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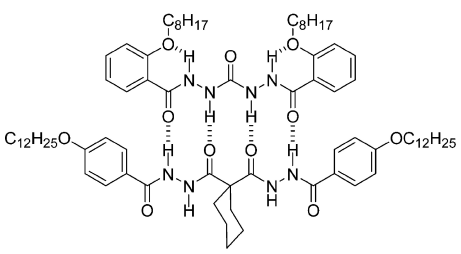

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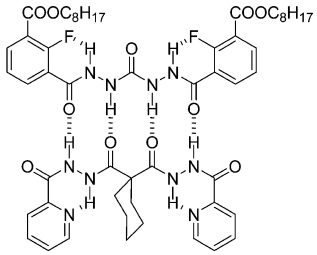

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Hydrazide-Based Quadruply Hydrogen-Bonded Heterodimers. Structure, Assembling Selectivity, and Supramolecular Substitution

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Abstract: This paper describes the synthesis, self-assembly, and characterization of a new class of highly stable hydrazide-based quadruply hydrogen-bonded heterodimers. All of the hydrazide-derived heterodimers possess the complementary ADDA−DAAD hydrogen-bonding sequences. Hydrazide derivatives **1**, which has two intramolecular S(6) RO···H−N hydrogen bonds, and **2** complex to afford two fastly exchanging isomeric heterodimers **1·2** and **1·2′** in chloroform, as a result of two different conformational arrangements of **2**. An average binding constant K_{assoc} of 4.7×10^4 M^{-1} was determined for heterodimer **1·2** and **1·2′** by ^{1}H NMR titration of **1** with changing **2** in chloroform-*d*. In contrast, **1** binds **11** and **12**, both of which are introduced with two intramolecular S(6) hydrogen bonds, to exclusively afford heterodimers **1·11** and **1·12**, with K_{assoc} values of 1.8×10^4 and 5.0×10^2 M^{-1}, respectively. Fluorine-containing **19**, which has a hydrazide skeleton identical to that of **1** but two intramolecular S(6) F···H−N hydrogen bonds, can also complex with **2**, **11**, and **12**, to afford heterodimers **19·2**, **19·2′**, **19·11**, and **19·12**, with K_{assoc} values of of 1.2×10^4 (average value for **19·2** and **19·2′**), 5.4×10^3, and 1.9×10^2 M^{-1}, respectively. The structures of the new heterodimers have been proven with NOESY, IR, and VPO (for some of the heterodimers) experiments. Moreover, **1** and **19** can also strongly bind 2,7-dilauroylamido-1,8-naphthyridine **23** to afford dimers **1·23** and **19·23** with K_{assoc} values of 6.0×10^5 and 1.4×10^5 M^{-1}, respectively. Adding **1** to the 1:1 solution of **23** and 1-octyl-3-(4-oxo-3,4-dihydro-pyrido[2,3-*d*]pyrimidin-2-yl)urea **24** or 1-octyl-3-(4-oxo-1,4-dihydro-pyrimidin-2-yl)urea **25**, which had been developed initially by Zimmerman and Meijer, respectively, induces dimers **23·24** and **23·25** to dissociate, leading to the formation of dimers **1·23** and **24·24** or **25·25**, respectively. The new hydrazide-based hydrogen-bonding modules described are useful building blocks for self-assembly and open a new avenue to recognition between discrete supramolecular species.

Introduction

The construction of new supramolecular architectures with well-established structures and functions would be greatly facilitated if a diverse set of structural motifs with strong and specific intermolecular interactions becomes available. Because of their directionality and strength, hydrogen bonds are one of the most important interactions in the self-assembly of supramolecular structures.[1] Although early study had established that simple doubly hydrogen-bonded systems, such as amide,[2] sulfamide,[3] carboxylic acid,[4] pyridone derivatives, and 2-aminopyridine-carboxylic acid complexes,[5] and triply hydrogen-bonded systems, such as cyanuric acid-melamine and cytosine-guanine motifs,[1a,6] could be used to construct various molecular aggregators, recent investigations have demonstrated that multiply (>3) hydrogen-bonded modules are even more powerful assembling tools due to their increased binding strength, specificity, and directionality.[1j−l,7] Particularly, the self-complementary quadruply hydrogen-bonded homodimers based on rigid heterocyclic derivatives had found extensive applications in the construction of well-defined supramolecular oligomers and polymers.[8,9] Nevertheless, the self-complementary

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[§] Beijing Normal University.

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(5) (a) Boucher, E.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1995**, *60*, 1408. (b) Yang, J.; Fan, E.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 5314.

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feature of homodimers also makes it difficult to use this kind of binding motif to selectively assemble specific heterodimeric supramolecular structures from distinct monomers, because a mixture of possible dimers consisting of different monomers would always be generated statistically on account of their comparable binding stability.[8f,10] In principle, non-self-complementary binding arrays are ideal tools to selectively assemble heterodimeric systems. However, the number of this kind of quadruply hydrogen-bonding modules available for use in supramolecular assembly is notably limited.[11] Therefore, there is a strong need to develop new types of non-self-complementary quadruply hydrogen-bonding units of high stability and specificity.

We were interested in developing new unnatural molecular recognition units with programmable strength and specificity. Moreover, we also hoped to use new binding modules as model systems to explore, if any, new recognition or interaction between discrete supramolecular species with distinct structural skeletons and binding motifs. We envisioned that investigations along this line would lead to a new possibility for creating recognition diversity and, more importantly, for developing new principles to construct new supramolecular architectures. Herein, we describe (1) the design, self-assembly, and characterization of a new class of quadruply hydrogen-bonded heterodimers from readily available hydrazide derivatives and (2) the competitive associating behaviors of the new supramolecular species with two rigid heterocyclic homodimers, which were initially reported by Zimmerman and Meijer.[7d,e] To our knowledge, the construction of the new class of highly stable hydrazide-based ADDA−DAAD (A = hydrogen-bond acceptor, D = hydrogen-bond donor) heterodimers also represents the first successful application of hydrazide derivatives in the self-assembly of hydrogen-bond-mediated supramolecular systems with well-established structures.[12,13]

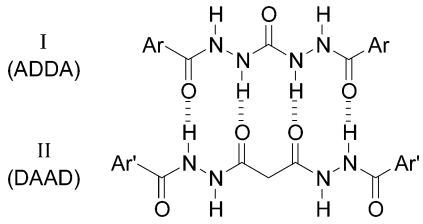

Figure 1. The designed binding motif of the new generation of hydrazide-based quadruply hydrogen-bonded heterodimers.

Results and Discussion

The underlying assembling strategy for the new type of quadruply hydrogen-bonded heterodimers involves the combination of two series of readily available hydrazide derivatives I and II, as shown in Figure 1. In principle, monomers I and II are expected to give rise to the complementary DAAD and ADDA hydrogen-bonding sequences, leading to the formation of a new generation of hydrogen-bonded supramolecular species. The hydrogen-bonding components, that is, C═O and NH units in both series, are designed to be arranged as closely as possible to reduce the influence of structural flexibility. Also, additional intramolecular RO···H−N and F···H−N hydrogen bonds are introduced to increase the binding stability and selectivity of the new class of heterodimers.

Compounds **1** and **2**, which possess the complementary ADDA and DAAD hydrogen-bonding sequence, respectively, were first designed and synthesized. The octyloxy groups were incorporated into **1** for the formation of two highly favorable intramolecular S(6)-type hydrogen bonds,[14] which should facilitate its complexation with complementary counterpart molecules. The introduction of the dodecyloxy and cyclohexyl groups in **2** provided good solubility in organic solvents, and the latter group was also expected to facilitate the complexation of **2** with **1** as a result of steric hindrance between it and the adjacent hadrazide groups. The syntheses of both **1** and **2** are outlined in Scheme 1. Treatment of **3** with commercially available carbohydrazide **4** in the presence of EDCI afforded **1** in 60% yield. For preparation of **2**, malonic acid diethyl ester **5** was first treated with dibromide **6** in the presence of sodium ethoxide to yield **7**, which was hydrolyzed and then converted to diacyl chloride **8** with thionyl chloride. Subsequent reaction of **8** with **10** in chloroform with triethylamine as base yielded compound **2** in 67% yield. Compound **10** could be conveniently prepared from the reaction of **9** with hydrazine.

