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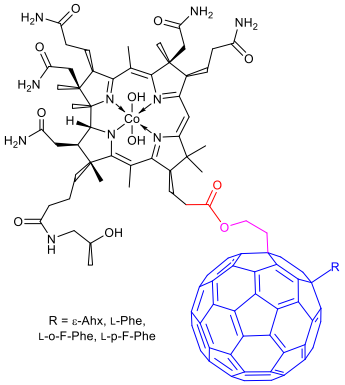
HYBRID NANOSTRUCTURES BASED ON MONO(AMINO ACID) DERIVATIVES OF FULLERENE C_{60} AND VITAMIN B_{12}

N. Yu. Shepeta*

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, str. 1, Moscow, 119334 Russia

Abstract

This minireview highlights the author's own works on the synthesis and investigations of the properties of hybrid nanostructures (HNSs) based on mono(amino acid) derivatives of fullerene C_{60} and vitamin B_{12}. The synthetic routes to monoderivatives of fullerene C_{60} with various amino acids and the methods for obtaining their hybrid nanostructures with vitamin B_{12} derivatives were developed. The structures of the resulting compounds and the sizes of their nanoparticles were studied by different physicochemical methods. It was shown that the HNSs with catalytically active derivatives of vitamin B_{12} retain the activity in the autoxidation of ascorbic acid, which is characteristic of some derivatives of vitamin B_{12}.



Key words: amino acids, vitamin B_{12}, fullerene C_{60}, hybrid nanostructures.

Introduction

Fullerene derivatives are known to exhibit a broad spectrum of biological activity [1, 2]. Water-soluble derivatives of fullerene C_{60} exhibit antioxidant, membranotropic, neuroprotective, antiviral, antibacterial, and antitumor properties and also act as effective low-toxic delivery systems of drugs for various diseases to their targets [3, 4].

This work was envisioned by the full member of the Academy of Sciences of USSR M. E. Volpin and carried out by his colleagues at INEOS RAS. V. S. Romanova was the first to develop a unique method for the synthesis of mono(amino acid) and peptide derivatives of fullerene [5]. The resulting compounds appeared to be non-toxic, are easily excreted from the body, and display different types of biological activity.

Mono(amino acid) derivatives of fullerene C_{60} and vitamin B_{12}

According to M. E. Volpin [6], the catalytic sources of reactive oxygen species (ROS), which selectively accumulate in a tumor, can actively suppress the growth of malignant cells. Of particular interest are natural macrocyclic complexes of cobalt: vitamin B_{12} and its derivatives (cobalamins, including B_{12} e-monocarboxylic acid (e-COOH-Cbl-CN, **1**) and e-carboxy-dihydroxycobinamide (e-COOH-Cbi-$(OH)_2$, **2**), Fig. 1).

It was established that cobalamins can be used as delivery systems of drugs to a tumor [7]. However, the molecule of vitamin B_{12} itself hardly passes through cell membranes. This can be mitigated by the partial hydrophobization of the vitamin molecule, which, in turn, can be achieved by attaching it to a hydrophobic compound, for example, a derivative of fullerene C_{60}.

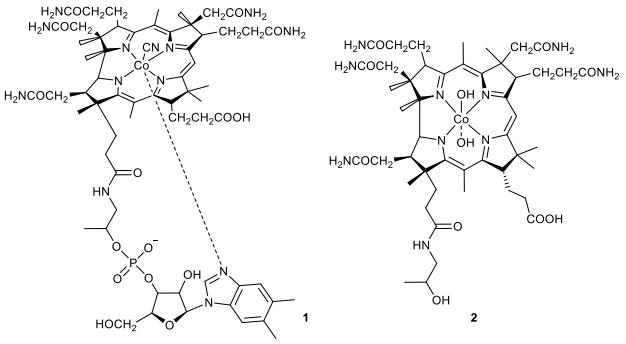


Figure 1. Structures of B_{12} e-carboxylic acid (**1**) and e-carboxy-dihydroxycobinamide (**2**).

