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To assemble or fold?†

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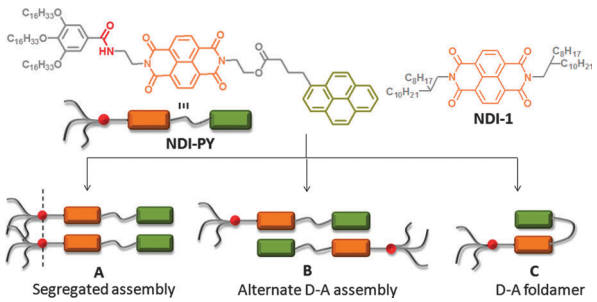
This communication reports an elegant structure formation by an amide functionalized donor (D)–acceptor (A) dyad by stepwise folding and assembly. It adopts a folded conformation by intra-chain CT-interaction that subsequently dimerizes by inter-molecular H-bonding to produce a folded dimer (FD) with a DAAD stacking sequence. Incompatibility of the aromatic stacked face with MCH triggers macroscopic assembly by solvophobically driven edge-to-edge stacking of the FD with concomitant growth in the orthogonal direction by D–D π-stacking leading to the formation of a reverse-vesicle.

Charge-transfer (CT)-interaction mediated alternate stacking of donor (D) and acceptor (A) π-systems,[1] has successfully promoted many ingenious supramolecular architectures[2] with relevance to optoelectronic applications. On the other hand, their segregated-assembly[3] has also been studied with considerable interest owing to its potential application in organic solar cells. However, hierarchical growth is limited in either case by the inherently weak nature of π-stacking or CT-interaction. Nature has cited innumerable examples where H-bonding governs the self-assembly and thereby the function of biotic systems. Inspired by nature, several synthetic systems have been reported on H-bonding-promoted supramolecular assembly of isolated D and A chromophores by our group[4] and others.[5] These examples show that the mode of co-assembly (alternate or segregated stack) is governed by relatively strong H-bonding rather than D–A CT-interaction.[2] This encouraged us to examine whether H-bonding interaction can similarly dictate the mode of self-assembly in covalently linked D–A systems which is more challenging due to its possible conflict with intra-chain CT-interaction which is much stronger compared to inter-molecular D–A complexation.[4,5]



Scheme 1 Top: structure of **NDI-PY** and the control molecule; bottom: possible modes of folding and assembly of the **NDI-PY**.

To test this, in this communication we have studied the self-assembly of a D–A dyad (**NDI-PY**) (Scheme 1) that contains an electron deficient naphthalenediimide (NDI) chromophore connected to a pyrene (PY) moiety which is a well known D–A pair for CT-complex formation.[2] The NDI-chromophore is connected to a trialkoxybenzamide wedge that has a dual role of solubilising the building block in a non-polar solvent as well as promoting self-assembly through H-bonding among the amide groups. **NDI-PY** is so designed that in principle it can adopt different modes of self-assembly (Scheme 1) by interplay of H-bonding and intra- or inter-molecular CT-interaction. **NDI-PY** in MCH (C = 2.0 mM) produces an intense red solution (inset, Fig. 1a) suggesting the formation of a CT-complex,[2] which is also confirmed from the appearance of a broad CT-band at around 525 nm (Fig. 1a). This observation rules out the possibility of a segregated assembly (mode A, Scheme 1). Interestingly, an equimolar mixture of **PY** and **NDI-1** (Scheme 1) shows neither red coloration nor a CT-band (Fig. 1a) substantiating the formation of an intramolecular CT-complex (mode C, Scheme 1).

