Chinese Journal of Chemistry, **2006**, *24*, 1200—1208

Full Paper

Self-assembly of Hydrazide-based Heterodimers Driven by Hydrogen Bonding and Donor-Acceptor Interaction†

FENG, Dai-Jun(冯代军) WANG, Peng(王鹏) LI, Xiao-Qiang(李小强)
LI, Zhan-Ting*(黎占亭)

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

A new series of hydrogen bonding-driven heterodimers have been self-assembled in chloroform from hydrazide-based monomers. Additional intermolecular donor-acceptor interaction between the electron-rich bis(*p*-phenylene)-34-crown-10 unit and the electron-deficient naphthalene diimide unit has been utilized to increase the stability of the dimmers, and pronounced cooperativity of the two discrete non-covalent forces to stabilize the dimer has been revealed by the quantitative ^{1}H (2D) NMR and UV-Vis experiments.

Keywords hydrazide, heterodimer, self-assembly, hydrogen bonding, donor-acceptor interaction

Introduction

Cooperative interaction of different non-covalent forces plays a critical role in the formation of the controlled structures and functions of biomacromolecules such as DNA, peptides and proteins.[1] One of the challenges in supramoleulcar chemistry is the self-assembly of new supramolecular systems with defined structures or functions.[2-6] In the past decade, a large number of supramolecular architectures have been constructed based on single non-covalent forces such as transition metal-ligand interaction,[7-10] hydrophobic interaction,[11-13] hydrogen bonding,[14-19] and electrostatic interaction.[20-22] More recently, it has been demonstrated that, based on elaborate molecular design, combination of two or more different non-covalent interactions could also function well or even more efficiently in constructing new generation of supramolecular architectures.[23-25]

We recently found that 2-ureido-4[1*H*]-pyrimidinone-based quadruply hydrogen bonded homodimers, reported first by Beijer *et al.*[26] could be forced by additional intermolecular donor-acceptor interaction between electron-rich bis(*p*-phenylene)-34-crown-10 and electron-deficient pyromellitic dimide (PDI) or naphthalene diimide (NDI),[27-29] to form hydrogen bonded heterodimers.[30-32] Rearrangement of hydrogen bonded homodimers to heterodimers regulated by donor-acceptor interaction represents a general, useful strategy for supramolecular self-assembly. Previously we also described the self-assembly of hydrazide-based quadruply hydrogen bonded heterodimers.[33] In this paper, we report that donor-acceptor interaction and hydrogen bonding can be utilized to cooperatively induce the generation of a new series of heterodimers from hydrazide-derived monomers.

Experimental

General procedure[33]

1,5-Bis(2-(decyloxy)benzoyl)carbonohydrazide (3) To a stirred solution of **8**[34] (0.60 g, 2.16 mmol) in dichloromethane (15 mL) was added oxalyl chloride (0.54 g, 4.00 mmol). After stirring for another 3 h at room temperature, the solvent was removed under reduced pressure. The resulting residue was dissolved in dichloromethane (15 mL) and the solution was added slowly to a solution of carbonohydrazide (0.09 g, 1.00 mmol) and triethylamine (1 mL) in dichloromethane (10 mL). The mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The resulting residue was triturated with chloroform (25 mL) and the organic phase was washed with water (2×10 mL), brine (10 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the crude product was subjected to column chromatography (EtOAc) to afford compound **3** as a waxy solid (0.40 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.89 (s, 2H), 8.12 (br, 2H), 8.11 (dd, J=1.8, 7.5 Hz, 2H), 7.40—7.36 (m, 2H), 7.02—6.98 (m, 2H), 6.90 (d, J=8.1 Hz, 2H), 4.06 (t, J=6.6 Hz, 4H), 1.92—1.85 (m, 4H), 1.39—1.18 (m, 14H), 0.80 (t, J=6.6 Hz, 3H); ESI-MS calcd for $C_{35}H_{54}N_4O_5Na$ ([M+Na]$^+$) 633.3989, found 633.3986.

3,5-Dioxane-1,1-dicarboxylic acid hydrazide (10): A solution of **9**[35] (1.50 g, 6.30 mmol) and hydrazine monohydrate (2 mL, 85%) in ethanol (10 mL) was heated under reflux for 2 h and then cooled to room temperature. The solvent was then removed under reduced pressure and the resulting residue was dissolved

* E-mail: ztli@mail.sioc.ac.cn; Tel.: 021-54925122; Fax: 021-64166128
Received January 11, 2006; revised April 20, 2006; accepted May 16, 2006.
Project supported by the National Natural Science Foundation of China (Nos. 20321202, 20332040, 20425208).
† Dedicated to Professor Xikui Jiang on the occasion of his 80th birthday.

in methanol (3 mL). Ethyl acetate (10 mL) was then added dropwise. The white precipitate formed was filtered, washed with ether, and dried over 24 h under reduced pressure at 90 ℃ to afford compound **10** as white powder (1.10 g, 84%). m.p. 205—207 ℃; ^{1}H NMR (300 HMz, $CDCl_3$) δ: 8.40 (br, 2H), 4.79 (s, 2H), 4.33 (s, 4H), 4.20 (br, 4H); EI-MS calcd for $C_6H_{12}N_4O_4$ ([M+Na]$^+$) 227.0773, found 227.0751. Anal. calcd for $C_6H_{12}N_4O_4$: C 35.29, H 5.92, N 27.44; found C 35.60, H 5.74, N 27.31.

***N*,*N*'-bis(4-(octyloxy)benzoyl)-1,3-dioxane-5,5-dicarbohydrazide (4)**: To a stirred solution of compounds **10** (0.10 g, 1.00 mmol), **11**[36] (0.30 g, 1.25 mmol) and triethylamine (0.30 mL) in DMF (3 mL), cooled in ice-bath, was added tri(dimethylamino)benzotriazol-1-yloxyl phosphonium hexafluorophosphate (BOP) (0.45 g, 1.00 mmol). The solution was stirred at 0 ℃ for 1 h and then for 12 h at room temperature. Upon removal of the solvent under reduced pressure, dichloromethane (25 mL) was added and the organic phase was washed with hydrochloric acid (2 mol•L^{-1}, 10 mL), saturated sodium bicarbonate solution (10 mL), water (10 mL×2), brine (10 mL), and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the resulting residue was purified by column chromatography (petroleum ether/AcOEt, 2/1, *V*/*V*) to afford compound **4** as a white solid (0.16 g, 50%). m.p. 65—67 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.05 (s, 2H), 9.13 (s, 2H), 7.67 (d, J=9.0 Hz, 4H), 6.74 (d, J=9.0 Hz, 4H), 4.79 (s, 2H), 4.33 (s, 4H), 8.86 (t, J=6.0 Hz, 4H), 1,71—1.67 (m, 4H), 1.20—1.80 (m, 36H), 0.83 (t, J=6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 167.0, 162.6, 129.3, 113.0, 114.4, 114.4, 94.2, 69.9, 68.2, 51.2, 51.1, 31.8, 29.3, 29.2, 26.0, 22.7, 14.1; HRMS (MALDI-Tof) calcd for $C_{36}H_{52}N_4O_8Na$ ([M+Na]$^+$) 691.3672, found 691.3677.