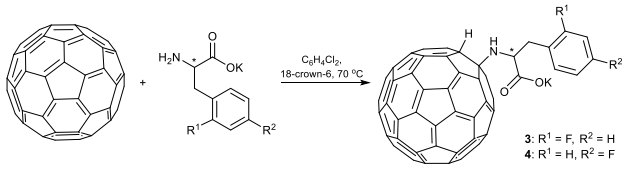
At the first stage of investigations, the principal possibility of obtaining new compounds based on a conjugate of catalytically inactive B_{12} e-carboxylic acid **1** and a derivative of fullerene C_{60} with ε-aminocaproic acid [8] in two ways was demonstrated.

After that, a hybrid nanostructure combining a catalytically active form of vitamin B_{12}, e-carboxy-dihydroxycobinamide **2**, and *N*-(monohydrofullerenyl)-ε-aminocaproic acid was synthesized. It was found that the resulting HNS retains the catalytic activity in the oxidation of a natural substrate, namely, ascorbic acid, inherent in compound **2** [9].

It was shown that the biological activity of the resulting conjugate changes upon variation of the structure of the amino acid incorporated into the composition of the fullerene C_{60} derivative [10]. Recently, the successful production of a hybrid nanostructure based on a salt of fullerene-L-phenylalanine acid

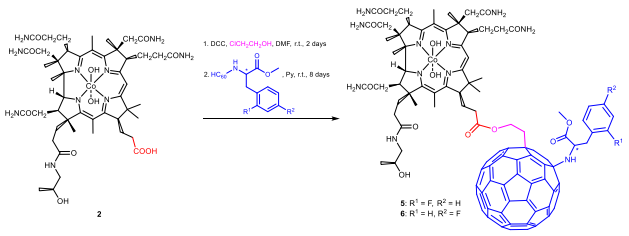
and e-carboxy-dihydroxycobinamide **2** was reported [11]. This HNS was also found to be catalytically active, just like initial compound **2**.

The introduction of a fluorine atom into an amino acid molecule usually imparts new biological properties to the final product [12, 13]. To expand the spectrum of biological activity of amino acid and peptide derivatives of fullerenes, the following amino acids were used as starting compounds for the synthesis of water-soluble derivatives of fullerene C_{60}: L-phenylalanine, *o*-fluoro-L-phenylalanine, and *p*-fluoro-L-phenylalanine. The first stage was the synthesis of the fullerene derivatives with *o*-fluoro-L-phenylalanine and *p*-fluoro-L-phenylalanine. L-Phenylalanine derivatives of fullerene C_{60} [14] were obtained by our research group (Scheme 1) according to the earlier suggested method [5].



Scheme 1. Synthesis of the salts of the fullerene-substituted L-phenylalanine acids.

Next, the resulting nanostructures of *N*-(monohydrofullerenyl)amino acids (**3**, **4**) were combined with a derivative of vitamin B_{12}, namely, e-carboxy-dihydroxycobinamide (**2**). Since complex **2** contains several free hydroxy groups, the addition should be carried out without the use of thionyl chloride. Therefore, a synthetic approach based on the introduction of an ethylene spacer and the application of DCC as a coupling agent was suggested (Scheme 2).



Scheme 2. Synthesis of the derivatives of *N*-(monohydrofullerenyl)-L-phenylalanine and e-carboxy-dihydroxycobinamide (**5**, **6**).

The structures of all HNSs obtained based on mono(amino acid) derivatives of fullerene C_{60} and e-carboxy-dihydroxycobinamide were confirmed by various physicochemical methods [14].

It was found that the resulting HNSs exhibit catalytic activity in the autoxidation of ascorbic acid, but their activity is slightly lower than that of the derivatives of vitamin B_{12} [9, 14]. This can be explained by a decrease in the relative concentration of a vitamin B_{12} moiety in the molecules of the hybrid nanostructures and partial deactivation of the resulting ROS by the fullerene framework. It should be noted that the data obtained by us are consistent with the results for similar structures based on pure chlorin and its fullerene derivative [15]. The substituted fullerene unit in the resulting conjugate will likely to be able to compensate for a decrease in the catalytic activity by imparting the lipophilic properties to a hybrid nanostructure, which is facilitated by amino acid derivatives of fullerene, capable of entering the cell without destroying a lipid bilayer of the cell membrane.

