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Association of Liquid-Assisted Grinding with Aging Accelerates the Inherently Slow Slipping-on of a Dibenzo-24-Crown-8 over the *N*-hydroxysuccinimide Ester of an Ammonium-Containing Thread

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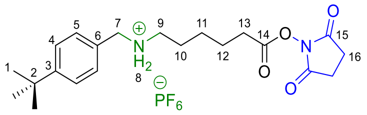
1 General methods

All reagents were used as received without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates. The grinding was carried out using a Mixer Mill Retsch® MM200 or MM400 high speed vibrating ball mill (operated at 25 Hz, 1 stainless steel ball with a diameter of 10 mm in a 10 mL stainless steel reactor). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 600 Avance III spectrometer (respectively at 600.27 and 150.94 MHz), a Bruker 400 Avance III HD spectrometer (respectively at 400.13 and 100.62 MHz), and a Bruker 300 Avance spectrometer (respectively at 300 and 75 MHz). Chemical shifts of ^{1}H NMR and ^{13}C NMR are given by using CH_3CN as reference (1.94 ppm for ^{1}H spectrum, and 118.26 ppm respectively for ^{13}C spectrum). ^{1}H NMR signal assignments were deduced from 2D ^{1}H-^{1}H NMR COSY while ^{13}C assignments were deduced from 2D ^{13}C-^{1}H NMR HSQC. Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), quint (quintuplet), m (multiplet). High-resolution mass spectra (HRMS) were recorded respectively on a ZQ Micromass apparatus and a Q-TOF Micro apparatus.

2 Synthesis of the ammonium-containing molecular axle 1



1[1]

Compound **1** has been synthesized in a four-step sequence according to the procedure described by Coutrot.[1]

^{1}H NMR (400 MHz, CD_2Cl_2, 298K): δ ppm = 7.48 (d, 2H, $^{3}J_{H4\text{-}H5}$ = 8.5Hz, H_4), 7.39 (d, 2H, $^{3}J_{H5\text{-}H4}$ = 8.5Hz, H_5), 6.89 (br s, 2H, H_8), 4.24 (t, 2H, $^{3}J_{H7\text{-}H8}$ = 5.4Hz, H_7), 3.13-3.05 (m, 2H, H_9), 2.79 (s, 4H, H_{16}), 2.60 (t, 2H, $^{3}J_{H13\text{-}H12}$ = 7Hz, H_{13}), 1.83-1.69 (m, 4H, H_{10} H_{12}), 1.54-1.42 (m, 2H, H_{11}), 1.31 (s, 9H, H_1).
^{13}C NMR (100 MHz, CD_2Cl_2, 298K): δ ppm = 170.7 (C_{14}), 169.1 (C_{15}), 154.0 (C_3), 130.1 (C_5), 126.8 (C_4), 126.7 (C_6), 52.6 (C_7), 47.9 (C_9), 35.1 (C_2), 31.3 (C_1), 30.8 (C_{13}), 26.0 & 25.3 (C_{10} C_{11} C_{16}), 24.0 (C_{12}).
HRMS (ESI): $[M\text{-}PF_6]^+$ calcd for $C_{21}H_{31}N_2O_4^+$: 375.2284, found: 375.2281.

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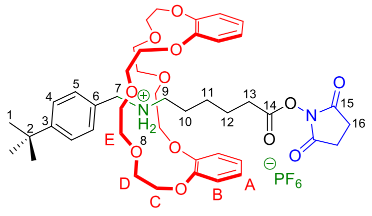
[1] T. Legigan; B. Riss-Yaw, C. Clavel, F. Coutrot, *Chem. Eur. J.* **2016**, *22*, 8835-8847.

3 Synthesis of rotaxane 2



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3.1 Procedure for the synthesis of rotaxane 2 in solution

Compound **2** was synthesized in solution from the ammonium salt **1** according to the procedure described by Coutrot.[1] To a solution of the NHS ester **1** (0.18 mmol, 1 equiv.) in dry CD_3CN ([**1**]=3.10^{-2} M) was added DB24C8 (3 equiv.). The mixture was stirred at 333 k and the kinetic of the reaction monitored by ^1H NMR spectroscopy.

^1H NMR (600 MHz, CD_3CN, 298K): δ ppm = 7.27 (d, 2H, $^3J_{H5\text{-}H4}$ = 8.3Hz, H_5), 7.21 (d, 2H, $^3J_{H4\text{-}H5}$ = 8.3Hz, H_4), 7.21 (br s, 2H, H_8), 6.91 (s, 8H, H_A H_B), 4.55-4.51 (m, 2H, H_7), 4.19-4.14 & 4.11-4.04 (2m, 2x4H, H_C $H_{C'}$), 3.85-3.76 (m, 8H, H_D $H_{D'}$), 3.68-3.63 & 3.58-3.53 (2m, 2x4H, H_E $H_{E'}$), 3.37-3.30 (m, 2H, H_9), 2.77 (s, 4H, H_{16}), 2.34 (t, 2H, $^3J_{H13\text{-}H12}$ = 7.4Hz, H_{13}), 1.51 (quint, 2H, $^3J_{H10\text{-}H11}$ = $^3J_{H10\text{-}H9}$ = 7.4Hz, H_{10}), 1.45 (quint, 2H, $^3J_{H12\text{-}H13}$ = $^3J_{H12\text{-}H11}$ = 7.4Hz, H_{12}), 1.23 (s, 9H, H_1), 1.17 (quint, 2H, $^3J_{H11\text{-}H12}$ = $^3J_{H11\text{-}H10}$ = 7.4Hz, H_{11}).
^{13}C NMR (150 MHz, CD_3CN, 298K): δ ppm = 171.1 (C_{15}), 169.8 (C_{14}), 153.1 (C_3), 148.5 ($C_{IV\ arom\ DB24C8}$), 130.4 (C_5 C_6), 126.5 (C_4), 122.4 & 113.6 (C_A C_B), 71.6 (C_E $C_{E'}$), 71.2 (C_D $C_{D'}$), 69.0 (C_C $C_{C'}$), 52.8 (C_7), 49.3 (C_9), 35.2 (C_2), 31.4 (C_1), 31.0 (C_{13}), 26.7 (C_{10}), 26.4 (C_{16}), 26.1 (C_{11}), 24.5 (C_{12}).
HRMS (ESI): $[M-PF_6]^+$ calcd for $C_{45}H_{63}N_2O_{12}^+$: 823.4381, found: 823.4382.

3.2 General procedure for the synthesis of rotaxane 2 through solvent-free and solvent-less methods

3.2.1 General procedure for mixing solids

a. Mixing with a spatula (entries 2, 4, and 7 of table 1)

The compound **1** (1.4 mg, 0.0027 mmol, 1 equiv.) and DB24C8 (3.6 mg, 0.0080 mmol, 3 equiv.) were added to a vial and mixed with the spatula.

