Supporting Information for

Amphiphilic Calixresorcinarene Associates as Effective Solubilizing Agents for Hydrophobic Organic Acids: Construction of Nano-Aggregates

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Table S1. The data of pH-titration of mixed solutions of calixresorcinarenes and substrates (Nap, IF) (pH^0 - the pH value of solution before titration, pH_{pr} - the pH value of solution when precipitation is occurs).

	C, mM	pH^0/ pH_{pr}	ν(HCl)/ν(1-5)	C_S, mM[a]
Naproxen				
C5A + Nap	1	7.49/4.42	4	4
	5	8.69/3.36	6	-
C5DMA + Nap	1	7.32/4.36	4	7
	5	8.82/3.35	7	-
C8A + Nap	1	7.53/3.30	6	5
	2	7.73/3.34	5	-
	5	8.35/2.46	7	-
C8DMA + Nap	1	7.16/4.03	5	7
	2	7.99/3.26	7	-
	5	8.09/2.86	8	-
C11DMA + Nap	1	7.27/3.23	6	6
	5	8.27/3.08	6	-
Ibuprofen				
C5A + IF	1	5.42/3.35	5	5
C8A + IF	1	7.81/3.40	5	5
C5DMA + IF	1	6.98/3.69	5	5

[a] the concentration of substrate accordingly ^{1}H NMR data

Table S2. The data of pH-titration of mixed solutions of calixresorcinarenes and DDA (pH^0 - the pH value of solution before titration, pH_{pr} - the pH value of solution when precipitation is occurs).

	C(calix), mM	pH^0/ pH_{pr}	ν(HCl)/ν(1-5)	ν(calix)/ν(DDA)
C5A	1	5.82/3.94	1.5	2/3
C8A	1	6.07/2.70	1	1/1
C5DMA	1	6.65/2.79	1.5	1/2
C8DMA	1	6.20/3.13	3.5	2/7
C11DMA	1	5.91/2.89	3	1/3

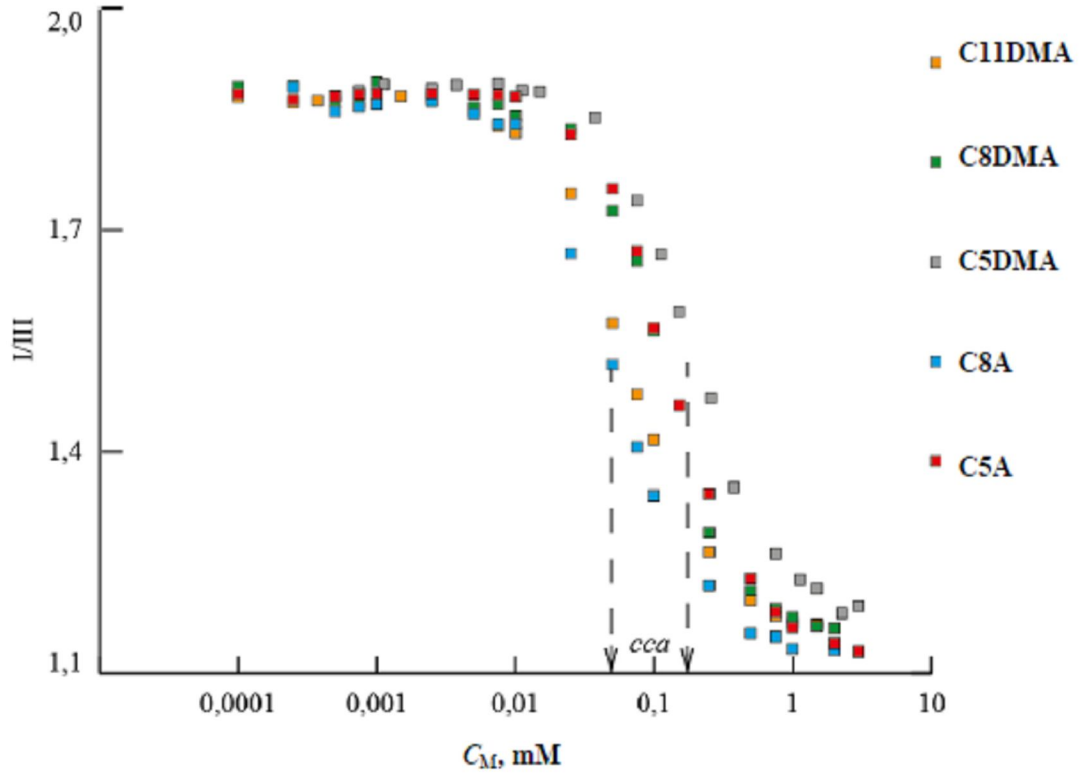


Figure S1. The dependence of I/III values of pyrene (0.002 mM) on concentration of calixresorcinarenes.

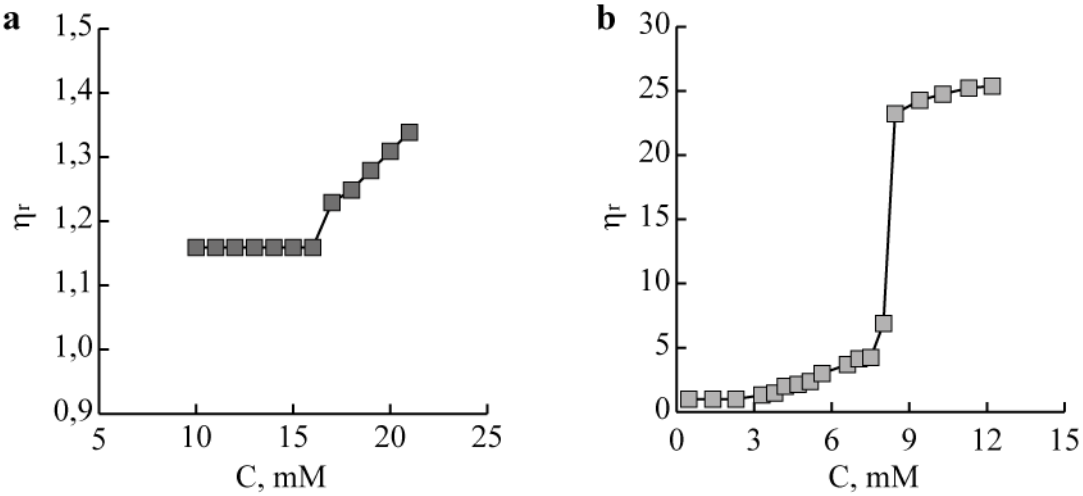


Figure S2. The dependence of relative viscosity (η_r) of C5DMA (a) and C11DMA (b) aqueous solutions on macrocycle concentration.

Table S3. Cloud point (CP) of aqueous solutions of macrocycles C5DMA, C8DMA and C11DMA

	C_M, mM	CP, °C
C5DMA	2	74
	5	72
	10	60
	15	55
C8DMA	2	66
	5	73
	10	44
	15	44
C11DMA	5	52

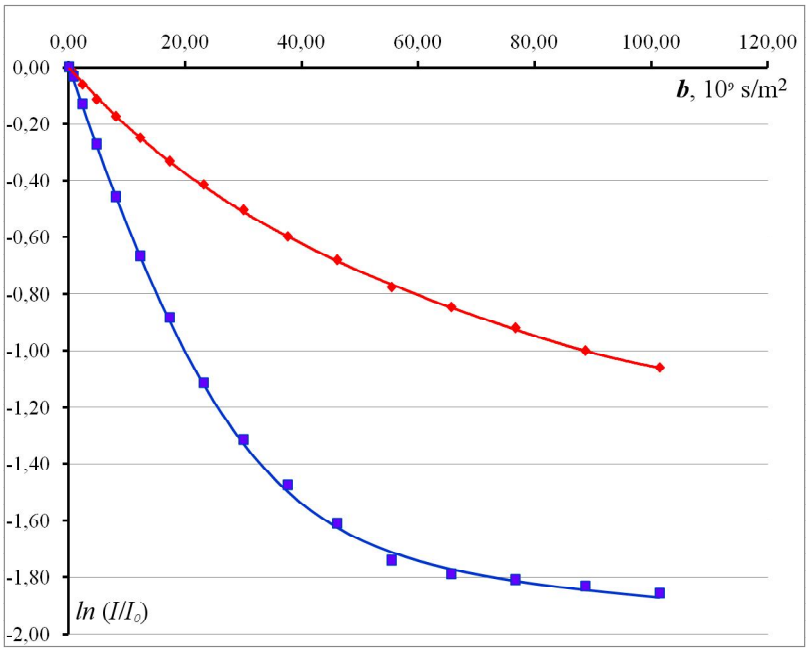


Figure S3. Natural logarithm of the normalized signal attenuation (ln I/I_0) in the FT-PGSE experiments as a function of the gradient amplitude b. Diffusion curves of protons of $(CH_3)_2N$-groups of C11DMA before (♦) and after (■) addition of naproxene. The concentrations in the aqueous solutions of C11DMA are 1.0 mM in both cases. The markers are points of experimental diffusion curves, the solid lines are the simulated diffusion decay curves for two component fitting in "T1/T2 Analysis" module of Breker Xwinnmr software package. Results for simulated diffusion decay curve: for individual aqueous solutions of C11DMA ratio weigh of component P_{fast}/P_{slow}=1/1, D_s(fast) = 4.5 · 10^{-11} m^2s^{-1}, D_s(slow) = 4.8 · 10^{-12} m^2s^{-1}, root mean square (RSS) = 1.118e-006 and standard deviation (SD) = 2.643e-004. For mixed C11DMA-Nap aqueous solutions: ratio of weigh of component P_{fast}/P_{slow}=4/1, D_s(fast) = 9.7 · 10^{-11} m^2s^{-1}, D_s(slow) = 4.1· 10^{-12} m^2s^{-1}, RSS = 4.639e-006 and SD = 5.385e-004.

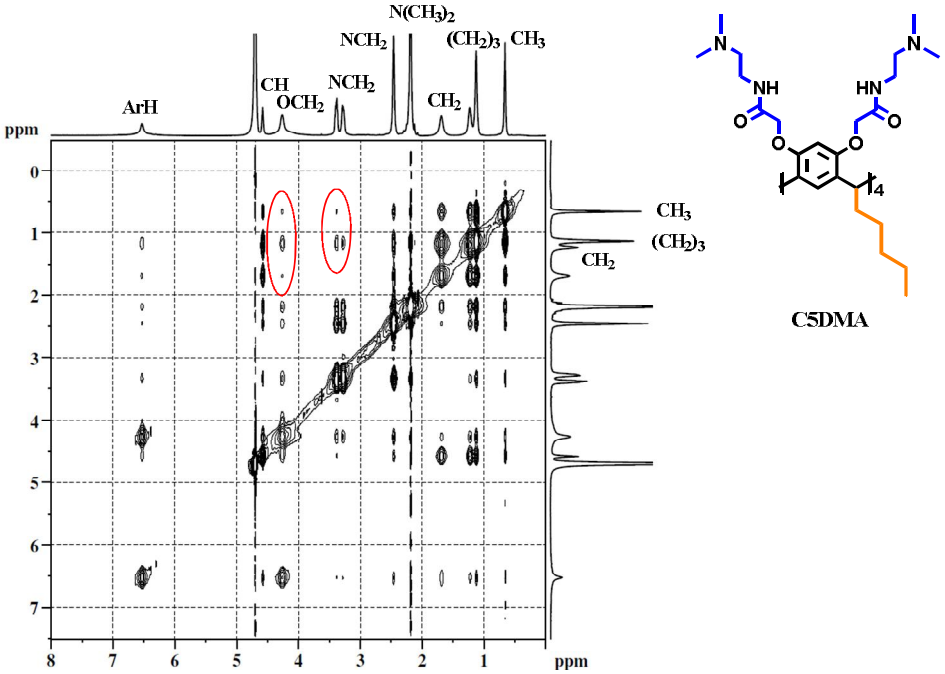


Figure S4. 2D NOESY spectra of C5DMA in D_2O (1 mM).