Furthermore the CT-band intensity (λ_{max} = 525 nm) shows a linear relationship with concentration (Fig. S1, ESI,† and Fig. 1b) confirming intra-chain folding (mode C, Scheme 1).[6] Variable temperature UV/vis studies (Fig. 1c) show a gradual decrease in the CT-band intensity with increasing temperature up to 65 °C followed by a sharp downfall and saturation at 85 °C

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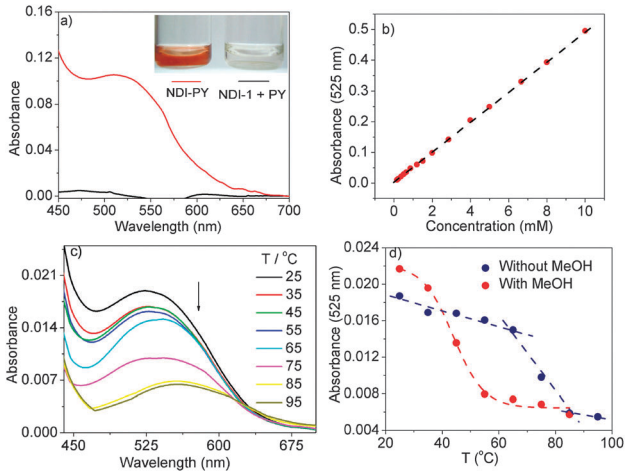


Fig. 1 (a) UV/Vis spectrum of the red solution (inset left) of **NDI-PY** and colorless solution (inset right) of **NDI-1** + **PY** (1:1) in MCH; C = 2.0 mM. (b) Variation of absorbance (λ_{max} = 525 nm) of **NDI-PY** as a function of concentration (10.0–0.16 mM). (c) Effect of temperature on the CT-band intensity of **NDI-PY** (C = 0.4 mM). (d) Variation of the CT-band intensity of **NDI-PY** (λ_{max} = 525 nm) with temperature in the absence and presence of MeOH.

indicating (i) appreciable stability and (ii) possibly a two-step melting of the D–A foldamer. However in the presence of a H-bond breaking protic solvent MeOH (Fig. S2, ESI,† and Fig. 1d) shows a sharp fall in the CT-band intensity at a relatively much lower temperature suggesting significantly less stability of the CT-complex or the folded state when the H-bonding effect is decoupled. The FT-IR spectrum of **NDI-PY** in MCH (Fig. S3, ESI†) looked almost identical to that in the solid state and showed sharp peaks at 1666 and 1580 cm^{-1} for amide-I and amide-II, respectively, and a broad peak at 3410 cm^{-1} for –NH stretching confirming H-bonding among the amide groups[7] in the folded state. Combining all these spectroscopic pieces of evidence, it is now apparent that in solution, the flexible dyad (**NDI-PY**) adopts a folded structure utilizing both intramolecular CT-interaction as well as intermolecular H-bonding.

To examine whether the **NDI-PY** foldamer remains as a discrete structure or further propagates to form a higher ordered assembly in MCH, we looked into the morphology. Transmission electron microscopy (TEM) images revealed nearly spherical hollow particles (diameter ~100 to 120 nm) with a thin wall (thickness ~1.6 nm as indicated by the white arrow in Fig. 2a)

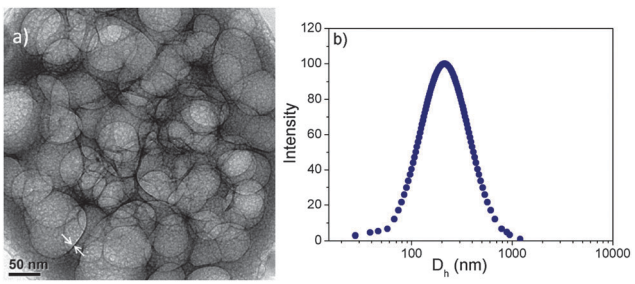
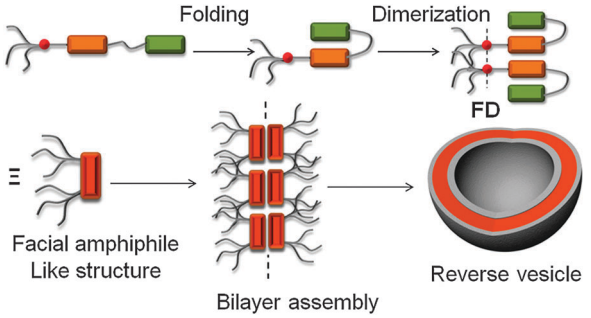


Fig. 2 (a) TEM image of **NDI-PY** showing vesicular assembly. (b) DLS data in MCH. C = 0.4 mM.