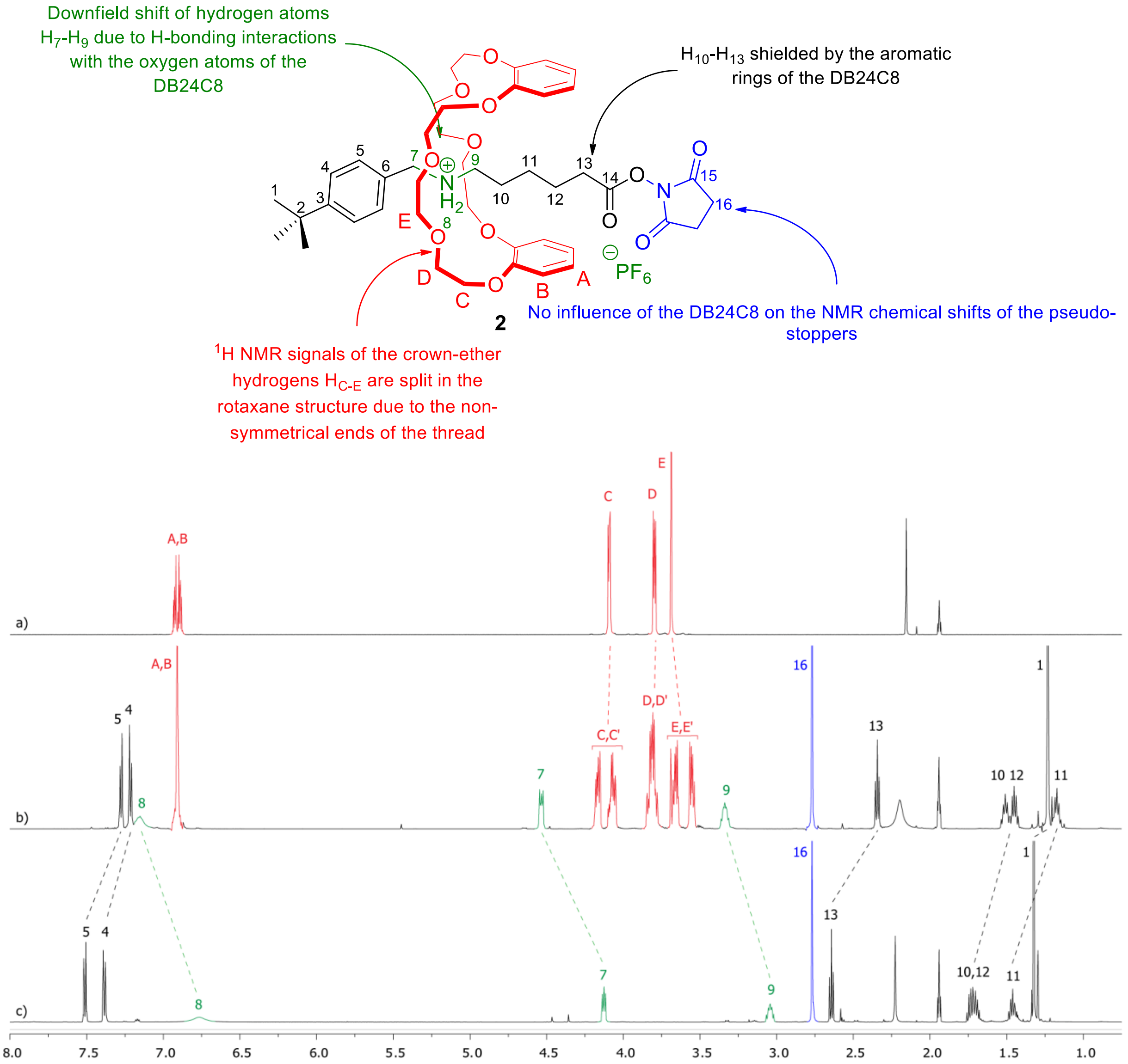
b. Mixing by grinding (entries 3, 5, 6 and 8 of table 1)

Compound **1** (19.7 mg, 0.0375 mmol, 1 equiv.), DB24C8 (50.7 mg, 0.113 mmol, 3 equiv.) and acetonitrile (14 µL, corresponding to 0.2 µL/mg of mixture for entries 3, 6 and 8, no acetonitrile for entry 5) were added to a 10 mL stainless steel reactor containing 1 stainless steel ball of 10 mm diameter. Then, the reactor was closed and subjected to milling at 25 Hz for 1 h at room temperature in a high-speed vibrating ball mill. Then, the solid mixture was split in 14 uncapped vials, each containing 5 mg of the solids.

3.2.2 General procedure of the slipping-on process through aging method

In a 100 mL round-bottom flask was disposed uncapped vials containing 5 mg of the ball-milled solid mixture. Aging was then carried out in the presence of an atmosphere of acetonitrile (the atmosphere of acetonitrile was created by adding 0.1 mL of acetonitrile in the 100 mL stoppered round-bottom flask) (entries 7 and 8, Table 1) or argon (the atmosphere of argon was introduced by alternating vacuum/Ar gas sequences) (entries 4 to 6, Table 1). The round-bottom flask was stoppered, and then placed in an oven at 333 K for the kinetics times. Each vial was analyzed by ^{1}H NMR spectroscopy after a given time and gave rise to only one data of figure 1.

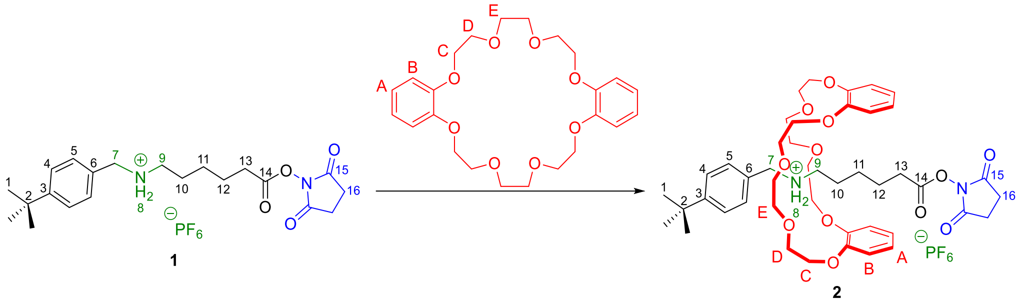
3.3 ^{1}H NMR characterization of rotaxane 2

