Supporting Information

Synthesis and Characterization of pH-Responsive Mesalazine-Polynorbornene Supramolecular Assembly

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This document contains 18 Figures and 2 Tables over 27 pages.

1. General information

All metathesis reactions were conducted under nitrogen atmosphere using *Schlenk*-technique or under argon using a glovebox. DMSO-d_6, CD_2Cl_2 (Eurisotop), reagents and solvents (Aldrich) were used as received.

(4-(bicyclo[2.2.1]hept-5-en-2-ylmethoxy)pyridine-2,6-diyl)dimethanol (**7**), 5-(perfluoro-tertbutoxymethyl)bicyclo[2.2.1]hept-2-ene, polymer **4**,[1] and tetraethylene glycol ditosylate[2] were synthetized as reported.

Solution state NMR spectra were obtained on a Varian Unity INOVA spectrometer operating at an equivalent ^{1}H frequency of 500 MHz, and ^{19}F frequency of 282 MHz. Notation for the ^{1}H NMR spectral splitting patterns includes singlet (s), doublet (d), triplet (t), broad (br) and multiplet/overlapping peaks (m). Chemical shifts (δ values) are given in ppm, coupling constants (*J*) are expressed in Hertz. The 2D-NOESY measurement was performed according to standard procedure and a mixing time of 50 ms was applied.

Solid state NMR spectra were recorded on a Varian NMR system operating at a ^{1}H frequency of 400 MHz (100 MHz for ^{13}C) with a Chemagnetics 4.0 mm narrow-bore double resonance T3 probe. The spinning rate of the rotor was 8 kHz in all cases. For the ^{13}C cross-polarization (CP) MAS 8000 transients were recorded with SPINAL-64 decoupling with a strength of 83 kHz and 1.0 ms of contact time with 5 s of recycle delay, which is five times larger than T_{1H} of the crystalline mesalazine. CP MAS ^{13}C spectra were collected by varying the contact time to gain the cross-polarization build-up curves. The temperature of all the measurements was 20 °C. Adamantane was used as external chemical shift reference (38.55 and 29.50 ppm). The 90° pulse lengths were 3 μs for the carbon and 4.2 μs for the proton channels.

GPC measurements were carried out using Waters 2695 separation unit and Waters 2414 RI detectors (Waters, Milford, USA) at 35 °C column and detector temperature. The sample compartment was used at 25 °C. Column bank contained four columns (4.6×300 mm): Styragel HR 0.5, Styragel HR 1, Styragel HR 2 and Styragel HR 4 (Waters, Milford, USA). A third order calibration curve was used, and the calibration standards were Polystyrenes in the 500-310000 Da molecular weight range. The eluent was HPLC grade THF (VWR International, Leuven, Belgium). The flow rate was 0.5 ml/min. For the calculations of the molecular weights,

Millennium[32] Chromatography Manager was used. The concentration of the samples was 5 mg/mL, and the volumes of injections were in the range of 10-50 μL.

The Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometric (MALDI-TOF MS) measurements were performed with an AutoFlex Speed mass spectrometer equipped with a time-of-flight (TOF) mass analyzer. In all cases, 19.5 kV (IonSource 1) and 18.3 kV (IonSource 2) acceleration voltages were used with pulsed ion extraction (PIE™). The positive ions were detected in the linear mode. A Bruker smartbeam™-II solid phase laser (355 nm, ≥ 100 μJ/pulse) operating at 500 Hz was used to produce laser desorption, and 5000 shots were summed. The MALDI-TOF MS spectra were externally calibrated using polyethylene glycol (PEG) standard (M_n = 1450 g/mol, Sigma-Aldrich, Taufkirchen, Germany).

Samples for MALDI-TOF MS were prepared with 2,5-dihydroxybenzoic acid (DHB) (Sigma-Aldrich, Taufkirchen, Germany) matrix dissolved in tetrahydrofuran (VWR International, Leuven, Belgium) at a concentration of 20 mg/mL. The concentrations of the analyte solutions were 5 mg/mL, and sodium trifluoroacetate (NaTFA) (Sigma-Aldrich, Taufkirchen, Germany) was dissolved in THF at a concentration of 5 mg/mL (used as the cationization agent to promote ionization). The solutions were mixed in a 10:2:1 (v/v) ratio (matrix/analyte/cationization agent). A volume of 0.5 μL of the solution was deposited onto a metal sample plate and allowed to air-dry.

The glass transition temperature (T_g) was determined by a Setaram DSC92 differential scanning calorimeter from -140 °C to 130 °C. The samples, with an average mass of 30-40 mg were pressed in 120 μL aluminum crucibles and sealed with pierced lids. On each sample, at least three measurements were performed, with two different scanning rates (two measurements with 20 °C/min, and one measurement with 10 °C/min). During the measurement, the calorimeter was purged with high purity nitrogen (flow rate 20 mL/min). Calcined α-alumina powder was used as reference material. The calorimeter was calibrated with high purity metals (five different metals, with at least three different scanning rates). The data obtained from the first measurement was not evaluated (the thermal history of the sample is removed). Thermal stability was investigated by simultaneous thermogravimetry-differential scanning calorimetry

(TG-DSC) on a Setaram LabsysEvo system. The measurements were performed under pyrolytic conditions in a flowing (80 mL/min) high purity argon (99.999%) atmosphere, in 25–500 °C temperature range, with a scanning rate of 10 °C/min. An average of 10-15 mg sample was placed in 100 μL aluminum pan; the samples were used as received. The measurements were blank corrected. All measurement results were evaluated with Calisto Processing software.

The released mesalazine was determined by Metertech SP-8001 UV/Visible Spectrophotometer at maximum wavelength.

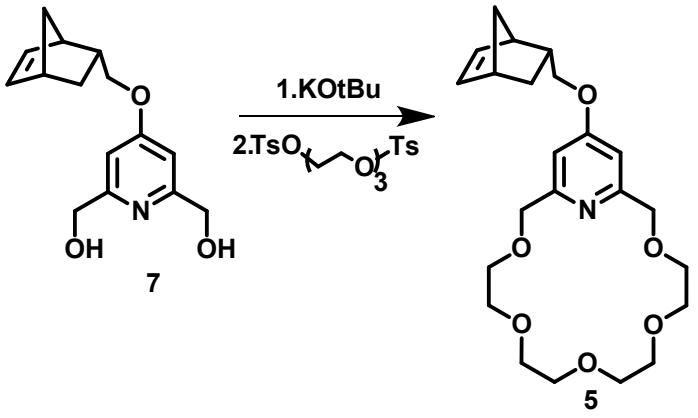
TLC was performed on Merck Kieselgel 60 F_{254} plates or Merck Aluminium oxide 60 F_{254} plates and spots were visualized by UV light or by exposing it with iodine or aqueous solution of $(NH_4)_6Mo_7O_{24}$, $Ce(SO_4)_2$ and sulfuric acid.

Flash column chromatography was performed on a CombiFlash Rf 150 apparatus using gradient elution in normal (silica or alumina column; hexane−ethyl acetate or dichloromethane−methanol or dichloromethane−ethanol as eluent) phase mode. Sample loadings were performed in the case of silica flash chromatography by coating the sample onto a silica cartridge.

Gradient elution preparative HPLC was applied (Armen) on a Gemini 250×50.00 mm; 10 μm, C18, 110 Å.

2. Synthesis of polymer 4

Modified synthesis of **5**



In a Schlenk tube diol **7** (558 mg, 2.14 mmol) was dissolved in THF (50 mL) and KOtBu (1 M THF solution, 4.6 mL, 4.6 mmol) was added to this stirred solution. In another Schlenk tube ditosylate (1.00 g, 1.99 mmol) was dissolved in THF (45 mL). The solution of ditosylate was added to the suspension of the diol's potassium salt at –78 °C. The mixture was let to warm up to room temparature and refluxed for 18 hours. The solvent was evaporated and the crude product (2 g) was purified by flash chromatography on alumina (eluent: dichloromethane and methanol 0 to 5% using gradient elution) to give 1.1 g as a light brown oil. The crude product was further purified by preparative HPLC (gradient method: 95% water, 4.9% acetonitrile, 0.1% HCOOH to 95% acetonitrile, 4.9% water, 0.1% HCOOH). The solvent was evaporated and the residue formate salt was liberated by dissolving it in dichloromethane (50 mL) and washed with tetramethyl-ammonium hydroxide (20 mL, 25 m/m% in water). The phases were separated and the aqueous phase was extracted with dichloromethane (3×30 mL). The organic phases were combined. The solvent was evaporated under reduced pressure to give 500 mg of **5** (60%) as a colorless oil. The ^{1}H NMR spectrum of **5** was identical than that of reported.[1]

Characterization of polymer **4**:

