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Tetrahedron
Tetrahedron 62 (2006) 10147–10151

Reactions of chlorofullerene $C_{60}Cl_6$ with *N*-substituted piperazines

Olesya A. Troshina,[a] Pavel A. Troshin,[a,*] Alexander S. Peregudov,[b] Elena M. Balabaeva,[a] Vyacheslav I. Kozlovski[c] and Rimma N. Lyubovskaya[a]

[a]*Institute of Problems of Chemical Physics of RAS, Semenov Prospect 1, Chernogolovka, Moscow Region 142432, Russia*
[b]*A. N. Nesmeyanov Institute of Organoelement Compounds of RAS, Vavilova St. 28, B-334, Moscow 119991, Russia*
[c]*Institute for Energy Problems of Chemical Physics of RAS (Branch), Semenov Prospect 1/10, Chernogolovka, Moscow Region 142432, Russia*

Received 13 May 2006; revised 27 July 2006; accepted 10 August 2006
Available online 6 September 2006

Abstract—It was shown for the first time that reactions of C_{60} halides with aliphatic amines provide a facile route for the synthesis of aminofullerenes, valuable precursors for water-soluble cationic fullerene derivatives. Particularly, chlorofullerene $C_{60}Cl_6$ and *N*-substituted piperazines were investigated in this work. It was shown that substitution of chlorine atoms in $C_{60}Cl_6$ by amine groups is accompanied by partial elimination of addends from the fullerene cage that yields mixtures of di-, tetra- and, hexaaminofullerenes as the final products. Separation of these mixtures by column chromatography resulted in isolation of pure 1,4-diaminofullerenes; this procedure gives much higher and more reproducible yields of these compounds than direct oxidative photoaddition of secondary amines to C_{60}. ESI mass spectrometry and NMR spectroscopy data showed that hexaaminofullerene isomers are major components in inseparable mixtures of polyaddition products. Polyaminofullerenes were found to be readily soluble in aqueous acids; these solutions are unstable because of a facile substitution of protonated amine groups with hydroxyls. Nevertheless, the use of other amine substrates in the investigated reaction can potentially allow the preparation of more stable water-soluble cationic fullerene derivatives for biological studies.

1. Introduction

Halofullerenes are valuable substrates for preparation of novel fullerene derivatives by substitution of halogen atoms with appropriate organic groups. Chlorofullerene $C_{60}Cl_6$ is one of the most available [60]fullerene halides.[1] The symmetrical molecular structure as well as the low number of halogen addends allows for their selective substitution by various nucleophiles with formation of one or several major products. Thus, $C_{60}Cl_6$ undergoes Friedel–Crafts reaction with aromatics under Lewis acid catalysis to yield mainly $C_{60}Ar_5Cl$. Isolation of $C_{60}Ar_2$ and $C_{60}Ar_4$ compounds as side products points to the partial halogen elimination that competes with substitution.[2] Treatment of $C_{60}Cl_6$ with sodium alkoxides affords substitution products $C_{60}(OR)_5Cl$ (R=Me, Et), while reactions with less nucleophilic alcohols give mainly $C_{60}(OR)_2$ (R=Me, *i*Pr) through elimination of four chlorine atoms from the fullerene cage.[3] Reaction of the chlorofullerene with MeLi shows poor selectivity and yields mixtures of $C_{60}Me_6$, $C_{60}Me_5Cl$, $C_{60}Me_5O_2OH$, $C_{60}Me_5OOH$, etc.[4] Allyltrimethylsilane also reacts with $C_{60}Cl_6$ in the presence of $TiCl_4$ as a catalyst to give predominantly $C_{60}(CH_2CH{=}CH_2)_6$ and $C_{60}(CH_2CH{=}CH_2)_5Cl$ as a side product.[5]