Scheme 2 Proposed mode of folding followed by assembly by **NDI-PY**. The other possibility (Fig. S6, ESI†) of stacking of the foldamer with more usual ...DADADA... sequence is eliminated as in that case H-bonding among the amides was found to be not allowed by geometrical constraints (Fig. S6, ESI†).

that is reminiscent of reverse vesicles[8] (Fig. 2a and Fig. S4, ESI†). The average hydrodynamic diameter (D_h) of ~200 nm obtained from dynamic light scattering (DLS) (Fig. 2b) showed a larger particle size compared to that obtained from TEM possibly due to the shrinkage of the membrane in the dry state.[9] Static light scattering (SLS) measurements (Fig. S5, ESI†) revealed the radius of gyration (R_g) to be 106 nm. The $R_g/R_h(D_h/2)$ value (1.06) very close to unity further confirming a hollow spherical morphology.[9]

Based on these experimental results it is proposed (Scheme 2) that initially **NDI-PY** adopts a folded structure by intramolecular CT-interaction that dimerizes by H-bonding to produce a folded dimer (FD). Now a structural similarity can be drawn between the FD and a typical facial amphiphile.[10] The stacked rigid chromophores constitute a MCH incompatible face (similar to the hydrophobic face of a facial amphiphile in water) while the presence of the alkyl chains make the other face of the FD suitable for interaction with MCH. Thus the FD forms a bilayer structure by stacking of the edges that propagates orthogonally through **PY–PY** interaction to form an extended assembly which eventually bends to produce reverse vesicle (Fig. 2a) to avoid the unfavourable exposure of the edges to the medium.

The MALDI experiment (Fig. 3a) showed a prominent peak at m/z = 2919.54 corresponding to the dimer [dimer of **NDI-PY** + Na]$^+$ of the **NDI-PY** and thus confirmed the formation of the FD. The zoomed image (inset, Fig. 3a) shows a typical isotope distribution with a 1 mass unit difference between the peaks confirming a singly charged species. This model (Scheme 2) was also supported by various other experimental pieces of evidence. Firstly it accounts for the reduced stability of the CT-complex in the presence of MeOH (Fig. 1d). Because H-bonding among the amides restricts the conformational freedom of the acceptor arm and thus reduces the number of possible conformations of the unfolded D–A dyad. Thus the folding process happens with a relatively less entropy loss. Fluorescence studies (Fig. 3b) show a strong emission band (λ_{max} ~ 450 nm), which can be attributed to pyrene excimer emission,[11] as in that region neither the monomeric NDI nor pyrene emits. This supports the model (Scheme 2) for a higher order assembly through PY–PY stacking. A relatively less intense peak at ~650 nm appears possibly due to emission from the CT-complex.[12]

