Synthesis of water-soluble cyclen-functionalised fullerene C_{60} derivatives

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The fullerene family has interesting photophysical, electrochemical and mechanical properties with applications in organic solar cells, nanotechnology, superconductivity, chemosensors and biomedicine. Water-soluble cyclen-functionalised fullerene derivatives cyclen-C_{60}-**1** and bis(cyclen)-C_{60}-**2** have been synthesised. The whole synthetic routes are simple and the total yields are relatively high.

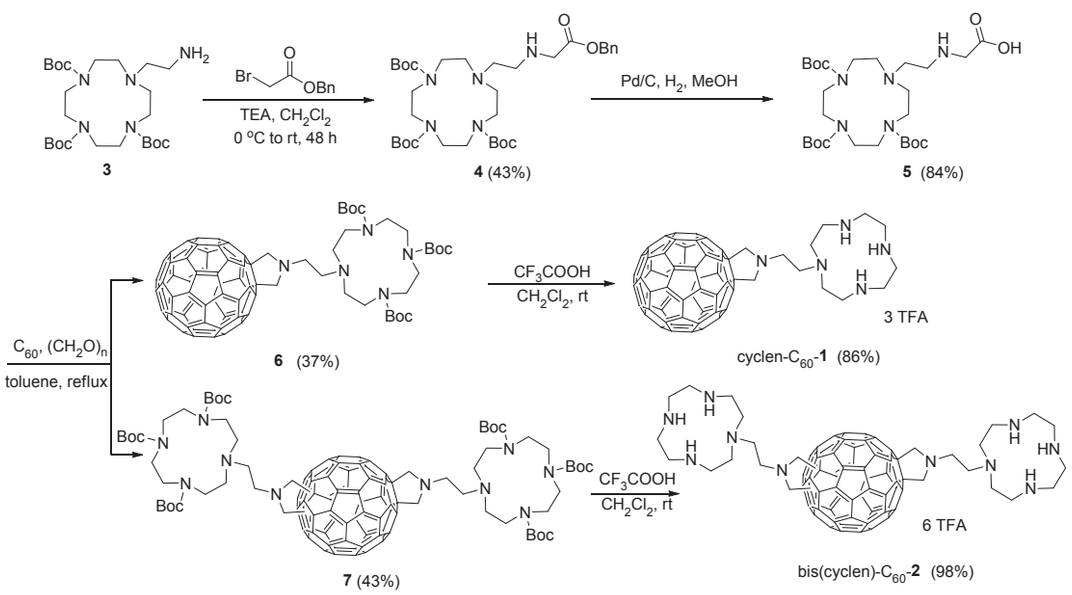
Keywords: fullerene, C_{60}, cyclen, water-soluble synthesis

Since their discovery in 1985, fullerenes have attracted considerable attentions in different fields of science.[1–6] The fullerene family, especially C_{60}, possesses interesting photophysical, electrochemical, and mechanical properties for utilisation in organic solar cells, nanotechnology, superconductivity, chemosensors and body armour construction.[7–17] Due to their size, hydrophobicity, three-dimensionality and electronic configurations, fullerenes have also been studied in the field of biomedicine including as anti-HIV agents, radical scavengers, antioxidants, antibiotics, antiviral drugs, DNA photocleavage, and carriers in gene and drug delivery.[18–20] However, unfunctionalised fullerenes are completely insoluble in water, which limits their use in biomedical studies.[21,22] Cyclen (1,4,7,10-tetraazacyclododecane) is known to have a very high binding constant with transition-metal ions such as Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+}.[5] What is more, in neutral buffer solution, cyclen is partially protonated by an uptake of two protons, and so possesses good water-solubility.[23,24] We now present the design and synthesis of water-soluble cyclen-functionalised fullerene C_{60} derivatives.

