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Diamide-based fullerosteroidal and disteroidal [2] rotaxanes: solvent-induced macrocycle translocation and/or unthreading†

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The synthesis, characterization and behaviour of two novel Leigh-type amide [2]rotaxanes are reported. NMR study shows that fullerosteroidal and disteroidal rotaxanes occur in a *peptide* co-conformation in $CDCl_3$. [D_6]DMSO induces fast unthreading of disteroidal rotaxane, which includes *steroid* co-conformers as intermediates. On the other hand, fullerosteroidal rotaxane undergoes predominantly a shuttling process occupying the *stacked* co-conformation, whereas unthreading is very slow in comparison with its disteroidal analogue (25% after 7 days). Moreover, organogelation and self-organization properties were studied. It was found that disteroidal rotaxane is an organogelator and its SEM image shows that it forms a branched film-like network in a PhMe/EtOAc 1 : 1 mixture.

1. Introduction

Rotaxanes are mechanically interlocked supramolecular architectures composed of one or more linear moieties (thread, axle) surrounded by macrocyclic ring(s) (wheel) and sufficiently large stopper groups positioned at the axle termini in order to prevent the dissociation process.[1] Due to their abacus like structure,[2] rotaxanes have attracted great attention in studies of non-covalent bonding interactions, as well as in wide ranges of applied research. Such compounds have proven to be valuable in biomedical exploration (enzyme-sensitive rotaxane-based propeptides,[3] supramolecular nanovalves as anticancer drug carriers,[4] rotaxanes with oligomeric axles as intracellular transport agents,[5] squaraine-rotaxanes as molecular probes for *in vitro* and *in vivo* fluorescence cell imaging[6]), but also as components of nanoelectrochemical devices.[7] Besides careful design based on a choice of axle–wheel interactions (hydrophobic, ionic, π–π stacking, hydrogen bonding, metal–ligand coordination) and consequent rational subunit selection, the development of template-directed synthetic strategies[1a,8] expanded the possibility to obtain a large number of rotaxanes. The notable mobility of the macrocyclic ring within the supramolecular system enables its rotation around the thread[1a] and translational movement along the axle allows reversible (shuttling)[9] or irreversible (unthreading) movement.[10] In addition, the shuttling process in rotaxanes possessing two or more different stationary units causes co-conformational isomerism,[11] and the predominance of one of the translational isomers in response to external stimuli. The position of the ring component of the molecular shuttle can be controlled by variation of the electrochemical potential,[12] pH,[13] illumination,[14] solvent,[9] or by cooperative effects of various driving forces[15] which allow the manipulation of binding affinities. Efficient switching without further chemical transformations can be performed using solvents of different polarity (dichloromethane and dimethyl sulfoxide), as described by the examples of two hydrogen bond-assembled fullerene-stoppered rotaxanes.[2,16] However, poor solubility of Leigh-type fullerene-stoppered rotaxanes is one of the major obstacles to their application.[2,17] It was also observed that the presence of the steroidal subunit in mechanically interlocked molecules played an essential role in their self-organization to more complex, morphologically well defined architectures.[18]

Willing to examine individual as well as mutual effects of steroidal and fullerenic stoppers on properties of mechanically interlocked systems, here we describe the template-directed synthesis and detailed characterization of two novel hydrogen bond assembled rotaxanes – disteroidal, with pregnenolone-derived stoppers, and fullerene-pregnenolone stoppered. Their shuttling/unthreading behaviour in solvents of different polarity as well as the self-organization process are also examined and discussed.

2. Experimental

General information

The amine-TFA salt **1**,[19] fulleropyrrolidinic acid **2a**,[20] pregnenolone hemisuccinate **2b**[21] and the thread **3a**[19] were synthesized

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according to the literature procedures. Chloroform and triethylamine (TEA) were dried by refluxing with P_2O_5 and with CaH_2, respectively, and distilled prior to use. Flash column chromatography (FCC) and dry-column flash chromatography (DCFC) were carried out with Merck silica gel 0.04–0.063 mm and 0.015–0.04 mm, respectively. Thin layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} plates. Melting points were determined on a Digital melting point WRS-1B apparatus and are uncorrected. IR spectra (ATR) were recorded with a Perkin-Elmer-FT-IR 1725X spectrophotometer; ν values are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with Varian Gemini 200 (^1H at 200 MHz, ^{13}C at 50 MHz) and Bruker Avance spectrometers (^1H at 500 MHz, ^{13}C at 125 MHz). Chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hz. TMS was used as an internal reference. The homonuclear 2D (DQF-COSY) and the heteronuclear 2D ^1H–^{13}C spectra (HSQC, HMBC) were recorded with the usual settings. UV spectra were recorded with a GBC-Cintra 40 UV/Vis spectrophotometer. The high-resolution MS spectra were taken with Agilent 6210 LC ESI-MS TOF and LTQ Orbitrap XL spectrometers. Standard steroidal numbering was used together with abbreviations for 4-aminobutanoic and succinate fragments (GABA and Succ, respectively). Labels of the peptide/diamide moieties and the macrocycle ring in threads and rotaxanes are given in Scheme 2. SEM: the morphology investigations were carried out with SEM, using a JEOL JSM-840A instrument, at an acceleration voltage of 30 kV. The dried samples obtained from a drop of dilute solutions of rotaxanes **4a** (0.1 mM in $CHCl_3$) and **4b** (0.1 mM in PhMe/EtOAc 1 : 1, v/v) were deposited on the surface of a Si substrate (5 × 5 mm) and left overnight to slowly evaporate in a glass Petri dish (diameter 10 cm) under a PhMe atmosphere at room temperature. The investigated samples were gold sputtered in a JFC 1100 ion sputter device and then subjected to SEM observations.

Thread 3a.[19] UV/Vis ($CHCl_3$): $\lambda_{max}(\varepsilon)$ = 430 nm (2.33 × 10^3 mol^{-1} dm^3 cm^{-1}); ^1H NMR (500 MHz, [D_6]DMSO): δ = 8.11 (br t, J = 5.0 Hz, 1H, NH(Gly)), 7.83 (br t, J = 5.5 Hz, 1H, NH(GABA)), 5.34 (m, 1H, HC(6)), 4.49 (m, 1H, HC(3)), 4.45 (s, 4H, H_2C(pyrr)), 3.78 (br d, J = 5.0 Hz, 2H, H_2C(Gly)), 3.16 (q, J = 6.5 Hz, 2H, $H_2C(4')$), 3.13 (t, J = 7.0 Hz, 2H, H_2C (4″)), 2.54 (m, 3H, $H_2C(2'')$ and HC(17)), 2.29 (m, 4H, $H_2C(2')$ and H_2C(4)), 2.19 (quint, J = 7.0 Hz, 2H, $H_2C(3'')$), 2.08 (s, 3H, H_3C(21)), 2.06 (m, 1H, HC(16)), 2.02 (m, 1H, HC(12)), 1.95 (m, 1H, HC(7)), 1.85 (m, 1H, HC(1)), 1.81 (m, 1H, HC(2)), 1.72 (m, 2H, $H_2C(3')$), 1.64 (m, 1H, HC(15)), 1.60 (m, 1H, HC(11)), 1.58 (m, 1H, HC(16)), 1.56 (m, 1H, HC(2)), 1.55 (m, 1H, HC(7)), 1.43 (m, 5H, HC(8), HC(11) and HC(12)), 1.16 (m, 2H, HC(14) and HC(15)), 1.00 (m, 1H, HC(9)), 0.98 (s, 3H, H_3C(19)), 0.55 (s, 3H, H_3C(18)); ^{13}C NMR (125 MHz, [D_6] DMSO): δ = 208.2 (C(20)), 172.7 (C(1″)), 171.9 (C(1′)), 169.1 (CO(Gly)), C_{full} (155.2, 146.7, 145.9, 145.7, 145.5, 144.8, 144.7, 144.1, 142.6, 142.1, 141.8, 141.6, 141.3, 139.5, 135.8), 139.3 (C(5)), 121.9 (C(6)), 73.1 (C(3)), 70.5 (C_{full}-sp^3), 67.1 (C(pyrr)), 62.7 (C(17)), 56.1 (C(14)), 53.6 (C(4″)), 49.3 (C(9)), 43.3 (C(13)), 42.3 (C(Gly)), 38.1 (C(12)), 37.9 (C(4′)) 37.7 (C(4)), 36.5 (C(1)), 36.1 (C(10)), 33.4 (C(2″)), 31.3 (C(8)), 31.1 (C(7)), 27.4 (C(2)), 24.5 (C(3″)), 24.3 (C(15)), 24.0 (C(3′)), 22.3 (C(16)), 20.6 (C(11)), 19.0 (C(19)), 12.9 (C(18)).

