Molecular Recognition

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C–H···O Hydrogen Bonding Induced Triazole Foldamers: Efficient Halogen Bonding Receptors for Organohalogens**

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Halogen bonding is the noncovalent interaction between halogen atoms (Lewis acids) and neutral or anionic Lewis bases.[1,2] In the past decade, it has emerged as a new useful noncovalent force, which has found wide applications in supramolecular crystal engineering and materials design,[3] and its importance in controlling the structures and functions of biological molecules[4] and promoting organic reactions[5] has also been recognized. Detailed investigations of discrete halogen bonding patterns in the gas phase have provided valuable data about their directional preferences and binding trends.[6] However, single halogen bonds, particularly those of neutral organohalogens, are considerably weak in solution.[7] Thus, further applications of halogen bonds in solution-phase supramolecular chemistry would heavily depend on the development of new efficient binding patterns. We envisioned that one straightforward strategy to achieve increased binding affinity in solution is to utilize the cooperativity of single binding patterns by the multivalent principle.[8–10] Our research group and Hecht et al. recently reported that 1,4-diphenyl-1H-1,2,3-triazoles could form intramolecular six-membered C–H···O hydrogen bonding patterns.[11,12] Herein, we describe that i) this hydrogen bonding pattern can be utilized to construct a new kind of triazole-derived foldamer, and ii) the new foldamers are capable of binding tri- and didentate organohalogens through multiple N···X (X = Cl, Br, and I) halogen bonds to form stable 1:1 complexes.

A number of structurally flexible triazole oligomers have been reported to bind chloride anions through the intermolecular C–H···Cl$^-$ hydrogen bond.[13–17] We conjectured that long oligomers with repeated 1,4-diphenyl-1*H*-1,2,3-triazole units might be induced, by the repeated intramolecular C–H···O hydrogen bonds, to form folded structures with all the triazole units being positioned inward to bind multidentate organohalogens by halogen bonds.[18] We thus synthesized oligomers **1a–e** (Scheme 1, see the Supporting Information, Scheme S1 for details), which contain 2, 4, 6, 8, and 10 repeated triazole units, respectively. Hexamer **1b** is attached to two pyrene units as fluorescent probes to detect the formation of the folded conformation in solution, while dimer **1e** is designed as a control compound.

Numerous attempts to crystallize oligomers **1a–e** were unsuccessful. However, crystals of short analogues **2a** and **2b**, suitable for the X-ray analysis, were grown by slow evaporation of their chloroform and ethyl acetate (1:1) solution.[19] It can be concluded that both compounds form two pairs of three-center C–H···O hydrogen bonds because the C*H*···O distances all are shorter than the sum (2.72 Å) of the van der Waals radium of hydrogen and oxygen atoms (Figure 1). The geometry of the two model compounds in the crystals also suggested that oligomers with eight repeated triazole units would give rise to one turn, which could produce a cavity that is approximately 1.8 nm in diameter. The crystal structure of **2b** also showed that one of the N2 atoms of its triazoles formed a weak N···Cl halogen bond (3.29 Å) with one chlorine atom of the entrapped chloroform (Figure 1), thus pointing to the potential of these type of triazole foldamers to form intermolecular halogen bonds in solution.

The downfield sections of the ^{1}H NMR spectra of oligomers **1a–e** and short oligomers **2a–c** in [D]chloroform are provided in Figure 2. The signals of the protons of the triazole and the linker benzene units of **2a–c** could be assigned easily based on the integrated intensity of the signals, while the signals of these type of protons of **1a–e** were assigned by comparing their spectra with those of **2a–c** and also using 2D ^{1}H NMR NOESY techniques. The NH signals of **1b** and **1e** were assigned using ^{1}H NMR H_2O/D_2O exchange experiments (see the Supporting Information). In comparison to the triazole proton of **2c**, which cannot form the intramolecular C–H···O hydrogen bonding,[11] the triazole ^{1}H NMR signals (marked by stars in Figure 2) of **1a–e** and **2a** and **2b** all shift downfield pronouncedly ($\Delta\delta = 0.28$–0.44 ppm), except the signals of the benzoyl-bearing triazole units of **1a** and **1c** (marked by triangles in Figure 2), as these units form only one C–H···O hydrogen bond. These observations support the hypothesis that the longer oligomers also form the three-center C–H···O hydrogen bonding in solution.

