Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2015, **13**, 9938

Received 15th July 2015,
Accepted 25th August 2015

DOI: 10.1039/c5ob01448d

www.rsc.org/obc

The molecular recognition controlled stereomutation cycle in a dynamic helical assembly†

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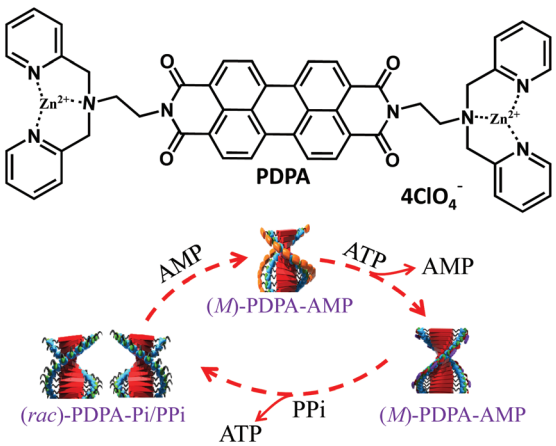
Perylene bisimide functionalized with a phosphate recognition unit assembles into a left-handed, right-handed or racemic helical assembly on binding with AMP, ATP and inorganic phosphates, respectively. Thus, competitive binding among these multivalent guests was utilized for completing an unprecedented helix mutation cycle in a dynamic supramolecular assembly.

Natural helical macromolecules display elegant control over their helix handedness through preferred configurations of homochiral building blocks.[1] In artificial helical polymers[2] and supramolecular assemblies,[3] handedness has been controlled by employing monomers of opposite enantiomers. Such an approach involves the additional synthetic challenge of obtaining both enantiomeric monomers. However, homochiral guest (chiral auxiliaries) induced helicity into the assembly of achiral molecules presents a smart design strategy, whose handedness can be easily controlled by configuration of the easily accessible guest molecules.[4] Very recently, this design has been further utilized for the construction of metastable states, enantioselective sensing and other chiroptical applications.[5] An evolved level of control over the helical assembly would demand dynamic switching of main chain chirality without affecting the configuration of stereocenters. Such a rational design of precise control over the helix handedness of one-dimensional (1-D) supramolecular polymers has not been reported.

Biomacromolecules like polynucleotides represent a class of polymers which are shown to display stimuli responsive reversible stereomutation.[6] A biomimetic approach of stereomutation in synthetic helical polymers has been demonstrated by controlling parameters like temperature, solvent, pH, light, redox states, guest molecules, metastable assemblies, *etc.*[7] However, a rational design for dynamic switching of helical states leading to complete control over the helix mutation cycle in a synthetic supramolecular polymer remains unprecedented. Here we report, an efficient strategy of competitive guest binding among multivalent guests for dynamic switching of helical states of a receptor functionalized supramolecular polymer, from a racemic to left-handed followed by a right-handed helix before converting them back to racemic stacks, thus completing a helix mutation cycle. Our recent report on the dipicolylethylenediamine–zinc (DPA–Zn) functionalized perylene diimide derivative (**PDPA**) shows the opposite helical assembly of **PDPA** molecules upon interaction with AMP (left-handed, *M*-helix) and ATP (right-handed, *P*-helix).[8] Taking advantage of the competitive guest binding among multivalent guests, AMP can be replaced by ATP leading to dynamic helix reversal from *P*-helix to *M*-helix. Using this strategy, we could replace bound AMP with ATP, which can be further replaced by achiral pyrophosphate (PPi, $P_2O_7^{4-}$). This results in a helix transformation from racemic to *M*-helix followed by *P*-helix and finally converting them back to the racemic assembly, completing one helix cycle (Scheme 1). Thus, we demonstrate



Scheme 1 Chemical structure of PDPA along with schematic representation of step-wise change in helix handedness by competitive replacement of phosphate guests.