Thread 3b. To an ice bath cooled solution of the TFA salt **1** (135 mg, 0.236 mmol, 1 equiv.) in DCM (10 mL), pregnenolone hemisuccinate **2b** (147 mg, 0.354 mmol, 1.5 equiv.), TEA (30 mg, 41 μL, 0.295 mmol, 1.25 equiv.), and HOBT (58 mg, 0.378 mmol, 1.6 equiv.) were added. A solution of DCC (78 mg, 0.378 mmol, 1.6 equiv.) in DCM (5 mL) was added dropwise over 2 h and the reaction mixture was stirred for 24 h. The solvent was evaporated *in vacuo* and the residue chromatographed by DCFC on SiO_2 column using PhMe/EtOAc/MeOH 5 : 5 : 2 to obtain **3b** as a colourless oil (128 mg, 63%), which was precipitated from the DCM solution with *n*-hexane. R_f = 0.54 (PhMe/EtOAc/MeOH 5 : 5 : 1); mp 119–120 °C; IR: $\tilde{\nu}$ = 3305, 3079, 2941, 1729, 1707, 1650, 1553, 1440, 1358, 1253, 1177, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.79 (t, J = 6.0 Hz, 1H, NH(GABA)), 6.47 (t, J = 5.5 Hz, X part of ABX system, 1H, NH(Gly)), 5.37 (t, J = 5.0 Hz, 2H, HC(6)), 4.60 (m, 2H, HC(3)), 3.93 (two AB quartets, AB part of ABX system, J(AB) = 15 Hz, J(AX, BX) = 5.5 Hz, 2H, H_2C(Gly)), 3.29 (q, J = 7.0 Hz, 2H, H_2C(4)-GABA), 2.70 (dt, J = 2.0 and 6.5 Hz, 2H, H_2C(3)-succ), 2.53 (two t, 2H, J = 9 Hz, HC(17)), 2.49 (t, J = 6.5 Hz, 2H, H_2C(2)-succ), 2.33 (t, J = 10 Hz, 2H, H_2C(2)-GABA), 2.31 (m, 4H, HC(4)), 2.17 (m, 2H, HC(16)), 2.12 (s, 6H, H_3C(21)), 2.05 (m, 2H, HC(12)), 2.00 (m, 2H, HC(7)), 1.88 (m, 2H, HC(1)), 1.86 (m, 2H, HC(2)), 1.84 (quint, J = 10 Hz, 2H, H_2C(3)-GABA), 1.69 (m, 2H, HC(15)), 1.65 (m, 2H, HC(16)), 1.61 (m, 2H, HC(11)), 1.58 (m, 2H, HC(2)), 1.57 (m, 2H, HC(7)), 1.49 (m, 2H, HC(8)), 1.48 (m, 2H, HC(11)), 1.45 (m, 2H, HC(12)), 1.21 (m, 2H, HC(15)), 1.15 (m, 2H, HC(14)), 1.12 (m, 2H, HC(1)), 1.02 (s, 6H, H_3C(19)), 1.01 (m, 2H, HC(9)), 0.63 (s, 6H, H_3C(18)); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.5 (C(20)), 172.8 (CO-succ, ester)), 172.7 (CO(GABA)), 172.1 (CO-succ, amide), 169.0 (CO(Gly)), 139.6 and 139.5 (C(5)), 122.4 (C(6)), 74.6 and 74.0 (C(3)), 63.6 (C(17)), 56.8 (C(14)), 49.9 and 49.8 (C(9)), 43.9 (C(13)), 43.3 (C(Gly)), 39.0 (C(4)-GABA), 38.8 (C(12)), 38.0 (C(4)), 36.9 (C(1)), 36.6 (C(10)), 32.0 (C(2)-GABA)), 31.8 (C(8)), 31.7 (C(7)), 31.5 (C(21)), 30.9 (C(2)-succ), 29.8 (C(3)-succ), 27.7 (C(2)), 24.5 (C(3)-GABA), 24.4 (C(15)), 22.8 (C(16)), 21.0 (C(11)), 19.3 (C(19)), 13.2 (C(18)); ^1H NMR (500 MHz, [D_6]DMSO): δ = 8.16 (t, J = 6.0 Hz, 1H, NH(Gly)), 7.68 (*t*, J = 6.0 Hz, 1H, NH (GABA)), 5.33 (m, 2H, HC(6)), 4.45 (m, 2H, HC(3)), 3.61 (d, J = 5.5 Hz, 2H, H_2C(Gly)), 3.06 (q, J = 6.5 Hz, 2H, H_2C(4)-GABA), 2.56 (two t, J = 9.0 Hz, 2H, HC(17)), 2.49 (t, J = 6.5 Hz, 2H, H_2C(3)-succ), 2.39 (t, J = 6.5 Hz, 2H, H_2C(2)-succ), 2.25 (bt, J = 7.5 Hz, 6H, H_2C(4) and H_2C(2)-GABA), 2.05 (s, 6H, H_3C(21)), 2.02 (m, 2H, HC(16)), 2.00 (m, 2H, HC(12)), 1.94 (m, 2H, HC(7)), 1.84 (m, 2H, HC(1)), 1.75 (m, 2H, HC(2)), 1.63 (quint, J = 7.0 Hz, 2H, H_2C(3)-GABA), 1.61 (m, 2H, HC(15)), 1.56 (m, 4H, HC(11), HC(16)), 1.54 (m, 4H, HC(2), HC(7)), 1.42 (m, 2H, HC(12)), 1.40 (m, 4H, HC(8), HC(11)), 1.14 (m, 4H, HC(14), HC(15), 1.06 (m, 2H, HC(1)), 0.96 (m, 2H, HC(9)), 0.96 (s, 6H, H_3C(19)), 0.52 (s, 6H, H_3C(18)); ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 208.8 (C(20)), 172.2 (CO-succ, ester; CO-GABA), 171.5 (CO-succ, amide), 169.1 (CO(Gly), 139.7 and 139.6 (C(5)), 122.1 and 122.0 (C(6)), 73.4 and 73.3 (C(3)), 62.7 (C(17)), 56.1 (C(14)), 49.4 (C(9)), 43.4 (C(13)), 42.3 (C(Gly)), 38.0 (C(12)), 37.9 (C(4)-GABA), 37.8 and 37.7 (C(4)), 36.6 (C(1)), 36.2 (C(10)), 31.4 (C(8) and C(7)), 31.3 (C(21)), 31.2 (C(2)-GABA), 29.9 (C(2)-succ), 29.4 (C(3)-succ), 27.4 (C(2)), 24.6 (C(3)-GABA), 24.1

(C(15)), 22.4 (C(16)), 20.7 (C(11)), 19.1 (C(19)), 13.0 (C(18)); HRMS (ESI-TOF) (*m*/*z*): calcd for $C_{52}H_{77}N_2O_8$ $(M + H)^+$: 857.5674, found: 857.5664.