Organic fullerene derivatives prepared from $C_{60}Cl_6$ possess all addends attached around one five-membered ring at the fullerene cage; this addition pathway cannot be achieved using commonly used cycloaddition reactions. Therefore, we considered $C_{60}Cl_6$ as a particularly valuable substrate for the preparation of water-soluble fullerene derivatives. There is a limited number of known derivatives of [60]fullerene that possess solubility in water above 1 mg/mL; most of them are represented by compounds bearing multiple addends (>5–6) that cover almost the whole fullerene surface.[6] Such fullerene derivatives cannot be applied as inhibitors of HIV-1 protease since its active center has good attraction to the hydrophobic [60]fullerene core.[7] Efficiencies of photosensitized generation of singlet oxygen (potential for photodynamic therapy of cancer) on the one hand, and quenching of radical species on the other (neuroprotection activity) also depend on the degree of distortion of the fullerene π-system in C_{60} derivatives.[8] Therefore, only a few water-soluble fullerene derivatives have potential to find some medicinal applications. Their syntheses usually require several steps and give relatively low overall product yields.[9] Replacement of 4–5–6 chlorine atoms in $C_{60}Cl_6$ with addends bearing masked ionic groups (–COO^-, –SO_3^-,

Keywords: Fullerene; Amines; C_{60}; $C_{60}Cl_6$; Nucleophilic substitution.
* Corresponding author. Fax: +7 496 522 18 52; e-mail: troshin@cat.icp.ac.ru

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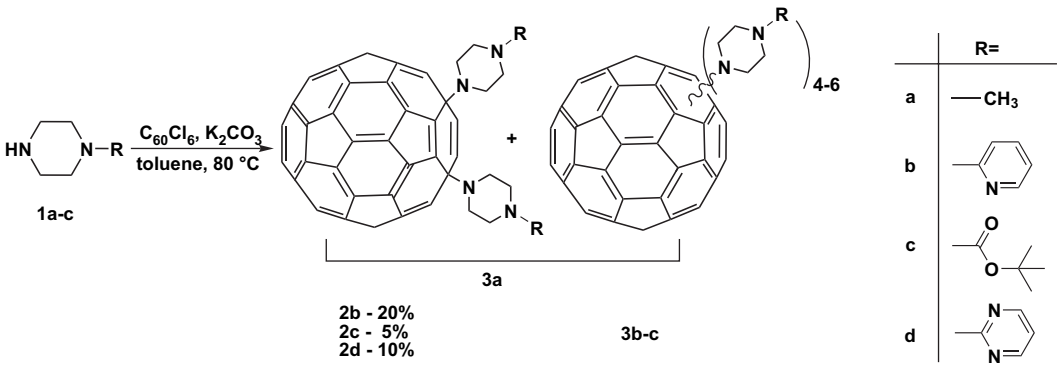
doi:10.1016/j.tet.2006.08.033



Scheme 1.

R_4N^+, etc.) can be considered as a superior approach to the synthesis of water-soluble fullerene derivatives.

It has been reported recently that cationic fullerene derivatives inhibit HIV and hepatitis C viruses quite efficiently and possess good antiproliferative and antibacterial activities.[10] Therefore, we address here the reaction of $C_{60}Cl_6$ with amines as a promising route to polyaminofullerenes and their water-soluble cationic derivatives.

2. Results and discussion

It was shown that $C_{60}Cl_6$ readily reacts with *N*-substituted piperazines **1a–d** with the formation of a mixture of products (Scheme 1).

Typically, hexachlorofullerene was dissolved in dry toluene at 80 °C, then rigorously dried potassium carbonate and the corresponding amine were added. The resulting mixture was stirred for 20 h at 80 °C and afterwards cooled down to room temperature.[†] All insoluble products were filtered off, while the filtrate was concentrated in vacuum to give brown solids that were washed with hexane and dried in air.