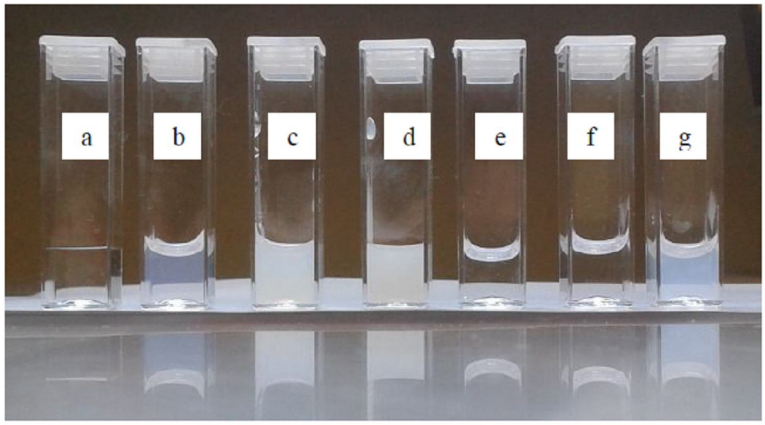


Figure S5. Aqueous solutions of C5A (a), C5DMA + IF (b), C5A + Nap (c), C8A + Nap (d), C8A (e), C5DMA (f), C5DMA + DDA (g).

Table S4. The values of ξ-potentials and pH of individual and mixed aqueous solutions of macrocycles (C_M = 1 mM).

	C_S, mM[a]	ξ, mV	pH
C5A	-	+70	8.64
C5A + IF	5	+50	5.37
C5A + Nap	4	+43	6.03
C5A + DDA	1.5	+29	6.65
C8A	-	+62	7.97
C8A + IF	5	+44	5.08
C8A + Nap	5	0	5.58
C8A + DDA	2	+16	6.69
C5DMA	-	+60	8.36
C5DMA + DDA	2	+47	6.04
C8DMA	-	+46	8.36
C8DMA + DDA	3.5	-3	6.20
C11DMA	-	+20	8.19
C11DMA + DDA	3	+30	5.88

[a] C_S - the concentration of substract in mixed solution, C_S were estimated by pH-titration method.

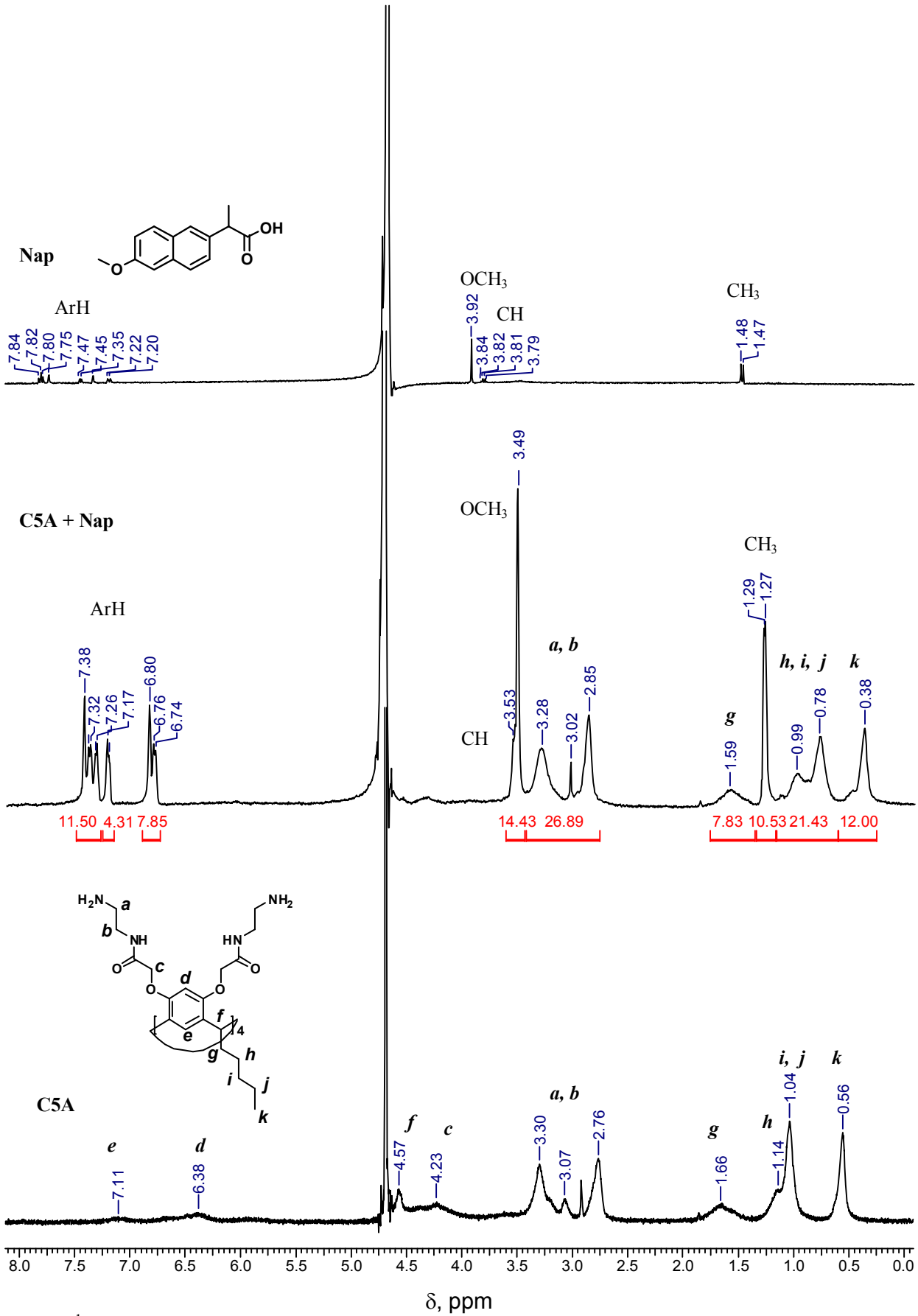


Figure S6. ^{1}H NMR spectra of the individual solutions of Nap (0.1 mM[a], pH 5.22) and C5A (1 mM, pH 8.96), and C5A-Nap mixture (pH 7.67) after solubilization in D_2O.

[a] The solubility of naproxen in water is ≈ 0.1 mM[1]

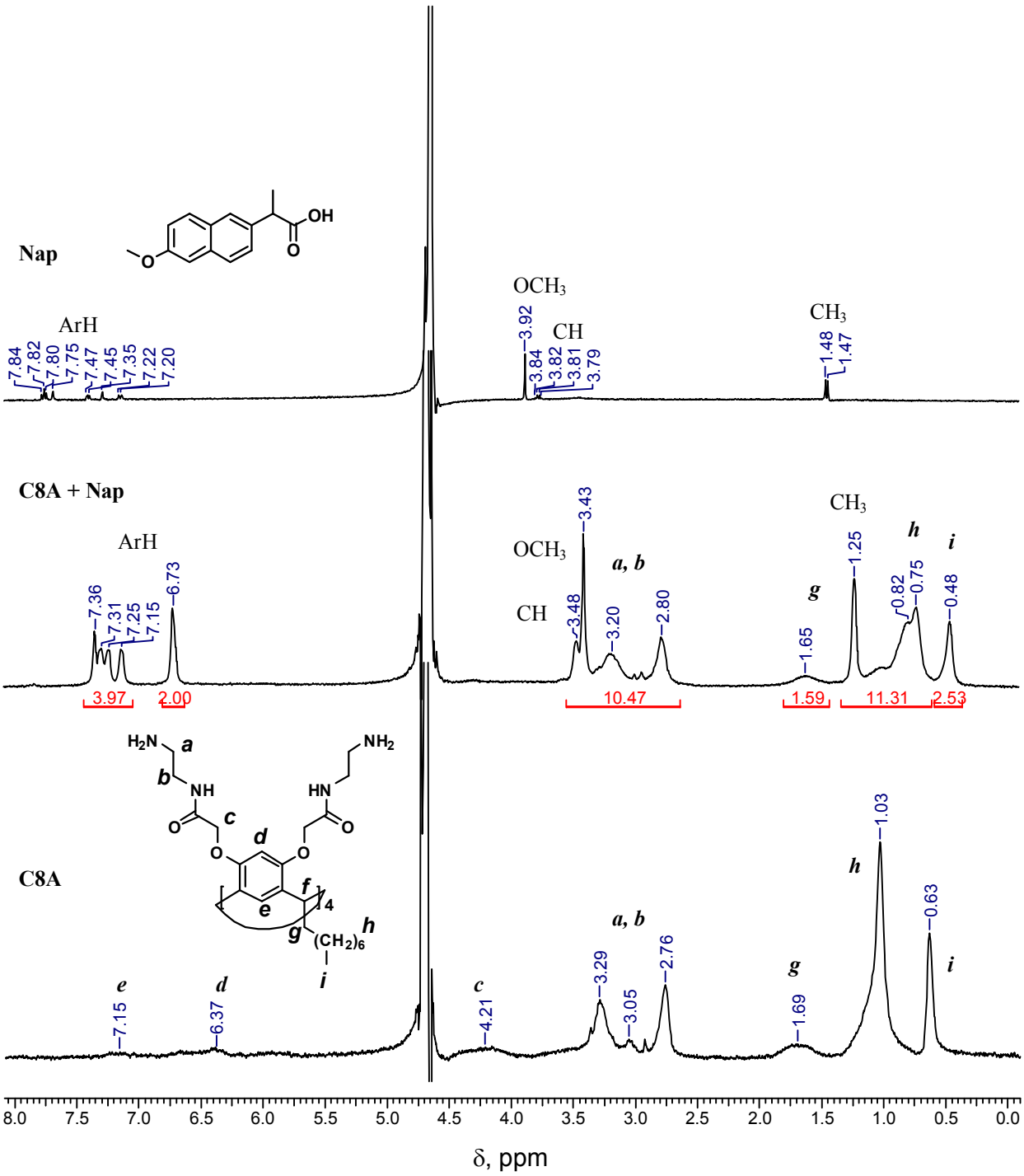


Figure S7. ^{1}H NMR spectra of the individual solutions of Nap (0.1 mM[a], pH 5.22) and C8A (1 mM, pH 8.26), and C8A-Nap mixture (pH 7.78) after solubilization in D_2O.