Result and discussion

Scheme 1 shows the synthetic strategy used to obtain cyclen-functionalised fullerene C_{60} derivatives. The cyclen-C_{60}-**1** anchored with one cyclen pendant was successfully synthesised by a four-step reaction with tri-*tert*-butyl-10-(2-aminoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (**1**) and C_{60} as starting materials, in 11% overall yield. This product was soluble in MeOH, EtOH, DMSO, and most importantly, it was slightly soluble in water. The bis(cyclen)-C_{60}-**2** was also obtained *via* the similar method, and exhibited a very good water-solubility (> 10 mg mL^{-1}). Unfortunately, bis(cyclen)-C_{60}-**2** was a mixture of various isomers, which could not been purified through silica gel chromatography.

The Boc-protected cyclen **3** was prepared according to the literature.[25] The electrophilic substitution was then performed between amino group of **3** and benzyl 2-bromoacetate to give the intermediate cyclen **4** in a yield of 43%. In the next step, benzyl group was removed through hydrogenation catalysed by Pd/C in a good yield of 84%. This resulting carboxyl cyclen **5** was then reacted with C_{60} to form fulleropyrrolidine



Scheme 1 Synthesis routes of cyclen-functionalised fullerene C_{60} derivatives.

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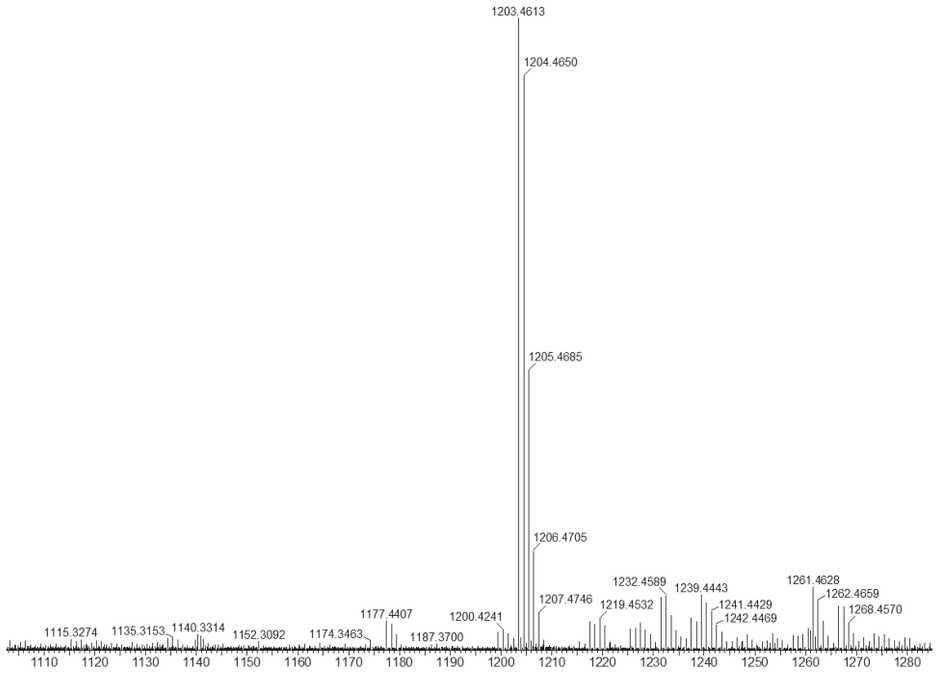

Fig. 1 The ESI-TOF mass spectrum of bis(cyclen)-C_{60}-**2**.

6 and **7** according to the classic procedure developed by Prato and co-workers.[26,27] Boc-protection was finally removed under a strong acid condition to give cyclen-functionalised fullerene C_{60} derivatives cyclen-C_{60}-**1** and bis(cyclen)-C_{60}-**2**. The cyclen-C_{60}-**1** and its intermediates were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The ^{1}H NMR and ^{13}C NMR of bis(cyclen)-C_{60}-**2** did not give meaningful results,[28,29] but its TOF-MS spectrum showed the expected molecular ions peaks in high intensity (Fig. 1, *m/z* 1203.4613).

