### **Thioamides: Versatile Bonds To Induce Directional and Cooperative** Hydrogen Bonding in Supramolecular Polymers

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Abstract: The amide bond is a versatile functional group and its directional hydrogen-bonding capabilities are widely applied in, for example, supramolecular chemistry. The potential of the thioamide bond, in contrast, is virtually unexplored as a structuring moiety in hydrogen-bonding-based self-assembling systems. We report herein the synthesis and characterisation of a new self-assembling motif comprising thioamides to induce directional hydrogen bonding. N,N',N"-Trialkylbenzene-1,3,5-tris-(carbothioamide)s (thioBTAs) with either achiral or chiral side-chains have been readily obtained by treating their amide-based precursors with P<sub>2</sub>S<sub>5</sub>. The thioBTAs showed thermotropic liquid crystalline behaviour and a columnar mesophase was assigned. IR spectroscopy revealed that strong, three-fold, intermolecular hydrogen-bonding interactions stabilise the columnar structures. In apolar alkane solutions, thio-BTAs self-assemble into one-dimensional, helical supramolecular polymers stabilised by three-fold hydrogen bonding. Concentration- and temperaturedependent self-assembly studies performed by using a combination of UV and CD spectroscopy demonstrated a cooperative supramolecular polymerisation mechanism and a strong amplification of supramolecular chirality. The high dipole moment of the thioamide bond in combination with the anisotropic shape of the resulting cylindrical aggregate gives rise to sufficiently strong depolarised light scattering to enable depolarised dynamic light scat-

Keywords: dynamic light scattering • polymers • self-assembly • supramolecular chemistry thioamides

tering (DDLS) experiments in dilute alkane solution. The rotational and translational diffusion coefficients,  $D_{\text{trans}}$  and  $D_{\text{rot}}$ , were obtained from the DDLS measurements, and the average length, L, and diameter, d, of the thio-BTA aggregates were derived (L =490 nm and d=3.6 nm). These measured values are in good agreement with the value  $L_w = 755 \text{ nm}$  obtained from fitting the temperature-dependent CD data by using a recently developed equilibrium model. This experimental verification validates our common practice for determining the length of BTA-based supramolecular polymers from model fits to experimental CD data. The ability of thioamides to induce cooperative supramolecular polymerisation makes them effective and broadly applicable in supramolecular chemistry.

good proteolytic stability, strong hydrogen-bond-donating capacity and easy synthetic accessibility.<sup>[3]</sup> The introduction of thioamide bonds into peptides at specific positions allows tuning of the stability of  $\alpha$ -helical structures and investigation of the folding dynamics of  $\beta$ -sheet formation.<sup>[4]</sup> Also, the thioamide group is an effective fluorescence quencher and useful for investigating conformational changes in oligopeptides and proteins.<sup>[5]</sup> The thioamide group normally resides in a trans conformation; however, under UV light, the trans conformer readily isomerises to the cis conformer.<sup>[6]</sup> This characteristic has been successfully applied to generate a photoswitchable element within a peptide backbone and allows the on/off switching of catalytic activity in enzymes.<sup>[7]</sup> Apart from the potential of the thioamide in elucidating protein dynamics and folding, the replacement of proteolytically sensitive amides by thioamides has been a successful strategy in the design of new inhibitors; closthioamide was recently described as a very potent antibiotic for several resistant bacteria strains.<sup>[8]</sup> Despite all these attractive properties, the thioamide bond has received remarkably little at-

#### Introduction

The importance of amide groups for directional hydrogenbonding interactions is well recognised in proteins, polyamides and in supramolecular chemistry.<sup>[1,2]</sup> In contrast, the thioamide group is much less explored, although it possesses many beneficial properties such as a high dipole moment,

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204273.

Chem. Eur. J. 2013, 00, 0-0

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tention in the field of supramolecular chemistry. Although thioamide-containing macrocycles and polymers are effective metal chelators<sup>[9]</sup> and anion binders,<sup>[10]</sup> the ability of the thioamide bond as a structuring moiety in hydrogen-bond-ing-based self-assembling systems is virtually unexplored.

In recent years, we and others have explored in detail the properties of N,N',N"-trialkylbenzene-1,3,5-tricarboxamides (BTAs), discotic molecules consisting of a central benzene and three alkyl chains coupled to the core through amide bonds.<sup>[11]</sup> These simple compounds show considerable application potential as thermotropic liquid crystals,<sup>[12]</sup> organogels,<sup>[13]</sup> nucleating agents for isotactic polypropylene<sup>[14]</sup> and multivalent scaffolds for biomedical applications.<sup>[15]</sup> In addition, the effect of subtle changes in the molecular structures of BTAs on their self-assembling properties has been studied by our group. For example, the effect of variations in amide connectivity<sup>[16]</sup> and the number of stereogenic centres,<sup>[17]</sup> and the introduction of isotope chirality<sup>[18]</sup> and hydrophilic<sup>[19]</sup> or fluorophilic<sup>[20]</sup> side-chains into the BTA structures have been analysed. In all cases, the self-assembly is highly cooperative and governed by the formation of three hydrogen bonds between consecutive discs.<sup>[21]</sup>

