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First Zipper-Featured Molecular Duplexes Driven by Cooperative Donor−Acceptor Interaction

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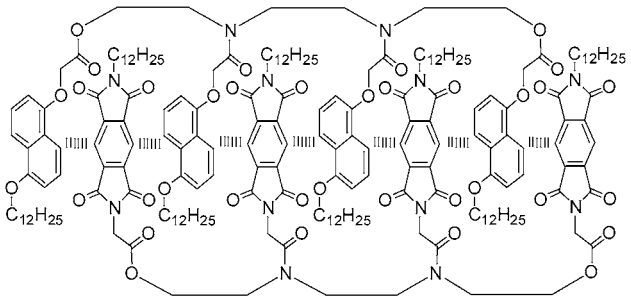
ABSTRACT



The first class of zipper-shaped artificial duplexes, which are driven by multiple donor−acceptor interactions between electron-rich 1,5-dioxynaphthalene or 1,4-dioxybenzene and electron-deficient pyromellitic dimide units, have been studied in organic media by ^{1}H NMR, UV−vis, and vapor pressure osmometry. ^{1}H NMR binding investigations reveal substantial cooperativity of the donor−acceptor interaction in the duplexes.

Self-assembly of linear molecules into double, triple, and higher order multistranded complexes is a common structural motif in biological systems. Biological zipper motif is of fundamental importance for self-replication, fiber behavior, and formation of functional multicomponent complexes.[1] In the past decade, synthetic zipper systems have received increasing attention for mimicking biological structures and self-assembly of functional supramolecular structures. Metal ion−ligand coordination,[2,3] electrostatic interaction,[4] and intermolecular hydrogen bonds[5,6] have been successfully utilized to construct a number of discrete bimolecular zippers. However, to our knowledge, no stable linear synthetic duplexes, induced by donor−acceptor interaction, have ever been reported. We describe here the first class of donor−acceptor interaction-driven duplexes with a zipper-like binding motif.

It has been well-established that electron-rich 1,5-dialkoxynaphthalene and electron-deficient pyromellitic dimide (PDI)

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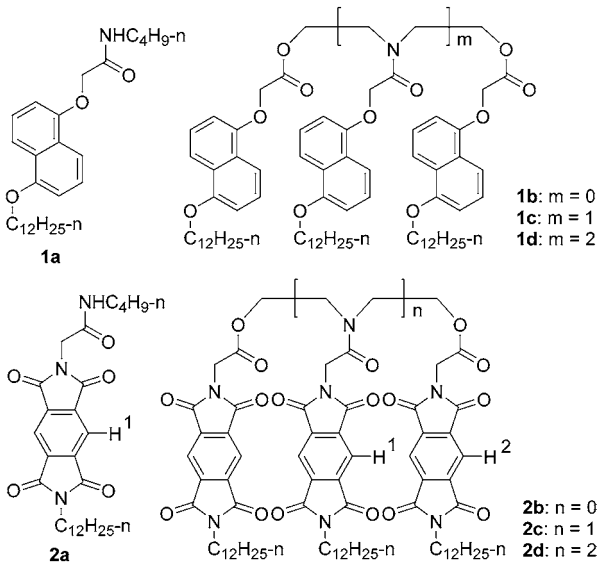
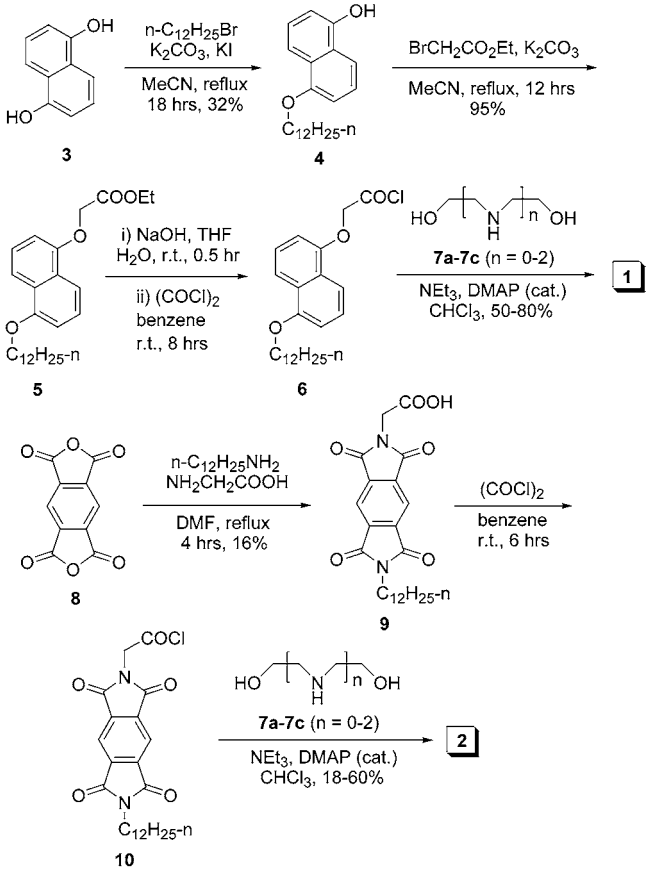
could form a donor−acceptor complex.[7] In recent years, this kind of noncovalent interaction has been utilized to self-assemble neutral [2]catenanes by using macrocyclic crown ether, incorporated with two 1,5-dioxynaphthalene units, as a template.[8,9] We envisioned that structurally matched linear molecules incorporated with multiple electronic donor or acceptor units might also be used to generate new stable dimers through multisite binding. Therefore, compounds **1** and **2** were designed.



