

Supplementary Information

Unidirectional Rotation in a Mechanically Interlocked Hydrogen Bonded Molecular Motor

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I. Synthetic experimental procedures

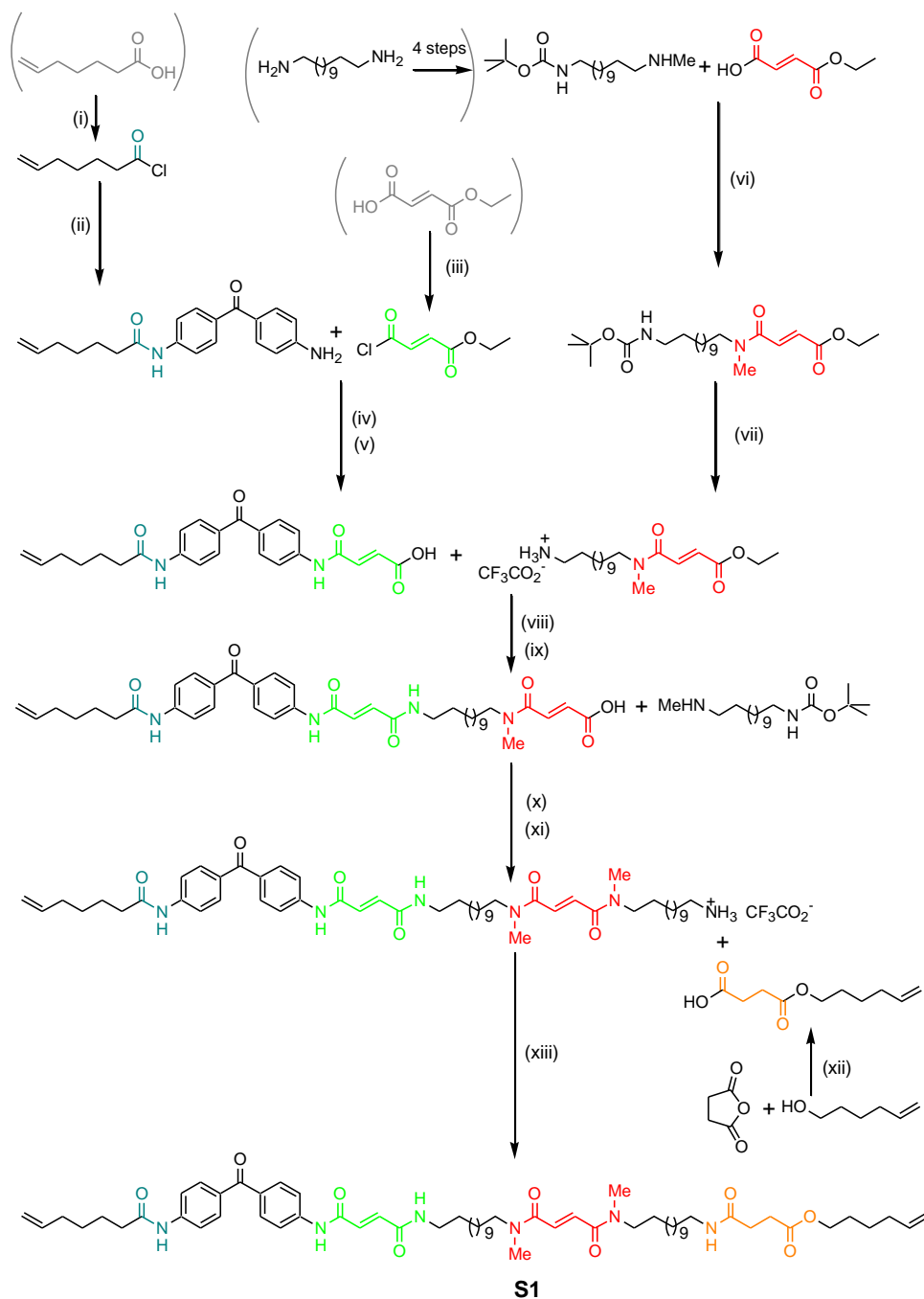
- (i) Preparation of macrocycle precursor, **S1**
- (ii) Preparation of each diastereomer of **1-3**.

II. Computational studies

III. Determination of shuttling rates

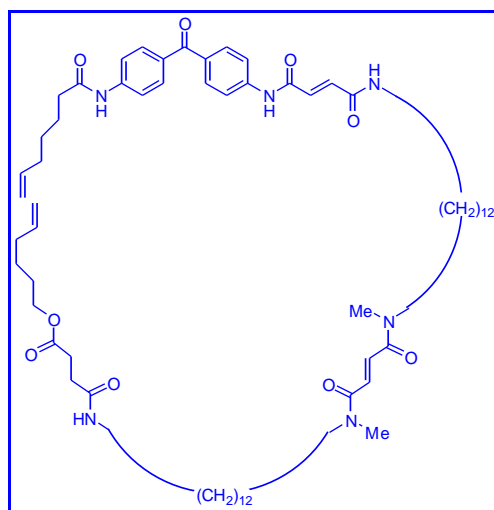
- (i) Symmetrical [2]rotaxanes
- (ii) Energy barrier for random circumrotation

I. Synthetic experimental procedures (i) Preparation of macrocycle precursor, S1



(i) thionyl chloride, CH_2Cl_2 , 65 °C, 2 h, quantitative. (ii) 4,4'-diaminobenzophenone, Et_3N , THF, 2 h, 96%. (iii) thionyl chloride, CH_2Cl_2 , 40 °C, 2 h, quantitative. (iv) Et_3N , THF, 2 h, 90%. (v) 1M $\text{NaOH}(\text{aq})$, THF, 16 h, 83 %. (vi) $\text{EDCI}\cdot\text{HCl}$, DMAP, CH_2Cl_2 , 16 h, 89%. (vii) trifluoroacetic acid, CHCl_3 , 30 min., quantitative. (viii) BOP, Et_3N , 1/5 THF/ CHCl_3 , 1 h, 69%. (ix) 1 M $\text{NaOH}(\text{aq})$, THF, 16 h, quantitative. (x) BOP, Et_3N , 1/5 THF/ CHCl_3 , 1 h, 74%. (xi) trifluoroacetic acid, CHCl_3 , 30 min., 95%. (xii) Et_3N , CHCl_3 , 16 h, 98%. (xiii) BOP, Et_3N , 1/5 THF/ CHCl_3 , 2 h, 86%.

[12-({3-[(12-{3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid hex-5-enyl ester, S1

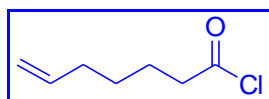


To a stirred suspension of [12-({3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid *tert*-butyl ester-trifluoro-acetate salt, **S18** (1.35 g, 1.43 mmol, 1 equiv.) in 25 mL of THF was added succinic acid monohex-5-enyl ester, **S19** (0.37 g, 1.86 mmol, 1.3 equiv.) in 25 mL of CHCl_3 , followed by 0.5 mL of triethylamine until pH 14. This was followed by addition of BOP (0.95 g, 2.15 mmol, 1.5 equiv.) and a further 0.5 mL of triethylamine to maintain a basic mixture. After 10 minutes a pale yellow solution was obtained and the reaction mixture stirred at room temperature for a further 2 hours. Concentration under reduced pressure gave a yellow oil which was subjected to column chromatography (silica gel, 3:97 MeOH/ CHCl_3). Excess HMPA remained in the yellow oil, which was washed with Et_2O to give the product as a colourless solid.

Selected data for [12-({3-[(12-{3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid hex-5-enyl ester, S1: Yield 1.22 g (86%); ^1H NMR (400 MHz, $\text{CDCl}_3/1\%$ MeOD): $\delta = 10.26$ (brs, 1H, ArNHCO), 8.65 (brs, 1H,

ArNHCO), 7.76–7.64 (m, 10H, CH=CHCONH & NHCOCH₂ & ArH, benzophenone), 7.32 (m, 2H, NCH₃COCH=CHNCH₃), 6.98 & 6.91 (d, *J* = 15.2 Hz, 2H, NHCOCH=CHCONH), 5.77 (m, 2H, CH₂=CH), 4.94 (m, 4H, CH₂=CH), 4.04 (t, *J* = 6.6 Hz, CO₂CH₂), 3.39 (m, 4H, CH₂NCH₃), 3.29 (m, 2H, CH₂NHCO), 3.16 (m, CH=CHCONHCH₂), 3.08 & 2.98 (s, 6H, NCH₃), 2.62 (t, *J* = 6.8 Hz, NHCOCH₂CH₂CO₂), 2.42 (t, *J* = 6.8 Hz, NHCOCH₂CH₂CO₂), 2.37 (t, *J* = 7.3 Hz, 2H, CH₂CONHAr), 2.05 (m, 4H, CH₂=CHCH₂), 1.72 (quint, *J* = 7.6 Hz, 2H, CH₂CH₂CONHAr), 1.57 (m, 8H, CO₂CH₂CH₂ & 2 x CH₂CH₂NCH₃ & CH₂CH₂NHCO), 1.44 (m, 6H, CO₂CH₂CH₂CH₂ & CH₂=CHCH₂CH₂ & CH=CHCONHCH₂CH₂), 1.23 (brs, 32H, CH₂, alkyl); ¹³C NMR (100 MHz, CDCl₃/1% MeOD): δ = 195.05, 191.35, 173.49, 172.45, 171.79, 165.41, 164.78, 163.56, 142.36, 142.03, 138.38, 138.25, 134.02, 133.44, 132.78, 132.64, 131.37, 131.32, 131.00, 119.26, 119.18, 118.67, 114.81, 114.71, 64.79, 50.39, 49.98, 49.76, 49.55, 49.34, 49.12, 48.91, 48.70, 48.41, 39.91, 39.68, 39.54, 37.26, 35.57, 34.26, 33.42, 33.20, 30.85, 29.62, 29.46, 29.41, 29.36, 29.28, 29.24, 29.19, 29.04, 28.42, 27.89, 27.01, 26.85, 26.55, 25.06, 24.93; HRMS (FAB, THIOG matrix): *m/z* = 1093.73126 [(M+H)⁺] (anal. calcd for C₆₄H₉₇N₆O₉: *m/z* = 1093.73170).

Hept-6-enoyl chloride, **S2**

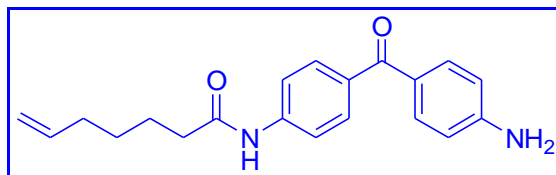


To a stirred solution of 6-heptenoic acid (4.60 mL, 33.8 mmol, 1 equiv.) in 90 mL of CH₂Cl₂ was added thionyl chloride (19.7 mL, 270 mmol, 8 equiv.), one drop of DMF (cat.) and stirred at 65 °C for 2 hours. Distillation of thionyl chloride and CH₂Cl₂ yielded the acid chloride as a yellow oil.

Selected data for hept-6-enoyl chloride, S2: Yield 4.98 g (quantitative); ¹H NMR (400 MHz, CDCl₃): δ = 5.78 (m, 1H, CH₂=CH), 5.01 (m, 2H, CH₂=CH), 2.90 (m, 2H, CH₂COCl), 2.08 (m, 2H, CH₂=CHCH₂), 1.74 (m, 2H, CH₂CH₂COCl), 1.47 (m, 2H,

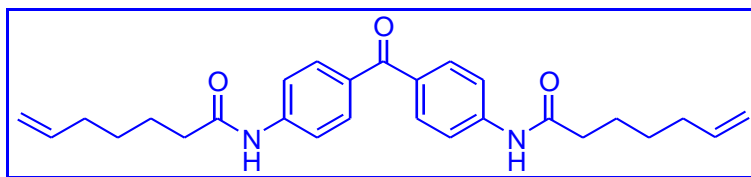
$\text{CH}_2=\text{CHCH}_2\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 174.14, 138.20, 115.60, 47.32, 33.50, 27.95, 24.85$.

Hept-6-enoic acid {4-[1-(4-amino-phenyl)-2-oxo-vinyl]-phenyl}-amide, S3



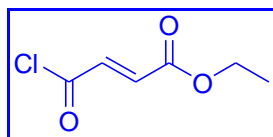
To a stirred solution of 4,4'-diaminobenzophenone (10.00 g, 47.1 mmol, 1 equiv.) and triethylamine (9.9 mL, 70.7 mmol, 1.5 equiv.) in 700 mL of THF was added hept-6-enoyl chloride, **S2** (3.30 g, 22.6 mmol, 0.48 equiv.) in 100 mL of THF at 0 °C over 10 minutes. The reaction mixture was stirred at room temperature for 2 hours. The volume of THF was reduced to 50 mL and 500 mL of CHCl_3 was added. The organic phase was washed with 1 M aqueous HCl (3 x 350 mL), saturated aqueous NaHCO_3 (3 x 350 mL), brine (350 mL), dried over anhydrous MgSO_4 and concentrated under reduced pressure to give a mixture of monosubstituted and disubstituted benzophenone as a yellow oil. The yellow oil was subjected to column chromatography (silica gel, 40:60 CHCl_3 /cyclohexane) to elute the disubstituted benzophenone and CHCl_3 to elute the mono- (**S3**) and di- (**S4**) substituted products.