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†Electronic supplementary information (ESI) available: Supporting figures and experimental details. See DOI: 10.1039/c5ob01448d

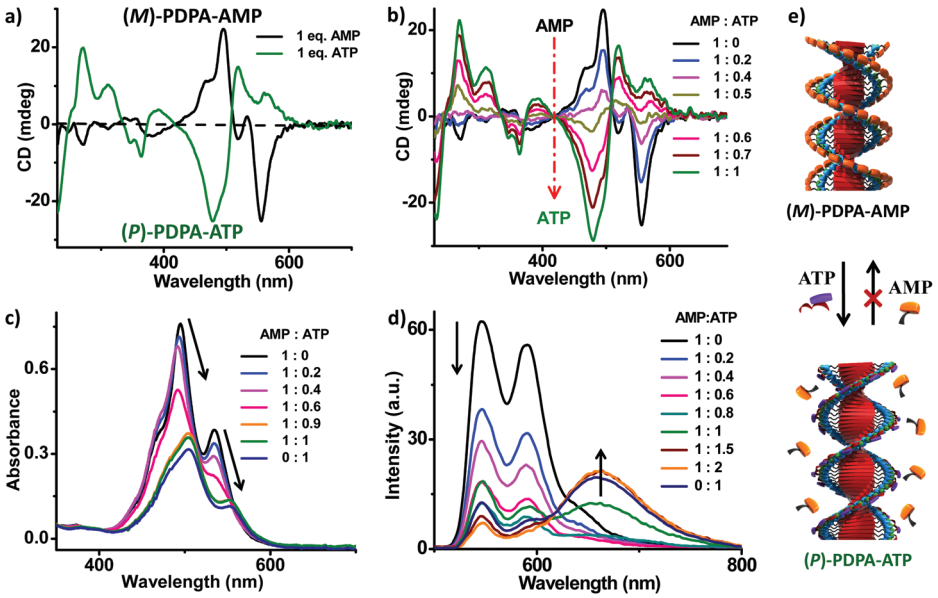

Fig. 1 (a) CD spectra of (*M*)-**PDPA-AMP** and (*P*)-**PDPA-ATP** assemblies showing their mirror image relationship. Variation in (b) CD signal, (c) absorption spectra and (d) emission spectra (λ_{ex} = 470 nm) upon addition of ATP to (*M*)-**PDPA-AMP** solution (90% aq. HEPES in MeCN, $c = 2 \times 10^{-5}$ M). (e) Schematic representation of dynamic helix reversal through competitive replacement of AMP by ATP.

a tandem guest exchange for step-wise control of the helix handedness of a synthetic assembly, resulting in one complete helix mutation cycle.

Towards this goal, homochiral stacks with a preferred handedness were constructed by binding chiral adenosine phosphates to **PDPA** racemic assemblies. Addition of AMP to (***rac***)**-PDPA** stacks (90% HEPES in MeCN, 2×10^{-5} M) resulted in a negative bisignated circular dichroism (CD) signal (negative and positive maxima at 557 nm, 496 nm, respectively, Fig. 1a and S1†). This indicates a left-handed (*M*-helix type) organization of PBI chromophores, *i.e.* (***M***)**-PDPA-AMP**. On the other hand, addition of adenosine triphosphate (ATP) to (***rac***)-**PDPA** stacks induced a positive bisignated CD signal (positive and negative maxima at 518 nm, 480, nm respectively, Fig. 1a). This is a clear signature of right-handed (*P*-helix type) organization, *i.e.* (***P***)**-PDPA-ATP**, which is opposite in handedness compared to (***M***)**-PDPA-AMP** assemblies as shown in Fig. 1a. The origin of opposite helicity upon AMP and ATP binding to the DPA derivative was previously attributed to the differences in their mode of binding and the differential positioning of the adenosine moiety with respect to the stacks.[9]