Rotaxane 4a. A solution of *p*-xylenediamine (135 mg, 0.988 mmol) in anh. $CHCl_3$ (42 mL) and a separate solution of isophthaloyl dichloride (200 mg, 0.988 mmol) in anh. $CHCl_3$ (42 mL) were simultaneously added dropwise over 4 h to a stirred solution of the thread **3a** (85 mg, 0.066 mmol) and dry TEA (200 μL, 1.403 mmol) in dry $CHCl_3$ (25 mL) under Ar. After the addition, the reaction mixture was stirred overnight at ambient temperature. The mixture was filtered through Celite, evaporated to dryness and chromatographed on silica gel by FCC. The pure unconsumed thread **3a** (68 mg, 80%) was eluted with PhMe/EtOAc/MeOH 10 : 10 : 3 while the mixture of rotaxane and free macrocycle (14 mg) was eluted with PhMe/EtOAc/MeOH 10 : 10 : 7 and further separated by size exclusion chromatography on Sephadex G-25. Sephadex G-25 (10 g) was suspended in $CHCl_3$ (stabilized with 1% EtOH), left to swell overnight and the solution of the mixture of **4a** and free macrocycle (14 mg) in $CHCl_3$/MeOH (95 : 5, 0.5 mL) was applied to the column. Elution with $CHCl_3$, precipitation from highly concentrated $CHCl_3$ solution with MeOH and subsequent drying under vacuum afforded the rotaxane **4a** (9 mg, 8%) as a brown powder. $R_f = 0.35$ (PhMe/EtOAc/MeOH 5 : 5 : 1); UV/Vis ($CHCl_3$): $\lambda_{max}(\varepsilon) = 428$ nm (6.15×10^3 mol^{-1} dm^3 cm^{-1}); IR: $\tilde{\nu} =$ 3428, 2951, 1726, 1141 cm^{-1}. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ at a concentration of 15 mg mL^{-1} was obtained with low resolution due to the high level of self-aggregation. Dilution to 2.5 mg mL^{-1} provided an acceptable ^{1}H NMR spectrum with slightly broadened signals (data given below) and a ^{13}C NMR spectrum with a low signal-to-noise ratio (see S10;† data not given); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.41$ (s, 2H, M4), 8.13 (d, J = 8.0 Hz, 4H, M2), 7.60 (m, 6H, M1 and NH(M)), 7.26 (s, 8H, M6), 6.85 (br s, 1H, NH(GABA)), 5.90 (br s, 1H, NH(Gly)), 5.30 (m, 1H, HC(6)), 4.56 (s, 8H, H_2C(M)), 4.51 (m, 1H, HC(3)), 4.27 (s, 4H, H_2C(pyrr)), 3.06 (br s, 2H, $H_2C(4')$), 2.94 (br s, 2H, $H_2C(4'')$), 2.83 (br s, 2H, H_2C(Gly)), 2.54 (t, 1H, J = 8.0 Hz, HC(17)), 2.25 (m, 2H, $H_2C(2'')$), 2.17 (m, 2H, $H_2C(2')$, 1.91 (m, 2H, $H_2C(3'')$), 2.13 (s, 3H, H_3C(21)), 1.66 (m, 2H, $H_2C(3')$), 0.97 (s, 3H, H_3C(19)), 0.63 (s, 3H, H_3C(18)); ^{1}H NMR (500 MHz, [D_6]DMSO + 1 drop of $CDCl_3$): $\delta = 8.84$ (m, 4H, NH(M)), 8.31 (s, 2H, M4)), 7.96 (m, 2H, NH(Gly) and NH(GABA)), 7.91 (d, $J = 8.0$ Hz, 4H, M2), 7.40 (br t, $J = 8.0$ Hz, 2H, M1), 7.24 (s, 8H, M6), 5.23 (m, 1H, HC(6)), 4.48 (m, 4H, H_2C(M)), 4.32 (m, 4H, H_2C(M)), 4.29 (m, 1H, HC(3)), 3.66 (s, 2H, H_2C(Gly)), 3.38 (s, 4H, H_2C(pyrr)), 2.92 (br s, 2H, $H_2C(4')$), 2.05 (m, 2H, $H_2C(4'')$), 2.03 (m, 2H, $H_2C(2')$), 1.88 (m, 2H, $H_2C(2'')$), 1.48 (m, 2H, $H_2C(3')$), 1.45 (m, 2H, $H_2C(3'')$), 0.91 (m, 1H, HC(9)), 0.86 (s, 3H, H_3C(19)), 0.50 (s, 3H, H_3C(18)); ^{13}C NMR (125 MHz, [D_6]DMSO + 1 drop of $CDCl_3$): $\delta = 208.6$ (C(20)), 173.6 (CO(1″)), 172.1 (CO(1′)), 169.3 (CO(Gly)), 165.7 (CO(M)), C_{full} (155.1, 146.8, 146.1, 145.7, 145.5, 145.3, 144.7, 144.1, 142.5, 142.1, 141.9, 141.6, 141.4, 139.4, 135.7), 139.5 (C(5)), 138.1 (C(6)-M), 134.5 (C(3)-M), 130.1 (C(2)-M), 128.8 (C(5)-M), 128.0 (C(1)-M), 126.1 (C(4)-M), 121.9 (C(6)), 73.1 (HC(3)), 69.9 (C_{full}-sp^3), 66.2 (C(pyrr)), 62.7 (C(17)), 56.1 (C(14)), 52.9 (C(4″)), 49.3 (C(9)), 43.3 (CH_2(M)), 43.2 (C(13)), 42.2 (C(Gly)), 38.0 (C(12)), 37.9 (C(4′)), 37.5 (C(4)), 36.5 (C(1)), 36.1 (C(10)), 32.6 (C(2′)), 31.4 (C(8), C(7)), 31.2 (C(21)), 27.2 (C(2)), 24.5 (C(3″)), 24.1 (C(3′)), 22.3 (C(15)), 22.2 (C(16)), 20.6 (C(11)), 19.0 (C(19)), 13.0 (C(18)); HESI-Orbitrap MS (*m*/*z*): calcd for $C_{125}H_{80}N_7O_9$ $(M + H)^+$: 1822.5939, found: 1822.6164.