Mixtures of aminofullerenes were obtained in all syntheses as revealed by TLC and NMR spectroscopy. A crude product formed in the reaction of $C_{60}Cl_6$ with 1-methylpiperazine possesses an average composition of C_{60}(1-methylpiperazinyl)$_{4–5}$; this mixture could not be separated by column chromatography on silica because of almost irreversible absorption of the material at the stationary phase (due to strongly basic properties of amine residues). Addition of tertiary amines (triethylamine, pyridine) or acids (CF_3COOH, CH_3COOH) to the eluent ($CHCl_3$–methanol 2:1) resulted in elution of inseparable mixtures of partially hydrolyzed compounds with composition C_{60}(piperazinyl)$_x$(OH)$_y$. Electrospray mass spectrometry analysis (ESIMS) of a crude product with an average composition of C_{60}(1-methylpiperazinyl)$_{4–5}$ revealed intensive signals at *m*/*z*=819 (C_{60}(1-methylpiperazinyl)$_1^+$), 919 (C_{60}(1-methylpiperazinyl)$_2\cdot H^+$), 1017 (C_{60}(1-methylpiperazinyl)$_3^+$), and 1133 (C_{60}(1-methylpiperazinyl)$_4O\cdot H^+$). Less intensive peaks were observed at *m*/*z*=837 and 1035 due to C_{60}(1-methylpiperazinyl)$OH\cdot H^+$ and C_{60}(1-methylpiperazinyl)$_3OH\cdot H^+$, respectively. The later appeared most likely because of a partial hydrolysis of aminofullerenes (Fig. 1).

Application of the less basic piperazines **1b–d** bearing electron withdrawing groups allowed for separation of the crude reaction products using column chromatography on silica. In the course of separation, diaminofullerenes **2b–d** (toluene–methanol 125:1) were followed by distinct fraction that represented a mixture of polyaminofullerenes **3b–d**. Variation of the eluent composition and repeatable column chromatography did not result even in partial separation of components of **3b–d** presumably because of the strong similarity in their properties.

The composition and structure of **2b–d** was confirmed by chemical analysis data, ^1H and ^{13}C NMR spectrometry. The ^1H NMR spectrum of **2b** consists of two doublets and two triplets corresponding to pyridyl protons and a multiplet at

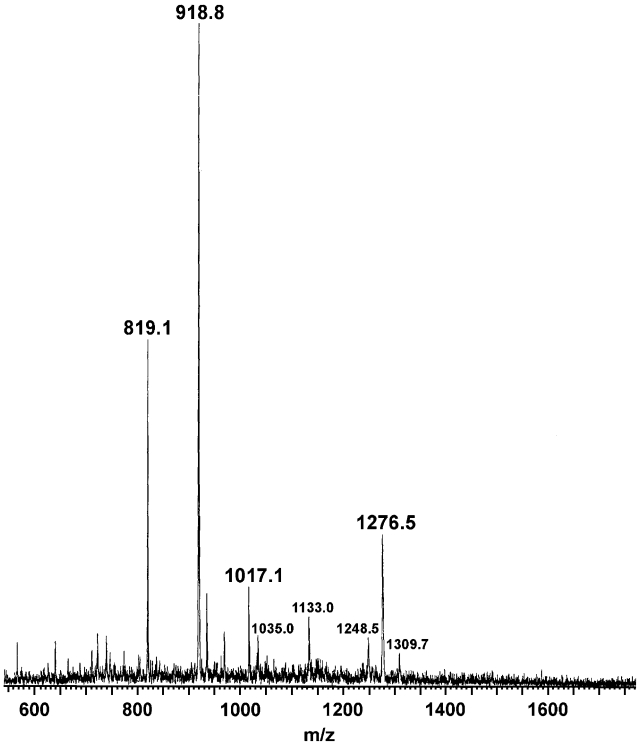


Figure 1. The ESIMS of the crude product formed in the reaction of $C_{60}Cl_6$ with *N*-methylpiperazine.

[†] If the reaction is conducted at room temperature, the result is essentially the same except for lower yields of **2b-d**.

