Supporting information to be published electronically

Sterically demanding benzene-1,3,5-tricarboxamides: tuning the mechanisms of supramolecular polymerization and chiral amplification

Martijn Veld (M.A.J.Veld@tue.nl), Daniël Haveman (D.Haveman@tue.nl), Anja Palmans (A.Palmans@tue.nl), E.W. Meijer (E.W.Meijer@tue.nl)

Molecular Science and Technology

Department of Chemical Engineering and Chemistry

Eindhoven University of Technology

P.O. Box 513, 5600 MB Eindhoven, the Netherlands

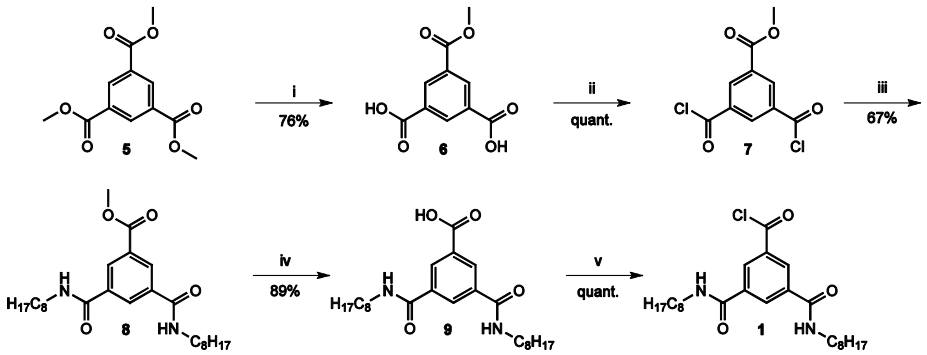
Table of contents

Detailed general information on syntheses

All chemicals were ordered from Sigma-Aldrich-Fluka and used as received unless stated otherwise. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at a Varian Mercury 400 MHz spectrometer at 400 and 100 MHz, respectively. Peaks are noted as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qui) or heptet (h), broadened peaks are noted as (br). Chemical shifts are reported in ppm and are relative to TMS for ^{1}H-NMR spectra (δ = 0 ppm) and the solvent peak for ^{13}C-NMR spectra ($CDCl_3$, $\delta = 77.16 \pm 0.32$ ppm; MeOD-d_4, $\delta = 49.00 \pm 0.01$ ppm; DMSO-d_6, $\delta = 39.52 \pm 0.06$ ppm).[1] MALDI-TOF-MS spectra were recorded on a PerSeptive Biosystems Voyager DE PRO spectrometer using the acidic α-cyano-4-hydroxycinnamic acid (CHCA) or neutral trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) matrix. FT-IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer. Elemental analysis was carried out on a Perkin Elmer 2400 apparatus.

Synthesis of 3,5-bis(octylaminocarbonyl)benozyl chloride (1)

This mono acid chloride was prepared according to a modified literature procedure[2] for the desymmetrization of commercially available trimethyl benzene-1,3,5-tricarboxylate (Scheme SI-1).



Scheme SI-1: Synthesis of 3,5-bis(octylaminocarbonyl)benzoic acid (**1**); (i) 1) 2.2 mol eq. NaOH, MeOH, 12 h, reflux; 2) Aq. HCl; (ii) 2.8 mol eq. oxalyl chloride, THF, argon, 1 h, 0 °C to r.t.; (iii) 2.5 mol eq. *n*-octylamine, 4.5 mol eq. Et_3N, DCM, argon, 12h, 0 °C to r.t.; (iv) 1) LiOH, $MeOH/H_2O$, 40 h, r.t.; 2) Aq. HCl.