Irradiation of the Hb signal of decamer **1d** at 6.40 ppm caused the Ha signal at 8.35 ppm to strengthen notably (see Scheme 1 for the atom labelling). The 2D ^{1}H NMR NOESY

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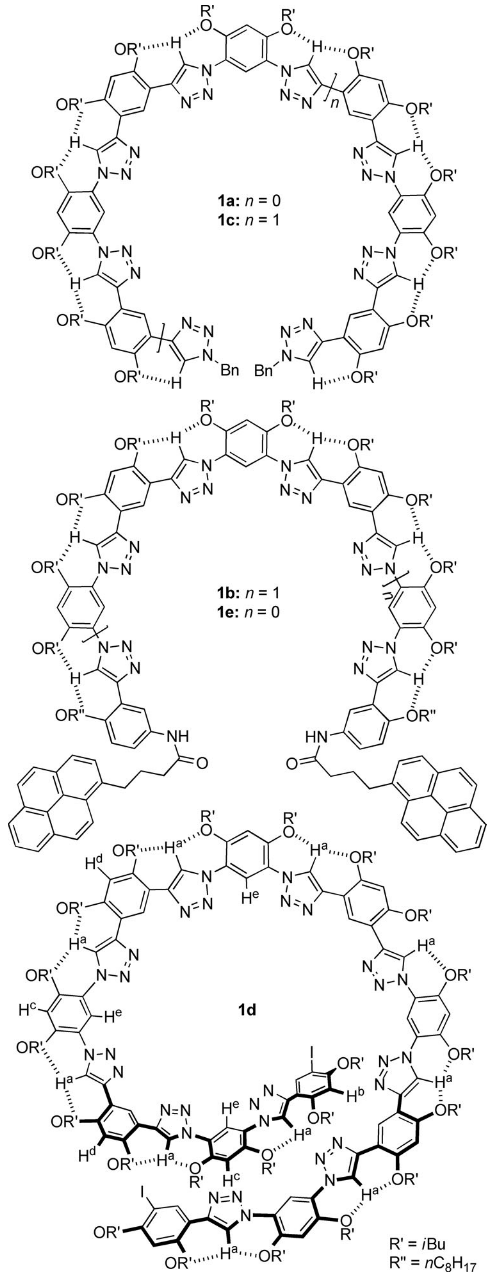
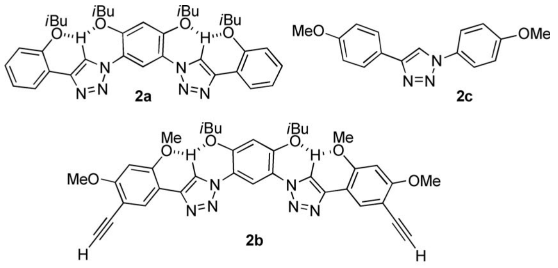


Scheme 1. Oligomers **1a–e**.



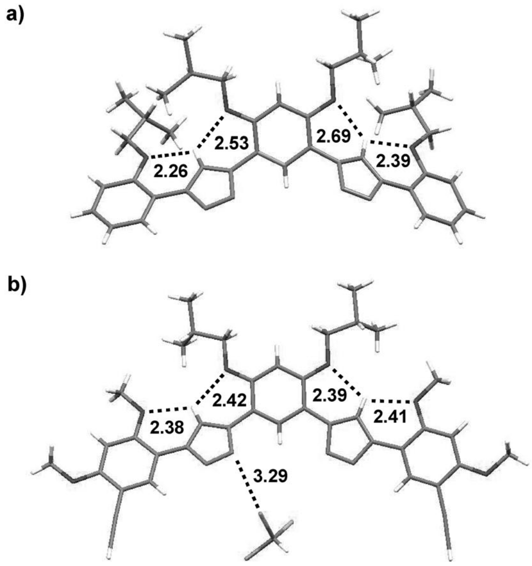


Figure 1. The crystal structures of compounds a) **2a** and b) **2b**. The crystal structure of **2b** highlights an intermolecular N···Cl halogen bond formed with the entrapped chloroform.