3.8–4.0 ppm from the CH_2 protons of piperazine ring (Fig. 2). The ^{13}C NMR spectrum exhibited a signal at 73.5 ppm corresponding to the fullerene cage sp^3 carbon; 34 peaks of fullerene and pyridyl sp^2 carbons were detected in low field region (100–160 ppm) that prove unambiguously the C_s symmetry of the product corresponding to structure **2b**. Both ^1H and ^{13}C NMR spectra of **2C** and **2d** also correspond to the suggested structures. The UV–vis spectrum of **2b** exhibited a broad band at 445 nm typical for fullerene derivatives with 1,4-addition pathway.[11] Similar spectroscopic data were reported previously for 1,4-dimorpholinofullerene.[11]

It should be noted that although oxidative photochemical addition of secondary amines to parent C_{60} also yields 1,4-diaminofullerenes as minor products, their yields are lower than in our method based on $C_{60}Cl_6$ (0–8%).[11,12] Reactions of [60]fullerene with active amines such as piperazines **1a** and **1b** give mostly oxygen-containing tetraaminofullerenes $C_{60}[NR_2]_4O$ and other polyaddition products, while the corresponding 1,4-$C_{60}[NR_2]_2$ are not formed or form in very low yields (1–3%). Application of $C_{60}Cl_6$ as a substrate for preparation of 1,4-diaminofullerenes is also advantageous in the case of amines possessing labile functional groups. In particular, it is illustrated by the preparation of diaminofullerene **2c** reported here. This compound cannot be obtained directly in the reaction of [60]fullerene with *N*-(*tert*-butoxycarbonyl)piperazine because of degradation of this reagent even under mild photochemical conditions (irradiation from conventional 50 W incandescent light bulb) and formation of unsubstituted piperazine monoaddition product ($C_{60}N_2C_4H_8$).[12] Therefore, reaction of $C_{60}Cl_6$ with secondary amines can find useful application for preparation of some specific 1,4-diaminofullerenes under mild conditions. Compounds obtained here **2b** and **2c** possess chelating groups and can be used for construction of noncovalently linked donor–acceptor assembles with metalloporphyrins and formation of complexes with transition metals.

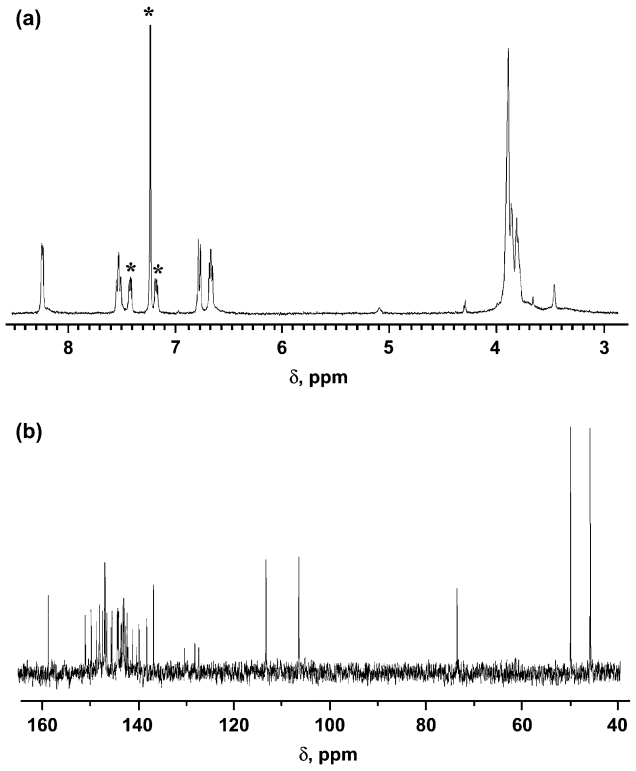


Figure 2. The ^1H and ^{13}C NMR spectra of **2b**. Symbol '*' denotes signals of residual $CHCl_3$ in $CDCl_3$ and 1,2-dichlorobenzene solvent impurities.