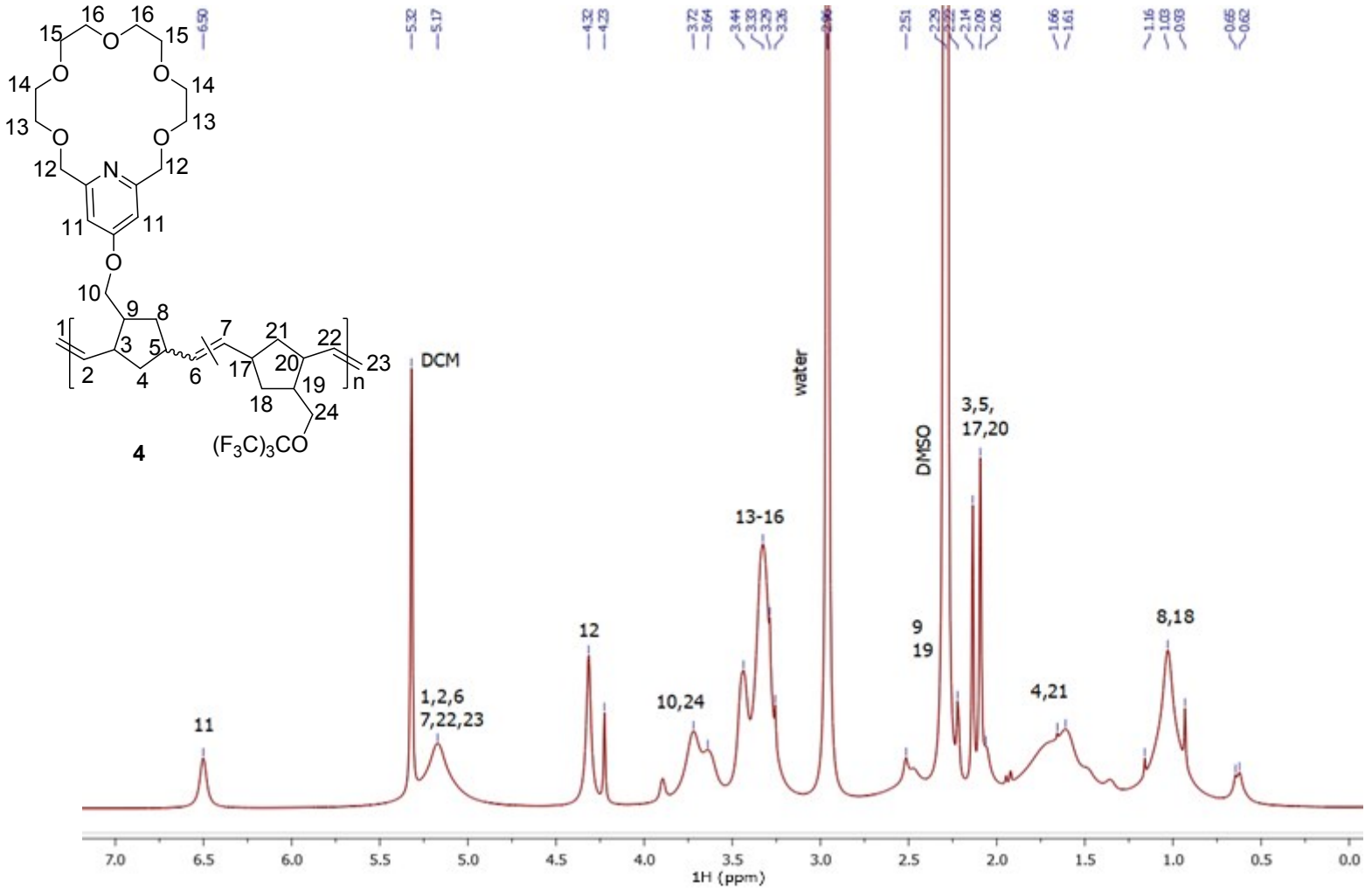


Figure S1. ^{1}H NMR spectrum of **4-*cp-1-5*** (1/5 equivalent, **G2**) (DMSO-*d6*:CD_2Cl_2=1:1).

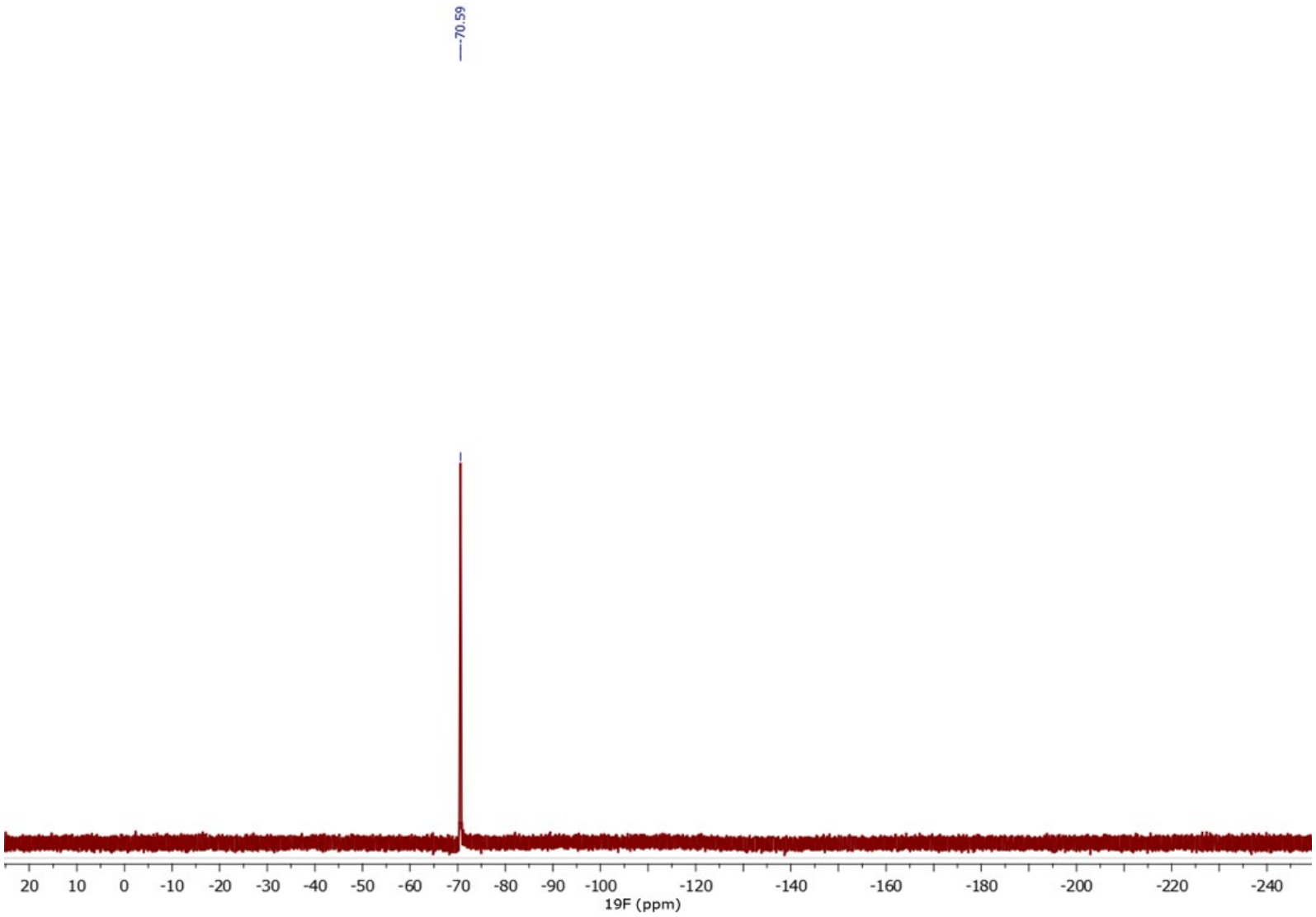


Figure S2. ^{19}F NMR spectrum of **4-*cp-1-5*** (DMSO-*d6*:CD_2Cl_2=1:1).

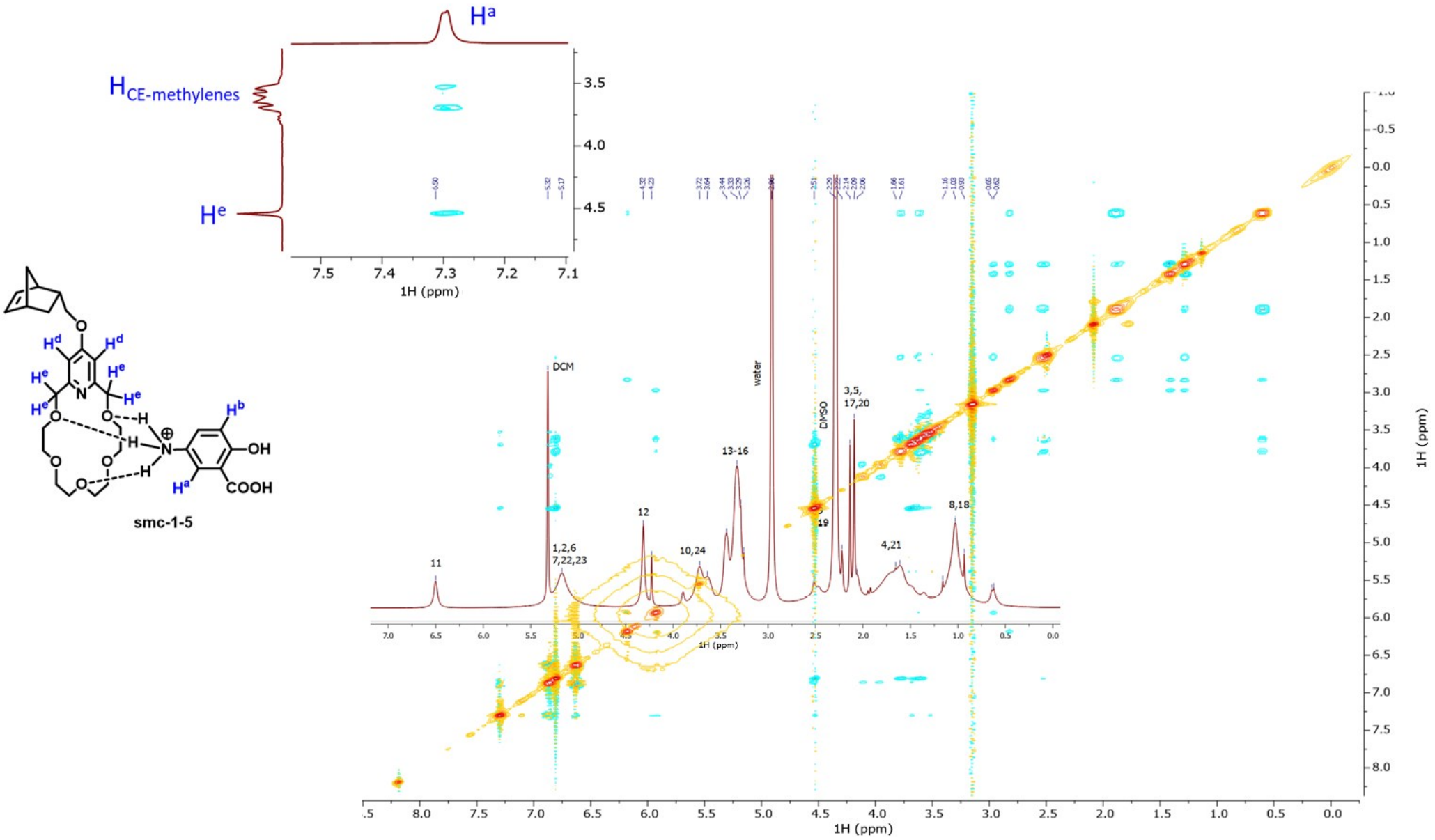


Figure S3. NOESY spectrum of **smc-1-5** in DMSO-*d6*:CD_2Cl_2=1:1, with a mixing time of 500 ms.

