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Single- and double-helices of α,α'-dibenzylaminotripyrrin: solution and solid state studies.

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The dimeric association of α,α'-di(benzylamino)tripyrrin in chloroform was found to be 40 times less effective than previously reported α,α'-dianilinotripyrrin, which, however, led us to observe the co-crystal structure of single and double helix forms. Attachment of chiral phenylethylamines on the same tripyrrin platform was also performed to induce helical chirality.

The double helix structure of DNA has inspired the synthesis of a wide range of artificial systems with an ever growing interest in this area.[1] Indeed, since early 2000, a variety of artificial double helical molecules have been reported by employing hydrogen bonding interactions (**A**),[2,3] salt-bridge formations (**B**)[4,5] and π-stacking interactions (**C**) (Chart 1.).[6] In most cases, the X-ray crystal structures offer solid evidence of double-helix structures as well as deep insights into the interstrand interactions. However, as the complexity of the system increases, it generally becomes difficult to grow crystals suitable for XRD analysis. In these cases, as well as in molecular systems exhibiting small dimerization constant, the spectroscopic measurements become the methods of choice in characterizing double helices.

Recently, we have developed a new helical system based on α,α'-dianilinotripyrrin **1**, which is capable of forming a double helical structure.[7] This fully π-conjugated molecule bearing two amine NH, two imine N and one pyrrolic NH can form interstrand hydrogen-bonds in non-polar solvents, while a monomeric single-helical structure was confirmed in polar solvents by XRD analysis. An equilibrium of monomeric and dimeric structures was observed by ^{1}H NMR analysis, allowing for determination of the association constant K_{dim} to be 270 M^{-1} in $CDCl_3$ at 25 °C. Interestingly, the dimerisation association constants as well as other physicochemical parameters (ΔH, ΔS) were tuneable by the substituents installed on the aniline moieties. For example, the K_{dim} values were increased by one-order of magnitude upon installation of *tert*-butyl or trifluoromethyl groups at the 3,5-positions of the aniline groups. To extend the scope of the substituents and to compare the association kinetics, we planned to examine a similar substitution reaction with benzylamine. Herein, the study on the reactivity and the characterization of newly obtained di(benzylamino)tripyrrin is reported. Fortunately, we obtained a co-crystal structure containing single- and double-helices as a rare example.

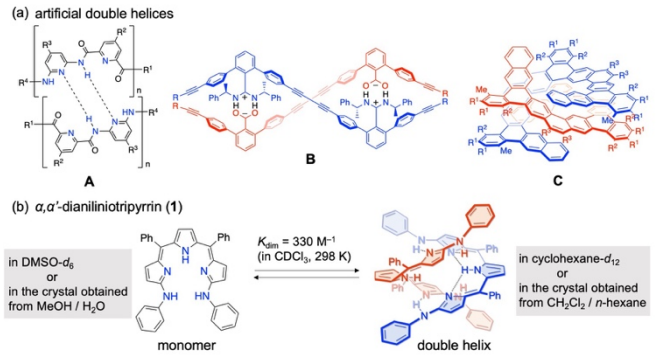

Chart 1. (a) Examples of artificial double helix molecules. (b) An equilibrium of single- and double-helical forms of α,α'-dianilinotripyrrin **1**.

As reported for the synthesis of **1**, the substitution reaction was performed in THF with benzylamine on α,α'-dibromotripyrrin **2** (Scheme 1). Unfortunately, at room temperature or even at elevated temperature, only mono-substitution reaction proceeded effectively to give α-benzylamino-α'-bromotripyrrin **3** in a quantitative yield. Further reaction of isolated **3** with benzylamine under heating did not afford bis-adducts. This can be rationalized with the electron-density of the tripyrrin core of **3** that becomes more electron rich due to the alkylamino group.[8] To mitigate this problem, we prepared 5,10-bis(*p*-trifluoromethylphenyl)tripyrrin **4**, which bears electron withdrawing groups at the *meso* positions. By slightly modifying the reported procedure for **2**, **4** was synthesized from the