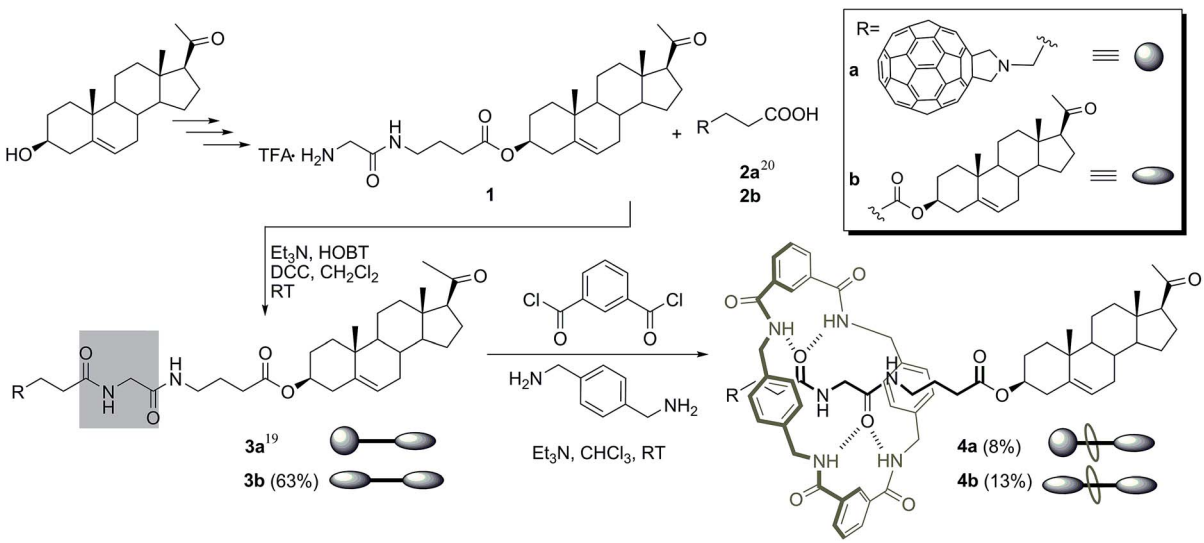
Rotaxane 4b. A solution of *p*-xylenediamine (96 mg, 0.701 mmol) in $CHCl_3$ (anhydrous, 15 mL) and a separate solution of isophthaloyl dichloride (143 mg, 0.701 mmol) in $CHCl_3$ (15 mL) were added dropwise simultaneously for 4 h to a stirred solution of the thread **3b** (40 mg, 0.047 mmol) and TEA (200 μL, 1.403 mmol) in dry $CHCl_3$ (45 mL) under an atmosphere of Ar. After the addition, the reaction mixture was stirred overnight at ambient temperature. The mixture was filtered through Celite, evaporated to dryness and chromatographed on SiO_2 by FCC. The unreacted thread (34 mg, 85%) was eluted with PhMe/EtOAc/MeOH 10 : 10 : 1 while rotaxane **4b** was eluted with PhMe/EtOAc/MeOH 10 : 10 : 5 and precipitated from DCM solution with *n*-hexane. Yield: 8.2 mg (13%); $R_f = 0.49$ (PhMe/EtOAc/MeOH 5 : 5 : 1); IR: $\tilde{\nu} =$ 3481, 3439, 3308, 3062, 2942, 2851, 1729, 1701, 1647, 1622, 1535, 1270, 1172, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.33$ (s, 2H, M4), 8.14 (dd, $J = 1.0$ and 8.0 Hz, 4H, M2), 7.58 (t, $J = 8.0$ Hz, 2H, M1), 7.52 (m, 4H, NH(M)), 7.22 (s, 8H, M6), 7.10 (br t, $J = 5.5$ Hz, 1H, NH(GABA)), 5.95 (br t, X part of ABX system, $J = 4.0$ Hz, 1H, NH(Gly)), 5.29 (m, 1H, HC(6)), 5.21 (m, 1H, HC(6)), 4.64 (m, 4H, H_2C(M)), 4.45 (m, 4H, H_2C(M)), 4.46 (m, 1H, HC(3)), 4.42 (m, 1H, HC(3)), 3.06 (q, $J = 6.5$ Hz, 2H, H_2C(4)-GABA), 2.89 and 2.85 (two AB quartets, AB part of ABX system, J(AB) = 17 Hz, J(AX, BX) = 4.0 Hz, 2H, H_2C(Gly)), 2.53 (t, $J = 9.0$ Hz, 2H, HC(17)), 2.32 (br t, $J = 6.5$ Hz, 2H, H_2C(3)-succ), 2.19 (m, 6H, HC(4) and HC(16)), 2.14 (m, 2H, H_2C(2)-GABA), 2.13 (s, 3H, H_3C(21)), 2.12 (s, 3H, H_3C(21)), 2.09 (br t, $J = 6.5$ Hz, 2H, H_2C(2)-succ), 2.06 (m, 2H, HC(12)), 1.98 (m, 2H, HC(7)), 1.79 (m, 2H, HC(1)), 1.70 (m, 2H, HC(2)), 1.67 (m, 2H, HC(15)), 1.66 (m, 4H, HC(16) and H_2C(3)-GABA), 1.59 (m, 2H, HC(11)), 1.55 (m, 2H, HC(7)), 1.49 (m, 2H, HC(2)), 1.46 (m, 2H, HC(11)), 1.45 (m, 4H, HC(8) and HC(12)), 1.23 (m, 2H, HC(15)), 1.15 (m, 2H, HC(14)), 0.99 (m, 2H, HC(1)), 0.97 (m, 2H, HC(9)), 0.95 (s, 6H, H_3C(19)), 0.62 (s, 6H, H_3C(18)); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 209.6$ (C(20)), 172.8 (CO-succ, ester), 172.5 (CO-GABA), 172.2 (CO-succ, amide), 169.1 (CO-Gly), 166.5 (CO-M), 139.2, 139.0 (C(5)), 137.7 (C(6)-M), 133.9 (C(3)-M), 131.5 (C(2)-M), 129.2 (C(1)-M), 129.1(C(5)-M), 124.0 (C(4)-M), 122.7 and 122.6 (C(6)), 74.8 and 74.4 (C(3)), 63.6 (C(17)), 56.8 (C(14)), 49.8 and 49.7 (C(9)), 44.1 (H_2C-M), 44.0 (C(13)), 42.4 (C(Gly)), 39.2 (C(4)-GABA), 38.7 (C(12)), 37.9 (C(4)), 36.8 and 36.7 (C(1)), 36.5 (C(10)), 31.7 (C(7), C(8), C(20)), 31.5 (C(2)-GABA), 30.1 (C(2)-succ), 29.7 (C(3)-succ), 27.7 and 27.6 (C(2)), 24.5 (C(15)), 24.3 (C(3)-GABA), 22.8 (C(16)), 21.0 (C(11)), 19.2 (C(19)), 13.2 (C(18)); the unthreading of the rotaxane **4b** started immediately after dissolution in [D_6]DMSO, so the corresponding ^{1}H and ^{13}C chemical shifts were determined by comparative analysis of the NMR data of the sample, pure thread **3b** and pure M. ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 8.60$ (br q, $J = 5.0$ Hz, 4H, NH(M)), 8.15 (s, 2H, M4), 7.94 (dd, $J = 1.5$ and 8.0 Hz, 4H, M2), 7.86 (br t, $J = 5.5$ Hz, 1H, NH(Gly)), 7.64 (br t, $J = 5.5$ Hz, 1H, NH(GABA)), 7.54 (t, $J = 7.5$ Hz, 2H, M1), 7.16 (s, 8H, M6), 5.16 (m, 1H, HC(6)), 5.12 (m, 1H, HC(6)), 4.39 (m, 4H, H_2C(M)), 4.32 (m, 4H, H_2C(M)), 4.12 (m, 1H, HC(3)), 3.99 (m, 1H, HC(3)), 3.38 ($J = 5.5$