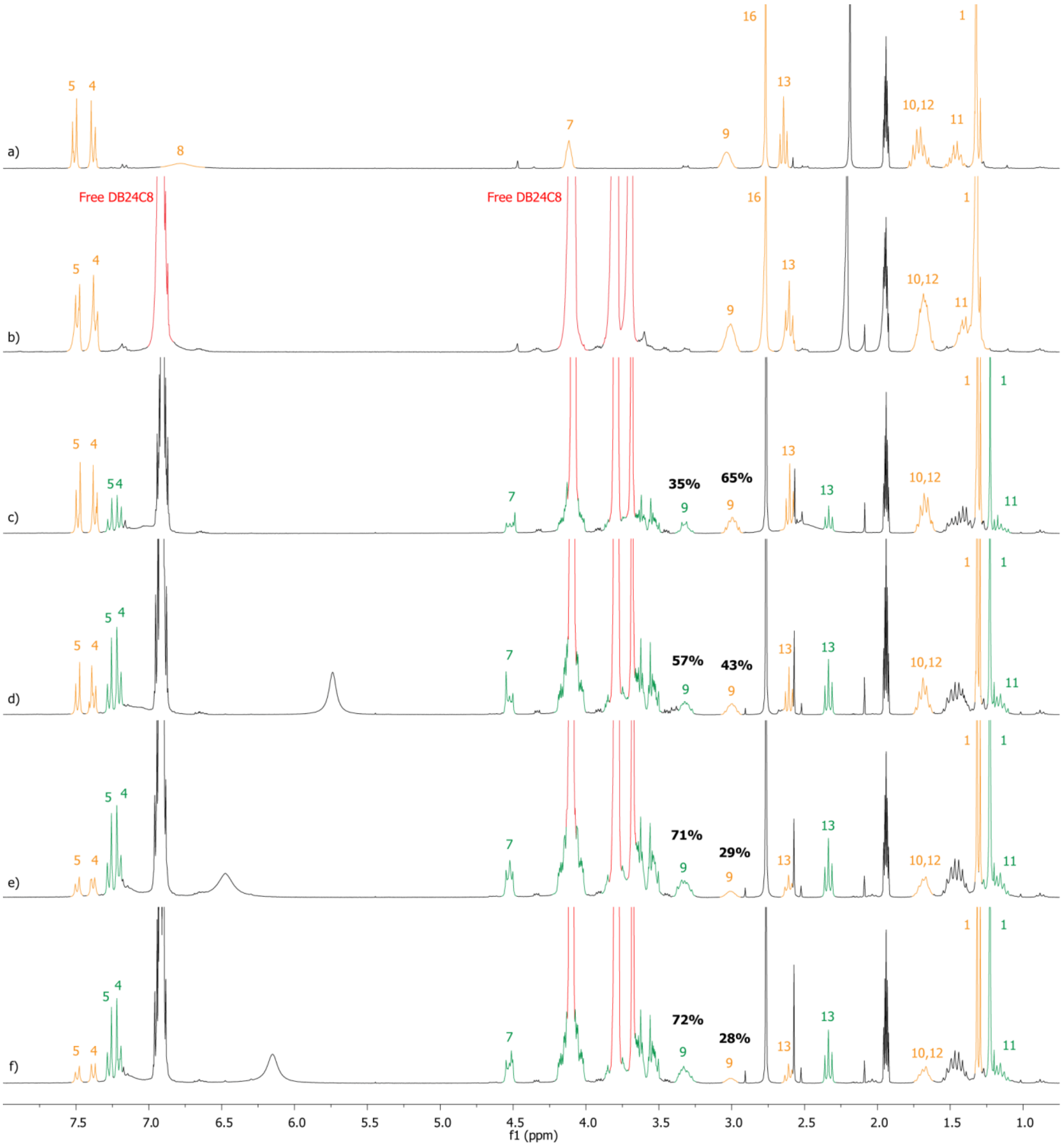


^{1}H NMR spectra (600 MHz, CD_3CN, 298K) of: (a) DB24C8; (b) the [2]rotaxane **2** and (c) the uncomplexed thread **1**

4 Kinetic studies of the slipping-on process relative to the formation of rotaxane 2

4.1 Slipping-on process in solution



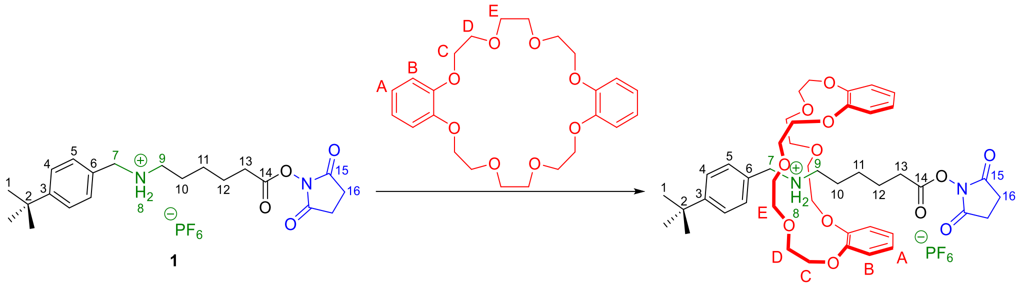


^{1}H NMR spectra (300 MHz, CD$_3$CN, 298K) of the entry 1, table 1: (a) the uncomplexed protonated ester **1** (3.10^{-2}M); (b) the mixture of uncomplexed protonated ester **1** (3.10^{-2}M) and DB24C8 (3 equiv.) at initial time; (c) the reaction mixture at t=48,8h; (d) the reaction mixture at t=119,3h; (e) the reaction mixture at t=312,5h; (f) the reaction mixture at t=528h. Non-overlapped signals of the uncomplexed thread **1** are represented in orange, signals of the free DB24C8 in red and signals of the rotaxane **2** in green.

4.2 General procedure for solvent-free and solvent-less procedures

The progress of the slipping-on process was monitored by carrying out ^{1}H NMR analysis of each vial (see paragraph 3.2) over time (5 mg of mixture, **1**:DB24C8 1:3 equivalents, respectively) in CD_3CN (0.6 mL) at 298 K. The relative percentages of the unthreaded molecular axle **1** and the [2]rotaxane **2** were determined by integrating the H_9 signal for each compound. Examples of ^{1}H-NMR spectra are given below.

