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Decoding the Consequences of Increasing the Size of Self-Assembling Tricarboxamides on Chiral Amplification

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ABSTRACT

A complete series of experimental and theoretical investigations on the supramolecular polymerization of chiral (**1** and **2**) and achiral (**3**) oligo(phenylene ethynylene) tricarboxamides (OPE-TAs) is reported. The performance of seargents-and-soldiers (*SaS*) and majority rules (*MR*) experiments has allowed deriving a full set of thermodynamic parameters, including the helix reversal penalty (HRP) and the mismatch penalty (MMP). The results described illustrate the influence exerted by the number of stereogenic centers per monomeric unit and the temperature on the chiral amplification phenomena. Whilst the HRP decreases upon decreasing the number of chiral side chains, the MMP follows an opposite trend. The experimental trend observed in *MR* experiments contrasts with that reported for benzenetricarboxamides (BTAs), for which the chiral amplification ability increases by lowering the number of stereogenic centers or increasing the temperature. Theoretical calculations predict that the rotational angle between adjacent monomeric units in the stack (ca. 18°) gradually decreases when decreasing the number of branched chiral side chains, and leads to higher MMP values in good accord with the experimental trend. The reduction of the rotational angle gives rise to less efficient H-bonding interactions between the peripheral amide functional groups and is suggested to provoke a decrease of the HRP as experimentally observed. In BTAs, increasing the number of stereogenic center per monomeric units results in a negligible change of the rotation angle between adjacent units (ca. 65°) and, consequently, the steric bulk increases with the number of chiral side chains leading to higher MMP values. The data presented herein contribute to shed light on the parameters controlling the transfer and amplification of chirality processes in supramolecular polymers, highlighting the enormous influence exerted by the size of the self-assembling unit on the final helical outcome.

INTRODUCTION

The discovery of the spontaneous resolution in ammonium sodium tartrate, made by Pasteur, initiated the challenging task of deciphering the origin of asymmetry in Nature and, more specifically, the phenomenon of chirality and how chirality is transferred to the different levels of hierarchy.[1] A large number of scientific areas like asymmetric synthesis,[2] enantioseparation,[3] or molecular motors[4] relies on chiral amplification at molecular or supramolecular level. The use of amplification of chirality in molecular reactions, especially for asymmetric catalysis, has experienced an outstanding advance by the synergy of both experimental and theoretical data.[5] However, the establishment of clear rules and structure-property relationships for achieving an accurate knowledge on the chiral amplification observed in self-assembling systems is more challenging.[6] Taking advantage of the principles extracted from chiral covalent polymers, such as polyisocyanates and polyacetylenes,[7] the chiral amplification of self-assembling systems has been investigated by following two strategies known as *sergeants-and-soldiers (SaS)* and *majority rules (MR)*.[6,8] In the *SaS* experiments, a minute number of chiral units (the sergeants) command a large number of achiral units (the soldiers) to yield enantiomerically enriched mixtures. In the *MR* experiments, mixing unequal amounts of two enantiomers makes the whole mixture to adopt the chiral sign dictated by the chiral component added in excess.[6,8]

Supramolecular polymers,[9] that is, macromolecular species in which the monomeric units are joined together by non-covalent forces, are an exceptional benchmark to perform chiral amplification studies that contribute to shed light into the origin of homochirality.[6] The rotated one-dimensional self-assembly of a number of organic scaffolds affords helical columnar stacks that are very valuable to investigate the processes of transfer and amplification of chirality. Merocyanines,[10] naphtalene bisimides,[11] perylene bisimides,[12] π-conjugated systems,[13] and C_3-symmetric tricarboxamides[14] are some examples of organic platforms utilized to investigate the chiral transmission and/or amplification in supramolecular polymers.[15]

Despite the number of studies reporting the generation of chiral supramolecular structures making use of axial chirality,[16] in the vast majority of the examples described, the construction of helical supramolecular polymers is achieved by the peripheral decoration of the self-assembling units with stereogenic centers.[10-14] However, few studies report clear rules to understand the requirements of a self-assembling unit to generate chiral supramolecular ensembles. Only for the case of C_3-symmetric benzenetricarboxamides (BTAs)[17] and oligo(phenylene

ethynylene) tricarboxamides (OPE-TAs, compounds **1-3** in Figure 1),[18] a systematic investigation of the molecular structural factors that lead to an efficient transfer of chirality has been carried out.

The derivation of all the thermodynamic parameters associated to the polymerization mechanism, isodesmic or cooperative,[9] is required to obtain a detailed description of the chiral amplification phenomena in supramolecular polymers. This goal can be readily achieved by applying the equilibrium (EQ) model, which considers the monomeric, oligomeric, and larger supramolecular polymeric species present during the formation of the corresponding supramolecular polymer.[19] In addition, the two-component version of the EQ model also allows deriving the mismatch enthalpy ΔH_{mm}. This parameter that quantifies the mismatch penalty (MMP) due to the incorporation of a monomer into an aggregate of its unpreferred helicity, has been estimated in ~2 kJ·mol^{-1} for BTAs and OPE-TAs.[18a,19] Together with the MMP, it is important to consider the helix reversal penalty (HRP) as an additional energy penalty for a chiral amplification phenomenon. The HRP penalizes the creation of different helical domains within a columnar stack and, to the best of our knowledge, this parameter has only been calculated for the supramolecular polymerization of BTAs.[17] The balance between all these thermodynamic parameters, and especially the MMP and the HRP, conditions the final outcome obtained from *SaS* and *MR* experiments in the chiral amplification of supramolecular polymers.