In general, hydrogen bonds between thioamides are reported to be weaker than in secondary amides.<sup>[22]</sup> In addition, thioamides show UV/CD absorption at higher wavelengths than amides.<sup>[23]</sup> This latter feature facilitates the probing of their self-assembly in systems with additional chromophores. Herein, we show that the replacement of the amide bond by a thioamide in BTAs results in a supramolecular motif with self-assembling properties similar to those of amide-based BTAs. The supramolecular polymers formed show a comparable stability to their amide counterparts and a strong amplification of the supramolecular chirality. Remarkably, the high dipole moment of thioamides in combination with the highly anisotropic shape of the formed aggregates allows an in-depth depolarised dynamic light scattering analysis from which the length of the supramolecular polymers can be derived. Although theoretical models that describe cooperative self-assembly allow prediction of the average number of monomer units per polymer chain,<sup>[24]</sup> the experimental validation of these predictions for BTA-based supramolecular polymers proved to be a challenging task. The depolarised dynamic light scattering experiments have enabled us, for the first time, to relate the theoretically predicted lengths of thioBTA-based supramolecular polymers to measured quantities.

#### **Results and Discussion**

**Synthesis and characterisation**: A number of synthetic methods are available for converting amides into thioamides.<sup>[25]</sup> We selected  $P_2S_5$  because of its ease of reaction and accessibility.<sup>[25d]</sup> After optimisation of the reaction conditions, thio-BTAs **2a–c** were prepared by treating their amide counterparts **1a–c** with an excess of  $P_2S_5$  at reflux in toluene (Scheme 1). Three derivatives were prepared, comprising



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Scheme 1. Synthesis of the thioBTAs **2a–c** from the corresponding BTAs **1a–c**.

either an achiral *n*-dodecyl (**2a**), a chiral (*S*)-3,7-dimethyloctyl ((*S*)-**2b**) or an (*R*)-3,7-dimethyloctyl side-chain ((*R*)-**2c**). All compounds were purified by column chromatography and isolated in reasonable yields (48, 66 and 25%, respectively). IR spectroscopy showed the complete disappearance of the C=O stretch at 1640 cm<sup>-1</sup>, indicative of the full conversion of the amides **1** into thioamides **2** (see Figure S1 in the Supporting Information). <sup>1</sup>H and <sup>13</sup>C NMR analysis in combination with MALDI-TOF MS further confirmed the proposed structures and high purity of compounds **2a–c**.

Behaviour of thioBTAs 2a-c in the solid state: With the help of polarised optical microscopy (POM) and differential scanning calorimetry (DSC), the thermal behaviour of thio-BTAs 2a,b was investigated. Under crossed polarisers, compound 2a is mobile and birefringent at room temperature indicating the presence of a mesophase. In contrast, compound **2b** is an amorphous solid at room temperature with birefringent textures starting to appear above 100°C. The clearing temperatures into the isotropic liquid are around 263 and 288°C for 2a and 2b, respectively.<sup>[26]</sup> The phasetransition temperatures and corresponding enthalpies were then accurately determined by DSC. The results are discussed for the second heating (heating/cooling rates of 10 Kmin<sup>-1</sup>, see Figure S2 in the Supporting Information for full traces). Compound 2a shows two thermal transitions at -4.5 ( $\Delta H$  = 3.30 kJ mol<sup>-1</sup>) and 254 °C ( $\Delta H$  = 6.05 kJ mol<sup>-1</sup>) whereas compound **2b** shows two transitions at 95 ( $\Delta H =$ 3.65 kJ mol<sup>-1</sup>) and 260 °C ( $\Delta H = 11.30 \text{ kJ mol}^{-1}$ ). The first transition is attributed to the transition into the mesophase and the second one to the clearing temperature. Interestingly, the clearing temperatures are about 30 K higher than those reported for the corresponding amide derivatives (see Table S1), which indicates a more stable mesophase for thio-BTAs.<sup>[12a, c, 27]</sup>

The textures grown by the slow cooling of compounds **2a,b** are typical of the presence of a columnar mesophase (see Figure S3 in the Supporting Information for representative examples). The nature of the mesophase was deter-

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mined on the basis of the X-ray diffraction (XRD) measurements performed on compound 2a. The diffraction pattern of compound 2a at 100 °C is presented in Figure S4 and the data are summarised in Table S2 in the Supporting Information. In the small-angle area, three reflections at 1.82, 1.05 and 0.92 nm are found. The spacings show a reciprocal ratio of  $1:\sqrt{3:2}$ , which is consistent with hexagonal packing of the columnar structures. In addition, two reflections are found in the wide-angle area, a diffuse reflection at 0.45 nm and a sharper reflection at 0.35 nm. The first corresponds to the disordered aliphatic side-chains and the second is representative of the interdisc distance. The sharpness of the reflection at 0.35 nm indicates an ordered packing of the discs within the columnar structures. The intercolumnar distance is approximately 2.10 nm. The mesophase of compound 2a could thus be assigned as Col<sub>ho</sub>.