A crystal of compound **1** suitable for X-ray analysis was grown from chloroform by slow evaporation. Figure 2 shows the X-ray structure of the centrosymmetric homodimer **1**·**1**. The two molecules are held together by four intermolecular tricenter hydrogen bonds (O···H distances = 2.230 and 2.383 Å, respectively) between the two hydrazide skeletons which are arranged within a slightly twisted plane. A similar type of tricenter hydrogen bonds had been observed for simple sym-

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(12) Ureas derivatives have been investigated extensively for hydrogen-bond-mediated self-assembly and molecular recognition. However, to our knowledge, no examples of hydrogen-bond-driven supramolecular systems from hydrazine derivatives with well-established structures have ever been reported.

(13) Hydrazide units have been successfully used by Nowick et al. to control the folding structures of artificial peptides, see: (a) Nowick, J. S.; Smith, E. M.; Pairish, M. *Chem. Soc. Rev.* **1996**, *25*, 401. (b) Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1997**, *1*, 120. (c) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287.

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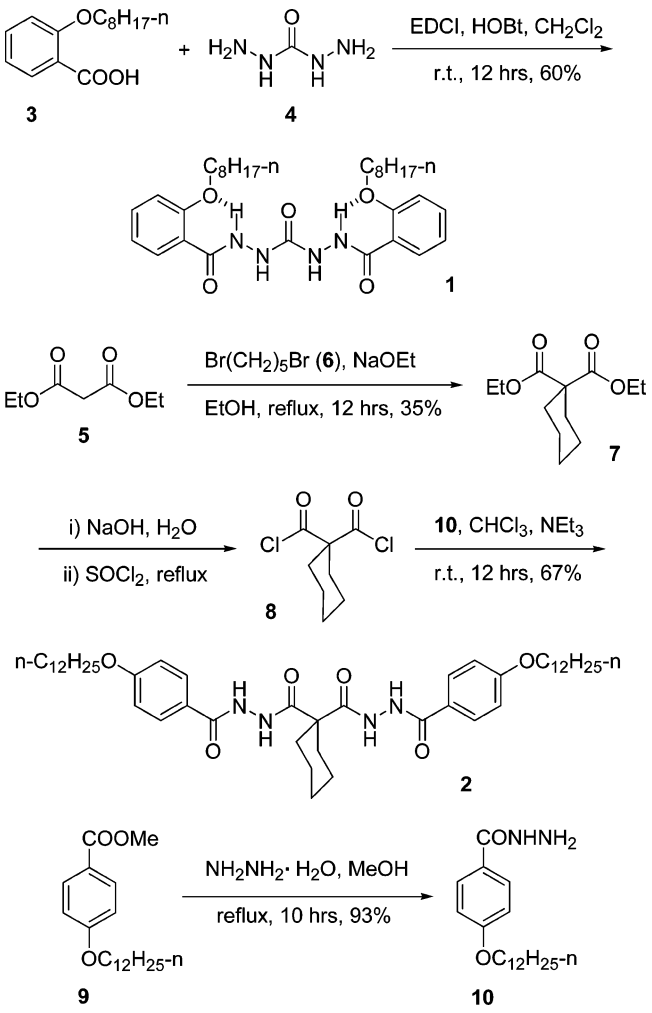
Scheme 1



metric aryl urea derivatives.[15] As expected, there are two intramolecular S(6)-type hydrogen bonds (O···H distance = 1.983 Å) for every molecule, that rigidify the backbone of the molecule.

The NH signals of compounds **1** and **2** in ^{1}H NMR spectra were assigned by the NOE and gradient experiments (Chart 1). The peak of NH-2 protons was substantially shifted downfield (9.99 ppm) relative to that of the NH-1 protons (8.48 ppm) in **1**, suggesting that the NH-2 protons were involved in strong intramolecular hydrogen bonds.[16] Dilution studies (50 mM to 100 μM) in $CDCl_3$ revealed weak self-binding for both compounds at room temperature. A fit of the chemical shift data for both NH-1 of **1** and **2** to a 1:1 isotherm afforded binding constant K_{assoc} values of 55 M^{-1} for dimer **1·1** and 112 M^{-1} for dimer **2·2** (Chart 1), respectively.[17] No obvious chemical shift changes ($\Delta\delta$ < 0.03 ppm) were observed for the NH-2 signals of both **1** and **2**, indicating that these protons did not involve important intermolecular hydrogen bonds.

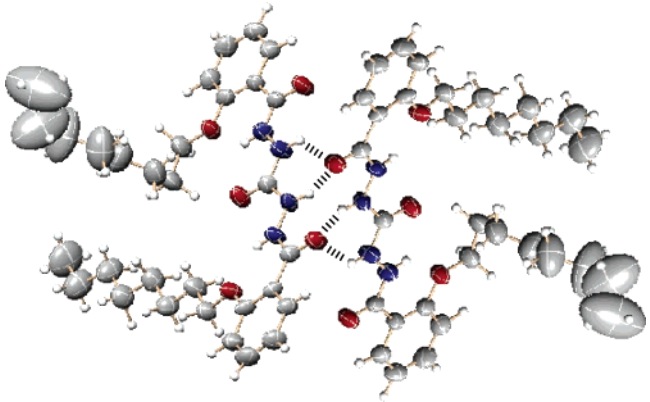


Figure 2. X-ray structure of **1**, showing the intermolecular tricenter hydrogen-bonded dimerization and the intramolecular S(6)-type hydrogen bonds.

Mixing 1 equiv of **1** (5 mM) and 1 equiv of **2** (5 mM) in $CDCl_3$ led to a substantial downfield change of the chemical shifts for the NH-1 signal ($\Delta\delta$ = 0.81 ppm) of **1** and for both the NH-1 ($\Delta\delta$ = 0.71 ppm) and the NH-2 ($\Delta\delta$ = 0.57 ppm) signals of **2** as compared to those of the pure samples of **1** and **2** at the same concentration, initially suggesting that there might be two isomeric dimers **1·2** and **1·2′** generated as a result of the distinct arrangements of **2** (Chart 2). No important shift ($\Delta\delta$ < 0.02 ppm) was observed for the NH-2 signal of **1**, which was involved in the formation of the strong intramolecular hydrogen bond. The ^{1}H NMR dilution study in $CDCl_3$ at room temperature also supported the formation of two isomeric dimers. Reducing the concentration of the 1:1 solution from 80 mM to 80 μM led to the signals of the NH-1 ($\Delta\delta$ = 0.94 ppm) of **1** and the NH-1 ($\Delta\delta$ = 0.82 ppm) and NH-2 ($\Delta\delta$ = 0.72 ppm) of **2** to shift upfield remarkably. In contrast, the NH-2 signal of **1** showed no significant concentration dependence ($\Delta\delta$ < 0.04 ppm). Variable-temperature ^{1}H NMR experiments in $CDCl_3$ from 10 to 55 °C revealed that the signals of the NH-1 of **1** and the NH-1 and NH-2 of **2** exhibited much greater temperature dependence than that of the NH-2 of **1**.[18] All of these observations are consistent with the formation of two dimeric isomers **1·2** and **1·2′**.