In conclusion, we have synthesised water-soluble cyclen-functionalised fullerene derivatives cyclen-C_{60}-**1** and bis(cyclen)-C_{60}-**2**. The whole synthetic routes are simple and the total yields are relatively high. This result may be advantageous for the application of fullerenes in biomedical field.

Experimental

NMR spectra were obtained on a Bruker AMX-400. The ^{1}H NMR (400 MHz) chemical shifts were measured relative to $CDCl_3$ or DMSO-d_6 as the internal reference ($CDCl_3$: δ 7.26 ppm; DMSO-d_6: δ 2.50 ppm). The ^{13}C NMR (100 MHz) chemical shifts were given using $CDCl_3$ or DMSO-d_6 as the internal standard ($CDCl_3$: δ 77.16 ppm; DMSO-d_6: δ 39.52 ppm). The molecular weights were tested on Autoflex MALDI-TOF-MS (Bruker, USA) in the linear mode with (*R*)-cyano-4-hydroxycinnamic acid as a matrix. High-resolution mass spectra (HRMS) were obtained with a Waters-Q-TOF-Premier (ESI). Progress of their reactions was monitored by TLC. Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification.

Tri-tert-butyl 10-(2-aminoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (**3**): Prepared according to the literature.[25]

Tri-tert-butyl-10-(2-(2-(benzyloxy)-2-oxoethylamino)ethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate (**4**): Benzyl 2-bromoacetate (2.5 mL, 16 mmol) in CH_2Cl_2 (10 mL) was added to a solution of Boc-protected cyclen (**3**) (6.9 g, 13.4 mmol) and triethylamine (2.8 mL, 20 mmol) in CH_2Cl_2 (180 mL) at 0 °C over a period of 30 minutes, and the solution was stirred at room temperature for 48 hours.

The mixture was then concentrated under reduced pressure, and the product was purified by column chromatography on silica gel (ethyl acetate) to provide the desired product (**4**) (3.8 g, 43%) as a clear sticky liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (m, 5H), 5.14 (s, 2H), 3.52–3.25 (m, 14H), 2.74–2.63 (m, 8H), 1.45 (s, 9H), 1.42 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 156.2, 155.8, 155.5, 135.6, 128.7, 128.54, 128.51, 79.7, 79.6, 79.4, 66.7, 55.8, 54.5, 53.1, 51.2, 50.2, 48.6, 48.2, 48.0, 47.7, 45.1, 28.8, 28.6 ppm; IR: ν_{max}/cm^{-1} = 2973, 1680, 1457, 1412, 1363, 1247, 1153; HRMS (ESI^{+}): calcd for $C_{34}H_{58}N_5O_8$ $[M+H]^{+}$ 664.4285; found 664.4286.

2-(2-(4,7,10-tris(Tert-butoxycarbonyl)-1,4,7,10-tetraazacyclododecan-1-yl)ethylamino)acetic acid (**5**): 3% Pd/C (1.05 g) catalyst was added to a solution of **4** (3.6 g, 5.4 mmol) in 50 mL of methanol, and the mixture was reacted under 1.5 MPa of hydrogen at room temperature for 3 hours. Then the mixture was filtered through a Celite pad and washed with methanol. The solution was concentrated under reduced pressure affording the carboxyl derivative (**5**) (2.6 g, 84%) as a white solid, m.p. 91–93 °C. **5** was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49–3.32 (m, 14H), 3.07–3.01 (m, 4H), 2.68 (s, 4H), 1.44 (s, 9H), 1.42 (s, 18H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 155.9, 155.3, 79.7, 79.4, 54.6, 53.9, 50.1, 49.7, 47.7, 42.9, 41.9, 28.6, 28.5 ppm; IR: ν_{max}/cm^{-1} = 2976, 1656, 1462, 1414, 1402, 1315, 1249, 1155; HRMS (ESI^{+}): calcd for $C_{27}H_{52}N_5O_8$ $[M+H]^{+}$ 574.3816; found 574.3814.