Selected data for hept-6-enoic acid {4-[1-(4-amino-phenyl)-2-oxo-vinyl]-phenyl}-amide, S3: Yield 7.23 g (96%); m.p. 136 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 10.12$ (brs, 1H, CONH), 7.73 (d, $J = 8.6$ Hz, 2H, ArH, benzophenone), 7.61 (d, $J = 8.6$ Hz, 2H, ArH, benzophenone), 7.53 (d, $J = 8.6$ Hz, 2H, ArH, benzophenone), 6.62 (d, $J = 8.6$ Hz, 2H, ArH, benzophenone), 6.11 (brs, 2H, NH_2), 5.83 (m, 1H, $\text{CH}_2=\text{CH}$), 5.02 (m, 2H, $\text{CH}_2=\text{CH}$), 2.38 (t, $J = 7.6$ Hz, 2H, CH_2CONH), 2.06 (q, $J = 7.6$ Hz, 2H, $\text{CH}_2=\text{CHCH}_2$), 1.62 (quintet, $J = 7.6$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CONH}$), 1.41 (quintet, $J = 7.6$ Hz, 2H, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 192.41, 171.60, 153.36, 142.05, 138.52, 133.13, 132.32, 130.14, 124.18, 118.02, 114.81, 112.48, 36.26, 32.90, 27.82, 24.50$; HRMS (FAB, THIOG matrix): $m/z = 323.17639$ $[(\text{M}+\text{H})^+]$ (anal. calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$: $m/z = 323.17595$).



Selected data for hept-6-enoic acid {4-[1-(4-hept-6-enoylamino-phenyl)-2-oxo-vinyl]-phenyl}-amide, S4: Yield 0.88 g (4%); m.p. 179 °C; ^1H NMR (400 MHz, DMSO- d_6): δ = 10.27 (brs, 2H, CONH), 7.78 (d, J = 8.8 Hz, 4H, ArH, benzophenone), 7.71 (d, J = 8.8 Hz, 4H, ArH, benzophenone), 5.83 (m, 2H, $\text{CH}_2=\text{CH}$), 5.01 (m, 4H, $\text{CH}_2=\text{CH}$), 2.39 (t, J = 7.3 Hz, 4H, CH_2CONH), 2.07 (q, J = 7.3 Hz, 4H, $\text{CH}_2=\text{CHCH}_2$), 1.63 (m, 4H, $\text{CH}_2\text{CH}_2\text{CONH}$), 1.42 (m, 4H, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 193.31, 171.75, 143.04, 134.51, 131.64, 130.82, 118.13, 114.81, 36.28, 32.89, 27.81, 24.46; HRMS (FAB, THIOG matrix): m/z = 433.25903 [(M+H) $^+$] (anal. calcd for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_3$: m/z = 433.24912).

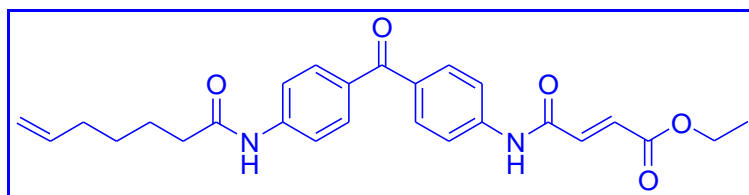
3-Chlorocarbonyl-acrylic acid ethyl ester, S5



To a suspension of fumaric acid monoethyl ester (4.00 g, 47 mmol, 1 equiv.) in 30 mL of CH_2Cl_2 was added one drop of DMF (cat.) and thionyl chloride (16 mL, 222 mmol, 8 equiv.) and heated to 40 °C for 30 minutes until complete dissolution. Distillation of thionyl chloride and CH_2Cl_2 yielded the acid chloride as a pale yellow oil.

Selected data for 3-chlorocarbonyl-acrylic acid ethyl ester, S5: Yield 4.51 g (quantitative); ^1H NMR (400 MHz, CDCl_3): δ = 7.01 (d, J = 15.3 Hz, 1H, $\text{CH}=\text{CH}$), 6.96 (d, J = 15.3 Hz, 1H, $\text{CH}=\text{CH}$), 4.30 (q, J = 7.0 Hz, 2H, CH_2CH_3), 1.34 (t, J = 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ = 165.80, 164.15, 138.30, 137.12, 62.46, 14.44; MS (ESI): m/z = 197.7 [(M+Cl) $^-$].

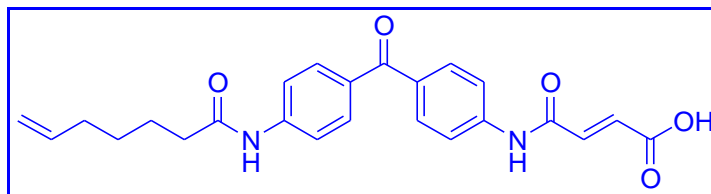
3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acrylic acid ethyl ester, S6



To a stirred solution of hept-6-enoic acid {4-[1-(4-amino-phenyl)-2-oxo-vinyl]-phenyl}-amide, **S3** (6.00 g, 17.9 mmol, 1 equiv.) and triethylamine (5 mL, 70.9 mmol, 2 equiv.) in 80 mL of THF was added 3-chlorocarbonyl-acrylic acid ethyl ester, **S5** (4.40 g, 26.9 mmol, 1.5 equiv.) in 20 mL of THF at 0 °C over 10 minutes. The reaction mixture was stirred at room temperature for 2 hours. The volume of THF was reduced to 20 mL and 50 mL of CHCl₃ was added. The organic phase was washed with 1 M aqueous HCl (3 x 50 mL), saturated aqueous NaHCO₃ (3 x 50 mL), brine (50 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure to give the product as a yellow solid.

Selected data for 3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acrylic acid ethyl ester, S6: Yield 7.24 g (90%); m.p. 225 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.91 (brs, 1H, CONH), 10.27 (brs, 1H, CONH), 7.86, (d, *J* = 8.8 Hz, 2H, ArH, benzophenone), 7.78 (d, *J* = 8.8 Hz, 2H, ArH, benzophenone), 7.76 (d, *J* = 9.0 Hz, 2H, ArH, benzophenone), 7.73 (d, *J* = 9.0 Hz, 2H, ArH, benzophenone), 7.26 (d, *J* = 15.3 Hz, 1H, CH=CH), 6.77 (d, *J* = 15.3 Hz, 1H, CH=CH), 5.83 (m, 1H, CH₂=CH), 5.01 (m, 2H, CH₂=CH), 4.24 (q, *J* = 7.0 Hz, 2H, CH₂CH₃), 2.39 (t, *J* = 7.3 Hz, 2H, CH₂CONH), 2.08 (q, *J* = 7.3 Hz, 2H, CH₂=CHCH₂), 1.64 (q, *J* = 7.3 Hz, 2H, CH₂CH₂CONH), 1.42 (quintet, *J* = 7.3 Hz, 2H, CH₂=CHCH₂CH₂), 1.29 (t, *J* = 7.3 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 193.31, 171.79, 164.78, 161.76, 143.19, 142.11, 138.51, 137.23, 132.74, 131.43, 130.90, 130.86, 129.99, 118.75, 118.16, 114.82, 60.85, 36.28, 32.89, 27.81, 24.45, 13.98; HRMS (FAB, THIOG matrix): *m/z* = 449.20833 [(M+H)⁺] (anal. calcd for C₂₆H₂₉N₂O₅: *m/z* = 449.20765).

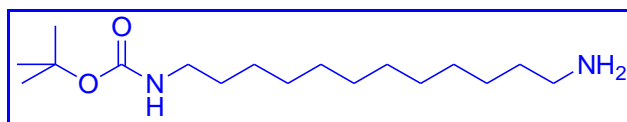
3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acrylic acid, S7



To a stirred solution of 3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acrylic acid ethyl ester, **S6** (2.00 g, 4.5 mmol, 1 equiv.) in 20 mL of THF was added 1 M aqueous NaOH (0.20 g in 5 mL H₂O, 4.9 mmol, 1.1 equiv.). The yellow solution was stirred at room temperature for 16 hours after which TLC indicated some unreacted ester remained. Additional 1 M aqueous NaOH (0.04 g in 1 mL H₂O, 0.98 mmol, 0.2 equiv.) was added and stirred for a further 6 hours. Water was added to the reaction mixture, followed by dropwise addition of concentrated HCl until pH 1. The reaction mixture extracted with 1:5 THF/CHCl₃ (3 x 50 mL), dried with anhydrous MgSO₄ and concentrated under reduced pressure to give the acid as a yellow solid.

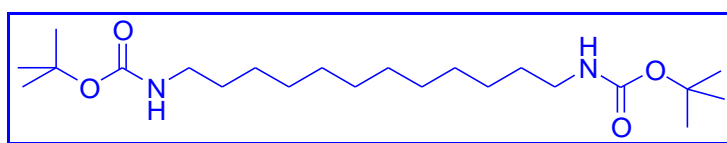
Selected data for 3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acrylic acid, S7: Yield 1.64 g (83%); m.p. 263 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.92 (brs, 1H, CONH), 10.32 (brs, 1H, CONH), 7.92–7.77 (m, 8H, ArH, benzophenone), 7.25 (d, *J* = 15.3 Hz, 1H, CH=CH), 6.77 (d, *J* = 15.3 Hz, 1H, CH=CH), 5.88 (m, 1H, CH₂=CH), 5.07 (m, 2H, CH₂=CH), 2.44 (t, *J* = 7.3 Hz, 2H, CH₂CONH), 2.12 (q, *J* = 7.3 Hz, 2H, CH₂=CHCH₂), 1.68 (m, 2H, CH₂CH₂CONH), 1.47 (quintet, *J* = 7.3 Hz, 2H, CH₂=CHCH₂CH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 193.31, 171.79, 166.17, 162.05, 143.17, 142.16, 138.51, 136.73, 132.66, 131.42, 131.28, 130.93, 130.89, 118.73, 118.13, 114.84, 36.28, 32.91, 27.80, 24.42; HRMS (FAB, THIOG matrix): *m/z* = 421.17715 [(M+H)⁺] (anal. calcd for C₂₄H₂₅N₂O₅: *m/z* = 421.17635).

(12-Amino-dodecyl)-carbamic acid *tert*-butyl ester, S8



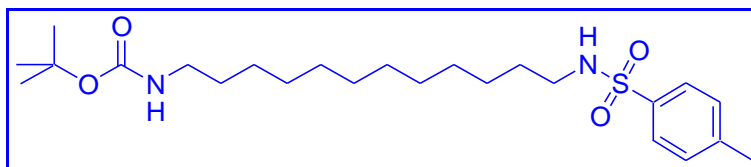
To a solution of 1,12-diaminododecane (20 g, 100 mmol, 1 equiv.) in 600 mL of CHCl_3 (slight suspension) was added a solution of di-*tert*-butyl dicarbonate (10.90 g, 50 mmol, 0.5 equiv.) in 200 mL of CHCl_3 . Immediate precipitation occurred on addition and the resulting suspension was stirred for 16 hours at room temperature. The precipitate was filtered and the filtrate concentrated under reduced pressure to give a white solid (a mixture of diamine, monoprotected and diprotected amine). The white solid was subjected to column chromatography (silica gel, 5:95 MeOH/ CHCl_3 and 1:10:89 NH_4OH /MeOH/ CHCl_3) to yield in order of elution the di- (**S9**) and mono- (**S8**) protected amines.

Selected data for (12-amino-dodecyl)-carbamic acid *tert*-butyl ester, S8: Yield 8.53 g (57%); m.p. 96 °C; ^1H NMR (400 MHz, CDCl_3): δ = 4.54 (brs, 1H, CONH), 3.09 (m, 2H, CONHCH_2), 2.67 (t, J = 6.8 Hz, 2H, CH_2NH_2), 1.43 (brs, 13H, CH_3 , *t*-butyl & CH_2 , alkyl), 1.38 (brs, 2H, NH_2), 1.25 (brs, 16H, CH_2 , alkyl); ^{13}C NMR (100 MHz, CDCl_3): δ = 157.64, 79.69, 42.24, 40.63, 33.86, 30.06, 29.60, 29.55, 29.53, 29.48, 29.28, 28.42, 26.88, 26.80; HRMS (FAB, THIOG matrix): m/z = 301.28491 $[(\text{M}+\text{H})^+]$ (anal. calcd for $\text{C}_{17}\text{H}_{37}\text{N}_2\text{O}_2$: m/z = 301.28550).



Selected data for (12-*tert*-butoxycarbonylamino-dodecyl)-carbamic acid *tert*-butyl ester, S9: Yield 3.7 g (43%); m.p. 115 °C; ^1H NMR (400 MHz, CDCl_3): δ = 4.51 (brs, 2H, CONH), 3.10 (m, 4H, CONHCH_2), 1.45 (brs, 13H, CH_3 , *t*-butyl & CH_2 , alkyl), 1.27 (m, 16H, CH_2 , alkyl); ^{13}C NMR (100 MHz, CDCl_3): δ = 157.62, 79.69, 40.63, 30.06, 29.51, 29.27, 28.43, 26.79, 20.60; HRMS (FAB, THIOG matrix): m/z = 401.33864 $[(\text{M}+\text{H})^+]$ (anal. calcd for $\text{C}_{22}\text{H}_{45}\text{N}_2\text{O}_4$: m/z = 401.33793).