The synthesis of **1** and **2** is outlined in Scheme 1. Compound **3** was first alkylated to afford **4**, which reacted with ethyl bromoacetate to produce ester **5**. Subsequent hydrolysis followed by treatment of the resulting acid with oxalyl chloride produced intermediate **6**. Compound **6** reacted with butylamine or diol **7** in the presence of triethylamine in chloroform to afford the desired naphthalene derivatives **1a** and **1b**−**d**, respectively. The synthesis of **2** proceeded with acyl chloride **10** as the key intermediate. Compound **8** first reacted with *n*-dodecylamine and glycine in refluxing DMF[10] to afford acid **9**, which was readily converted to **10** with oxalyl chloride. Compound **10** reacted with butylamine or diol **7** under the conditions described for the synthesis of **1**, leading to the formation of **2a** or **2b**−**d**, respectively. The introduction of the long dodecyl groups to compounds **1b**−**d** and **2b**−**d** provides them good solubility in common organic solvents such as chloroform and dichloromethane, making both series of monomers ideal for ^{1}H NMR binding analysis.

Scheme 1. The Synthesis of Monomers **1** and **2**



^{1}H NMR dilution experiments in $CDCl_3$ from ca. 40 mM to ca. 0.3 mM were first performed for compounds **1** and **2**, which revealed no pronounced chemical shifts ($\leq$0.03 ppm) for the aromatic protons. These observations indicate that these compounds do not self-aggregate substantially in chloroform.[11] Quantitative binding studies were then carried out in $CDCl_3$ solutions by titrating acceptors **2a**−**d** with **1a**−**d** and observing the changes in the chemical shifts of H-1 or H-2 of **2a**−**d**.[12] These protons exhibited sharp signals within the investigated concentration range. In contrast, the signals of the naphthalene protons in compounds **1a**−**d** overlapped each other, and were not suitable for titration analysis. Figure 1 shows as an example the titration curve for the H-1 signal of **2c** (0.5 mmol) during titration with **1c** (from 0.1 to 40 mmol). The association constants (K_{assoc}) for complexes **1·2** in $CDCl_3$ were calculated by the fitting a function containing K_{assoc} as a variable parameter to the

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(12) The H-1 and H-2 signals of **2c** could be easily assigned by comparing their ^{1}H NMR integral intensities, while the two sharp Ar−H signals of **2d** could not be differentiated by ^{1}H NMR and one of them was used for titration analysis.