IR spectroscopy is a sensitive tool for assessing the presence of hydrogen-bonding interactions in the solid state. Previous research from our group unambiguously showed that three-fold intermolecular hydrogen bonding is present in the mesophase and in the crystalline state of the amide-BTAs, characterised by peaks at around 3240 (NH stretch), 1640 (amide I) and 1564 cm<sup>-1</sup> (amide II).<sup>[11,12c]</sup> The IR spectrum of compound **2a** in the mesophase (Figure 1) shows an



Figure 1. IR spectrum of compound **2a** (bulk, mesophase) at room temperature.

NH stretch at 3180 cm<sup>-1</sup>, a CN vibration at 1539 cm<sup>-1</sup> and a C=S vibration at 693 cm<sup>-1,[28]</sup> The low value for the NH stretch in the thioBTAs is indicative of the presence of strong hydrogen bonding; the N–H stretch in non-hydrogen-bonded systems is at around 3400 cm<sup>-1,[29]</sup> Although **2b** is crystalline at room temperature, its IR spectrum is very similar to that of **2a** (see Figure S1 in the Supporting Information), which indicates that the helical columnar packing of the thioamides is retained in the crystalline state.

**Self-assembly of thioBTAs in dilute alkane solution**: We selected methylcyclohexane (MCH) as the solvent of choice to evaluate the self-assembly of thioBTAs because it is apolar

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yet offers good solubility for the thioBTAs. The IR spectra of compound **2b** in MCH (c=2 mM, T=20 °C) shows identical NH and CN stretches to the solid-state sample (see Figure S4 in the Supporting Information). These similar values indicate that the columnar structures stabilised by hydrogen bonds in the solid state are retained in MCH solution.

The UV spectra of the thioBTAs in MCH are significantly redshifted compared with those of the amide-based BTAs.<sup>[30]</sup> The UV spectrum of **2c** (Figure 2A), for example, shows a



Figure 2. a) Overlay of the UV and CD spectra of compound 2c; b) mirror-image CD spectra of 2b,c in MCH ( $c=2.2 \times 10^{-5}$  M); c) UV spectra and d) CD spectra of 2b between 20 and 80 °C (the arrows show the shifts upon increasing the temperature;  $c=1.7 \times 10^{-5}$  mol L<sup>-1</sup> in MCH).

 $\lambda_{max}$  at 228 nm with a pronounced shoulder at 305 nm, whereas the  $\lambda_{max}$  of **1c** is located at 195 nm in MCH. In addition, the CD spectrum of 2c is more complicated than that of 1c. The CD spectrum of 2c shows several positive and negative extrema ( $\Delta \varepsilon = -53.3 \text{ Lmol}^{-1} \text{ cm}^{-1}$  at 216 nm,  $\Delta \varepsilon =$ 20.7 L mol<sup>-1</sup> cm<sup>-1</sup> at 228 nm,  $\Delta \varepsilon = -48.2$  L mol<sup>-1</sup> cm<sup>-1</sup> at  $\Delta \varepsilon = 55.9 \,\mathrm{L}\,\mathrm{mol}^{-1}\,\mathrm{cm}^{-1}$ 238 nm, at 316 nm,  $\Lambda \epsilon =$  $11.6 \text{ Lmol}^{-1} \text{ cm}^{-1}$  at 377 nm), whereas that of **1b** shows one positive extremum at 195 nm and one negative extremum at 223 nm. The enantiomers 2b,c display perfect mirror-image CD spectra (Figure 2B). These observations indicate that thioBTAs self-assemble in MCH in helical supramolecular polymers, similarly to amide-based BTAs, and that the presence of stereogenic centres biases the helicity. Increasing the temperature to 80°C results in a redshift of the UV maximum of 2b to 237 nm whereas the shoulder is blueshifted to 295 nm (Figure 2C). Increasing the temperature also results in the disappearance of the Cotton effect (Figure 2D). The shifts in the  $\lambda_{max}$  in the UV spectra and the reduction of the Cotton effect upon increasing the temperature are consistent with reaching the molecularly dissolved state of thio-

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BTAs at higher temperatures. In fact, the UV spectrum at 80 °C is similar to the UV spectrum of molecularly dissolved thioamide BTAs in THF in which the shoulder is also located at 293 nm (see Figure S5 in the Supporting Information).