2-Ethoxybenzohydrazide (13): A solution of **12**[37] (1.80 g, 10.0 mmol) and hydrazine monohydrate (4 mL, 85%) in ethanol (25 mL) was heated under reflux for 2 h. Upon cooling to room temperature, the precipitate formed was filtered and washed with cool water to give **13** as a white solid (1.80 g, 100%). The product was recrystallized from ethyl acetate for analysis. m.p. 80—82 ℃ (73—74 ℃ lit.[38]). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 9.85 (s, 1H), 8.16 (br, 1H), 8.14 (d, d, J=1.5, 7.5 Hz, 1H), 7.45—7.41 (m, 1H), 7.01 (t, J=6.6 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 4.22 (q, J=6.6 Hz, 2H), 3.79 (s, 2H), 1.51 (t, J=6.9 Hz); MS (EI) *m/z*: 180 [M]$^+$.

***N*'-(2-Ethoxybenzoyl)hydrazinecarboxylic acid phenyl ester (14)**: To a stirred solution of **13** (2.50 g, 14.0 mmol) and pyridine (1 mL) in dichloromethane (15 mL) was added dropwise a solution of phenyl chloroformate (1 mL) in dichloromethane in 30 min at 0 ℃. Stirring was continued for 3 h at room temperature. The solution was then washed with diluted hydrochloric acid (2 mol/L, 10 mL), water (10 mL×2), brine (10 mL), and dried over sodium sulfate. After removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography (CH_2Cl_2 : AcOEt=3 : 1, *V* : *V*) to give compound **14** as a white solid (3.57 g, 85%). m.p. 65—67 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.83 (s, 1H), 8.16 (br, 1H), 8.14 (dd, J=1.5, 7.5 Hz, 1H), 7.45—7.32 (m, 5H), 7.01 (t, J=6.6 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 4.22 (q, J=6.6 Hz, 2H), 1.51 (t, J=6.9 Hz). MS (EI) *m/z*: 300 [M]$^+$. Anal. calcd for $C_{16}H_{16}N_2O_4$: C 63.99, H 5.37, N 9.33; found C 64.10, H 5.40, N 9.20.

1-(2-Ethoxybenzoyl)carbonohydrazide (15): A solution of compound **14** (0.87 g, 2.70 mmol) and hydrazine monohydrate (1.1 mL, 85%, 2.70 mmol) in methanol (10 mL) was heated under reflux for 3 h and then cooled to room temperature. Upon removal of the solvent under reduced pressure, the resulting residue was recrystallized from ethyl acetate to give compound **15** as a white solid (0.48 g, 75%). m.p. 85—87 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.86 (s, 1H), 8.17 (br, 1H), 8.17 (dd, J=1.5, 7.5 Hz, 1H), 7.41—7.45 (m, 1H), 7.04 (t, J=6.6 Hz, 1H), 6.93 (d, J=8.4 Hz, 1H), 6.45 (s, 1H), 4.21 (q, J=6.6 Hz, 2H), 3.77 (s, 2H), 1.51 (t, J=6.9 Hz). HRMS (ESI) calcd for $C_{10}H_{14}N_4O_3Na$ ([M+Na]$^+$) 261.0958, found 261.0958. Anal. calcd for $C_{10}H_{14}N_4O_3$: C 50.41, H 5.92, N 23.52; found C 50.64, H 5.74, N 23.31.

2-(Decyloxy)-5-iodobenzoic acid (16): A suspension of **8** (2.80 g, 10.0 mmol), iodine (2.50 g, 10.0 mmol) and silver sulfate (3.11 g, 10.0 mmol) in methanol (25 mL) was stirred for 2 h. The yellow solid was filtered off and the filtrate concentrated *in vacuo*. The resulting residue was triturated with dichloromethane (50 mL) and the organic phase washed with aqueous sodium sulfite solution (5%, 20 mL), water (20 mL×2), brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was recrystallized from petroleum ether to give compound **16** as a white solid (3.4 g, 90%). m.p. 75—77 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.48 (br, 1H), 8.49 (d, J=2.4 Hz, 1H), 7.84 (dd, J=8.4, 2.4 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 4.23 (t, J=6.0 Hz, 2H), 1.96—1.87 (m, 2H), 1.53—1.43 (m, 2H), 1.36—1.28 (m, 12H), 0.89 (t, J=3.0 Hz, 3H). MS (EI) *m/z*: 404 [M]$^+$. Anal. calcd for $C_{17}H_{25}IO_3$: C 50.50, H 6.23; found C 50.26, H 6.14.

2-(Decyloxy)-5-(2-(trimethylsilyl)ethynyl)benzoic acid (17): To a stirred solution of compound **16** (4.00 g, 10.0 mmol), $Pd(PPh_3)_4$ (0.65 g, 0.50 mmol), and cupric iodide (96 mg, 0.50 mmol) in triethylamine (10 mL) was added a solution of trimethylsilylethyne (1.00 g) in triethylamine (5 mL). The mixture was stirred at room temperature for 3 h and then concentrated *in vacuo*. The resulting residue was triturated with dichloromethane (50 mL) and the organic phase washed with hydrochloric acid (1 mol•L^{-1}, 50 mL), water (50 mL×2), brine (50 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was subjected to column chromatography (petroleum ether/AcOEt 5/1 *V*/*V*) to give compound **17** as a white solid (2.80 g, 80%). m.p. 79—82 ℃; ^{1}H NMR (300 HMz, $CDCl_3$) δ: 7.93 (d, J=2.0 Hz, 1H), 7.59 (dd, J=

2.0, 9.0 Hz, 1H), 6.91 (d, J=9.0 Hz, 1H), 4.04 (t, J=6.0 Hz, 2H), 1.86—1.81 (m, 2H), 1.49—1.27 (m, 14H), 0.90 (t, J=6.0 Hz, 3H), 0.25 (s, 9H); MS (EI) *m/z*: 374 $[M]^+$. Anal. calcd for $C_{22}H_{34}O_3Si$: C 70.54, H 9.15; found C 70.61, H 9.02.

2-(Decyloxy)-5-ethynylbenzoic acid (18): Compound **17** (0.39 g, 1.00 mmol) was dissolved in methanol (10 mL) and powered potassium carbonate (0.28 g, 2.00 mmol) was added. The suspension was stirred at room temperature for 2 h and then concentrated under reduced pressure. The resulting residue was triturated with chloroform (20 mL). After workup, the crude product was purified by column chromatography (petroleum ether/AcOEt, 5/1, *V*/*V*) to give compound **18** as a white solid (0.27 g, 98%). m.p. 80—82 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, J=2.0 Hz, 1H), 7.63 (dd, J=2.0, 9.0 Hz, 1H), 6.93 (d, J=9.0 Hz, 1H), 4.03 (t, J=6.0 Hz, 2H), 2.79 (s, 1H), 1.85—1.80 (m, 2H), 1.49—1.26 (m, 14 H), 0.90 (t, J=6.0 Hz, 3H); MS (EI) *m/z*: 302 $[M^+]$. Anal. Calcd for $C_{22}H_{26}O_3$: C 75.46, H 8.67; found C 75.61, H 8.62.