3. Synthesis of Mesalazine (1) - polymer 4 supramolecular assembly, smc-1-4

A vial was charged with polymer **4** (100 mg) and it was dissolved in dichloromethane (10 mL). 1 equivalent [per crown ether unit (**5**)] of **1** (7 mg, 0.046 mmol) was dissolved in methanol (20 mL). Then the solution of the polymer was added to the stirred solution of mesalazine (**1**). After the addition of the solution of the polymer, the mixture became pale purple. The mixture was stirred for 1 hour and the solvent was removed under reduced pressure.

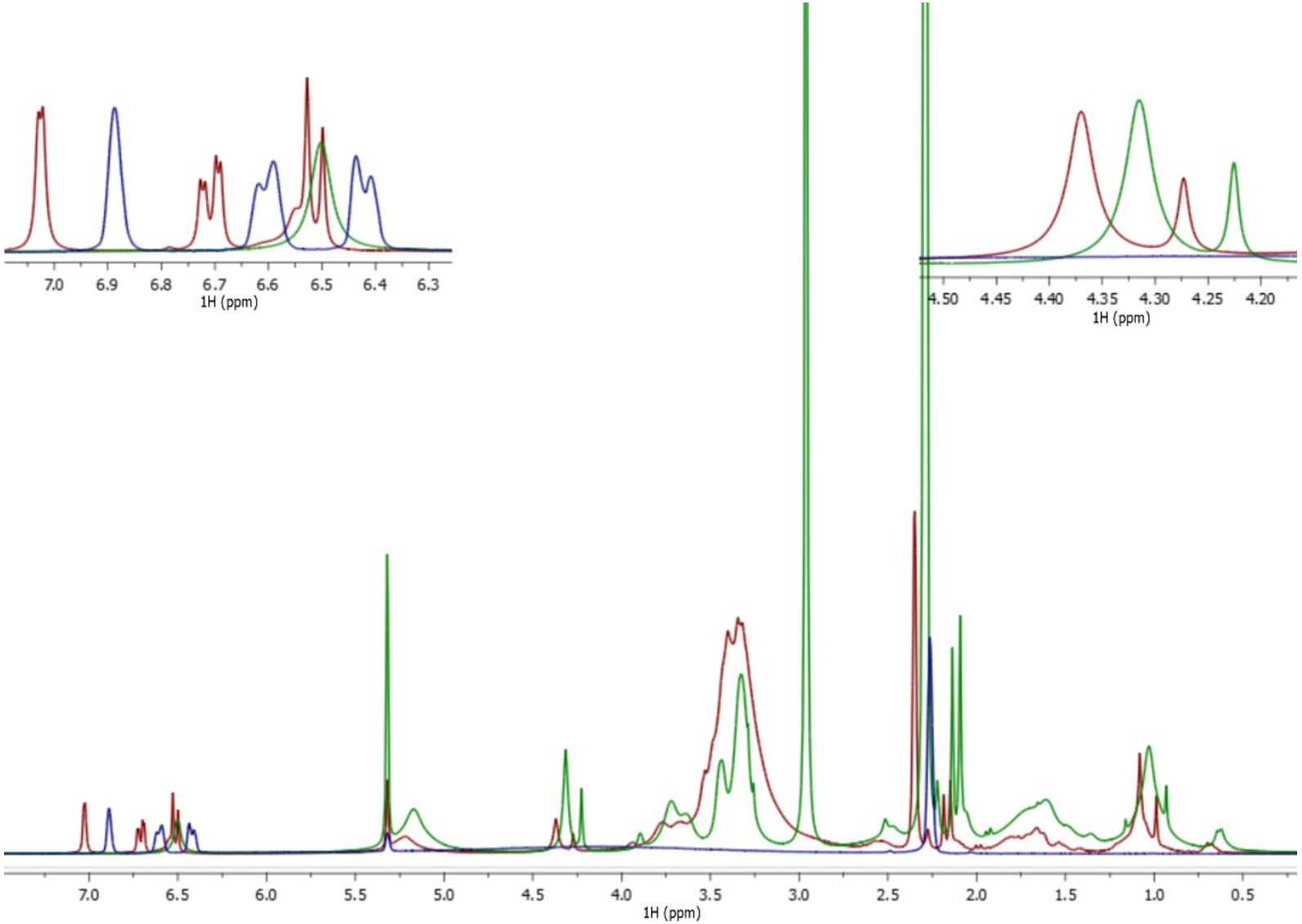


Figure S4. Superimposed ^{1}H NMR spectra of **4-*cp-1-5*** (green), **1** (blue) and **smc-1-4-*cp-1-5*** (red) (1:1 mixture of CD_3OD and CD_2Cl_2, [**4**] = [**1**] = 0.06 mmol/mL).

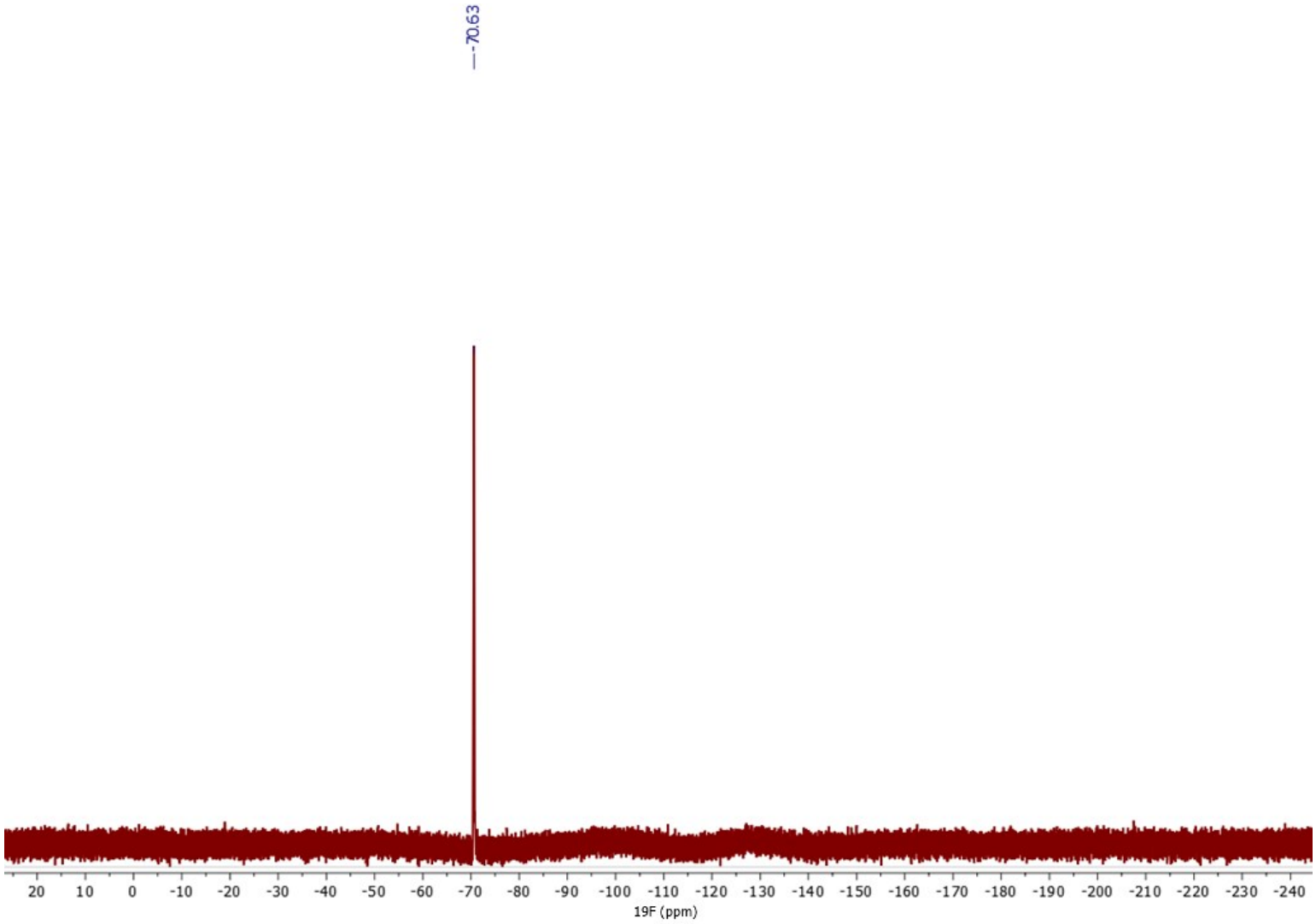


Figure S5. ^{19}F NMR spectrum of **smc-1-4-*cp-1-5*** (DMSO-*d6*:CD_2Cl_2=1:1).