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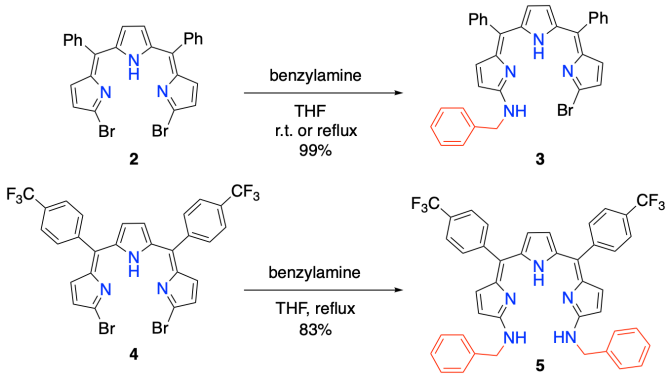
corresponding tripyrrane through α,α'-dibromotripyrrane in 53% yield in 2 steps (See ESI). Noteworthy, the synthesis of 5,10-bis(*p*-trifluoromethylphenyl)tripyrrane failed when using Gryko's method[9] employing an *N*-tosylated precursor. The tripyrrane was obtained in 31% yield from pyrrole and aldehyde using the acid-catalyzed synthesis in aqueous medium.[10] With **4** in hand, the reaction with 4 equivalents of benzylamine in refluxing THF gave α,α'-dibenzylamino-5,10-bis(*p*-trifluoromethylphenyl)tripyrrin (**5**) in 83% yield. This is the first example of di(alkylamino)tripyrrin derivative.[11]



Scheme 1. Synthesis of α,α'-dibenzylaminotripyrrin.

^{1}H NMR spectrum of **5** in DMSO-d_6 exhibited signals corresponding to the monomeric form due to the hydrogen-bonding between the external amine NH and the solvent (Fig. 1a). The spectral pattern was similar to that of **1** in DMSO-d_6 except for the presence of the benzyl protons at 4.66 ppm. In $CDCl_3$, the ^{1}H NMR spectra of **1** displayed a mixture of monomeric and dimeric forms, the ratio of which depended on the concentration and temperature.[7] This behaviour was not mirrored by **5**, instead, at room temperature at a concentration of 10 mM in $CDCl_3$, we observed relatively sharp peaks at 7.63, 7.56, 7.30, 7.27, 6.66 and 6.23 ppm and broad peaks at 6.15 and 4.54 ppm (Fig. 1b). Cooling down the solution to –20 °C led to the appearance of new peaks, including the interstrand NH peak at –12.74 ppm (Fig. 1c). In cyclohexane-d_{12}, **5** showed clear signals of NH protons at 12.78 and 11.02 ppm and a set of tripyrrin signals, suggesting the exclusive formation of the dimer (Fig. 1d).

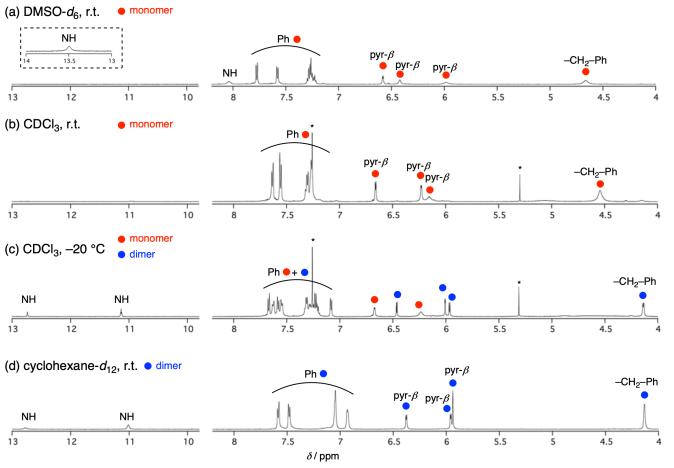


Fig. 1 ^{1}H NMR spectra of **5**; a) in DMSO-d_6 at rt, b) in $CDCl_3$ at rt, c) in $CDCl_3$ at –20 °C and d) in cyclohexane-d_{12} at rt.

The physicochemical parameters for dimerisation of **5** were determined by variable temperature ^{1}H NMR spectral analysis (See ESI). The K_{dim} value of **5** (6.7 M^{-1} at 298 K) is much smaller than that of **1** (270 M^{-1} at 298 K). The van't Hoff plot gave ΔH and ΔS values to be = –35.8 kJ mol^{-1} and –104.4 J mol^{-1} K^{-1}, respectively. Although the dimerisation is mostly enthalpy-driven, the enthalpic gain is smaller than the one observed for **1** (ΔH = –53.6 kJ mol^{-1}).

In the optimized structure (DFT calculation at B3LYP-D3(BJ)/6-311++G(d,p) level, Fig. 2b), [12] effective π-π contacts are seen with the distance of ca. 3.68 Å between the two pyrrole moieties. However, the benzylic methylene moieties likely disturb effective CH-π interaction between the terminal phenyl segment and the tripyrrin core, which is responsible for the higher dimerisation constants observed for **1** or its derivatives.