4.2.1 Aging at 333 K under Argon atmosphere after homogenization using a spatula (entry 4, Table 1)



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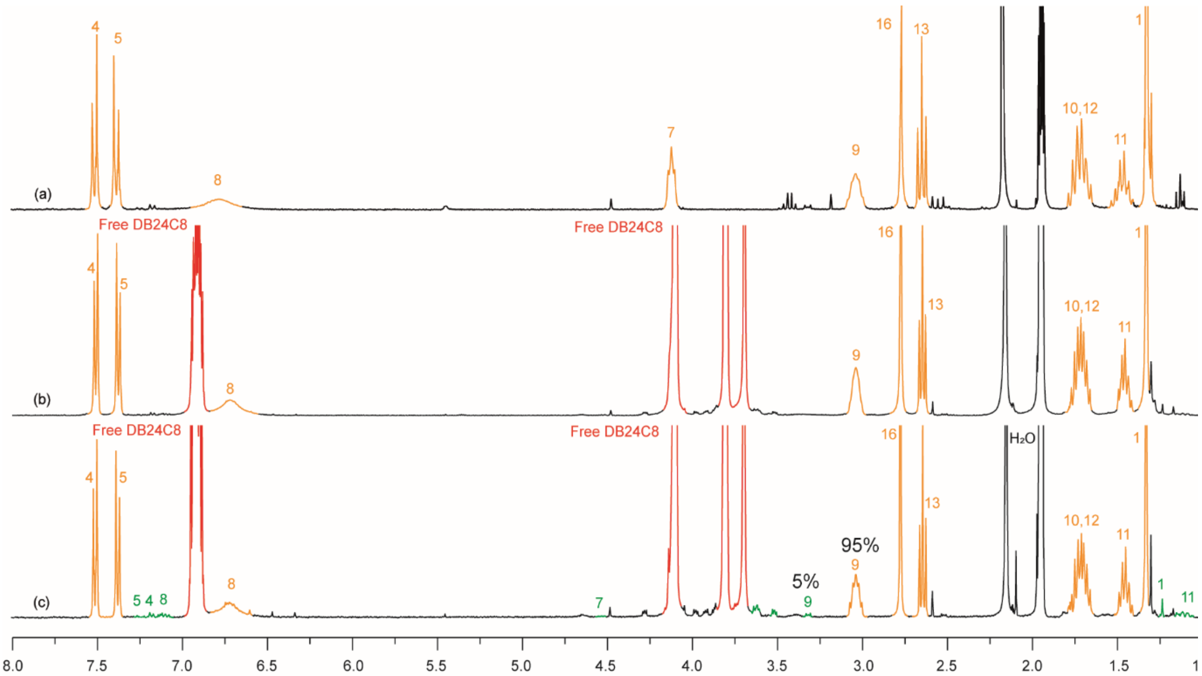
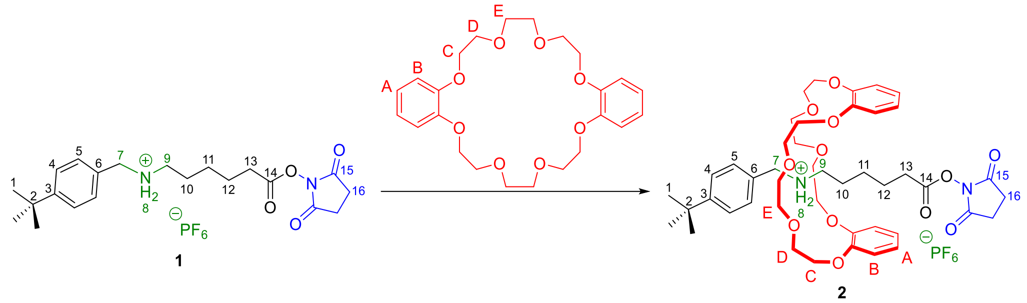
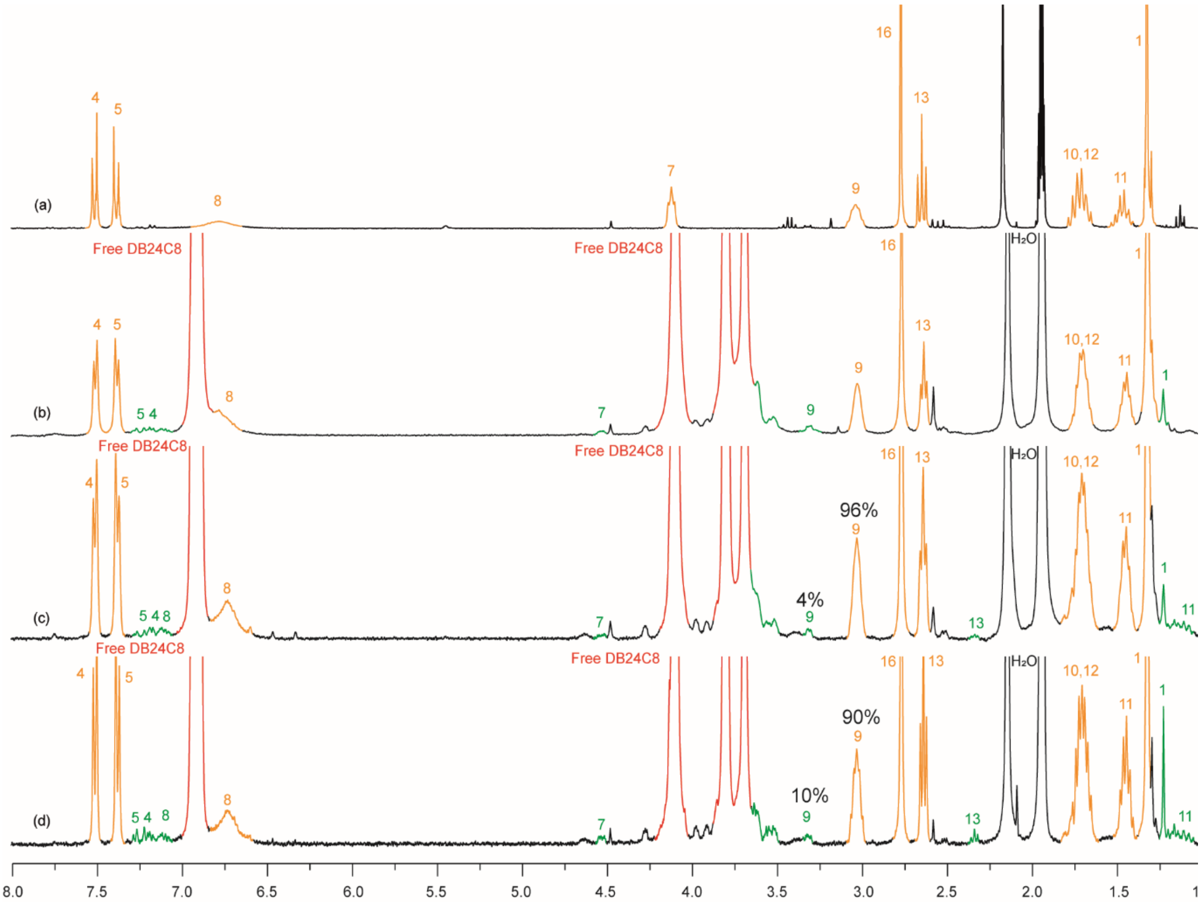


^{1}H NMR spectra (400 MHz, CD_3CN, 298K) of the entry 4, table 1: (a) the uncomplexed protonated ester **1**; (b) the mixture of uncomplexed protonated ester **1** (1 equiv.) and DB24C8 (3 equiv.) at initial time; (c) the reaction mixture at t=504 h. Non-overlapped signals of the uncomplexed thread **1** are represented in orange, signals of the free DB24C8 in red and signals of the rotaxane **2** in green.