*5-Methoxycarbonylbenzene-1,3-dicarboxylic acid (**6**)*

A 1000 mL flask was equipped with a cooler and charged with MeOH (500 mL) and NaOH pellets (8.84 g, 221 mmol). After complete dissolution of the NaOH, a suspension of trimethyl benzene-1,3,5-tricarboxylate (25.25 g, 100 mmol, 0.45 eq) in MeOH (250 mL) was added. The clear solution was refluxed for 12 h and cooled to r.t. Half of the solvent was removed *in vacuo*, and the reaction mixture was poured into 1 M HCl (1300 mL). The aqueous solution was extracted with Et_2O (4 ×

250 mL) and the combined organic layers were washed with 1 M HCl (150 mL) and subsequently dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to give a white solid in quantitative yield (23.83 g). To remove mono- and tri-acid side products, the crude product was finely ground, suspended in a mixture of $CHCl_3$ (575 mL) and EtOH (5.5 mL) and refluxed for 15 min. The hot solution was filtered over a Büchner funnel, after which the grinding and filtration procedure was repeated another five times until no side products were present according to LC-MS analysis. The product was dried overnight under reduced pressure at 50 °C and obtained as a fine white powder (17.14 g, 76.5 mmol, 76%). ^{1}H-NMR (DMSO-d_6) δ: 13.6 (br. s, 2H, -COOH), 8.65 (s, 1H, -ArH), 8.62 (s, 2H, -ArH), 3.94 (s, 3H, -$COOCH_3$) ppm. ^{13}C-NMR (DMSO-d_6) δ: 165.7, 164.8, 133.9, 133.4, 132.1, 130.7, 52.7 ppm. FT-IR: ν = 1714, 1702, 1410, 1267 cm^{-1}. Elemental analysis: $C_{10}H_8O_6$ (224.17) Calcd: C: 53.58 H: 3.60 Obs: C: 49.38 H: 3.85. (The observed elemental analysis data are in better correspondence with the monohydrate of **6** $C_{10}H_8O_6 \cdot H_2O$ (242.18) Calcd: C: 49.59 H: 4.16).

Methyl 3,5-dichlorocarbonylbenzoate (7)

Under an argon atmosphere, 5-methoxycarbonyl-benzene-1,3,-dicarboxylic acid (**6**) (3.12 g, 13.9 mmol) was dissolved in dry THF (15 mL) and DMF (2 drops) was added. Oxalyl chloride (5.01 g, 39.5 mmol, 2.8 eq) was dissolved in dry THF (15 mL) and slowly added over a 25 min interval while stirring at 0 °C. The reaction mixture was stirred at r.t. for another 30 min after which all volatiles were removed under reduced pressure. Compound **7** was obtained as a light yellow solid in quantitative yield (3.97 g) and directly used without further workup. ^{1}H-NMR ($CDCl_3$) δ: 9.03 (d, 1H, J = 1.6 Hz, -ArH), 8.98 (m, 2H, J = 1.6 Hz, -ArH), 4.04 (s, 3H, -COOMe) ppm. ^{13}C-NMR ($CDCl_3$) δ: 166.8, 164.2, 137.6, 136.8, 135.1, 132.8, 53.4 ppm. FT-IR: ν = 1757, 1729, 1600, 1446, 1431, 1307, 1210, 1143 cm^{-1}. According to ^{1}H-NMR and ^{13}C-NMR measurements, approximately 10% of 1,3,5-benzenetricarbonyl trichloride was present as contamination from the starting material, although no trimesic acid was visible during LC-MS analysis.

*Methyl 3,5-bis(octylaminocarbonyl)benzoate (**8**)*

Under an argon atmosphere, methyl 3,5-bis-chlorocarbonyl-benzoate (**7**) (3.97 g, 12.4 mmol) was dissolved in dry DCM (50 mL). While stirring at 0 °C, a solution of *n*-octylamine (3.97 g, 30.7 mmol, 2.5 eq) and Et_3N (5.65 g, 55.9 mmol, 4.5 eq) in dry DCM (50 mL) was added over a 30 min interval. Stirring was continued overnight while allowing the solution to warm to r.t. The clear, yellow reaction mixture was diluted with DCM (30 mL) and washed with 0.1 M HCl (3 × 50 mL) and brine (70 mL). When required, more DCM and water were added to improve the phase separation. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was