spectrum of **1d** (2 mM) in [D]chloroform also displayed NOE contacts between the Ha signal and the Hb–d signals and between Hc,d signals and He signals (see the Supporting Information). When the solution was diluted from 5 mM to 0.5 mM these signals did not shift significantly, thus excluding the possibility of strong intermolecular stacking. Under identical conditions, similar signal strengthening and NOE contacts were not observed for the shorter oligomers **1a** and **1c**. Thus, although the signal overlapping made it difficult to assign the triazole and benzene ring proton signals to the different positions in the backbone, the above observations for **1d** still provide evidence for the helical conformation because only this conformation could cause the two types of

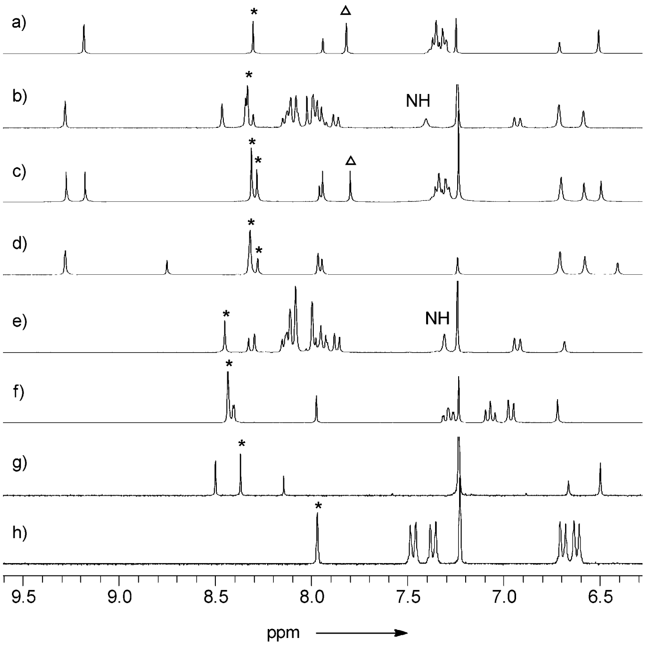


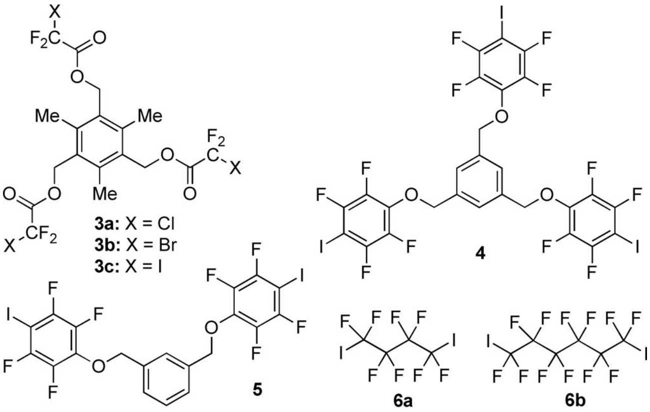
Figure 2. Sections of the ^{1}H NMR spectra (400 MHz, 10 mM) of triazole oligomers: a) **1a**, b) **1b**, c) **1c**, d) **1d**, e) **1e**, f) **2a**, g) **2b**, and h) **2c** in [D]chloroform at 25 °C.

