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Rotaxane axle as an effective scaffold: synthesis of functionalized [3]rotaxane and connection of the wheel components arranged on the axle

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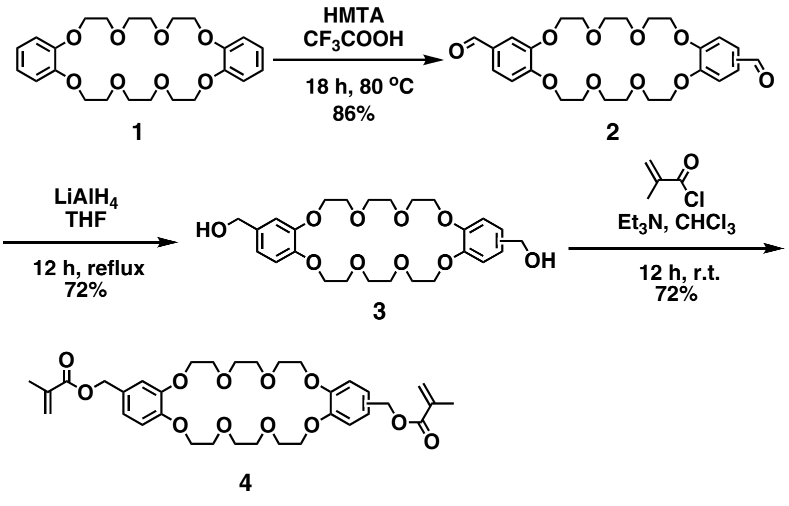
Abstract—A [3]rotaxane consisting of a bis(*sec*-ammonium)-type axle and two functionalized dibenzo-24-crown-8-ether wheels was prepared in a good yield. The two point connection of the wheel components placed on the axle of the rotaxane was achieved by the Michael addition of hexanedithiol to the methacrylate C=C bonds of the wheels to afford the corresponding [2]rotaxanes.

Polyrotaxanes[1] including oligo ones have interesting structures where two or more macrocyclic wheel components are regularly arranged on the axle component. In particular, the axles of the polyrotaxanes can provide excellent scaffolds that are quite suitable for multi-point connection of the macrocyclic wheels because undesirable *intermolecular* linear connection of the wheels can be avoided easily by the concentration control. Harada et al. reported the successive connection of many cyclodextrin wheels integrated on a poly(ethylene glycol) axle of a polyrotaxane to yield molecular nanotubes.[2] Zhu and Chen synthesized [2]catenane from pseudo[4]rotaxane using the wheel component as a template.[3] Stoddart and co-workers linked two crown ether wheels placed on an axle of a pseudorotaxane.[4] To establish and apply such polyrotaxane systems for the macrocycle connection, the significance and advantages of the polyrotaxane should be studied by using structure-distinct



Scheme 1.

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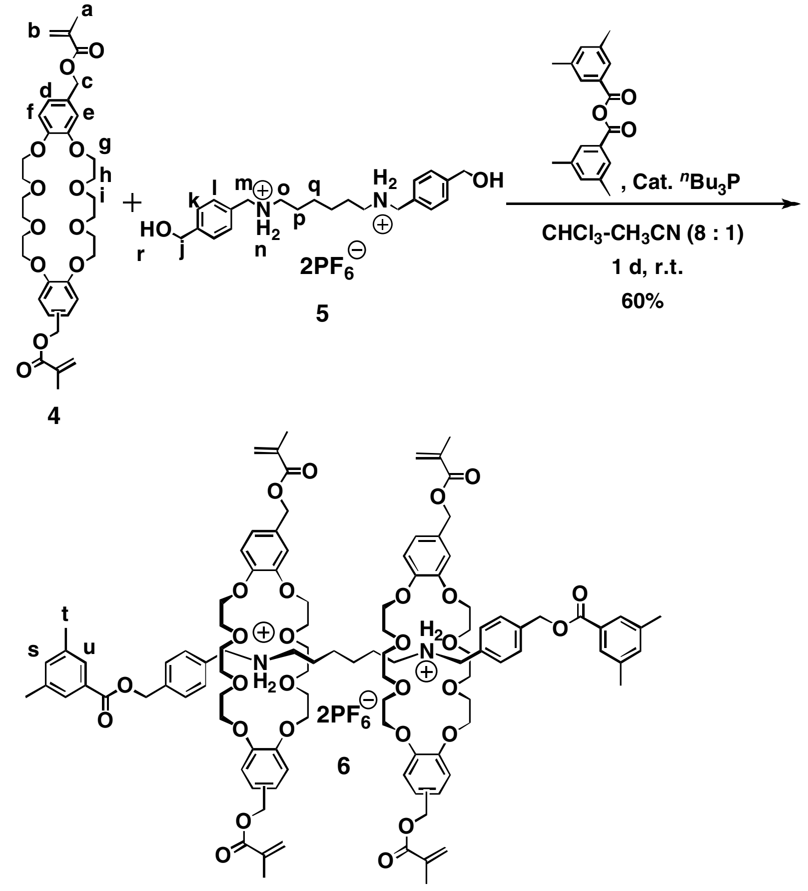


