First synthesis of a new fullerene oximes bis(9-[hydroxo]-1-[1’-hydroxymino-2’-oxo-2’-alkyl-ethyl])1,9-dihydro-[C₆₀-I₄]₁₁[5,6]fullerenes via reaction of C₆₀ with ketones and NaNO₂ promoted by HCl

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ABSTRACT
A mixture of cis-2 and cis-3 isomers of new fullerene derivatives bis(9-[hydroxo]-1-[1’-hydroxymino-2’-oxo-2’-alkyl-ethyl])1,9-dihydro-[C₆₀-I₄]₁₁[5,6]fullerenes have been selectively synthesized with high yields at the reaction of C₆₀ fullerene with ketones Me₂CO, EtMeCO, i-PrMeCO, PhMeCO in the presence of NaNO₂ and HCl.

Introduction
Oxime derivatives of [60]fullerene are prospective as complexation reagents, physiologically active compounds and precursors for further chemical functionalization leading to fullerene derivatives with desired properties (1–5). At the same time, the works on the synthesis of fullerene oximes are limited. For example, the reaction of C₆₀ with nitroalkanes (RCH₂NO₂; R = H, Me, CH₂CH₂COOEt) in the presence of trimethylamine Et₃N and trimethylsilylchloride Me₃SiCl (−20°C, Ar, 30 min) results in the intermediate isoioxolidine cycloadduct of C₆₀, which then converts into β-hydroxyxime of C₆₀ fullerene (34–65% yields) via its treatment with tetraethylammonium chloride (−20°C, Ar, 60 min) and neutralization by HCl (6). However, this synthetic methodology requires cooling and involves formation of two intermediate products. One-pot room-temperature synthesis of β-hydroxyximes of fullerene C₆₀ (34–46% yields, 2 hrs) has been performed by using of nitroalkane excess (C₆₀:RCH₂NO₂ = 1:20; R = H, Me, CO₂Et, CH₂CH₂CO₂Et, CH₂CH₂CO₂Bu¹, Bn) (7). Chemical modification of cyclopropane derivative of C₆₀ with oxylamine group has been used to attach diverse oligosaccharides to fullerene cage via strong oxime bonds (yields of the target compounds are not provided) (8). To our knowledge hitherto not been obtained fullerene oximes containing a carbonyl group.

Materials and methods
We used a commercial C₆₀ (99.9%), produced by arc discharge between graphite electrodes (Institute of Organometallic Chemistry, G.A. Razuvaev, RAS, Nizhny Novgorod). The solvent CCl₄ was purified according to the procedure (9). NaNO₂, acetone, acetonaphone, methyl ethyl ketone and methyl isopropyl ketone were analytical grade and used as purchased. High performance liquid chromatography (HPLC) was performed on Hewlet Packard, series 1090, with a UV detector (λ_max = 340 nm), Buckyprep Waters 4.6 × 250 mm column at a temperature of 30°C, toluene as a mobile phase, flow rate 1.0 mL/min. The components of the mixture were separated using a Cosmosil Buckyprep Waters semi-column 250 × 10 mm at room temperature; mobile phase: toluene; flow rate: 2.0 mL/min. UV-Visible spectra were recorded on a Perkin Elmer Lambda 750 spectrometer (I = 0.1; 1 cm). IR spectra have been recorded by a Vertex 70 V spectrometer (Bruker) in CHCl₃. The NMR spectra of ¹H and ¹³C were recorded on Bruker Avance-400 spectrometer (operating frequency of 400.13 MHz and 100.62). CDCl₃ was used as a solvent (δ 77.1 ppm), internal standard—(CH₃)₂Si. Mass spectra were obtained on the Bruker MALDI TOF/TOF Autoflex-III instrument with a laser desorption and registration of positive and negative ions in the reflective mode. The elementary sulfur Sₙ was used as a matrix.

General procedure for the synthesis of the C₆₀ bisadducts 1–4
To solution of C₆₀ in CCl₄ (30 mg, 0.04 mmol) were sequentially added ketones (Me₂CO, EtMeCO, i-PrMeCO, PhMeCO) (0.4 mol), NaNO₂ (0.1 mol), and HCl (0.2 mol). Immediately after the addition of HCl, were observed vigorous evolution of brown gas and the deep purple solution became dark brown and white precipitate is formed. The reaction solution was mixed in brown gas and the deep purple solution became dark brown and white precipitate is formed. The reaction solution was mixed in 30 min and then neutralized by CaCO₃. The liquid phase was separated by filtration and analyzed by HPLC. Reaction kinetics was monitored by the decrease of the C₆₀ peak up to the 100% conversion. HPLC of the solution after reaction contains the single broadened peak with the retention time equal to 6.2 min. The reaction products were isolated by semipreparative HPLC with toluene as an eluent. Unfortunately, the replacement of toluene by the polar eluent CH₃CN:H₂O = 4:1 also did not allow separating the regioisomeric bisadducts. Additional purification

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was successfully performed by water washing (3 × 50 mL). When water added, two liquid layers aroused, so by-products were removed to the water layer. A liquid organic residue was dried under anhydrous MgSO₄, and toluene was distilled off. The obtained precipitates 1–4 were dried in vacuo.