Another important feature of the investigated reaction is high-yield formation of polyaminofullerenes (ca. 60–70%) that most likely have all amine groups arranged at one hemisphere of the fullerene cage (like chlorine atoms in the starting $C_{60}Cl_6$). Thus, a mixture of polyaminofullerenes **3b** with average composition C_{60}(4-(2-pyridyl)piperazin-1-yl)$_{4.5}$ as determined from chemical analysis was characterized by ESI mass spectrometry. The most intensive peaks were observed at m/z=1693 and 847 amu, these correspond to molecular ions $[C_{60}(4\text{-}[2\text{-pyridyl}]piperazin\text{-}1\text{-}yl)_6\cdot H]^+$ and $[C_{60}(4\text{-}[2\text{-pyridyl}]piperazin\text{-}1\text{-}yl)_6\cdot 2H]^{2+}$, respectively. Surprisingly, signals of the corresponding tetraaminofullerenes were much less intensive. Both ^1H and ^{13}C NMR spectra of **3b** consisted of numerous partially overlapped peaks thus ruling out the possibility of high compositional and isomeric purity of **3b**.

As expected, polyaminofullerenes **3a**–**d** were readily soluble in organic and inorganic acids thus yielding the corresponding salts. Isolation of these salts by precipitating it by addition of acetone or acetonitrile or by concentration of these acidic solutions at room temperature and reduced pressure was challenged by competing solvolysis with exchange of amine groups with –OH or RCOO– residues. Thus, in contrast to the recently reported conversion of C_{60}[amine]$_4$O derivatives into water-soluble salts,[12] polyaminofullerenes **3a**–**d** give under the same conditions insoluble in water material. Nevertheless, we continue our investigations on $C_{60}Cl_6$ reactions with less bulky secondary and primary amines in order to obtain stable water-soluble cationic fullerene derivatives that can exhibit promising biological activities.

3. Conclusions

A reaction of $C_{60}Cl_6$ with amines was investigated for the first time. It was shown that it allows for superior preparation of 1,4-diaminofullerenes; the compounds reported here possess chelating pyridyl and pyrimidinyl groups and can potentially be utilized for construction of supramolecular assembles with metalloporphyrins and complexes with transition metals.

Isolated mixtures of polyaminofullerenes were characterized by ^1H and ^{13}C NMR and ESIMS; a peak for hexaaminated species $[C_{60}(NR_2)_6\cdot H]^+$ strongly dominated in the mass spectrum. The observed very high solubility of polyaminofullerenes in acidic media opens easy route for preparation of water-soluble fullerene derivatives, particularly, ones that can exhibit promising biological properties.

4. Experimental

4.1. Reagents and solvents

Chlorofullerene $C_{60}Cl_6$ was prepared by chlorination of C_{60} with ICl in 1,2-dichlorobenzene as described before.[13]

The solid $C_{60}Cl_6$ was obtained as a 1:1 solvate with 1,2-dichlorobenzene. Surprisingly, this 1,2-dichlorobenzene was observed as trace solvent impurity in the ^1H NMR spectra of some 1,4-diaminofullerenes (for instance, **2b**). Toluene for reactions of $C_{60}Cl_6$ with amines was distilled over metal sodium–benzophenone. All other reagents and solvents were purchased from Acros Organics and used as received.

4.2. General experimental procedure for reactions of $C_{60}Cl_6$ with *N*-substituted piperazines

Hexachlorofullerene (200 mg, 0,278 mmol) was dissolved in 100 mL of dry toluene under stirring at 80 °C within 3 h. Then vigorously dried potassium carbonate (5–10 g) was added to the hot chlorofullerene solution that was followed by dropwise addition of amine **1a–d** (2 mmol) dissolved in 40 mL of toluene. Resulting mixture was stirred for 20 h at 80 °C, afterwards cooled down to the room temperature. All insoluble products were filtered off, while the filtrate was concentrated in vacuum to give brown solids that were washed with hexane and dried in air.

