisaddition with bridged bisaldehydes.[21,22] In all cases the spacer geometry strongly influenced the distribution of regioisomers, i.e., its rigidity favoured some of the addition patterns. Thus, tether templated bis-Prato reaction with biphenyl-bridged dialdehyde afforded in good yield even commonly low-yielding *trans*-1 product (together with *trans*-2 isomer).[22] Selective templated tandem addition of nitrile oxide and azomethine ylide connected with short alkyl chain (3 or 4C-atoms) gave exclusively *cis*-1 products in excellent yield (65% and 67%, respectively), but the increase of the tether flexibility to 5C led to a mixture of *cis*-1, *cis*-2 and *cis*-3 adducts in 54%, 2%, and 31% yield, respectively.[23] Furthermore, employing dialdehydes as templating moieties always enlarges the number of products due to introduction of the stereocenter on the pyrrolidinic ring. It should be

---

* Corresponding author. Tel.: +381 11 263 5104; fax: +381 11 263 6061; e-mail address: dmilic@chem.bg.ac.rs (D. Milić).

http://dx.doi.org/10.1016/j.tet.2015.05.038
0040-4020/© 2015 Elsevier Ltd. All rights reserved.

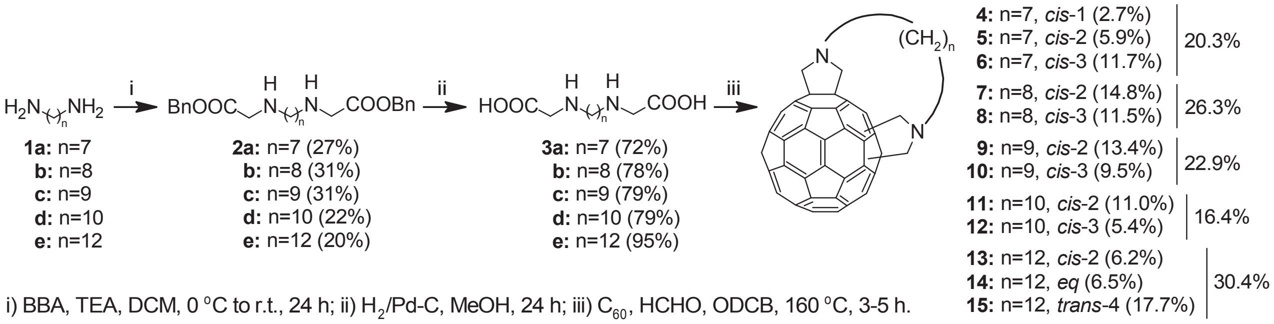
Please cite this article in press as: Kop, T.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.038

mentioned that bisadducts were also obtained by regioselctive intramolecular reactions involving [2+2]-cycloaddition[24] and nucleophilic addition.[25]

Increasing functionalization of the fullerene reduces the aggregation of obtained derivatives and consequently improves their solubility, expanding at the same time the possibility of application. Therefore we supposed that formation of bis(pyrrolidino)fullerenes, bridged by a flexible alkyl chain could contribute to the study of the bisaddition selectivity, as well as to the development of upgraded, more soluble fullerene derivatives. In this work we present the synthesis, characterization and morphological properties, as well as in vitro antioxidant activity of alkyl bridged bis(pyrrolidino)fullerenes. In addition, the influence of the tether length on several parameters was examined, including the selectivity and efficacy of the one-pot biscycloaddition to $C_{60}$, spectroscopic properties, morphology and radical scavenging capacity of obtained compounds.