"bis(9-[hydroxo]-1-[1'-hydroximino-2'-oxo-2'-methyl-ethyl])-1,9-dihydro-[C₆₀-Ih] [5,6]fullerene 1." 95% (37 mg). ¹³C NMR (100.62 MHz, CDCl₃): δ 17.85–30.76, 69.94, 76.86, 107.18, 113.59, 138.6, 141.91, 142.06, 143.29, 144.80, 145.99, 147.93, 149.00, 151.27, 162.66, 166.85, 167.30, 167.54, 185.79, 189.15, 193.45. ¹H NMR (400.13 MHz, CDCl₃): δ 2.34 (s, 3H); 6.44 (s, 1H), 6.50 (s, 1H); 8–10 (s, 1H). MALDI TOF (m/z): 926.876 [M] (C₆₆H₁₀O₆N₂) (calcd 926.825). IR ν/cm⁻¹: 3651, 3402 (O–H), 3013, 2926, 2852, 1803 (C–H), 1709, 1606, 1420, 1367, 1159, 947 (N–O), 600.

"bis(9-[hydroxo]-1-[1'-hydroximino-2'-oxo-2'-ethyl-ethyl])-1,9-dihydro-[C₆₀-Ih] [5,6] fullerene 2." 2.91% (36 mg). ¹³C NMR (100.62 MHz, CDCl₃): δ 7.96–10.54, 18.84–28.76, 66.84, 74.86, 103.56, 108.06, 135.6, 140.06, 143.31, 143.99, 144.85, 146.99, 147.83, 149.33, 152.26, 161.40, 166.85, 167.30, 167.54, 173.26, 183.17, 189.15, 192.77. ¹H NMR (400.13 MHz, CDCl₃): δ 1.74 (s, 3H); 2.65 (s, 2H); 6.25 (s, 1H); 8–10 (s, 1H). MALDI TOF (m/z): 954.868 [M] (C₆₈H₁₄O₆N₂) (calcd 954.879). IR ν/cm⁻¹: 3410 (O–H), 1830 (C–H), 1700, 1604, 1420, 1369, 1159, 948 (N–O), 595.

"bis(9-[hydroxo]-1-[1'-hydroximino-2'-oxo-2'-isopropyl-ethyl])-1,9-dihydro-[C₆₀-Ih] [5,6] fullerene 3." 3.89% (36 mg). ¹³C NMR (100.62 MHz, CDCl₃): δ 18.96–20.54, 30.94–35.77, 62.34, 75.67, 100.56, 110.15, 136.87, 137.64, 138.11, 140.98, 142.29, 143.14, 144.85, 146.27, 155.21, 160.39, 162.44, 168.53, 170.16, 175.57, 180.66, 190.07. ¹H NMR (400.13 MHz, CDCl₃): δ 1.64 (s, 3H); 2.81 (s, 1H); 6.00 (s, 1H); 8–10 (s, 1H). MALDI TOF (m/z): 1050.969 [M] (C₇₀H₁₄O₆N₂) (calcd 1050.968). IR ν/cm⁻¹: 3415 (O–H), 1830 (C–H), 1706, 1601, 1363, 1156, 948 (N–O), 595.

**Analysis carbonyl groups of the 1 adduct**

To 1 mL of 1 solution (15 mg) in methanol, we added 1 mL of 2,4-dinitrophenylhydrazine solution and a drop of concentrated HCl. The test-tube was closed and heated at water bath at 60°C for 5 min. A yellow precipitate occurred. After the
cooling and addition of 5 mL of 10% aqueous solution of KOH, the solution immediately obtained intensive red color as a manifestation of formation of quinoid ion 6 (Scheme 2).

Analysis oxime groups of the 1 adduct

Distilled water (10 mL) and concentrated HCl (0.5 mL) was added to solid yellow adduct 1 (37 mg). This mixture was heated in 30 min without reflux of liquid phase. Then solid was washed by water to pH 7 and dried in vacuum. This way, solid powder 7 was obtained (Scheme 3).