Additional compelling evidence for the formation of both **1·2** and **1·2′** came from 2D-NOESY experiments (see the Supporting Information). Important NOE connections were observed between all of the NH signals of both **1** and **2**, all with comparable intensities (Chart 2). Considering that, in dimer **1·2**, the distances between the NH-1 or NH-2 of **1** and the NH-2 of **2** are remarkably longer than those between the NH-1 or NH-2 of **1** and the NH-1 of **2**, respectively, the comparably strong NOE correlation between the NH-2 of **2** and the NH's of **1** should more reasonably correspond to the structure of dimer **1·2′**. Reducing the temperature to −20 °C led to broadening but not splitting of the NH signals of both **1** and **2** in a 1:1 solution (5 mL) in $CDCl_3$, indicating that the exchange between the two conformationally isomeric heterodimers was still rapid on the ^{1}H NMR time scale at this temperature.

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(16) Similar intramolecular hydrogen bonds have been established in several folded artificial peptides, see: (a) Smith, E. M.; Holmes, D. L.; Shaka, A. J.; Nowick, J. S. *J. Org. Chem.* **1997**, *62*, 7906. (b) Nowick, J. S.; Pairish, M.; Lee, I. Q.; Holmes, D. L.; Ziller, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 5413. (c) Holmes, D. L.; Smith, E. M.; Nowick, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 7665.

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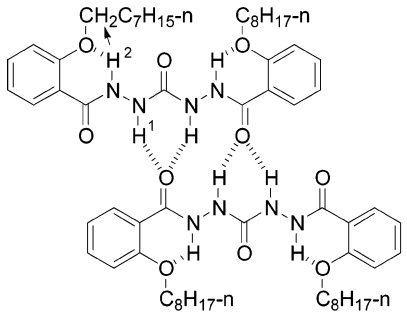
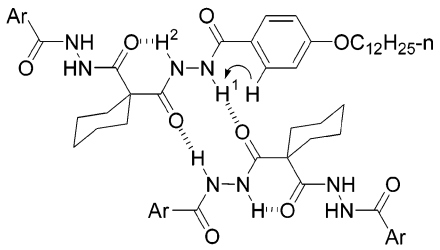
(18) (a) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529. (b) Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587.

Chart 1

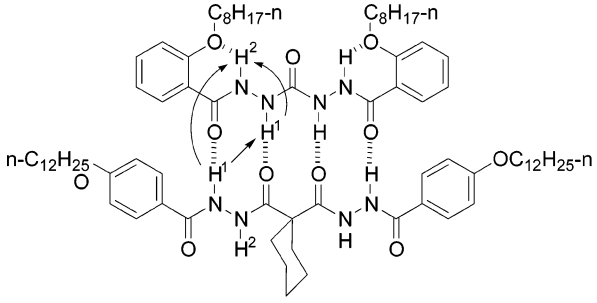


1·1

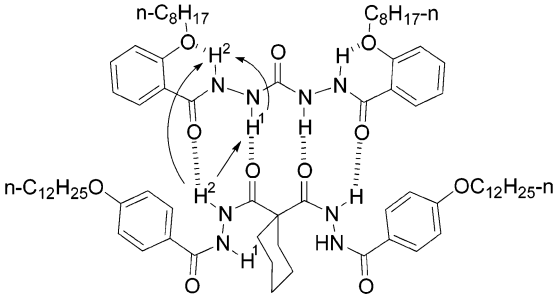


2·2

Chart 2



1 · 2



1 · 2'

An average molecular mass of 1300 ± 100 u was determined with vapor pressure osmometry (VPO) in toluene at 30 °C, which agrees well with that calculated for the dimeric structure (1330 u). FT-IR data were also consistent with dimerization. The pure samples displayed one hydrogen-bonded NH-stretch at 3150 cm^{-1} for **1** and 3155 cm^{-1} for **2**, respectively, and one hydrogen-bond-free NH-stretch at 3430 cm^{-1} for **1** and 3433 cm^{-1} for **2**, respectively, in $CHCl_3$ solution (30 mM), while a mixture of **1** and **2** (20 mM) in $CHCl_3$ exhibited a substantially increased hydrogen-bonded NH-stretch at 3157 cm^{-1} and a decreased NH-stretch at ca. 3430 cm^{-1} as compared to the pure samples, showing that the previously hydrogen-bond-free N−H's had been involved in intermolecular hydrogen bonding in the mixture.

^{1}H NMR titration was carried out for the solution of **1** in $CDCl_3$ with **2**, and the representative results are presented in Figure 3. Fitting the chemical shift data for the NH-1 signals of **1** to a 1:1 binding isotherm afforded an average K_{assoc} value of approximately 4.7×10^4 M^{-1} for the complex of **1** and **2**.[19] In contrast, only small chemical shift changes ($\Delta\delta \leq 0.04$ ppm) were observed for the NH-2 of **1**, which implies that this proton was not importantly involved in intermolecular hydrogen bonding. Heterodimer **1·2** represents one of the most stable examples of quadruply hydrogen-bonded heterodimers that are assembled from nonheterocyclic monomers.[11,20]

Because what is formed from **1** and **2** in chloroform is a mixture of two isomeric dimers, which exchange fastly to each other at room temperature, further improvement of the assembling selectivity of this new class of quadruply hydrogen-bonded modules would be important for future application in the self-assembly of new supramolecular systems. Therefore, two new hydrazide derivatives **11** and **12**, both with the ADDA hydrogen-bonding sequence, were designed and synthesized (Scheme 2). It was conceived that, for **11**, two stable intramolecular S(6)-type hydrogen bonds would be generated from the central NH protons and, as a result, only the peripheral NH protons were free for any intermolecular complexation.[1h] In contrast to **11**, compound **12** would possess two intramolecular S(6)-type hydrogen bonds formed from the peripheral NH protons, as has been observed for **1**. As a result, the selective formation of a dimeric structure similar to that of **1·2′** would be greatly facilitated. The syntheses of compounds **11** and **12** are straightforward, as shown in Scheme 2. Thus, treatment of pyridine-2-carboxylic acid hydrazide **14**, which was prepared in high yield from compound **13** and hydrazine, with diacyl

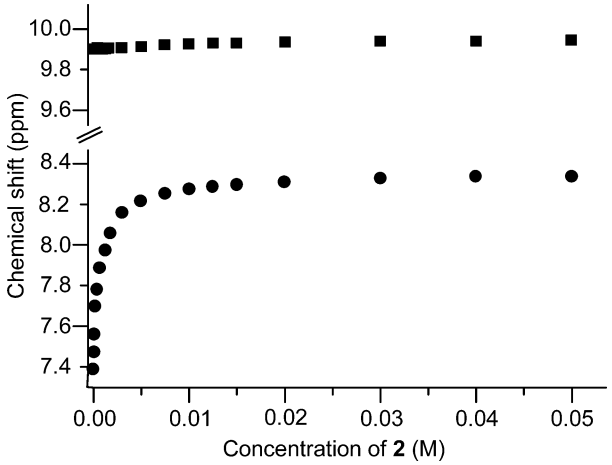
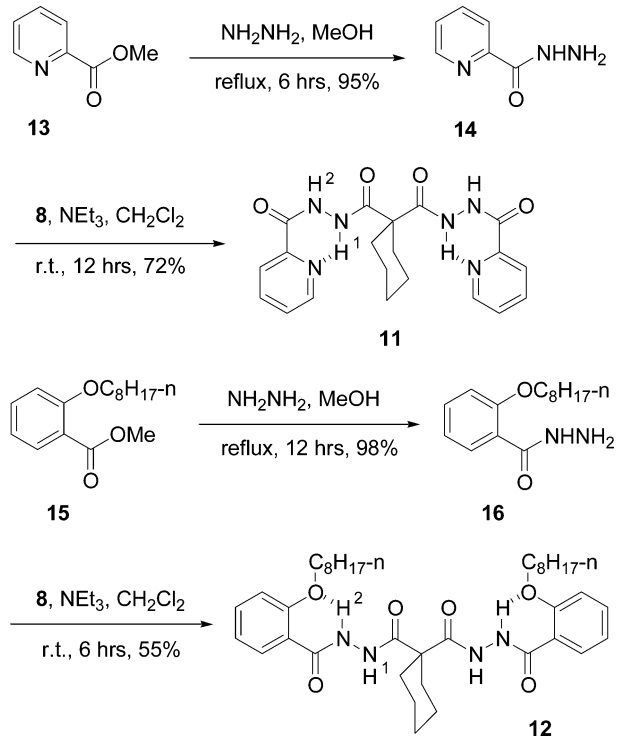


Figure 3. Chemical shift summaries of the NH-1 (●) and NH-2 (■) signals of **1** (1.0 mM) titrated with **2** in $CDCl_3$ at 25 °C.