Compound 20: To a stirred solution of compound **19**[30] (0.60 g, 0.86 mmol) and $Pd(PPh_3)_4$ (0.80 g, 0.04 mmol) in pyrrolidine (5 mL) was added a solution of compound **18** (0.25 g, 0.86 mmol) in pyrrolidine (1.5 mL). The mixture was stirred at 80 ℃ for 2 h and then concentrated *in vacuo*. The resulting residue was triturated with dichloromethane (50 mL) and the organic phase washed with hydrochloric acid (2 mol•L^{-1}, 5 mL), water (5 mL), brine (5 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was subjected to column chromatography (EtOAc/MeOH, 20/1, *V*/*V*) to give compound **20** as a white solid (0.40 g, 50%). m.p. 60—62 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=2.4 Hz, 1H), 7.59 (dd, J=2.4, 9.0 Hz, 1H), 6.95—6.91 (m, 2H), 6.75—6.66 (m, 6H), 4.15 (t, J=3.0 Hz, 2H), 4.04 (t, J=3.0 Hz, 2 H), 3.95—3.60 (m, 30H), 1.86—1.84 (m, 2H), 1.41—1.20 (m, 14H), 0.81 (t, J=6.6 Hz). HRMS (MALDI-TOF) calcd for $C_{47}H_{64}O_{13}Na$ ($[M+Na]^+$) 859.4229, found 859.4239.

Compound 5: It was prepared as a white solid (60%) from the reaction of **15** and **20** (2 equiv.) according to the method described above for **3**. m.p. 125—127 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.93 (s, 1H), 9.73 (s, 1H), 8.23 (d, J=2.1 Hz, 1H), 8.10 (d, J=6.3 Hz, 1H), 8.07 (br, 2 H), 7.53—7.50 (m, 1H), 7.40—7.38 (m, 1H), 7.01—6.98 (m, 1H), 6.91—6.85 (m, 2H), 6.71—6.66 (m, 8H), 4.19—3.61 (m, 36H), 1.90—1.85 (m, 2H), 1.51 (t, J=7.2 Hz, 3H), 1.40—1.31 (m, 16H), 0.80 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 164.1, 163.6, 157.1, 156.8, 156.1, 154.0, 153.1, 153.0, 152.8, 136.5, 135.5, 133.7, 132.3, 121.2, 119.5, 119.1, 118.5, 116.7, 115.5, 114.5, 113.7, 112.5, 112.3, 92.2, 85.7, 76.9, 76.6, 71.1, 70.9, 70.9, 69.8, 69.7, 68.3, 68.2, 65.1, 31.9, 29.6, 29.3, 28.9, 26.0, 22.7, 14.8, 14.2; HRMS (MALDI-TOF) calcd for $C_{57}H_{76}N_4O_{15}Na$ ($[M+Na]^+$) 1079.5209, found 1079.5199.

***N*'-(4-(Octyloxy)benzoyl)-1,3-dioxane-5,5-dicarbohydrazide (21)**: It was prepared as colorless oil in 60% yield from the reaction of **10** and **11** (1∶1, molar ratio) according to the method described above for compound **4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.28 (br, 1H), 8.94 (s, 1H), 8.85 (br, 1H), 7.78 (d, J=8.1 Hz, 2H), 6.91—6.88 (d, J=8.1 Hz, 2H), 6.91 (d, J=2.0 Hz, 2H), 4.92 (s, 2H), 4.38 (s, 4H), 3.98 (t, J=6.6 Hz, 3H), 1.82—1.77 (m, 2H), 1.45—1.25 (m, 10H), 0.90 (t, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 162.7, 129.2, 123.2, 114.5, 94.1, 77.0, 68.3, 36.9, 36.8, 31.8, 29.3, 29.1, 26.0, 22.6, 14.1. HRMS (MALDI-TOF) calcd for $C_{21}H_{32}N_4O_6Na$ ($[M+Na]^+$) 459.2212, found 459.2214.

(*E*)-4-(2-Cyanovinyl)benzoic acid (23): To a stirred aqueous solution of tetrafluoroboric acid (3 mL, 30%) was added compound **22** (2.50 g, 18.0 mmol). The solution was stirred for 20 min in an ice-bath and a solution of sodium nitrite (2.40 g, 40.0 mL) in water (2 mL) was added dropwise within 30 min. Stirring was continued for another 1 h and then a solution of acrylonitrile (1 mL) in methanol (10 mL) and palladium acetate (80 mg, 0.36 mmol) was added. The mixture was heated at 50 ℃ for 3 h and then cooled to room temperature. The precipitate was filtered and dissolved in minimal amount of methanol and the solution poured into water (10 mL) of 60 ℃. Upon cooling to room temperature, the precipitate was filtered again. This process was repeated for another two times to afford compound **23** a yellow solid (1.20 g, 40%). m.p. 260—262 ℃ [lit.[39], 256—257 ℃]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.73 (d, J=9.0 Hz, 2H), 6.37 (d, J=9.0 Hz, 2H), 6.30 (d, J=16 Hz, 1H), 5.07 (d, J=16 Hz, 1H). MS (EI) *m/z*: 173 $[M]^+$.

4-(3-Aminopropyl)benzoic acid hydrochloric acid salt (24): A suspension of **23** (0.50 g, 3.00 mmol) and Pd-C (50 mg, 5%) in hydrochloric acid (20%, 3 mL) and ethanol (15 mL) was stirred under hydrogen gas (0.04 Pa) at room temperature for 10 h. The solid was filtered off and the filtrate concentrated *in vacuo*. The resulting residue was washed thoroughly with ether and then dissolved in methanol (5 mL). Ether was added to produce yellow solid. The solid was filtered and dried in vacuo to afford compound **24** as a yellow solid (0.60 g, 95%). m.p. 280—282 ℃ (lit.[40], 285—290 ℃); ^{1}H NMR (DMSO-d_6) δ: 12.81 (br, 1H), 7.89 (d, J=7.5 Hz, 2H), 8.03 (br, 3H), 7.36 (d, J=7.5 Hz, 2H), 2.74—2.72 (m, 4H), 1.88 (br, 2H).