Herein, we expand the studies on chiral amplification by investigating the helical supramolecular polymerization of OPE-TAs, both by *SaS* and *MR* experiments (Figure 1). We demonstrate the influence exerted by molecular structural factors, i.e., the number of stereogenic centers at the peripheral side chains, and also the influence of external factors, such as the temperature, on the ability of these systems to experience amplification of chirality. A detailed energetic investigation has been performed, and the HRP and MMP penalties have been derived for these dynamic supramolecular polymers, showing important differences with respect to previous studies reported for the family of BTAs.[17] In contrast to BTAs, decreasing the number of stereogenic centers results in a negligible chiral amplification, and increasing the temperature results in an increase of the MMP, thus hindering the chiral amplification phenomenon. Theoretical calculations have been utilized to confirm the preferential handedness of OPE-TAs, and to rationalize the experimental trends by invoking key structural parameters. The theoretical results indicate that the small rotational dihedral angle between adjacent OPE-TAs along the helical stack, compared to BTAs, stands as a crucial factor that conditions the chiral amplification in these and related supramolecular polymers. The data presented in this work illustrate the enormous influence exerted by the size of the self-assembling unit on the final helical outcome, and allows establishing more clear rules on the structure/property relationship for chiral supramolecular polymers.

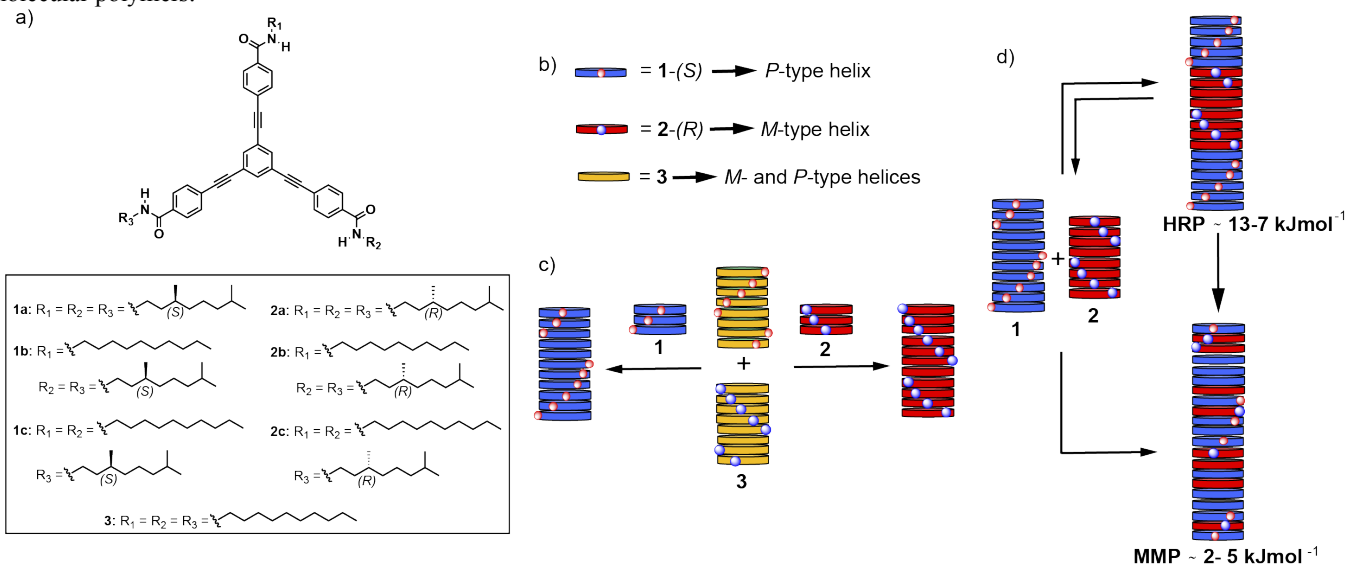

Figure 1. (a) Chemical structure of the symmetrically and asymmetrically substituted oligo(phenylene ethynylene) tricarboxamides **1-3**. (b) Schematic illustration of the relationship between the point chirality embedded in the side chains of tricarboxamides **1-3** and the helical outcome upon supramolecular polymerization. (c) Sergeants-and-soldiers experiments between chiral **1** or **2** and achiral **3**. (d) Majority rules experiments for chiral **1** and **2** indicating the HRP and MMP effects.

RESULTS AND DISCUSSION

Synthesis, supramolecular polymerization mechanism and transfer of chirality. The synthesis of chiral tricarboxamides **1** and **2a** as well as achiral tricarboxamide **3** has been previously described by our research group.[18a,18b] Chiral tricarboxamides **2b** and **2c**, endowed with two or one stereogenic centers, respectively, of absolute configuration (*R*), were prepared by following a similar synthetic strategy to that described for asymmetrically substituted **1b** and **1c** (Scheme S1). A full spectroscopic characterization of all new compounds is included in the Supporting Information.

In good analogy with BTAs, the supramolecular polymerization of OPE-TAs **1-3** proceeds through the formation of a triple array of H-bonding interactions between the amide functional groups and the consequent π-stacking of the aromatic moieties.[17] The synergy of these two non-covalent interactions yields helical columnar stacks governed by a cooperative or nucleation-elongation mechanism. Theoretical calculations showed that, in these columnar stacks, adjacent monomeric units are rotated by ca. 18°. In addition, both experimental and theoretical data demonstrated that the presence of stereogenic centers of absolute configuration (*S*) at the side chains affords right-handed *P*-type helices and those with an absolute configuration

(*R*) gives rise to left-handed *M*-type helices.[18] In good agreement with these preliminary data, new tricarboxamides **2b** and **2c** are also expected to form *M*-type helical structures, as indicate the corresponding circular dichroism (CD) spectra. Figure 2 shows the CD spectra registered for chiral OPE-TAs **1** and **2** in methylcyclohexane (MCH) at a total concentration (c_T) of 10 μM. Similarly to tricarboxamides **1**, the supramolecular polymerization of **2a-c** yields the same dichroic pattern and, consequently, the same helical outcome regardless the presence of one (**2c**), two (**2b**) or three (**2a**) stereogenic centers at the side chains. This implies that only one stereogenic center is sufficient to bias the efficient transfer of chirality to the whole supramolecular structure.[18b]