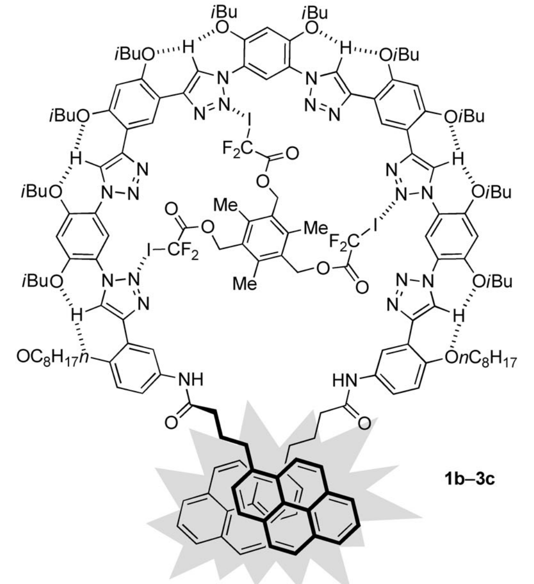
protons to be in close proximity to each other by the cross-ring stacking of the end segments.[18b]

The fluorescent spectra of hexamer **1b** in both dichloromethane and polar acetonitrile (1.0 μM) exhibited a strong excimer emission around 449 nm (see the Supporting Information). In contrast, the shorter analogue **1e** at the same concentration did not display this emission. The extremely dilute concentration excludes any important intermolecular stacking interactions, therefore the formation of the excimer emission by **1b** in the two solvents should also be attributed to the formation of the folded conformation of the backbone; this folded conformation induced the two appended pyrene units to stack intramolecularly. The shorter oligomer **1e** should also have a slightly crescent-shaped conformation, which, however, caused the two appended pyrene units to separate spatially, making their stacking impossible.

With the assumption that an oligomer of eight 1,2,3-triazole units forms a helicate of one turn, molecular modeling revealed that the aromatic backbone of foldamers **1c** and **1d** would produce a polar internal cavity approximately 1.8 nm in diameter, while shorter analogues **1a** and **1b** could also form a crescent-shape conformation of similar internal size. The binding affinity of these compounds for tridendates **3a–c** and **4** were then investigated. Molecular modelling showed that, when adopting an extended conformation, **3a–c** have a diameter of 1.4–1.5 nm, while **4** has diameter of approximately 1.8 nm. In view of the conformational flexibility of the molecules, we anticipated multivalent binding between them and the triazole foldamers through the formation of multiple N···X halogen bonds.

The addition of 1 equivalent of the foldamers **1a–c** to a solution of **3c** (10 mM) in dichloromethane caused the CF_2 signal of **3c** in the ^{19}F NMR spectrum to shift upfield by 0.02, 0.04, and 0.04 ppm (with $PhCF_3$ as internal standard), respectively, and an increase in the amount of **1c** to 3.5 equivalents could lead to an upfield shift of 0.20 ppm (see the Supporting Information). The shifts were not as large as that reported for the halogen bonding with a chloride anion as donor,[20] but were repeatable, thus supporting the formation of the N···I halogen bonding between the triazole N2 and N3 atoms of the foldamers and the iodo atom of the tridentate guests. The addition of 1 equivalent of the short analogues **2a** and **2b** to the solution of **3c** (10 mM) in dichloromethane did not cause an observable change for the chemical shift of its CF_2 signal, thus indicating that the above shift of the ^{19}F signal of **3c** resulted through the cooperative interaction of the weak intermolecular N···I halogen bonding. Molecular modeling of the aromatic backbones of **1a–e** (Spartan/PM3 Semi-Empirical) also revealed that the N2 and N3 atoms of their triazole units bear a partial negative charge,[15b] which produces a crescent or helical domain for the longer **1a–d** (see the Supporting Information) and thus should remarkably favor multivalent binding with the guests, as exemplified in Scheme 2 for the complex between **1b** and **3c**.





Scheme 2. The folded structure of **1b** binded to **3c** by multiple N···I halogen bonds, which further intensify the folded state of **1b**, thus leading to an increase of the excimer emission of the appended pyrene units. Other N2 and/or N3 atoms of the triazole units may also form the halogen bonds as a result of the dynamic nature of this non-covalent interaction.