4-[(6-Octyl-1,3,5,7-tetraoxo-3,5,6,7-tetrahydro-1*H*-pyrrolo[3,4-*f*]isoindol-2-propyl)]benzoic acid (26): A suspension of **24** (0.45 g, 2.00 mmol), **25** (0.44 g, 2.00 mmol), octyl amine (0.26 g, 2.00 mmol) and triethylamine (2 mL) in pyridine (10 mL) was heated under reflux for 12 h. The solvent was then removed under reduced pressure. The resulting residue was added to *N*,*N*-dimethylformamide (35 mL) and acetate acid (5 mL). The suspension was stirred at 100 ℃ for 10 min and then cooled to room temperature. The solid formed was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was then

washed with water (5 mL), methanol (5 mL) and dichloromethane (5 mL) to give compound **26** as a white solid (0.19 g, 20%). m.p. 193—195 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.14 (s, 2H), 7.79 (d, J=7.5 Hz, 2H), 7.33 (d, J=7.5 Hz, 2H), 3.66—3.58 (m, 4H), 2.71—2.75 (m, 2H), 2.00—1.98 (m, 2H), 1.61—1.65 (m, 2H), 1.27—1.24 (m, 10H), 0.85—0.80 (m, 3H); ^{13}C NMR (DMSO-d_6) δ: 166.3, 166.2, 136.9, 136.7, 129.3, 128.3, 117.0, 37.9, 37.7, 32.3, 31.1, 28.7, 28.4, 27.7, 26.2, 22.0, 13.8. MS (EI) *m/z*: 491 $[M+H]^+$. Anal. calcd for $C_{28}H_{30}N_2O_6$: C 68.56, H 6.16, N 5.71; found C 67.74, H 6.23, N 5.44.

4-[(7-Octyl-1,3,6,8-tetraoxo-3,6,7,8-tetrahydro-1*H*-benzo[lmn][3,8]phenanthrolin-2-propyl)]benzoic Acid (28): It was prepared as a white solid (15%) from the reaction of **24**, **27** and octyl amine in hot pyridine according to the method described for **26**. m.p. 220—222 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.53 (br, 1H), 8.53—8.52 (d, J=2.7 Hz, 4H), 7.71—7.68 (d, J=8.1 Hz, 2H), 4.05—3.93 (m, 4H), 2.74—2.67 (m, 2H), 1.97—1.93 (m, 2H), 1.57—1.55 (m, 2H), 1.29—1.19 (m, 10H), 0.78 (t, J=6.0 Hz, 2H); ^{13}CNMR (DMSO-d_6) δ: 162.1, 161.2, 146.0, 129.8, 128.7, 127.7, 125.9, 125.8, 40.0, 39.0, 32.2, 30.6, 28.1, 27.9, 27.7, 26.9, 26.0, 21.4, 13.1; MS (EI) *m/z*: 540 $[M]^+$. Anal. calcd for $C_{32}H_{32}N_2O_6$: C 71.09, H 5.97, N 5.18; found C 69.66, H 5.69, N 5.32.

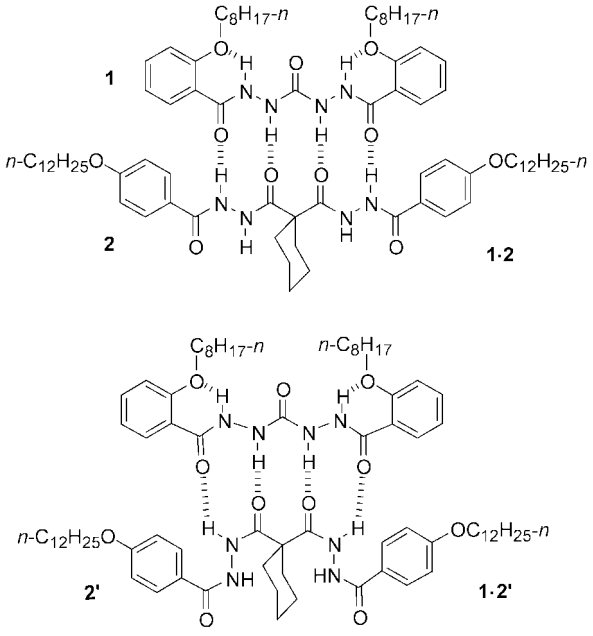
Compound 6: It was prepared as a white solid (40%) from the reaction of **21** and **26** according to the method described for **4**. m.p. 207—209 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.13 (s, 2H), 9.07 (s, 1H), 8.99 (s, 1H), 8.17 (s, 2H), 7.69 (d, J=9.0 Hz, 2H), 7.61 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 6.77 (d, J=9.0 Hz, 2H), 4.87 (s, 2H), 4.62 (s, 4H), 3.87 (t, J=7.0 Hz, 2H), 3.72—3.63 (m, 4H), 1.97 (t, J=7.0 Hz, 2H), 1.72—1.61 (m, 4H), 1.37—1.22 (m, 20H), 0.79 (t, J=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 166.7, 166.2, 164.6, 162.6, 145.6, 137.4, 137.1, 129.2, 129.0, 128.6, 128.1, 123.0, 118.1, 114.4, 94.1, 76.6, 69.5, 68.3, 51.1, 38.8, 38.2, 33.0, 31.8, 29.7, 29.3, 29.2, 28.4, 26.8, 26.0, 22.6, 22.5, 14.0. HRMS (MALDI-TOF) calcd for $C_{49}H_{60}N_6O_{11}Na$ ($[M+Na]^+$) 931.4207; found 931.4212.

Compound 7: It was prepared as a white solid in 25% yield from the reaction of **21** and **28** according to the method described above for **4**. m.p. 246—248 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.18 (s, 2H), 9.22 (s, 1H), 9.18 (s, 1H), 8.89—8.62 (m, 4H), 7.72 (d, J=9.0 Hz, 2H), 7.61 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 6.77 (d, J=9.0 Hz, 2H), 4.86 (s, 2H), 4.36 (s, 4H), 4.13—3.89 (m, 4H), 3.87 (t, J=6.0 Hz, 2H), 1.97 (t, J=7.0 Hz, 2H), 1.72—1.61 (m, 4H), 1.37—1.22 (m, 20H), 0.81 (t, J=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 166.2, 164.3, 162.9, 162.8, 162.7, 131.0, 130.9, 129.2, 128.7, 127.4, 114.5, 94.2, 70.1, 68.3, 51.0, 41.0, 40.5, 38.8, 33.3, 31.8, 29.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.6, 28.1, 27.1, 27.0, 21.7, 21.6, 14.1; HRMS (MALDI-TOF) calcd for $C_{53}H_{62}N_6O_{11}Na$ ($[M+Na]^+$) 981.4375; found 981.4369.