Another important aspect of these multivalent guests is their strength of interaction which is easily tunable based on the number of available binding groups. For example, AMP being a monophosphate can be competitively replaced by ATP with three phosphate binding groups, due to the significant differences in the association constant (K_a). The highest value of K_a (ATP) was 1.2×10^6 M^{-1}, whereas K_a (AMP) was 8.8×10^4 M^{-1} (Fig. S2–4†). These data were obtained by fitting the titration curves using "GraphPad PRISM" software. We note that indeed ATP binding is much stronger than AMP, thus AMP can be replaced easily by ATP. This strategy was recently employed for demonstrating helix reversal in naphthalenediimide (NDI) derivatives.[10] We envisaged that such an approach could be used to impose well-defined control over the helix handedness of stacks. Thus, aliquots of ATP were added to the (***M***)**-PDPA-AMP** solution while monitoring the CD spectra. We note that the CD spectra inverts gradually from a negative bisignated signal to a positive bisignated signal, passing through an isodichroic point at a zero crossing of 418 nm (Fig. 1b). These changes were very fast, where the addition of aliquots of ATP to (***M***)**-PDPA-AMP** led to a sharp jump in the CD signal (Fig. S5†). Moreover, the final CD signal obtained after replacement of AMP by ATP was the same in intensity as compared to the (***P***)**-PDPA-ATP**, confirming complete substitution of guest molecules. Apart from the opposite CD signal, the replacement of AMP by ATP was further confirmed by the bathochromic shift of the band maxima from 499 nm to 514 nm and from 535 nm to 564 nm on formation of **PDPA**-ATP stacks (Fig. 1c). Fluorescence spectra also show the evolution of a new red shifted band at 665 nm upon addition of ATP (Fig. 1d). These spectral features were shown to be characteristic of (***P***)**-PDPA-ATP**, confirming the complete replacement of AMP from the **PDPA** stacks (Fig. S6†).

To gain further insights into the supramolecular organization replacement of **PDPA** bound AMP by ATP, microscopic investigations were undertaken. The transmission electron micrograph of (***M***)**-PDPA-AMP** shows the formation of irregular nanostructures (Fig. 2a). However, upon competitive replacement of AMP by ATP, we observe a morphology transition to well-defined one-dimensional (1-D) nanofibers (Fig. 2b). The widths of these fibers were nearly 5 nm, which is close to the

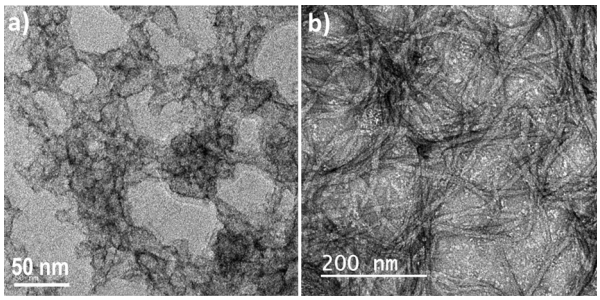

Fig. 2 TEM micrographs of the **PDPA** assembly in the presence of (a) 1 eq. AMP, (b) 4 eq. AMP followed by 1 eq. ATP showing the morphology transition from ill-defined aggregates to 1-D nanofibers confirming replacement of bound AMP by ATP (90% water in MeCN, 2×10^{-5} M). Helical structures could not be visualized in their microscopic images probably due to bundling of aggregates.

length of the **PDPA**-ATP complex (ATP bound on both sides of **PDPA**). Moreover, these fibers closely resemble the nanostructure obtained by **(*P*)-PDPA-ATP** (Fig. S7†). This unambiguously confirms the transformation from **(*M*)-PDPA-AMP** to **(*P*)-PDPA-ATP**, presenting a very simple strategy for the dynamic reversal of supramolecular helicity.