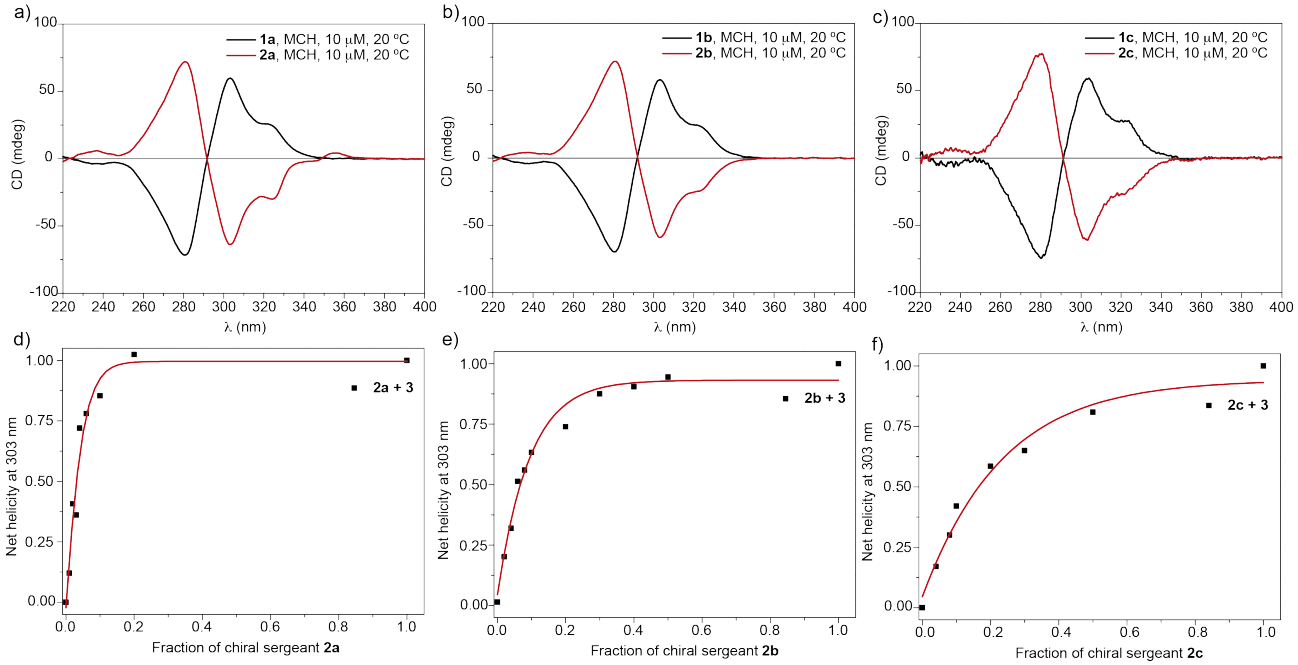

Figure 2. (a-c**)** CD spectra of chiral tricarboxamides **1** and **2** in MCH, c_T = 10 μM, 20 °C. *SaS* experiments for achiral **3** upon mixing with chiral **2a** (d), **2b** (e), and **2c** (f) (MCH, c_T = 10 μM, 20 °C). The red curves in (d-f) correspond to a sigmoidal fitting to guide the eye.

To confirm the preferential *M*–type helical handedness in our novel tricarboxamide **2a-c** derivatives decorated with chiral aliphatic chains with stereogenic centres with an absolute configuration *R*, theoretical calculations using the GFN2-xTB approach were performed (see the SI for computational details).[20] The geometry of large supramolecular stacks of 20 monomeric units was fully optimized, and the energy of right- and left-handed helices was compared. Note that for derivatives **2b** and **2c**, two types of supramolecular arrangements can be obtained by considering the relative disposition of the achiral and chiral aliphatic chains in vicinal molecules along the stack (see Figure 3a-b for **2c** and Figure S1 for **2b**). In the *eclipsed* disposition, achiral and chiral chains are placed in different arms of the helix, whereas in the *staggered* disposition achiral and chiral chains are intercalated along the growing direction of the helix. Fully chiral **2a** can only stack in an eclipsed configuration. Theoretical calculations for **2a** indicate that the energy difference per monomeric unit between *P* and *M* helices is 6.3 kJ·mol^{-1} in favor of the *M* helix. Similarly, the eclipsed left-handed stacking of **2b** is found 7.0 kJ·mol^{-1} per monomeric unit more stable than the analogous right-handed column. Staggered stackings of **2b** lie in between in energy (Figure S2). Finally, the staggered stackings of **2c** are found more stable than the eclipsed growth. For this derivative, the alternated *M*-type 20-mer is predicted 5.0 kJ·mol^{-1} per monomeric unit more stable than the corresponding *P*-type aggregate. Minimum-energy geometries for the most stable *M*-type stacks of **2a** and **2c** are displayed in Figure 3c-d. Regardless of the number of chiral aliphatic chains, GFN2-xTF calculations demonstrate that derivatives **2a-c** arrange supramolecularly in a preferentially left-handed orientation. Considering that the stereogenic centres of **1a-c** display the opposite absolute configuration to that present in **2**, the most stable arrangements for **1a-c** are right-handed helices (in good accord with previous reports).[18]

By making use of the one-component version of the EQ model and variable temperature (VT) UV-Vis experiments,[19] a complete set of thermodynamic parameters – nucleation enthalpy (ΔH_n), elongation enthalpy (ΔH_e), elongation entropy (ΔS), nucleation (K_n) and elongation (K_e) binding constants, and cooperativity factor (σ) – have been derived for tricarboxamides **2** to complement those already reported for compounds **1** and **3** (Table 1). As expected, compounds **2** present very similar thermodynamic parameters to those obtained for chiral **1** and achiral **3** and also for BTAs,[17,19] thus confirming the cooperative character of the supramolecular polymerization of these tricarboxamides.[18]