Results and discussion

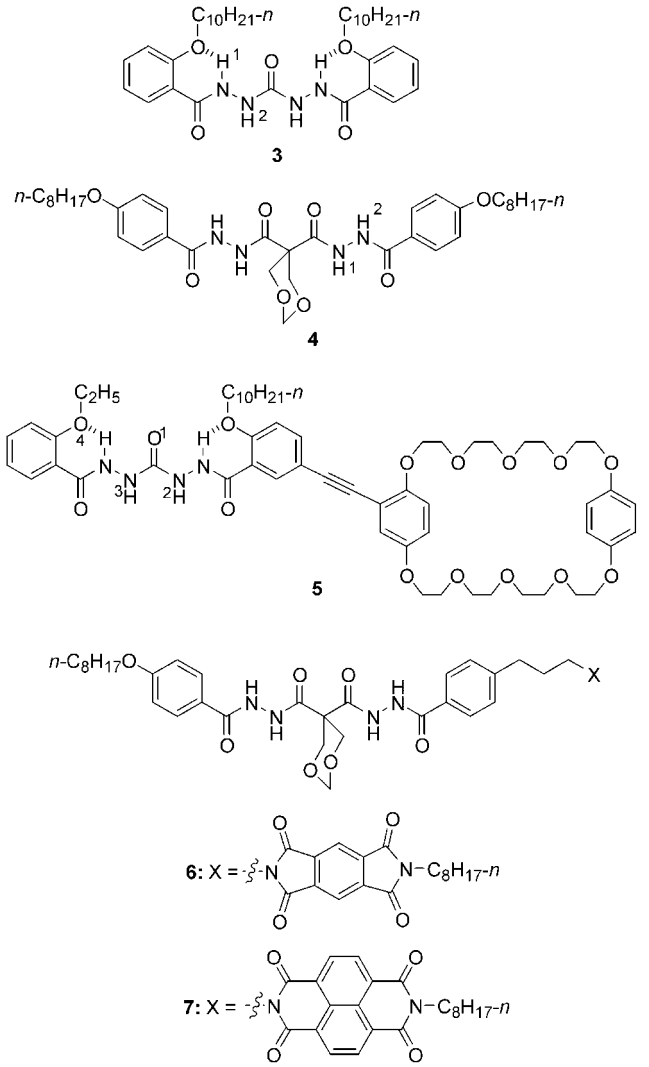
Previous study demonstrated that monomers **1** and **2** could bind each other in chloroform to form hetereodimeric isomers **1•2** and **1•2'** with an average association constant of 4.7×10^4 mol•L^{-1} in chloroform. In order to improve the assembling selectivity of this kind of heterodimers, the cyclohexane unit in **2** was replaced with a 1,3-dioxane unit in the new monomers **4**, **6** and **7** for the present investigation. It was envisioned that intramolecular six-membered hydrogen bonding would be formed in this monomers, which would decrease the stability of the conformational isomer similar to that of **2'** in dimer **1•2'** (Scheme 1). In addition, electron rich bis(*p*-phenylene)-34-crown-10 was introduced to **5**, while the electron deficient PDI or NDI unit was incorporatedin **6** and **7** (Scheme 2), respectively. It was expected that the additional intermolecular donor-acceptor interaction between these binding sites would be generated in the heterodimers formed from these structurally matched monomers, which would promote the stability of the corresponding dimers.

Scheme 1

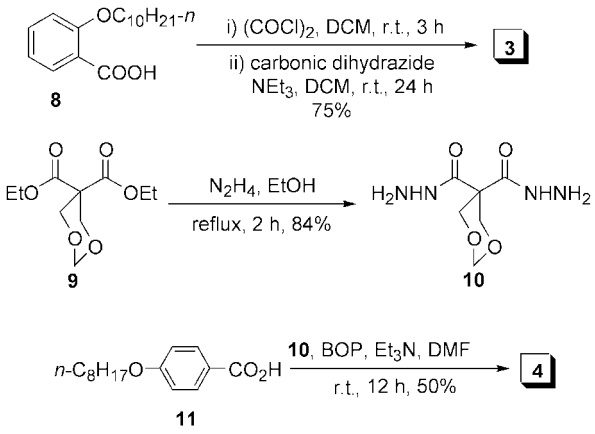


Monomer **3** was prepared from the corresponding acyl chloride and carbonic dihydrazide in dichloromethane (Scheme 3). For the preparation of **4** (Scheme 3), compound **9** was first transformed to **10** with excess hydrazine in refluxing ethanol. The latter (1 equiv.) was then treated with 2 equiv. of **11** in DMF with BOP as coupling reagent to produce **4** in 50% yield.