4.2.2 Aging at 333 K under Argon atmosphere after homogenization by grinding without LAG (entry 5, Table 1)

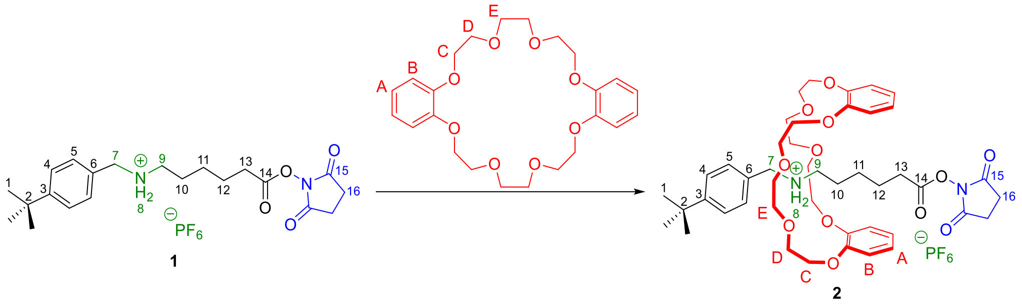


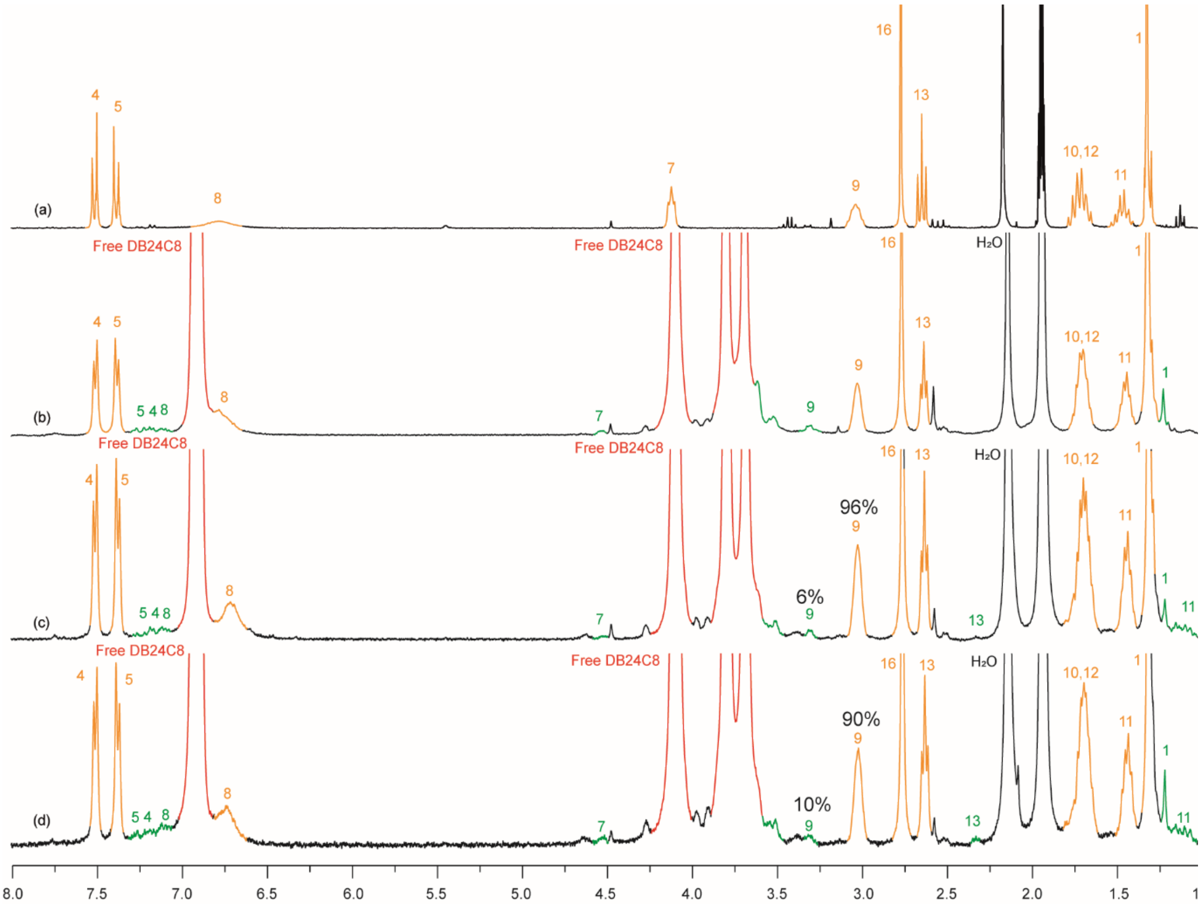
1 2



^{1}H NMR spectra (400 MHz, CD_3CN, 298K) of the entry 5, table 1: (a) the uncomplexed protonated ester **1**; (b) the mixture of uncomplexed protonated ester **1** (1 equiv.) and DB24C8 (3 equiv.) at initial time after grinding; (c) the reaction mixture at t=168 h; (d) the reaction mixture at t=504 h. Non-overlapped signals of the uncomplexed thread **1** are represented in orange, signals of the free DB24C8 in red and signals of the rotaxane **2** in green.

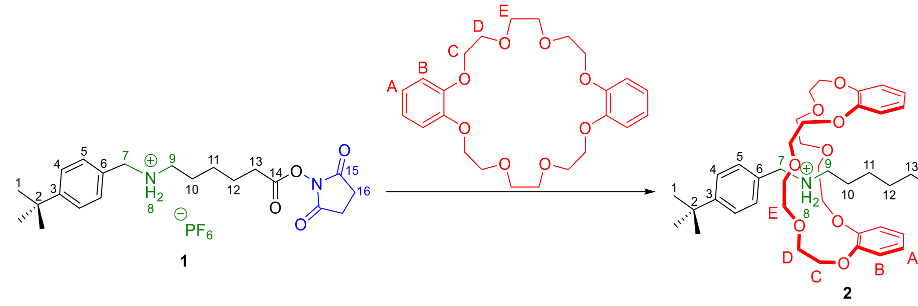
4.2.3 Aging at 333 K under Argon atmosphere after homogenization by grinding with LAG (entry 6, Table 1)

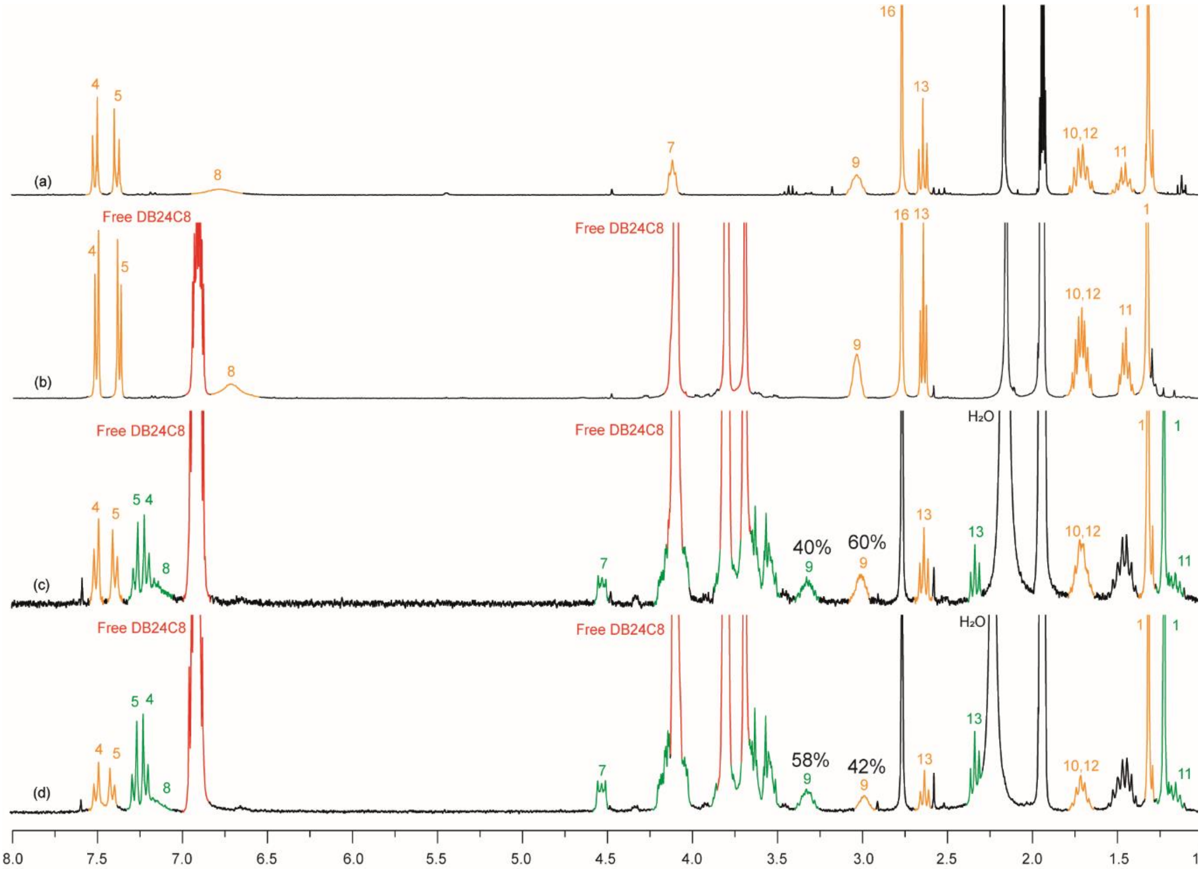




^{1}H NMR spectra (400 MHz, CD_3CN, 298K) of the entry 6, table 1: (a) the uncomplexed protonated ester **1**; (b) the mixture of uncomplexed protonated ester **1** (1 equiv.) and DB24C8 (3 equiv.) at initial time after grinding; (c) the reaction mixture at t=168 h; (d) the reaction mixture at t=504 h. Non-overlapped signals of the uncomplexed thread **1** are represented in orange, signals of the free DB24C8 in red and signals of the rotaxane **2** in green.