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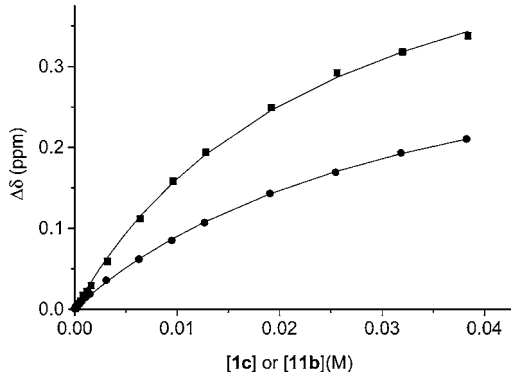


Figure 1. ^{1}H NMR titration curves of **2c** with **1c** (●) and **11b** (■) (vide infra) in $CDCl_3$ at room temperature.

experimental data and are summarized in Table 1.[13,14] The 1:1 binding stoichiometry of the complexes was proved by the Job's plot of the probe signals vs the mole fraction of **1** in the mixture solution, in which the maximum chemical shift change was observed at 0.5 mol fraction.[15] The K_{assoc} values of complex **1b·2c** in solvents of higher polarity were also obtained and are provided in Table 1.

Several important features can be found for the new class of heterodimers from Table 1: (1) The association constants increase substantially with the increase of the number of the aromatic units in both **1** and **2**. (2) For complexes with a totally identical number of aromatic units, the complexes consisting of longer **1** and shorter **2** are usually more stable than those consisting of shorter **1** and longer **2**. For example, the K_{assoc} of complex **1c·2b** is considerably larger than that of complex **1b·2c**. (3) The stability of the complexes is reduced with the addition of solvents of high polarity, such as methanol-*d*, acetone-d_6, and DMSO-d_6. This observation suggests that the formation of the new complexes is mainly driven by the intermolecular donor−acceptor interaction but not by the possible solvophobic interaction, although Iverson et al. had demonstrated that solvophobic interaction was the major driving force for a similar, simpler dimeric system.[11b]

Table 1. Association Constants (K_{assoc}) of Novel Donor−Acceptor Interaction-Driven Artificial Heterodimers **1·2** in $CDCl_3$ at Room Temperature[a]

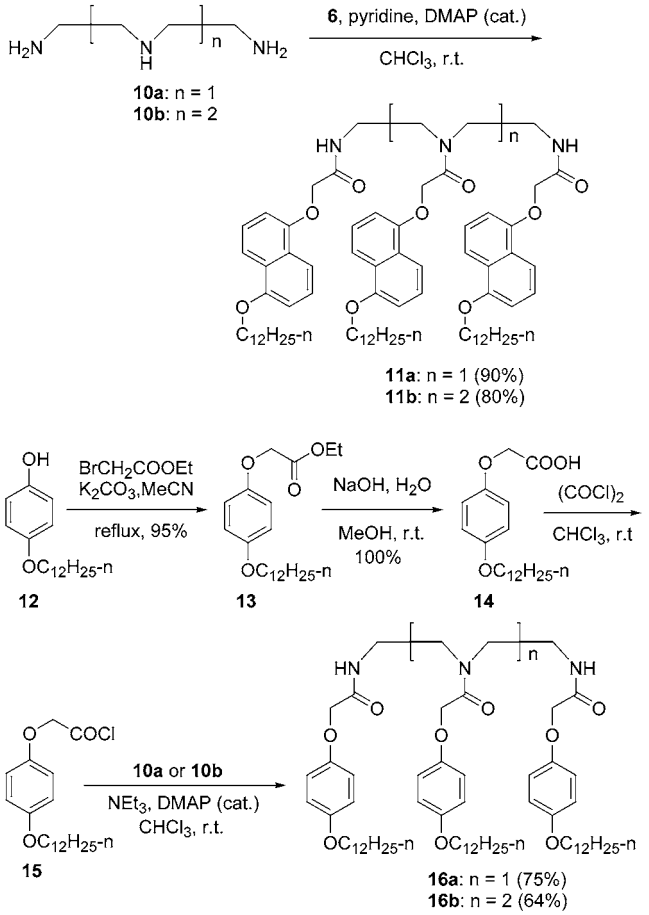
complex	K_{assoc} (M^{-1})	complex	K_{assoc} (M^{-1})
1a·2a	10	**1a·2b**	25
1b·2a	40	**1b·2b**	130
1c·2b	670	**1b·2c**	290
1c·2b	450[b]	**1c·2b**	500[d]
1c·2b	360[c]	**1c·2b**	290[g]
1c·2b	380[f]	**1c·2b**	410[e]
1c·2c	1200	**1d·2c**	4200
1c·2d	3100	**1d·2d**	8800