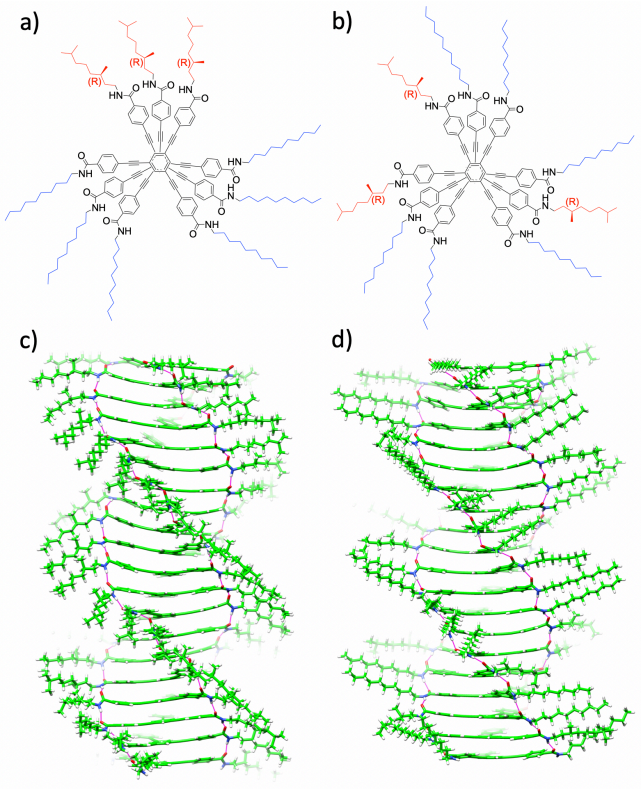

Figure 3. Eclipsed (a) and staggered (b) disposition of chiral chains along the helical stack of **2c**. Minimum-energy geometry calculated at the GFN2-xTB level for the most stable 20-mer columnar *M*-helical stacks of **2a** (c) and **2c** (d).

Table 1. Thermodynamic parameters for tricarboxamides 1-3

Compound	ΔH_e[a]	ΔS_e[b]	ΔH_n[a]	K_n[c]	K_e[c]	σ[d]
1a	–79.3	–140	–27.7	52	3.9 e+6	1.3e-5
1b	–76.9	–130	–24.3	265	4.9 e+6	5.4e-5
1c	–83.9	–150	–26.3	184	7.5 e+6	2.4e-5
2a	–80.6	–140	–22.5	761	2.9 e+6	1.1e-5
2b	–76.8	–130	–23.1	417	4.8 e+6	8.6e-5
2c	–78.5	–130	–17.7	750	9.5 e+6	7.9e-5
3	–78.0	–140	–26.9	15	0.2 e+6	7.0e-5

[a] In kJ·mol^{-1}; [b] in J·K^{-1}·mol^{-1}; [c] in L·mol^{-1}; [d] $\sigma = K_n/K_e$. The values of the two binding constants (K_n *and* K_e) and σ were calculated at 298 K. MCH as solvent.

Amplification of chirality. *SaS* experiments. The influence of the number of stereogenic centers per monomeric unit on the chiral amplification ability by mixing chiral tricarboxamides **1** with achiral **3** has been previously reported.[18b] The data extracted from the corresponding *SaS* experiments, carried out by adding increasing amounts of chiral tricarboxamides **1** to a solution of achiral **3** and keeping the total concentration c_T constant, reveal that decreasing the number of stereogenic centers at the side chains is accompanied with a drastic decrease on the ability to amplify the chirality by the chiral self-assembling unit.[18b] In good correlation, analogous results have been obtained by mixing increasing amounts of chiral **2** and achiral **3**. In these *SaS* experiments, a direct correlation between the number of stereogenic centers and the amplification of chirality is observed. Thus, when mixing **2a**, endowed with three stereogenic centers, and **3** in MCH at c_T = 10 μM, a molar fraction of around 0.2 is sufficient to bias the whole helicity of the mixture (Figure 2d). This molar fraction increases to 0.4 for the mixture of **2b**, which contains two stereogenic centers, and achiral **3,** and is negligible for **2c** (Figure 2e and 2f, respectively).

We have checked the influence of temperature on the extent of chiral amplification by performing the *SaS* experiments at three different temperatures with the mixture of achiral **3** and chiral **2a** (Figure S3). As expected, and in good analogy with BTAs,[17a] increasing the temperature results in the addition of a higher fraction of chiral sergeant **2a** to achieve a homochiral system with a net helicity equal to unity. This effect confirms that temperature weakens the strength of the non-covalent interactions responsible for the supramolecular polymerization of these tricarboxamides, and reduces the degree of aggregation and the average stack length despite the cooperative character of the mechanism.

To energetically quantify the effect that the number of stereogenic centers in the chiral self-assembling unit exerts in obtaining a complete homochiral sytems in a *SaS* experiment, we have used the mathematical model described for BTAs, in which the two possible penalties for incorporating chiral units, MMP, or chiral fragments, HRP, within a helical columnar stack of unpreferred helicity is calculated.[17a] Considering that in the cooperative supramolecular polymerization of achiral **3**, a racemic mixture of both the left-and right-handed helical structures are formed upon self-assembly, the MMP contribution can be neglected. The chiral unit added to the racemic mixture will be incorporated in the supramolecular polymer of its preferred helicity since this situation prevents the system to be energetically penalized. Consequently, we have derived the HRP parameter for the six *SaS* experiments performed by mixing chiral tricarboxamides **1a-c** and **2a-c** with achiral **3**, at c_T = 10 μM and 20 °C (Table 2). The value estimated for the HRP is maximum (~13 kJ·mol^{-1}) for the mixtures of the tricarboxamides with three stereogenic centers, **1a** and **2a**, with achiral **3**, and decreases by decreasing the number of stereogenic centers in the self-assembling unit (~11 kJ·mol^{-1} for **1b** and **2b** with **3**, and ~8 kJ·mol^{-1} for **1c** and **2c** with **3**). Despite the error produced by the model utilized for deriving the HRP parameter,[17a] the values of the HRP are rather high and follow a clear tendency that provide a justification for the chiral amplification features experimentally observed in the *SaS* experiments. The high HRP value calculated for the mixtures of **1a** and **2a** with **3** hampers the formation of domains with inversed helicity within a columnar stack and, hence, favors the generation of homochiral supramolecular polymers at relatively low excess of the fraction of the chiral sergeant. However, decreasing the number of stereogenic centers per monomeric unit results in a lower energy penalty for those stacks with domains of inversed helicity, and yields a poor

and even a negligible ability for chiral amplification in the case of tricarboxamides **1b-2b** and **1c-2c**, respectively**.**

Table 2. Helix Reversal Penalty (HRP) determined from fitting the *SaS* data

Mixture[a]	3 + 1a	3 + 1b	3 + 1c	3 + 2a	3 + 2b	3 + 2c
HRP[b]	13.2	11.6	7.7	12.4	10.2	7.7

[a] c_T = 10 μM; 20 °C; [b] in kJ·mol^{-1}

Amplification of chirality. *MR* experiments. The above-described *SaS* experiments demonstrate that reducing the number of stereogenic centers per monomeric unit decreases the ability of these tricarboxamides to transfer the chiral information and, consequently, the ability to achieve a fully amplified chiral state. However, a further step is to determine the influence of the number of stereogenic centers on the amplification of chirality by performing *MR* experiments. In a *MR* experiment, mixing unequal amounts of two enantiomers with invariable c_T can give rise to homochiral, fully amplified mixtures.