The mechanism of self-assembly was further investigated by performing temperature-dependent CD spectroscopy on compound **2b** at concentrations between  $2 \times 10^{-5}$  and  $5 \times 10^{-5}$  mol L<sup>-1</sup> in MCH (Figure 3). The temperature-depend-



Figure 3. Temperature-dependent CD effect for **2b** probed at  $\lambda = 317$  nm and  $c = 5 \times 10^{-5}$  ( $\blacksquare$ ),  $4 \times 10^{-5}$  ( $\square$ ),  $3 \times 10^{-5}$  ( $\bullet$ ) and  $2 \times 10^{-5}$  mol L<sup>-1</sup> ( $\bigcirc$ ) in MCH.

ent cooling curves are typical for a cooperative aggregation process in which a nucleation and elongation phase can be distinguished. The two phases are separated by the (concentration-dependent) temperature of elongation,  $T_{e}$ . To quantify the thermodynamic parameters of the self-assembly of **2b**, the CD cooling curves were analysed by applying a recently developed mathematical model for supramolecular polymerisation reactions (see Figure S6A in the Supporting Information).<sup>[31]</sup> In this model, which is based on equilibria between monomers, oligomers and polymers, the aggregation process is divided into a nucleation and elongation regime. In the nucleation regime, the formation of a dimer, described by the equilibrium constant  $K_2$ , for dimerisation is assumed to result in a stable nucleus. In the elongation regime, in which additional monomers add to the growing polymer chain, all equilibrium constants K  $(K_2 \neq K)$  are assumed to be equal. Because the nucleation step is highly unfavourable, the equilibrium constant for nucleation is much smaller than that for elongation  $(K_2 \ll K)$ .

The thermodynamic parameters describing the nucleation and elongation processes are derived by performing nonlinear least-squares analyses on the experimental melting curves. The simultaneous fit of the different concentrations gives values to the enthalpy of elongation,  $\Delta H_{\rm ELO}$ , the associated entropy,  $\Delta S$ , and the nucleation penalty,  $\Delta H_{\rm NP}$  From these values, the equilibrium constants for the nucleation,  $K_2$ , and elongation phase, K, can be calculated. Importantly, the cooperativity factor  $\sigma$ , defined as  $K_2/K$  and a direct measure of the cooperativity of the system, can be calculated from the obtained results. The results are summarised in Table 1. Increasingly small numbers for  $\sigma$  indicate an increasingly cooperative system. As a reference, the values

Table 1. Thermodynamic parameters for the self-assembly of 1b and 2b in MCH as obtained from the equilibrium model.

BTA	$\Delta H_{\rm ELO}$ [kJ mol <sup>-1</sup> ]	$\frac{\Delta S}{[\mathrm{J}\mathrm{mol}^{-1}\mathrm{K}^{-1}]}$	$\Delta H_{\mathrm{NP}}^{[\mathrm{a}]}$ [kJ mol <sup>-1</sup> ]	$K^{[\mathrm{b}]}$ [ $10^5 \mathrm{m}^{-1}$ ]	$K_2^{[b]}$ [m <sup>-1</sup> ]	$\sigma^{[b]}$
1b <sup>[c]</sup>	-72	-128	-30	8.7	5	$5.4 \times 10^{-6}$
20	-54	-/1	-19	4.9	185	$3.7 \times 10^{-5}$

[a] The nucleation penalty,  $\Delta H_{\rm NP}$  has a negative value, which implies that the enthalpy associated with the nucleation process is positive and hence unfavourable. [b] The equilibrium constant for elongation, *K*, the equilibrium constant for dimerisation,  $K_2$ , and the cooperativity factor,  $\sigma$ , were calculated at 298 K. [c] Data obtained from ref. [31].

previously determined for the amide BTA **1b** are included in Table 1.<sup>[31]</sup>

The thermodynamic values derived for thioBTA self-assembly show notable differences compared with amidebased BTA self-assembly. First, both the enthalpy and entropy of elongation are less negative for thioBTA **2b** ( $\Delta H_{\rm ELO}$  =  $-54.0 \text{ kJ mol}^{-1}$ ,  $\Delta S = -71 \text{ J mol}^{-1} \text{K}^{-1}$ ) than for the amide BTA **1b**  $(\Delta H_{\rm ELO} = -72.0 \text{ kJ mol}^{-1}, \Delta S = -128 \text{ J mol}^{-1} \text{K}^{-1}).$ To ensure that this difference is not related to a fitting error, we also derived a van't Hoff plot for both compounds (see Figure S7 and Table S3 in the Supporting Information).<sup>[17]</sup> Also, the enthalpy and entropy associated with thio- $(\Delta H = -54.2 \text{ kJ mol}^{-1})$ BTA self-assembly  $\Delta S =$  $-56.0 \,\mathrm{J}\,\mathrm{mol}^{-1}\mathrm{K}^{-1}$ ) are less negative than those for the BTA  $(\Delta H = -73.0 \text{ kJ mol}^{-1})$ amide-based 1b  $\Delta S =$  $-113.0 \text{ Jmol}^{-1}\text{K}^{-1}$ ). The elongation of the thioBTA **2b** and the amide BTA 1b starts at similar temperatures under identical concentrations, although the solubility of 2b in MCH is much better than that of 1b. Importantly, the results show that the cooperativity factor,  $\sigma$ , is around 100 times larger for the thioBTAs, which indicates a less cooperative self-assembly behaviour. The self-assembly of the achiral thioBTA (see Figure S6B in the Supporting Information) is similar to that of chiral 2b, albeit the cooperativity is slightly lower ( $\sigma = 7 \times 10^{-4}$ ) and the enthalpy release is slightly more negative ( $\Delta H_{\rm ELO} = -64.1 \text{ kJ mol}^{-1}$ ).