Scheme 2.

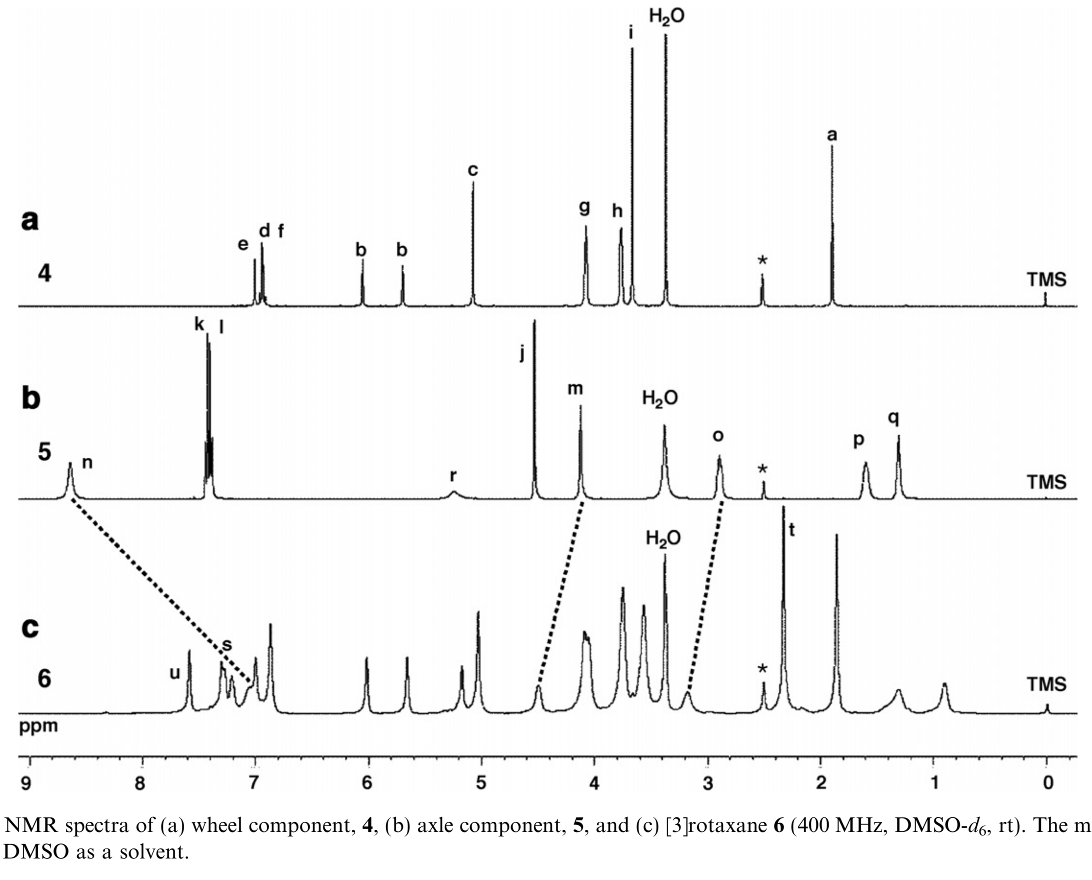


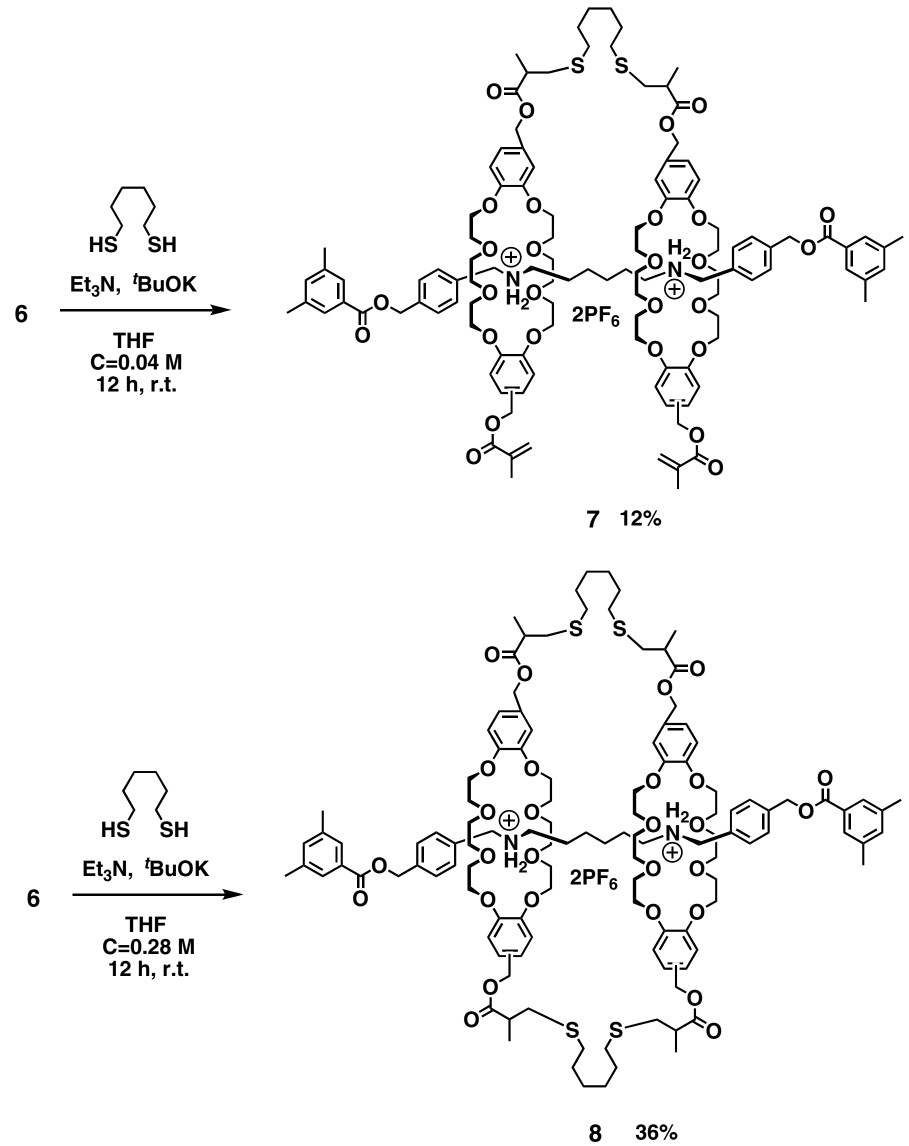
Figure 1. ^{1}H NMR spectra of (a) wheel component, **4**, (b) axle component, **5**, and (c) [3]rotaxane **6** (400 MHz, DMSO-d_6, rt). The mark ★ denotes the signal of DMSO as a solvent.

oligorotaxanes consisting of wheels containing reactive groups. While synthetic method of higher order rotaxanes than [2]rotaxane required for the wheel connection is limited,[5] we previously succeeded in synthesizing oligorotaxanes consisting of *sec*-ammonium-crown ether couples in high yields using the acylative end-capping protocol for the corresponding hydroxy-terminated axle-containing pseudorotaxanes.[6] Thus, we have been hitherto interested in and have examined the connection of two crown ether wheels of [3]rotaxane. In this Letter, we wish to describe the synthesis of [3]rotaxane bearing functionalized crown ether wheels and its transformation to [2]rotaxane through the efficient successive connection of the two wheel components at the two reactive sites.

Bis(methacrylate)-functionalized wheel **4** was prepared in three steps starting from DB24C8 (**1**) as shown in Scheme 1. Typical formylation of **1** with hexamethylenetetramine (HMTA) was followed by LiAlH$_4$-reduction to yield bis(hydroxymethyl)DB24C8 **3**. Reaction of **3** with methacryloyl chloride afforded **4** as a mixture of two regioisomers in 72% yield. The bis(ammonium)-type axle **5** was synthesized according to our previous report.[6] The structures of **4** and **5** were fully characterized by ^{1}H NMR, IR, and MS spectra.