(19) Titration of **2** (1.33 mM) with **1** in $CDCl_3$ revealed important chemical shift changes for both NH-1 ($\Delta\delta$ 0.90 ppm) and NH-2 ($\Delta\delta$ 0.85 ppm) signals of **2**, indicating that both protons were involved in important intermolecular hydrogen bonding. Because both dimers **1·2** and **1·2′** exist and exchange fastly to each other in the solution, no binding constants of separate isomeric dimers could be obtained by titration of **2** with **1**. We thank one of the reviewers for critical comments concerning this issue.

Scheme 2



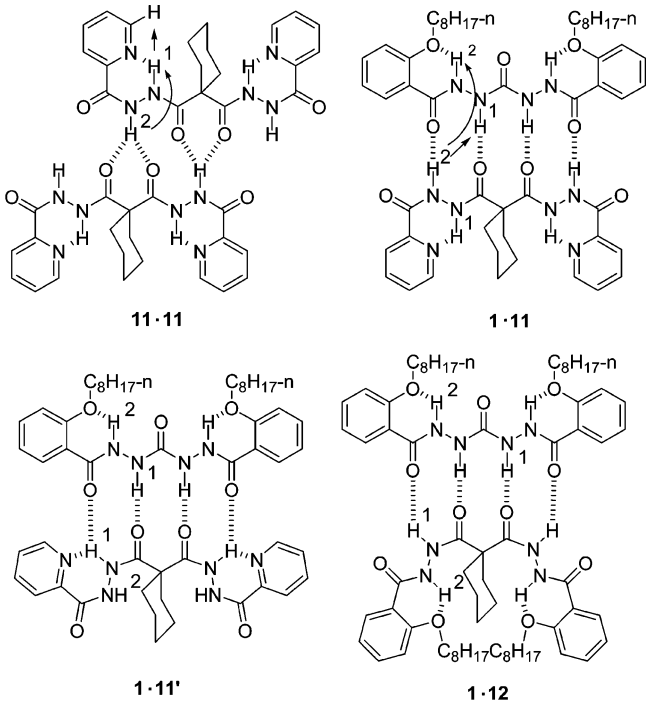
chloride **8** in dichloromethane in the presence of triethylamine afforded **11** in 72% yield. For preparation of **12**, hydrazide **16** was first generated in quantitative yield from the reaction of 2-octyloxybenzoic acid methyl ester **15** and hydrazine. Subsequent reaction of **16** with **8** afforded **12** in 55% yield under the reaction conditions described for preparing **11**.

^{1}H NMR spectra in $CDCl_3$ (5 mM) supported the existence of intramolecular S(6)-type hydrogen bonds in both **11** and **12**. All of the NH protons in both compounds were assigned with the NOESY techniques (numbered in Scheme 2). For **11**, the NH-1 peak (9.89 ppm) was remarkably downfield shifted as compared to its NH-2 peak (9.37 ppm). In contrast, the NH-2 peak (10.66 ppm) in **12** was substantially more downfield than its NH-1 peak (9.58 ppm). These observations clearly showed that the former two NH protons were involved in intramolecular hydrogen bonds. Variable-temperature ^{1}H NMR investigations from 10 to 55 °C revealed an obviously lower temperature dependence of the former two signals in both compounds, which was also consistent with their involvements with intramolecular hydrogen bonds. The self-association of **11** and **12** in $CDCl_3$ was then investigated by ^{1}H NMR spectroscopy. A pronounced upfield shift was observed only for the NH-2 signal (ca. 0.15 ppm) in **11** upon dilution of the solution from 50 to 0.5 mM, which afforded a K_{dim} value of 25 M^{-1} for homodimer **11·11** (Chart 3). No important shifts ($\Delta\delta$ < 0.04 ppm) were observed for the NH-1 signal in **11** and for both NH signals in **12**, implying that these protons did not involve important intermolecular hydrogen bonding.

The binding ability of **11** toward **1** was then investigated with the ^{1}H NMR titration method. The representative results are presented in Figure 4. By fitting a 1:1 binding motif for the

(20) Gong et al. have recently reported a nonheterocyclic DADD−ADAA binding motif with a K_{assoc} of approximately 1250 M^{-1} in 5% DMSO-d_6/$CDCl_3$. No binding constant of the dimer in pure chloroform was provided, see ref 11c.

Chart 3



NH-2 data of **11**, we derived a K_{assoc} value of approximately 1.8×10^4 M^{-1} for heterodimer **1·11** (Chart 3). Only small chemical shift changes (≤0.08 ppm) were observed for the NH-1 signal of **11**, which suggested an obviously smaller binding stability for **1·11′**. The 2D-NOESY experiment also supported the binding selectivity of **1** and **11**. Different from the case of **1** and **2** in which both the NH-1 and the NH-2 of **2** exhibited important intermolecular NOEs, NOE was observed only between the NH-2 signal of **11** and the NH signals of **1**, while the NH-1 signal in **11** did not display any intermolecular connection. The lower K_{assoc} value of dimer **1·11** relative to dimer **1·2** can be rationalized by considering that steric hindrance should exist between the pyridine group and the cyclohexyl group of **11** in dimer **1·11**.

The ^{1}H NMR titration study of **12** with **1** in $CDCl_3$ (Figure 4) revealed that these two compounds exhibited a binding affinity that is opposite to that between compounds **1** and **11**: No important change of chemical shift (≤0.04 ppm) was found

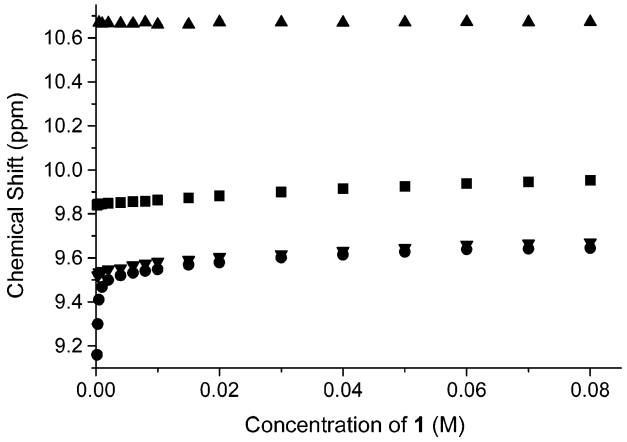
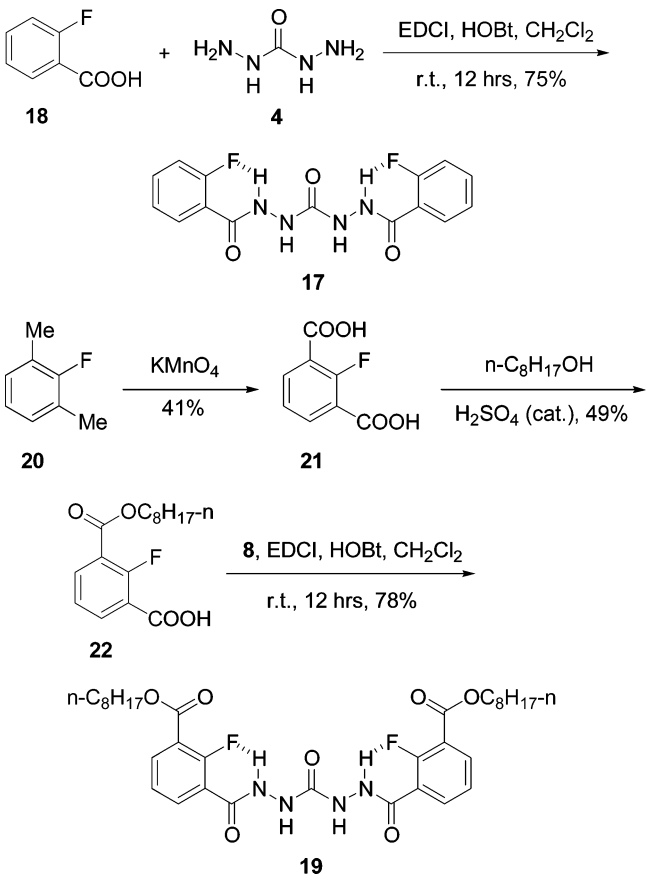