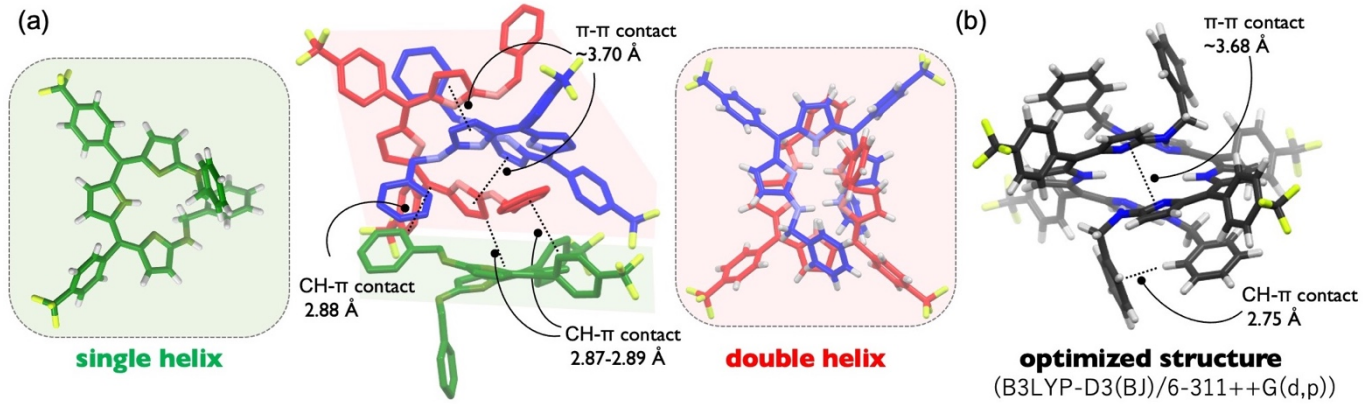


Fig. 2 (a) X-Ray crystal structure of **5** (CCDC 2054819). Red and blue molecules form a double helical structure and green one exists as a monomer. Intermolecular interactions are highlighted. Hydrogen atoms were omitted for clarity in the center. (b) Optimized structure of the double helical structure calculated at the B3LYP-D3(BJ)/6-311++G(d,p) level of theory.

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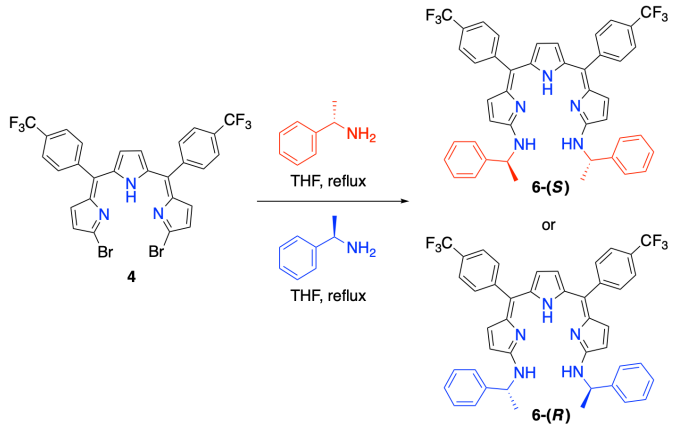
Fortunately, single crystals suitable for XRD analysis were obtained from an *n*-hexane solution of **5** by slow evaporation (Fig. 2a). We thought that the dimeric form of **5** should be dominant in *n*-hexane as observed in the ^{1}H NMR spectrum in cyclohexane-d_{12}. However, to our surprise, the solved structure is a mixture of two tripyrrin units, one of which forms double-helix, and the other exists as a monomer. In other words, this "co-crystal" is a snap-shot of an equilibrium between single-strand and double-strand tripyrrins. Such co-crystal structure of artificial π-conjugated helices is unprecedented, to the best of our knowledge. In the crystal structure, several CH-π contacts are observed between the benzyl aromatic C-H and other benzyl π-plane or tripyrrin π-plane within 2.9 Å. No solvent molecules are included in the unit cell, indicating that such 1:1 mixture allows as good crystal packing.



Scheme 2. Synthesis of (*S*)/(*R*)-phenylethylamine-substituted-diaminotripyrrin **6**.