Amplification of chirality: Amplification of supramolecular chirality, that is, a small enantiomeric excess or a small amount of chiral compound biases the supramolecular helicity in a non-linear fashion, is typically investigated by performing majority rules (MR) and sergeants-and-soldiers (SaS) experiments.<sup>[32]</sup> The MR experiment is performed by mixing the two enantiomers and the MR effect is operative when the intensity of the CD effect at a certain wavelength changes non-linearly as a function of the enantiomeric excess (ee).<sup>[33]</sup> In this case, the enantiomer present in the majority dictates the helical sense to which the minority enantiomer adjusts. Alternatively, the SaS experiment involves mixing of a few chiral units (sergeants) with large number of achiral units (soldiers) consisting of equal amounts of P (right-handed)- and M (left-handed)-type supramolecular polymers.<sup>[34]</sup> When the SaS effect is operative, a strong non-proportional increase in the CD effect is observed. Previous results from our group showed a pro-

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nounced amplification of supramolecular chirality in C=Oand N-centred BTAs.

A majority rules experiment was performed by mixing the enantiomer pair **2b** and **2c** in different ratios and probing the magnitude of the CD effect at 317 nm (Figure 4). The CD effect is non-linear with respect to the *ee*. For 100 % > 1



Figure 4. Majority rules experiment performed on **2b** and **2c** in MCH  $(c=2.2 \times 10^{-5} \text{ mol L}^{-1}, \text{ CD effect probed at 317 nm}).$ 

ee | > 15%, the CD effect is constant, which indicates the presence of only one type of helical column. For 15% > |ee| > 0%, the *ee* linearly decreases, which is indicative of the formation of columnar structures with the opposite helicity. An *ee* of 15% is needed to fully bias one helicity, which indicates that a ratio of enantiomers of 57.5:42.5 is sufficient for there to be only one helical sense. This also implies that helical columns tolerate up to 42.5% of the unpreferred enantiomer. In addition, an SaS experiment was performed that showed that chiral compound **2c** biases the helical sense of achiral thioBTAs (see Figure S8 in the Supporting Information). The MR and SaS effects found for thioBTAs are similar in magnitude to those observed in the previously studied C=O- and N-centred BTAs.<sup>[16,17]</sup>

Dimensions of thioBTA-based supramolecular polymers: To date, the experimental determination of the length of rigid cylindrical supramolecular polymers by scattering techniques has proved a challenge. Although several systems forming rigid one-dimensional supramolecular polymers have been analysed by scattering techniques, the exact determination of the length and diameter of the supramolecular polymer is not trivial and often only lower limits can be obtained.<sup>[35]</sup> Depolarised dynamic light scattering (DDLS) measurements, in contrast, have been successfully applied to quantify the mean length and diameter of rigid nanorods in solution.<sup>[36]</sup> Because the rotational and translational diffusion display different functional dependencies on rod length and diameter, the length and diameter of the nanorods can be determined from these two measurements. Remarkably, the DDLS measurements of (rigid) supramolecular polymers have not been reported, presumably because they require a large anisotropy in the polarisability of the particle.<sup>[37]</sup>

In this work we conducted DDLS measurements to determine the rotational and translational diffusion coefficients,  $D_{\rm trans}$  and  $D_{\rm rot}$ , of the supramolecular thioBTAs. Because of the nature of the hydrogen-bonding array in aggregated thioamides, the thioamides are rotated out-of-the-plane in a parallel fashion giving rise to a strong dipole moment. An increase in the size of the aggregate results in an anisotropy of the polarisability. Thus, the high dipole moment of a thioamide bond in combination with the highly anisotropic shape of the resulting cylindrical aggregate gives rise to sufficiently strong depolarised scattering to enable DDLS measurements of the rotational and translational diffusion coefficients,  $D_{\rm trans}$  and  $D_{\rm rot}$ .