Hz, 2H, H_2C(Gly)), 2.58 (q, J = 6.0 Hz, 2H, H_2C(4)-GABA), 2.54 (br t, J = 9.0 Hz, 2H, HC(17)), 2.10 (m, 4H, H_2C(2)-succ and H_2C(3)-succ), 2.04 (s, 3H, H_3C(21)), 1.99 (m, 2H, HC(16)), 1.95 (m, 2H, HC(12)), 1.86 (m, 2H, HC(7)), 1.76 (m, 4H, HC(4)), 1.73 (m, 2H, H_2C(2)-GABA), 1.62 (m, 2H, HC(1)), 1.57 (m, 2H, HC(15)), 1.54 (m, 2H, HC(16)), 1.48 (m, 2H, HC(11)), 1.45 (m, 2H, HC(7)), 1.38 (m, 2H, HC(12)), 1.31 (m, 4H, HC(8) and HC(12)), 1.22 (m, 2H, HC(2)), 1.18 (m, 2H, H_2C(3)-GABA), 1.10 (m, 4H, HC(14) and HC(15)), 0.99 (m, 2H, HC(2)), 0.82 (m, 2H, HC(9)), 0.81 (s, 3H, H_3C(19)), 0.78 (m, 2H, HC(1)), 0.75 (s, 3H, H_3C(19)), 0.49 (s, 6H, H_3C(18)); ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 208.9 (C(20)), 172.3 (CO(GABA)), 172.1 (CO-succ, ester), 171.9 (CO-succ, amide), 169.0 (CO(Gly)), 166.0 (CO-M), 139.5 (C(5)), 137.7 (C(6)-M), 134.6 (C(3)-M), 130.1 (C(2)-M), 128.7 (C(1)-M), 128.5 (C(5)-M), 126.1 (C(4)-M), 121.8, 121.7 (C(6)), 73.3 and 73.0 (C(3)), 62.7 (C(17)), 56.1 (C(14)), 49.3 (C(9)), 43.2 (H_2C-M), 42.8 (C(13)), 42.1 (C(Gly)), 38.0 (C(12)), 37.8 (C(4)-GABA), 37.3 and 37.1 (C(4)), 36.5 (C(1)), 36.1 (C(10)), 31.4 (C(8) and (C(7)), 31.3 (C(21)), 31.0 (C(2)-GABA), 29.7 (C(2)-succ), 28.9 (C(3)-succ), 27.0 and 26.8 (C(2)), 24.3 (C(3)-GABA), 24.1 (C(15)), 22.4 (C(16)), 20.6 (C(11)), 19.0 and 18.9 (C(19)), 13.0 (C(18)). HRMS (ESI-TOF) (m/z): calcd for $C_{84}H_{105}N_6O_{12}$ $(M + H)^+$: 1389.7785, found: 1389.7765.

3. Results and discussion

Target compounds were prepared according to Scheme 1 considering the observation that labile hydrogen bonding in rotaxanes allows solvent-induced molecular motion.[9a,b] Hereof, the presence of the *GABA-Gly-GABA* diamide fragment and suitable bulky terminal subunits in the previously synthesized, quite soluble fullerene-peptide-steroid triad **3a**[19] generated an optimal thread for the unsymmetrical, fullerene-steroid-stoppered molecular shuttle. By analogy, a *Succ-Gly-GABA* component as the molecular recognition core as well as pregnenolone subunits as endpoints were used to design the thread **3b** for a steroid-stoppered, interlocked system. The new compound **3b** was prepared analogous to **3a**, following the DCC/HOBT assisted amidation of the amine-TFA salt **1** using pregnenolone hemisuccinate **2b** in the presence of triethylamine in dichloromethane. Following the Leigh procedure,[22] isophthaloyl dichloride and *p*-xylylenediamine were simultaneously added to a solution of the corresponding threads **3**. Their diamide *GABA-Gly-GABA* and *GABA-Gly-Succ* subunits, containing two amide carbonyl functions in the 1,4-position, templated the macrocycle clipping around the axes, providing rotaxanes **4**. The careful flash column chromatography (FCC) of the crude, unsymmetrically stoppered, non-covalent hybrid on SiO_2 gave a mixture of rotaxane **4a** and the free tetraamide macrocycle (M). The conditions for their purification by chromatography on silica gel were not found, since both compounds showed equal R_f values in many applied eluents (numerous binary and ternary mixtures of $CHCl_3$, PhMe, EtOAc and MeOH). The favorable π–π interactions between the free macrocycle and the outer side of the fullerene subunit might be a reason for unsuccessful separation on the silica column. Nevertheless, pure rotaxane **4a** was obtained by gel filtration on Sephadex G-25 in $CHCl_3$, subsequent precipitation from $CHCl_3$ solution with MeOH and drying in a vacuum oven for two days (45 °C, 15 mbar). In the NMR spectrum in $CDCl_3$, signals corresponding to poorly soluble free M did not appear, while in [D_6]DMSO diluted with one drop of $CDCl_3$ (1 drop of $CDCl_3$ was necessary to completely dissolve the mixture **4a**/M) they were clearly visible, providing a way to check unambiguously the purity of rotaxane **4a**.

In contrast, a careful FCC of the disteroidal rotaxane **4b** proceeded smoothly, providing a pure target compound. Although performing hydrogen bond-templated interlocking afforded rotaxanes in quite a moderate yield (Scheme 1), their precursors were successfully recovered (80% of **3a** and 85% of **3b**) and reused. In addition to the structural requirements, the achieved yield might be attributed to the poor solubility of



Scheme 1 Synthesis of fullerosteroidal and disteroidal rotaxanes 4 with a tetraamide macrocycle.

thread precursors and the unthreading process in the presence of polar medium during column chromatography.

The structures of all compounds were determined from IR, NMR (^{1}H, ^{13}C, COSY, HSQC and HMBC) and HRMS spectra supported also by the UV/Vis data of the fullerene containing thread **3a** and rotaxane **4a**. The presence of a steroidal moiety in the rotaxane **4a** significantly improved its solubility in chloroform, but concentrations higher than 1.4 mM (2.5 mg mL^{-1}, used for ^{1}H NMR recording) led to solution jellification, indicating the compounds self-aggregate. Also, in the ^{13}C NMR spectrum in $CDCl_3$ no response for thread carbonyls was observed, while [D_6]DMSO (with addition of one drop of $CDCl_3$) enabled assignment of all carbons. Comparison of the ^{1}H NMR spectra of rotaxanes **4** and the corresponding threads **3** in $CDCl_3$ (Fig. 1) affirmed the interlocked architecture anchored by hydrogen bonds between the four macrocyclic amide H and the two amide carbonyl oxygen atoms. The location of the macrocycle on the diamide station (*GABA-Gly-GABA* in **4a** and *Succ-Gly-GABA* in **4b**, Scheme 2) was clearly determined from the chemical shift differences of the pyrrolidine, amide and steroid protons in rotaxanes and corresponding threads (Fig. 1, Tables S1 and S2 in ESI†).