Figure 4. Chemical shift summaries of the NH-1 (■) and NH-2 (●) protons of **11** (1.0 mM) and the NH-1 (▼) and NH-2 (▲) of **12** (10 mM), both titrated with **1** in $CDCl_3$ at 25 °C.

Scheme 3



for its NH-2 signal, which was proven to be involved in strong intramolecular S(6)-type hydrogen bonds. From nonlinear regression of the titration data of the NH-1 signal of **12** with a 1:1 binding motif, a K_{assoc} value of approximately 500 M^{-1} was obtained for dimer **1·12** (Chart 3). The binding constant is remarkably lower than that of dimer **1·11**, which might be attributed to the substantially increased spatial hindrance between the cyclohexyl group and the intramolecularly hydrogen-bonded moiety of **12**.

The formation of intramolecular S(6)-type hydrogen bonds in compound **1** is obviously crucial for efficient self-assembly of the new class of heterodimeric structures. Considering that fluorine has the highest electronegativity and its van der Waals radius (1.35 Å) is very close to that of oxygen (1.40 Å), it was envisioned that the octyloxy group might be replaced with fluorine to form similar intramolecular S(6) F···H−N hydrogen bonds.[21] To test this hypothesis, compound **17** was first prepared from the coupling reaction of commercially available **18** and **4** in the presence of EDCI (Scheme 3). Unfortunately, compound **17** was found to be insoluble in nonpolar solvents such as chloroform or dichloromethane. Therefore, another fluorine-containing compound **19** was synthesized, as outlined in Scheme 3. In brief, the immediate precursor to **19**, fluorine-containing acid **22**, was prepared from the monoesterification of diacid **21**,

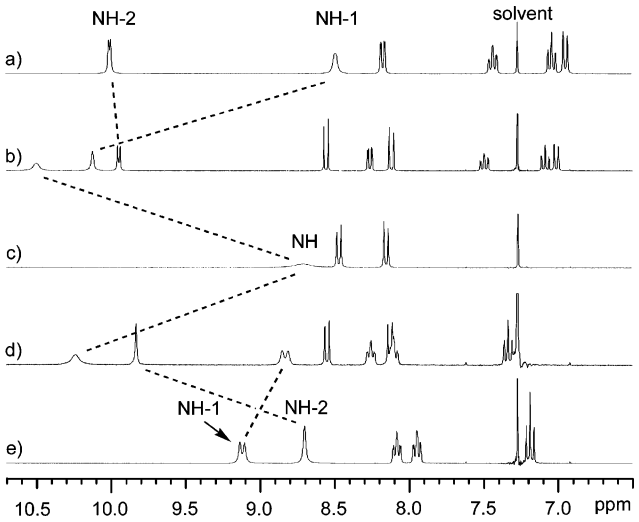


Figure 5. Partial ^{1}H NMR spectrum (400 MHz, 10 mM) of (a) **1**, (b) **1** + **23** (1:1), (c) **23**, (d) **19** + **23**, and (e) **19** in $CDCl_3$ at room temperature, highlighting the formation of heterodimer **1·23** and **19·23**.

which, in turn, was obtained from the oxidation of commercially available 2-fluoro-*m*-xylene **20** with potassium permanganate. The initial attempt to prepare **22** from the selective hydrolysis of 2-fluoro-*iso*-phthalic acid dioctyl ester was not successful, which always afforded **21** as the sole product. As expected, the incorporation of two octoxycarbonyl groups into **19** provided good solubility in common solvents such as chloroform and benzene.

Prior to binding studies with compounds **2**, **11**, and **12**, the self-association of **19** in $CDCl_3$ was investigated by ^{1}H NMR spectroscopy. Different from **1** where only the chemical shift of the H-1 peak exhibited important concentration dependence, both NH signals (numbered in Chart 4) of **19** moved upfield upon dilution of its solution in $CDCl_3$ from 100 mM to 80 μM, which gave K_{assoc} values of 75 and 20 M^{-1} for homodimers **19·19** and **19′·19′**, respectively, after fitting to a dimeric binding motif. Moreover, it can be found that the NH-1 signal (ca. 9.12 ppm) of **19** is less downfield shifted than the NH-1 signal (ca. 10.00 ppm) of **1** at the same concentration (20 mM). The results appear to indicate that the intramolecular S(6) F···H−N hydrogen bond in **19** is notably weaker than the intramolecular S(6) RO···H−N hydrogen bond in **1**.[22]

^{1}H NMR titration studies were then carried out in $CDCl_3$ for compound **19** with **2**, and for compounds **11** and **12** with **19**, respectively. Fitting the chemical shift data for the NH-1 of **19**, **11**, and **12** to a 1:1 binding model gave association constants of approximately 1.2×10^4, 5.4×10^3, and 1.9×10^2 M^{-1} for dimers **19·2** (a mixture with **19·2′**, the existence of which was proven with ^{1}H NMR dilution and NOESY experiments), **19·11**, and **19·12** (Chart 5), respectively. The signals of the NH-2 protons of **19** (<0.07 ppm), **11**, and **12** (<0.04 ppm) did not shift obviously within the concentration range studied, indicating that these protons, which were involved in strong intramolecular hydrogen bonds, were not engaged in important intermolecular hydrogen bonding. NOESY experiments revealed important intermolecular NOE connections between the NH signals of the

(21) It has been reported that fluorine can act as a weak hydrogen-bond acceptor. Nevertheless, to the best of our knowledge, no examples of F···H−N hydrogen-bond-promoted self-assembly of supramolecular systems with defined structures have been available, see: (a) Vinogradov, S. N.; Linnell, R. H. *Hydrogen Bonding*; Van Nostrand Reinhold: New York, 1971; pp 124−135. (b) Jones, D. A. K.; Watkinson, J. G. *J. Chem. Soc.* **1964**, 2366. (c) Kool, E. T. *Acc. Chem. Res.* **2002**, *35*, 936.

(22) Intramolecular S(7) F···H−N hydrogen bonds might also be formed from the H-2 protons of **19**, which compete with the S(6) hydrogen bonds and reduce the latter's strength.