To isolate **2b–d**, the crude product mixture was re-dissolved in toluene and then diluted by hexane to give 1:1 v/v solvent mixture. Resulting solution was filtered and poured at the top of silica gel column (silica gel purchased from Acros Organics, 30–75 μ, 90 Å). Very small amount of fullerene C_{60} (less than 1–2 mg, formed from $C_{60}Cl_6$ via loss of all chlorine atoms) was washed out from the column in the course of product deposition; following elution by toluene–methanol mixtures (toluene–MeOH 99.2:0.8 v/v) resulted in the fractions of diaminofullerenes **2b–d**. Increase in the methanol content in the solvent mixture (toluene–MeOH 98:2–97:3 v/v) resulted in elution of polyaminofullerenes **3b–d** as single fractions. Repeatable separation of **3b–d** on silica and alumina stationary phases using different solvent compositions did not result in any resolution of the components. The solutions of **2b–d** were concentrated at the rotary evaporator to the volume 10–15 mL; then hexane was added (40–50 mL) and the precipitate was collected by centrifugation and dried in air to afford compounds **2b–d** as brown solids in 5–20% yield.

4.2.1. Compound 2b. Found: C, 89.28; H, 2.77; N, 7.96. $C_{78}H_{24}N_6$ requires C, 89.64; H, 2.31; N, 8.04%; ν_{max} (KBr)=528, 729, 772, 940, 983, 1007, 1130, 1160, 1244, 1434, 1483, 1592, 2917 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.40–4.20 (16H, br m), 6.70 (2H, t, *J* 8.0 Hz), 6.81 (2H, d, *J* 8.8 Hz), 7.56 (2H, t, *J* 9.2 Hz), 8.27 (2H, d, *J* 3.7 Hz); δ_C (100 MHz, CS_2–C_6D_{12} 10:1) 45.8, 49.9, 73.5, 106.4, 113.3, 127.4, 128.2, 130.4, 136.8, 138.2, 139.8, 140.4, 141.1, 142.1, 142.3, 142.5, 143.0, 143.1, 143.2, 143.4, 143.5, 144.1, 144.2, 144.2, 144.3, 144.4, 145.4, 145.6, 146.5, 146.9, 147.0, 147.4, 148.0, 148.6, 149.8, 151.0, 158.7.

4.2.2. Compound 2c. Found: C, 85.74; H, 3.16; N, 5.07. $C_{78}H_{34}N_4O_4$ requires C, 85.86; H, 3.14; N, 5.13%; ν_{max} (KBr)=528, 1001, 1126, 1167, 1251, 1286, 1365, 1421, 1458, 1698, 1743, 2851, 2921 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.55 (18H, s), 3.60–3.90 (16H, br m); δ_C (150 MHz, CS_2–C_6D_{12} 10:1) 28.3, 30.1, 49.9, 73.4, 78.6, 138.2, 139.7, 140.4, 141.1, 142.1, 142.2, 142.5, 142.9, 143.0, 143.0, 143.1, 143.2, 143.4, 143.4, 143.6, 144.0, 144.1, 144.2, 144.3, 145.3, 145.6, 146.1, 146.5, 146.6, 146.7, 146.9, 147.0, 147.2, 148.6, 149.5, 150.7, 153.1.

4.2.3. Compound 2d. Found: C, 86.83; H, 2.45; N, 10.81. $C_{76}H_{22}N_8$ requires C, 87.18; H, 2.12; N, 10.70%; δ_H (400 MHz, $CDCl_3$) 3.72–4.07 (8H, br m), 4.22 (8H, br s), 6.56 (2H, t, *J* 4.8, 1.3 Hz), 8.39 (4H, dd, *J* 4.8, 1.6 Hz); δ_C (100 MHz, CS_2–C_6D_{12} 10:1) 44.3, 50.0, 73.6, 109.9, 138.2, 139.8, 140.4, 141.1, 142.1, 142.3, 142.5, 143.0, 143.1, 143.2, 143.4, 143.5, 143.7, 144.1, 144.2, 144.2, 144.3, 145.4, 145.6, 146.5, 146.9, 147.0, 147.3, 148.6, 149.8, 151.0, 157.1, 157.2, 157.3, 161.3.