Thus, as a result of the anisotropic effect of the macrocycle aromatic rings, both methylene and amide Gly protons of rotaxanes **4** are significantly upfield shifted in comparison to threads **3** ($\Delta\delta \sim 1$ ppm for CH_2; 1.0 and 0.5 ppm for NH of **4a** and **4b**, respectively). Somewhat weakened shielding of protons near the Gly N-side resulted in lesser shifting of ~0.4 ppm (*GABA* 2″, 3″ and *Succ* 2, 3 in **4a** and **4b**, respectively, Tables S1 and S2†). The smallest difference (up to 0.2 ppm) in the chemical shifts of the remaining signals belonging to the pyrrolidine ring, the rest of GABA and characteristic steroidal protons (H-3, H-6 and the angular methyl groups) confirmed the position of the macrocycle around the diamide binding site, as shown in Scheme 2. In addition, diverse shielding of the steroidal stoppers by the macrocycle aromatic rings led to the splitting of the olefinic H-6 signal (Fig. 1c and d and 2d and e).

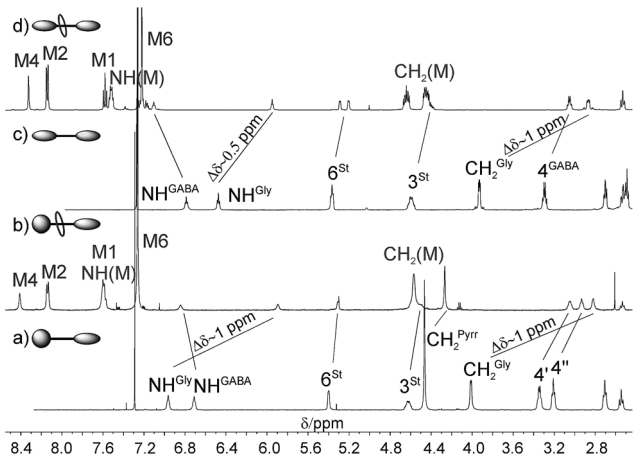
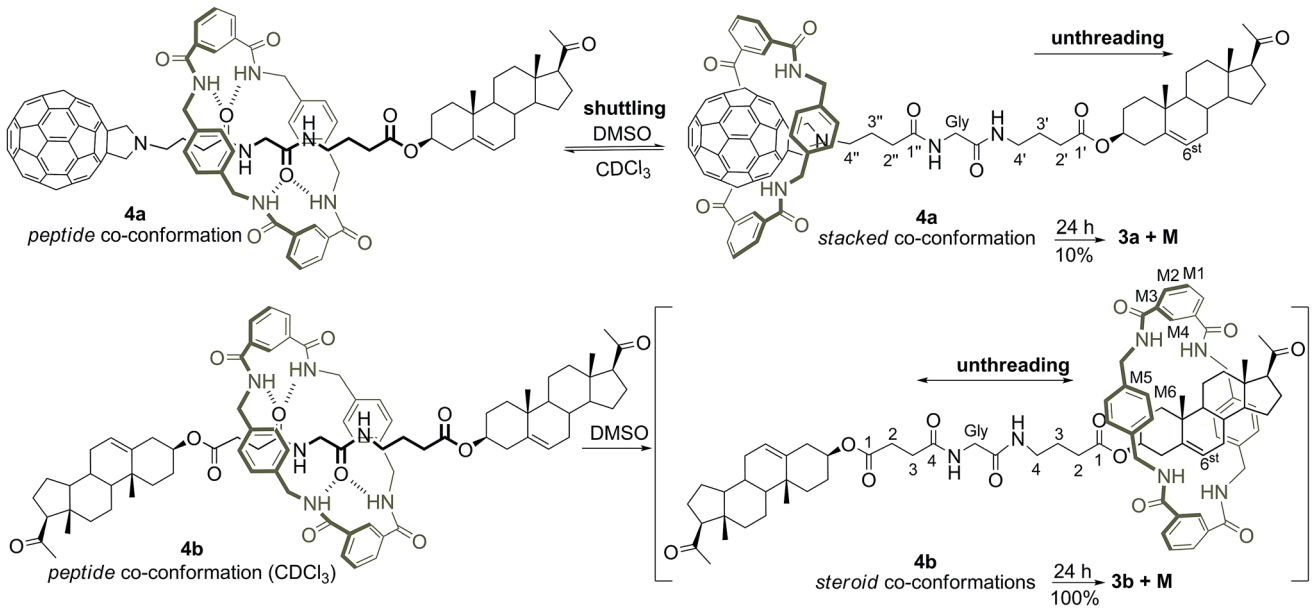


Fig. 1 Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of (a) thread **3a**, (b) rotaxane **4a**, (c) thread **3b**, and (d) rotaxane **4b**. Labels correspond to those indicated in Scheme 2.

Samples of both rotaxanes were kept in $CDCl_3$ solution for a week at room temperature with no NMR evidence of macrocycle release.

Exposing these compounds to solvents possessing strong H-bond accepting properties, such as DMSO, induced macrocycle shuttling along the corresponding threads. Thanks to the fullerene stopper and the resulting π–π interactions with four aromatic rings of the wheel,[9a,b] the mechanically interlocked architecture of rotaxane **4a** was mainly preserved, while under the same conditions, the disteroidal analogue **4b** appeared less stable. A striking upfield shift of the pyrrolidinic signal of rotaxane **4a** in DMSO (δ 3.38 ppm, Fig. 2b) in comparison to the same structure in $CDCl_3$ (δ 4.27 ppm, Fig. 1b), as well as to thread **3a** in DMSO (δ 4.45 ppm, Fig. 2a), was noticed, indicating wheel displacement to the fullerene proximity (see also Table S1†). Also, the resonances associated with methylene protons belonging to the GABA moiety adjacent to the pyrrolidine (2″–4″, Scheme 2) followed the same trend. Observed shifts (reducing the distance from the C_{60} moiety) additionally supported the macrocycle position (Fig. 2a–c and Table S1†) and formation of the *stacked* co-conformer of **4a** in [D_6]DMSO (Scheme 2). The resonance of macrocycle benzylic protons (CH_2(M)) appeared as a broad singlet only in rotaxane **4a** in $CDCl_3$ (Fig. 1b), indicating their fast exchange. The signal splitting (two multiplets for AB part of ABX system) in rotaxane **4b** in $CDCl_3$ (Fig. 1d) and in both rotaxanes in [D_6]DMSO (Fig. 2b and e) supports its reduced symmetry and indicates slow rotation of the macrocycle around the thread on the NMR time scale at room temperature.