Scheme 2

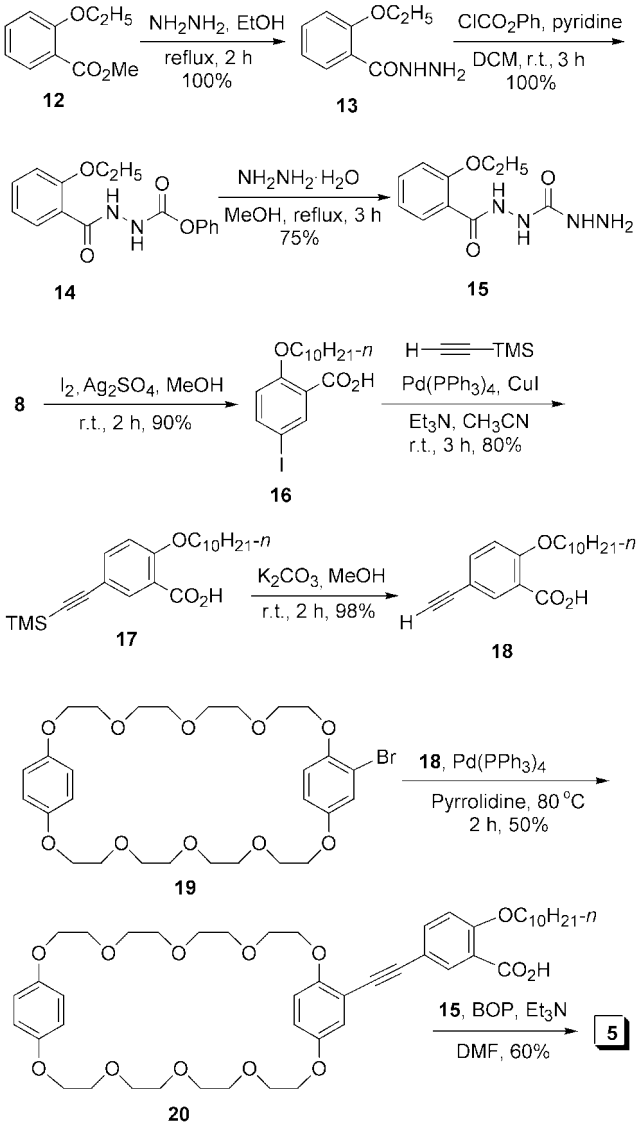


Scheme 3



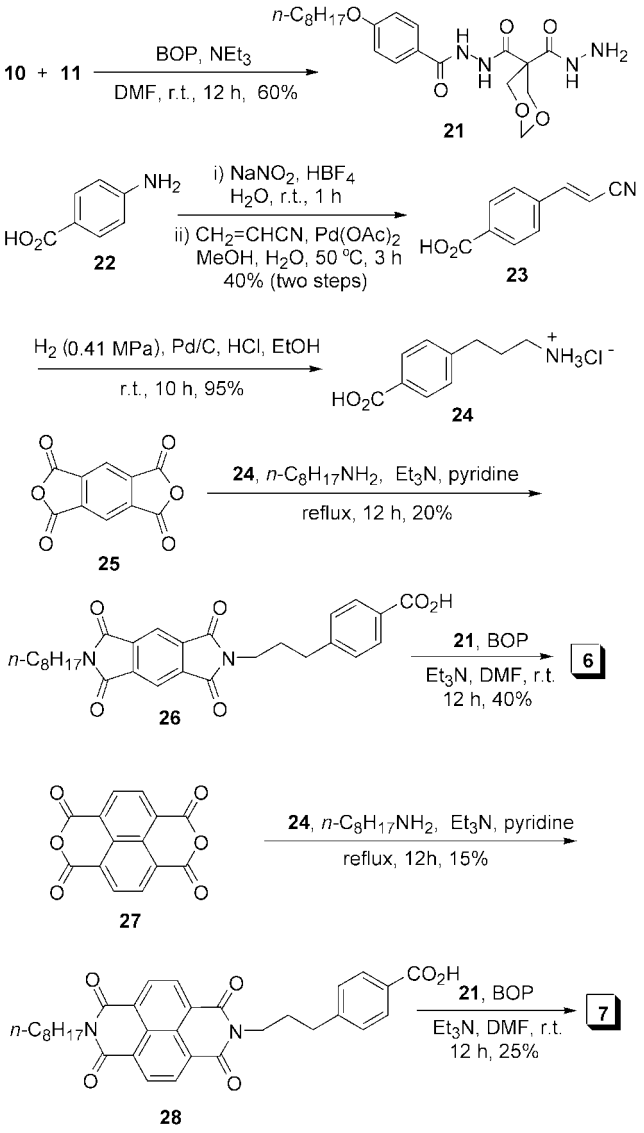
The synthetic route for compound **5** is presented in Scheme 4. Thus, **13** was first prepared from the reaction of **12** and hydrazine in quantitative yield and then transformed to **14** with phenyl chloroformate in dichloromethane in the presence of pyridine. Treatment of **14** with hydrazine afforded intermediate **15** in 75% yield. Then, compound **8** was treated with iodine and silver sulfate in methanol to afford **16** in 90% yield. The latter was coupled with trimethylsilylacetylene in acetonitrile in the presence of palladium(0) to give **17** in 80% yield. Treatment of **17** with potassium carbonate in methanol produced **18** quantitatively. Pd-catalyzed reaction of **18** with bromide **19** in hot pyrrolidine afforded intermediate **20** in 50% yield. Finally, 1 equiv. of **20** was treated with 1 equiv. of **15** in DMF in the presence of BOP to give **5** in 60% yield.

Scheme 4



For the preparation of **6** and **7** (Scheme 5), compound **21** was first prepared in 60% yield from the reaction of **10** and **11** in the presence of BOP. Then, intermediate **23** was prepared from acid **22** in 40% yield through diazotization, followed by a Pd-catalyzed coupling reaction. Palladium-catalyzed hydrogenation of **23** in hydrochloric acid afforded amine **24** as a salt in 95% yield. The latter was then treated with pyromellitic

Scheme 5



anhydride **25** and octyl amine in hot pyridine to produce **26** in 20% yield. Finally, coupling of **26** with **21** in DMF afforded monomer **6** in 40% yield. In the similar way, compound **28** was obtained in 15% yield from the reaction of **24**, **27** and octyl amine. The coupling reaction of **28** with **21** in DMF afforded monomer **7** in 25% yield.

The ^{1}H NMR experiments in chloroform-d revealed that, upon dilution, the NH-2 signal of both **3** and **4** was shifted downfield pronouncedly, suggesting self-binding for these protons and the formation of homodimer **3•3** and **4•4**. A fit of the chemical shift data to a 1∶1 isotherm afforded association constant K_{assoc} values of 60 and 65 mol^{-1}•L for **3•3** and **4•4**, respectively.[33,41] In contrast, the NH-1 signal of both compounds displayed no important shifting. This observation is similar to that of **1** and **2**[33] and consistent with the fact that these protons are involved in intramolecular hydrogen bonding. In principle, the NH-1 of **4** could form intramolecular six-membered hydrogen bonding with both the central C=O oxygen and the dioxane oxygen.[33] The fact that only one singlet was observed for these protons indicates that the exchange between the discrete conformational isomers, as shown in Figure 1, is fast on the ^{1}H NMR time scale.

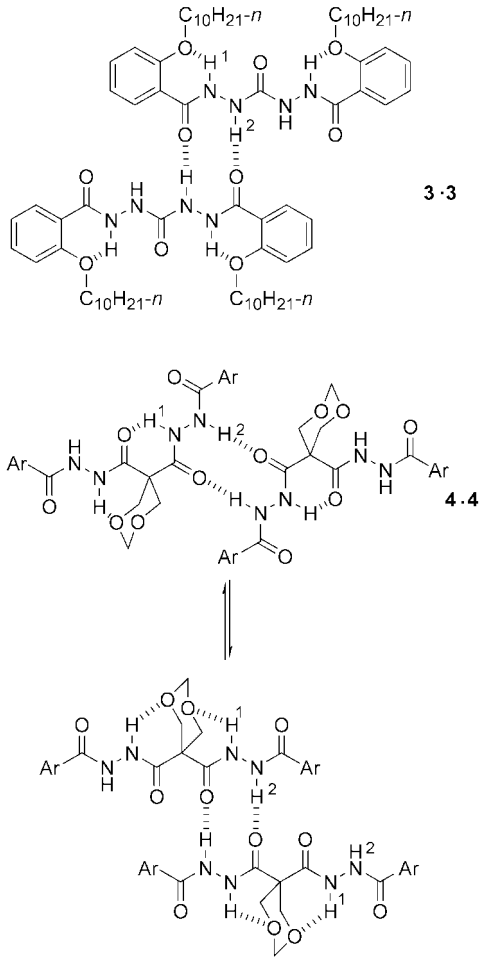


Figure 1 The structure of dimer **3•3** and the possible exchange process between conformational isomers of dimer **4•4**.