[3]Rotaxane **6** was synthesized according to the acylative end-capping protocol[7] by treating a mixture of **4** and **5** with 3,5-dimethylbenzoic anhydride in the presence of a catalytic amount of tributylphosphane (Scheme 2). Oily product **6** was obtained in 60% yield.[8] The ^{1}H NMR spectrum of **6** clearly suggested its [3]rotaxane structure in comparison with those of **4** and **5** (Fig. 1).

The most reliable ^{1}H NMR characteristic is, as shown in Figure 1, the clear downfield shift of benzylic protons (from 4.11, 2.89 ppm to 4.66, 3.22 ppm) neighboring to the *sec*-ammonium group (signals m and o) of **5**, undoubtedly due to the intramolecular hydrogen bond-



Scheme 3.

ing of the CH_2 group with the crown ether wheel (NH–O) in **6**.[9] In addition, *m*/*z* 1191.78 signal in the MALDI-TOF mass spectrum assignable to that of [**6**$-2PF_6^-$] also strongly suggested the [3]rotaxane structure (calcd *m*/*z* 1910.94).[9]

The connection of the wheel components was carried out by Michael addition of hexanedithiol to **6** in the presence of both 10 mol % of potassium *tert*-butoxide and triethylamine in dry THF for 12 h at room temperature (Scheme 3). The main product obtained by preparative HPLC separation was [2]rotaxane **7** (12% yield) when the concentration of **6** was 0.04 M, suggesting that one of the two functional groups of the wheel was unreacted. Meanwhile, [2]rotaxane **8** having fully reacted functional groups was obtained in 36% yield by HPLC purification when the concentration increased up to 0.28 M.

Figure 2 lists the ^{1}H NMR spectra of **6**, **7**, **8**, and the reference compound **9**.[10] It is obvious that a part of vinyl proton signals of **6** still remained in **7**. Whereas the multiplet signals around 2.7 ppm, assignable to the methine and methylene proton signals derived from the methacrylate (6.10 and 5.55 ppm) moiety formed by the thiol addition, appeared in the spectrum of **7**, the NMR integration suggested that the major product is [2]rotaxane **7**[11] formed by one-hand linking of the wheels of **6**. Meanwhile, the vinyl proton signals of **6** completely disappeared in the ^{1}H NMR spectrum of the product formed at high concentration ([**6**] = 0.28 M), being consistent with the structure of [2]rotaxane **8**.[12] The methyl proton (1.92 ppm) of the methacrylate moiety of **6** was shifted to upfield (1.25 ppm) by the thiol addition. These results were in good accordance with the occurrence of the intramolecular successive Michael addition of hexanedithiol at high concentration ([**6**] = 0.28 M). Further, MALDI-TOF mass spectra clearly supported the above results: **7**; *m*/*z* 2060.37 for [**7**$-2PF_6^-$] (calcd *m*/*z* 2061.00) and **8**; *m*/*z* 2211.78 for [**8**$-2PF_6^-$] (calcd *m*/*z* 2211.05).

The Michael addition of hexanedithiol to macrocycle **4** alone was also carried out under the same condition, as a control experiment. Only a polymeric product instead of **7** or **8** was obtained,[13] undoubtedly revealing the significance of the arrangement of the wheels along the rotaxane skeleton (Scheme 4).