removed *in vacuo* to give a yellow oil that slowly crystallized. The crude product was recrystallized from EtOAc (25 mL) and placed at –20 °C to induce crystallization. Filtration over a Hirsch funnel and washing with cold EtOAc (3 × 5 mL) gave compound **8** as an off-white powder. (3.72 g, 8.3 mmol, 67% combined yield from three crops). ^{1}H-NMR ($CDCl_3$) δ: 8.52 (d, 2H, *J* = 1.6 Hz, -ArH), 8.41 (t, 1H, *J* = 1.6 Hz, -ArH), 6.36 (t, 2H, *J* = 4.9 Hz, -CONH-), 3.97 (s, 3H, -$COOCH_3$), 3.47 (dt, 4H, *J* = 7.1, 6.7 Hz, -CONHC$\underline{H}_2$-), 1.77-1.52 (m, 4H, -$CONHCH_2C\underline{H}_2$-), 1.46-1.19 (m, 20H, -CH_2-), 0.88 (t, 6H, *J* = 6.7 Hz, -CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 165.9, 165.8, 135.7, 131.1, 130.48, 129.9, 52.8, 40.6, 31.9, 29.7, 29.4, 29.3, 27.1, 22.8, 14.2 ppm. FT-IR: ν = 3261, 3089, 2956, 2921, 2852, 1730, 1661, 1633, 1598, 1561, 1466, 1439, 1388, 1324, 1268, 1259, 1199, 1179, 990, 916, 710, 700 cm^{-1}. MALDI-TOF-MS: Calculated M = 446.31 g/mol, observed m/z = 469.15 $[M + Na]^+$, 447.18 $[M + H]^+$ g/mol.

*3,5-Bis(octylaminocarbonyl)benzoic acid (**9**)*

A 100 mL flask was equipped with a stirring bar and methyl ester **8** (2.31 g, 5.18 mmol) was dissolved in MeOH (50 mL). Solid $LiOH{\cdot}H_2O$ (325.8 mg, 7.77 mmol, 1.5 eq) was added, after which a white precipitate formed. After addition of H_2O (2.6 mL), the precipitate slowly redissolved and a clear solution was obtained. The reaction mixture was stirred at r.t. until all methyl ester was hydrolyzed according to ^{1}H-NMR analysis (complete conversion after 40 h). The product was precipitated in 1 M HCl (400 mL), filtered over a Büchner funnel, washed with 1 M HCl (3 × 10 mL) and dried overnight under vacuum at 50 °C. Compound **9** was isolated as a fine white powder (1.98 g, 4.59 mmol, 89%). ^{1}H-NMR ($CDCl_3$:MeOD-d_4 98:2 v/v) δ: 8.50 (s, 2H, -ArH), 8.38 (s, 1H, -ArH), 7.06-6.82 (br. s., 2H, -CONH-), 3.43 (t, 4H, *J* = 7.1 Hz, -CONHC$\underline{H}_2$-), 1.66-1.56 (m, 4H, -$CONHCH_2C\underline{H}_2$-), 1.44-1.17 (m, 20H, -CH_2-), 0.86 (t, 6H, *J* = 6.2 Hz, -CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 166.5, 164.9, 135.3, 131.2 130.3, 130.1 39.4 31.24, 28.9, 28.7, 28.6, 26.5, 22.1, 13.9 ppm. FT-IR: ν = 3323, 3075, 2956, 2923, 2854, 1702, 1642, 1596, 1538, 1450, 1288, 1235, 1182 cm^{-1}. MALDI-TOF-MS: Calculated M = 432.30 g/mol, observed m/z = 455.18 $[M + Na]^+$, 433.20 $[M + H]^+$. Elemental analysis: $C_{25}H_{40}N_2O_4$ (432.60) Calcd: C: 69.41 H: 9.32 N: 6.48 Obs: C: 69.49 H: 9.20 N: 6.48.