The synthesis of **5** proved that it is possible to install sp^3 carbons next to the amine moieties in these tripyrrin derivatives. This allowed us to examine the substitution reaction of **4** with (*S*)- or (*R*)-1-phenylethylamine (Scheme 2). The reactions proceeded smoothly under heating in THF, affording (*S*)- and (*R*)-1-phenylethylamine-substituted tripyrrins **6-(*S*)** and **6-(*R*)** in 62% and 58% yields, respectively. The ^{1}H NMR spectra of **6-(*S*)** and **6-(*R*)** were measured in $CDCl_3$, both showing a single set of peaks at room temperature or even at –40 °C. This indicates that the dimerization constant of **6-(*S*)/(*R*)** is much smaller than **5** probably due to the steric effects. In cyclohexane-d_{12}, **6-(*S*)/(*R*)** exhibited two sets of signals indicating the equilibrium between monomer and dimer even in a 10 mM solution (See ESI). Thus, association constant K_{dim} in cyclohexane-d_{12} was calculated to be 851 M^{-1}, which was quite small considering that **5** exclusively forms a dimeric form in cyclohexane-d_{12}. Mixing an equimolar amount (each 5 mM) of **6-(*S*)** and **6-(*R*)**, in cyclohexane-d_{12} at room temperature, leads to an NMR spectrum *quasi*-identical with those of the enantiopure samples (See ESI). This implies that **6-(*S*)** and **6-(*R*)** self-sort to form homodimers rather than producing a statistical mixture in which the mixed chirality heterodimer would be present.

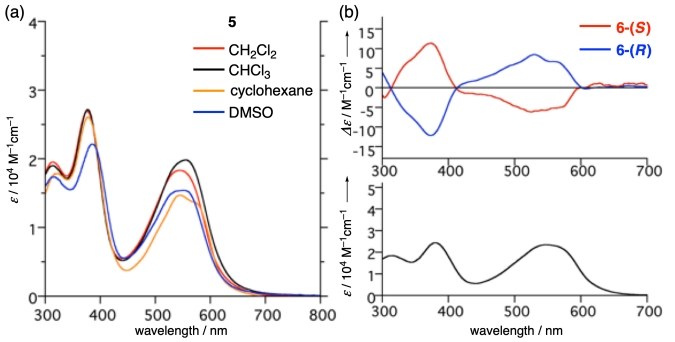


Fig. 3 (a) UV/vis absorption spectra of **5** in CH_2Cl_2 (black), $CHCl_3$ (red), cyclohexane (orange) and DMSO (blue). (b) CD (top) and absorption (bottom) spectra of **6-(*S*)** and **6-(*R*)** in $CHCl_3$.

UV-Vis absorption spectra of **5** were measured in various solvents (CH_2Cl_2, $CHCl_3$, cyclohexane and DMSO) as shown in Fig. 3. In all cases, two main absorption bands around 380 and 550 nm were observed, and the solution colors were deep purple. Compound **5** is not emissive under these conditions probably due to the rapid structural changes and association in non-polar solvents. This process, however, does not affect the absorption spectrum and the solvent specific NH-tautomerization driven color change, which was observed in the case of **2**,[7] was not present. Chiral tripyrrins **6-(*S*)** and **6-(*R*)** essentially displayed the same absorptions, but they showed Cotton effects in the circular dichroism (CD) spectra due to the presence of enantiopure single helices in $CHCl_3$. Although the intensity is relatively small ($\Delta\varepsilon$ = 12 M^{-1} cm^{-1} at 374 nm), mirror-imaged patterns were confirmed for **6-(*S*)** and **6-(*R*)**.[13] This is the first example of chirality transfer from the terminal substituents to the tripyrrin core.[14]

In summary, a new double helical molecule, α,α'-di(benzylamino)tripyrrin, was synthesized by the substitution reaction of CF_3-activated α,α'-dibromotripyrrin with benzylamine. This tripyrrin exclusively formed a double helical structure in cyclohexane, while the association constant in $CDCl_3$ was smaller than that of α,α'-dianilinotripyrrin. The structural requirements to form a double helix were deduced from the DFT-optimized structure. The decreased dimerisation constant allowed us to obtain a co-crystal containing single- and double-strand helices, which enables us to visualize the actual interaction between helices. Chiral phenylethylamine-substituted diaminotripyrrins were synthesized, which

demonstrate chirality transfer from the carbon point chirality to the tripyrrin chromophore. Further study on the design and characterizations of new tripyrrin derivatives are actively in progress.

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Conflicts of interest

There are no conflicts to declare.

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