Having shown the dynamic reversal of supramolecular helicity in these self-assembled stacks, a method to convert homochiral to racemic stacks is essential in gaining complete control over their helical states. In this regard, we utilized an inorganic achiral phosphate, PPi [$(P_2O_7)^{4-}$], which can replace AMP as well as ATP due to their high charge density. Addition of PPi to either **(*M*)-PDPA-AMP** or **(*P*)-PDPA-ATP** led to complete loss of the bisignated CD signal (Fig. S8†) due to the formation of **(*rac*)-PDPA-PPi** stacks. With these experiments, we have shown switching of helicity from a left-handed to right-handed assembly as well as dynamically converted them into their racemic forms.

With the demonstration of control over various single step transitions like inversion of helicity, racemic to homochiral and *vice versa*, the next challenge was to perform them in a sequential manner in one pot (Fig. 3). This was attempted by tandem addition of different phosphates, in order to complete one helix cycle from a racemic to left-handed followed by a right-handed helix before converting them to racemic stacks again. Thus, we started with **PDPA** stacks pre-bound with

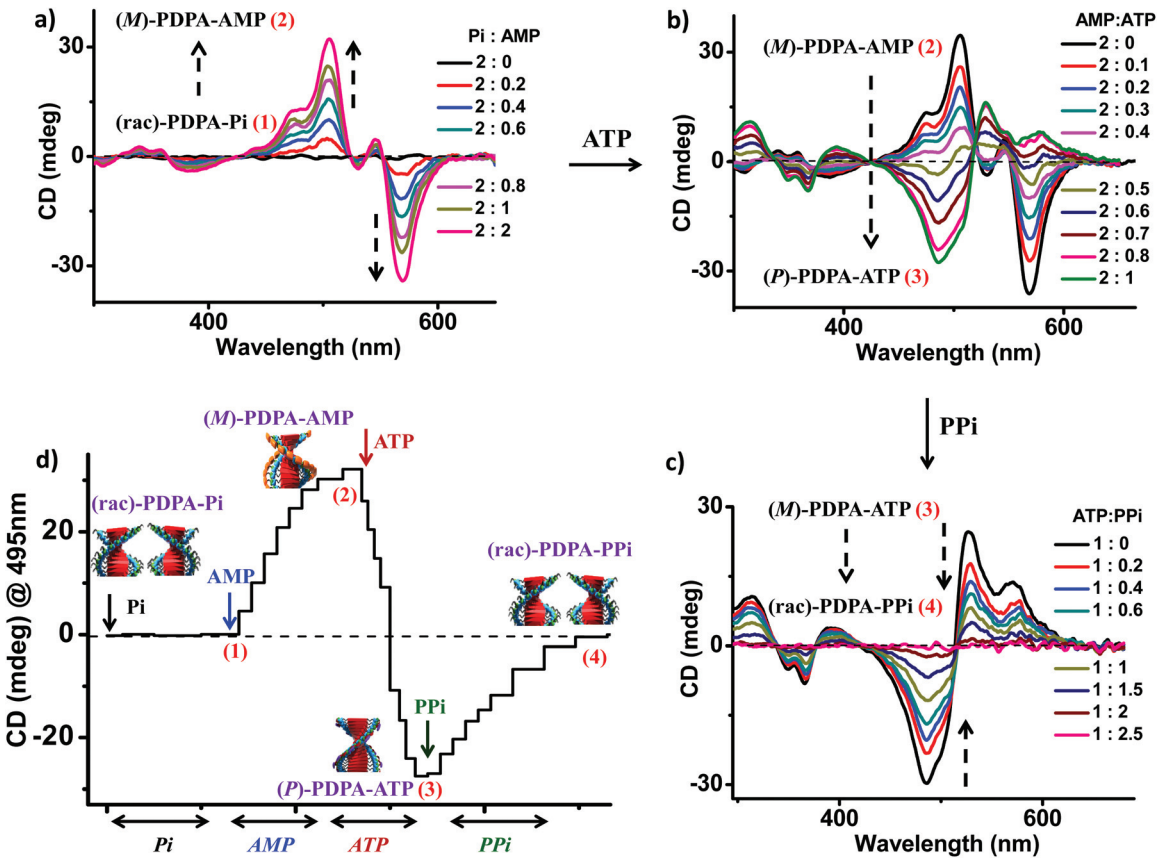

Fig. 3 Variation in CD signals upon sequential addition of (a) AMP to **(*rac*)-PDPA-Pi** followed by (b) ATP and subsequently (c) PPi (90% aq. HEPES in MeCN, $c = 2 \times 10^{-5}$ M). (d) The plot of CD maxima near 495 nm upon sequential addition of various phosphates, whereas the schematic represents the respective helical states obtained. All spectra in a, b and c were obtained from the same solution with subsequent addition of different phosphates each time.

achiral inorganic mono-phosphate, Pi [$(PO_4)^{3-}$] to give the racemic assembly (***rac*)-PDPA-Pi**. To this solution aliquots of AMP were added, which can replace Pi, thereby converting them into a homochiral left-handed assembly. This could be easily monitored by the evolution of the negative bisignated CD signal, confirming the formation of (***M*)-PDPA-AMP** stacks (Fig. 3a). Subsequent addition of ATP to the above solution resulted in reversal of the CD signal from the negative to positive bisignated CD signals, passing through an isodichroic point with a zero crossing at 423 nm (Fig. 3b). This clearly indicates the transition between two states, *i.e.