The addition of **3a–c** and **4** to the dichloromethane solution of **1a**, **1c**, and **1d** remarkably decreased the emission intensity of the foldamers, while adding the organohalogens to the solution of **1b** caused its excimer emission to increase. Both observations support that the foldamers complexed the organohalogens. The latter observation also shows that the complexation further stabilized the folded state of **1b** (Scheme 2). Fluorescent titrations were then conducted to evaluate the binding constants of the related 1:1 complexes by applying the results to the Benesi–Hildebrand plot, which showed the required linear relationship (see the Supporting Information).[21] The derived binding constants are listed in Table 1. It can be seen that the binding stability of the complexes of the same foldamer increases from **3a** to **3b** and then to **3c**; this finding is consistent with the fact that the organoiodine is a better halogen donor then its chlorine or bromine counterpart.[1] In the mixture of dichloromethane and n-hexane, the complex becomes more stable (Table 1, entries 6–8), thus implying that dichloromethane as weak halogen donor might compete with the guest to bind the triazole. The binding affinity of **1c** toward didentates **5** and **6a**

Table 1: Binding constants of triazole foldamers **1a–d** with organohalogens **3–6** in dichloromethane at 298 K.[a]

Entry	Foldamer host	Guest	K_a [M^{-1}]	ΔG [kJ mol^{-1}]
1	**1a**	**3a**	2.0×10^{3}	18.8
2	**1a**	**3b**	4.1×10^{3}	20.6
3	**1a**	**3c**	7.0×10^{3}	21.9
4	**1b**	**3c**	3.0×10^{4}	25.6
5	**1b**	**3c**	3.2×10^{4}[b]	25.7
6	**1b**	**4**	1.4×10^{4}	23.6
7	**1b**	**4**	8.6×10^{4}[c]	28.1
8	**1b**	**4**	1.0×10^{5}[d]	28.5
9	**1b**	**4**	1.0×10^{5}[b,d]	28.5
10	**1c**	**3a**	4.0×10^{2}	14.8
11	**1c**	**3b**	2.7×10^{3}	19.6
12	**1c**	**3c**	6.8×10^{3}	21.9
13	**1c**	**3c**	5.9×10^{3}[b]	21.5
14	**1c**	**4**	2.8×10^{3}	19.7
15	**1c**	**5**	7.4×10^{2}	16.4
16	**1c**	**6a**	1.6×10^{3}	18.3
17	**1c**	**6b**	4.3×10^{3}	20.7
18	**1d**	**3a**	24	7.9
19	**1d**	**3b**	1.0×10^{3}	17.1
20	**1d**	**3c**	1.0×10^{4}	22.8
21	**1d**	**3c**	7.7×10^{3}[b]	22.2

[a] Binding constants, K_a, are determined by using the Benesi–Hildebrand method. [b] Data is evaluated by using nonlinear regressions. [c] In dichloromethane and *n*-hexane (1:1 v/v). [d] In dichloromethane and *n*-hexane (1:9 v/v).

and **6b** was also evaluated (Table 1, entries 15–17). As expected, the value of **5** is lower than that of **4**, but all the values are still remarkably higher than the reported values for the complexes stabilized by single a N···I halogen bond.[7]

In conclusion, we have demonstrated for the first time that intramolecular C–H···O hydrogen bonding can be utilized to induce aromatic 1,2,3-triazole oligomers to form folded and helical secondary structures. All the triazole units of the new foldamers are positioned inward to form a cavity approximately 1.8 nm in diameter and tridentate organohalogen guests can be bound within this cavity. The resulting 1:1 complexes are remarkably stable as a result of the cooperativity of the formed halogen bonds, thus suggesting that halogen bonding may be as useful as hydrogen bonding in solution-phase molecular recognition when the multivalent principle is applied. Given the extensive applications of the N–H···N hydrogen bonding in supramolecular chemistry, a future goal will be to exploit the affinity of the new triazole foldamers toward hydrogen bonding guests of matching sizes and binding sites.

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[1] *Halogen Bonding: Fundamentals and Applications* (Eds.: P. Metrangolo, G. Resnati), Springer, Berlin, **2008**.

[2] a) P. Metrangolo, H. Neukirch, T. Pilati, G. Resnati, *Acc. Chem. Res.* **2005**, *38*, 386–395; b) P. Metrangolo, F. Meyer, T. Pilati, G. Resnati, G. Terraneo, *Angew. Chem.* **2008**, *120*, 6206–6220; *Angew. Chem. Int. Ed.* **2008**, *47*, 6114–6127.