In order to monitor shuttling processes in more detail, ^{1}H NMR titration of rotaxane **4a** in $CDCl_3$ with [D_6]DMSO was performed (Fig. 3). As can be seen, the first addition of [D_6]DMSO (1%, Fig. 3b) led to complete solvation of the GABA-amide proton provoking its strong downfield shift from δ 6.85 to 7.79 ppm, practically to the value observed for the free thread. In such conditions the chemical shift of the Gly amide proton was not changed, probably due to sterically hindered solvent access. A gradual increase of the medium polarity induced the progressive breakage of the wheel-thread H-bonds and the solvation of the macrocycle amide protons (NH(M)), leading to their deshielding of almost 1 ppm – from δ 7.79 ppm in the presence of 1% [D_6]DMSO to δ 8.76 ppm in the mixture containing 52% [D_6]DMSO (Fig. 3b–i). After addition of 15% [D_6]DMSO (Fig. 3f), several changes in the ^{1}H NMR spectrum were observed, all together suggesting the parallel existence of macrocycle conformational changes and solvation of Gly-NH. Thus, a broad singlet of CH_2(M) changed to two multiplets and the CH_2^{Pyrr} singlet was slightly shifted upfield ($\Delta\delta \sim 0.2$ ppm), while Gly-NH proton was shifted downfield ($\Delta\delta \sim 0.8$ ppm). A low level of unthreading was first detected with 42% [D_6]DMSO, resulting in the appearance of weak signals corresponding to the free thread as well as the macrocycle (Fig. 3h). Increasing the medium polarity to 52% [D_6]DMSO led to the upfield shift of the pyrrolidine singlet to $\delta < 3.70$ (overlapped with water signal) and further deshielding of both amide protons (Fig. 3i), indicating macrocycle motion preferentially toward the fullerene stopper and formation of the stable *stacked* co-conformer (Scheme 2).



Scheme 2 Solvent-induced translocation of the macrocyclic ring (M) with the proposed structures of co-conformers followed by partial and complete dissociation of rotaxanes **4a** and **4b**, respectively.

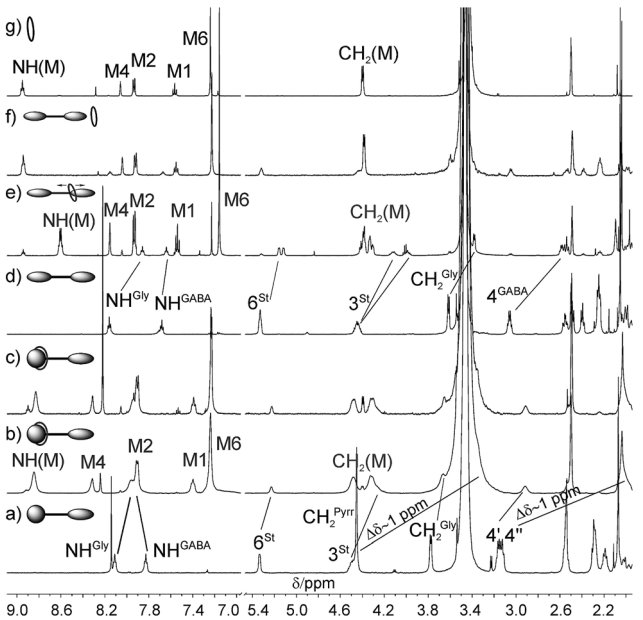


Fig. 2 Partial ^{1}H NMR spectra (500 MHz, [D$_6$]DMSO) of (a) thread **3a**, (b) rotaxane **4a** immediately after dissolution, (c) rotaxane **4a** after 24 h, (d) thread **3b**, (e) rotaxane **4b** immediately after dissolution, (f) rotaxane **4b** after 24 h, and (g) free macrocycle M. For labels, see Scheme 2.

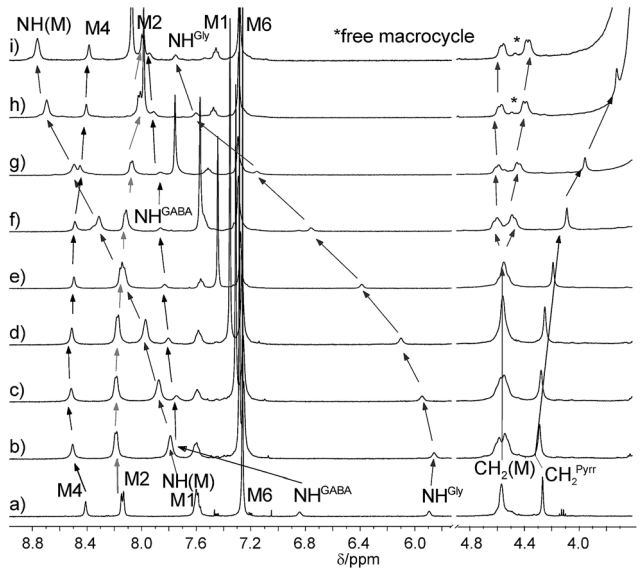


Fig. 3 ^{1}H NMR monitoring of macrocycle translocation in the rotaxane **4a** in CDCl$_3$ (a) induced by [D$_6$]DMSO (b: 1%, c: 2%, d: 4%, e: 8%, f: 15%, g: 30%, h: 42%, i: 52%).

No significant dissociation of fullerosteroidal rotaxane **4a** in [D$_6$]DMSO was detected over 24 h (2 and 10% after 1 and 24 h, respectively), while after 7 days in the same solvent 25% of the mechanically interlocked system underwent unthreading. In contrast, rigid but not sufficiently bulky pregnenolone units in the steroidal rotaxane **4b** allowed the macrocycle to slip over them, enabling a much faster dissociation process (4% after 1 h, 100% after 24 h). In such a case, many intermediate *steroid* co-conformers (Scheme 2) might be suggested. Due to the fast unthreading in a polar solvent at room temperature, in such conditions the supramolecular assembly **4b** could be considered as a pseudorotaxane.

Previously reported results confirming organogelation behaviour of the fullerene–cholesterol conjugate[23] and cholesterol-stoppered rotaxane,[18] prompted us to examine the self-organization properties of synthesized rotaxanes **4**. To that purpose, the solubility in individual solvents (CHCl$_3$, PhMe, THF, dioxane and EtOAc) and their binary mixtures was

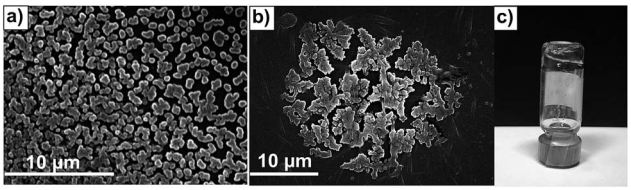


Fig. 4 SEM images of (a) rotaxane **4a** (0.1 mM in $CHCl_3$), (b) rotaxane **4b** (0.1 mM in PhMe/EtOAc = 1 : 1), and (c) photo of **4b** gel (1 mM in PhMe/EtOAc = 1 : 1).

checked, while the form of the aggregates obtained after solvent evaporation was followed by scanning electron microscopy (SEM). The presence of the fullerene moiety in rotaxane **4a** reduced its solubility, affording a clear solution only in chloroform. The jellification noticed at higher concentration (1.4 mM) during NMR recording indicated reorganization at the supramolecular level. The direct evidence for the tendency for self-ordering was obtained by SEM, the image of which revealed the association of quite uniform, round structures to micrometer-sized elongated particles (Fig. 4a). As expected, both disteroidal structures (thread **3b** and rotaxane **4b**) were easily soluble in all media used. However, unlike compound **3b**, after few minutes at room temperature a clear 1 mM solution of **4b** in PhMe/EtOAc 1 : 1 mixture was transformed into transparent gel, stable up to 50 °C (Fig. 4c). Prolonged drying of a drop of 0.1 mM solution allowed organization of **4b** into a branched film-like network (Fig. 4b) or into irregularly shaped large microstructures in the case of **3b** (Fig. S1 in ESI†), confirming their different affinities for aggregation. The observed difference in the gelation ability between the disteroidal thread **3b** and the corresponding rotaxane **4b** strongly indicates that hydrogen bonding interactions of the mechanically interlocked structure plays an important role in self-assembly, thereby controlling the gelation process.