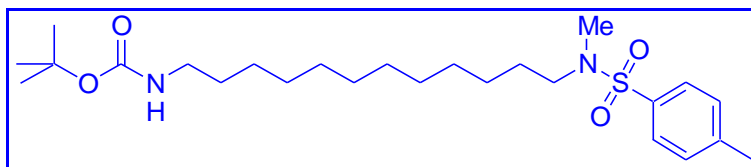
[12-(Toluene-4-sulfonylamino)-dodecyl]-carbamic acid *tert*-butyl ester, S10



To a stirred solution of (12-amino-dodecyl)-carbamic acid *tert*-butyl ester, **S8** (3.80 g, 12.6 mmol, 1 equiv.) and triethylamine (2.1 mL, 15.2 mmol, 1.2 equiv.) in 10 mL of CHCl_3 was added *p*-toluenesulfonyl chloride (2.70 g, 13.9 mmol, 1.1 equiv.) in 15 mL of THF over 10 minutes. The reaction mixture was stirred for 16 hours after which, 50 mL of CHCl_3 was added. The organic phase was washed with 1 M aqueous HCl (3 x 50 mL), saturated aqueous NaHCO_3 (3 x 50 mL), brine (50 mL), dried over anhydrous MgSO_4 and concentrated under reduced pressure to give a white solid. The white solid was found to contain both the product and unreacted *p*-toluenesulfonyl chloride, which was removed by washing with warm hexane (3 x 50 mL).

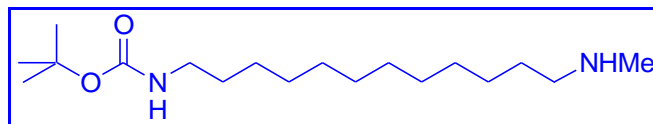
Selected data for [12-(toluene-4-sulfonylamino)-dodecyl]-carbamic acid *tert*-butyl ester, S10: Yield 5 g (88%); m.p. 98 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.75 (d, J = 8.1 Hz, 2H, ArH, phenyl), 7.30 (d, J = 8.1 Hz, 2H, ArH, phenyl), 4.57 (brs, 1H, NHSO_2), 4.52 (brs, 1H, CONH), 3.10 (m, 2H, CONHCH_2), 2.92 (q, J = 6.8 Hz, 2H, CH_2NHSO_2), 2.43 (s, 3H, ArCH_3), 1.44 (brs, 13H, $\text{CONHCH}_2\text{CH}_2$ & $\text{CH}_2\text{CH}_2\text{NHSO}_2$ & CH_3 , *t*-butyl), 1.28–1.20 (m, 16H, CH_2 , alkyl); ^{13}C NMR (100 MHz, CDCl_3): δ = 156.40, 143.60, 137.49, 130.03, 127.50, 79.69, 43.61, 41.02, 30.44, 29.91, 29.88, 29.86, 29.82, 29.78, 29.65, 29.43, 28.83, 27.17, 26.89, 21.90; HRMS (FAB, THIOG matrix): m/z = 455.29346 [(M+H) $^+$] (anal. calcd for $\text{C}_{24}\text{H}_{43}\text{N}_2\text{O}_4\text{S}$: m/z = 455.29436). Anal. calcd for $\text{C}_{24}\text{H}_{42}\text{N}_2\text{O}_4\text{S}$: C 63.40, H 9.31, N 6.16. Found C 63.25, H 9.44, N 5.85.

{12-[Methyl-(toluene-4-sulfonyl)-amino]-dodecyl}-carbamic acid *tert*-butyl ester, S11



To a solution of [12-(toluene-4-sulfonylamino)-dodecyl]-carbamic acid *tert*-butyl ester, **S10** (6.60 g, 14.5 mmol, 1 equiv.) in 85 mL of acetone was added methyl iodide (27 mL, 435 mmol, 30 equiv.) followed by addition of vacuum dried K₂CO₃ (21.1 g, 145 mmol, 10 equiv.). The resulting suspension was heated at 40 °C for 16 hours; TLC showed some unreacted **S10** remained. Additional methyl iodide (10.8 mL, 174 mmol, 12 equiv.) was added and stirred at 40 °C for a further 16 hours until completion. The suspension was filtered and concentrated under reduced pressure to give a viscous oil. This was dissolved in 100 mL of CHCl₃ and washed with water (50 mL), brine (2 x 50 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure to give a white solid.

Selected data for {12-[methyl-(toluene-4-sulfonyl)-amino]-dodecyl}-carbamic acid *tert*-butyl ester, **S11:** Yield 6.63 g (98%); m.p. 51 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.66 (d, *J* = 8.1 Hz, 2H, ArH, phenyl), 7.31 (d, *J* = 8.1 Hz, 2H, ArH, phenyl), 4.52 (brs, 1H, CONH), 3.10 (m, 2H, CONHCH₂), 2.96 (t, *J* = 7.1 Hz, 2H, CH₂NCH₃SO₂), 2.70 (s, 3H, ArCH₃), 2.48 (s, 3H, NCH₃), 1.52–1.44 (m, 13H, CONHCH₂CH₂ & CH₂CH₂NCH₃SO₂ & CH₃, *t*-butyl), 1.28–1.25 (m, 16H, CH₂, alkyl); ¹³C NMR (100 MHz, CDCl₃): δ = 155.99, 143.14, 134.55, 129.60, 127.41, 78.99, 50.11, 40.63, 34.55, 30.06, 29.71, 29.53, 29.51, 29.29, 29.22, 28.43, 27.59, 26.81, 26.51, 21.51; HRMS (FAB, THIOG matrix): *m/z* = 469.30959 [(M+H)⁺] (anal. calcd for C₂₅H₄₅N₂O₄S: *m/z* = 469.31001). Anal. calcd for C₂₅H₄₄N₂O₄S: C 64.04, H 9.46, N 5.98. Found C 64.18, H 9.44, N 5.85.

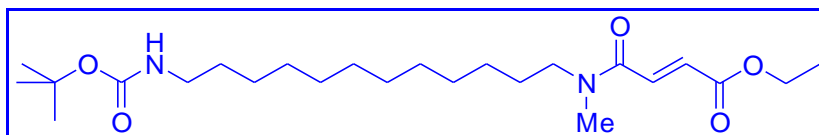
(12-Methylamino-dodecyl)-carbamic acid *tert*-butyl ester, S12

A sodium naphthalide solution [made from addition of sodium (1.30 g, 56.5 mmol, 5 equiv.) to a stirred solution of naphthalene (7.25 g, 56.5 mmol, 5 equiv.) in 300 mL of DME (freshly distilled over sodium and benzophenone) under a nitrogen atmosphere and stirred for 1 hour at room temperature after the solution had turned dark green] was added dropwise to a solution of {12-[methyl-(toluene-4-sulfonyl)-amino]-dodecyl}-carbamic acid *tert*-butyl ester, **S11** (5.30 g, 11.3 mmol, 1 equiv.) in 100 mL of anhydrous DME over 30 minutes under a nitrogen atmosphere at $-35\text{ }^{\circ}\text{C}$. The resulting dark green solution was stirred for a further 10 minutes at $-35\text{ }^{\circ}\text{C}$ until TLC indicated no starting compound remained. The reaction was quenched with water (10 mL) and concentrated under reduced pressure to give a colourless solid. The colourless solid was dissolved in CHCl_3 and filtered through a silica plug using petroleum ether (60/80) to remove the naphthalene. This was followed by 20:80 MeOH/ CHCl_3 washings which were combined, concentrated and purified using column chromatography (silica gel, 2:98 MeOH/ CHCl_3 followed by 0.5:5:94.5 NH_4OH /MeOH/ CHCl_3 as eluent) to give the desired product as a colorless solid.

Selected data for (12-methylamino-dodecyl)-carbamic acid *tert*-butyl ester, S12:

Yield 3.02 g (85%); m.p. $53\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ = 4.54 (brs, 1H, OCONH), 3.09 (m, 2H, OCONHCH₂), 2.55 (t, J = 7.3 Hz, 2H, CH₂NHCH₃), 2.42 (s, 3H, NHCH₃), 1.44 (brs, 14H, OCONHCH₂CH₂ & CH₂CH₂NHCH₃ & NHCH₃ & CH₃, *t*-butyl), 1.25 (m, 16H, CH₂, alkyl); ^{13}C NMR (100 MHz, CDCl_3): δ = 157.64, 78.94, 52.23, 40.62, 36.55, 30.05, 29.93, 29.56, 29.54, 29.53, 29.27, 28.42, 27.34, 26.79; HRMS (FAB, THIOG): m/z = 315.30068 [(M+H)⁺] (anal. calcd for $\text{C}_{18}\text{H}_{39}\text{N}_2\text{O}_2$: m/z = 315.30115). Anal. calcd for $\text{C}_{18}\text{H}_{38}\text{N}_2\text{O}_2$: C 68.74, H 12.18, N 8.91. Found C 68.75, H 12.17, N 8.80.

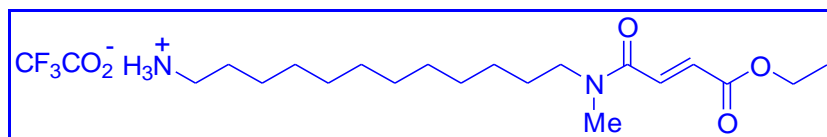
3-[(12-*tert*-Butoxycarbonylamino-dodecyl)-methyl-carbamoyl]-acrylic acid ethyl ester, S13



A solution of fumaric acid monoethyl ester (1.46 g, 10.1 mmol, 1 equiv.), (12-methylamino-dodecyl)-carbamic acid *tert*-butyl ester, **S12** (3.50 g, 11.1 mmol, 1.1 equiv.) and DMAP (1.24 g, 10.1 mmol, 1 equiv.) in 250 mL of CH₂Cl₂ was stirred at 0 °C for 10 minutes followed by addition of EDCI.HCl (1.94 g, 10.1 mmol, 1 equiv.). The reaction mixture was stirred for 16 hours at room temperature. The organic layer was washed with 1 M aqueous HCl (3 x 150 mL), saturated aqueous NaHCO₃ (3 x 150 mL), brine (150 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure to give a yellow oil. The yellow oil was subjected to column chromatography (silica gel, 40:60 hexane/EtOAc) to yield the product as a colourless oil.

Selected data for 3-[(12-*tert*-butoxycarbonylamino-dodecyl)-methyl-carbamoyl]-acrylic acid ethyl ester, S13: Yield 3.97 g (89%); ¹H NMR (400 MHz, CDCl₃): δ = 7.39 (d, *J* = 15.4 Hz) & 7.38 (d, *J* = 15.2 Hz)[(1H, CH=CH)], 6.80 (d, *J* = 15.2 Hz) & 6.78 (d, *J* = 15.4 Hz) [(2H, CH=CH)], 4.51 (brs, 1H, CONH), 4.26 (q, *J* = 7.1 Hz, 2H, CH₂CH₃), 3.44 & 3.37 (m, 2H, CH₂NCH₃), 3.11–3.02 (m, 5H, CONHCH₂ & NCH₃), 1.55 (m, 2H, CH₂, alkyl), 1.45 (brs, 13H, OCONHCH₂CH₂ & CH₂CH₂NCH₃ & CH₃, *t*-butyl), 1.34–1.26 (m, 16H, CH₂CH₃, CH₂, alkyl); ¹³C NMR (100 MHz, CDCl₃): δ = 165.85, 164.59, 164.33, 155.98, 134.15, 133.84, 131.03, 130.98, 78.95, 61.06, 60.37, 50.27, 48.17, 40.61, 35.57, 33.98, 30.04, 29.49, 29.34, 29.25, 28.94, 28.41, 27.02, 26.89, 26.82, 26.78, 26.53, 21.03, 14.15; HRMS (FAB, THIOG matrix): *m/z* = 441.33215 [(M+H)⁺] (anal. calcd for C₂₄H₄₅N₂O₅: *m/z* = 441.33285).

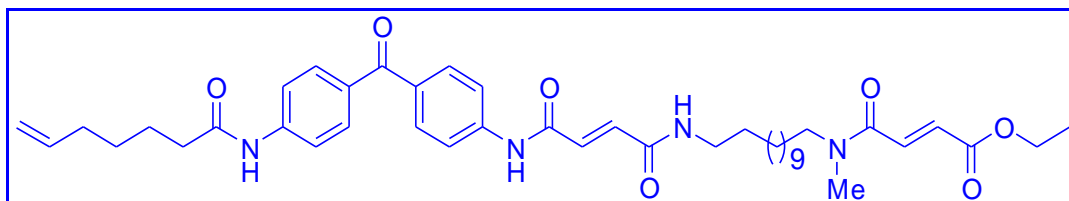
12-[(3-ethoxycarbonyl-acryloyl)-methyl-amino]-dodecyl-trifluoro-acetate salt, S14



To a stirred solution of 3-[(12-*tert*-butoxycarbonylamino-dodecyl)-methyl-carbamoyl]-acrylic acid ethyl ester, **S13** (1.70 g, 3.86 mmol, 1 equiv.) in 10 mL of CHCl_3 was added trifluoroacetic acid (20 mL, 38.6 mmol, 10 equiv.) and stirred at room temperature for 30 minutes until completion. The reaction mixture was concentrated under reduced pressure to give the product as a pale yellow oil.