We performed all the DDLS measurements at 25 °C in MCH with  $c=9 \times 10^{-4}$  mol L<sup>-1</sup>. The initial decay rate,  $\Gamma$ , can be extracted from the intensity autocorrelation functions. Then the rotational and translational diffusion coefficients,  $D_{\text{trans}}$  and  $D_{\text{rot}}$ , can be extracted from  $\Gamma=6D_{\text{rot}}+D_{\text{trans}}q^2$  in which q is the scattering wave vector (Figure 5). We used a hydrodynamic model for the diffusion of spherical endcapped cylinders to compute the length L and diameter d of the thioBTA aggregates from the measured diffusion coefficients.<sup>[38]</sup> Values of L=490 nm and d=3.6 nm were obtained (Table 2). In addition, the degree of polymerisation, DP, of 1439 was extracted.<sup>[39]</sup>

Table 2. Measured translational diffusion coefficient,  $D_{\text{trans}}$ , rotational diffusion coefficient,  $D_{\text{rot}}$  length, L, diameter, d, and average degree of polymerisation, DP, and calculated values weight average degree of polymerisation,  $DP_{w}$ , number average degree of polymerisation,  $DP_n$ , aggregate length based on  $DP_w$ ,  $L_w$ , and aggregate length based on  $DP_n$ ,  $L_n$  for **2b**<sup>[a]</sup>

	Measured
$D_{\rm rot}  [{ m s}^{-1}]$	$196 \pm 5$
$D_{\text{trans}} \left[ \text{m}^2 \text{s}^{-1} \right]$	$(6.24\pm0.15)\times10^{-12}$
η [Pas]	$7.36 \times 10^{-4}$
$L [{\rm nm}^{-1}]$	490
<i>d</i> [nm]	3.6
DP	1439
	Calculated
$DP_{w}$	2157
DP <sub>n</sub>	1080
$L_{\rm w}$ [nm]	755
L <sub>n</sub> [nm]	348

[a] Determined at  $c = 9 \times 10^{-4} \text{ mol } \text{L}^{-1}$  and 25 °C.

From the thermodynamic parameters discussed in Table 1, we can calculate the number-average degree of polymerization,  $DP_n$ , and the weight-average degree of polymerisation,  $DP_w$ , of the supramolecular polymers at a selected temperature and concentration (Table 2).<sup>[24a]</sup> At  $c=9\times10^{-4}$  M and 25 °C, the  $DP_n$  and  $DP_w$  are approximately 1080 and 2157, respectively.<sup>[40]</sup> This corresponds to a chain length of around 755 nm (based on the  $DP_w$  and an interdisc distance of 0.35 nm). The calculated chain length of 755 nm is in good agreement with the experimentally obtained value of 490 nm. In addition, XRD measurements revealed an intercolumnar distance of 2.1 nm for the LC phase of **2a** at 100 °C, conditions under which the aliphatic chains are molten and highly disordered. Taking into account the inter-

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Figure 5. a) Field autocorrelation functions at different angles with corresponding cumulant fit (full line) and b) angular dependence of extracted decay rates ( $\Gamma$ ) and linear fit (—) to determine the values of  $D_{\rm rot}$  and  $D_{\rm trans}$  (full line) for **2b** ( $c=9\times10^{-4}$  in MCH, T=25 °C).

calation of solvent molecules within the aggregates,<sup>[18d,41]</sup> the experimentally determined diameter of the aggregates of 3.6 nm is in good agreement with the expected value.

#### Conclusion

We have reported a facile synthesis and molecular characterisation of chiral and achiral N,N',N''-trialkylbenzene-1,3,5tris(carbothioamide)s (thioBTAs). The thioBTAs show thermotropic liquid crystalline behaviour. IR spectroscopy revealed that three-fold intermolecular hydrogen bonding stabilises the columnar structures in the mesophase and in methylcyclohexane. In analogy to their amide counterparts, thioBTAs self-assemble cooperatively into one-dimensional, helical supramolecular polymers and the presence of stereogenic centres biases one helicity. In addition, strong amplification of the supramolecular chirality was observed. Depolarised DLS experiments showed that the average length, L, and diameter, d, of the thioBTA stacks are 490 and 3.6 nm, respectively. These measured values are in good agreement with the value of  $L_w$ =755 nm obtained from fitting the temperature-dependent CD data and the intercolumnar distance of 2.1 nm in the columnar mesophase. This is the first experimental verification in which we have validated our common practice for determining the length of the supramolecular BTA-based polymers from model fits to experimental CD data.

The ability of a thioamide to induce cooperative, directional hydrogen bonding in supramolecular polymerisations makes it versatile and broadly applicable. Compared with the amide bond, thioamides offer a number of additional advantages when designing new supramolecular motifs. First, the absorption wavelength is shifted to higher values, which facilitates the performance of spectroscopic experiments in the presence of other chromophores. Secondly, the high dipole moment of the thioamide bond enables DDLS measurements, which allows the lengths and diameters of rodlike aggregates to be determined. Thirdly, thioamides can be switched to a cis conformation with UV light. We are currently exploring the possibility of such a photochemical trigger to turn "off" or "on" the self-assembly behaviour of this new class of self-assembling discotics by switching between the *trans* and *cis* conformations of the thioamide bonds.