"bis(9-[hydroxo]-1-[1'-hydroxymino-2'-oxo-2'-alkyl-ethyl])-1,9-dihydro-[C60-Ih][5,6]fullerene 7." 98% (35 mg). 13C NMR (100.62 MHz, CDCl3): δ 27.97, 28.14, 29.69, 67.76, 69.95, 95.31, 98.15, 103.82, 129.76, 137.31, 139.53, 139.85, 142.44, 143.99, 145.17, 145.59, 146.15, 147.96, 148.95, 150.48, 151.17, 151.36, 151.64, 153.65, 153.48, 189.45, 190.34, 191.51, 192.99, 193.45, 193.96. 1HNMR (400.13 MHz, CDCl3): δ 2.64–2.67 (s, 3H). MALDI TOF (m/z): 896.701 (calcd 896.796).

Results and discussion

The chemical transformations underlying a new one-pot selective synthesis of bis(9-[hydroxo]-1-[1'-hydroxymino-2'-oxo-2'-alkyl-ethyl])-1,9-dihydro-[C60-Ih][5,6]fullerenes are shown in Scheme 1. Dark brown solutions of bisadducts 1–4 are produced in 30 min at the reaction of the C60 fullerene with ketones (Me2CO, EtMeCO, i-PrMeCO, PhMeCO) in CCl4 in the presence of sodium nitrite and HCl at ~20°C. The bisadducts were purified by semipreparative HPLC. The synthesized compounds were identified by NMR 1H and 13C, HMBC, IR, UV-Vis and mass-spectrometry.

Interaction of C60 with acetone has been used to define the optimal ratio of regents (Table 1, entry 1–5). The highest yield of fullerene oxime 1 (isolated yield 95%) is achieved at the molar ratio C60:Me2CO:NaNO2:HCl = 0.01:100:25:50. When other carbonyl compounds are involved in the reaction under study (α- and β-diketones, cyclic ketones, aliphatic aldehydes, or carboxylic acids), fullerene oximes are not produced (Table 1, entry 9–14).

Contents of 1 compound have been found from MALDI-TOF/TOF mass-spectra. Its spectrum contains a peak of the molecular ion with m/z 926.876 (1%) [M = C60(C(NOH)COCH3)2(OH)2] (calcd 926.825) and peaks of fragmentary ions with m/z 909.497 (2%) [M-OH], 892.050 (4%) [M-(OH)2], 822.777 (8%) [M-(C(NOH)COCH3)(OH)-1], 806.643 (19%) [M-(C(NOH)COCH3)(OH)2], 752.662 (2%) [M-(C(NOH)COCH3)2-2], 735.805 (8%) [M-(C(NOH)COCH3)2(OH)-2], and 720.000 (100%) [M-(C(NOH)COCH3)2(OH)2]. The peak with m/z 926.876 was assigned to molecular ion because its intensity increased in elementary sulfur matrix in the cases of both positive and negative ions.

The structure of compound 1 has been determined by 1H NMR and 13C NMR spectra. The 1H NMR spectrum of 1 has the broadened signals of the protons of the methyl group in the range δ 2.34 and OH groups of oxime moiety at 6.50 ppm, which correspond to E-isomers. In addition, the proton signals in the range of 8–10 ppm correspond to Z-isomers are registered. The ratio of the signals from E- and Z-isomers is estimated as 17:1. In the 1H NMR spectrum, the signals of hydrogen atoms of OH addends are absent. We explain this absence with their intra- and intermolecular interactions. In contrary, the signals of hydrogen atoms of oxime moieties are registered at 6.5 ppm due to their

| Entry | Carbonyl compound (Carb) | Molar ratio C60(Carb):NaNO2:HCl | Yield of fullerene oximes (%)a |
|-------|--------------------------|--------------------------------|-------------------------------|
| 1     | Me2CO                    | 0.01:0:0:1:0:0:0:01              | 24                            |
| 2     |                           | 0.01:0:1:0:1:0:1:1              | 55                            |
| 3     |                           | 0.01:1:1:1                     | 70                            |
| 4     |                           | 0.01:10:1:0:10                 | 85                            |
| 5     |                           | 0.01:100:25:50                | 100                           |
| 6     | EtMeCO                   | 0.01:100:25:50                | 95                            |
| 7     | i-PrMeCO                 | 0.01:100:25:50                | 94                            |
| 8     | MePhCO                   | 0.01:100:25:50                | 97                            |
| 9     | PhCO                     | 0.01:100:25:50                | 0                             |
| 10    | MeCO2H                  | 0.01:100:25:50                | 0                             |
| 11    | MeCOCOMe                 | 0.01:100:25:50                | 0                             |
| 12    | C6H12O                   | 0.01:100:25:50                | 0                             |
| 13    | RCH2COH (R = Me, Et, Pr) | 0.01:100:25:50                | 0                             |
| 14    | RCH2COOH (R = Me, Et, Pr)| 0.01:100:25:50                | 0                             |