Selected data for 12-[(3-ethoxycarbonyl-acryloyl)-methyl-amino]-dodecyl-trifluoro-acetate salt, S14: Yield 1.55 g (quantitative); ^1H NMR (400 MHz, CDCl_3): δ = 8.82 (brt, 3H, $\text{CF}_3\text{CO}_2^- \text{NH}_3^+$), 7.36 (2d, J = 15.4 Hz, 1H, $\text{CH}=\text{CH}$), 6.74 (2d, J = 15.4 Hz, 1H, $\text{CH}=\text{CH}$), 4.26 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.43 (m, 2H, CH_2NCH_3), 3.13–3.05 (m, 5H, H_2^+NCH_2 & NCH_3), 1.68–1.57 (m, 4H, CH_2 , alkyl), 1.32 (t, J = 7.1, 3H, CH_2CH_3), 1.26 (brs, 16H, CH_2 , alkyl); ^{13}C NMR (100 MHz, CDCl_3): δ = 166.28, 166.17, 165.93, 160.35 (q, CF_3), 133.21, 132.80, 132.24, 132.08, 61.91, 61.39, 50.97, 49.03, 40.88, 36.12, 34.69, 29.11, 29.07, 29.04, 29.02, 28.93, 28.81, 28.62, 28.54, 28.48, 27.56, 27.26, 27.23, 26.64, 26.47, 26.25, 25.89, 25.82, 13.91.

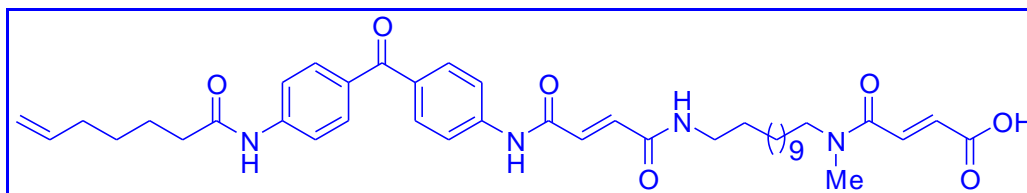
3-[(12-{3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acrylic acid ethyl ester, S15



To a stirred solution of 12-[(3-ethoxycarbonyl-acryloyl)-methyl-amino]-dodecyl-trifluoroacetate salt, **S14** (2.63 g, 5.80 mmol, 1.3 equiv) in 35 mL of CHCl_3 was added an excess of triethylamine (4 mL) until pH 10. This was followed by addition of a slight suspension of 3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acrylic acid, **S7** (2.00 g, 4.46 mmol, 1 equiv.) in 25 mL of THF to obtain a dark brown solution; a further 0.5 mL of triethylamine was added to maintain a basic pH. To the resulting reaction mixture was added BOP (2.96 g, 6.69 mmol, 1.5 equiv.) and stirred at room temperature for 1 hour. Concentration under reduced pressure gave a brown oil which was subjected to column chromatography (silica gel, 2:98 MeOH/ CHCl_3) to give the product as a yellow solid.

Selected data for 3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acrylic acid ethyl ester, S15: Yield 2.46 g (69%); m.p. 234 °C; ^1H NMR (600 MHz, $\text{DMSO-}d_6$): δ = 10.79 (brs, 1H, ArNHCO), 10.27 (brs, 1H, ArNHCO), 8.50 (brt, 1H, CONH), 7.87–7.71 (m, 8H, ArH, benzophenone), 7.41 (d, J = 15.4 Hz, 1H, $\text{NCH}_3\text{COCH}=\text{CHCO}_2$), 7.10 & 7.03 (d, J = 15.1 Hz, 2H, $\text{NHCOCH}=\text{CHCONH}$), 6.55 (2d, J = 15.4 Hz, 1H, $\text{NCH}_3\text{COCH}=\text{CHCO}_2$), 5.83 (m, 1H, $\text{CH}_2=\text{CH}$), 5.01 (m, 2H, $\text{CH}_2=\text{CH}$), 4.20 (q, J = 7.10 Hz, 2H, CH_2CH_3), 3.18 (m, 2H, $\text{CH}=\text{CHCONHCH}_2$), 3.05 & 2.90 (s, 3H, NCH_3), 2.39 (t, J = 7.4 Hz, 2H, CH_2CONHAr), 2.08 (q, J = 7.2 Hz, $\text{CH}_2=\text{CHCH}_2$), 1.64 (m, 2H, $\text{CH}_2\text{CH}_2\text{CONHAr}$), 1.46 (m, 6H, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & CH_2NCH_3 & CH_2 , alkyl), 1.25 (m, 19H, CH_2CH_3 , CH_2 , alkyl); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 193.33, 171.82, 165.06, 163.82, 163.54, 163.16, 162.76, 143.13, 142.43, 138.51, 135.13, 134.74, 134.63, 132.51, 132.41, 132.22, 132.06, 131.53, 130.89, 129.50, 129.43, 118.60, 118.13, 114.86, 60.66, 49.06, 47.08, 36.27, 35.01, 33.36, 32.90, 28.92, 28.80, 28.70, 28.65, 28.52, 28.18, 27.79, 26.36, 26.16, 25.76, 24.45, 13.98; HRMS (FAB, THIOG matrix): m/z = 743.44061 [(M+H) $^+$] (anal. calcd for $\text{C}_{43}\text{H}_{59}\text{N}_4\text{O}_7$: m/z = 743.43838). Anal. calcd for $\text{C}_{43}\text{H}_{58}\text{N}_4\text{O}_7$: C 69.52, H 7.87, N 7.54. Found C 69.14, H 7.80, N 7.33.

3-[(12-{3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acrylic acid, S16

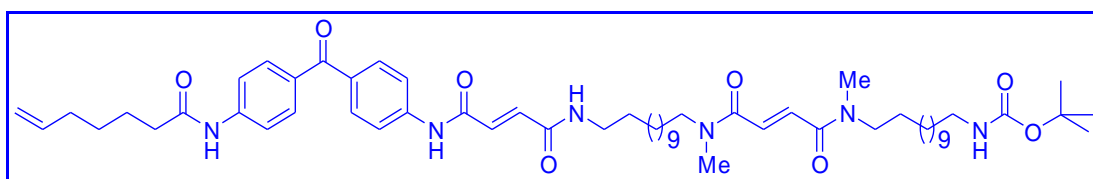


To 3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acrylic acid ethyl ester, **S15** (1.50 g, 2.02 mmol, 1 equiv.) was added 60 mL of THF and 10 mL MeOH, which resulted in the formation of a yellow viscous solution. This was followed by addition of 1 M aqueous NaOH (0.10 g in 2.5 mL H₂O, 2.42 mmol, 1.2 equiv.), after 5 minutes, a brown solution was obtained that was left to stir at room temperature for 16 hours. Water was added to the reaction mixture followed by dropwise addition of concentrated HCl until pH 1. The reaction mixture extracted with 1:5 THF/CHCl₃ (3 x 80 mL), combined, dried over anhydrous MgSO₄ and concentrated under reduced pressure to give the acid as a yellow solid.

Selected data for 3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acrylic acid, S16: Yield 1.44 g (quantitative); m.p. 242 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.80 (brs, 1H, ArNHCO), 10.28 (brs, 1H, ArNHCO), 8.51 (brt, 1H, CONH), 7.87–7.72 (m, 8H, ArH, benzophenone), 7.35 (d, *J* = 15.4 Hz, 1H, NCH₃COCH=CHCO₂), 7.10 & 7.03 (d, *J* = 15.2 Hz, 2H, NHCOCH=CHCONH), 6.50 (2d, *J* = 15.4 Hz, 1H, NCH₃COCH=CHCO₂), 5.83 (m, 1H, CH₂=CH), 5.02 (m, 2H, CH₂=CH), 3.18 (q, *J* = 6.8 Hz, 2H, CH=CHCONHCH₂), 3.05 & 2.90 (s, 3H, NCH₃), 2.39 (t, *J* = 7.6 Hz, 2H, CH₂CONHAr), 2.08 (q, *J* = 7.1 Hz, CH₂=CHCH₂), 1.63 (m, 2H, CH₂CH₂CONHAr), 1.46 (m, 6H, CH₂=CHCH₂CH₂ & CH₂NCH₃ & CH₂, alkyl), 1.26 (m, 19H, CH₂CH₃, CH₂, alkyl); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 193.31, 171.79, 166.45, 163.59, 163.14, 162.76, 143.15, 142.43, 138.52, 134.63, 134.48, 134.05, 132.41, 132.22,

131.45, 130.94, 130.90, 130.80, 130.70, 118.59, 118.12, 114.86, 49.10, 47.08, 36.27, 34.99, 33.40, 32.91, 28.94, 28.81, 28.67, 28.29, 27.80, 26.38, 26.20, 25.84, 24.45; HRMS (FAB, THIOG matrix): $m/z = 715.40873$ [(M+H)⁺] (anal. calcd for C₄₁H₅₅N₄O₇: $m/z = 715.40708$).

[12-({3-[(12-{3-[4-(4-Hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid *tert*-butyl ester, S17

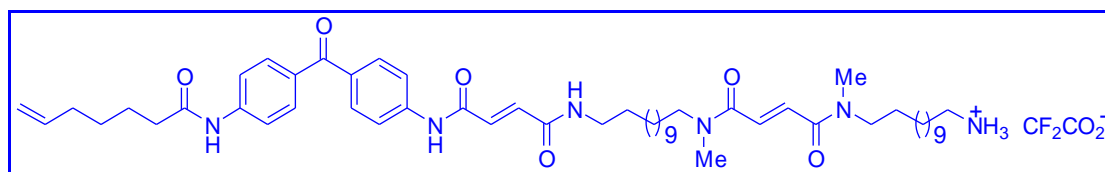


To a stirred solution of (12-methylamino-dodecyl)-carbamic acid *tert*-butyl ester, **S12** (0.85 g, 2.69 mmol, 1.3 equiv) in 30 mL of CHCl₃ was added a slight suspension of 3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acrylic acid **S16** (1.48 g, 2.07 mmol, 1 equiv.) in 35 mL of THF to give an orange suspension. Triethylamine (1 mL) was added until pH 10 followed by BOP (1.37 g, 3.11 mmol, 1.5 equiv.). The resulting suspension was stirred at room temperature for 10 minutes, after which, an orange solution was obtained which was stirred for a further 90 minutes. Concentration under reduced pressure gave a yellow oil which was subjected to column chromatography (silica gel, 3:97 MeOH/CHCl₃) to give the product as a pale yellow solid.

Selected data for [12-({3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid *tert*-butyl ester, **S17:** Yield 1.54 g (74%); m.p. 204 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.78 (brs, 1H, ArNHCO), 10.26 (brs, 1H, CONHAr), 8.49 (brt, 1H, CH=CHCONH), 7.87–7.71 (m, 8H, ArH, benzophenone), 7.20 (m, 2H, NCH₃COCH=CHCONCH₃), 7.10 & 7.03 (d, *J* = 15.1 Hz, 2H, NHCOCH=CHCONH), 6.74 (brt, 1H, NHCO₂), 5.83 (m, 1H, CH₂=CH), 5.01 (m, 2H, CH₂=CH), 3.38 (m, 2H, CH₂, alkyl), 3.19 (m, 2H, CH=CHCONHCH₂), 3.04 (brs, 2H,

NCH₃), 2.90 (m, 6H, NCH₃ & CH₂NHCO₂), 2.39 (t, *J* = 7.3 Hz, 2H, CH₂CONHAr), 2.08 (q, *J* = 7.1 Hz, CH₂=CHCH₂), 1.64 (m, 2H, CH₂CH₂CONHAr), 1.46 (m, 8H, CH₂=CHCH₂CH₂ & CH₂NCH₃ & CH₂, alkyl), 1.38 (s, 9H, NHCO₂C(CH₃)₃), 1.24 (m, 38H, CH₂, alkyl); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 193.29, 171.77, 164.42, 164.14, 163.16, 162.77, 157.69, 143.15, 142.44, 138.51, 134.64, 132.43, 132.21, 131.48, 131.09, 131.04, 130.90, 130.86, 130.74, 130.70, 118.59, 118.13, 114.03, 77.19, 49.12, 47.05, 36.28, 34.99, 33.37, 32.90, 29.42, 28.93, 28.82, 28.74, 28.67, 28.38, 28.21, 27.81, 26.51, 26.38, 26.21, 25.91, 24.45; HRMS (FAB, THIOG matrix): *m/z* = 1011.69013 [(M+H)⁺] (anal. calcd for C₅₉H₉₁N₆O₈: *m/z* = 1011.68984).

[12-({3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid *tert*-butyl ester-trifluoro-acetate salt, **S18**

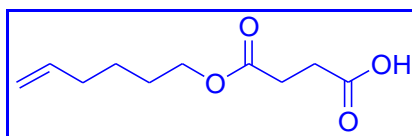


To a stirred suspension of [12-({3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid *tert*-butyl ester, **S17** (1.45 g, 1.43 mmol, 1 equiv.) in 10 mL of CHCl₃ was added trifluoroacetic acid (5 mL, excess) and the resulting yellow solution was stirred at room temperature for 30 minutes until completion. The reaction mixture was concentrated under reduced pressure to give a yellow oil that was titrated with Et₂O to give a pale yellow solid.