Boc-Cyclen-C_{60} (**6**): A mixture of **5** (58 mg, 0.1 mmol), C_{60} (72 mg, 0.1 mmol), paraformaldehyde (4.5 mg, 0.05 mmol, 1.5 equiv.) and toluene (15 mL) was stirred at 110 °C and then refluxed for 6 hours. The mixture was concentrated under reduced pressure to remove toluene. The crude product was purified by column chromatography on silica gel (toluene/ethyl acetate = 5/1, v/v) to give the desired product **6** (47 mg, 37%) as a black solid. m.p. > 260 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (s, 4H), 3.71 (s, 2H), 3.62 (s, 2H), 3.45 (s, 8H), 3.30–3.27 (m, 2H), 3.18–3.15 (m, 2H), 2.96–2.90 (m, 4H), 1.49–1.47 (m, 27H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 147.4, 146.3, 146.2, 146.1, 145.8, 145.5, 145.4, 144.6, 143.2, 142.7, 142.3, 142.2, 142.0, 140.3, 136.3, 79.8, 79.7, 79.5, 70.8, 68.5, 55.6, 54.8, 51.2, 50.2, 48.3, 28.8, 28.73, 28.67 ppm; IR: ν_{max}/cm^{-1} = 2924, 1683, 1455, 1411, 1363, 1246, 1154; HRMS (ESI^{+}): calcd for $C_{87}H_{52}N_5O_6$ $[M+H]^{+}$ 1262.3918; found 1262.3911.

Boc-bis(cyclen)-C_{60} (**7**): A mixture of **5** (570 mg, 1.0 mmol), C_{60} (720 mg, 1.0 mmol), paraformaldehyde (45 mg, 0.5 mmol, 1.5 equiv.) and toluene (200 mL) was stirred at 110 °C and then refluxed for 6 hours. The mixture was concentrated under reduced pressure

to remove toluene. The crude product was purified by column chromatography on silica gel (toluene/ethyl acetate = 1/1, v/v) to give the desired product **7** (389 mg, 43%) as a black solid. HRMS (ESI^+): calcd for $C_{114}H_{102}N_{10}O_{12}Na$ $[M+Na]^+$ 1826.7610; found 1826.7611.

Cyclen-C_{60}-**1**: Trifluoroacetic acid (1.0 mL, 13.4 mmol) was added slowly to a solution of **6** (90 mg, 71.3 µmol) in 50 mL of CH_2Cl_2, at room temperature. The solution was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to remove the solvent and then washed with CH_2Cl_2 to remove the impurities. Deprotected product cyclen-C_{60}-**1** (80 mg, 86%) was obtained as a brownish solid. m.p. > 260 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 4.75–4.62 (m, 4H), 3.53 (s, 2H), 3.28 (s, 4H), 3.16–3.06 (m, 10H), 2.91 (s, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.5, 146.6, 145.9, 145.6, 145.4, 145.2, 144.71, 144.68, 144.0, 142.6, 142.1, 141.8, 141.5, 141.3, 139.5, 135.4, 72.1, 67.1, 48.2, 44.3, 42.2, 42.0 ppm; IR: ν_{max}/cm^{-1} = 3400–2500, 1667, 1424, 1123; UV-Vis: λ_{max}/nm = 253, 325; HRMS (ESI^+): calcd for $C_{72}H_{28}N_5$ $[M+H]^+$ 962.2345; found 962.2342.

Bis(cyclen)-C_{60}-**2**: Trifluoroacetic acid (1.0 mL, 13.4 mmol) was added slowly to a solution of **7** (90 mg, 49.9 µmol) in 50 mL of CH_2Cl_2, at room temperature. The solution was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to remove the solvent and then washed with CH_2Cl_2 to remove the impurities. Deprotected product bis(cyclen)-C_{60}-**2** (92 mg, 98%) was obtained as a brownish solid. IR: ν_{max}/cm^{-1} = 3434, 1677, 1198, 1128; HRMS (ESI^+): calcd for $C_{84}H_{55}N_{10}$ $[M+H]^+$ 1203.4611; found 1203.4613.

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