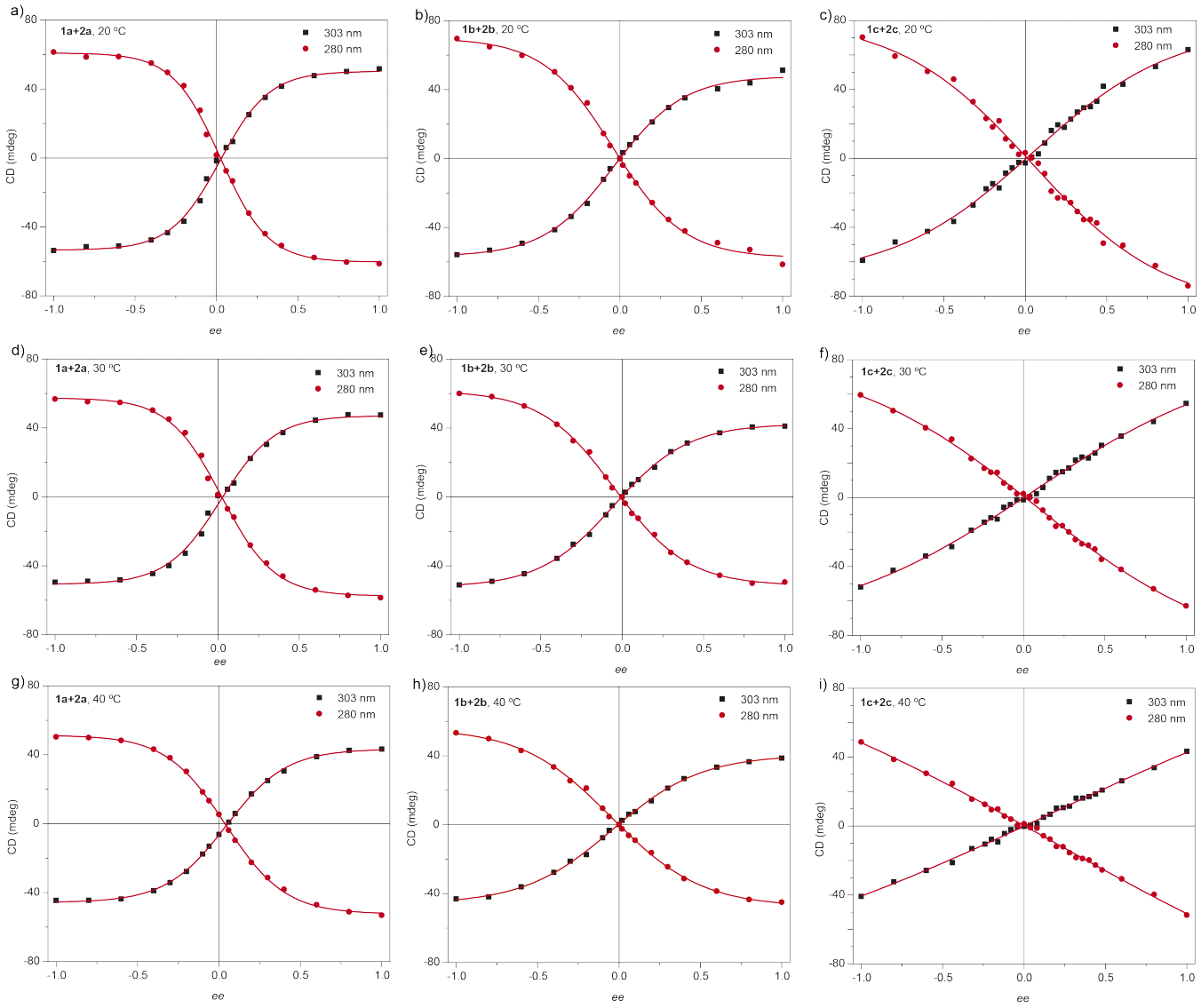

Figure 4. Changes in CD intensity (red circles: λ = 280 nm, black squares: λ = 303 m) as a function of *ee* upon adding ***(S)*-1** to a solution of ***(R)*-2** (MCH, c_T = 10 μM) at 20 °C (a-c), 30 °C (d-f), and 40 °C (g-i) . *ee* = 1.0 corresponds to pure ***(S)*-1** and *ee* = -1.0 corresponds to pure ***(R)*-2**. The red curves correspond to a sigmoidal fitting to guide the eye.