Mixing 1 equiv. of **3** (0.07 mol•L^{-1}) and 1 equiv. of **4** (0.07 mol•L^{-1}) in chloroform-d led to important downfield movement of the chemical shift of NH-2 of **3** ($\Delta\delta$ 0.25) and **4** ($\Delta\delta$ 0.56), as compared to that of the pure sample of the identical concentration. Small downfield shift ($\Delta\delta$ 0.09) was also exhibited for NH-1 of **4**. In contrast, no obvious shift ($\Delta\delta<0.01$) was observed for the NH-1 signal of **3**. ^{1}H NMR NOESY experiment in chloroform-d revealed important intermolecular NOE connection between the NH-2 signals of **3** and **4** but not any other intermolecular NOE connections. This observation supports that the NH-2 protons of **3** and **4** were strongly involved in intermolecular hydrogen bonding, leading to the formation of **3•4**. Dilution of the 1∶1 solution of **3** and **4** (from 0.07 mol•L^{-1} to 0.0005 mol•L^{-1}) in chloroform-d caused substantial upfield shifting of the NH-2 signal of **3** ($\Delta\delta$ −0.76) and **4** ($\Delta\delta$ −0.69), which can be attributed to weakening of the

intermolcular hydrogen bonding involved for these protons. The NH-1 signal of **4** in the 1∶1 solution also moved downfield notably ($\Delta\delta=0.20$) upon dilution. Such downfield shift might reflect that the NH-1 protons in **4** in the mixture was involved in both inter- and intramolecular hydrogen bonding and, upon dilution, the intermolecular hydrogen bonding shifted to intramolecular hydrogen bonding. Because the above upfield shifting of the NH-2 signal of **3** and **4** in the mixture solution at the reduced concentration could be partially caused by the dissociation of their homodimers, the association constant of heterodimer **3•4** could not be derived from the dilution experiments.[33] Therefore, ^{1}H NMR titration experiments were carried out in chloroform-d and the change of the chemical shift of the NH-2 signal of **3** with the concentration change of **4** was fitted to a 1∶1 binding isotherm to afford an average K_{assoc} value of *ca*. 360 L^{-1}•mol for heterodimer **3•4**.[33,41]

The binding stability of heterodimer **3•4** is remarkably smaller than that of heterodimer **1•2** ($K_{assoc}=4.7\times10^4$ L^{-1}•mol in chloroform-d).[33] This reduced binding affinity may be ascribed to the formation of the intramolecular hydrogen bonding between the central NH-1 protons and the dioxane oxygen atoms of **4**, which induces a nonplanar conformation for its carbonic dihydrazide moiety and consequently decreases its binding ability toward **3**.

The 1∶1 solution of **4** and **5** in chloroform-d was also investigated by the ^{1}H NMR spectroscopy, which revealed similar change as observed for the 1∶1 solution of **3** and **4**. Due to the existence of the cyclophane, the NH-2 and NH-3 protons of **5** exhibited two discrete singlets in the ^{1}H NMR spectrum of the solution of the pure and mixture samples. Both signals appeared in the downfield area compared to the corresponding signals in the ^{1}H NMR spectrum of pure **5** and moved upfield remarkably upon dilution. The NH protons of **4** exhibited two singlets, although in principle four discrete signals might be displayed upon complexation with **5**. Intermolecular NOE connections were also observed in the NOESY spectrum of the 1∶1 mixture (0.01 mol•L^{-1}), which are shown in the text. These results indicate that complex **4•5** was also formed in the solution (Figure 2). On the base of the ^{1}H NMR titration experiments in chloroform-d, the association constant of complex **4•5** was estimated to be *ca*. 270 L^{-1}•mol ($\Delta G=13.9$ kJ/mol). The value is notably smaller that that of complex **3•4**, possibly as a result of the steric hindrance of the cyclophane in **5**.

The binding behavior of **5** with **6** and **7** was then investigated in chloroform. The central two NH protons of both **6** and **7** in the pure solution of chloroform-d exhibited two singlets due to the existence of the electron deficient PDI or NDI subunit, while the peripheral two NH protons gave rise to one single signal. Mixing the identical amount of **5** with **6** or **7** in chloroform-d led to substantial downfield movement of the central NH signals of **5** and the peripheral NH signals of **6** and **7**, indicating the formation of heterodimers **5•6** and **5•7** (Figure 2). Additional evidence for the formation of the heterodimers also came from the ^{1}H NMR NOESYexperiments of the 1∶1 solution of **5** with **6** and **7** in chloroform-d, which revealed strong intermolecular NOEs (see the text). Interestingly, both H-2 and H-3 of **5** exhibited NOE connections with the H-1 and H-4 signals of **6** and **7**. The intermolecular NOEs displayed from the hydrazide protons with longer distance may be attributed to two different arrangement of the monomers relative to each other or reflect an increased binding stability of the dimers compared to dimer **4•5**, which did not displayed the NOE of longer distance. At present, we are unable to differentiate between the two possibilities.

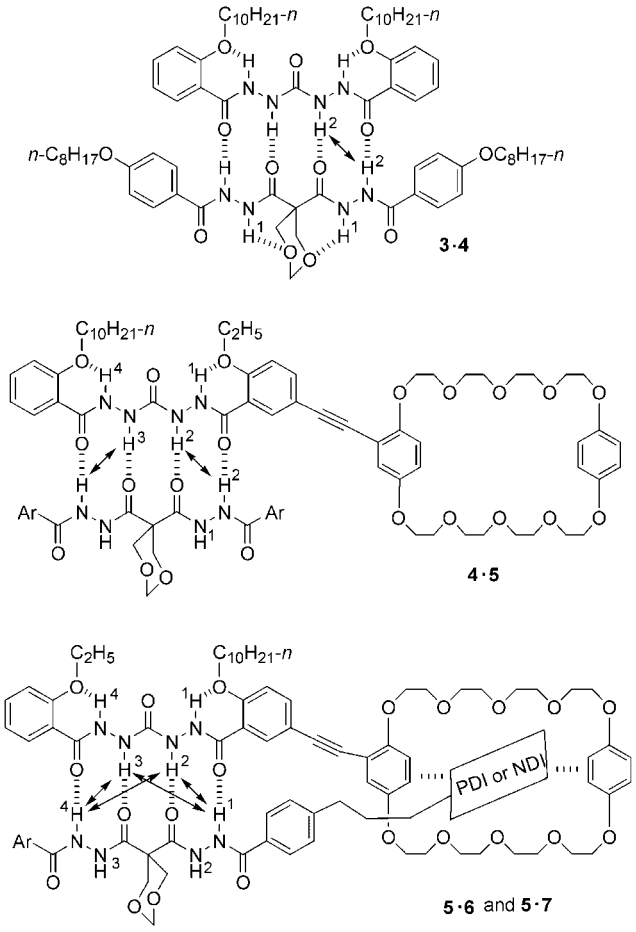


Figure 2 The intermolecular NOE connections observed for dimers **3•4**, **4•5**, **5•6** and **5•7** in chloroform-d (0.02 mol•L^{-1}).