*3,5-Bis(octylaminocarbonyl)benzoyl chloride (**1**)*

Under an argon atmosphere, 1-chloro-*N*,*N*,2-trimethylpropenylamine (194 mg, 1.45 mmol, 200 µL, 1.45 eq) was dissolved in dry DCM (10 mL). Compound **9** (431 mg, 1.00 mmol) was added divided over 3 portions. New carboxylic acid was added as soon as a clear solution was obtained. After complete addition of **9**, stirring was continued for 1 h at r.t. All volatiles were removed *in vacuo* and crude **1** was quantitatively obtained as a off-white solid together with *N*,*N*-dimethylisobutyramide

(total mass: 575 mg). The product was directly used without any further purification. ^{1}H-NMR ($CDCl_3$) δ: 8.59 (s, 2H, -ArH), 8.51 (s, 1H, -ArH), 6.39 (s, 1H, -CONH-), 3.58-3.39 (dt, 4H, J = 6.8, 6.4 Hz, -CONHC$\underline{H}_2$-), 1.71-1.59 (m, 4H, -CONHCH$_2$C$\underline{H}_2$-), 1.45-1.21 (m, 20H, -CH$_2$-), 0.89 (t, 6H, J = 6.6 Hz, -CH$_3$) ppm. ^{13}C-NMR ($CDCl_3$) δ: 167.7, 165.4, 136.0, 134.0, 132.4, 132.0, 40.7, 31.9, 29.6, 29.4, 29.3, 27.2, 22.7, 14.2 ppm. FT-IR (crude product): ν = 3289, 3075, 2956, 2926, 2855, 1761, 1640, 1543, 1466, 1437, 1292, 1216, 1130, 977, 910, 732 cm^{-1}. Additional peaks from the *N*,*N*-dimethylisobutyramide side product are also visible in the ^{1}H-NMR ($CDCl_3$) δ: 3.00 (s, 6H, -N(CH$_3$)$_2$) 2.83 (h, 1H, J = 6.9 Hz, -C$\underline{H}$(CH$_3$)$_2$), 1.13 (d, 6H, J = 6.7 Hz, -CH(C$\underline{H}_3$)$_2$) and ^{13}C-NMR ($CDCl_3$) δ: 177.5, 30.3, 29.5, 19.3 ppm.

Comparison of the CD spectra of BTAs (*S*)-2 and (*S*,*S*,*S*)-4

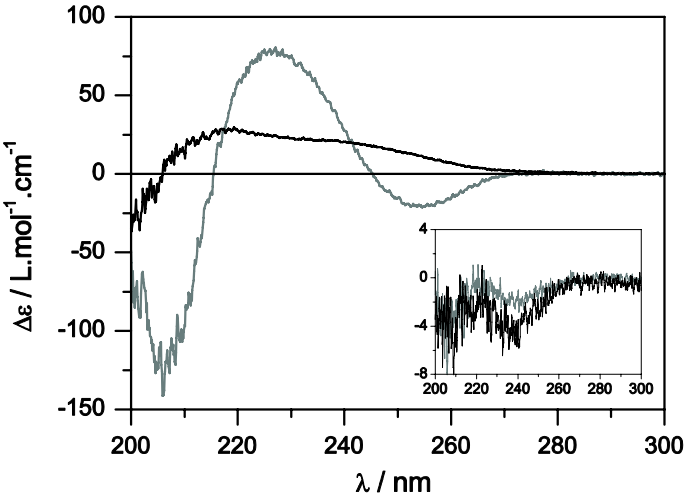


Figure SI-1: CD spectra of (*S*)-**2** (black line, c = $5 \cdot 10^{-5}$ M) and (*S*,*S*,*S*)-**4** (gray line, c = $1.0 \cdot 10^{-5}$ M) in MCH at 20 °C. The inset shows the residual CD effect in the molecularly dissolved state as measured at the same concentration in MeCN.

CD and UV-vis characterization of (PheOct)(octyl)$_2$ BTA (2)