Our previous studies indicate that mixing solutions at c_T = 10 μM of tricarboxamides **1a** and **2a**, both endowed with three stereogenic centers, results in a non-linear variation of the dichroic response indicative of an efficient chiral amplification at a 48 % of enantiomeric excess (*ee*).[18c] Applying the two-component version of the EQ model,[19] a MMP value of around ~2 kJ·mol^{-1} was derived. This value is very similar to that derived for BTAs with three stereogenic centers (~2.1 kJ·mol^{-1}).[17] As in the previous section, we have investigated the influence of the number of stereogenic centers per monomeric unit in the ability to yield a fully homochiral mixture. Thus, we have performed *MR* experiments at c_T = 10 μM and at temperature of 20 °C by mixing tricarboxamides **1b** and **2b**,

with two (*S*) and two (*R*) stereogenic centers, respectively, and also by mixing tricarboxamides **1c** and **2c**, with only one (*S*) and one (*R*) stereogenic center, respectively (Figure S4). The experimental results show that reducing the chiral information per monomeric unit is accompanied by a reduced ability of the system to achieve a complete amplified state. Thus, whilst a 48 % of *ee* is required for the mixture **1a+2a** to provide a homochiral mixture, higher values of ee (57 % for **1b+2b** and >80 % for **1c+2c)** are necessary to get a complete chiral response (Figure 4). These experimental data are in good accordance with that inferred from the *SaS* experiments, but are in clear contrast to that described for BTAs, for which reducing the number of stereogenic centers per monomeric unit yields a more efficient chiral amplification.[17]

To justify the experimental findings, we have calculated the MMP factor.[19] The high HRP value derived from the *SaS* experiments suggests that reversing the handedness of a helical columnar stack is highly unfavorable; thus, the incorporation of a chiral unit into a columnar helical stack of its unpreferred helicity is energetically more favorable. Consequently, in the *MR* experiments, the HRP factor can be neglected and, from an energetic point of view, only the MMP factor has to be considered. Thus, we have determined the MMP (Figure S5 and Table 3) by applying the two-component version of the EQ model[19] and the thermodynamic data extracted from the variable-temperature experiments.

Table 3. Mismatch Penalty (MMP) determined from fitting the *MR* data[a]

	1a+2a	1b+2b	1c+2c
MMP 20 °C[b]	2.0 ± 0.2	2.5 ± 0.1	5.4 ± 0.4
MMP 30 °C[b]	2.5 ± 0.1	2.9 ± 0.2	8.6 ± 1.2
MMP 40 °C[b]	3.3 ± 0.2	3.7 ± 0.2	12.0 ± 0.2

[a] All the experiments performed in MCH at c_T = 10 μM; [b] in kJ·mol^{-1}.

The values derived for the MMP clearly show that this penalty notably increases by decreasing the number of stereogenic centers. Especially interesting is the case of the mixture of tricarboxamides **1c** + **2c**, endowed with only one stereogenic center, for which the calculated MMP is 5.4 kJ·mol^{-1}. This value is comparable to that obtained for the HRP from the *SaS* experiments by using the mixtures of **3** + **1c** and **3** + **2c** (Table 2). The similarity between the MMP and the HRP in the chiral amplification processes involving tricarboxamides **1c** and **2c** indicate that it is energetically possible to have helical reversals within a stack.

To complement all the studies related with the chiral amplification properties of these tricarboxamides, we have also investigated the influence of temperature on the *MR* experiments (Figure 4). Increasing the temperature to 30 and 40 °C hinders the formation of the helical aggregates and, consequently, a less intense dichroic response for the enantiopure samples and for the mixture of both tricarboxamides is observed. The values calculated for the MMP (Table 3) clearly show that the larger the number of stereogenic centers, the higher the amplification of chirality, and that temperature decreases the ability of the tricarboxamides for the amplification of chirality. These data are in clear contrast with those reported for BTAs, in which the effect is the opposite. In BTA discotics, a full homochirality is afforded more easily by increasing the temperature, and the MMP range from ~2 kJ·mol^{-1} at room temperature to ~1 kJ·mol^{-1} at 50 °C.[17]To achieve a better knowledge of the effect exerted by temperature on the chiral amplification phenomenon experienced by the reported tricarboxamides, we have also performed VT-CD experiments for different *ee* values. These VT-CD measurements were done only for mixtures of compounds **1a+2a** and **1b+2b** because the mixture of tricarboxamides **1c+2c** experiences a weak chiral amplification that decreases, becoming negligible, by raising the temperature. The comparison of the cooling curves obtained for the **1a+2a** mixture and the enantiopure tricarboxamides **1a** and **2a** allows the determination of the influence exerted by temperature to bias the degree of chiral amplification. As in the previous CD experiments, the VT-CD measurements were accomplished in MCH as solvent and at c_T = 10 μM, by using a cooling rate of 1 K·min^{-1} and temperature ranging from 90 to 20 °C.

In the case of the pure enantiomers **1a** and **2a**, a gradual decrease of the dichroic response is observed upon heating the solution. The reduction of the intensity of the dichroic signal is rapid at intermediate temperatures (~33 °C), and it is cancelled at the temperature of elongation T_e = 67 °C (Figure 5). Similar curves are obtained for pure **1b** and **2b** (Figure S6). The non-sigmoidal shape of the cooling curves is characteristic of the cooperative supramolecular polymerization mechanism that governs the formation of the helical, columnar stacks for these chiral tricarboxamides.

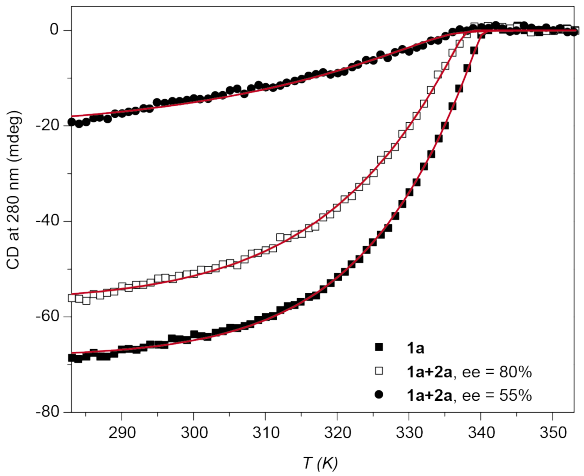

Figure 5. Cooling curves of mixtures of tricarboxamides **1a** and **2a** with variable values of the *ee* (MCH, c_T = 10 μM, cooling rate 1 K·min^{-1}). The red lines depict the fitting to the one-component EQ model.