[a] With an error ≤20%. [b] With 10% CD_3OD (v/v). [c] With 20% CD_3OD (v/v). [d] With 10% CD_3COCD_3 (v/v). [e] With 20% CD_3OD (v/v). [f] With 10% CD_3SOCD_3 (v/v).). [g] With 20% CD_3SOCD_3 (v/v).

It was envisioned that replacing the PDI unit in **2** with the naphthalene-1,8:4,5-tetracarboxydiimide (NDI) unit,[16] a more electron-deficient acceptor than PDI, should lead to the construction of heterodimers of similar binding motif but with higher binding stability. Therefore, compounds with the skeletons of **2b**−**d** but incorporating two to four NDI units have also been prepared. However, these compounds were found to be insoluble in organic solvents such as chloroform and DMSO and a quantitative binding study with compounds **1** could not be performed.

Then, another four donor molecules **11a**, **11b**, **16a**, and **16b** were prepared, as outlined in Scheme 2, to investigate

Scheme 2. The Synthesis of Monomers **11** and **16**



the diversity of the new binding motif. In brief, treatment of amines **10a** and **10b** with **6** and base afforded **11a** and **11b**, respectively, while **16a** and **16b** were prepared starting from **12**[17] with use of the methods described for the synthesis of **1**. Both compounds **11** and **16** are soluble in chloroform.

(14) Table 1 lists the association constants of the 1:1 complexes, which consist of **1** and **2** incorporating the same number of aromatic units, or with one more or less aromatic units compared to each other. The complexing behavior of **1** toward **2** with more or less than one number of aromatic units was also investigated in $CDCl_3$. Although an important change of the chemical shifts of the H-1 of **2** was also exhibited, no good results of association constants could be derived by fitting to a nonlinear binding equation appropriate for a 1:1 or 1:2 binding model, revealing that more complicated binding models might exist.

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The binding study of **11** and **16** toward **2b**−**d** in $CDCl_3$ was then carried out by ^1H NMR titration of **2b**−**d** with **11** and **16**. The corresponding association constants K_{assoc} are derived by nonlinear regression for a 1:1 binding model and provided in Table 2. It can be found that **11a** and **11b** exhibit

Table 2. Association Constants (K_{assoc}) of Donor−Acceptor Interaction-Driven Heterodimers **11·2** and **16·2** in $CDCl_3$[a]

complex	K_{assoc} (M^{-1})	complex	K_{assoc} (M^{-1})
11a·2b	700	**11b·2c**	4300
11a·2c	1800	**11b·2d**	11000
11a·2d	3300	**16a·2b**	90
16b·2c	260	**16a·2c**	210
16b·2d	420	**16a·2d**	350

[a] Performed at 25 °C with an error ≤20%.

similar binding ability toward acceptors **2** compared to compounds **1b** and **1c**, respectively, suggesting that the possible intra- and intermolecular hydrogen bonds produced by the two peripheral amide groups have no substantial effect on the formation of the donor−acceptor interaction-driven heterodimers. In contrast, **16** exhibits significantly lower complexing ability than those of **1** or **11** with the same number of donor units. These results are not unexpected considering that 1,5-dioxynaphthalene-incorporating macrocyclic ether is a much more effective template than the 1,4-dioxybenzene-incorporated analogue for donor−acceptor interaction-induced self-assembly and molecular recognition.[18] NOESY experiments were also performed for the most strong complexes **1d·2d** and **11b·2d** in $CDCl_3$, which did not reveal intermolecular NOEs for the aromatic protons.