Chart 4

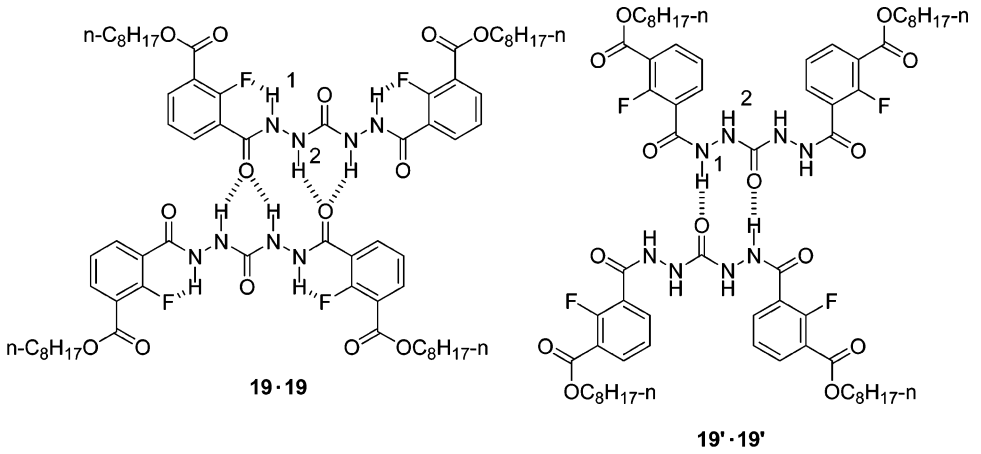
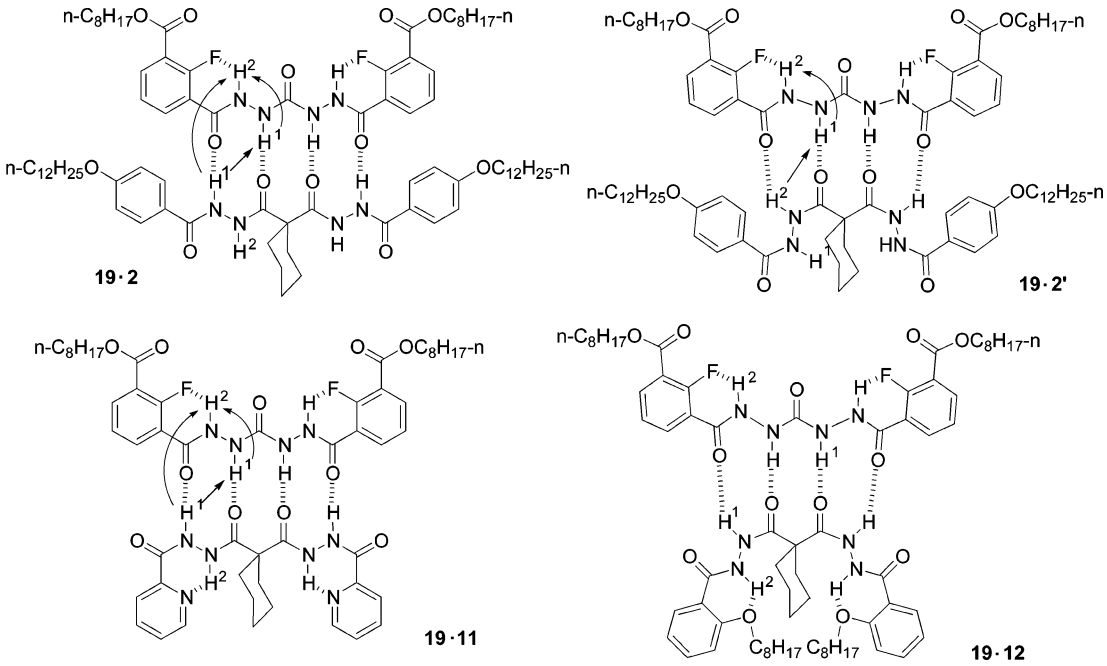


Chart 5



former three complexes (Chart 5), which were consistent with the formation of the heterodimers.

The fact that two conformationally isomeric heterodimers were generated, respectively, between **1** or **19** and **2** revealed that these flexible nonheteroaromatic hydrazide derivatives could readily adjust their conformations to facilitate the self-assembly of new kinds of heterodimers. Previous studies by Meijer and Zimmerman et al. have revealed that quadruply hydrogen-bonded dimers from rigid heterocyclic monomers usually exhibited very strong binding affinity.[7d,e] Therefore, it was conceived that more stable binding modules might be constructed from hydrazide monomers and complementary rigid heteroaromatic monomers. To investigate this potential, the binding behaviors of **1** and **19** with **23** in $CDCl_3$ were investigated. Mixing 1 equiv of **1** with 1 equiv of **23** in $CDCl_3$ (10 mM) caused substantial downfield shifting for the NH-1 signal ($\Delta\delta$ = 2.03 ppm) of **1** and the N−H signal ($\Delta\delta$ = 1.54 ppm) of **23**, while the chemical shift of the NH-2 of **1** did not change downfield greatly ($\Delta\delta$ = ca. 0.10 ppm), as shown in Figure 5. These observations clearly indicated that a new heterodimer **1·23** was formed (Chart 6), which was further evidenced by the observation of strong NOE connections between the NH signals of the two compounds, as shown in Chart 6. The VPO experiment afforded an average mass of 1050 ± 100 u in chloroform (calculated value for dimer **1·23**: 1078 u), which is also consistent with the formation of the dimer. ^{1}H NMR titration studies of **23** (0.7 mM) with **1** were then performed in $CDCl_3$, which gave a K_{assoc} value of approximately 6.0×10^5 M^{-1} for heterodimer **1·23**.

A remarkable downfield shift ($\Delta\delta$ = 1.17 ppm) was also observed for the NH-1 signal of **19** upon mixing it with **23** in a 1:1 ratio (Figure 5d), as a result of the formation of heterodimer **19·23**, which was further evidenced by intermolecular NOE connections (Chart 6). A ^{1}H NMR titration study in $CDCl_3$ afforded this heterodimer a K_{assoc} value of approximately 1.4×10^5 M^{-1}.

Development of new approaches to efficiently regulate the assembling processes of supramolecular recognition modules is potentially useful for the design of novel molecular device and functional materials.[23] The facts that the hydrazide-based hydrogen-bonded heterodimers display varying stability and affinity and that the monomers display good conformational

Chart 6

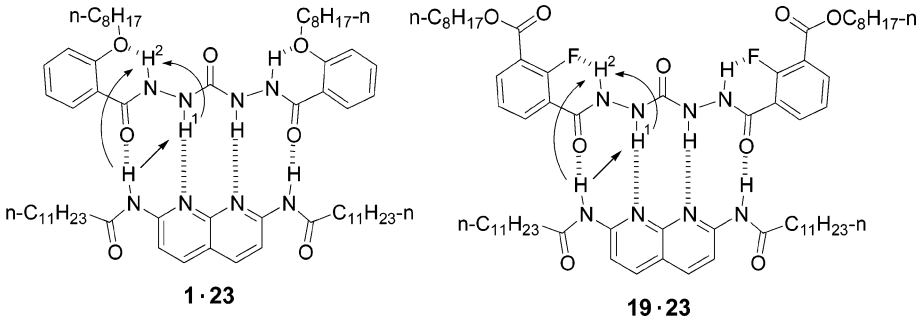
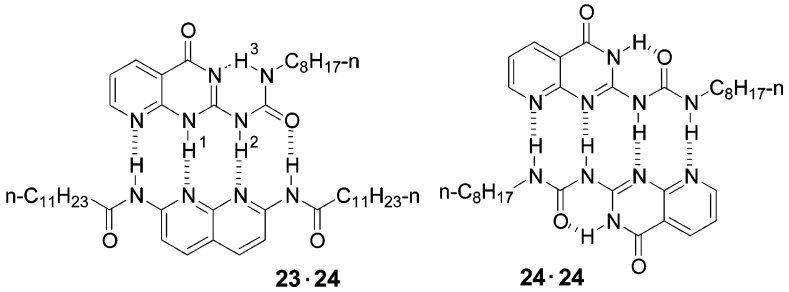