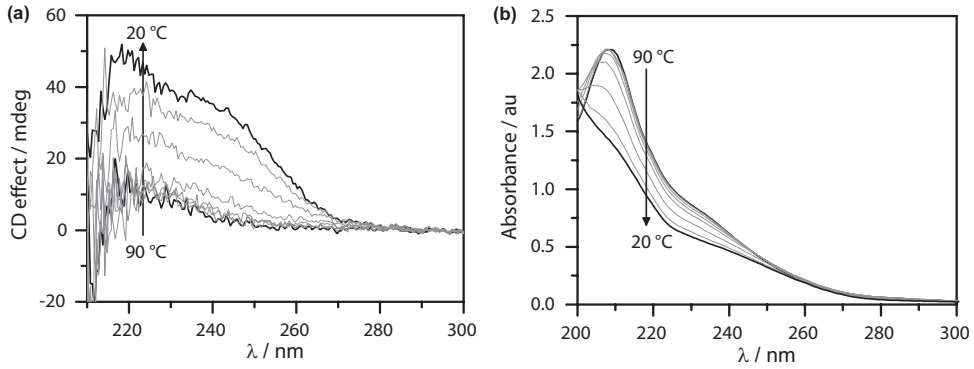


Figure SI-2: (a) CD and (b) UV-vis spectra for **(*S*)-2** at temperatures between 90 and 20 °C (data shown at 10 °C increments, $c = 5 \cdot 10^{-5}$ M, MCH).

At temperatures between 90 and 60 °C, a small residual CD effect was visible for BTA **2** (+8 mdeg at $\lambda = 225$ nm), which is different from the molecularly dissolved state as measured in acetonitrile at the same concentration. According to the UV-vis spectra, BTA **2** is completely molecularly dissolved at elevated temperature in MCH. The differences in the spectral features of the molecularly dissolved state at high temperature in MCH and acetonitrile are therefore attributed to the largely different polarity of the solvents ($\varepsilon_r = 2.02$ and 37.5, respectively), which can result in a difference in preferential conformation and thus spatial ordering of the chromophores in both situations.

CD and UV-vis characterization of $(PheOct)_3$ BTA (4)

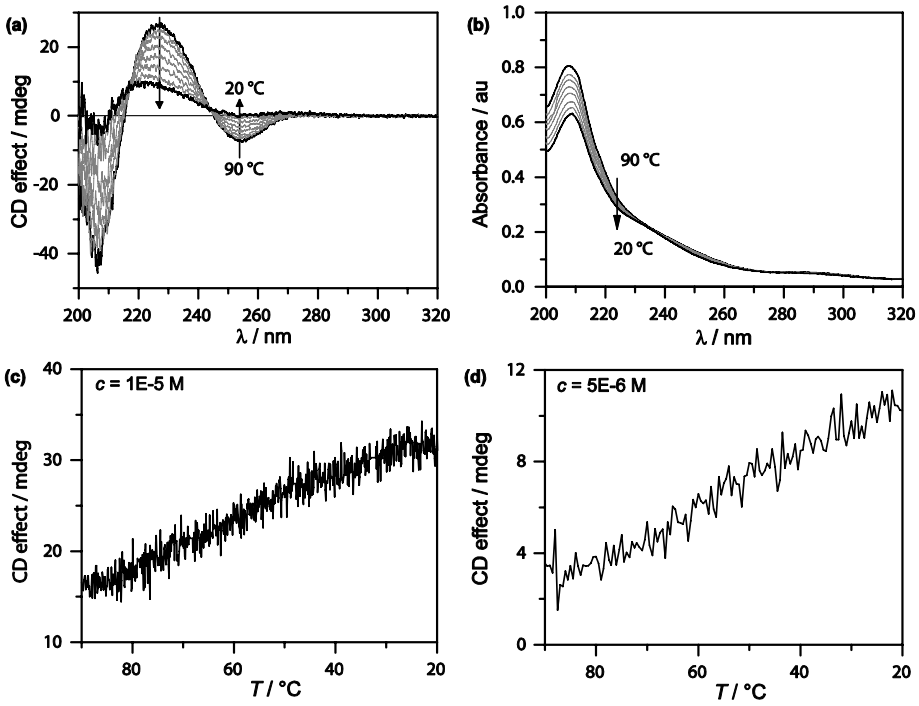


Figure SI-3: (a)-(b) Full CD (a) and UV-vis spectra (b) for (*S*,*S*,*S*)-**4** at temperatures between 90 and 20 °C (10 °C increments, $c = 1 \cdot 10^{-5}$ M, MCH); (c)-(d) Temperature dependence of the CD effect of (*S*,*S*,*S*)-**4** at λ = 225 nm showing a nearly linear dependence of the spectral changes on temperature for: $c = 1 \cdot 10^{-5}$(c) and $c = 5 \cdot 10^{-6}$ M (d).