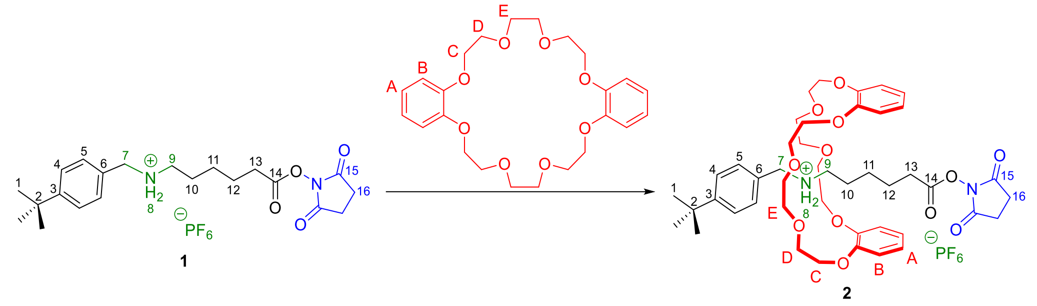
4.2.4 Aging at 333 K under acetonitrile atmosphere after homogenization with a spatula (entry 7, Table 1)

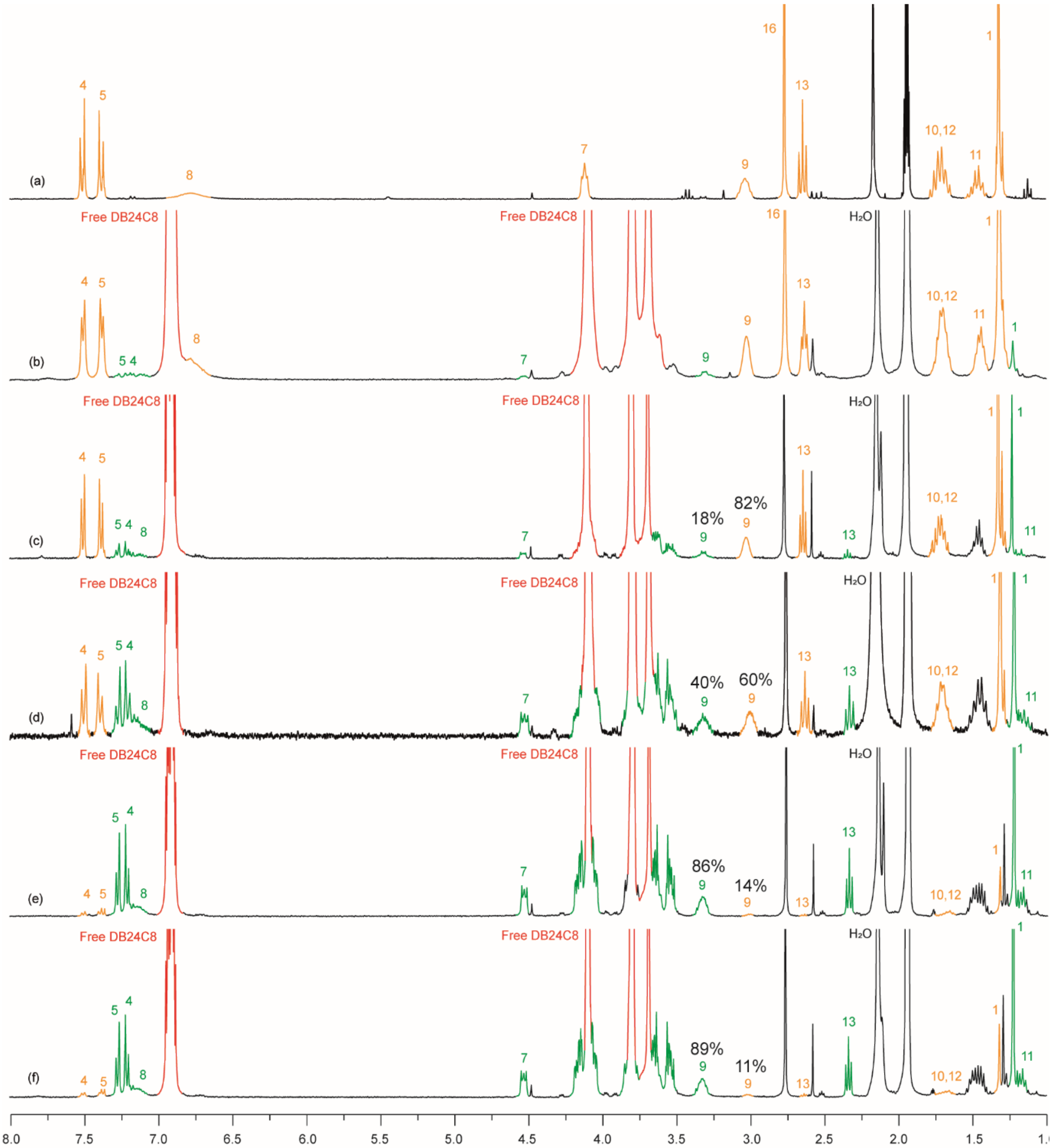




^{1}H NMR spectra (400 MHz, CD_3CN, 298K) of the entry 7, table 1: (a) the uncomplexed protonated ester **1**; (b) the mixture of uncomplexed protonated ester **1** (1 equiv.) and DB24C8 (3 equiv.) at initial time; (c) the reaction mixture at t=22.1 h; (d) the reaction mixture at t=72.1 h. Non-overlapped signals of the uncomplexed thread **1** are represented in orange, signals of the free DB24C8 in red and signals of the rotaxane **2** in green.