4. Conclusions

Two novel hydrogen-bond assembled fullerosteroidal and disteroidal[2]rotaxanes are synthesized by *GABA-Gly-GABA* and *Succ-Gly-GABA* templated macrocycle clipping over the axles containing corresponding stoppers. ^{1}H NMR spectroscopy was used to investigate solvent-induced macrocycle movement along the threads, as well as the stability of the interlocked architectures, expressed as the affinity for unthreading. The target compounds have proven to be stable in a non polar environment ($CDCl_3$) regardless of the stopper nature, occupying the *peptide* co-conformation with the macrocycle anchored by the axle–wheel interamide H-bonds. In the case of the fullerene-stoppered rotaxane **4a**, the solvation of amide groups by [D_6]DMSO caused macrocycle translocation toward the fullerene and formation of a quite stable *stacked* co-conformer, stabilized by wheel-stopper π–π interactions. In contrast, rigid steroidal moieties turned out to be insufficiently bulky to protect the macrocycle from slipping, leading to practically quantitative unthreading of the disteroidal rotaxane **4b** after 24 h. In addition, both rotaxanes expressed a strong tendency to self-order, while a rotaxane with terminal pregnenolone units also showed organogelation behaviour. Based on their dynamic properties, these novel supramolecular architectures could be of use for designing new interlocked systems with controlled dissociation in polar medium.

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Notes and references

1 (*a*) M. Xue, Y. Yang, X. Chi, X. Yan and F. Huang, *Chem. Rev.*, 2015, **115**, 7398; (*b*) H. Tian and Q.-C. Wang, *Chem. Soc. Rev.*, 2006, **35**, 361; (*c*) X. Ma and H. Tian, *Chem. Soc. Rev.*, 2010, **39**, 70; (*d*) F. Vögtle, T. Dünwald and T. Schmidt, *Acc. Chem. Res.*, 1996, **29**, 451.

2 A. Mateo-Alonso, G. Fioravanti, M. Marcaccio, F. Paolucci, D. C. Jagesar, A. M. Brouwer and M. Prato, *Org. Lett.*, 2006, **8**, 5173–5176.

3 (*a*) A. Fernandes, A. Viterisi, F. Coutrot, S. Potok, D. A. Leigh, V. Aucagne and S. Papot, *Angew. Chem., Int. Ed.*, 2009, **48**, 6443; (*b*) R. Barat, T. Legigan, I. Tranoy-Opalinski, B. Renoux, E. Péraudeau, J. Clarhaut, P. Poinot, A. E. Fernandes, V. Aucagne, D. A. Leigh and S. Papot, *Chem. Sci.*, 2015, **6**, 2608.

4 R. Hernandez, H.-R. Tseng, J. W. Wong, J. F. Stoddart and J. I. Zink, *J. Am. Chem. Soc.*, 2004, **126**, 3370.

5 J. Zhu, M. McFarland-Mancini, A. F. Drew and D. B. Smithrud, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 520.

6 J. R. Johnson, N. Fu, E. Arunkumar, W. M. Leevy, S. T. Gammon, D. Piwnica-Worms and B. D. Smith, *Angew. Chem., Int. Ed.*, 2007, **46**, 5528.

7 (*a*) A. Rescifina, C. Zagni, D. Iannazzo and P. Merino, *Curr. Org. Chem.*, 2009, **13**, 448; (*b*) E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72; (*c*) C. J. Bruns and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2186; (*d*) T. D. Nguyen, H.-R. Tseng, P. C. Celestre, A. H. Flood, Y. Liu, J. F. Stoddart and J. I. Zink, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 10029.

8 (*a*) D. B. Amabilino and J. F. Stoddart, *Chem. Rev.*, 1995, **95**, 2725; (*b*) D.-H. Qu and H. Tian, *Chem. Sci.*, 2011, **2**, 1011; (*c*) G. Barin, R. S. Forgan and J. F. Stoddart, *Proc. R. Soc. London, Ser. A*, 2012, **468**, 2849.

9 (*a*) A. Mateo-Alonso, D. M. Guldi, F. Paolucci and M. Prato, *Angew. Chem., Int. Ed.*, 2007, **46**, 8120; (*b*) A. Mateo-Alonso, *Top. Curr. Chem.*, Fullerene-stoppered bistable rotaxanes, Springer Press, Berlin, Heidelberg, 2014, 348, pp. 127–137; (*c*) A. S. Lane, D. A. Leigh and A. Murphy, *J. Am. Chem. Soc.*, 1997, **119**, 11092.

10 J. J. Gassensmith, E. Arunkumar, L. Barr, J. M. Baumes, K. M. DiVittorio, J. R. Johnson, B. C. Noll and B. D. Smith, *J. Am. Chem. Soc.*, 2007, **129**, 15054.

11 E. A. Neal and S. M. Goldup, *Chem. Commun.*, 2014, **50**, 5128–5142.
12 (*a*) H. R. Tseng, S. A. Vignon and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2003, **42**, 1491; (*b*) A. Altieri, F. G. Gatti, E. R. Kay, D. A. Leigh, D. Martel, F. Paolucci, A. M. Z. Slawin and J. K. Y. Wong, *J. Am. Chem. Soc.*, 2003, **125**, 8644; (*c*) F. Durola and J. P. Sauvage, *Angew. Chem., Int. Ed.*, 2007, **46**, 3537.
13 (*a*) A. M. Elizarov, S. H. Chiu and J. F. Stoddart, *J. Org. Chem.*, 2002, **67**, 9175; (*b*) C. M. Keaveney and D. A. Leigh, *Angew. Chem., Int. Ed.*, 2004, **43**, 1222.
14 (*a*) A. M. Brouwer, C. Frochot, F. G. Gatti, D. A. Leigh, L. Mottier, F. Paolucci, S. Roffia and G. W. H. Wurpel, *Science*, 2001, **291**, 2124; (*b*) V. Balzani, M. Clemente-León, A. Credi, B. Ferrer, M. Venturi, A. H. Flood and J. F. Stoddart, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 1178.
15 G. Bottari, F. Dehez, D. A. Leigh, P. J. Nash, E. M. Pérez, J. K. Y. Wong and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2003, **42**, 5886.
16 T. Da Ros, D. M. Guldi, A. F. Morales, D. A. Leigh, M. Prato and R. Turco, *Org. Lett.*, 2003, **5**, 689.
17 A. Mateo-Alonso and M. Prato, *Tetrahedron*, 2006, **62**, 2003.
18 Y.-L. Zhao, I. Aprahamian, A. Trabolsi, N. Erina and J. F. Stoddart, *J. Am. Chem. Soc.*, 2008, **130**, 6348.
19 M. S. Bjelaković, T. J. Kop, M. Vlajić, J. Đorđević and D. R. Milić, *Tetrahedron*, 2014, **70**, 8564.
20 M. S. Bjelaković, D. M. Godjevac and D. R. Milić, *Carbon*, 2007, **45**, 2260.
21 J. D. Cocker, J. Elks, P. J. May, F. A. Nice, G. H. Phillipps and W. F. Wall, *J. Med. Chem.*, 1965, **8**, 417.
22 D. A. Leigh, A. Murphy, J. P. Smart and A. M. Z. Slawin, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 728.
23 T. Ishi-i, Y. Ono and S. Shinkai, *Chem. Lett.*, 2000, **29**, 808.