Selected data for [12-({3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid *tert*-butyl ester, **S18:** Yield 1.4 g (95%); m.p. 195 °C; ¹H NMR (400 MHz, CDCl₃): δ = 10.81 (brs, 1H, ArNHCO), 10.30 (brs, 1H, ArNHCO), 8.52 (brt, *J* = 5.6 Hz, 1H, CONH), 7.87–7.71 (m, 8H, ArH, benzophenone), 7.68 (brs, 3H, CH₂NH₃), 7.20 (m, 2H, NCH₃COCH=CHCONCH₃), 7.10 & 7.03 (d, *J* = 15.6 Hz, 2H, NHCOCH=CHCONH), 5.83 (m, 1H, CH₂=CH), 5.01 (m, 2H, CH₂=CH),

3.36 (m, 2H, $\underline{\text{CH}}_2$, alkyl), 3.18 (m, 2H, CONHCH_2), 3.05 & 2.90 (s, 6H, NCH_3), 2.77 (m, 2H, $\underline{\text{CH}}_2\text{NH}_3$), 2.39 (t, $J = 7.3$ Hz, 2H, $\underline{\text{CH}}_2\text{CONHAr}$), 2.07 (q, $J = 7.1$ Hz, $\text{CH}_2=\text{CHCH}_2$), 1.63 (m, 2H, $\underline{\text{CH}}_2\text{CH}_2\text{CONHAr}$), 1.46 (m, 10H, $\text{CH}_2=\text{CHCH}_2\underline{\text{CH}}_2$ & $\underline{\text{CH}}_2\text{CH}_2\text{NCH}_3$ & $\text{CONHCH}_2\underline{\text{CH}}_2$, & CH_2 , alkyl), 1.25 (m, 34H, $\text{CH}_2\underline{\text{CH}}_3$, CH_2 , alkyl); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 193.30, 171.80, 164.36, 164.13, 163.15, 162.76, 143.16, 142.44, 138.51, 134.63, 132.41, 132.22, 131.44, 131.09, 131.03, 130.93, 130.89, 130.74, 130.68, 118.58, 118.12, 114.85, 49.11, 47.06, 36.27, 34.97, 33.41, 32.91, 28.94, 28.87, 28.81, 28.67, 28.48, 28.39, 27.80, 26.94, 26.51, 26.37, 26.22, 25.91, 25.72, 24.45$; HRMS (FAB, THIOG matrix): $m/z = 1046.60148$ [$\text{M}+\text{Na}$] $^+$ (anal. calcd for $\text{C}_{56}\text{H}_{82}\text{F}_3\text{N}_6\text{O}_8\text{Na}$: $m/z = 1046.60442$).

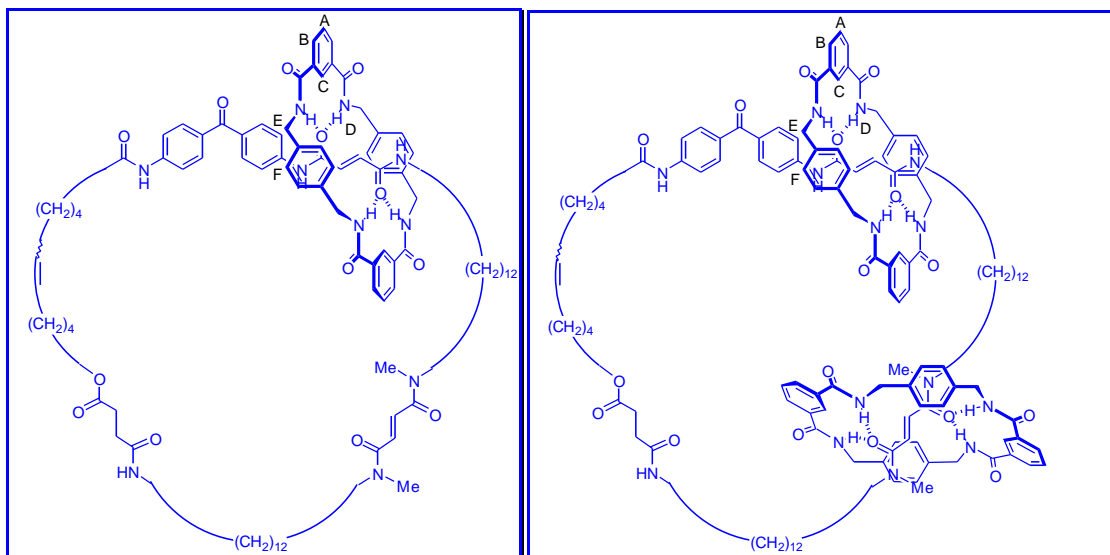
Succinic acid monohex-5-enyl ester, **S19**



To a solution of succinic anhydride (2.00 g, 20.0 mmol, 1 equiv.) in 90 mL of CH_2Cl_2 was added triethylamine (4.2 mL, 30.0 mmol, 1.5 equiv.) followed by 5-hexen-1-ol (2.4 mL, 20.0 mmol, 1 equiv.) and stirred at room temperature for 16 hours. The resulting solution mixture was washed with 1 M aqueous HCl (3 x 50 mL), brine (50 mL), dried with anhydrous MgSO_4 and concentrated under reduced pressure to give the product as a colourless oil.

Selected data for succinic acid monohex-5-enyl ester, S19: Yield 3.92 g (98%); ^1H NMR (400 MHz, CDCl_3): $\delta = 5.80$ (m, 1H, $\text{CH}_2=\underline{\text{CH}}$), 5.00 (m, 2H, $\underline{\text{CH}}_2=\text{CH}$), 4.12 (t, $J = 6.6$ Hz, 2H, $\underline{\text{CH}}_2\text{OCO}$), 2.69 (t, $J = 6.6$ Hz, 2H, OCOCH_2 or $\underline{\text{CH}}_2\text{CO}_2\text{H}$), 2.64 (t, $J = 6.6$ Hz, 2H, OCOCH_2 or $\underline{\text{CH}}_2\text{CO}_2\text{H}$), 2.09 (m, 2H, $\text{CH}_2=\text{CHCH}_2$), 1.66 (m, 2H, $\underline{\text{CH}}_2\text{CH}_2\text{OCO}$), 1.46 (m, 2H, $\text{CH}_2=\text{CHCH}_2\underline{\text{CH}}_2$); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 177.13, 172.15, 138.29, 114.83, 64.80, 33.22, 28.90, 28.80, 27.98, 25.12$; HRMS (FAB, NBA matrix): $m/z = 201.11250$ [$\text{M}+\text{H}$] $^+$ (anal. calcd for $\text{C}_{10}\text{H}_{17}\text{O}_4$: $m/z = 201.11268$).

(ii) Preparation of each diastereomer of 1-3.

[2]catenane, *E,E*-1 and [3]catenane, *E,E*-3

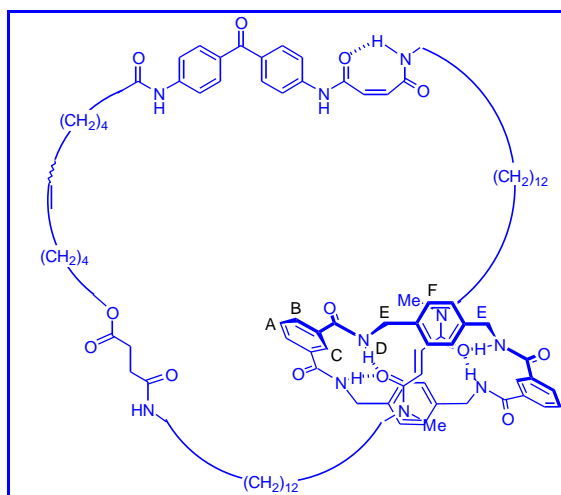
Macrocyclic *E,E*-2 (0.15 g, 0.14 mmol, 1 equiv.) and triethylamine (1.2 mL, 8.4 mmol, 60 equiv.) in 10 mL of CHCl_3 (stabilised with amylenes) was vigorously stirred whilst solutions of *para*-xylylene diamine (0.23 g, 1.7 mmol, 12 equiv.) in 15 mL of CHCl_3 and isophthaloyl dichloride (0.33 g, 1.6 mmol, 11.5 equiv.) in 15 mL of CHCl_3 were simultaneously added over a period of 2 hours using motor-driven syringe pumps. The resulting suspension was filtered and concentrated under reduced pressure and subjected to column chromatography (silica gel, first column 4:96 $\text{CHCl}_3/\text{MeOH}$ as eluent, second column 3:97 $\text{MeOH}/\text{CHCl}_3$ as eluent) to yield, in order of elution, the macrocycle, *E,E*-2, [2]catenane, *E,E*-1 and [3]catenane, *E,E*-3.

Selected data for the [2]catenane, *E,E*-1: Yield 63 mg (50%); ^1H NMR (600 MHz, CD_2Cl_2): δ = 8.86–8.81 (brs, 2H, ArH_C), 8.31–8.25 (m, 4H, ArH_B), 7.87–7.68 (m, 12H, NH_D & ArH , benzophenone), 7.65 (brt, 2H, ArH_A), 7.38–7.16 (m, 2H, NCH_3 - $\text{COCH}=\text{CHCONCH}_3$), 7.07–7.04 (brs, 8H, ArH_F), 6.07–6.01 (m, 2H, $\text{NHCOCH}=\text{CHCONH}$), 5.42 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 5.20–5.10 (m, 4H, CH_E), 4.06 (m, 2H, CH_2CO_2), 3.95–3.80 (m, 4H, CH_E), 3.43–3.02 (m, 6H, 2 x CH_2NCH_3 &

CH_2NHCO), 3.00–2.93 (s, 6H, NCH_3), 2.74 (m, 2H, $\text{CH}=\text{CHCONHCH}_2$), 2.62 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 2.45 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 2.41 (t, $J = 7.5$ Hz, 2H, CH_2CONHAr), 2.04 (m, 4H, 2 x $\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.72 (m, 2H, $\text{CH}_2\text{CH}_2\text{CONHAr}$), 1.56–0.64 (m, 46H, $\text{CO}_2\text{CH}_2\text{CH}_2$ & 2 x $\text{CH}_2\text{CH}_2\text{NCH}_3$ & $\text{CH}_2\text{CH}_2\text{NHCO}$ & $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$ & $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & $\text{CH}=\text{CHCONHCH}_2\text{CH}_2$ & CH_2 , alkyl); HRMS (FAB, NBA matrix): $m/z = 1597.91870$ [(M+H)⁺] (anal. calcd for $\text{C}_{94}\text{H}_{121}\text{N}_{10}\text{O}_{13}$: $m/z = 1597.91146$).

Selected data for [3]catenane *E,E*-3: Yield 63 mg (21%); ¹H NMR (600 MHz, CD_2Cl_2): $\delta = 8.78$ (m, 2H, CONH), 8.36–8.04 (m, 12H, ArH_B & ArH_C), 7.86–7.51 (m, 20H, NH_D & ArH , benzophenone & ArH_A), 7.20–7.01 (brs, 16H, ArH_F), 6.19 (m, 2H, $\text{NCH}_3\text{COCH}=\text{CHCONCH}_3$), 6.00 (m, 2H, $\text{NHCOCH}=\text{CHCONH}$), 5.40 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 5.14–4.98 (m, 8H, CH_E), 4.03 (m, 2H, CH_2CO_2), 3.95–3.74 (m, 8H, CH_E), 3.40–3.00 (m, 6H, 2 x CH_2NCH_3 & CH_2NHCO), 2.97–2.68 (m, 8H, NCH_3 , $\text{CH}=\text{CHCONHCH}_2$), 2.61 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 2.39 (m, 4H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$ & CH_2CONHAr), 2.02 (m, 4H, 2 x $\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.69–0.63 (m, 48H, $\text{CH}_2\text{CH}_2\text{CONHAr}$ & $\text{CO}_2\text{CH}_2\text{CH}_2$ & 2 x $\text{CH}_2\text{CH}_2\text{NCH}_3$ & $\text{CH}_2\text{CH}_2\text{NHCO}$ & $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$ & $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & $\text{CH}=\text{CHCONHCH}_2\text{CH}_2$ & CH_2 , alkyl); MS (FAB, NBA matrix): $m/z = 2131$ [(M+H)⁺].