4. Solid-State Nuclear Magnetic Resonance (ssNMR) Spectroscopy

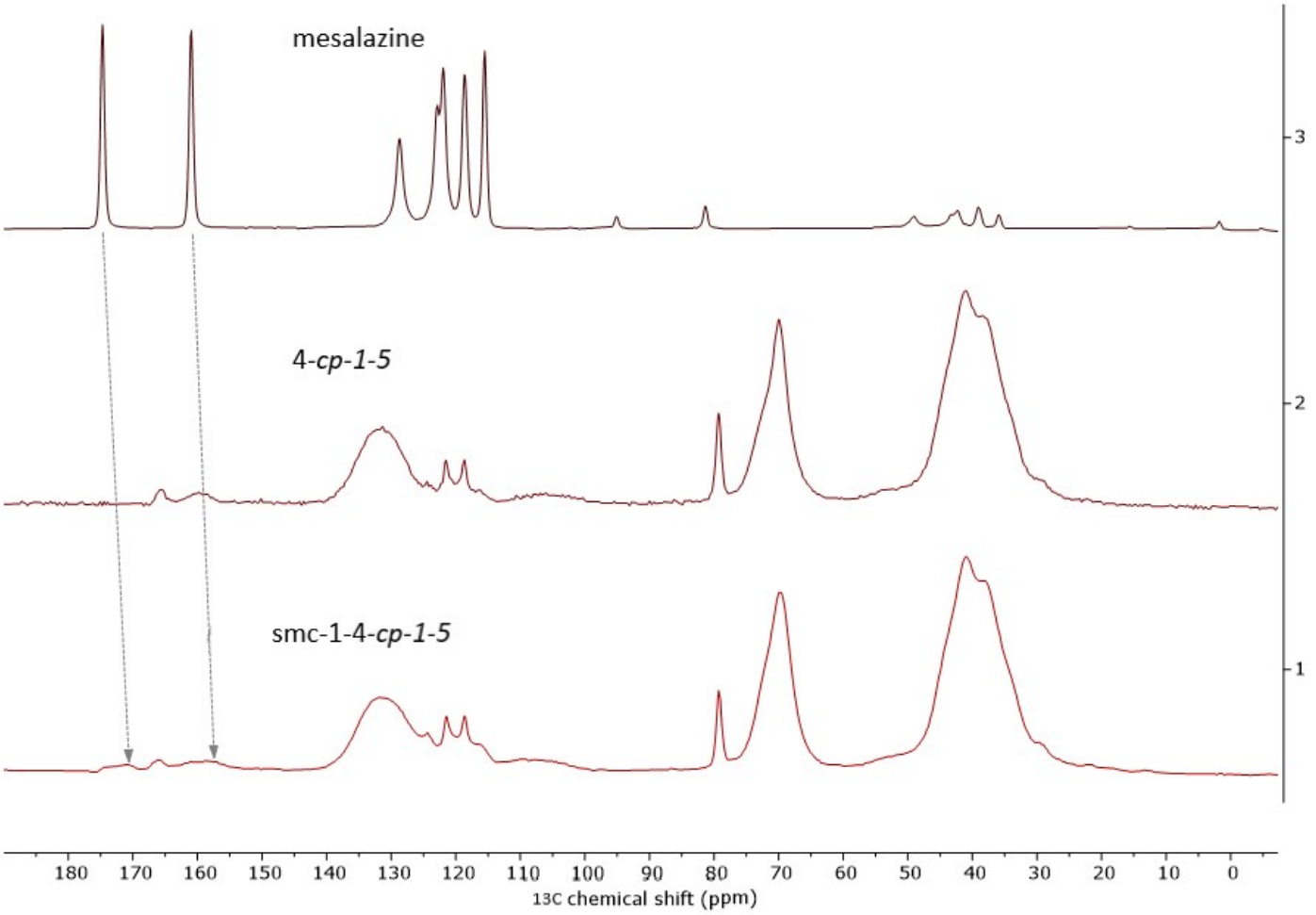


Figure S6. ^{13}C Solid-State NMR of **mesalazine (top), 4-*cp-1-5* (middle) and smc-1-4-*cp-1-5* (buttom)**

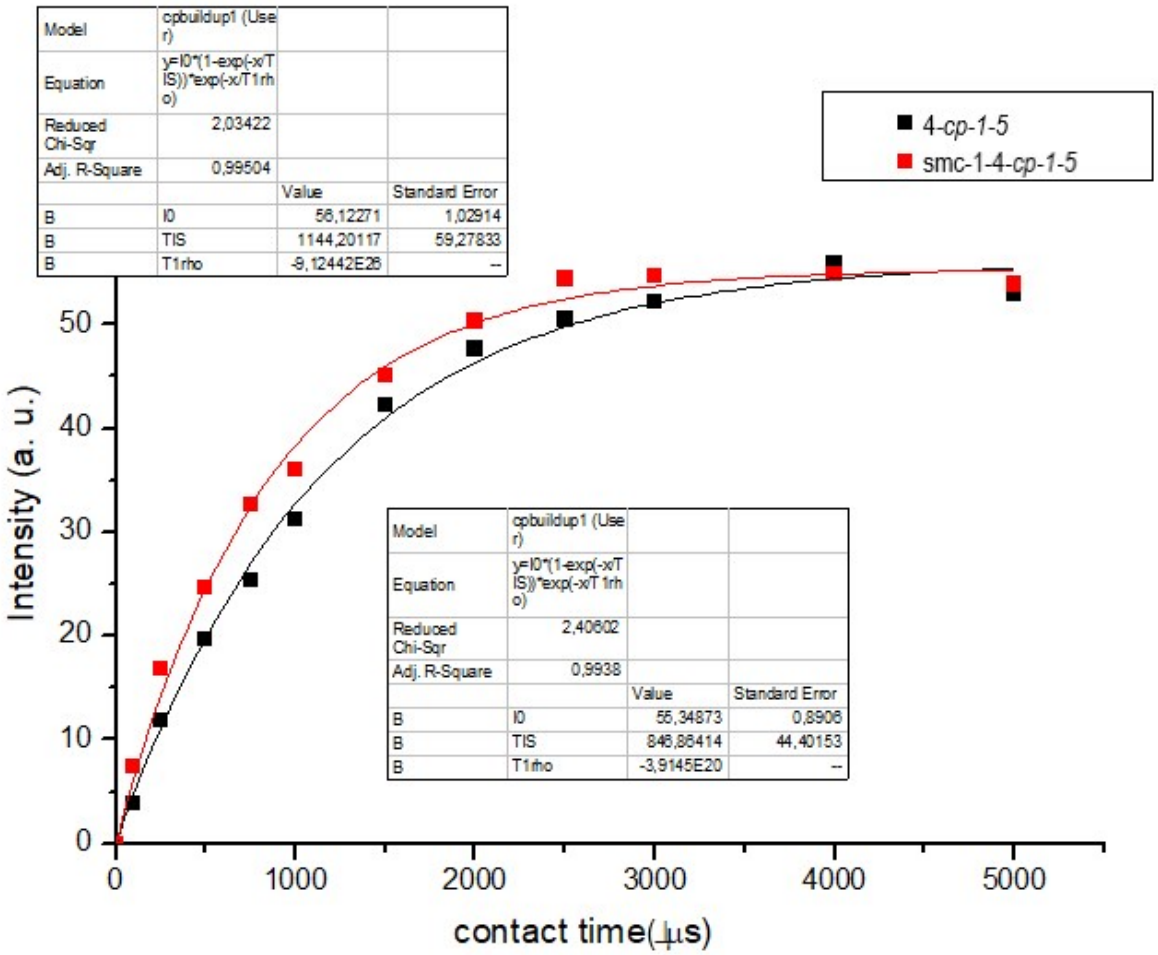


Figure S7. CP build-up curves for polymer **smc-1-4-*cp-1-5***'s crown ether unit.

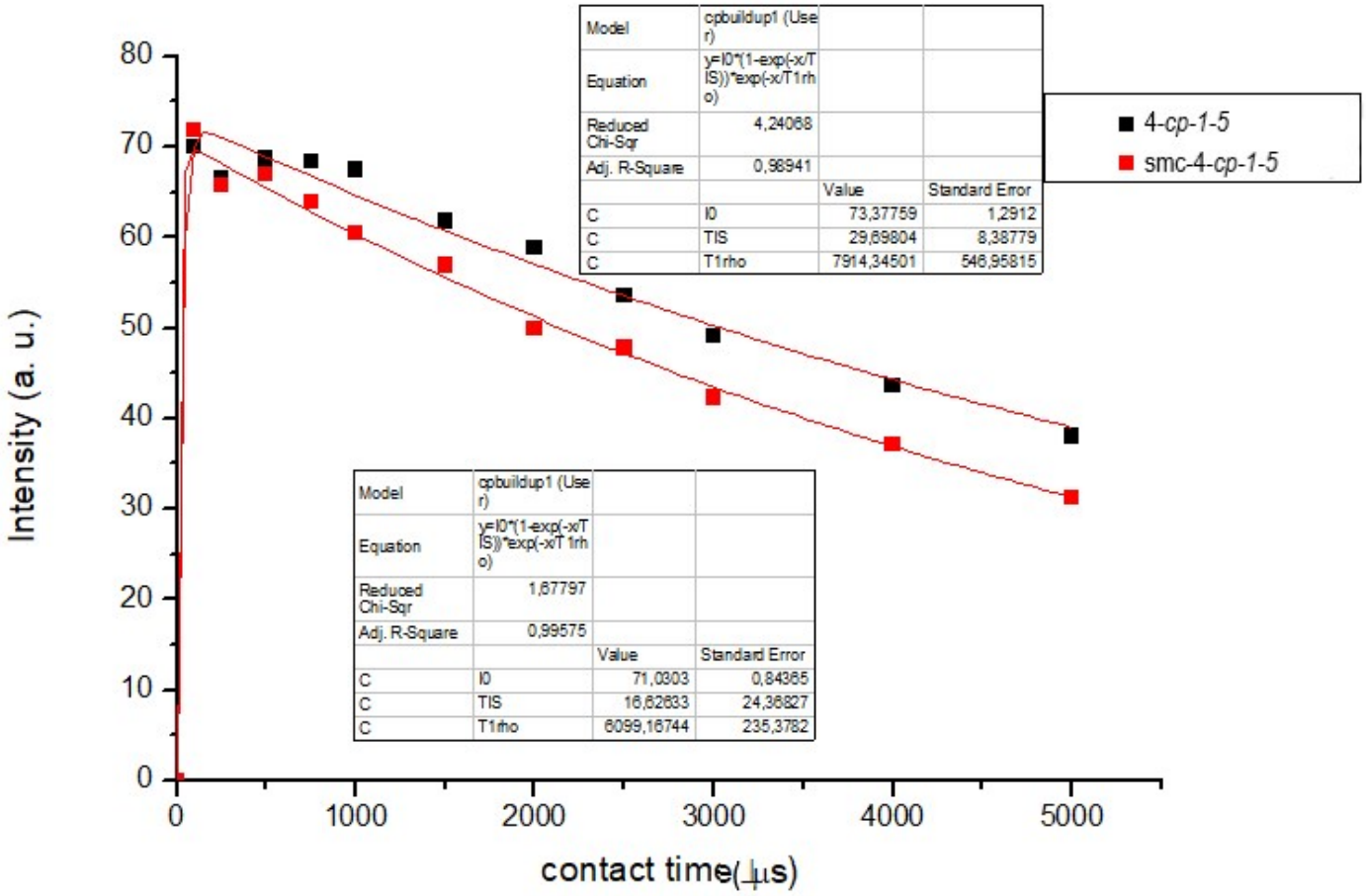


Figure S8. CP build-up curve for polymer **smc-1-4-*cp-1-5***'s backbone signal.