[a] The solubility of naproxen in water is ≈ 0.1 mM[1]

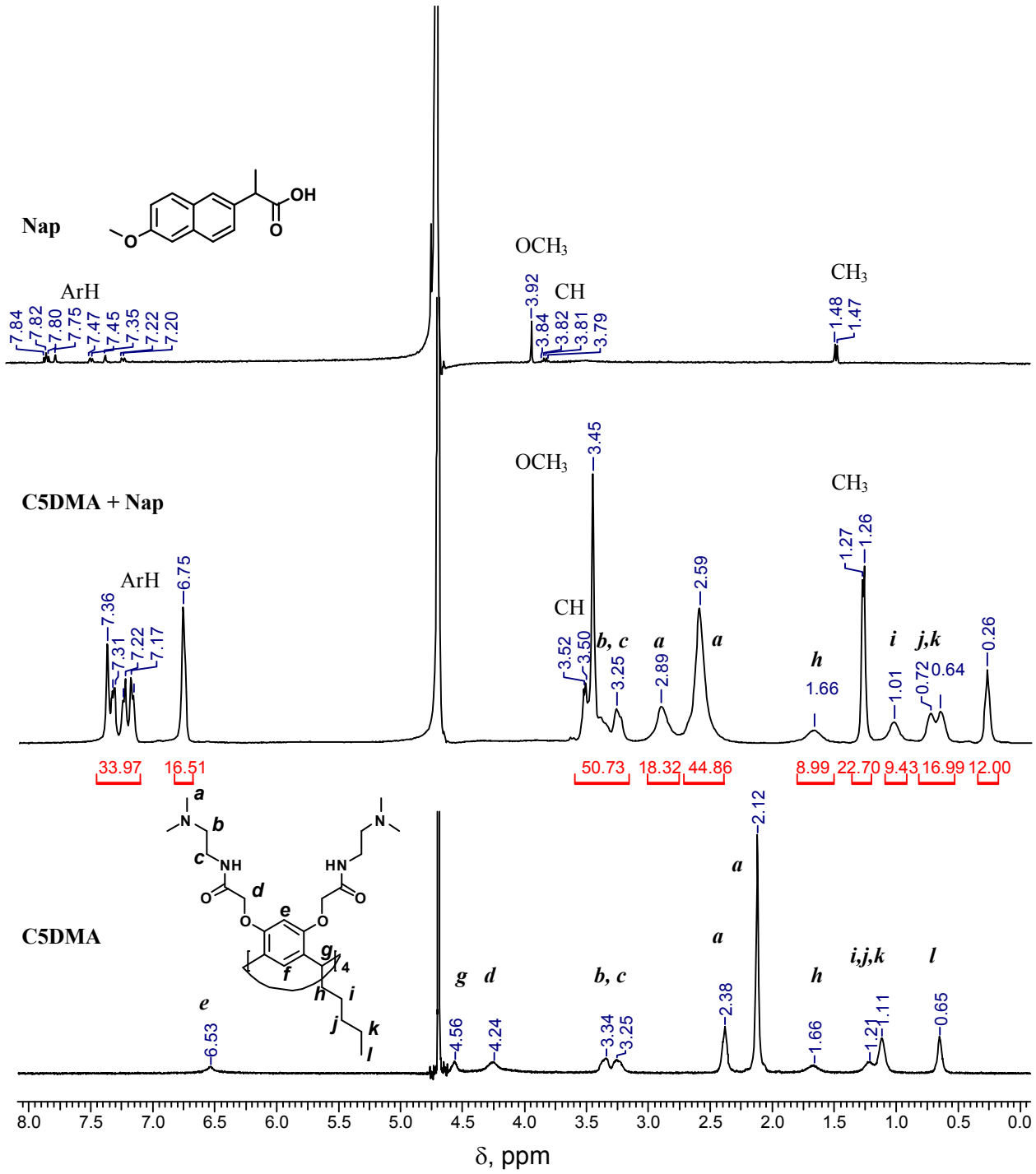


Figure S8. ^{1}H NMR spectra of the individual solutions of Nap (0.1 mM[a], pH 5.22) and C5DMA (1 mM, pH 9.26), and C5DMA-Nap mixture (pH 5.86) after solubilization in D_2O.

[a] The solubility of naproxen in water is ≈ 0.1 mM[1]

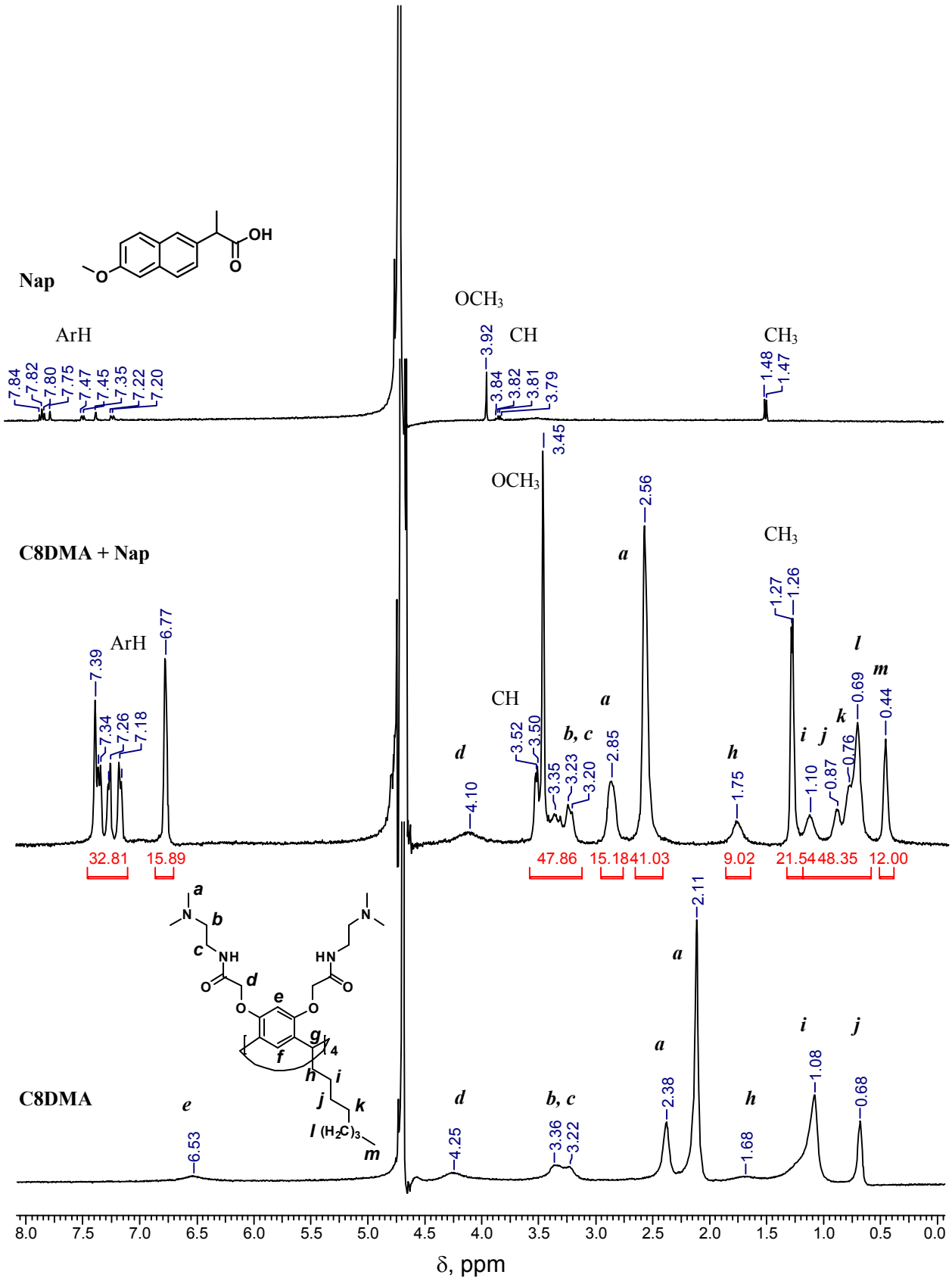


Figure S9. ^{1}H NMR spectra of the individual solutions of Nap (0.1 mM[a], pH 5.22) and C8DMA (1 mM, pH 8.32), and C8DMA-Nap mixture (pH 6.36) after solubilization in D_2O.

[a] The solubility of naproxen in water is ≈ 0.1 mM[1]

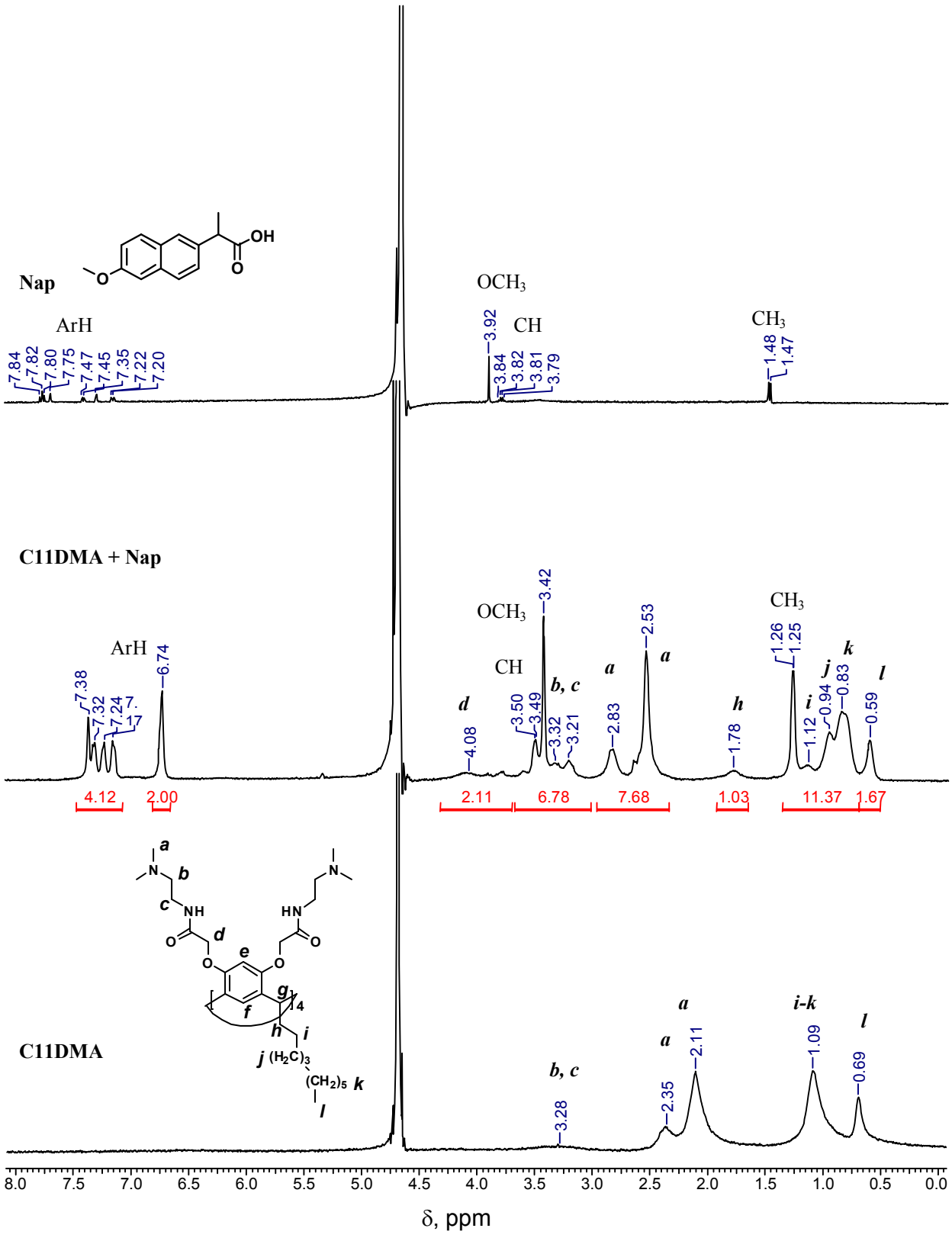


Figure S10. ^{1}H NMR spectra of the individual solutions of Nap (0.1 mM[a], pH 5.22) and C11DMA (1 mM, pH 8.34), and C11DMA-Nap mixture (pH 7.27) after solubilization in D_2O.