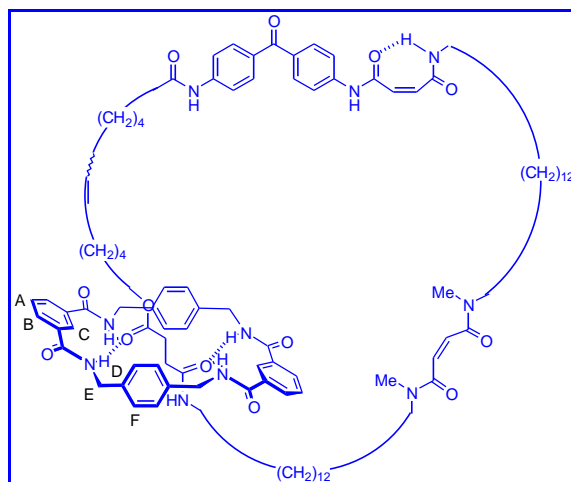
[2]catenane, *Z,E*-1



A 1×10^{-3} M solution of catenane *E,E*-**1** (7 mg) in CH_2Cl_2 (4.5 mL) was placed in a quartz vessel and directly irradiated at 350 nm using a multilamp photoreactor (model MLU18 manufactured by Photochemical Reactors Ltd, UK). The progress of the reaction was monitored by ^1H NMR spectroscopy and the photostationary state reached after 5 minutes irradiation. The reaction mixture (containing a mixture of *E,E*-**1** and *Z,E*-**1**) was concentrated under reduced pressure and subjected to column chromatography (silica gel, 3:97 MeOH/ CHCl_3) to obtain the pure *Z,E*-isomer.

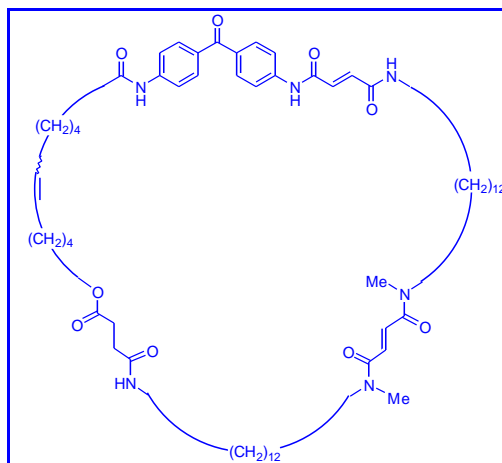
Selected data for [2]catenane *Z,E*-1**:** Yield 4.6 mg (66%); ^1H NMR (600 MHz, $\text{CD}_2\text{Cl}_2/1\%$ MeOD): $\delta = 8.82\text{--}8.74$ (brs, 2H, ArH_C), $8.26\text{--}8.21$ (m, 4H, ArH_B), $7.84\text{--}7.72$ (m, 12H, NH_D & ArH , benzophenone), 7.65 (m, 2H, ArH_A), $7.04\text{--}7.01$ (brs, 8H, ArH_F), $6.34\text{--}6.19$ (m, 2H, $\text{NCH}_3\text{COCH}=\text{CHCONCH}_3$), $6.09\text{--}5.96$ (m, 2H, $\text{NHCOCH}=\text{CHCONH}$), 5.41 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 5.12 (m, 4H, CH_E), 4.04 (m, 2H, CH_2CO_2), 3.78 (m, 4H, CH_E), $3.43\text{--}3.12$ (m, 8H, $2 \times \text{CH}_2\text{NCH}_3$ & CH_2NHCO & $\text{CH}=\text{CHCONHCH}_2$), $2.98\text{--}2.92$ & 2.72 & 2.68 (s, 6H, NCH_3), 2.60 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 2.41 (m, 4H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$ & CH_2CONHAr), 2.04 (m, 4H, $2 \times \text{CH}_2\text{CH}=\text{CHCH}_2$), 1.71 (m, 2H, $\text{CH}_2\text{CH}_2\text{CONHAr}$), $1.62\text{--}0.66$ (m, 46H, $\text{CO}_2\text{CH}_2\text{CH}_2$ & $2 \times \text{CH}_2\text{CH}_2\text{NCH}_3$ & $\text{CH}_2\text{CH}_2\text{NHCO}$ & $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$ & $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & $\text{CH}=\text{CHCONHCH}_2\text{CH}_2$ & CH_2 , alkyl); HRMS (FAB, NBA matrix): $m/z = 1597.91118$ $[(\text{M}+\text{H})^+]$ (anal. calcd for $\text{C}_{94}\text{H}_{121}\text{N}_{10}\text{O}_{13}$: $m/z = 1597.91146$).

[2]catenane, *Z,Z*-1****



A 1×10^{-3} M solution of catenane, *Z,E*-1 (16 mg) in CH_2Cl_2 (10 mL) was placed in a quartz vessel and directly irradiated at 254 nm using a multilamp photoreactor (model MLU18 manufactured by Photochemical Reactors Ltd, UK). The progress of the reaction was monitored by ^1H NMR spectroscopy and the photostationary state was reached after 20 minutes of irradiation. The reaction mixture (containing a mixture of *E,E*-1, *Z,E*-1, *E,Z*-1 and *Z,Z*-1) was concentrated under reduced pressure and subjected to column chromatography (silica gel, 3:97 MeOH/ CHCl_3 to 4:96 MeOH/ CHCl_3) to obtain pure *Z,Z*-1.

Selected data for [2]catenane *Z,Z*-1: Yield 5 mg (33%, ^1H NMR and HPLC of the crude reaction mixture indicates 48% *Z,Z*-1 present); ^1H NMR (600 MHz, CD_2Cl_2 /1% MeOD): δ = 8.31 (brm, 2H, ArH_C), 8.12 (m, 4H, ArH_B), 7.78–7.69 (m, 12H, NH_D & ArH, benzophenone), 7.59 (m, 2H, ArH_A), 7.18 & 7.17 (brs, 8H, ArH_F), 6.33 (brs, 2H, $\text{NCH}_3\text{COCH}=\text{CHCONCH}_3$), 6.21 (m, 2H, $\text{NHCOCH}=\text{CHCONH}$), 5.29 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 4.50 (m, 8H, CH_E), 3.87 (m, 2H, CH_2CO_2), 3.31–3.22 (m, 6H, 2 x CH_2NCH_3 & CH_2NHCO), 2.95 & 2.94 & 2.88 & 2.87 & 2.86 (s, 8H, NCH_3 & $\text{CH}=\text{CHCONHCH}_2$), 2.16 (m, 2H, CH_2CONHAr), 1.93–1.85 (m, 4H, 2 x $\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.77 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 1.52–1.23 (m, 50H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$ & $\text{CH}_2\text{CH}_2\text{CONHAr}$ & $\text{CO}_2\text{CH}_2\text{CH}_2$ & 2 x $\text{CH}_2\text{CH}_2\text{NCH}_3$ & $\text{CH}_2\text{CH}_2\text{NHCO}$ & $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$ & $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & $\text{CH}=\text{CHCONHCH}_2\text{CH}_2$ & CH_2 , alkyl); HRMS (FAB, NBA matrix): m/z = 1597.92985 [$(\text{M}+\text{H})^+$] (anal. calcd for $\text{C}_{94}\text{H}_{121}\text{N}_{10}\text{O}_{13}$: m/z = 1597.91146).

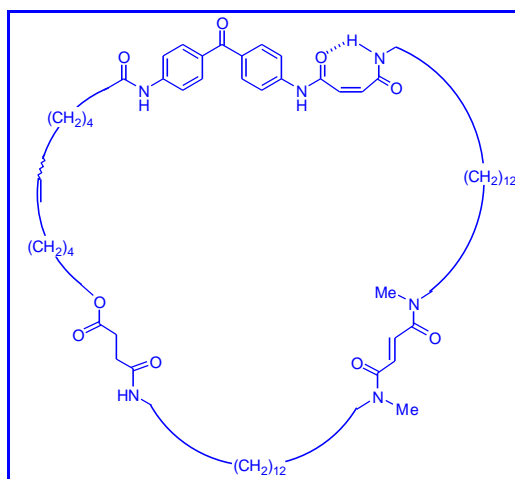
macrocycle, E,E-2

To a solution of 0.5 mM [12-({3-[(12-{3-[4-(4-hept-6-enoylamino-benzoyl)-phenylcarbamoyl]-acryloylamino}-dodecyl)-methyl-carbamoyl]-acryloyl}-methyl-amino)-dodecyl]-carbamic acid hex-5-enyl ester, **S1** (0.50 g, 0.46 mmol, 1 equiv.) in 50 mL of anhydrous THF and 900 mL of anhydrous CH₂Cl₂ was added Grubbs's catalyst (0.19 g, 0.23 mmol, 0.5 equiv.) and stirred under a nitrogen atmosphere. The pink reaction mixture was stirred for 16 hours at room temperature. The resulting brown solution was concentrated under reduced pressure and subjected to column chromatography (silica gel, 3:97 MeOH/CHCl₃) to give the product as an off-white solid.

Selected data for macrocycle *E,E-2*: Yield 0.29 g (59%); ¹H NMR (600 MHz, CD₂Cl₂/1% MeOD): δ = 10.32 (brs, 1H, ArNHCO), 9.11 (brs, 1H, ArNHCO), 7.82–7.70 (m, 10H, CH=CHCONH & NHCOCH₂ & ArH, benzophenone), 7.30 (m, 2H, NCH₃COCH=CHCONCH₃), 6.97 (m, 2H, NHCOCH=CHCONH), 6.55 (brm, 1H, NHCO), 5.41 (m, 2H, CH₂CH=CHCH₂), 4.04 (t, *J* = 6.6 Hz, 2H, CH₂CO₂), 3.44–3.28 (m, 4H, 2 x CH₂NCH₃ & CH₂NHCO), 3.13 (m, 2H, CH=CHCONHCH₂), 3.08 & 2.97 (s, 6H, NCH₃), 2.60 (m, 2H, NHCOCH₂CH₂CO₂), 2.42 (m, 2H, NHCOCH₂CH₂CO₂), 2.39 (t, *J* = 7.5 Hz, 2H, CH₂CONHAr), 2.04 (m, 4H, 2 x CH₂CH=CHCH₂), 1.70 (m, 2H, CH₂CH₂CONHAr), 1.55 (m, 8H, CO₂CH₂CH₂ & 2 x CH₂CH₂NCH₃ &

$\text{CH}_2\text{CH}_2\text{NHCO}$), 1.43 (m, 6H, $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$ & $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & $\text{CH}=\text{CHCONHCH}_2\text{CH}_2$), 1.34–1.21 (m, 32H, CH_2 , alkyl); HRMS (FAB, NBA matrix): $m/z = 1065.70618$ $[(\text{M}+\text{H})^+]$ (anal. calcd for $\text{C}_{62}\text{H}_{93}\text{N}_6\text{O}_9$: $m/z = 1065.70040$).

macrocycle, Z,E-2

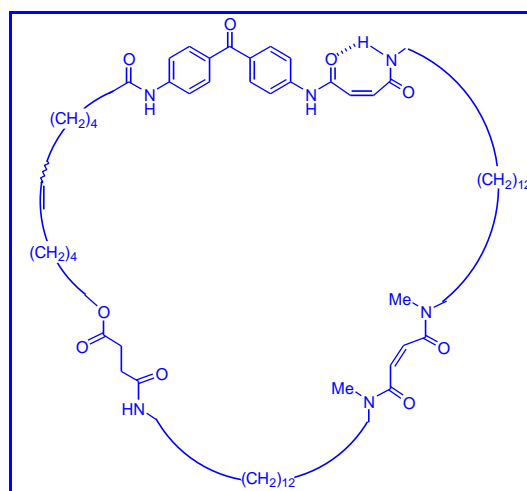


A 1×10^{-3} M solution of three-station macrocycle, *E,E-4* (10 mg) in CH_2Cl_2 (9 mL) was placed in a quartz vessel and directly irradiated at 350 nm using a multilamp photoreactor (model MLU18 manufactured by Photochemical Reactors Ltd, UK). The progress of the reaction was monitored by ^1H NMR spectroscopy and the photostationary state was reached after 5 minutes of irradiation. The reaction mixture (containing a mixture of *E,E-2* and *Z,E-2*) was concentrated under reduced pressure and subjected to column chromatography (silica gel, 3:97 MeOH/ CHCl_3) to obtain the pure *Z,E*-isomer.