5. MALDI-TOF characterization of 4 and 4-*cp-1-5* and smc-4-*cp-1-5*

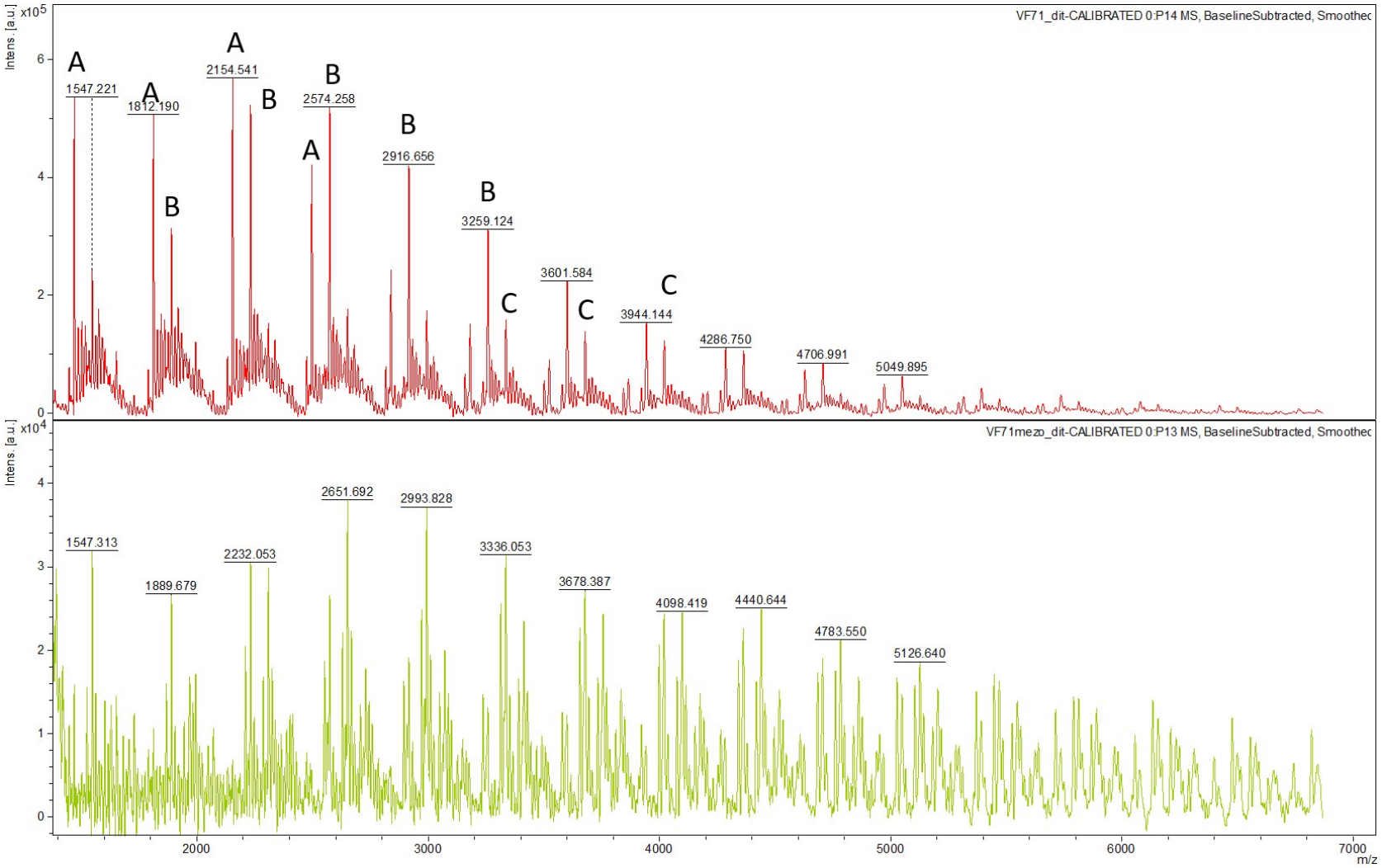


Figure S9. MALDI TOF spectra of **4-*cp-1-5*** (red) and **smc-4-*cp-1-5*** (green).

6. Optimized geometries

Structure: 1 : mesalazinium ion

Charge:1 SPIN MULTIPLICITY: 1

C	-1.905650	-0.353029	0.000000
C	-2.050756	1.037157	-0.000001
C	-0.664043	-0.949531	0.000002
C	-0.924204	1.837385	-0.000001
H	-3.045741	1.484030	-0.000002
H	-0.567250	-2.035150	0.000003
C	0.356960	1.260132	-0.000001
H	-1.005000	2.923715	-0.000002
O	1.415252	2.084922	0.000000
H	2.224337	1.520670	0.000001
C	0.483827	-0.144405	0.000000
C	1.830887	-0.748233	0.000000
O	1.831547	-2.076527	-0.000003
H	2.759655	-2.378819	-0.000003
O	2.864730	-0.091536	0.000003
N	-3.108075	-1.185001	0.000001
H	-3.693285	-1.001521	-0.828602
H	-2.877253	-2.188150	0.000017
H	-3.693299	-1.001496	0.828587

Structure: 5 : norbornene-functionalized pyridino-crown ether

CHARGE:0 SPIN MULTIPLICITY: 1

O	-0.388551	2.767491	1.435596	C	-1.898591	-0.121889	-1.689874
O	0.433852	4.211069	-1.026045	H	-2.018561	0.551218	-2.554833
O	0.230738	-0.116477	1.880505	H	-1.979936	0.477505	-0.767987
O	2.443222	-2.100009	1.204738	C	-2.938860	-1.220050	-1.696675
O	4.230445	-1.866870	-1.148294	C	-2.775497	-2.261063	-0.537180
C	-0.313131	4.733417	0.062282	C	-4.373045	-0.670794	-1.465379
H	0.363414	5.201667	0.797919	H	-2.881444	-1.757741	-2.654358
H	-0.961723	5.515279	-0.356261	C	-4.201607	-2.839174	-0.502501
C	-1.187453	3.710840	0.746159	H	-1.947953	-2.963003	-0.685559
H	-1.823696	3.196190	0.000409	C	-4.859507	-1.476080	-0.220404
H	-1.856615	4.232518	1.456354	H	-4.381535	0.413219	-1.277335
C	-1.204994	1.810400	2.083255	H	-5.019641	-0.870721	-2.330286
H	-1.851899	2.315125	2.824234	H	-4.347426	-3.562107	0.311329
H	-1.862320	1.307073	1.348371	H	-4.512932	-3.276175	-1.462896
C	-0.368890	0.784352	2.800534	H	-5.944043	-1.458267	-0.068690
H	-1.036573	0.226476	3.481151	C	-2.765714	-1.466112	0.756308
H	0.405529	1.280478	3.413319	H	-1.869430	-1.204833	1.321595
C	0.597931	-1.319922	2.538660	C	-4.008874	-0.996751	0.943300
H	1.376507	-1.125091	3.298409	H	-4.337803	-0.293020	1.709736
H	-0.287454	-1.733912	3.054105				
C	1.093971	-2.346946	1.554217				
H	0.455331	-2.341715	0.648566				
H	1.012115	-3.343078	2.024782				
C	2.979694	-3.194075	0.483632				
H	3.103284	-4.066051	1.153279				
H	2.292929	-3.490852	-0.330677				
C	4.320296	-2.817945	-0.097698				
H	4.775267	-3.718612	-0.532588				
H	4.985751	-2.443024	0.699039				
C	1.634576	3.552004	-0.677764				
H	2.447320	3.966296	-1.295654				
H	1.896366	3.737974	0.376652				
C	4.156322	-0.516058	-0.741065				
H	4.431928	-0.409431	0.321306				
H	4.888819	0.060375	-1.328411				
C	2.800141	0.114003	-0.949614				
C	1.595414	2.059238	-0.908005				
C	1.692472	-0.628875	-1.325861				
C	0.465522	0.029640	-1.454566				
H	1.754798	-1.704097	-1.482306				
C	0.415352	1.412856	-1.273431				
H	-0.498161	1.988677	-1.395425				
N	2.766645	1.439789	-0.737586				
O	-0.608445	-0.741823	-1.737021				

Structure: smc-1-5 : pyridino-crown ether + mesalazinium ion complex

CHARGE:1 SPIN MULTIPLICITY: 1

O	-3.017602	-3.315364	-0.775185	H	-2.734750	-0.552287	1.204403
O	-0.323248	-2.566303	-0.818707	H	-2.485763	-1.762249	0.041532
O	-4.677654	-2.081661	1.194621	N	0.447507	-0.129223	0.240702
O	-3.765573	0.290195	2.488776	O	4.486374	0.758052	0.301413
O	-1.039496	0.843749	2.349528	C	5.407643	0.028462	-0.523615
C	-0.834326	-3.586375	-1.661972	H	5.139723	0.180867	-1.581302
H	-1.175830	-3.150239	-2.618661	H	5.331557	-1.045121	-0.286658
H	-0.048410	-4.329199	-1.883910	C	6.793910	0.563123	-0.230277
C	-1.981604	-4.267087	-0.966698	C	7.889754	-0.202602	-1.042903
H	-1.659514	-4.675680	0.007100	C	7.240374	0.329865	1.239745
H	-2.343187	-5.098110	-1.595304	H	6.803664	1.629929	-0.494392
C	-4.212788	-3.891662	-0.267859	C	8.182227	-1.388711	-0.103005
H	-4.657430	-4.557672	-1.025974	H	7.604134	-0.429090	-2.076706
H	-3.992209	-4.483811	0.637219	C	8.559128	-0.485551	1.085345
C	-5.173595	-2.782044	0.067854	H	7.394586	1.265501	1.792390
H	-6.165974	-3.211741	0.290894	H	6.488393	-0.264414	1.780828
H	-5.279310	-2.097287	-0.794825	H	9.020439	-2.004848	-0.454825
C	-5.531342	-1.018198	1.577416	H	7.306120	-2.023070	0.096381
H	-5.602886	-0.271019	0.764523	H	8.896072	-0.975773	2.005030
H	-6.546509	-1.398469	1.787822	C	9.159302	0.611049	-0.854921
C	-4.972487	-0.382116	2.822107	H	9.576134	1.294258	-1.595764
H	-4.773618	-1.159429	3.580105	C	9.556078	0.444996	0.414668
H	-5.698761	0.337215	3.235872	H	10.369718	0.962043	0.924676
C	-3.038375	0.708333	3.634381	C	-2.672579	0.140884	-0.722762
H	-3.693679	1.280700	4.312247	C	-2.796377	-0.291107	-2.047016
H	-2.652904	-0.172566	4.176994	C	-2.843684	1.473063	-0.396971
C	-1.905253	1.592239	3.188696	C	-3.106013	0.620687	-3.043920
H	-1.358031	1.958776	4.074426	H	-2.663107	-1.348170	-2.282324
H	-2.296872	2.470838	2.641988	H	-2.755207	1.796631	0.638308
C	0.691092	-1.834497	-1.475868	C	-3.282164	1.977664	-2.735980
H	1.482063	-2.510493	-1.841832	H	-3.213913	0.305134	-4.081261
H	0.266490	-1.309158	-2.353789	O	-3.573293	2.820458	-3.745245
C	-0.015378	1.664940	1.825748	H	-3.661481	3.721192	-3.357211
H	-0.458870	2.441688	1.170868	C	-3.150789	2.403423	-1.397645
H	0.522435	2.180950	2.638672	C	-3.324369	3.829978	-1.068373
C	0.956234	0.842979	1.019422	O	-3.148794	4.118188	0.219310
C	1.289743	-0.811764	-0.544535	H	-3.281794	5.078517	0.335969
C	2.306689	1.151736	1.050318	O	-3.600972	4.689053	-1.896272
C	3.184533	0.430657	0.230891				
H	2.693432	1.936539	1.699946				
C	2.662088	-0.573920	-0.588593				
H	3.288731	-1.172332	-1.246697				
N	-2.263844	-0.786218	0.310745				
H	-1.213286	-0.672056	0.425131				