The cooling curves of **1a+2a** and **1b+2b** at *ee* of 55 % and 80 % present a different shape (Figure 5 and S6). In these mixtures, heating the solution produces a rapid reduction of the dichroic response. This effect is especially remarkable for those mixtures at *ee* = 55 %, in which the cooling curves can be visualized as two straight lines that intersect at the T_e. Furthermore, the destabilizing effect exerted by the minor enantiomer on the stability of the columnar stacks is demonstrated by the lower T_e values of the mixtures compared with that observed for the pure enantiomers (Table 4). The decrease in the dichroic response upon raising the temperature is a direct consequence of the increase of the MMP with temperature, and a

typical feature of cooperative processes. In the case of mixtures of the reported tricarboxamides, the increasing value of the MMP, together with the disassembly effect exerted by temperature, provokes a more rapid disassembly of the chiral supramolecular polymer into the constitutive monomers.

Table 4. T_e values extracted from the cooling curves of the pure (*S*) enantiomers 1a and 1b and the mixtures of 1a+2a and 1b+2b at *ee* = 55 and 80 %.[a]

	1a	1b	1a+2a (55%)	1a+2a (80%)	1b+2b (55%)	1b+2b (80%)
T_e[b]	67	65	61	64	61	64

[a] MCH, c_T = 10 μM; [b] in °C

These experimental findings strongly contrast to those previously described for BTAs. In BTAs, increasing the temperature allows reducing the energetic cost of incorporating a monomeric unit into a columnar stack of its unpreferred helicity. As a consequence, the consecution of a homochiral stack is favored at relatively high temperatures depending on the enantiomeric excess. The relaxation of the N–H···O=C H-bonding interactions between vicinal amide functional groups, upon increasing the temperature, has been considered to explain this trend.[17] A similar behavior could be expected for the described OPE-TAs **1-3** since the supramolecular polymerization of these tricarboxamides proceeds, as for BTAs, through the formation of a triple array of H-bonding interactions between the amide groups and, concomitantly, by the π-stacking of the aromatic units.[18] However, there is a clear geometrical difference between BTAs and tricarboxamides **1–3**. In the formation of the columnar stacks between BTAs, the rotation angle between the monomeric units is of ca. 60° to optimize the N–H···O=C bonds (2.1 Å) and the π-stacking of the benzene rings (ca. 3.5 Å).[21] This rotation angle between the stacked monomeric units produces a possible but weak interaction between the side chains on adjacent molecules. Raising the temperature weakens both the H-bonding interactions and the π-stacking of the benzene rings, and increases the distance between the BTA monomeric units. This reduces the interaction between the side chains, and especially of the stereogenic centers present in these chains, and favors the incorporation of monomeric units into columnar stacks of unpreferred helicity to yield fully homochiral aggregates. The larger size of the tricarboxamide discotics **1–3** drastically reduces the rotation angle between the monomeric units in the stack to ca. 18°.[18a] As discussed below, with this rotation angle the side chains are spatially close which originates van der Waals steric interactions. Increasing the temperature relaxes the distances between the aromatic units and the H-bonding interactions, but does not alleviate the hindrance between the side chains. Therefore, the incorporation of a monomeric unit of chiral tricarboxamides **1** or **2** into a stack of its unpreferred helicity would increase the steric interaction between the branched side chains, thus increasing the MMP and, consequently, the difficulty to achieve fully homochiral aggregates.

In order to provide a structural/energetic explanation of the chiral amplification trends in OPE-TAs, which differ from those reported for BTAs, we analyzed the minimum-energy geometry of the most stable supramolecular 20-mer stacks of **2a-c** (Figure 3c-d). Intermolecular parameters scrutinized comprise the rotation angle between adjacent monomeric units along the growing axis (θ), the intermolecular distance between central benzene centroids (d_I), and the H-bond distance (d_H) between adjacent amide groups (Figure 6a). Minimum-energy geometries obtained at the GFN2-xTB level of theory indicate that intermolecular distances d_I are scarcely affected by the number of chiral chains in our OPE-TAs, with average values of 3.25 Å and 3.26 Å for eclipsed **2a** and **2b**, respectively. As the minimum-energy stack of **2c** presents an alternated disposition of the chiral chains, the intermolecular distance between vicinal discotics in the stack is computed slightly shorter for this derivative (d_I = 3.20 Å). H-bond distances vary in the range of 1.73 to 1.95 Å, with average values of 1.81, 1.79 and 1.79 Å for **2a**, **2b** and **2c**, respectively.[22]

The optimized geometries, however, indicate that the stacking rotation per monomeric unit (θ) systematically decreases upon reducing the number of chiral chains in the discotic tricarboxamide, going from an average value of 18.51° in **2a** to 18.38° in **2b** and to 18.31° in **2c**. This leads to a small but noticeable 1.1% reduction of θ in passing from three-chiral-chains **2a** to one-chiral-chain **2c**. Larger values of the stacking rotation imply smaller steric hindrance between neighboring chains (Figure 6b), and thus smaller MMP values. To estimate the MMP, we computed the energy penalty of introducing a "wrong" chiral OPE-TA into a columnar 20-mer stack of its unpreferred handedness (see the Supporting Information for details). Theoretical calculations predict that this penalty increases upon decreasing θ, with MMP values of 1.40, 2.01, and 3.10 kJ·mol^{-1} per monomeric unit and per "wrong" chiral discotic for **2a**, **2b**, and **2c**, respectively, which nicely agree with the *MR* experimental results.

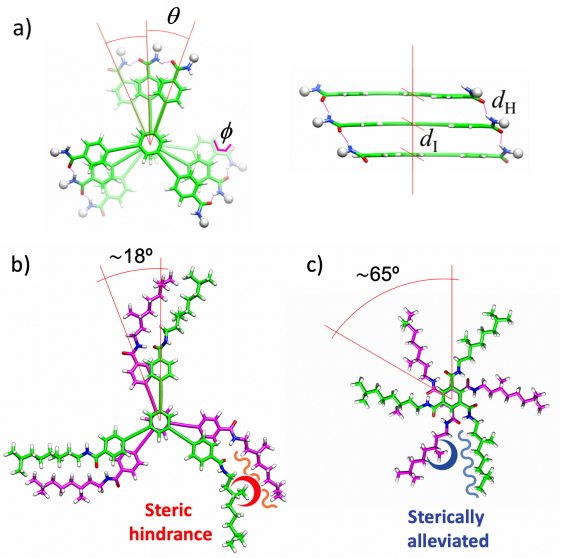

Figure 6. a) Inter- and intramolecular structural parameters characterizing the OPE-TA supramolecular helices: rotational angle between adjacent molecules along the stack (*θ*), twisting angle of the amide groups (*ϕ*), intermolecular discotic-discotic distance (d_I) and H-bond distance (d_H). Schematic illustration of the steric hindrance effect exerted by the chiral, aliphatic chains of vicinal units in OPE-TA **2a** (b) and the analogous BTA (c).