## 2. Results and discussion

Quite regioselective, but non-stereoselctive synthesis of bridged bis(pyrrolidino)fullerenes with a tether connected to the pyrrolidine stereogenic carbon (C-2) have already been performed using simple amino acids and dialdehydes containing rigid, aromatic linker.[21,22] In order to avoid stereocentre formation, as well as the steric influence of *C*-pyrrolidino-substituents on reaction selectivity, formaldehyde and *N*-linked diglycino derivatives were chosen as precursors. Bis(pyrrolidino)fullerenes bridged by medium ($n$=7–9C) to long ($n$=10 and 12C) alkyl chains were prepared by [3+2]-cycloaddition of azomethine ylides to $C_{60}$ following the synthetic pathway outlined in Scheme 1. Starting α,ω-diamines **1** underwent dialkylation-deprotection procedure, including simultaneous monoalkylation of both amino groups with benzyl bromoacetate (BBA), and Pd/*C*-catalyzed hydrogenolysis of obtained esters **2** to corresponding diglycino-derivatives **3**. In the presence of formaldehyde, thermally generated bis(azomethine)ylides underwent double 1,3-dipolar cycloaddition to $C_{60}$ providing target bis(pyrrolidino)fullerenes **4**–**15**. The last step was investigated using the medium-chain length diacid, $C_8$-diglycine **3b** as a model compound. Transformations of an equimolar mixture of $C_{60}$ and **3b** in the presence of 10-fold molar excess of paraformaldehyde were monitored under thermal and MW-assisted conditions, varying the temperature, solvent and reaction time (Table 1). In all experiments only two of eight theoretically possible regioisomers were formed—*cis*-2 (**7**) and *cis*-3 (**8**). No monoadduct, other bisregioisomers, nor dumbbell type difullerene derivative were detected. In all experiments, the remaining, highly polar fraction of the crude reaction mixture remained tightly adsorbed on the silica column. The relative ratio of the two synthesized bisadducts remained nearly constant over the experiments, but overall yield varied with reaction conditions. Using ODCB as a solvent under thermal conditions provided both better solubility of reactants and higher reaction temperature in comparison to toluene, affording notably higher overall yield of the products and elevated conversion of the fullerene (experiments 1 and 2 vs 3). Increasing the temperature of ODCB solution of reactants enabled better conversion of the $C_{60}$, but no improvement of the yield of bisadducts, nor significant change in *cis*-2/*cis*-3 ratio were achieved (experiments 1 and 2). Microwave irradiation did not give any improvement neither in efficiency nor selectivity (experiments 1–3 vs 4–6). Optimal reaction conditions included ODCB as a solvent, temperature range of 160–165 °C and reaction time of 4 h (Table 1, exp.1). Other diglycino-derivatives (**3a**, **3c**–**e**) were also exposed to them, and in all reactions significant regioselectivity was reached (Scheme 1, Fig. 1).



**Scheme 1.** Synthetic pathway for $n$-alkyl-tethered bispyrrolidino $C_{60}$ adducts **4**–**15**.

Results presented in Scheme 1 and Fig. 1 showed that even flexible alkyl-tethers guided the formation of bisadducts with considerable regioselectivity, but with no proportional relation between the length of the tether and the addition pattern. Thus, the shortest $C_7$-bridge afforded only *cis*-isomers in a moderate overall yield of 20%. Besides formation of sterically most demanding *cis*-1 bisadduct **4**, it is also important to emphasize the unusual regioselectivity of this reaction, yielding *cis*-3 regioisomer **6** as a main product (12%) in two- and four-fold excess over *cis*-2 **5** and *cis*-1 **4**, respectively. This is a rare example for bis(pyrrolidino)fullerene synthesis with *cis*-3 adduct as a dominant product. Frequently, no *cis*-3 isomer at all, or its very low contribution in the mixture of bisadducts was observed in Prato's bisadditions.[7] Further tether elongation to 8–10 methylene units led to even greater regioselectivity giving *cis*-2 and *cis*-3 isomers **7**–**12** exclusively, with *cis*-2 as a main product (11–15%). The $C_8$- and $C_9$-linkers provided a slight excess of corresponding *cis*-2 over *cis*-3 compound (1.4- and 1.3-fold, respectively), while with $C_{10}$-bridge a two times higher yield of *cis*-2 isomer was reached. Finally, the largest, $C_{12}$-flexible tether gave quite good regioselectivity affording the mixture of three bisadducts in a good yield (30%), with a clearly dominant *trans*-4 isomer **15** in almost three-fold excess over *cis*-2 **13** and *equatorial* **14**.

All compounds were characterized by FTIR, UV–vis, $^1H$–$^{13}C$ NMR spectroscopy and by HR mass spectrometry. The addition pattern of obtained regioisomers was elucidated by detailed analysis of their UV–vis and NMR spectra, and by spectral data comparison with those of known bispyrrolidine adducts of fullerene. All bisadduct isomers gave correct ESI quasimolecular $[M+1]^+$ ion peak in their ESI-TOF-MS spectra. UV–vis spectroscopy is a reliable tool in the determination of fullerene bisadducts structure since each addition pattern results in the specific schedule of absorption

Please cite this article in press as: Kop, T.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.05.038