#### **Experimental Section**

**Materials**: Compounds 1a-c were synthesised according to a published procedure.<sup>[12c]</sup> Toluene was dried on an activated alumina column and used immediately. All other chemicals were used as received.

Methods: CD and UV spectra were recorded on a Jasco J-815 CD spectrometer equipped with a Jasco PTC-348 WI temperature controller. Experiments were conducted by using spectroscopic-grade methylcyclohexane as the solvent. Cells with an optical path length of 1 cm were employed. The concentration-independent value of the Cotton effect, the molar circular dichroism ( $\Delta \varepsilon$ ), was calculated as  $\Delta \varepsilon = CD$  effect/(32980cl) in which c is the concentration in molL<sup>-1</sup> and l is the optical path length in cm. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer (400 MHz for  $^1\mathrm{H}\,\mathrm{NMR}$  and 100 MHz for <sup>13</sup>C NMR). <sup>1</sup>H chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) and <sup>13</sup>C chemical shifts are reported downfield from TMS with the resonance of the deuteriated solvent as the internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Polarised optical microscopy (POM) measurements were performed with a Jenaval polarisation microscope equipped with a Linkam THMS 600 heating device with crossed polarisers. The thermal transitions were determined by DSC from the second heating run by using a Perkin-Elmer DSC-7 instrument under nitrogen with heating and cooling rates of 20  $\mathrm{K\,min^{-1}}.$  MALDI-TOF mass spectrometry was performed with a PerSeptive Biosystems Voyager DE-PRO spectrometer or a Bruker autoflex speed spectrometer with  $\alpha$ -cyano-4-hydroxycinnamic acid (CHCA) as the matrix system.

**Wide- and small-angle X-ray diffraction measurements**: The samples for wide-angle X-ray diffraction (WAXD) and small-angle X-ray diffraction (SAXD) were prepared in 0.7 mm Lindemann glass capillaries. The samples were analysed on a Bruker–Nonius D8-Discover X-ray diffractometer with a 0.154 nm copper radiation source equipped with a home-built

sample oven (TU Delft, Prof. Dr. S. J. Picken and co-workers). The scattering data were recorded with a 2D detector ( $1024 \times 1024$ ) and the sample-to-detector distance was 8.4 (WAXD) or 34 cm (SAXD). The capillary was placed inside a vertically aligned graphite tube with a transversal hole, which allows the incident X-ray beam to cross freely. The temperature of the graphite tube was controlled by a system formed by a thermocouple connected to a proportional integral-derivative (PID) controller and power supply, which acts as a fast-response online oven ranging from room temperature to 350°C.

**Depolarised dynamic light scattering:** DDLS measurements were conducted on an ALV/CGS-3 MD-4 compact goniometer system equipped with a multiple tau digital real time correlator (ALV-7004; solid-state laser:  $\lambda = 532$  nm, 40 mW). In a typical experiment, the scattering angle  $\theta$  was varied between 20 and 150° in steps of 10 (first step) and 15° (subsequent steps) performing  $3 \times 30$  s experiments at each angle. The liquid samples were held in 5 mm borosilicate cells. The translational and rotational diffusion coefficients ( $D_{\text{trans}}$  and  $D_{\text{rot}}$ ) were obtained from the initial decay rate  $\Gamma$  extracted from the intensity autocorrelation functions by third-order cumulant analysis according to  $\Gamma = 6D_{\text{rot}} + D_{\text{trans}}q^2$ .<sup>[40]</sup>

Synthesis of thioBTAs 2a-c: N,N',N"-Tris(dodecyl)benzene-1,3,5-trithioamide (2 a): Compound 1a (2.0 g, 2.81 mmol) was dissolved in toluene (100 mL) and P<sub>2</sub>S<sub>5</sub> (2.10 g, 9.4 mmol) was added. The solution was heated at reflux for 4 h and then an additional amount of  $P_2S_5$  (1.5 g, 6.7 mmol) was added and the heating was continued for another 16 h. The solution was then cooled to 90 °C and MeOH (200 mL) was added. The clear solution was cooled to room temperature and evaporated to dryness. Dichloromethane (200 mL) was added and the solution extracted with water (200 mL), satd. NaHCO3 (3×200 mL) and brine (200 mL). After drying over MgSO4 the organic layer was evaporated to dryness and a viscous oil was obtained. Then MeOH (50 mL) was added and the mixture stirred for 5 min. MeOH was decanted and the procedure repeated with additional MeOH (50 mL). The combined MeOH layers were evaporated to dryness and the crude product was purified by column chromatography (SiO<sub>2</sub>, gradient CHCl<sub>3</sub> to CHCl<sub>3</sub>/EtOAc, 98:2) to afford a yellowish solid (1.03 g, 48 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 9.20$  (s, 3H; Ar-H), 7.20 (t, 3H; NH), 3.68 (m, 6H; NHCH<sub>2</sub>), 2.0-0.9 ppm (m, 63H; NHCH<sub>2</sub>(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 194.9, 138.8, 47.2, 32.0, 29.9, 29.8, 29.7, 29.6, 29.5, 27.9, 27.5, 22.7, 14.1 ppm; IR (20°C, film):  $\tilde{\nu} = 3180$  (NH), 1539 (amide II), 691 cm<sup>-1</sup> (C=S); MS (MALDI-TOF): m/z calcd for C<sub>45</sub>H<sub>81</sub>N<sub>3</sub>S<sub>3</sub>: 759.56; found: 760.57 [*M*+H]<sup>+</sup>, 782.55  $[M+Na]^+$ ; DSC:  $T_{m1} = -4.56$  °C ( $\Delta H = 3.29$  kJ mol<sup>-1</sup>),  $T_{m2} = 254$  °C ( $\Delta H =$  $6.0 \text{ kJ mol}^{-1}$ ).