Chart 7



adjustability make them ideal recognition modules for reversible regulation of hydrogen-bonded assemblies with discrete binding motifs. To test this potential, the competitive binding behavior of **1**, **23**, and **24** in $CDCl_3$ was investigated by ^{1}H NMR spectroscopy. Previously, Zimmerman and Corbin had reported that a heterocyclic compound similar to **23** could cause a dimer similar to **24·24** to dissociate to generate a new more stable heterodimer such as **23·24** (Chart 7).[7e] Adding 1 equiv of **1** to the 1:1 solution of **23** and **24** in $CDCl_3$ did induce dimer **23·24** to partially dissociate, leading to the release of **24**, which self-associated to form the stable dimer **24·24**, as indicated by the ^{1}H NMR spectra (Figure 6). The peaks of the NH protons of **1** and **23** in the mixture solution had been assigned by changing the ratio of **1** with **23** and **24** (Figure 6c). However, we could not quantitatively assess the dissociation process of **23·24** by ^{1}H NMR spectroscopy due to the fast exchange between the different dimers and the complicated tautomerization of dimer **24·24**.[24]

The competitive binding properties of **1** and **25** with **23** were then investigated by ^{1}H NMR spectroscopy. Previously, we had found that compound **23** could induce dimer **25·25**, the binding module of which had been initially reported by Meijer at al.,[7d] to dissociate to generate heterodimer **23·25** and the exchange process could be regulated with additional donor−acceptor interaction between *p*-dialkoxybenzene and naphthalene-1,4,5,8-tetracarboxylic diimide.[8f] The ^{1}H NMR results are presented in Figure 7. It can be found that approximately 70% (based on the relative integrative intensity of the H-4 signal of **25** in dimers **23·25** and **25·25** at 5.99 and 5.72 ppm, respectively) of dimer **23·25** was dissociated upon addition of 1 equiv of **1** to the 1:1

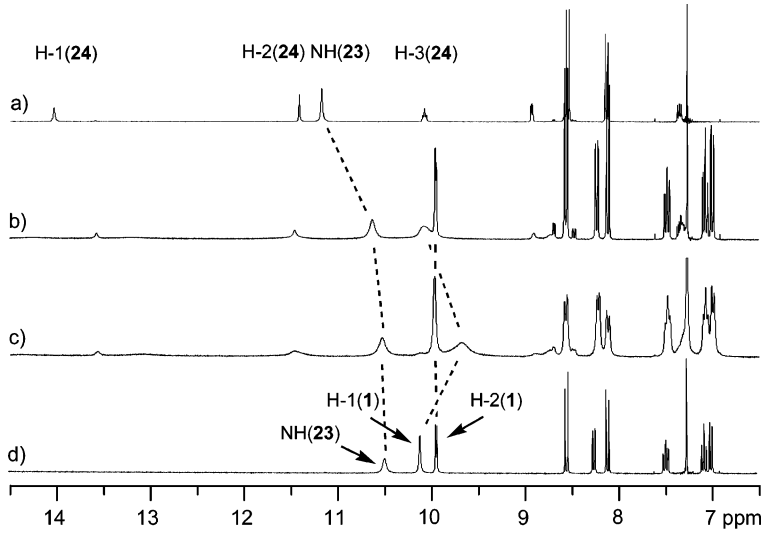


Figure 6. Partial 400 MHz ^{1}H NMR spectrum (10 mM) of (a) **23** + **24** (1:1), (b) **1** + **23** + **24** (1:1:1), (c) **1** + **23** + **24** (2:1:1), and (d) **1** + **23** (1:1) in $CDCl_3$ at 25 °C, highlighting the competitive complexing behavior of **1** and **24** to **23**.

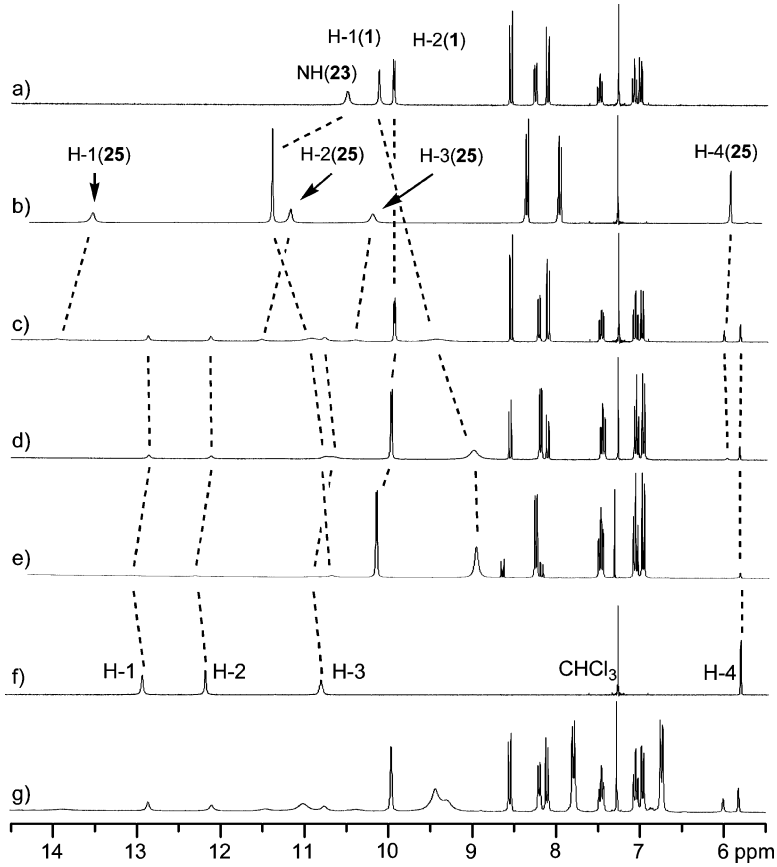
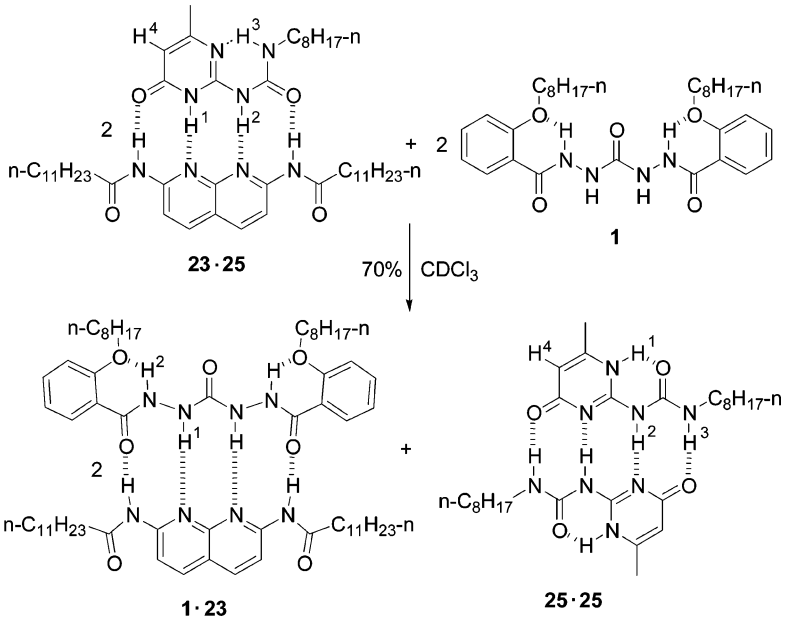


Figure 7. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 25 °C, [**23**] = 10 mM), highlighting the substitution process between **1** and **25** of **23·25**: (a) **1** + **23** (1:1), (b) **23** + **25** (1:1), (c) **1** + **23** + **25** (1:1:1), (d) **1** + **23** + **25** (3:1:1), (e) **1** + **23** + **25** (6:1:1), (f) **25** (10 mM), and (g) **1** + **2** + **23** + **25** (1:1:1:1).