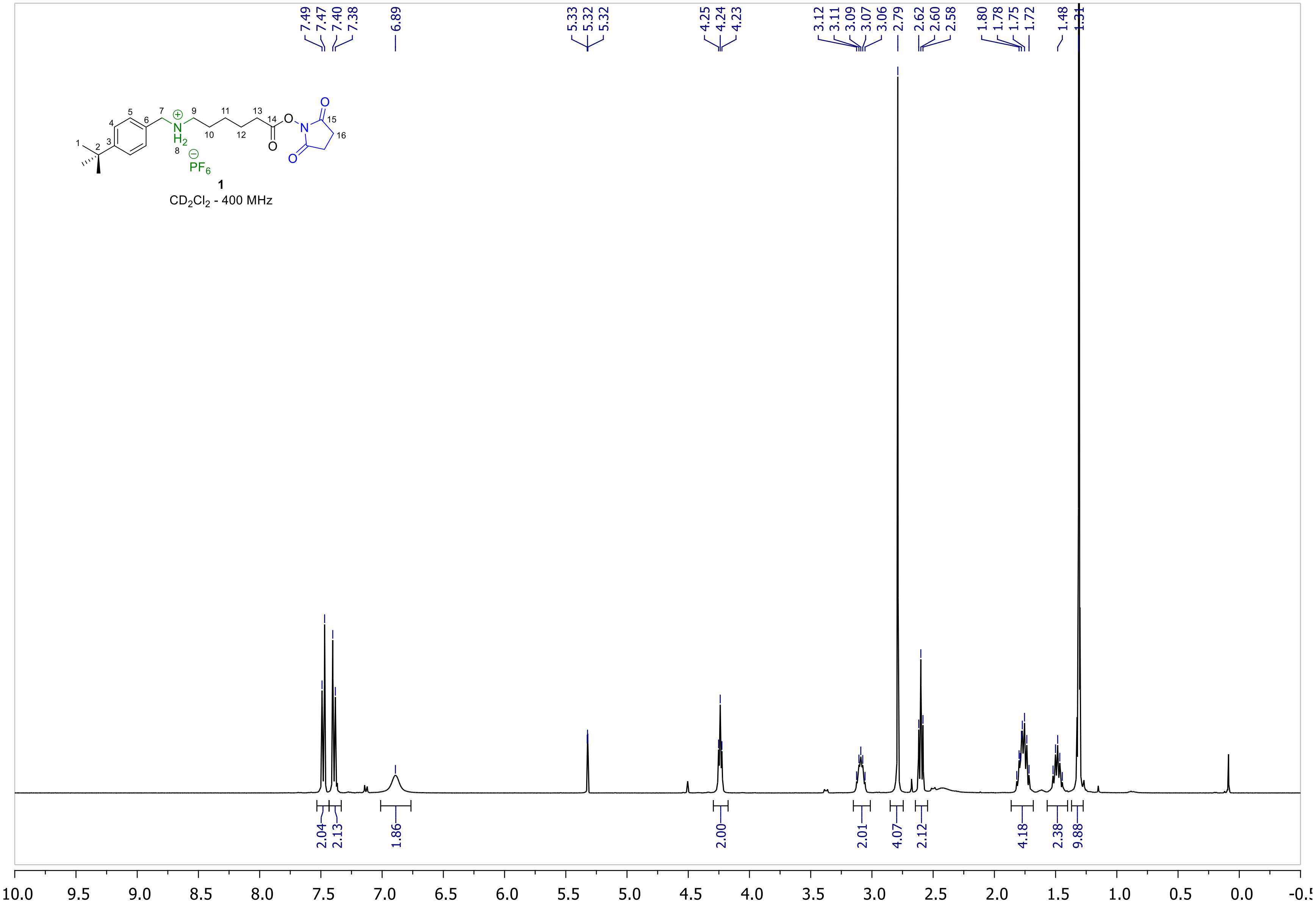
4.2.5 Aging at 333 K under acetonitrile atmosphere after homogenization by grinding with LAG (entry 8, Table 1)





^{1}H NMR spectra (400 MHz, CD_3CN, 298K) of the entry 8, table 1: (a) the uncomplexed protonated ester **1**; (b) the mixture of uncomplexed protonated ester **1** (1 equiv.) and DB24C8 (3 equiv.) at initial time after grinding; (c) the reaction mixture at t=4.3 h; (d) the reaction mixture at t=7.4 h; (e) the reaction mixture at t=89 h; (f) the reaction mixture at t=148.8 h. Non-overlapped signals of the uncomplexed thread **1** are represented in orange, signals of the free DB24C8 in red and signals of the rotaxane **2** in green.