Selected data for macrocycle *Z,E-2*: Yield 6.7 mg (67%); ^1H NMR (600 MHz, $\text{CD}_2\text{Cl}_2/1\%$ MeOD): $\delta = 7.81\text{--}7.71$ (m, 10H, $\text{CH}=\text{CHCONH}$ & NHCOCH_2 & ArH, benzophenone), 7.30 (m, 2H, $\text{NCH}_3\text{COCH}=\text{CHCONCH}_3$), 6.23 (s, 2H, $\text{NHCOCH}=\text{CHCONH}$), 5.41 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 4.05 (t, $J = 6.6$ Hz, 2H, CH_2CO_2), 3.43–3.31 (s, 6H, 2 x CH_2NCH_3 & CH_2NHCO), 3.15 (m, $\text{CH}=\text{CHCONHCH}_2$), 3.08 & 2.96 (s, 6H, NCH_3), 2.60 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 2.42 (m, 2H, $\text{NHCOCH}_2\text{CH}_2\text{CO}_2$), 2.38 (brt, 2H, CH_2CONHAr), 2.04 (m, 4H, 2 x

$\text{CH}_2\text{CH}=\text{CHCH}_2$), 1.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{CONHAr}$), 1.56 (m, 8H, $\text{CO}_2\text{CH}_2\text{CH}_2$ & 2 x $\text{CH}_2\text{CH}_2\text{NCH}_3$ & $\text{CH}_2\text{CH}_2\text{NHCO}$), 1.42 (m, 6H, $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_2$ & $\text{CH}_2=\text{CHCH}_2\text{CH}_2$ & $\text{CH}=\text{CHCONHCH}_2\text{CH}_2$), 1.24 (m, 32H, CH_2 , alkyl); HRMS (FAB, NBA matrix): $m/z = 1065.70091$ $[(\text{M}+\text{H})^+]$ (anal. calcd for $\text{C}_{62}\text{H}_{93}\text{N}_6\text{O}_9$: $m/z = 1065.70040$).

macrocycle, Z,Z-2

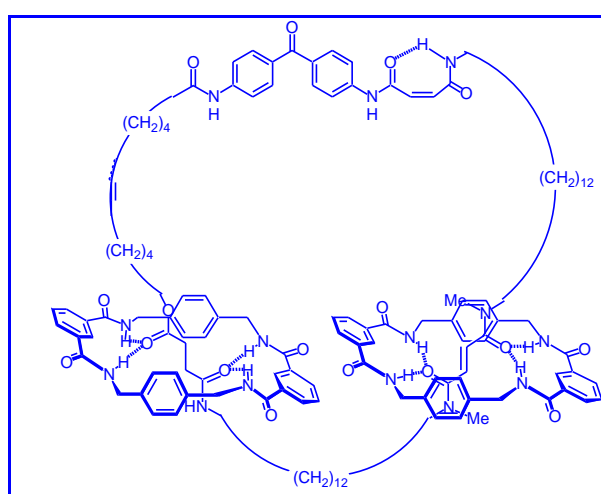


A 1×10^{-3} M solution of three-station macrocycle, *Z,E-2* (10 mg) in CH_2Cl_2 (9 mL) was placed in a quartz vessel and directly irradiated at 254 nm using a multilamp photoreactor (model MLU18 manufactured by Photochemical Reactors Ltd, UK). The progress of the reaction was monitored by ^1H NMR spectroscopy and the photostationary state was reached after 20 minutes of irradiation. The reaction mixture (containing a mixture of *E,E-2*, *Z,E-2*, *E,Z-2* and *Z,Z-2*) was concentrated under reduced pressure and subjected to column chromatography (silica gel, 3:97 MeOH/ CHCl_3) to obtain the pure *Z,Z*-isomer.

Selected data for macrocycle *Z,Z-2*: Yield 3.3 mg (33%, ^1H NMR and HPLC of the crude reaction mixture indicates 51% *Z,Z-2* present); ^1H NMR (600 MHz, $\text{CD}_2\text{Cl}_2/1\%$ MeOD): $\delta = 7.81\text{--}7.71$ (m, 8H, ArH, benzophenone), 6.35 (m, 2H, $\text{NCH}_3\text{COCH}=\text{CHCONCH}_3$), 6.24 (m, 2H, $\text{NHCOCH}=\text{CHCONH}$), 5.42 (m, 2H, $\text{CH}_2\text{CH}=\text{CHCH}_2$), 4.06 (m, 2H, CH_2CO_2), 3.33–3.15 (m, 8H, 2 x CH_2NCH_3 & CH_2NHCO & $\text{CH}=\text{CHCONHCH}_2$), 2.98–2.87 (s, 6H, NCH_3), 2.60 (m, 2H,

NHCOCH₂CH₂CO₂), 2.43 (m, 2H, NHCOCH₂CH₂CO₂), 2.39 (m, 2H, CH₂CONHAr), 2.05 (m, 4H, 2 x CH₂CH=CHCH₂), 1.70 (m, 2H, CH₂CH₂CONHAr), 1.56 (m, 8H, CO₂CH₂CH₂ & 2 x CH₂CH₂NCH₃ & CH₂CH₂NHCO), 1.42 (m, 6H, CO₂CH₂CH₂CH₂ & CH₂=CHCH₂CH₂ & CH=CHCONHCH₂CH₂), 1.36–1.22 (m, 32H, CH₂, alkyl); HRMS (FAB, NBA matrix): $m/z = 1065.69974 [(M+H)^+]$ (anal. calcd for C₆₂H₉₃N₆O₉: $m/z = 1065.70040$).

[3]catenane, Z,E-3

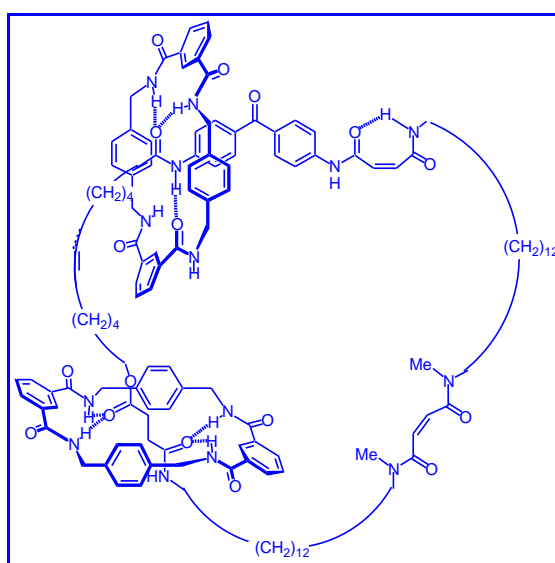


A 5×10^{-4} M solution of catenane *E,E-3* (12 mg) in CH₂Cl₂ (10 mL) was placed in a quartz vessel and directly irradiated at 350 nm using a multilamp photoreactor (model MLU18 manufactured by Photochemical Reactors Ltd, UK). The progress of the reaction was monitored by ¹H NMR spectroscopy and the photostationary state reached after 5 minutes irradiation. The reaction mixture (containing a mixture of *E,E-3* and *Z,E-3*) was concentrated under reduced pressure and subjected to column chromatography (silica gel, 4:97 MeOH/CHCl₃) to obtain the pure *Z,E*-isomer.

Selected data for [3]catenane *Z,E-3*: Yield 8 mg (67%); ¹H NMR (600 MHz, CD₂Cl₂): $\delta = 8.85$ – 8.76 (m, 4H, ArH_C), 8.38 – 8.14 (m, 8H, ArH_B), 7.78 – 7.69 (m, 16H, NH_D & ArH, benzophenone), 7.65 – 7.53 (m, 4H, ArH_A), 7.21 – 7.19 and 7.04 – 7.02 (m, 16H, ArH_F), 6.41 – 6.16 (m, 2H, NCH₃COCH=CHCONCH₃), 6.07 – 5.94 (m, 2H, NHCOCH=CHCONH), 5.35 (m, 2H, CH₂CH=CHCH₂), 5.13 and 3.79 (m, 8H, CH_E),

4.59–4.47 (m, 8H, CH_E), 3.93 (m, 2H, CH₂CO₂), 3.43–3.25 (m, 8H, 2 x CH₂NCH₃ & CH₂NHCO & CH=CHCONHCH₂), 2.96–2.93 & 2.72 & 2.68 (s, 6H, NCH₃), 2.41 (m, 2H, CH₂CONHAr), 1.96 (m, 4H, 2 x CH₂CH=CHCH₂), 1.66 (m, 2H, NHCOCH₂CH₂CO₂), 1.41 (m, 2H, NHCOCH₂CH₂CO₂), 1.35–0.68 (m, 50H, alkyl).

[3]catenane, Z,Z-3



A 5×10^{-4} M solution of catenane, *Z,E-3* (12 mg) in CH₂Cl₂ (10 mL) was placed in a quartz vessel and directly irradiated at 254 nm using a multilamp photoreactor (model MLU18 manufactured by Photochemical Reactors Ltd, UK). The progress of the reaction was monitored by ¹H NMR spectroscopy and the photostationary state was reached after 20 minutes of irradiation. The reaction mixture (containing a mixture of *E,E-3*, *Z,E-3*, *E,Z-3* and *Z,Z-3*) was concentrated under reduced pressure and subjected to column chromatography (silica gel, 4:97 MeOH/CHCl₃) to obtain pure *Z,Z-3*.

Selected data for [3]catenane *Z,Z-3*: Yield 6 mg (50%); ¹H NMR (600 MHz, CD₂Cl₂): δ = 8.34–8.31 (brm, 4H, ArH_C), 8.13–8.11 (m, 8H, ArH_B), 7.73–7.58 (m, 16H, NH_D & ArH, benzophenone), 7.55–7.52 (m, 4H, ArH_A), 7.16 (brs, 16H, ArH_F), 6.35–6.30 (m, 2H, NCH₃COCH=CHCONCH₃), 6.11–5.99 (m, 2H, NHCOCH=CHCONH), 5.18 (m, 2H, CH₂CH=CHCH₂), 4.55–4.45 (m, 16H, CH_E), 3.87

(m, 2H, CH₂CO₂), 3.24–3.04 (m, 6H, 2 x CH₂NCH₃ & CH₂NHCO), 2.93–2.80 (m, 8H, NCH₃ & CH=CHCONHCH₂), 1.85 (m, 4H, 2 x CH₂CH=CHCH₂), 1.61 (m, 2H, CH₂CONHAr), 1.44–1.14 (m, 50H, alkyl).

II. Computational studies

The calculations were performed with the MM3 force field model that has been found to be accurate for organic systems [1] and was parameterised explicitly to describe the hydrogen bonds and the π - π stacking interactions that govern intra- and intermolecular interactions in these systems. The molecular dynamics (MD) calculations were run with the Tinker 3.8 program [2] using the approach of Berendsen *et al.*[3] with periodic boundary conditions (PBC), a cubic box with a maximum linear dimension of ~ 45 Å, at constant volume and, unless otherwise specified, at a temperature equal to 298 K. The approach based on MM3 implemented in the Tinker program has been successful in a variety of applications carried out in our laboratory on similar systems.[4]

The catenanes were first optimised in the vacuum and then annealed repeatedly reaching a maximum temperature of 1000 K and cooling down to 0 K. During the simulations, it became evident that cutoff radii had to be quite long, i.e., 15 Å, however, care was taken that the catenane did not interact with its counterpart in an adjacent box. The minimum energy structure was embedded in a box of equilibrated CH_2Cl_2 solvent. Excess molecules were removed to conserve density. Up to 839 solvent molecules of CH_2Cl_2 were included explicitly. A first run of 200 ps of molecular dynamics was performed, keeping the solute rigid, in order to remove unphysical solvent-solute interactions. A combination of high temperature simulated annealing and 298 K equilibration dynamics yielded a number of similar structures. One of them was randomly selected and the whole system was then finally equilibrated for 300 ps. Data acquisition was run for 400 ps at 298 K.

Figures 1 and 2 represent two snapshots of the extreme structures observed during the

dynamics of [3]catenane, *E,E*-**3** in CH₂Cl₂. The molecule spontaneously smoothly switches from one to the other, conserving the total energy and without variations of temperature in the simulation box.

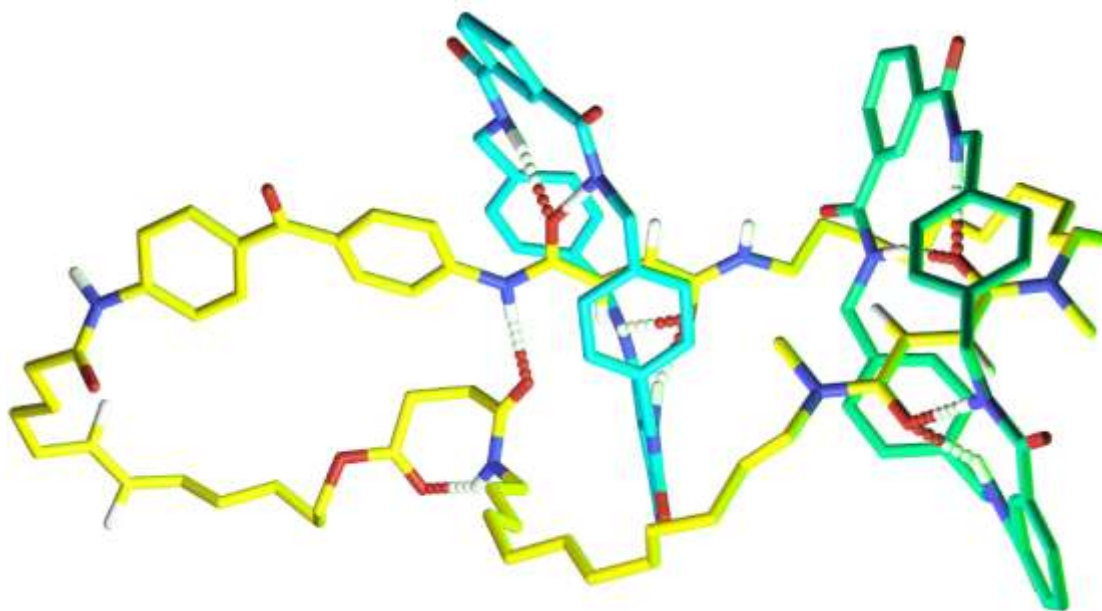


Figure 1. [3]Catenane *E,E*-**3** co-conformer 1.