7. Determination of the log*K* for the formation of complex 5-1 by NMR titration

Solutions of pyridino-18-crown-6 ether (**5**) and mesalazine (**1**) having the same concentration ($c_0 = 0.06M$) were mixed in various volume ratios and NMR spectra of the mixtures were taken. Complex stability constants were determined using the method described in ref. [3] , following the chemical shifts of the protons of the pyridine ring in the pyridino-18-crown-6 ether unit.

The equation of complex formation (see Table 1 for notations of concentrations):

5 + 1⇌**5 - 1**

Table S1. Concentration balances in the equilibrium of complexation between mesalazine (**1**) and pyridino-18-crown-6 (**5**) solutions ($c_0 = 0.06\ M$) during NMR titration.

	pyridino-18-crown-6 ether (5)	Mesalazin	complex
initial	$c_{5,0} = \frac{c_0 V_5}{V_5 + V_1}$	$c_{1,0} = \frac{c_0 V_1}{V_5 + V_1}$	0
change	$-x$	$-x$	$+x$
equilibrium	$c_{5,0} - x$	$c_{1,0} - x$	x

The equilibrium constant is calculated as:

$$K = \frac{c_{5\text{-}1}}{c_5 c_1} = \frac{x}{(c_{5,0} - x)(c_{1,0} - x)}$$

After rearranging, one arrives at the following quadratic equation:

$$Kx^2 - [K \underbrace{c_0}_{(c_{5,0} + c_{1,0})} + 1]x + Kc_{5,0}c_{1,0} = 0.$$

Dividing the previous equation by K and taking into account that $c_{5,0} + c_{1,0} = c_0$:

$$x^2 - \left[c_0 + K^{-1}\right]x + c_{5,0}c_{1,0} = 0.$$

The appropriate root of the quadratic equation, where $x < \min(c_{5,0}, c_{1,0})$, is:

$$x = \frac{\left[c_0 + K^{-1}\right] - \sqrt{\left[c_0 + K^{-1}\right]^2 - 4c_{5,0}c_{1,0}}}{2}$$

The δ_x chemical shift corresponding to the x complex concentration can be calculated by linear interpolation from the mole fractions and NMR chemical shifts of the crown ether in the free ($x_7;\delta_7$) and complex forms ($x_{5\text{-}1} = 1 - x_5;\delta_{5\text{-}1}$):

$$\delta^{calc}_{x} = x_5\delta_5 + x_{5\text{-}1}\delta_{5\text{-}1} = \frac{c_5\delta_5 + c_{5\text{-}1}\delta_{5\text{-}1}}{c_5 + c_{5\text{-}1}}$$

The sum of squared deviation of the experimental NMR shift (δ^{exp}_{x}) and calculated δ^{calc}_{x} NMR shift along the titration curve (i.e. for all x_i values) was minimized by optimizing the value of K, δ_7 and $\delta_{7\text{-}1}$:

$$\min_{K,\delta_5,\delta_{5\text{-}1}} \sum_i \left(\delta^{calc}_{x_i}(K,\delta_5,\delta_{5\text{-}1}) - \delta^{exp}_{x_i}\right)^2$$

The measured and fitted chemical shift values are shown in Figure S10 and Table S2.

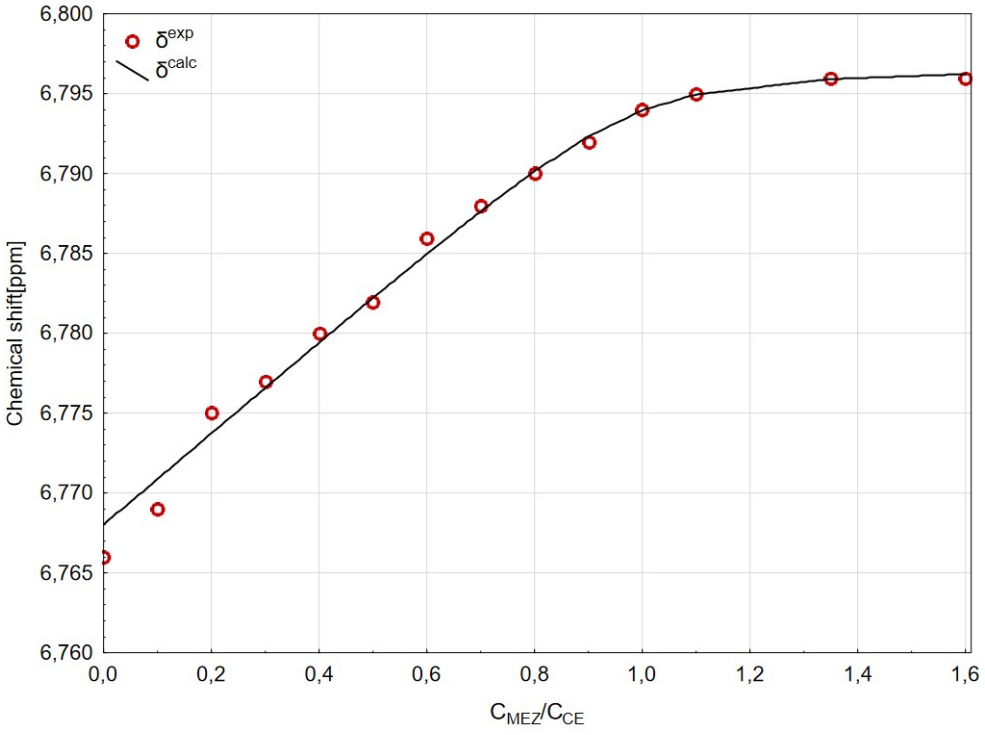


Figure S10. The experimental values and fitted theoretical curve of chemical shifts for methylene protons next to the pyridine-ring within the crown ether as a function of the mixing ratios of the mesalazine (**1**) and pyridino-18-crown-6 ether (**5**). The sum of concentrations in the mixture was constant: $c_{1,0} + c_{5,0} = 0.06\ M$.

Table S2. The experimental and fitted chemical shift values for methylene protons next to the pyridine ring within the crown ether as a function of the mixing ratios of the mesalazine (**1**) and pyridino-18-crown-6 ether (**5**). The sum of concentrations in the mixture was constant: $c_{1,0} + c_{5,0} = 0.06\ M$.

$\frac{c_{1,0}}{c_{5,0}} = \frac{V_{1,0}}{V_{5,0}}$	$\delta^{exp}_{x_i}/ppm$	$\delta^{calc}_{x_i}/ppm$
0	6.766	6.768
0.1	6.769	6.771
0.2	6.775	6.774
0.3	6.777	6.777
0.4	6.78	6.779
0.5	6.782	6.782
0.6	6.786	6.785
0.7	6.788	6.788
0.8	6.79	6.790
0.9	6.792	6.792
1.0	6.794	6.794
1.1	6.795	6.795
1.35	6.796	6.796
1.6	6.796	6.796

The optimized $\log K$ value and its 95% confidence interval (±2.2σ for 14-3 = 11 degrees of freedom from Student's t-distribution) are:

$$\log K = 3.4 \pm 0.5$$

Izatt *et al.* found $\log K$ values of 3.62 and 3.29 for similar complexes[4] shown in Figure S11 [R=Me; (*R*) and (*S*) enantiomers of PhEt]. These values are somewhat lower, which can be attributed to the presence of the extra alkyl groups hindering complexation sterically and by reducing the conformational flexibility of the crown ether macroring.