[a] The solubility of naproxen in water is ≈ 0.1 mM[1]

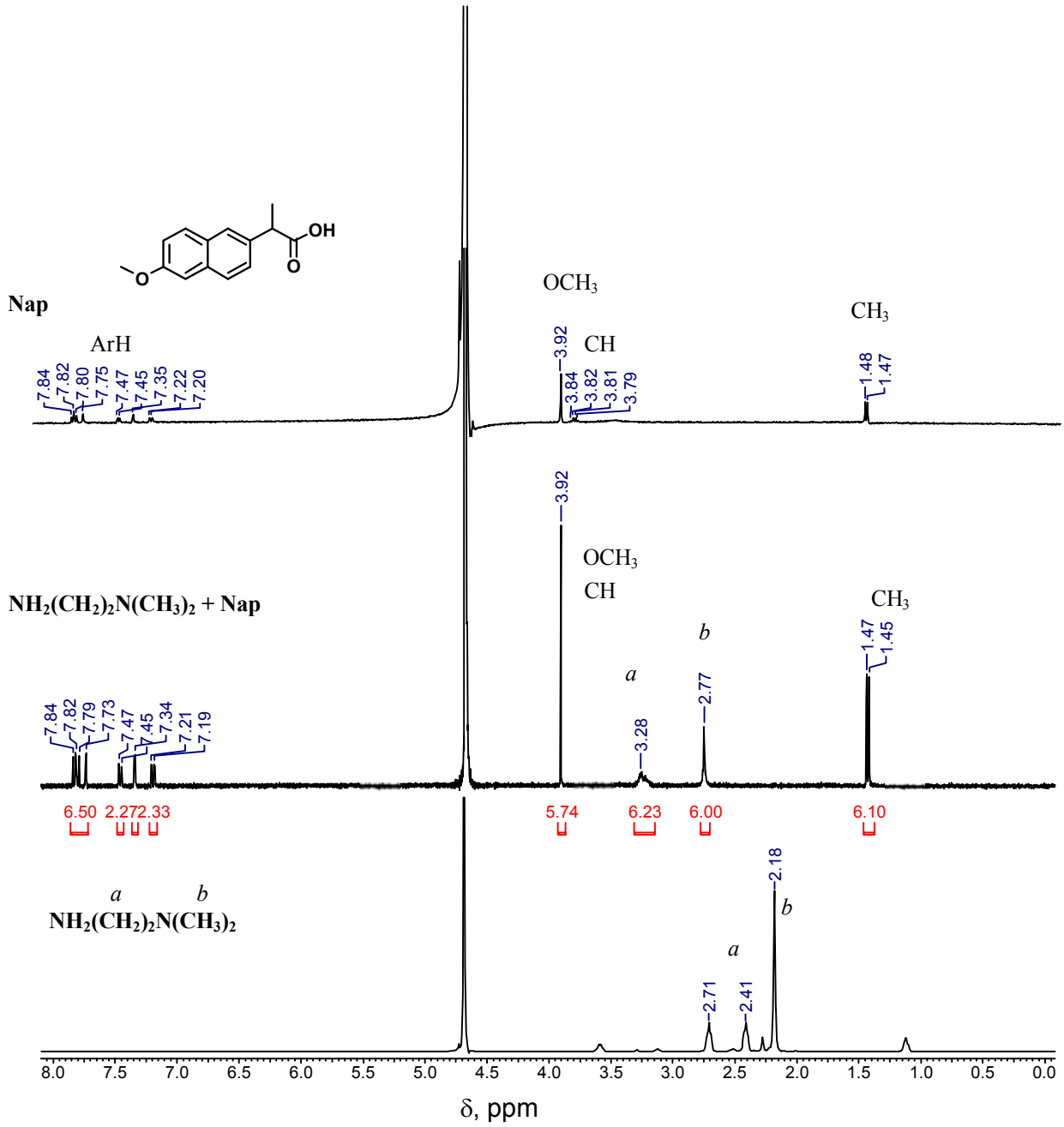


Figure S11. ^{1}H NMR spectra of the individual solutions of Nap (0.1 mM[a], pH 5.22) and N,N-dimethylethylenediamine (0.9 mM, pH 10.46), and their mixture (pH 10.10) after solubilization in D_2O.

[a] The solubility of naproxen in water is ≈ 0.1 mM[1]

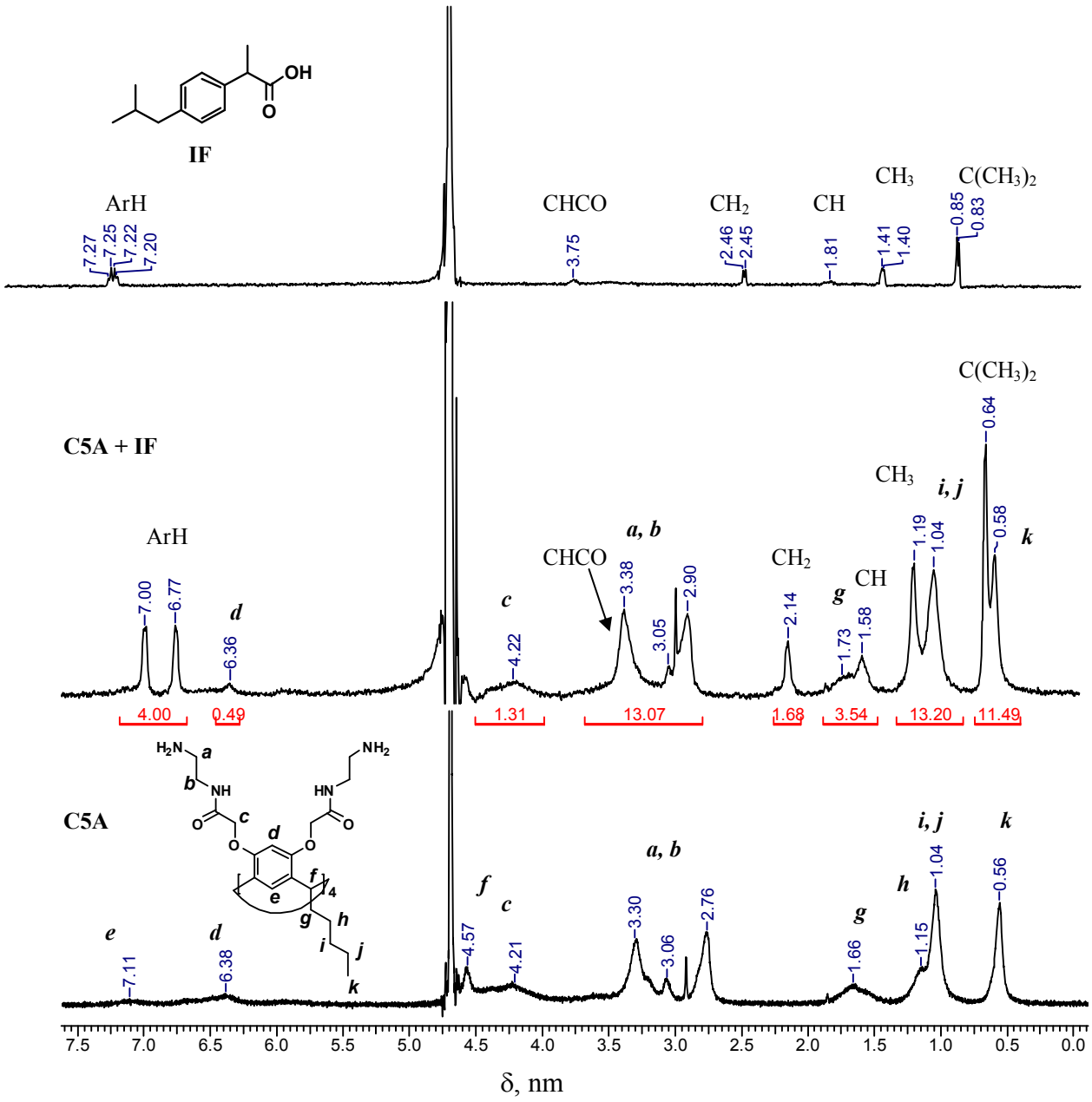


Figure S12. ^{1}H NMR spectra of the individual solutions of IF (0.2 mM[a], pH 3.77) and C5A (1 mM, pH 8.96), and C5A-IF mixture (pH 5.81) after solubilization in D_2O.

[a] The solubility of ibuprofen in water is ≈ 0.2 mM[2]

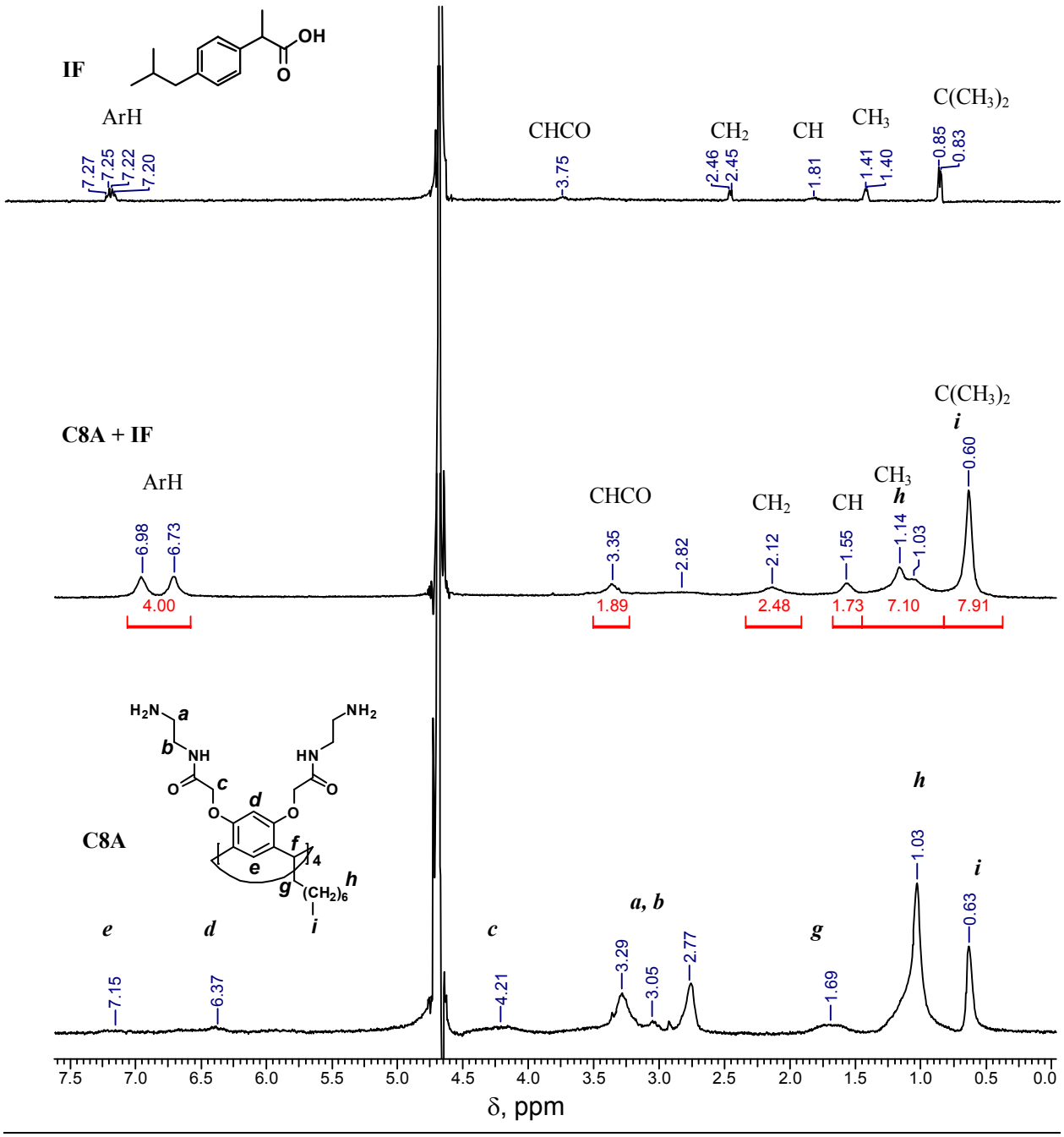


Figure S13. ^{1}H NMR spectra of the individual solutions of IF (0.2 mM[a], pH 3.77) and C8A (1 mM, pH 8.26), and C8A-IF mixture (pH 5.33) after solubilization in D_2O.