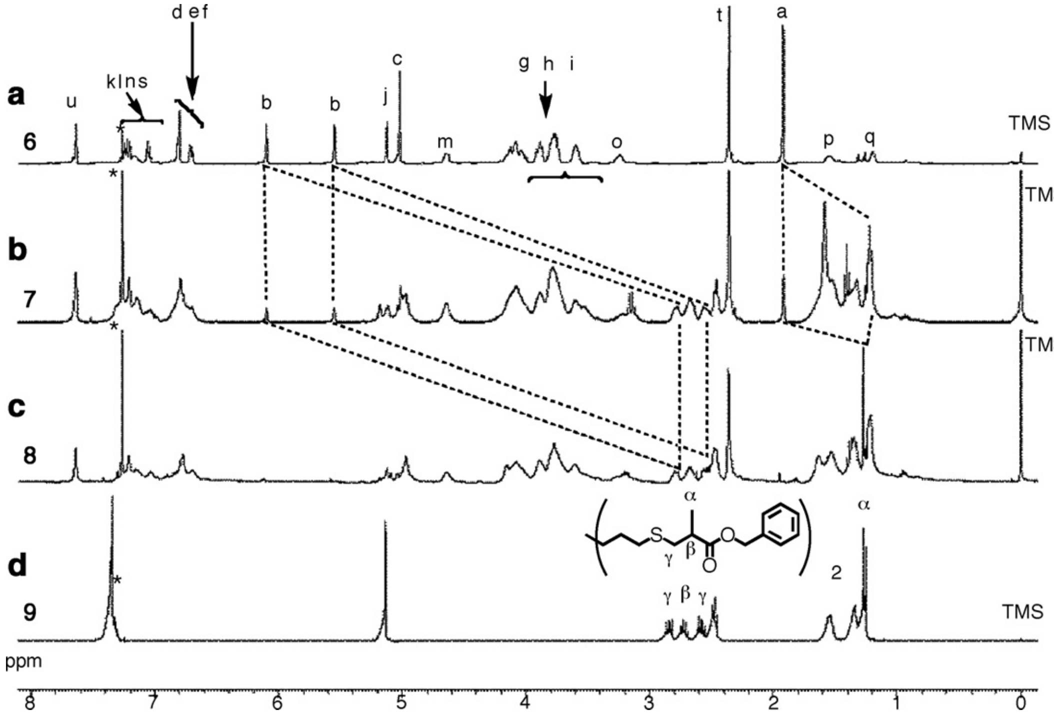
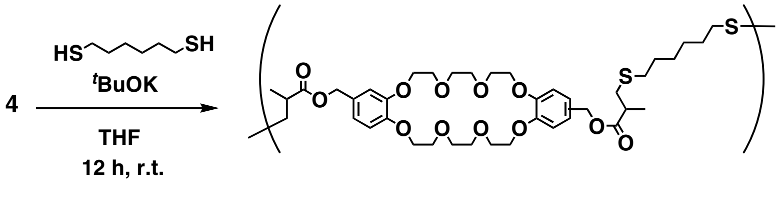


Figure 2. ^{1}H NMR spectra of (a) [3]rotaxane **6**, (b) [2]rotaxane **7**, (c) [2]rotaxane **8**, and (d) reference compound **9** (400 MHz, $CDCl_3$, rt). The mark ★ denotes the signal of $CHCl_3$ as a solvent.



Scheme 4.

In summary, we have successfully prepared functionalized [3]rotaxane **6** in a good yield from a bisammonium axle and bis(methacrylate)-tethered wheels. Rotaxane **6** can also be regarded as a tetrafunctionalized crosslinker for vinylic polymer. The advantageous use of the rotaxane scaffold has been demonstrated for the face-to-face connection of the wheels arranged on the axle of **6** by the Michael addition using an alkane dithiol. Further investigation on the development of the wheel-connection protocol is in progress.