The shape of the CD-effect of BTA **4** changes with temperature, which indicates that the state at high temperature displays a significant, non-zero CD-effect. The differences in the shape of the CD-effect were the same over the complete investigated concentration regime ($c = 5 \cdot 10^{-5}$ to $2 \cdot 10^{-6}$ M). However, the CD-spectra showed the existence of two isosbestic points at λ = 219 and 245 nm, meaning that two species are in equilibrium with each other.

Full CD-spectra of majority rules experiments

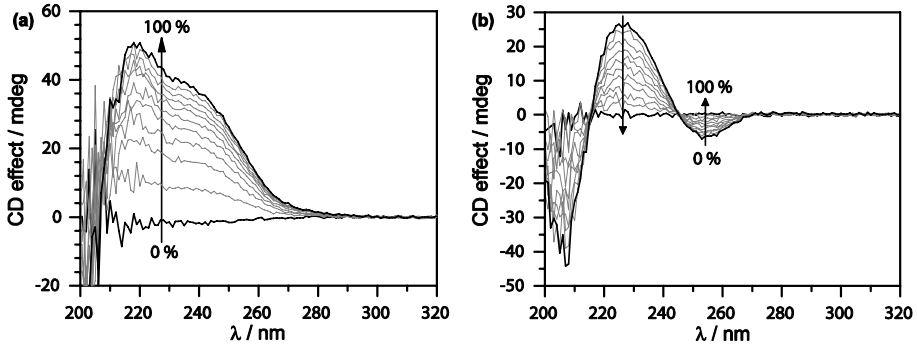


Figure SI-4: Full CD spectra at increments of 10% *e.e.* for majority rules experiments of BTAs: (a) **2** (c_{total} = 5·10^{-5} M) and (b) **4** (c_{total} = 1·10^{-5} M) (All measurements: MCH, 20 °C.)

Full CD spectra of mixing experiments between (*S*)-2 and (octyl)$_3$ BTA

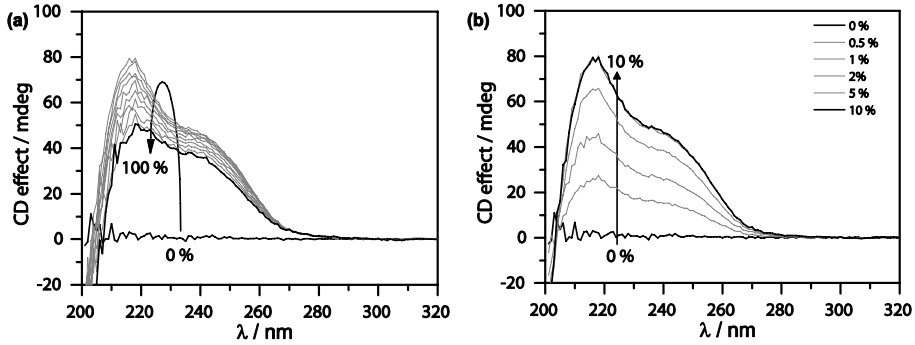


Figure SI-5: (a) Full CD spectra for a mixing experiment between (*S*)**-2** and (Octyl)$_3$ BTA as function of composition (data shown at 10 mol% increments); (b) Spectra for samples with a $x_{(S)\text{-}2}$ between 0 and 10 mol%. (λ = 225 nm, $c_{total} = 5 \cdot 10^{-5}$ M, MCH, 20 °C)