NMR Spectra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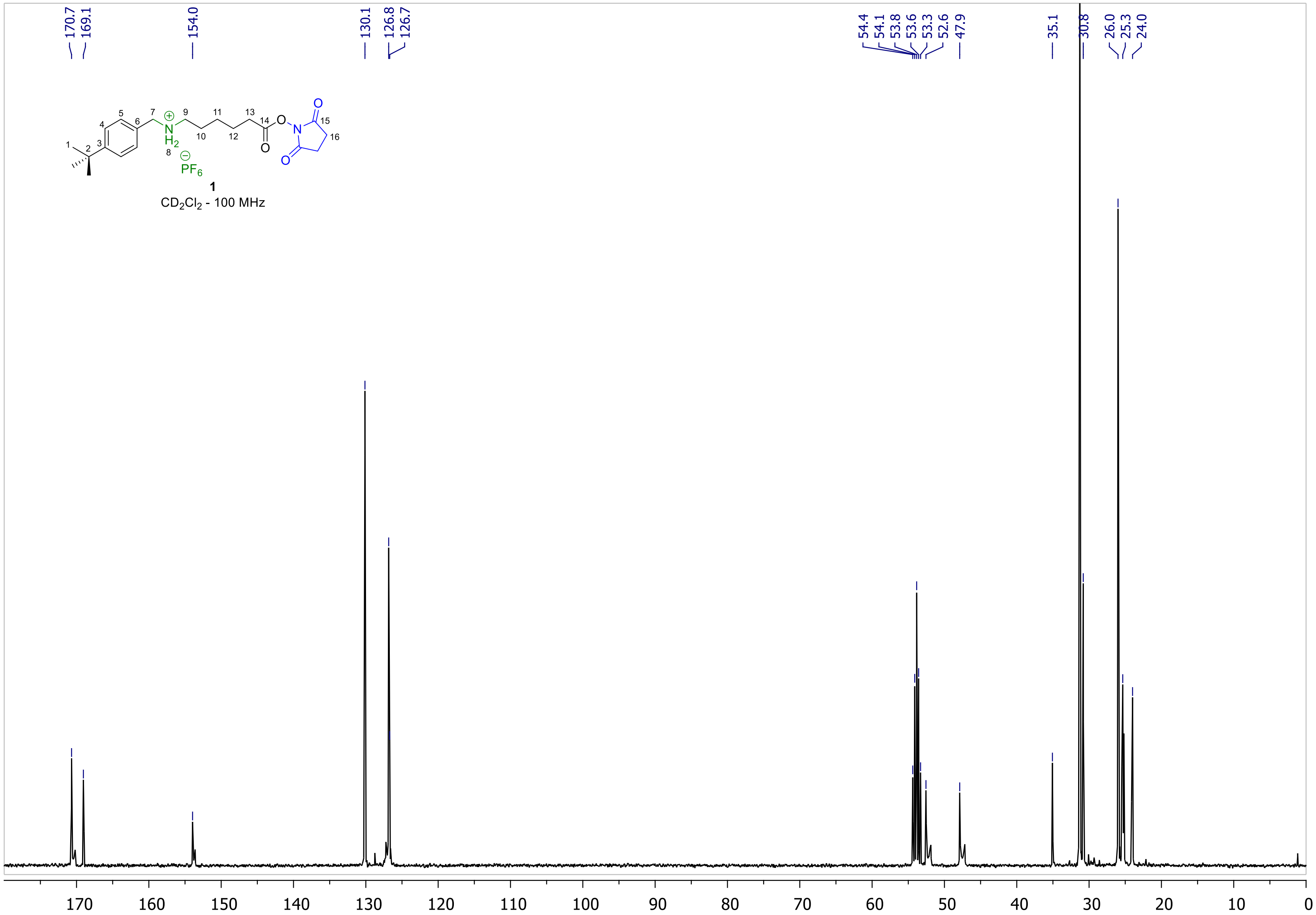
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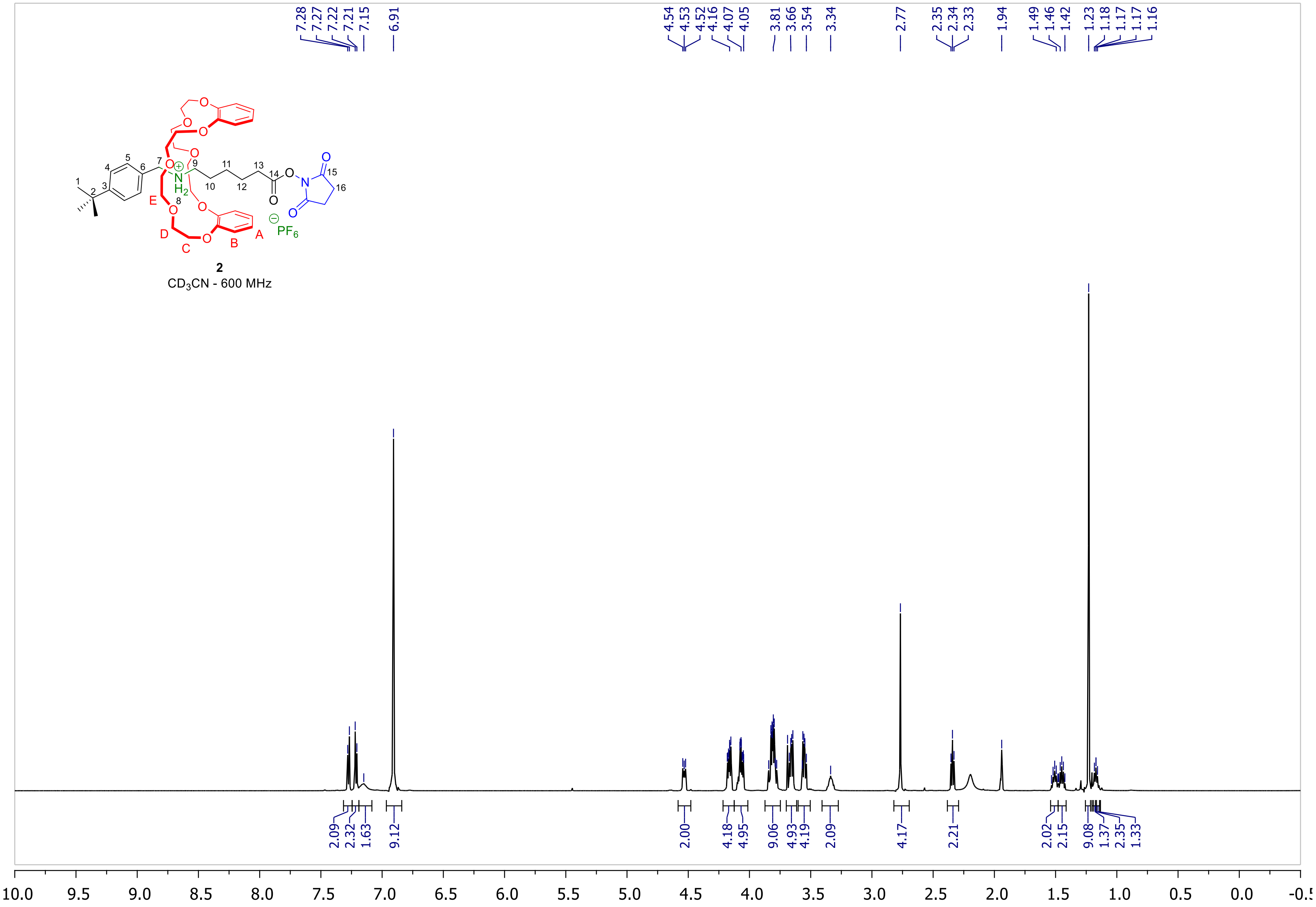
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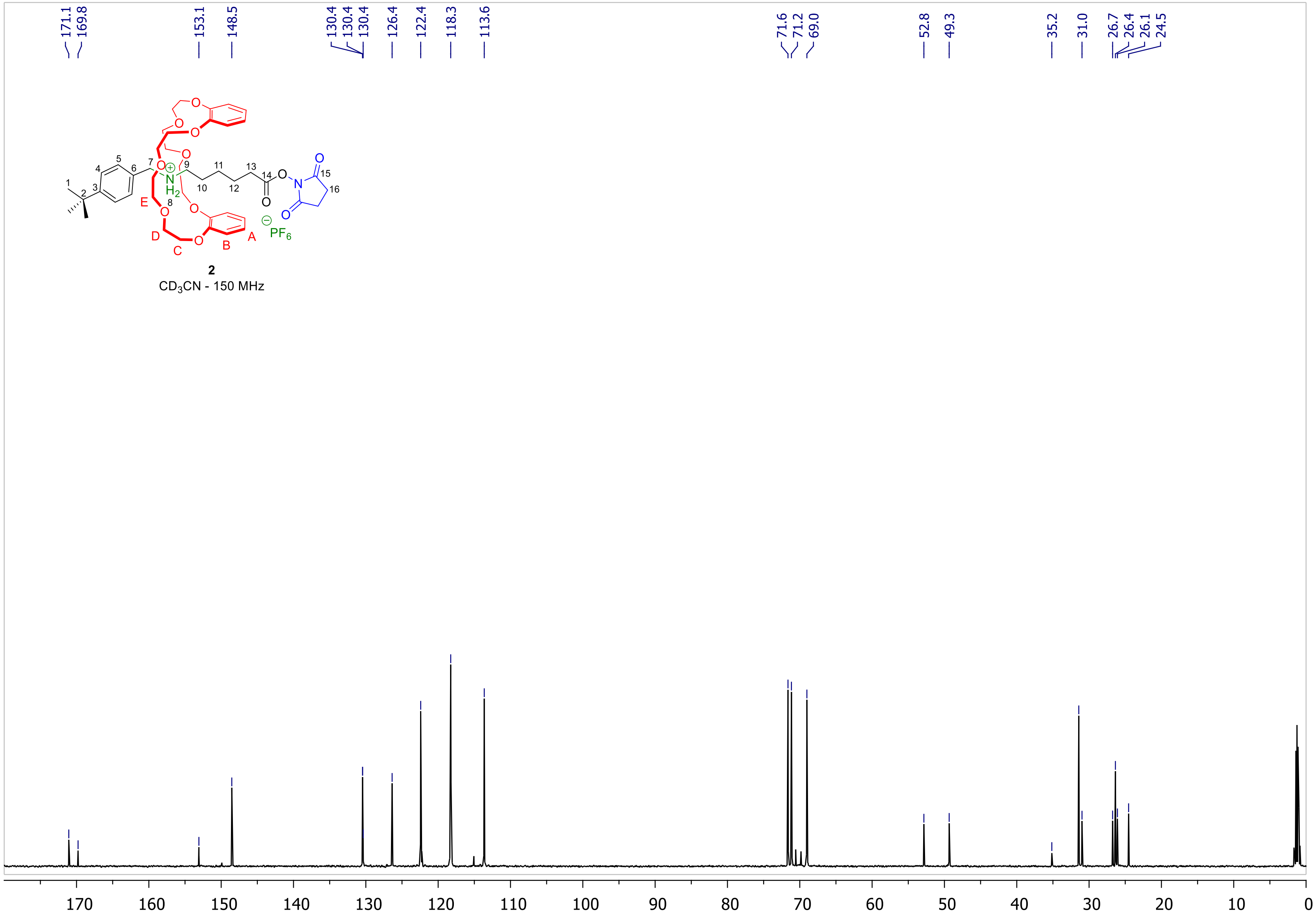

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