The occurrence of larger stacking rotations upon increasing the number of chiral chains could also explain the differences

found experimentally in the HRP. This penalty refers to the interaction along the growing axis between two helices of different handedness and, as already reported, can be related with the efficiency of H-bond interactions.[17] For larger stacking rotations (e.g. in **2a**), H-bond interactions become more directional (more handed oriented), and thus the penalty when two columns of different handedness interact is increased. The average twisting angle adopted by the amide groups (ϕ in Figure 6a) to form the intermolecular H-bonds is predicted to be 36.0° for **2a**.[23] In contrast, by reducing the rotating angle θ (e.g., in **2c**), H-bond interactions are less directed to a particular handedness (ϕ of 39.1° for **2c**), and thus the HRP is expected to be smaller. These trends follow the experimental behavior inferred from the *SaS* data.

A similar geometry analysis was performed for 20-mer columnar stacks of BTAs analogous to **2a-c** that were also fully optimized at the GFN2-xTB level (see the Supporting Information for details). Calculations show that the number of chiral chains barely impacts on the stacking rotation of BTAs, with a 0.3% increase of θ in going from the three-chiral-chains derivative to the one-chiral-chain discotic. The negligible effect of the number of chiral chains for θ can be rationalized by the absolute stacking rotation, which is computed of ca. 65° (Figure 6c). This large monomer rotation along the growing axis is due to the fact that the amide groups in BTAs are directly linked to the central benzene ring, and leads to a stacking arrangement where chiral chains of neighboring discotics do not interact as they are spatially distant (Figure 6c). As θ remains practically constant in BTAs, increasing the number of chiral centers inevitably increases the steric bulk in the column, and thus the MMP is meant to increase. Moreover, HRP is reported to be independent of the number of chiral chains for BTAs,[17b] in good accord with the stacking rotation invariance.

CONCLUSIONS

We have described a complete series of experimental and theoretical investigations on the supramolecular polymerization of oligo(phenylene ethynylene) tricarboxamides (OPE-TAs, compounds **1-3)**. We have expanded previous studies on transfer and amplification of chirality to demonstrate the influence exerted by the number of stereogenic centers per monomeric unit and the temperature on the chiral amplification phenomena by carrying out *SaS* and *MR* experiments. We have derived a full set of thermodynamic parameters including the helix reversal penalty (HRP) and the mismatch penalty (MMP). The values derived for the former demonstrate that the larger the number of chiral side chains, the higher the HRP, leading to a more efficient amplification of chirality. Otherwise, increasing the number of stereogenic centers per monomeric unit results in a lower MMP, enhancing the chiral amplification phenomenon. Decreasing the temperature also leads to a more efficient chiral amplification. These experimental data sharply contrast with those reported for BTAs, for which the chiral amplification ability in *MR* experiments increases by lowering the number of stereogenic centers or increasing the temperature.

To gain insight for this behavior, we performed theoretical calculations by utilizing the GFN2-xTB approach. Calculations first confirm that (*R*)-stereogenic centers favor the formation of *M*-type helical structures, the opposite being found for (*S*)-stereogenic centers. Second, they show that the rotational angle between neighboring OPE-TA units (ca. 18°) is conditioned by the steric hindrance between the peripheral side chains, larger values being found for larger number of chiral side chains. Larger stacking rotation angles imply smaller steric hindrance between neighboring chains and lead to smaller MMP values, thus explaining the experimental trends found for the MMP and HRP parameters. In contrast, the large rotational angle predicted for columnar stacks of BTAs (ca. 65°) gives rise to weak interactions between the side chains, and remains mostly unchanged with the number of stereogenic centers. Thus, increasing the number of chiral side chains in BTAs increases the steric hindrance, which results in larger MMP values whereas the HRP remains unaltered. The experimental consequence is that in BTAs the smaller the number of stereogenic centers per monomeric unit the larger the chiral amplification ability.

The data presented herein contribute to shed light on the parameters controlling the transfer and amplification of chirality processes in supramolecular polymers, highlighting the enormous influence exerted by the size of the self-assembling unit on the final helical outcome, and help to establish more clear rules on the structure/property relationships for the supramolecular polymerization of chiral self-assembling systems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Full experimental details, additional CD measurements, and theoretical calculations, including Figures S1-S6, Tables S1-S14 (PDF)

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ABBREVIATIONS

BTAs, 1,3,5-benzenetricarboxamides; OPE-TAs, oligo(phenylene ethynylene)-tricarboxamides; *SaS*, sergeants-and-soldiers; *MR*, majority rules; HRP, helix reversal penalty; MMP, mismatch penalty.

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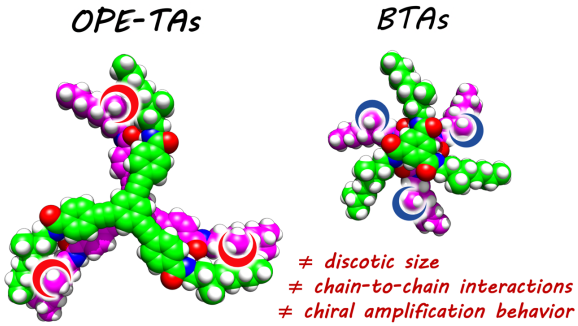
(22) It should be noted that the GFN2-xTB method tends to provide too short H-bond distances by 5−10 % compared to high-level DFT approaches. Please, see ref. 18e.

(23) Defective H-bond interactions with dihedral angles of < 15° or > 60° were not considered for the dihedral average computation.


OPE-TAs
BTAs
≠ discotic size
≠ chain-to-chain interactions
≠ chiral amplification behavior