An average molecular mass of 3100 ± 400 u was determined with vapor pressure osmometry (VPO) in chloroform−toluene (60:40 v:v) at 30 °C for complex **1d·2d**. The result is consistent with that calculated for the 1:1 binding motif (3468 u) of the complex.

All the complexes display pale to dark orange color in chloroform, depending on their stability and concentration. Consistently, UV−vis investigations also reveal broad electron-transfer absorbance between 400 and 600 nm for the new complexes. The corresponding molar extinction coefficients (ϵ) obtained in chloroform at room temperature

Table 3. Molar Extinction Coefficients (ϵ) of the 1:1 Complexes in Chloroform at [Monomer] = 0.016 M at Room Temperature

complex	ϵ ($M^{-1}\,cm^{-1}$)	λ_{max} (nm)	complex	ϵ (nm)	λ_{max} ($M^{-1}\,cm^{-1}$)
1a·2a[a,19]	12	441	**1b·2b**	30	449
1c·2c	118	452	**1d·2d**	225	440
11a·2c	155	450	**11b·2d**	260	445
16a·2c	65	430	**16b·2d**	110	433
11b·2d[b]	180	451			

[a] Obtained at [monomer] = 0.05 M. [b] Obtained at [monmomer] = 3.0 × 10^{-3} M.

are shown in Table 3. It can be found that the ϵ values are increased substantially with increasing monomer length. This observation also supports that important cooperative donor−acceptor interaction exists within the complexes.

All the above binding studies suggest that the new kind of duplexe may adopt a multisite zipper-like binding motif, as shown in Figure 2 with **1d·2d** as an example, which facilitates multisite donor−acceptor interactions and consequently promotes the stability of dimers consisting of long monomers.[20]

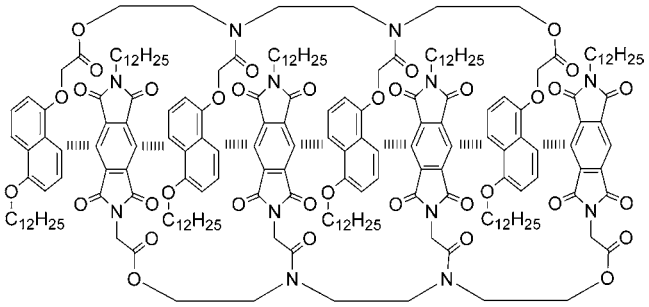

Figure 2. The proposed binding motif for duplex **1d·2d**.

In conclusion, donor−acceptor interaction has been, for the first time, successfully utilized for the formation of a new class of stable duplexes from readily available linear molecules. By modifying the molecular skeletons and introducing new, more electron deficient units into the acceptor molecules, more stable binding motifs are expected to be generated. Further applications of the new binding motif in self-assembly of a new generation of supramolecular species are also under investigation.

Acknowledgment. We thank the Ministry of Science and Technology (G2000078101) and the Natural Science Foundation (No. 20172069) of China for financial support.

Supporting Information Available: The synthesis and characterizations of all new compounds, ^1H NMR titration method, and UV−vis spectra of complexes **1b·2b**, **1c·2c**, and **1d·2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) No detectable absorbance was exhibited in the visible range at [**1a**] (=[**2a**]) = 0.016 M.

(20) This binding pattern requires a folding conformation for the monomers. Simple monomers such as **1b** and **2b** might also form complexes through linear, unfolded conformation, which, however, possess less donor−acceptor interaction sites than the proposed zipper-featured motif.