aThe yield is calculated based on HPLC data. Reaction time is 30 min.
stabilization by C = O groups located in α-positions relative to the H atoms. The 13C NMR spectrum of 1 has characteristic signals of oxime group and carbon atoms of the fullerene cage. Thus, the signals of sp²-hybridized atoms of the fullerene cage are registered in the range of δ 135–152 ppm. The oxime moieties are indicated by three signals at δ 17–30 ppm (CH₃ groups), δ 185–193 ppm (C=O) and δ 162–167 ppm (C=N). Additionally, the signals of sp³-carbons of the C₆₀ cage at δ 97–113 ppm and δ 65–69 ppm are detected. In addition to E-Z isomerism of fullerene oxime bisadducts (described above), positional isomerism likely takes place. It consists of different positional relationship of the oxime addends on the fullerene cage. According to theoretical considerations, there are minimally eight such regioisomers for the C₆₀ bisadducts (10). However, in the 13C spectrum, we do not observe single signals but deal with the sets of the signals of the C=O, C=N, C=O, and C=C groups of the isomers of the synthesized compound 1, which are chromatographically inseparable. In the HMBC experiments, the signals of methyl groups (δ 2.34) have the cross-peaks with carbon atoms of the C=O (δC 185–193) and C=N (δC 162–167) groups. Nevertheless, the above NMR data obtained well agree with the known data on the fullerene adducts (6, 7). The UV-Vis spectrum of the solution 1 in CC1₄ has the maximum at 258 and the bent at 420 nm (Figure 1) that is typical for cis-2 and cis-3 fullerene bisadducts (11–14). The IR spectrum of 1 contains the bands of valence vibrations of C=O (1803 cm⁻¹), C=N (1709 cm⁻¹), methyl linked with carbonyl (1367 and 1420 cm⁻¹), N–O (947 and 1159 cm⁻¹) and N–OH (3402 cm⁻¹). Deformation vibrations of N–O are registered at 596 cm⁻¹.

To approve additionally the considered structures of the synthesized compounds, we performed the qualitative chemical analysis of the oxime and carbonyl groups in 1 adduct. Detection of the C=O groups were performed according to the well-known method based on the formation of hydrazone via reaction of the C=O group with 2,4-dinitrophenylhydrazine (15) (Scheme 2).

This test is universal, especially if C=O is conjugated with another double bond (in the case of 1, it is C=N). Thus, we have confirmed the presence of C=O group in 1 by appearance of the maxima 225, 273 and 459 nm in the UV-Vis spectrum of the caustic soda solution of hydrazone 6 (Figure 2). Presence of oxime moiety in 1 was confirmed by formation of diketone 7 in the reaction of acidic hydrolysis of 1 (16) (Scheme 3).

The diketone was identified by NMR (¹H, ¹³C) and mass-spectrometry. The ¹H spectrum of 7 contains the signals of methyl protons at 2.6 ppm. The ¹³C spectrum of 7 has signals of carbon atoms in the range 130–152 ppm, C=O group at 189–193 ppm, CH₃ groups at 27–29 ppm as well as sp³-C atoms of C₆₀ at 95–98 and 67–69 ppm. The contents of 7 were deduced from mass-spectrum, which
shows the signal of molecular ion with $m/z$ 896.701 (1.7%) [M = C$_{60}$((CO)COCH$_3$)$_2$(OH)$_2$] (calcd 896.796) and fragmentary ions with $m/z$ 862.007 (3.3%) [M-(OH)$_2$], 791.081 (6.7%) [M-((CO)COCH$_3$(OH)$_2$], 720.000 (100%) [M-((CO)COCH$_3$)$_2$(OH)$_2$].

**Conclusion**

Thus, a mixture of cis-2 and cis-3 isomers of bis(9-[hydroxo]-1-[1’-hydroxymino-2’-oxo-2’-alkyl-ethyl])-1,9-dihydro-[C$_{60}$H$_{5}$]fullerenes has been selectively synthesized for the first time via the reaction of C$_{60}$ fullerene with ketones Me$_2$CO, EtMeCO, i-PrMeCO, PhMeCO in the presence of sodium nitrite and HCl.

**Funding**

The work was financially supported by Russian Foundation for Basic Research (project 16-03-00822 A).

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