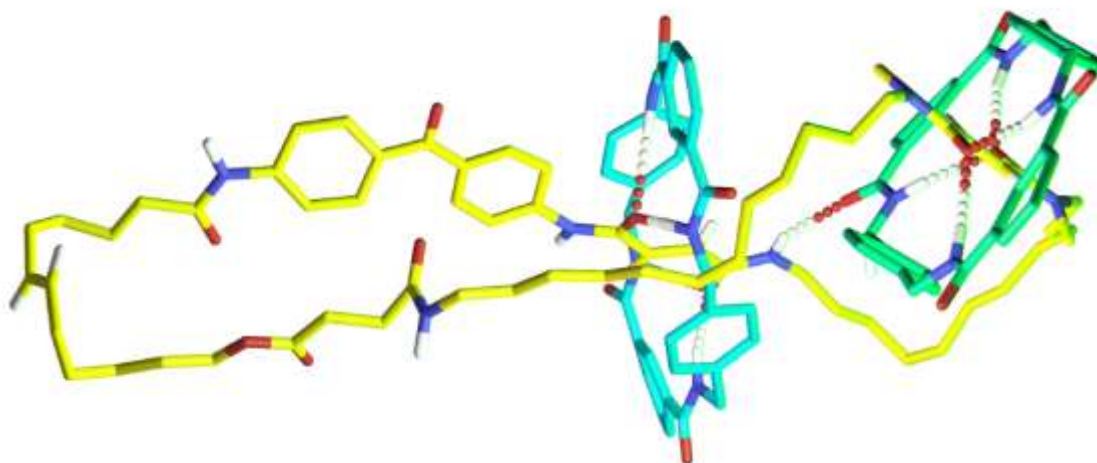


Figure 2. [3]Catenane *E,E*-**3** co-conformer 2.

Co-conformer **1** is present for about half of the time. It is characterised by two extra hydrogen bonds: the first internal to the succinic amide ester (C) station, the second

between the same succinic amide ester function and the fumaramide (A) station. For this co-conformer, comparison with similar calculations carried out for the [2]catenane *E,E*-2 in the same conditions in CH₂Cl₂ show the presence of a weaker interaction between the macrocycle and the tertiary amide fumaramide (B) station, which implies faster spinning in the [3]catenane.

Co-conformer **2** does not have the same extra two hydrogen bonds as co-conformer **1** and owes its stability to an extra hydrogen bond between the macrocycle sitting on station B and the fumaramide station A.

The actual rate of spinning for the macrocycle at the B station is the result of averaging these two types of structures weighted over their relative lifetimes.

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(2) (a) Ponder, J. W.; Richards, F. *J. Comput. Chem.* **1987**, *8*, 1016-1024; (b) Kundrot, C.; Ponder, J. W.; Richards, F. *J. Comput. Chem.* **1991**, *12*, 402-409; (c) Dudek, M. J.; Ponder, J. W. *J. Comput. Chem.* **1995**, *16*, 791-816.

(3) Berendsen, H.J.C.; Postma, J.P.M.; van Gusteren, W.F.; Di Nola, A.; Haak, J.R.; *J. Chem. Phys.* **1984**, *81*, 3684-3690.

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Leigh, D. A.; Léon, S.; Teat, S. J.; Wong, J. K. Y.; Zerbetto, F. *J. Am. Chem. Soc.* **2002**, *124*, 225-233.

Determination of shuttling rates

(i) Symmetrical [2]rotaxanes

The energy barriers for shuttling of the benzylic amide macrocycle from one station to another (Figure 3a) cannot be readily measured directly because the less-preferred binding site will be insufficiently populated if the macrocycle-binding energy differences of the two stations are large (as they are designed to be in **3**). However, they can be estimated using the assumption that the energy barrier of shuttling between two stations depends only on the strength of binding of the macrocycle to the initial station and the distance between the two stations, i.e. the energy barrier is not affected by the characteristics of the station being shuttled to. In this case, the barriers can be determined by using [2]rotaxanes containing two identical (i.e. degenerate energy) stations separated by the correct distance (Figure 3b).

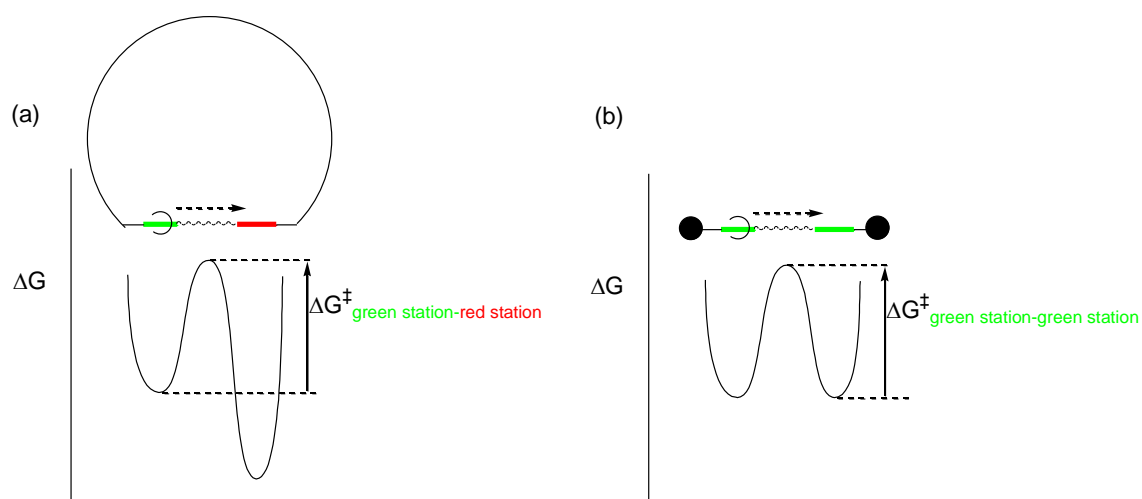
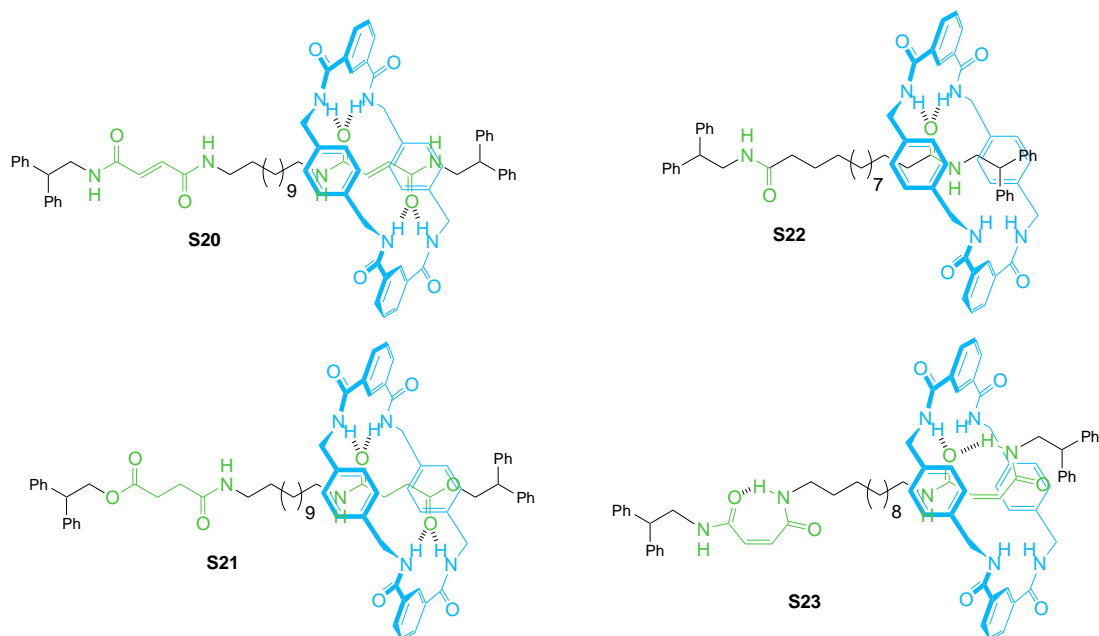


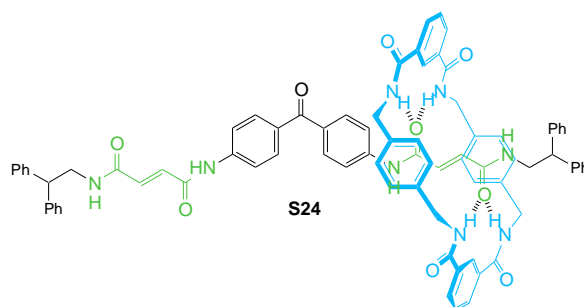
Figure 3. Energy barriers (ΔG^\ddagger) to shuttling between two stations that are of: (a) different energies, as in [3]catenane **3**; (b) identical energies, as in [2]rotaxanes **S20-S23**.

The contributions of the various processes to the stimuli-induced shuttling in **3** were thus estimated from the kinetics of various model compounds **S20-S23**.



The energy barriers for a benzylic amide macrocycle to move from each type of station (A and B, C, D, A' and B') to another station 12 carbon atoms away at 298 K in CDCl_3 were experimentally determined in the symmetrical two station [2]rotaxanes by variable temperature ^1H NMR spectroscopy (line shape analysis and spin polarisation transfer by selective inversion recovery (SPT-SIR) experiments).

The barriers for **S20-S23** (fumaramide and *bis-N*-methyl fumaramide $16.2 \pm 0.4 \text{ kcal mol}^{-1}$; succinic amide ester $11.3 \pm 0.2 \text{ kcal mol}^{-1}$; amide $< 8 \text{ kcal mol}^{-1}$; maleamide and *bis-N*-methyl maleamide $\ll 8 \text{ kcal mol}^{-1}$) mean that at 298 K in CDCl_3 stations A and B decomplex 4000 times less frequently than C and $>$ million times less frequently than D, A' and B' (the ratio of rates is given by $e^{\frac{\Delta\Delta G^\ddagger}{k_B T}}$). The benzophenone unit was shown not to significantly slow shuttling using model [2]rotaxane **S24**.



Thus, starting from *E,E*-**3**, when A is isomerised to A' the macrocycle moving from A' to C will be thousands of times more frequent an event to get to the equilibrium position of *Z,E*-**3** than the macrocycle originally at B moving to C and then the macrocycle at A' moving to B. Similarly, movement of the macrocycle from the B' station to D to give the most stable positional isomer of *Z,Z*-**3** will occur far more frequently than the macrocycles moving from C to D and B' to C. Finally, as long as the *N*-methyl maleamide station is not isomerised to the fumaramide unit at a significantly faster rate than the secondary maleamide station as *Z,Z*-**3** is converted to *E,E*-**3** (the rates we observe experimentally are the same for both types of station), then the macrocycle originally at D will move rapidly to A where it will be bound tightly and therefore be slower to move to the vacant B station than the macrocycle originally held at C. Thus the kinetics, like the thermodynamics, work in the right way to provide overwhelming directionality to the stimuli-induced motion in **3**.

(ii) Energy barrier for random circumrotation

The rate of random rotation can be calculated as twice the time taken by macrocycle 1 on the A station and macrocycle 2 on the B station, A(1)B(2), to reach the situation where macrocycle 1 is on the B station and macrocycle 2 is on the A station, A(2)B(1). In practice, initially, the system has only A(1)B(2) and the concentration of A(2)B(1) is zero, while at the end, the concentration of A(1)B(2) is the same of that of A(2)B(1). This time is then multiplied by two.

The free energy activation barriers, ΔG^\ddagger , to escape the four stations and shuttle over a C₁₂ spacer to another station were assumed to be 16.2, 16.2, 11.3, 8.0 kcal mol⁻¹ for A, B, C, and D (the values determined experimentally for the symmetrical [2]rotaxanes, *vide supra*). They were transformed into rate constants through [Pilling M.J. and Seakins P.W. Reaction kinetics, Oxford Science Publications, Oxford 1997, UK]

$$k(T) = \frac{k_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{k_B T}\right) \quad (1)$$

where $k(T)$ is the rate constant, k_B is Boltzmann constant, h is Planck constant, and T is the absolute temperature.

Numerical integration [Berberan-Santos M.N. and Martinho J.M.G. J. Chem. Ed. 67, 1990, 375-379] of the kinetic equations that considered the 12 possible isomers and their interconversions gave a time of random rotation, at 298K, of 13598 seconds. A simple Fortran programme which carries out these calculations is available from the authors [gatto@ciam.unibo.it].

The corresponding rate of random frequency rotation was obtained from the reciprocal as $3.7 \times 10^{-5} \text{ s}^{-1}$ (298 K). Equation 1 can be used to back-calculate the effective barrier as 23.5 kcal mol⁻¹ at 298 K. The significantly higher activation barrier for circumrotation of the large macrocycle compared to the stimuli-induced translational barriers (<8 kcal mol⁻¹ in CDCl₃ at 298 K for all except C→B which is 11.3 kcal mol⁻¹), means the random background rotation can be minimised by changing the reaction

conditions. The reaction sequence shown in Fig. 4 was repeated at $-78\text{ }^{\circ}\text{C}$ catalyzing the maleamide \rightarrow fumaramide isomerisation step with photochemically-generated bromine radicals. At this temperature the photo-stationary states for steps (i) and (ii) were still reached within 5 and 20 min, respectively, and after 2 min treatment with Br_2 (~ 1 equivalent) under a tungsten halogen lamp (400-670 nm) $\sim 100\%$ of *E,E*-**3** had been reformed. At 298 K the frequency of background circumrotation of *E,E*-**3** is approximately once every 8 hours.