[a] The solubility of ibuprofen in water is ≈ 0.2 mM[2]

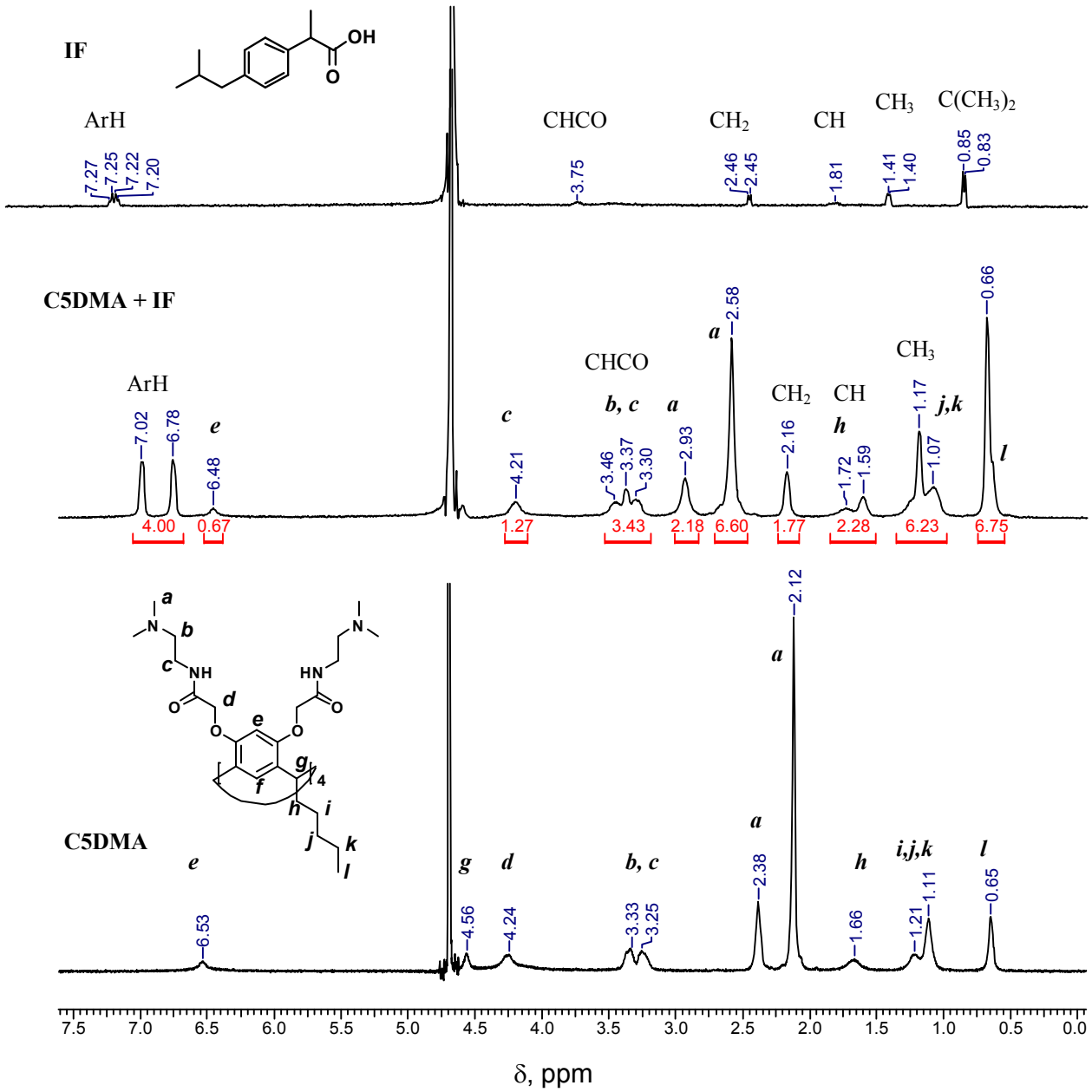


Figure S14. ^{1}H NMR spectra of the individual solutions of IF (0.2 mM[a], pH 3.77) and C5DMA (1 mM, pH 9.26), and C5DMA-IF mixture (pH 6.34) after solubilization in D_2O.

[a] The solubility of ibuprofen in water is ≈ 0.2 mM[2]

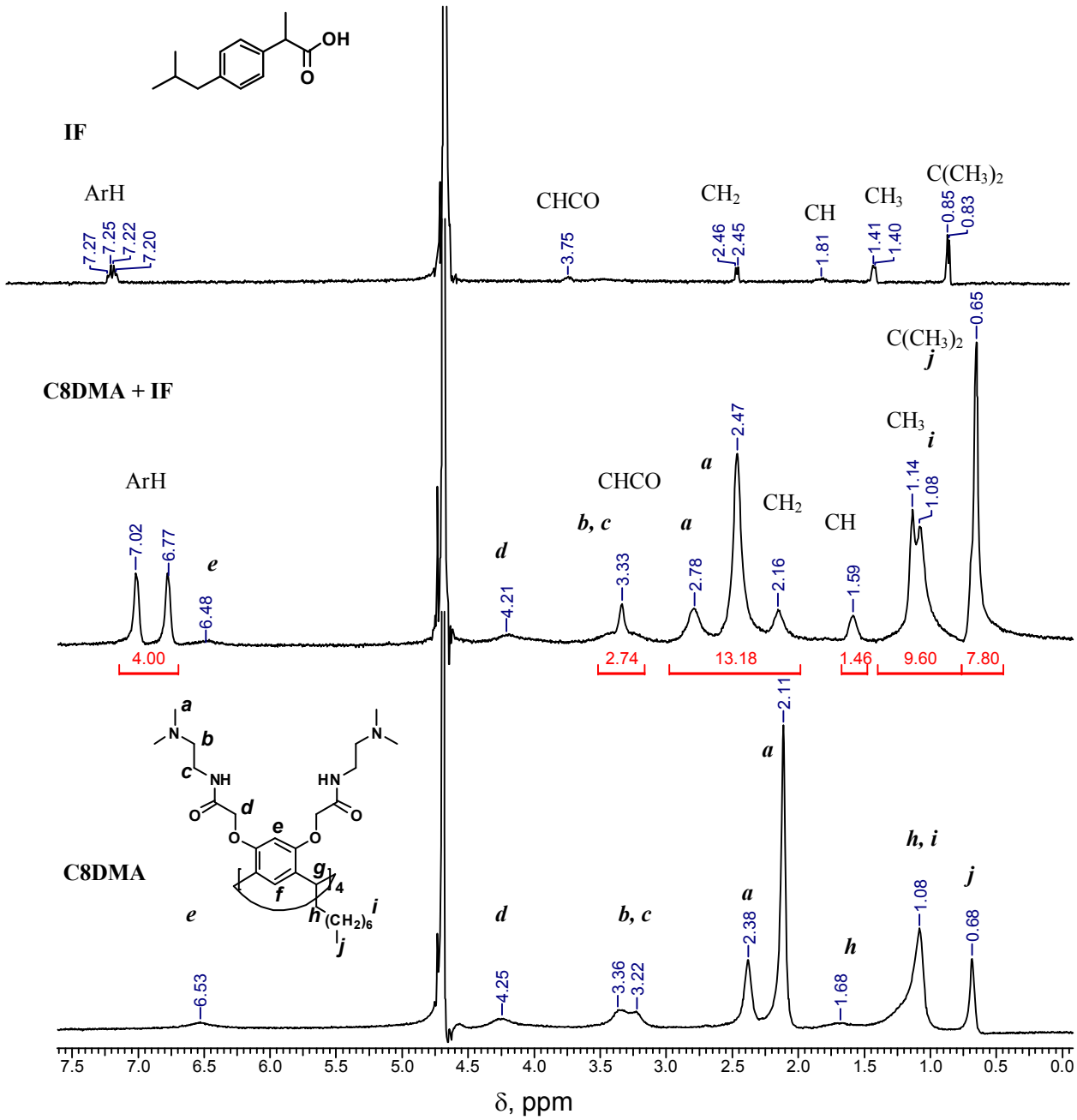


Figure S15. ^{1}H NMR spectra of the individual solutions of IF (0.2 mM[a], pH 3.77) and C8DMA (1 mM, pH 8.32), and C8DMA-IF mixture (pH 6.42) after solubilization in D_2O.

[a] The solubility of ibuprofen in water is ≈ 0.2 mM[2]