[3] a) M. D. Ward, *Dalton Trans.* **2010**, *39*, 8851–8867; b) K. Rissanen, *CrystEngComm* **2008**, *10*, 1107–1113; c) M. Fourmigue, *Struct. Bonding (Berlin)* **2008**, *126*, 181–207; d) D. W. Bruce, *Struct. Bonding (Berlin)* **2008**, *126*, 161–180; e) P. Metrangolo, G. Resnati, T. Pilati, S. Biella, *Struct. Bonding (Berlin)* **2008**, *126*, 105–136; f) K. Rissanen, *CrystEngComm* **2008**, *10*, 1107–1113; g) M. Fourmigué, *Curr. Opin. Solid State Mater. Sci.* **2009**, *13*, 36–45; h) G. Cavallo, P. Metrangolo, T. Pilati, G. Resnati, M. Sansotera, G. Terraneo, *Chem. Soc. Rev.* **2010**, *39*, 3772–3783; i) R. Bertani, P. Sgarbossa, A. Venzo, F. Lelj, M. Amati, G. Resnati, T. Pilati, P. Metrangolo, G. Terraneo, *Coord. Chem. Rev.* **2010**, *254*, 677–695; j) K. Merz, V. Vasylyeva, *CrystEngComm* **2010**, *12*, 3989–4002.

[4] a) A. R. Voth, P. S. Ho, *Curr. Top. Med. Chem.* **2007**, *7*, 1336–1348; b) E. Parisini, P. Metrangolo, T. Pilati, G. Resnati, G. Terraneo, *Chem. Soc. Rev.* **2011**, *40*, 2267–2278; c) P. Zhou, F. Tian, J. Zou, Z. Shang, *Mini-Rev. Med. Chem.* **2010**, *10*, 309–314.

[5] A. Bruckmann, M. A. Pena, C. Bolm, *Synlett* **2008**, 900–902.

[6] a) P. Politzer, P. Lane, M. C. Concha, Y. Ma, J. S. Murray, *J. Mol. Model.* **2007**, *13*, 305–311; b) A. Karpfen, *Struct. Bonding (Berlin)* **2008**, *126*, 1–15; c) A. C. Legon, *Phys. Chem. Chem. Phys.* **2010**, *12*, 7736–7747; d) P. Politzer, J. S. Murray, T. Clark, *Phys. Chem. Chem. Phys.* **2010**, *12*, 7748–7757.

[7] a) K. Xu, D. M. Ho, R. A. Pascal, *J. Org. Chem.* **1995**, *60*, 7186–7191; b) S. C. Blackstock, J. K. Kochi, J. P. Lorand, *J. Org. Chem.* **1987**, *52*, 1451–1460; c) S. Libri, N. A. Jasim, R. N. Perutz, L. Brammer, *J. Am. Chem. Soc.* **2008**, *130*, 7842–7844; d) R. Cabot, C. Hunter, *Chem. Commun.* **2009**, 2005–2007; e) M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras, M. S. Taylor, *J. Am. Chem. Soc.* **2010**, *132*, 1646–1653.

[8] P. L. Wash, S. Ma, U. Obst, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 7973–7974.

[9] C. A. Hunter, H. L. Anderson, *Angew. Chem.* **2009**, *121*, 7624–7636; *Angew. Chem. Int. Ed.* **2009**, *48*, 7488–7499.

[10] A. Mulder, J. Huskens, D. N. Reinhoudt, *Org. Biomol. Chem.* **2004**, *2*, 3409–3424.

[11] Y.-Y. Zhu, G.-T. Wang, R.-X. Wang, Z.-T. Li, *Cryst. Growth Des.* **2009**, *9*, 4778–4783.

[12] D. Zornik, R. M. Meudtner, T. E. Malah, C. M. Thiele, S. Hecht, *Chem. Eur. J.* **2011**, *17*, 1473–1484.

[13] Y. Hua, A. H. Flood, *Chem. Soc. Rev.* **2010**, *39*, 1262–1271.