Acknowledgment

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8. A mixture of 1:1 regio isomer **6**: mp 67–74.5 °C (EtOAc); IR (NaCl) 1686 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 4H, endcap Ar–H), 7.24 (m, 6H, axle and endcap ArH), 7.22 (m, 4H, axle-ArH), 7.02 (m, 4H, $NH_2{}^+$), 6.79 (m, 8H, crown-Ar–H), 6.70 (m, 4H, crown-Ar–H), 6.10 (s, 4H, methylene-CH_2), 5.55 (s, 4H, methylene-CH_2), 5.11 (s, 4H, axle-ArCH_2), 5.02 (s, 8H, crown-ArCH_2), 4.66 (br s, 4H, axle-Ar CH_2), 4.10–4.02 (m, 16H, crown-CH_2), 3.99–3.90 (m, 16H, crown-CH_2), 3.78–3.50 (m, 16H, crown-CH_2), 3.22 (br s, 4H, axle-CH_2), 2.36 (s, 12H, endcap-ArCH_3), 1.92 (s 12H, CH_3), 1.54 (br s, 4H, axle-CH_2), 1.20 (br s, 4H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 168.5, 151.1, 134.4, 125.4, 121.0, 60.2, 39.7, 34.9, 34.1, 31.3, 29.3, 26.4, 24.4, 14.2 ppm; MALDI-TOF–MS (Dithranol matrix) *m*/*z* 1911.78 $[M-2PF_6]^+$.
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10. Preparation of **9**: To a mixture of **4** (64.5 mg, 0.10 mmol) and 10 mol % potassium *tert*-butoxide (2.2 mg) in THF (0.36 mL) was added hexanedithiol (15.0 mg, 0.10 mmol). The mixture was stirred for 12 h at room temperature (*c* 0.28 M). The resulting mixture was extracted with $CHCl_3$, the combined $CHCl_3$ layer was washed with 3 M HCl and brine, and dried over anhydrous Mg_2SO_4. The solvent was evaporated and the residue was purified by preparative HPLC. Reference compound **9** was spectrosopically characterized.
11. Synthesis and charactarization of **7**: To a mixture of **4** (22.0 mg, 10.0 μmol) and 10 mol % potassium *tert*-butoxide (0.10 mg) in THF (0.036 mL) was added hexanedithiol (3.00 μL, 20.0 μmol) and triethylamine (2.78 μL, 20.0 μmol). The mixture was stirred for 12 h at room temperature (*c* 0.28 M). The resulting mixture was extracted with $CHCl_3$, the combined $CHCl_3$ layer was washed with 3 M HCl and brine, and dried over anhydrous Mg_2SO_4. The solvent was evaporated and the residue was purified by preparative HPLC. ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 4H, endcap Ar–H), 7.24 (m, 6H, axle and endcap ArH), 7.21 (m, 4H, axle-ArH), 7.04 (m, 4H, $NH_2{}^+$), 6.79 (m, 8H, crown-Ar–H), 6.70 (m, 4H, crown-Ar–H), 6.10 (s, 2H, methylene-CH_2), 5.55 (s, 2H, methylene-CH_2), 5.11 (m, 4H, axle-ArCH_2), 5.01 (s, 8H, crown-ArCH_2), 4.64 (br s, 4H, axle-ArCH_2), 4.15-4.02 (m, 16H, crown-CH_2), 3.99–3.60 (m, 16H, crown-CH_2), 3.60–3.42 (m, 16H, crown-CH_2), 3.22 (br s, 4H, axle-CH_2), 2.77, 2.57 (d m, 8H, CH_2), 2.67 (m, 4H, CH), 2.36 (s, 12H, endcap-ArCH_3), 1.92 (s 6H, CH_3), 1.54 (br s, 4H, axle-CH_3), 1.30 (br s, 4H, CH_2) 1.25 (s, 6H, CH_3) ppm, MALDI-TOF–MS (Dithranol matrix): *m*/*z* 2060.37 $[M-2PF_6]^+$.
12. Synthesis and charactarization of **8**: To a mixture of **4** (22.0 mg, 10.0 μmol) and 10 mol % potassium *tert*-butoxide (0.10 mg) in THF (0.250 mL) was added hexanedithiol (3.00 μL, 20.0 μmol) and triethylamine (2.78 μL, 20.0 μmol). The mixture was stirred for 12 h at room temperature (*c* 0.04 M). The resulting mixture was extracted with $CHCl_3$, the combined $CHCl_3$ layer was washed with 3 M HCl and brine, and dried over anhydrous Mg_2SO_4. The solvent was evaporated and the residue was purified by preparative HPLC. ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 4H, endcap Ar–H), 7.24 (m, 6H, axle and endcap ArH), 7.22 (m, 4H, axle-ArH), 7.02 (m, 4H, $NH_2{}^+$), 6.79 (m, 8H, crown-Ar–H), 6.70 (m, 4H, crown-Ar–H), 5.11 (s, 4H, axle-ArCH_2), 5.02 (s, 8H, crown-ArCH_2), 4.66 (br s, 4H, axle-ArCH_2), 4.10–4.02 (m, 16H, crown-CH_2), 3.99–3.90 (m, 16H, crown-CH_2), 3.78–3.50 (m, 16H, crown-CH_2), 3.22 (br s, 4H, axle-CH_2), 2.81, 2.60 (d m, 8H, CH_2), 2.73 (m, 4H, CH), 2.36 (s, 12H, endcap-ArCH_3), 1.54 (br s, 4H, axle-CH_3), 1.30 (br s, 4H, CH_2) 1.25 (s 12H, CH_3), ppm, MALDI-TOF–MS (Dithranol matrix): *m*/*z* 2211.78 $[M-2PF_6]^+$.
13. Reaction of **4** with hexanedithiol was carried out in the presence of *t*-BuOK in THF to give a polymeric product. The ^1H NMR spectrum of the product indicated the disappearance of the olefinic signals of **4** and appearance of methylene and methine proton signals, being consistent with the linear polymer formed by polyaddition (Scheme 4).