* from left-handed (***M*)-PDPA-AMP** to right-handed (***P*)-PDPA-ATP** through dynamic helix reversal. The next step in this sequential process was the addition of achiral diphosphate, PPi, to the above obtained (***P*)-PDPA-ATP** stacks. The CD spectra show continuous decrease in signal intensity, which finally resulted in a CD silent state at higher eq. of PPi (Fig. 3c). This confirms the transformation from the ATP bound right-handed helix to (***rac*)-PDPA-PPi** stacks. The absorption spectra of (***rac*)-PDPA-Pi** and (***rac*)-PDPA-PPi** confirmed that the molecules are not in their monomeric state, but are assembled as racemic stacks. A better picture of the whole process could be obtained by the plot of maximum CD intensity (near 495 nm) against sequential addition of various phosphates. Thus, the CD silent feature of (***rac*)-PDPA-Pi** shows an increase in the signal upon AMP addition (left-handed helix), followed by its reversal in the presence of ATP (right-handed helix), before further decreasing to zero CD signal in the presence of PPi (racemic) (Fig. 3d). Thus, we have shown a sequential change of helical states from racemic (***rac*)-PDPA-Pi** to left-handed (***M*)-PDPA-AMP**, followed by right-handed (***P*)-PDPA-ATP** before converting them back to racemic **PDPA** stacks (***rac*)-PDPA-PPi** (Fig. 3d), completing one helix cycle. These transitions were also confirmed by changes in the absorption spectra, which show the characteristic features of respective states (Fig. S9†).

In conclusion, we have shown a molecular recognition driven helical assembly of **PDPA**, whose handedness can be easily tuned based on the type of bound chiral auxiliary like AMP, ADP or ATP. Binding with AMP produced the *M*-helix, whereas ATP binding resulted in the formation of the opposite handed *P*-helix. Interestingly, an AMP bound *M*-form could be switched to its mirror imaged *P*-form by adding ATP, which competitively replaces AMP due to multivalent interactions. Thus we demonstrate a rational and simple competitive binding strategy for the dynamic helix reversal of **PDPA** assemblies. Such a design strategy was employed to gain step-wise control over the helix mutation cycle from racemic assemblies to left-helix followed by right-helix before converting them into racemic stacks again. Such a rational design for unprecedented control over the helix mutation cycle holds great promise as material for switchable enantioselective and other chiro-technological applications.

We thank Prof. C. N. R. Rao, FRS for his support throughout this work, JNCASR and DST, Govt. of India for financial support and Usha for the TEM. M. K. thanks CSIR for the fellowship. S. J. G. gratefully acknowledges the Sheikh Saqr Career Award Fellowship.

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