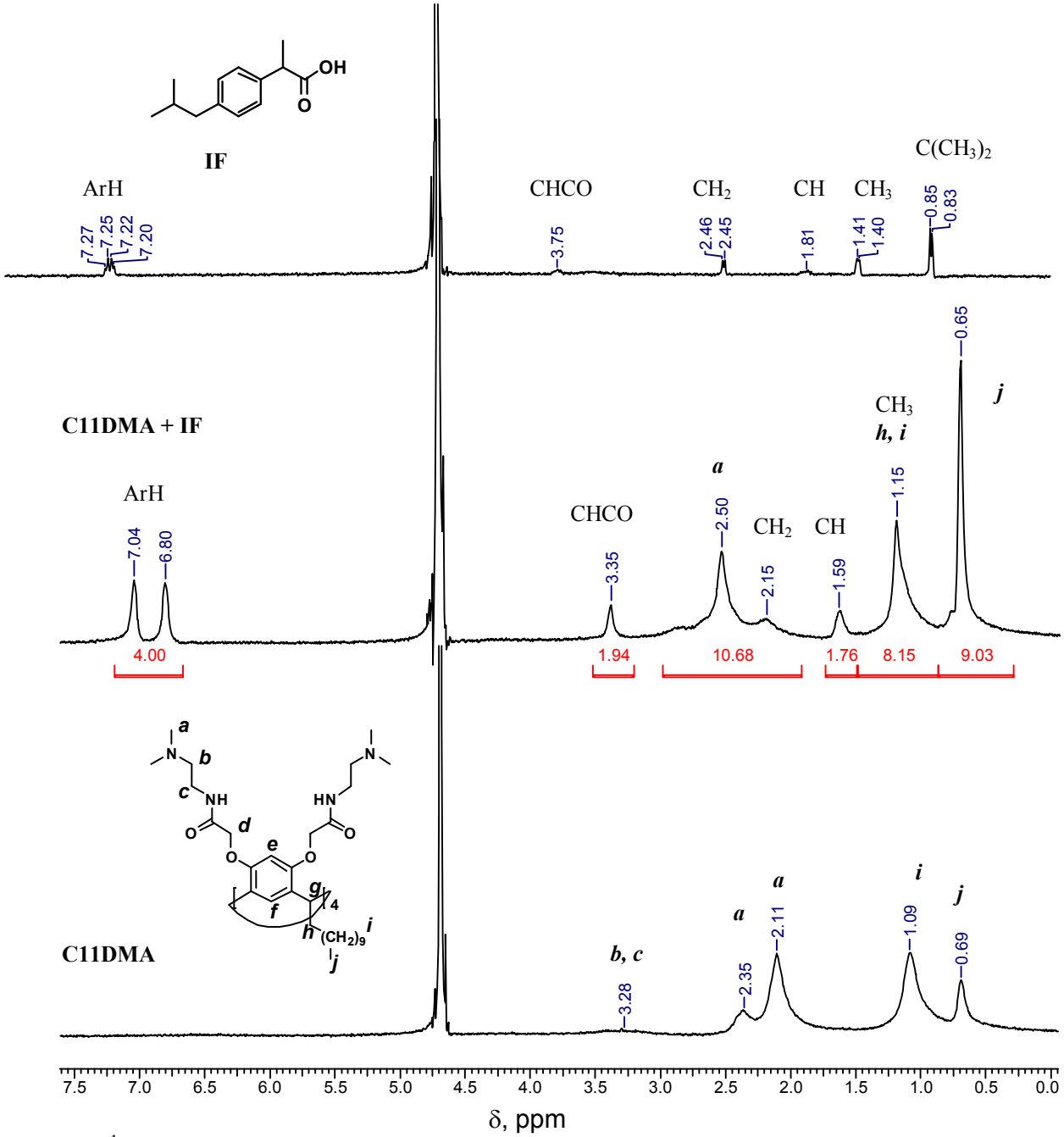


Figure S16. ^{1}H NMR spectra of the individual solutions of IF (0.2 mM[a], pH 3.77) and C11DMA (1 mM, pH 8.34), and C11DMA-IF mixture (pH 6.17) after solubilization in D_2O.

[a] The solubility of ibuprofen in water is ≈ 0.2 mM[2]

^{1}H NMR data for UDCA and macrocycles

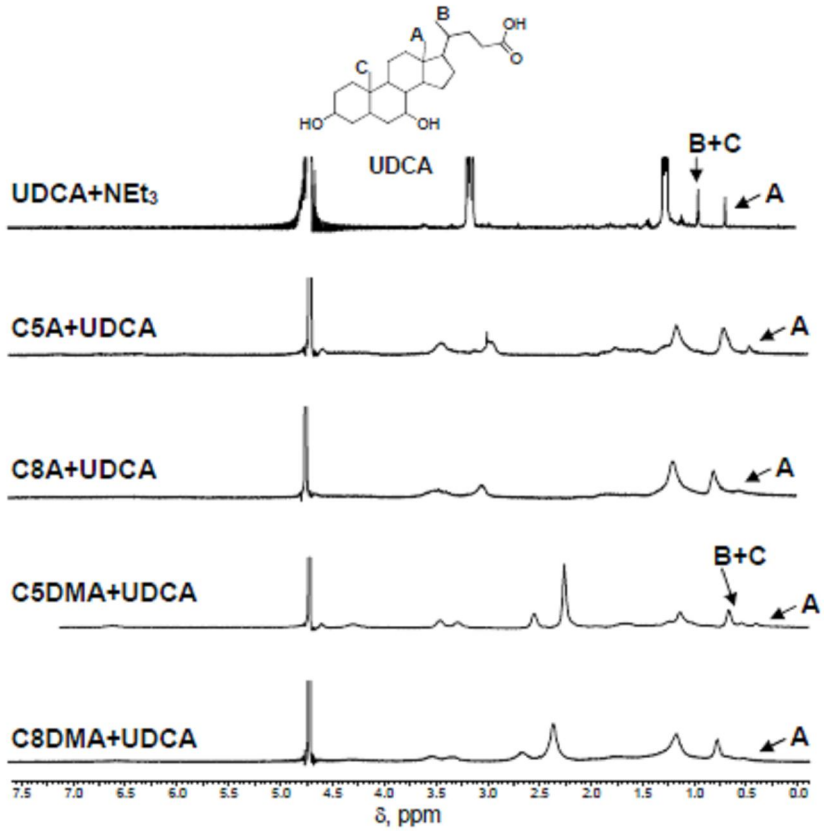


Figure S17. ^{1}H NMR spectra of UDCA in D_2O solutions in presence of NEt_3 and macrocycles. In some cases the signal of B and C groups are overlapped with the signals of aliphatic chains of macrocycles. For details see Table S5.

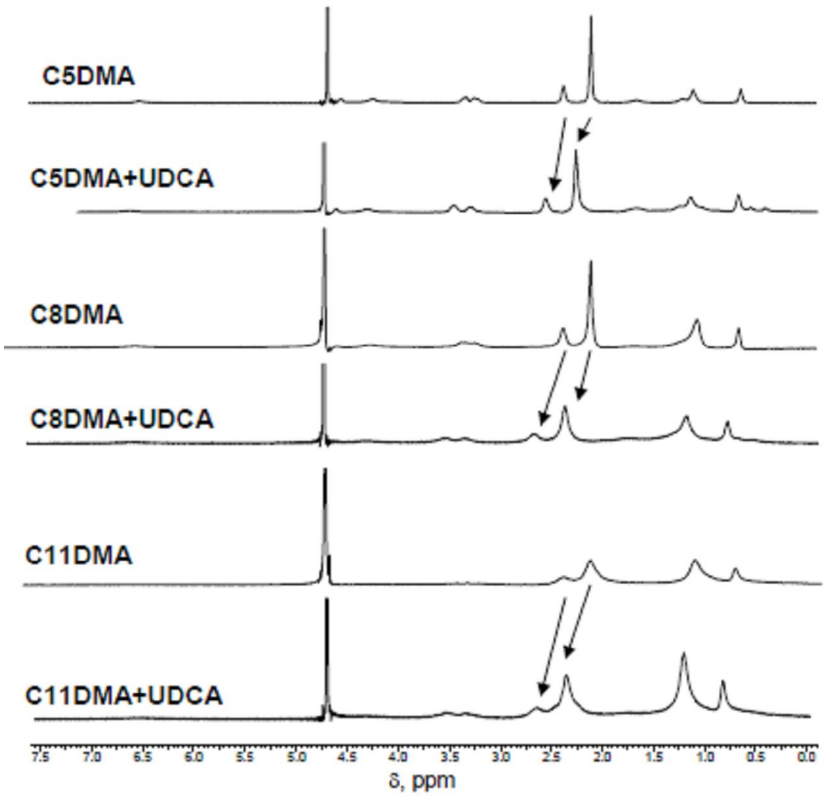
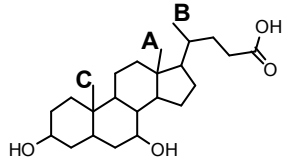


Figure S18. ^{1}H NMR spectra of individual D_2O solutions of dimethylamino-macrocycles and in the presence of UDCA. The downfield shifts of dimethylamino-groups of macrocycles in the presence of UDCA are indicated by solid arrows. For details see Table S5.

Table S5. The data of ^{1}H NMR spectrum of UDCA in DMSO-d_6, in NEt_3-D_2O solution and in 1 mM solutions of macrocycles in D_2O.



UDCA

	UDCA (DMSO-d_6)	**NEt_3 + UDCA**	**C5A + UDCA**	**Δδ[a]**	**C8A + UDCA**	**Δδ**	**C5DMA + UDCA**	**Δδ**	**C8DMA + UDCA**	**Δδ**	**C11DMA + UDCA**	**Δδ**
pH	-	*9.90*	*8.71*	-	*8.23*	-	*8.38*	-	*8.14*	-	*8.23*	-
Calix/ UDCA	**-**	**1/0.05**	**1/1**	**-**	**1/1**	**-**	**1/1**	**-**	**1/1**	**-**	ov[b]	**-**
CH_3(A)	0.62	0.65	0.42	-	0.46	-	0.45	-	0.50	-	ov	-
CH_3(B,C)	0.87	0.91	ov	-	ov	-	0.59	-	ov	-	ov	-
ArH	-	-	br[c]	-	br	-	6.56	0.03	6.54	0.03	br	-
CH	-	-	4.59	-0.02		-	4.58	0.02	ov	-	br	-
CH_2CO	-	-	4.17	-0.06	4.10	-0.11	4.26	0.01	4.28	0.03	br	-
NH-CH_2	-	-	3.42 3.09 2.97 2.92	0.12 0.03 0.05 0.16	3.39 br br 2.98	0.10 - - 0.22	3.43 3.27	0.09 0.02	3.51 3.31	0.19 0.09	3.48 3.29	- -0.01
CH_3N	-	-	-	-	-	-	2.57 2.27	0.19 0.15	2.63 2.33	0.25 0.24	2.60 2.32	0.25 0.22
CH_2	-	-	br	-	1.74	0.05	1.69	0.02	1.74	0.04	br	-
$(CH_2)_3$	-	-	1.25 1.12	0.09 0.08	1.11	0.08	1.28 1.16	0.06 0.05	1.14	0.06	1.15	0.06
CH_3	-	-	0.66	0.10	0.71	0.08	0.71	0.06	0.75	0.07	0.76	0.07

[a] $\Delta\delta = \delta_{complex} - \delta_{free}$; [b] ov - overlapping signal; [c] br – broadening signal