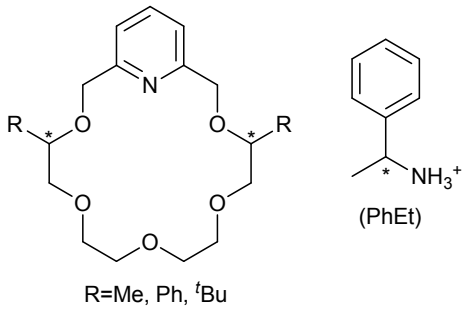


Figure S11. Complexation of molecules investigated by Izatt *et al.*[4]

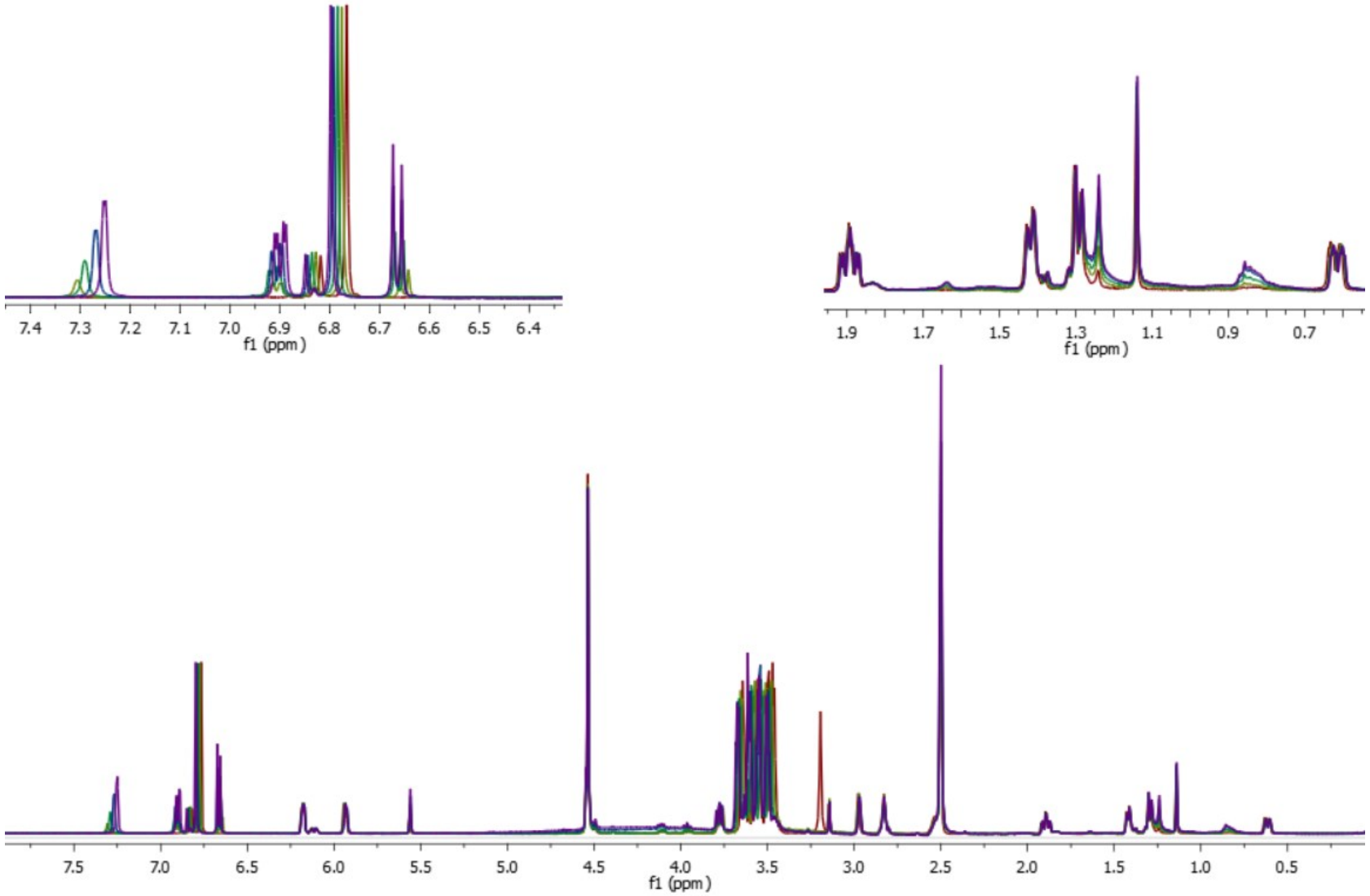


Figure S12. Investigation of the complexation of **5** (endo/exo mixture) with **1** by a titration ^{1}H NMR method. Red: 0; yellow: 0.3; green: 0.6; light blue: 1.0; purple: 1.3 equivalent (DMSO-d_6–CD_2Cl_2 1 : 1 mixture, [**5**] = [**1**] = 0.06 mmol mL^{-1}).

8. Thermal investigation studies of mesalazine (1) and smc-4-*cp-1-5*:

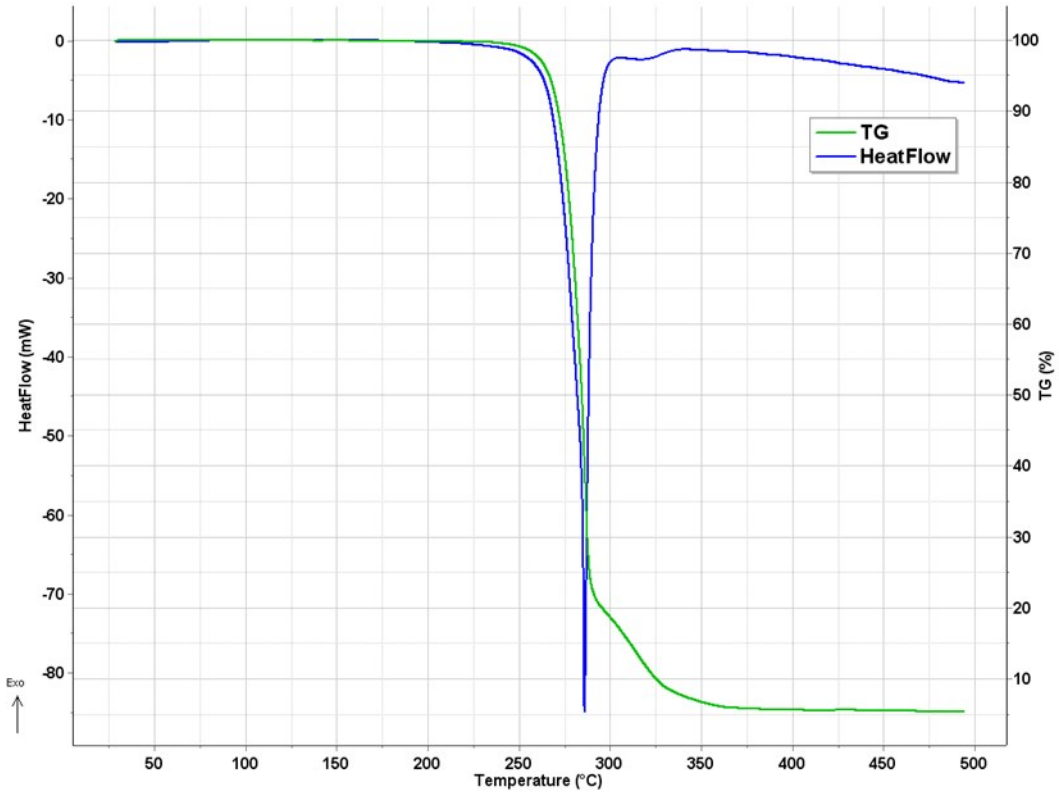


Figure S13. TG-DSC of **1**.

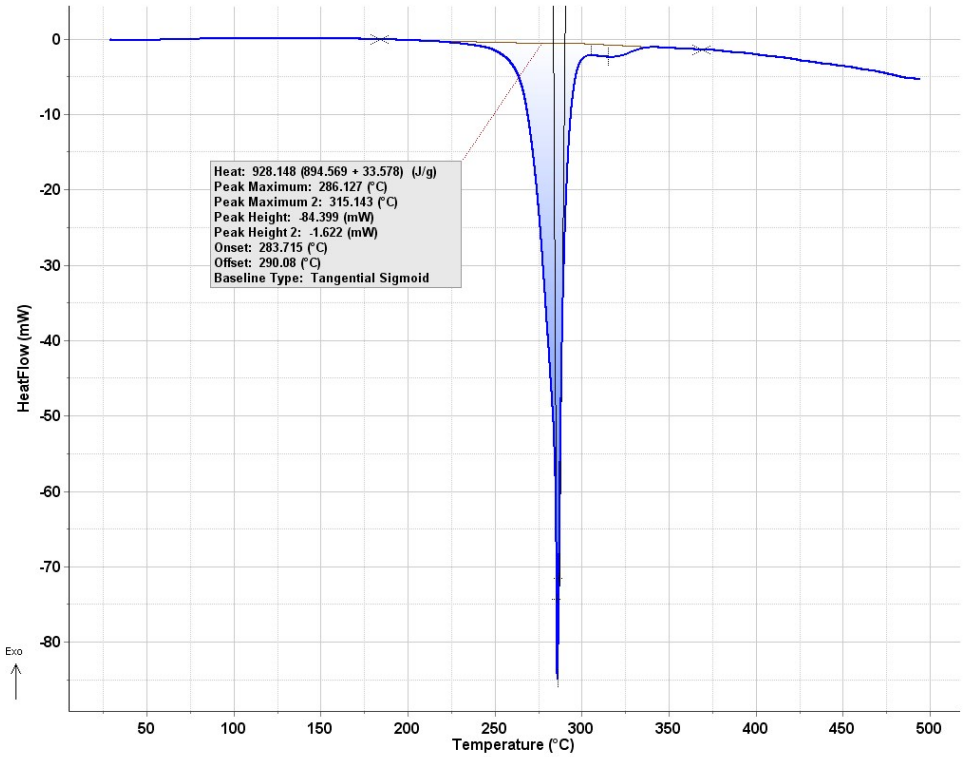


Figure S14. Quantitative DSC of **1**.

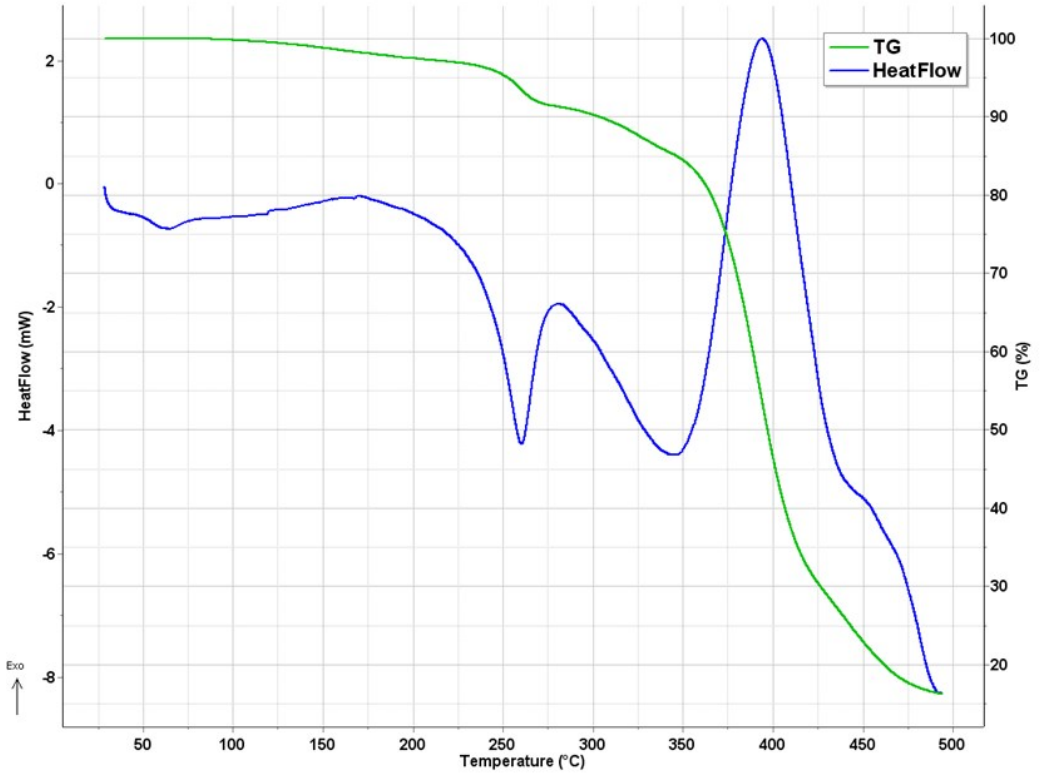


Figure S15. TG-DSC of **smc-1-4-*cp-1-5***.