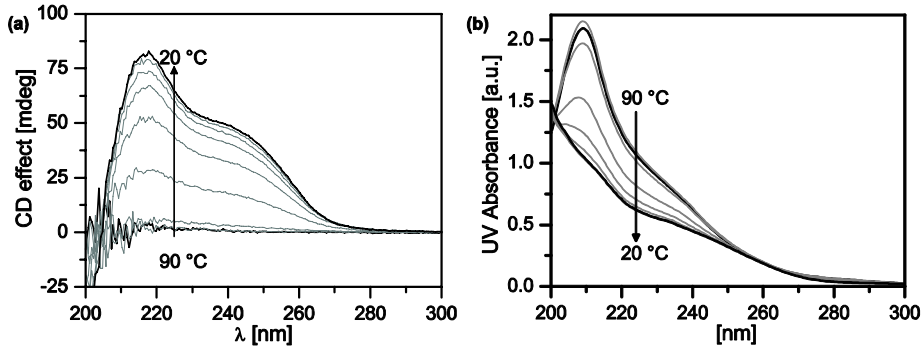


Figure SI-6: (a) CD and (b) UV-vis spectra at 10 °C increments for a mixture of (Octyl)$_3$ BTA and (*S*)**-2** with $x_{(S)\text{-}2} = 0.20$ (all measurements: $c_{total} = 5 \cdot 10^{-5}$ M, MCH).

Full CD spectra of mixing experiments between (*S*,*S*,*S*)-2 and (octyl)$_3$ BTA

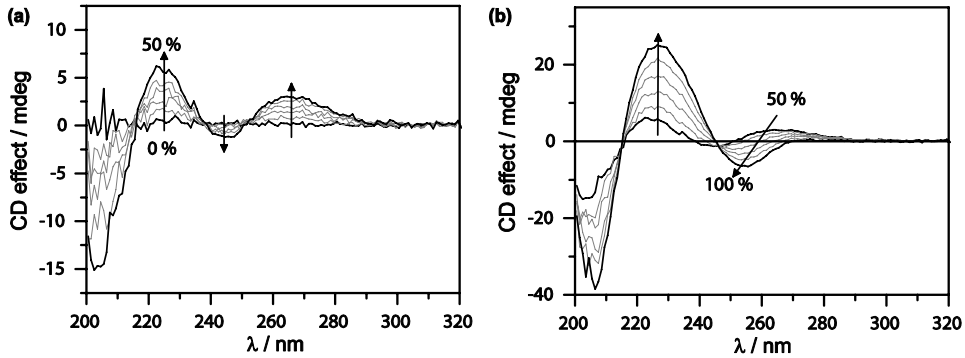


Figure SI-7: Full CD spectra for mixing experiment between (*S*,*S*,*S*)-**4** and (Octyl)$_3$ BTA as a function of composition (a) Regime I ($0 < x_{(S,S,S)\text{-}4} < 0.50$); (b) Regime II ($0.50 < x_{(S,S,S)\text{-}4} < 1.0$) (All measurements: $c_{total} = 1 \cdot 10^{-5}$ M, MCH, 20 °C.)

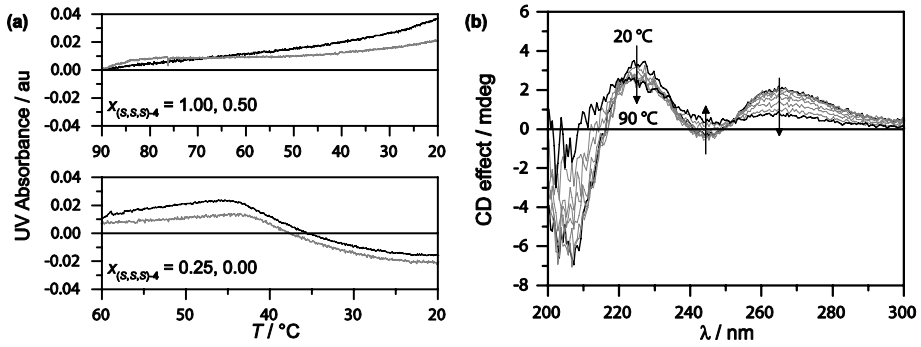


Figure SI-8: (a) Temperature-dependent wavelength monitoring at λ = 225 nm for mixtures of (*S*,*S*,*S*)-**4** and (Octyl)$_3$ BTA with varying compositions: $x_{(S,S,S)\text{-}4} = 1.0$ (black line top), $x_{(S,S,S)\text{-}4} = 0.50$ (gray line top), $x_{(S,S,S)\text{-}4} = 0.25$ (gray line bottom), and $x_{sergeant} = 0.0$ ($c = 5 \cdot 10^{-6}$ M, black line bottom) (All measurements: $c_{total} = 1 \cdot 10^{-5}$ M, unless otherwise stated, MCH); (b) Full CD spectra at increments of 10 °C for $x_{(S,S,S)\text{-}4} = 0.25$ showing a residual CD effect at 90 °C ($c_{total} = 1 \cdot 10^{-5}$ M).