[14] a) Y. Li, A. H. Flood, *Angew. Chem.* **2008**, *120*, 2689–2692; *Angew. Chem. Int. Ed.* **2008**, *47*, 2649–2652; b) Y. Li, M. Pink, J. A. Karty, A. H. Flood, *J. Am. Chem. Soc.* **2008**, *130*, 17293–17295; c) Y. Li, A. H. Flood, *J. Am. Chem. Soc.* **2008**, *130*, 12111–12122; d) S. Lee, Y. Hua, H. Park, A. H. Flood, *Org. Lett.* **2010**, *12*, 2100–2102.

[15] a) H. Juwarker, J. M. Lenhardt, D. M. Pham, S. L. Craig, *Angew. Chem.* **2008**, *120*, 3800–3803; *Angew. Chem. Int. Ed.* **2008**, *47*, 3740–3743; b) H. Juwarker, J. M. Lenhardt, J. C. Castillo, E. Zhao, S. Krishnamurthy, R. M. Jamiolkowski, K.-H. Kim, S. L. Craig, *J. Org. Chem.* **2009**, *74*, 8924–8934.

[16] a) R. M. Meudtner, S. Hecht, *Angew. Chem.* **2008**, *120*, 5004–5008; *Angew. Chem. Int. Ed.* **2008**, *47*, 4926–4930; b) M. Ostermeier, M.-A. Berlin, R. Meudtner, S. Demeshko, F. Meyer, C. Limberg, S. Hecht, *Chem. Eur. J.* **2010**, *16*, 10202–10213; c) R. M. Meudtner, S. Hecht, *Macromol. Rapid Commun.* **2008**, *29*, 347–351; d) L. Piot, R. M. Meudtner, T. El Malah, S. Hecht, P. Samori, *Chem. Eur. J.* **2009**, *15*, 4788–4792.

[17] a) Y. Wang, F. Li, Y. Han, F. Wang, H. Jiang, *Chem. Eur. J.* **2009**, *15*, 9424–9433; b) Y. Wang, J. Xiang, H. Jiang, *Chem. Eur. J.* **2011**, *17*, 613–619.

[18] Hydrogen bonded aromatic amide foldamers have been widely utilized for molecular recognition by intermolecular hydrogen bonds, see: a) C. Li, S.-F. Ren, J.-L. Hou, H.-P. Yi, S.-Z. Zhu, X.-K. Jiang, Z.-T. Li, *Angew. Chem.* **2005**, *117*, 5871–5875; *Angew. Chem. Int. Ed.* **2005**, *44*, 5725–5729; b) J. Garric, J.-M. Léger, I. Huc, *Angew. Chem.* **2005**, *117*, 1990–1994; *Angew. Chem. Int. Ed.* **2005**, *44*, 1954–1958; c) C. Bao, B. Kauffmann, Q. Gan, K. Srinivas, H. Jiang, I. Huc, *Angew. Chem.* **2008**, *120*, 4221–4224; *Angew. Chem. Int. Ed.* **2008**, *47*, 4153–4156; d) K. Yamato, L. Yuan, W. Feng, A. J. Helsel, A. R. Sanford, J. Zhu, J. Deng, X. C. Zeng, B. Gong, *Org. Biomol. Chem.* **2009**, *7*, 3643–3647; e) Q. Gan, Y. Ferrand, C. Bao, B. Kauffmann, A. Grélard, H. Jiang, I. Huc, *Science* **2011**, *331*, 1172–1175.

[19] CCDC 846798 (**2a**) and 846799 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] a) E. Dimitrijević, O. Kvak, M. S. Taylor, *Chem. Commun.* **2010**, *46*, 9025–9027; b) M. G. Sarwar, B. Dragisic, S. Sagoo, M. S. Taylor, *Angew. Chem.* **2010**, *122*, 1718–1721; *Angew. Chem. Int. Ed.* **2010**, *49*, 1674–1677; c) M. G. Chudzinski, C. A. McClary, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 10559–10567.

[21] H. A. Benesi, J. H. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.