(3S)-N,N',N''-Tris(3,7-dimethyloctyl)benzene-1,3,5-trithioamide (2b): Compound 1b (1.2 g, 1.9 mmol) was dissolved in toluene (35 mL) and  $P_2S_5$  (1.25 g, 5.6 mmol) was added. The solution was heated at reflux for 3 h, the solution was cooled to 90 °C and MeOH (75 mL) was added. The clear solution was cooled to room temperature and evaporated to dryness. Toluene (200 mL) and dichloromethane (100 mL) were added and the solution was extracted with water (200 mL), satd. NaHCO3 (2× 200 mL) and water (2×100 mL). The organic layer was evaporated to dryness and a viscous oil was obtained. The crude product was purified by column chromatography (SiO2, gradient CHCl3 to CHCl3/EtOAc, 98:2) to afford a yellowish solid (0.85 g, 66%). <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta = 8.60$  (s, 3 H; Ar-H), 7.62 (t, 3 H; NH), 3.73 (m, 6 H; CH<sub>2</sub>NH), 1.9–0.9 ppm (m, 51 H; NHCH<sub>2</sub>CHCH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>CH(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR  $(100 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 194.9, 138.9, 45.3, 39.3, 37.0, 34.9, 31.3, 28.0, 24.9,$ 22.8, 22.7, 19.5 ppm; IR (20°C, film):  $\tilde{\nu} = 3179$  (NH), 1543 (amide II), 693 cm<sup>-1</sup> (C=S); MS (MALDI-TOF): m/z calcd for  $C_{39}H_{69}N_3S_3$ : 675.45; found: 676.47  $[M+H]^+$ , 698.45  $[M+Na]^+$ ; DSC:  $T_{m1}=95$  °C  $(\Delta H = 3.65 \text{ kJ mol}^{-1}), T_{\text{m2}} = 260 \text{ °C} (\Delta H = 11.30 \text{ kJ mol}^{-1}).$ 

(3R)-N,N',N''-*Tris*(3,7-*dimethyloctyl*)*benzene*-1,3,5-*trithioamide* (2c): A procedure identical to that used for **2b** was applied. Compound **2c** was obtained as a yellowish solid (0.18 g, 25%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ =8.85 (s, 3H; Ar-H), 7.60 (t, 3H; NH), 3.68 (m, 6H; CH<sub>2</sub>NH), 1.9-0.9 ppm (m, 51 H; NHCH<sub>2</sub>CHCH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>CH(CH<sub>3</sub>)<sub>2</sub>); IR (20°C, film):  $\tilde{\nu}$ = 3180 (NH), 1540 (amide II), 695 cm<sup>-1</sup> (S=C); MS (MALDI-TOF): *m/z* calcd for C<sub>39</sub>H<sub>69</sub>N<sub>3</sub>S<sub>3</sub>: 675.45; found: 676.35 [*M*+H]<sup>+</sup>, 698.33 [*M*+Na]<sup>+</sup>.

#### Acknowledgements

This work was supported by the Dutch National Research School Combination Catalysis Controlled by Chemical Design (NRSC-Catalysis) and the Netherlands Organization for Scientific Research (Spinoza-NWO) foundations. I.K.V. gratefully acknowledges support from VENI-NWO and the European Union (FP7-PEOPLE-2011-CIG). The authors would like to thank Michel van Houtem and Carel Fitié for help with the X-ray diffraction measurements, Charley Schaefer and Peter Korevaar for providing assistance with fitting of the data and the ICMS animation studio for the artwork.

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Received: November 30, 2012 Revised: March 20, 2013 Published online: ■■ ■, 0000

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Thioamide bonds: The polymerisation of a thioamide-based supramolecular motif is elucidated by combining depolarised dynamic light scattering and temperature-dependent spectroscopic measurements (see figure). A cooperative polymerisation mechanism and strong amplification of chirality makes this a highly versatile structuring motif.



#### **Supramolecular Polymers** -

Thioamides: Versatile Bonds To Induce Directional and Cooperative Hydrogen Bonding in Supramolecular Polymers





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