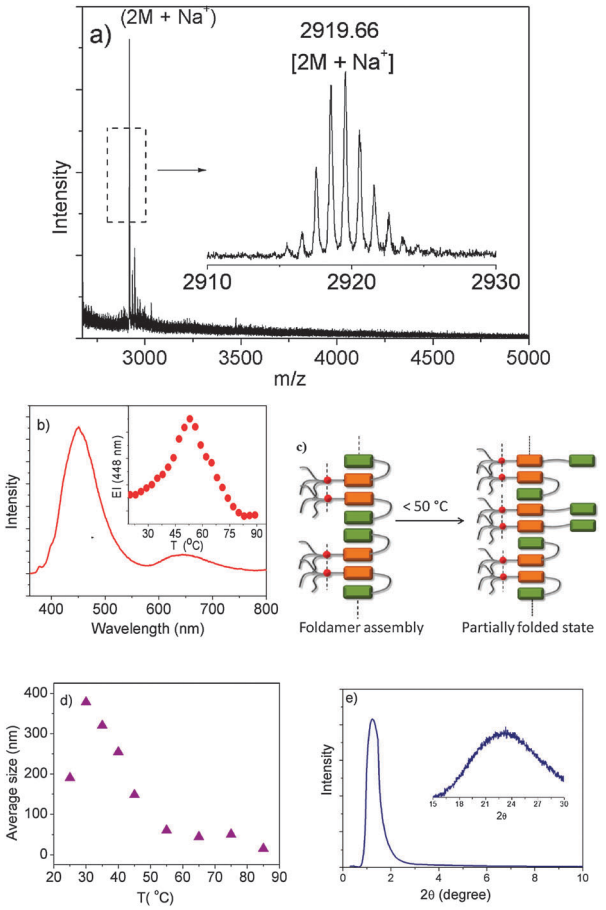


Fig. 3 (a) MALDI-TOF spectrum (selected region) of a film of **NDI-PY** made from a solution in MCH. (b) Emission spectrum of **NDI-PY** in MCH. Inset: plot of emission intensity at 448 nm (Fig. S7, ESI†) *vs.* temperature. λ_{ex} = 337 nm, concentration = 0.4 mM, solvent = MCH. (c) Transition from folded state to partially unfolded state at elevated temperature. (d) Variation in the particle size with temperature as obtained from the DLS experiment (Fig. S8, ESI†). *C* = 0.4 mM. (e) Powder XRD data of dried **NDI-PY** powder.

Intriguingly, variable-temperature fluorescence studies (inset, Fig. 3b and Fig. S7, ESI†) show a gradual increase in the emission intensity up to ~55 °C followed by a sharp decrease and saturation at ~85 °C. The initial increase in the excimer emission up to 50 °C possibly indicates partial unfolding (not complete melting) which still can allow **PY** excimer formation outside the D–A stack (Fig. 3c) but reduces the possibility of static quenching by the NDI acceptor. This also accounts for the decrease in the CT-absorption intensity in the same temperature window (Fig. 1d) at a slow rate possibly due to the gradual decrease of the relative population of the D units in the mixed stack. This also corroborates with the observed (Fig. S7, ESI†) decrease in the CT-emission band (650 nm) intensity with increasing temperature. However, above ~60 °C, thermal dissociation of the H-bonding leads to the melting of the whole assembled structure causing a sharp decrease in the intensity of the excimer emission (inset, Fig. 3b) as well as CT-absorption (Fig. 1d). The thermoresponsive disassembly was also probed using a variable-temperature DLS experiment (Fig. 3d and Fig. S8, ESI†). A very significant drop in the average particle size from 190 nm to 15 nm with increasing temperature from 25 °C to 85 °C illustrates rupture of the reverse vesicular assembly. Notably, an initial increase in the particle size around 30 °C may be due to the expansion of the membrane (Scheme 2) by partial unfolding (Fig. 3c). The powder X-ray diffraction (XRD) pattern (Fig. 3e) of a dried film generated from the solution of **NDI-PY** in MCH reveals a sharp peak in the low angle region (2θ = 1.23) corresponding to an interlayer spacing (*d*) of 71.2 Å that closely matches twice the estimated length (Fig. S9, ESI†) of the foldamer (37 × 2 = 74 Å) and thus further supports the proposed model for bilayer formation (Scheme 2). A relatively greater wall thickness (1.6 nm) of the vesicles (Fig. 2a) compared to the bilayer length indicates a multi-lamellar structure. A broad peak at around 2θ = 23.2 (inset, Fig. 3e) corresponding to a spacing of 3.83 Å confirms alternate stacking between pyrene and NDI.

A hierarchical assembly of an amide functionalized flexible D–A dyad has been demonstrated by maneuvering multiple weak interactions involving H-bonding, CT-interaction, π–π stacking and solvophobic forces. While a H-bonding driven segregated-assembly or intra-molecular CT-interaction promoted folding were the two limiting possibilities, the system smartly adopted an alternate path of self-organization to form a FD by satisfying both H-bonding and CT-interaction. Even after significant progress made in the field of foldamers in general[13] and D–A foldamers,[6] understanding their macroscopic assembly[14] is yet to be explored which may have far-reaching consequences for a more realistic bio-mimicking in terms of structure and function. Amidst the numerous possibilities, the formation of only a sequence specific (DAAD) structure that involves intra-chain folding followed by macroscopic-assembly is reminiscent of the protein structure by correlating the foldamer, FD and the bilayer membrane to be synthetic mimics of secondary, tertiary and quaternary structures of proteins, respectively.[15]

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