Conclusions

The effective chemical strategies for the synthesis of hybrid nanostructures based on e-carboxy-dihydroxycobinamide and *N*-(monohydrofullerenyl)amino acids were developed. The monoderivatives of fullerene C_{60} with ε-aminocaproic acid, L-phenylalanine, *o*-fluoro-L-phenylalanine, and p-fluoro-L-phenylalanine, as well as their hybrid nanostructures with the vitamin B_{12} derivatives were obtained and characterized. The catalytic activity of the resulting nanostructures in the ascorbic acid autooxidation was demonstrated.

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Corresponding author

* E-mail: nadshep@mail.ru. Tel: +7(916)248-7483 (N. Yu. Shepeta).

References

1. D. Petrovic, M. Seke, B. Srdjenovic, A. Djordjevic, *J. Nanomater*., **2015**, 565538. DOI: 10.1155/2015/565638
2. F. Moussa, in: *Nanostructured Materials for Biomedical Applications*, R. Narayan (Ed.), Elsevier, Duxford, **2018**, ch. 5, pp. 113–136. DOI: 10.1016/B978-0-08-100716-7.00005-2
3. L. B. Piotrovskii, O. I. Kiselev, *Fullerenes in Biology*, Rostok, St. Petersburg, **2006**, pp. 92–235 (in Russian).
4. M. A. Dumpis, D. N. Nikolayev, E. V. Litasova, V. V. Iljin, M. A. Brusina, L. B. Piotrovsky, *Rev. Clin. Pharmacol. Drug Ther.*, **2018**, *16*, 4–20. DOI: 10.17816/RCF1614-20
5. V. S. Romanova, V. A. Tsyryapkin, Yu. I. Lyakhovetsky, Z. N. Parnes, M. E. Vol'pin, *Russ. Chem. Bull.*, **1994**, *43*, 1090–1091. DOI: 10.1007/BF01558092
6. M. E. Vol'pin, N. Yu. Krainova, I. Ya. Levitin, Z. Ya. Mityaeva, G. N. Novodarova, V. K. Oganezov, A. A. Pankratov, V. I. Chissov, R. I. Yakubovskaya, *Ross. Khim. Zh.*, **1998**, *XLII*, 116–127.
7. D. V. Beigulenko, N. Yu. Shepeta, K. A. Kochetkov, S. E. Gelperina, *Macroheterocycles*, **2022**, *15*, 6–17. DOI: 10.6060/mhc224244k
8. V. S. Romanova, N. Yu. Shepeta, Z. S. Klemenkova, K. K. Babievskii, D. V. Beigulenko, I. A. Yamskov, K. A. Kochetkov, *INEOS OPEN*, **2019**, *2*, 41–44. DOI: 10.32931/io1907a
9. V. S. Romanova, N. Yu. Shepeta, Z. S. Klemenkova, K. A. Kochetkov, *Mendeleev Commun.*, **2021**, *31*, 844–846. DOI: 10.1016/j.mencom.2021.11.025
10. RU Patent 2196602, **2003**.
11. V. S. Romanova, N. Yu. Shepeta, *INEOS OPEN*, **2022**, *5*, 91–98. DOI: 10.32931/io2217r
12. S. Huhmann, B. Koksch, *Eur. J. Org. Chem*., **2018**, 3667–3679. DOI: 10.1002/ejoc.201800803

13. J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes, B. Koksch, *Chem. Rev*., **2019**, *119*, 10718–10801. DOI: 10.1021/acs.chemrev.9b00024
14. K. A. Kochetkov, V. S. Romanova, N. Yu. Shepeta, *Fullerenes, Nanotubes Carbon Nanostruct*., **2024**, *32*, 836–845. DOI: 10.1080/1536383X.2024.2334403
15. A. Yu. Belik, A. Yu. Rybkin, N. S. Goryachev, A. P. Sadkov, N. V. Filatova, A. G. Buyanovskaya, V. N. Talanova, Z. S. Klemenkova, V. S. Romanova, M. O. Koifman, A. A. Terentiev, A. I. Kotelnikov, *Spectrochim. Acta*, *Part A*, **2021**, *260*, 119885. DOI: 10.1016/j.saa.2021.119