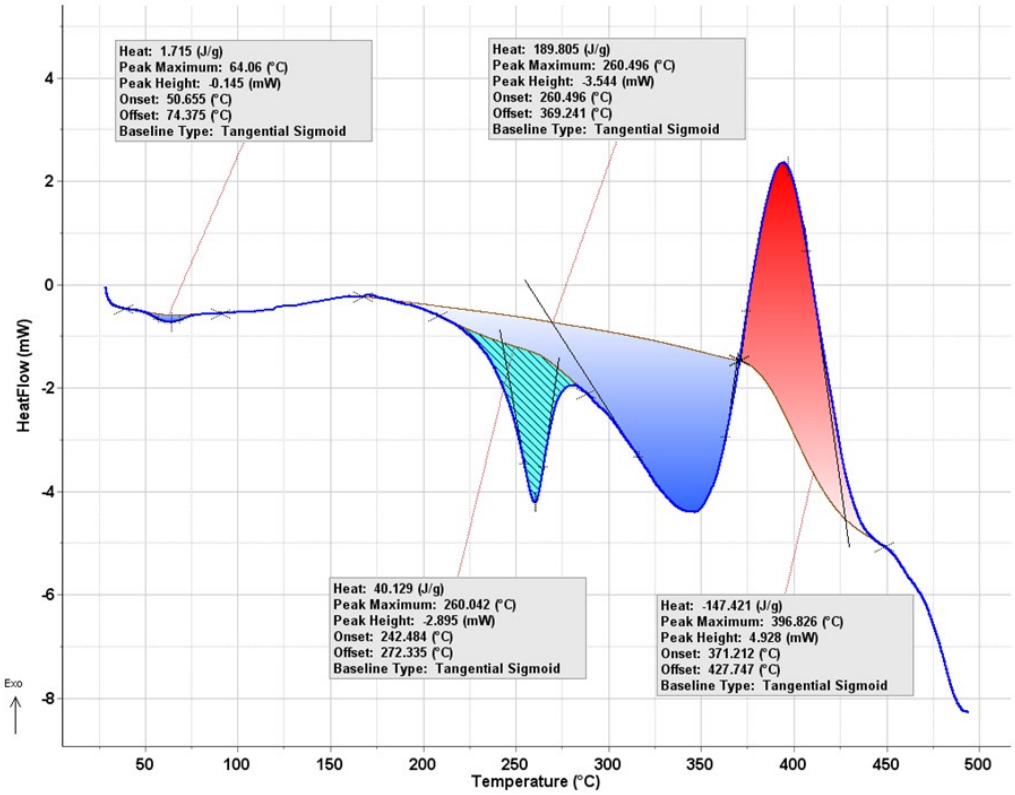


Figure S16. Quantitative DSC of **smc-1-4-*cp-1-5***.

9. Release tests of mesalazine (1) at different pH

During the pre-programmed drug release experiments mesalazine as a model compound was embedded into polymer **4-*cp-1-5***, from which mesalazine release was monitored in respect of pH at maximim wavelength. The pH levels were adjusted by acetate, phosphate and carbonate buffered aqueous solution (1.0 mL) and incubated at 37 °C with continuous shaking at 400 rpm. Samples were taken at 0^{th}, 5^{th}, 10^{th}, 20^{th}, 30^{th} minutes and 1^{st}, 2^{nd}, 4^{th}, 8^{th} hours of the experiments. In each case, the experiments were repeated at least three times, the standard deviation of the results was well within 10%.

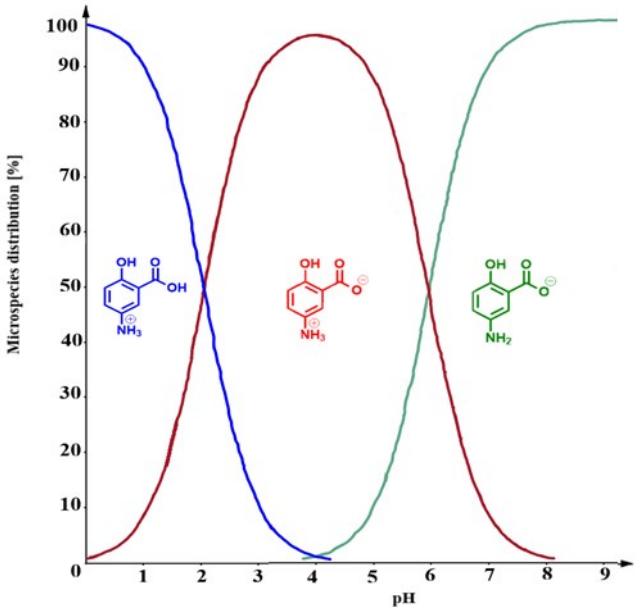


Figure S17. Distribution of mesalazine (**1**) species as the function of pH.

10. Release tests of mesalazine (1) at different NaCl concentrations

During the pre-programmed drug release experiments mesalazine as a model compound was embedded into polymer **4-*cp-1-5***, from which mesalazin release was monitored in respect of sodium ion concentration at maximim wavelength. The pH level was adjusted by phosphate buffered aqueous solution (1.0 mL) and incubated at 37 °C with continuous shaking at 400 rpm. Samples were taken at 0^{th}, 5^{th}, 10^{th}, 20^{th}, 30^{th} minutes and 1^{st}, 2^{nd}, 4^{th}, 8^{th} hours of the experiments. In each case, the experiments were repeated at least three times, the standard deviation of the results was well within 10%.

11. Evaluation of the drug release as a function of time

The drug-release with time was evaluated using a stretched exponential function (Weibull-distribution, eq. 1.). The paramaters of eq. 1, i.e., C_∞, k and λ were estimated by a home-made parameter estimation software (written in Turbo Pascal 7.0) employing the Gauss-Newton-Marquardt algorithm.[5]

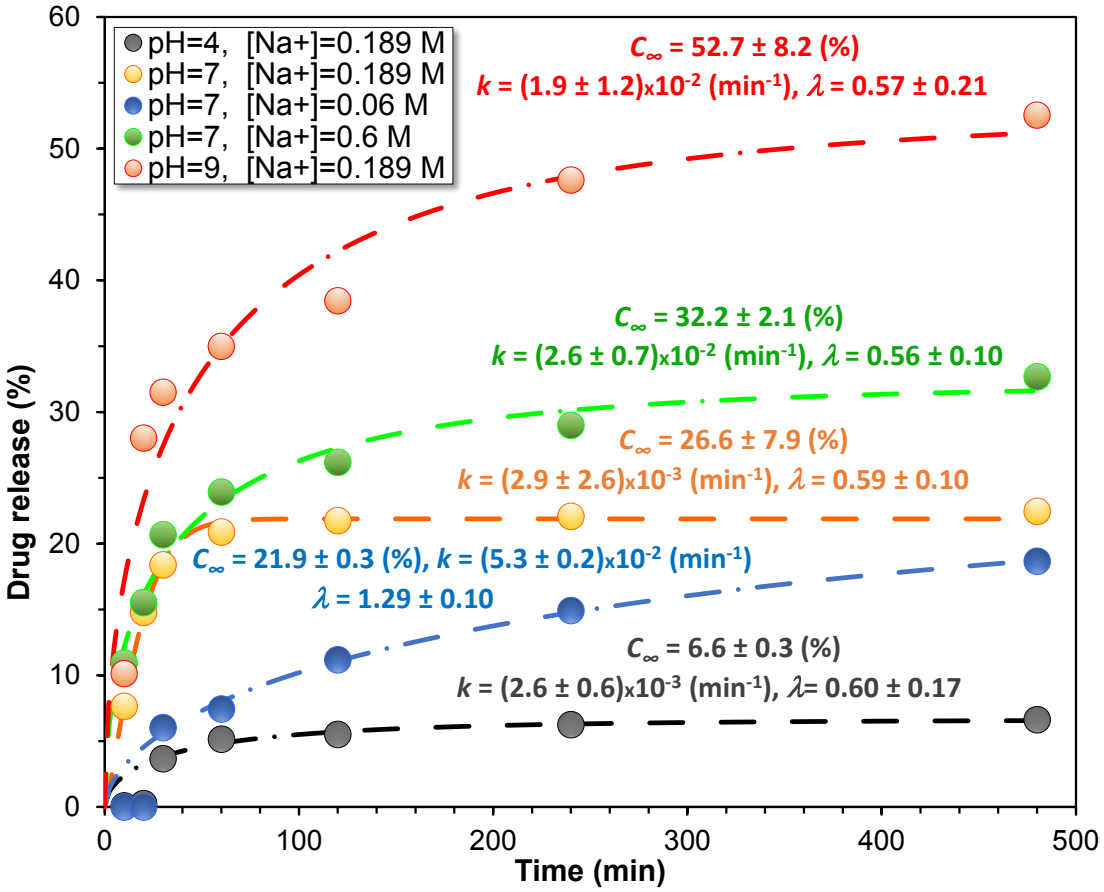


Figure S18. Release of mesalazine (**1**) from **smc-1-4** as a function of time at different pH and sodium ion concentrations (T = 37 °C). The dashed lines represent the fitted curves by eq. 1. The fitted parameters of eq. 1 are shown on the top of each curve.

12. References

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