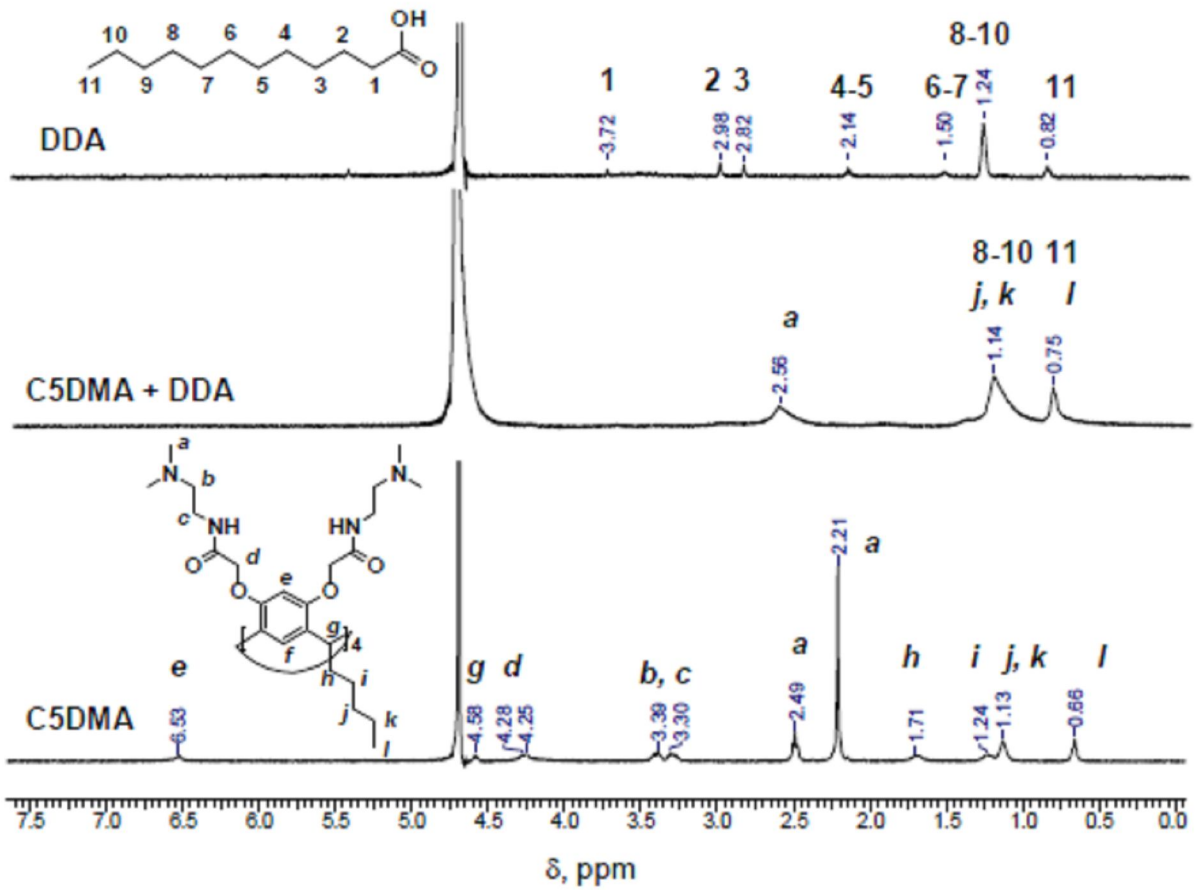
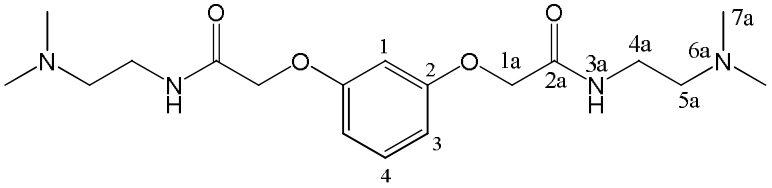


Figure S19. ^{1}H NMR spectra of the individual solutions of DDA (0.2 mM[a], pH 7.65) and C5DMA (1 mM, pH 8.66) and C5DMA-DDA mixture (pH 8.14) after solubilization and dilution by 1 mM solution of C5DMA in D_2O. The final C5DMA+DDA solution is opalescent thus the spectrum of mixture is broadened.

[a] The solubility of **DDA** in water is ~ 0.2 mM[3]

Table S6. The data of ^{1}H, ^{13}C и ^{15}N NMR spectra of RDMA (6 mM) in D_2O, D_2O + NEt_3 and D_2O + CF_3COOH.



	RDMA	NEt_3 (5μl)	$\Delta\delta^{[a]}$	NEt_3 (25μl)	Δδ	CF_3COOH (5μl)	Δδ	CF_3COOH (25μl)	Δδ
H1	6.60	6.58	-0.02	6.57	-0.03	6.61	0.02	6.40	-0.20
H3	6.66	6.64	-0.02	6.63	-0.03	6.66	0.00	6.44	-0.21
H4	7.29	7.27	-0.02	7.26	-0.03	7.29	0.00	7.08	-0.22
H1a	4.56	4.54	-0.01	4.53	-0.03	4.62	0.06	4.39	-0.16
H4a	3.39	3.36	-0.04	3.35	-0.05	3.65	0.26	3.45	0.05
H5a	2.51	2.45	-0.06	2.44	-0.07	3.30	**0.79**	3.40	**0.59**
H7a	2.22	2.16	-0.06	2.15	-0.07	2.89	**0.67**	2.68	**0.46**
C1	101.6	101.6	0	101.7	0.1	101.8	0.2	101.8	0.2
C2	157.9	157.9	0	157.9	0	157.9	0	157.9	0
C3	107.7	107.7	0	107.7	0	107.7	0	107.7	0
C4	130.3	130.3	0	130.3	0	130.4	0.1	130.4	0.1
C1a	66.3	66.3	0	66.3	0	66.3	0	66.3	0
C2a	170.6	170.6	0	170.5	0.1	171.7	1.1	171.7	1.1
C4a	36.0	36.1	0.1	36.1	0.1	33.8	-2.2	33.8	-2.2
C5a	56.3	56.3	0	56.3	0	56.1	-0.2	56.1	-0.2
C7a	43.5	43.5	0	43.5	0	42.6	-0.9	42.6	-0.9
N3a	111.3	111.9	**0.6**	111.7	**0.4**	106.5	**-4.8**	105.6	**-5.7**
N6a	20.4	20.1	**-0.3**	20.2	**-0.2**	31.5	**11.1**	31.2	**10.8**

[a] $\Delta\delta = \delta_{complex} - \delta_{free}$

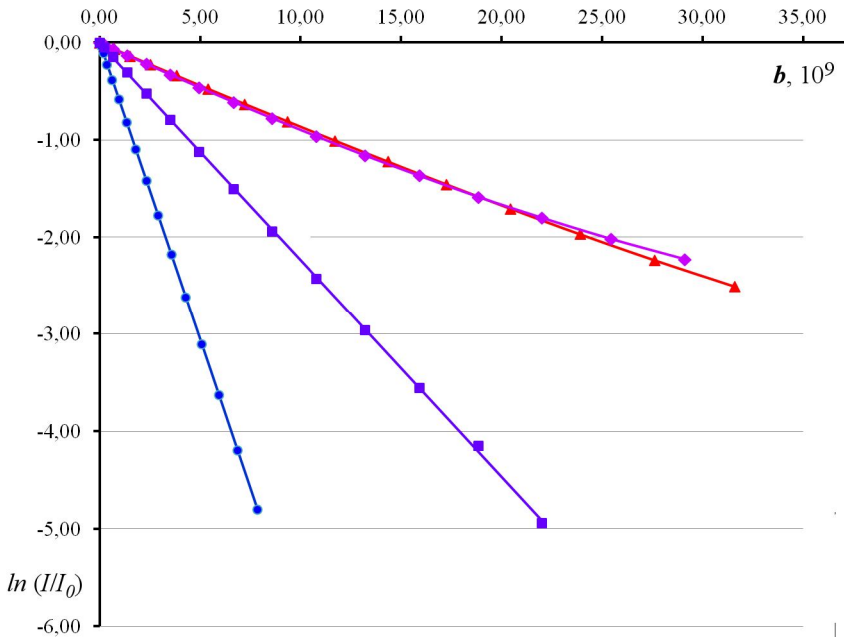


Figure S20. Natural logarithm of the normalized signal attenuation (ln I/I_0) in the FT-PGSE experiments as a function of the gradient amplitude b. Diffusion curves of aromatic protons of naproxene sodium (●) and protons of $(CH_3)_2N$-groups of C8DMA (▲) in individual aqueous solutions (1.0 mM), and diffusion curves of aromatic protons of Nap (■) and protons of $(CH_3)_2N$-groups of C8DMA (♦) in mixed aqueous solution (C (C8DMA) = 1 mM, C (Nap) = 7 mM).

Table S7. Self-diffusion coefficients (D_s), hydrodynamic radius (R_H), and aggregation numbers (N_{ag}) of macrocycles C5DMA in individual solutions and in complexes with naproxen (Nap) in D_2O solutions, the fraction of bound naproxen (P_{bD}) in the presence of C5DMA.

	C, mM		D_s ($\times 10^{-10}$ m^2/s)		R_H (Å)	N_{ag}	P_{bD}
	C5DMA	Nap	C5DMA	N			
C5DMA	1	-	1.05	-	27	12	-
C5DMA + Nap	1	4[a]	1.01	2.69	28	14	0.67
	1	2.5[b]	1.00	2.72	28	14	0.66
	1	1.25[b]	1.00	2.98	28	14	0.61
	1	0.4[b]	1.02	2.98	27	13	0.61
C5DMA	10	-	0.53	-	53	95	-
C5DMA + Nap	10	5[a]	0.50	1.15	56	113	0.88

[a] the concentration of naproxen is estimated by comparing of integral intensities of naproxen and macrocycle signals; [b] the solutions were obtained by dilution of C5DMA-Nap solution by solution of C5DMA (1 mM)

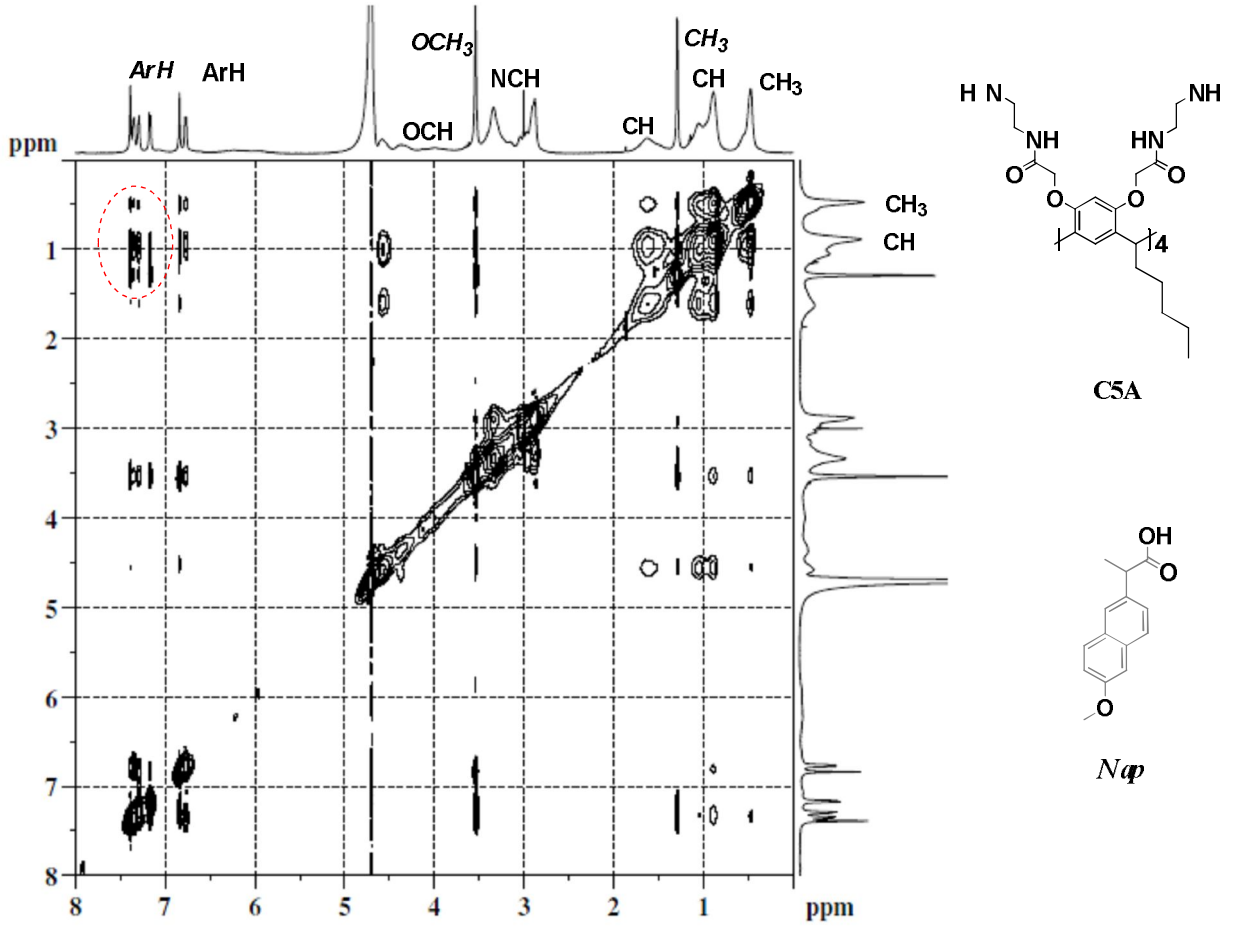


Figure S21. 2D NOESY spectra of C5A + Nap in D_2O (C_{C5A} = 1 mM), the dotted circle indicates the cross peaks between low-rim CH_2 and CH_3 groups of C5A and aryl groups of naproxen.