Due to important signal overlapping, quantitative binding investigations could not be performed for complexes **5•6** and **5•7** by the ^{1}H NMR titration method. Nevertheless, strong complexation of **5** and **7** caused the solution of their 1∶1 solution in chloroform to give rise to a strong charge transfer absorption band in the UV-Vis spectrum. Therefore, UV-Vis dilution experiments were carried out for the 1∶1 solution in chloroform (Figure 3). Association constant of 2.1 (±0.3)$\times10^4$ L^{-1}•mol ($\Delta G=24.6$ kJ/mol) was obtained for here-

rodimer **5•7** by a linear regression of the change data of the absorption with the concentration according to a 1∶1 binding mode.[42]

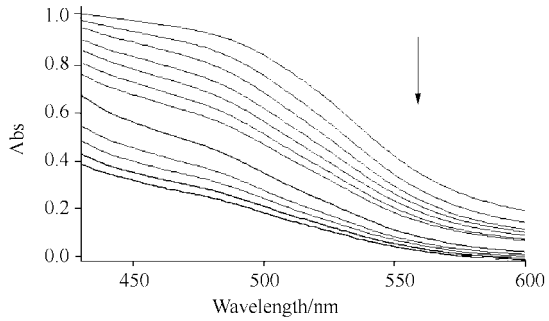
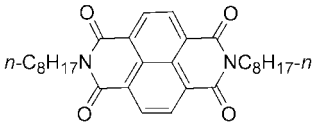


Figure 3 Plot of the charge-transfer absorption change of the 1∶1 solution of **5** and **7** vs. [**5**] (=[**7**]) in chloroform (from 0.013 to 0.038 mol•L^{-1}) at 25 ℃.

In order to establish if cooperativity exists for the two non-covalent forces to induce the formation of the dimer structure, compound **29** is also synthesized according to the reported method.[43] ^{1}H NMR dilution experiments performed in chloroform-d afforded an association constant of 35 L^{-1}•mol (ΔG=8.8 kJ/mol) for dimer **20•29**. Comparison of the stabilities of dimer **5•7** with that of dimers **4•5** and **20•29** indicates that the increase in the stability of **5•7** is not just a result of the additive effect of the two discrete binding forces. Instead, these data clearly show that the binding between the two monomers of **5•7** is a pronouncedly cooperative, entropically favorable process.



29

In summary, we have assembled a new series of heterodimers based on the combination of intermolecular hydrogen bonding and donor-acceptor interaction. Cooperativity has been observed for the discrete non-covalent forces to promote the stability of the dimers. Further work will focus on the modification of the binding moiety to achieve increased stability of the corresponding dimeric systems while keeping a high binding selectivity.

References

1 Dugas, H. *Bioorganic Chemistry*, 3rd ed., Springer Verlag, Berlin, **1996**.

2 Vögtle, F. *Supramolecular Chemistry*: *An Introduction*, Wiley, Chichester, U.K., **1991**.

3 Lehn, J.-M. *Supramolecular Chemistry*: *Concepts and Perspectives*, VCH, Meinheim, **1995**.

4 Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*, Wiley, New York, **2001**.

5 Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*, Wiley, New York, **2001**.

6 Badjic, J. D.; Nelson, A.; Cantrill, S. J.; Trunbull, W. B.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 723.

7 Sauvage, J.-P. *Transition Metals in Suparamolecular Chemistry*, Wiley, New York, **1999**.

8 Sanders, J. K. M. *Pure Appl. Chem*. **2000**, *72*, 2265.

9 Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev*. **2000**, *100*, 853.

10 Sun, W.-Y.; Yoshizawa, M.; Kusukawa, T.; Fujita, M. *Curr. Opin. Chem. Biol.* **2002**, *6*, 757.

11 Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev*. **2001**, *101*, 3893.

12 Bowden, N. B.; Weck, M.; Choi, I. S.; Whitesides, G. M. *Acc. Chem. Res*. **2001**, *34*, 231.

13 Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807.

14 Conn, M. M.; Rebek, J. Jr; *Chem. Rev*. **1997**, *97*, 1647.

15 Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63.

16 Schmuck, C.; Wienand, W. *Angew. Chem., Int. Ed*. **2001**, *40*, 4363.

17 Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2383.

18 Archer, E. A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, *57*, 1139.

19 Zhao, C.-C.; Tong, Q.-X.; Li, Z.-T.; Wu, L.-Z.; Zhang, L.-P.; Tung, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6807.

20 Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643.

21 Cubberley, M. S.; Iverson, B. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 650.

22 Jiang, X.-K.; Li, Z.-T. *Chin. J. Org. Chem.* **2004**, *24*, 753 (in Chinese).

23 Hirschberg, J. H. K. K.; Brunsveld, L.; Ramzi, A.; Vekemans, J. A. J. M.; Sijbesma, R. P.; Meijer, E. W. *Nature* **2000**, *407*, 167.

24 Zhao, X.; Jiang, X.-K.; Shi, M.; Yu, Y.-H.; Xia, W.; Li, Z.-T. *J. Org. Chem*. **2001**, *66*, 7035.

25 Liu, Y.; Zhao, Y. L.; Zhang, H. Y.; Song, H. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 3260.

26 Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761.

27 Hansen, J. G.; Feeder, N.; Hamilton, D. G.; Gunter, M. J.; Becher, J.; Sanders, J. K. M. *Org. Lett*. **2000**, *2*, 449.

28 Gabriel, G. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 15174.

29 Zhou, Q.-Z.; Jiang, X.-K.; Shao, X.-B.; Chen, G.-J.; Jia, M.-X.; Li, Z.-T. *Org. Lett.* **2003**, *5*, 1955.

30 Wang, X.-Z.; Li, X.-Q.; Shao, X.-B.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T.; Chen, Y.-Q. *Chem. Eur. J.* **2003**, *9*, 2904.

31 Li, X.-Q.; Jiang, X.-K.; Wang, X.-Z.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 2063.

32 Li, X.-Q.; Feng, D.-J.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 8275.

33 Zhao, X.; Wang, X.-Z.; Jiang, X.-L.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128.

34 Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. *J. Med. Chem.* **1990**, *33*, 2798.
35 MacCorquodale, F.; Walton, J. C.; Hughes, L.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1893.
36 Wan, W.; Guang, W.-J.; Zhao, K.-Q.; Zheng, W.-Z.; Zhang, L.-F. *J. Organomet. Chem.* **1998**, *557*, 157.
37 Pierce, J. S.; Salsbury, J. M.; Fredericksen, J. M. *J. Am. Chem. Soc.* **1942**, *64*, 1691.
38 Hogale, M. B.; Kharade, D. R. *J. Ind. Chem. Soc.* **1991**, *68*, 298.
39 Bol'shakova, S. A.; Goloshchapova, Z. A.; Tuzhilkova, T. N.; Grebenyuk, A. D.; Myakishev, V. M. *Pharm. Chem. J.* **1983**, *17*, 474.
40 Blicke; L. *J. Am. Chem. Soc.* **1943**, *65*, 2381.
41 Conners, K. A. *Binding Constants*: *The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**.
42 Feng, D.-J.; Li, X.-Q.; Wang, X.-Z.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 6137.
43 Katz, H. E.; Johnson, J.; Lovinger, A. J.; Li, W. *J. Am. Chem. Soc.* **2000**, *122*, 7787.

(E0601114 LU, Y. J.)