4.2.4. Compound 3b. ν_{max} (KBr)=525, 732, 773, 943, 980, 1007, 1097, 1126, 1160, 1246, 1280, 1313, 1437, 1482, 1594, 2851, 2925 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.88–3.96 (br m, 16H), 6.50–6.70 (br m, 4H), 7.36–7.53 (br m, 2H), 8.09–8.33 (br m, 2H) ppm. ^1H, ^{13}C NMR, and ESIMS spectra are shown in Supporting data.

Acknowledgements

This work was partially supported by INTAS (04-83-3733), Russian Foundation for Basic Research (04-03-32870) and Russian Science Support Foundation.

Supplementary data

Supporting information available: spectral data for compounds **2c–d** and **3b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.033.

References and notes

1. Birkett, P. R.; Avent, A. G.; Darwish, A. D.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *Chem. Commun.* **1993**, 1230–1231.
2. Birkett, P. B.; Avent, A. G.; Darwish, A.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *J. Chem. Soc. Perkin Trans. 2* **1997**, 457–461.
3. Avent, G.; Birkett, P. R.; Darwish, A. D.; Houlton, S. H.; Taylor, R.; Thomson, K. S. T.; Wei, X.-W. *J. Chem. Soc. Perkin Trans. 2* **2001**, 782–786.
4. Al-Matar, H.; Abdul-Sada, A. K.; Avent, A.; Fowler, P. W.; Hitchcock, P. B.; Rogers, K. M.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **2002**, 53–58.
5. Abdul Sada, A.; Avent, A.; Birkett, P. R.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *J. Chem. Soc. Perkin Trans. 1* **1998**, 393–395.
6. Tagmatarchis, N.; Shinohara, H. *Mini Rev. Med. Chem.* **2001**, *1*, 339–348; Da Ros, T.; Prato, M. *Chem. Commun.* **1999**, 663–669.
7. Wilson, S. R. *Perspectives of Fullerene Nanotechnology*; Osawa, E., Ed.; Kluwer: Dordrecht–Boston–London, 2001; Zhu, Z.; Wilson, S. *Biochemistry* **2003**, *42*, 1326–1333.
8. Guldi, D. M.; Asmus, K.-D. *Radiation Physics and Chemistry* **1999**, *56*, 449–456; Bensasson, R. V.; Berberan-Santos, M. N.; Brettreich, M.; Frederiksen, J.; Göttinger, H.; Hirsch, A.; Land, E. J.; Leach, S.; McGarvey, D. J.; Schonberger, H.; Schroder, C. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4679–4683.

9. Lamparth, I.; Hirsch, A. *Chem. Commun.* **1994**, 1727–1728; Brettreich, M.; Hirsch, A. *Tetrahedron Lett.* **1998**, *39*, 2731–2734.
10. Mashino, T.; Nishikawa, D.; Takanashi, K.; Usui, N.; Yamory, T.; Seki, M.; Endo, T.; Mochizuki, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4395–4397; Bosi, S.; Da Ros, T.; Spalluto, G.; Balzarini, J.; Prato, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4437–4440; Mashino, T.; Shimotohno, K.; Ikegami, N.; Nishikawa, D.; Okuda, K.; Takahashi, K.; Nakamura, S.; Mochizuki, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1107–1109.
11. Schick, G.; Kampe, K. D.; Hirsch, A. *Chem. Commun.* **1995**, 2023–2024.
12. Troshina, O. A.; Troshin, P. A.; Peregudov, A. S.; Kozlovski, V. I.; Lyubovskaya, R. N. *Chem.—Eur. J.* **2006**, *12*, 5569–5578.
13. Troshin, P. A.; Popkov, O.; Lyubovskaya, R. N. *Full. Nanot. Carb. Nanostruct.* **2003**, *11*, 163–182.