Table S8. The values of averaged hydrodynamic diameters of particles (d, nm), their intensities of scattering (%) and polydispersity index (PDI) in mixed solutions of macrocycles with naproxen (Nap), ibuprofen (IF) and dodecanoic acid (DDA) by DLS method.

	C_M, mM	fresh		after 7 d		after 14 d		after 21 d		after 28 d	
		d, nm (I, %)	*PDI*	d, nm (I, %)	*PDI*	d, nm (I, %)	*PDI*	d, nm (I, %)	*PDI*	d, nm (I, %)	*PDI*
C5A + IF	1	122 (24)	*0.042*	164 (29)	*0.052*	164 (23)	*0.092*	P[a]		-	
	0.5	91 (19)	*0.119*	122 (26)	*0.040*	122 (37)	*0.012*	142 (22)	*0.113*	n/c[b]	
	0.1	91	*0.082*	n/c	-	-		-		-	
C8A + IF	1	14 (17) 142 (6)	*0.395*	P	-	-		-		-	
C5A + Nap	1	142 (33)	*0.006*	190 (29)	*0.049*	220 (41)	*0.016*	P		-	
C8A + Nap	1	106 (26)	*0.050*	n/c	-	-		-		-	
	0.5	n/c	-	122 (11)	*0.040*	44 (0.5), 142 (22)	*0.176*	122 (14), 396 (9)	*0.256*	P	
C5A + DDA	1	33 (1.8), 122 (21)	*0.197*	44 (5), 142 (13)	*0.245*	51 (8), 220 (13)	*0.322*	P		-	
C8A + DDA	1	122 (17)	*0.181*	33 (3); 122 (15)	*0.262*	44 (7); 142 (14)	*0.269*	51 (7); 164 (11)	*0.288*	P	
C5DMA + DDA	1	91 (20)	*0.140*	122 (24)	*0.097*	142 (33)	*0.004*	142 (30)	*0.017*	142 (41)	*0.005*
C8DMA + DDA	1	164 (21)	*0.147*	164 (24)	*0.055*	164 (25)	*0.149*	164 (21)	*0.154*	59 (3), 220 (17)	*0.283*
C11DMA + DDA	1	10 (3), 33 (8), 106 (8)	*0.308*	14 (2), 44 (7), 164 (8)	*0.469*	18 (3), 164 (7)	*0.491*	38 (7), 164 (15)	*0.431*	44 (7), 220 (14)	*0.489*
C11DMA	1	4 (0.6), 8 (10), 28 (6), 79 (0.8), 4800 (0.1)	*0.269*	-		-		-		-	

[a] P – precipitation; [b] n/c – expone/ntial particle size–population curve is not correct

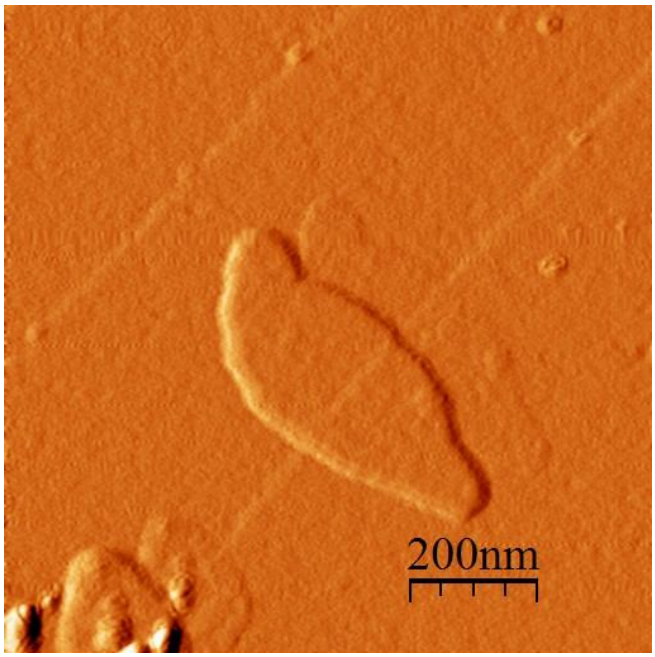


Figure S22. AFM image of C8A + Nap obtained on a surface of highly oriented pyrolytic graphite.

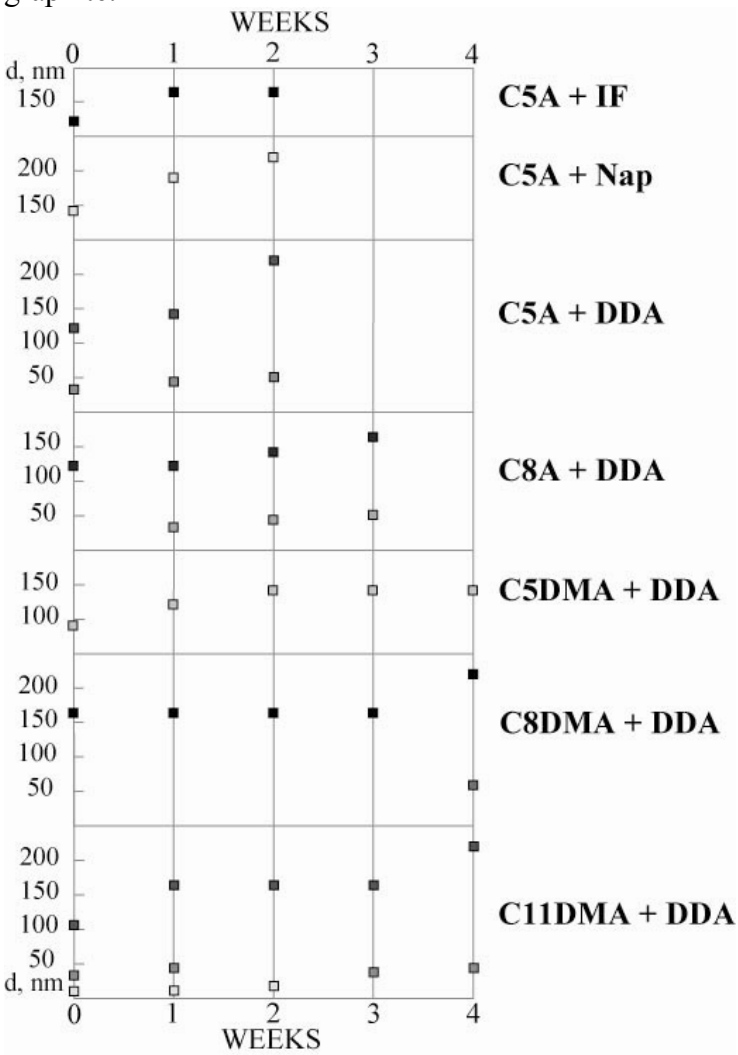


Figure S23. The dependence of averaged hydrodynamic diameter of particles in macrocycle-substrate solutions on time (DLS method, 25 °C).

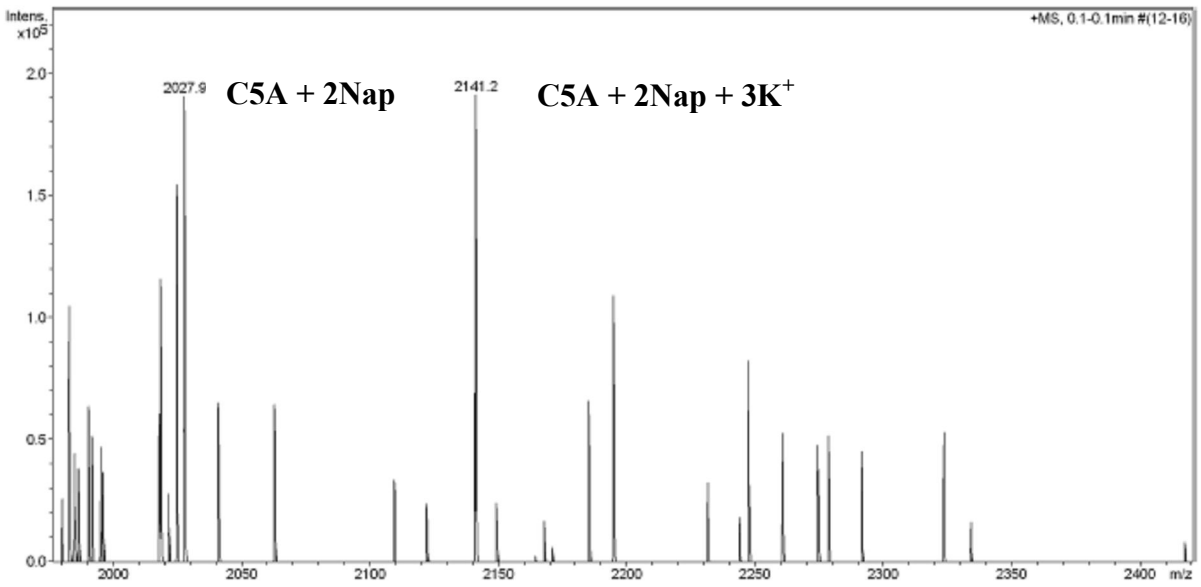


Figure S24. ESI MS spectra of C5A+Nap (molar ratio 1/2.5).

Table S9. The data of ^{1}H NMR spectrum of C5A, C5DMA, C5A + Nap and C5DMA + Nap solutions after addition[a] of 1N HCl in D_2O (C_M = 1 mM).

	Nap	C5A + HCl	C5A+ Nap + HCl	C5DMA + HCl	C5DMA + Nap + HCl
$CHC\underline{H}_3$	1.48, 1.47 d	-	-	-	-
$C\underline{H}CH_3$	3.83-3.79 q	-	-	-	-
OCH_3	3.92 s	-	-	-	-
ArH	7.84-7.20 m	-	-	-	-
ArH	-	br[b]	br	6.55	6.54
CH	-	ov[c]	ov	ov	ov
CH_2CO	-	3.54	3.58	3.71	br
$NH\text{-}CH_2$	-	3.1	3.15	3.60 3.34-3.30	3.68 3.56
CH_3N	-	-	-	2.91	2.89
CH_2	-	1.77	1.78	1.79	1.78
$(CH_2)_3$	-	1.22	1.20	1.25	1.21
CH_3	-	0.71	0.72	0.72	0.74

[a] the precipitate of naproxen after addition of HCl was removed; [b] br – broadening signal; [c] ov - overlapping signal

Table S10. The hemolytic activity data of calixresorcinarenes against human red blood cells in 0.15 M NaCl

	C, mM	Hemolysis of human red blood (%)
C5A	1	100
	0.1	100
C8A	1	100
	0.1	100
C5DMA	1	100
	0.1	84.8
C8DMA	1	100
	0.1	100
C11DMA	1	5.4
	0.1	2.7

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