Data analysis procedure for temperature-dependent spectroscopic data

The temperature-dependent data were corrected for differences in solvent absorption as a result of a temperature change. Subsequently, the data were normalized to and depending on the type of supramolecular aggregation behavior, data were fitted according to an isodesmic (equal K) model, or nucleation elongation model.

Procedure isodesmic temperature-dependent spectroscopic data

To obtain the thermodynamic parameters T_m and ΔH, and $K(T)$ characteristic for an isodesmic self-assembly process a procedure described in literature was used.[3] Spectral data were normalized between 0 and 1 to give the fraction of aggregated monomer (ϕ) at temperature T. These data were fitted using a sigmoidal relationship in equation (1) in which T_m is the temperature at which $\phi = 0.5$ and T^* is a characteristic temperature.

$$\phi(T) \cong \frac{1}{1+\exp\left[\frac{T-T_m}{T^*}\right]} \tag{1}$$

The following relationship between T^* and ΔH was used to calculate ΔH:

$$T^* = \frac{-RT_m^2}{0.908\Delta H} \tag{2}$$

The number average degree of polymerization $DP_N(T)$ was subsequently determined from the fitted data of $\phi(T)$ using equation (3):

$$DP_N(T) = \frac{1}{\sqrt{1-\phi(T)}} \tag{3}$$

The association constant $K(T)$ at a total monomer concentration c_T was calculated from the obtained expression for DP_N shown in equation (4).

$$DP_N(T) = \frac{1}{2} + \frac{1}{2}\sqrt{4K(T)c_T + 1} \tag{4}$$

Procedure for cooperative temperature-dependent spectroscopic data[4]

Data for the degree of aggregation (ϕ) were normalized based on the datapoints directly before T_e (value 0) and the datapoints at the lowest measured temperature (value 1). Then, a non-linear least squares curve fitting procedure using the nucleation elongation model was performed to the normalized data to extract the thermodynamic parameters describing the aggregation process.[4] Formula 6.1 was used to describe the data in the elongation regime between the temperature at which $\phi = 0.15$ and $\phi = 1.0$.

$$\phi = \phi_{sat}\left(1 - \exp\left[\frac{-h_e}{RT_e^2}(T - T_e)\right]\right) \tag{5}$$

The normalized data were subsequently divided by ϕ_{sat} and then the nucleation regime was fitted according to formula 6 to obtain a value for the nucleation constant Ka.[4] Data were fitted for the temperature regime between T_e and T_e + 10 K, while keeping the values for T_e and h_e at the previously determined values.

$$\phi_n = K_a^{1/3}\exp\left[\left(\frac{2}{3}K_a^{-1/3} - 1\right)\frac{h_e}{RT_e^2}(T - T_e)\right] \tag{6}$$

The obtained values for he are significantly different in the two different regions. When keeping both the values for h_e and T_e at their values as determined from the elongation regime as suggested in literature,[4] large deviations between the fitted curve and experimental data were found.

References

1. H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512-7515.
2. J. Roosma, T. Mes, P. Leclère, A. R. A. Palmans and E. W. Meijer, *J. Am. Chem. Soc.*, 2008, **130**, 1120-1121.
3. M. M. J. Smulders, M. M. L. Nieuwenhuizen, T. F. A. de Greef, P. van der Schoot, A. Schenning and E. W. Meijer, *Chem. Eur. J.*, 2010, **16**, 362-367.
4. M. M. J. Smulders, A. P. H. J. Schenning and E. W. Meijer, *J. Am. Chem. Soc.*, 2008, **130**, 606-611.