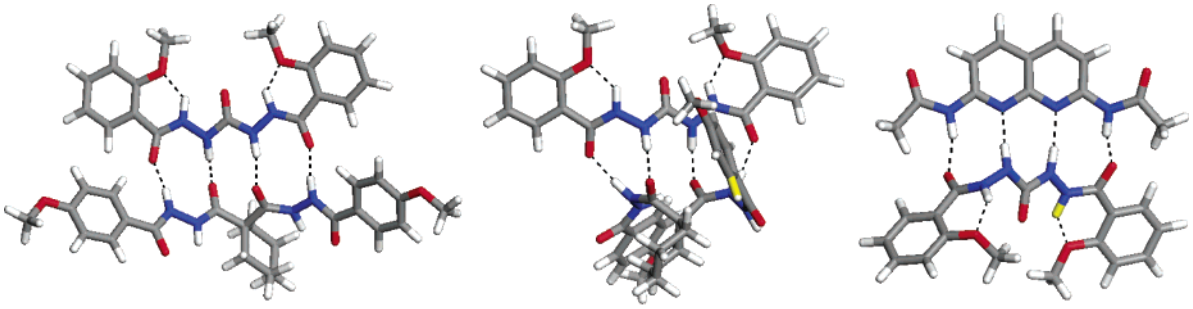
Scheme 4



solution of **23·25** in $CDCl_3$ (Figure 7c), as a result of the formation of heterodimer **1·23**. The dissociation was complete (with a lower limit of 95%, considering the sensitivity of the ^{1}H NMR measurement) after about 6 equiv of **1** was added (Figure 7e). Assuming that any other new complexes that might be formed in the mixture solution were negligible, we determined an equilibrium constant to be approximately 12 M^{-1} for the substitution process shown in Scheme 4, based on the integrating intensity of the sharp H-4 signal of **25** in the homo- and heterodimers. It is reasonable to assume that the binding constant of dimer **25·25** is the reported value of 5.7×10^7 M^{-1}

(23) (a) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (b) Ballardini, R.; Balzani, V.; Credi, A.; Gandolfi, M. T.; Venturi, M. *Acc. Chem. Res.* **2001**, *34*, 445.

(24) This kind of dimers had been reported to have four tautomeric isomers, see ref 7e.



1·2 **1·2′** **1·23**

Figure 8. Energy-minimized structures of dimers **1·2**, **1·2′**, and **1·23**. All 504of the side chains of monomers **1**, **2**, and **23** are replaced with methyl groups for clarity.

for this type of homodimers;[25] a lower limit K_{assoc} value of approximately 1.5×10^9 M^{-1} was estimated for dimer **23·25** from a simple thermodynamic circle. Direct measurement of the binding constants with the ^{1}H NMR method is obviously impossible for robust dimers such as **23·25**. This kind of competitive experiment represents an alternate approach for measuring the binding constants of highly stable hydrogen-bonded dimers.[26]

Addition of 1 equiv of **2** to the mixture solution could notably promote the reassociation of **23** and **25** to **23·25** (with an increase of ca. 10%) (Figure 7g), as a result of the competitive association of **2** with **1**. However, new low-resolved signals were also produced (Figure 7g), which indicated that new complexes might be formed between **2** and **23** or **25** in the mixture.

Because ADDA-sequenced hydrazide monomers **1** and **19** can efficiently associate with different kinds of DAAD-sequenced compounds **2**, **11**, **12**, and **23**, respectively, to form discrete heterodimers, these hydrazide monomers are obviously able to adopt quite varying conformations to achieve an optimal binding module. The density function method B3LYP at the level 3-21g basis was carried out to investigate the structures of three heterodimers, that is, **1·2**, **1·2′**, and **1·23**.[27] The energy-minimized conformations of these dimers are presented in Figure 8. It was revealed that both compounds **1** and **2** existed in a twisted conformation in all of the dimers, whereas the rigid **23** adopted a planar arrangement. The average hydrogen-bond lengths and angles between two molecules for **1·2**, **1·2′**, and **1·23** are 2.70 Å and 171.7°, 2.74 Å and 170.3°, 2.84 Å and 165.6°, respectively. As expectedly, monomer **2** displayed the most twisted conformation in dimer **1·2′**. The interaction energy of **1·2** is 49.3 kJ/mol larger than that of **1·2′**. The stronger interaction of **1·2** relative to its isomer **1·2′** is consistent with the ^{1}H NMR binding investigation mentioned above.

Conclusions

A new series of quadruply hydrogen-bonded ADDA−DAAD-sequenced heterodimers have been assembled in chloroform from readily available hydrazide derivatives, and their structures and binding stability have been investigated. Dimers **1·2** and **19·2** represent one of the most stable quadruply hydrogen-bonded modules that are constructed from nonheterocyclic building blocks.[28,29] A new kind of unique conformational isomerization of dimeric systems, generated as a result of distinct arrangement of the binding sites of the monomers, has been revealed. Selective self-assembly of single heterodimers can be achieved by simple introduction of additional intramolecular S(6) hydrogen bonds into the monomers. The association constants of the new heterodimers and the self-binding constants of the monomers are summarized in Table 1. Because the new class of heterodimers do not adopt an identical binding motif, the binding stability of these heterodimers does not fit a general incremental energy model,[30] but mainly depends on the arrangement of the binding sites and steric effect.

Table 1. A Summary of Association Constants of the New Generation of Hydrazide-Based Dimers[a]

dimer	K_{assoc} (M^{-1})	ΔG (kcal/mol)	dimer	K_{assoc} (M^{-1})	ΔG (kcal/mol)
1·1	55	2.4	**2·2**	1.1×10^2	2.8
11·11	25	1.9	**12·12**	<5	0.9
19·19	75	2.6	**19′·19′**	20	1.8
1·2	4.7×10^4	6.3	**1·11**	1.8×10^4	5.8
1·12	5.0×10^2	3.7	**19·2**	1.2×10^4	5.7
19·11	5.4×10^3	5.1	**19·12**	1.9×10^2	3.1
1·23	6.0×10^5	7.9	**19·23**	1.4×10^5	6.7

[a] The association constants are typically averages of two experiments at 25 °C, with an error of less than 15%.

For the first time, the intramolecular S(6)-type F···H−N hydrogen bond has been utilized to stabilize the binding conformation of monomers for self-assembly. Although this kind of hydrogen bond does not appear to be as strong as the classic S(6) O···H−N hydrogen bond, the considerably smaller size of fluorine, relative to the RO (even R = MeO) group, bodes well for the future application of the F···H−N hydrogen bond in self-assembly. Moreover, the unique substitution behavior displayed between **1** and dimers **23·24** and **23·25** to generate

(25) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487.
(26) Heath, R. E.; Dykes, G. M.; Fish, H.; Smith, D. K. *Chem.-Eur. J.* **2003**, *9*, 850.
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relatively weaker dimers **1·23** and **24·24** or **25·25** from stronger dimers demonstrates that inherent connections may exist between seemingly unrelated hydrogen-bonded assembling systems. Detailed investigations of these connections should point to new chemistry beyond supramolecules.

Experimental Section

General Methods. All reactions were carried out under a dry nitrogen atmosphere. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 600, 400, or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (chloroform, δ 7.27 ppm; DMSO, δ 2.49 ppm). Mass spectra (EI, ESI) were obtained on a Varian SATURN 2000 spectrometer. Vapor pressure osmometry (VPO) experiments were performed with a Knauer K-700 osmometer. IR spectra were recorded with a FT-185 infrared absorption spectrometer. X-ray analysis data were collected on an SMART APEX diffractometer. Elemental analysis was carried out at the SIOC analytical center. All solvents were dried before use following standard procedures. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica 60 coated on glass plates with F_{254} indicator. Compounds **23** was prepared according to the reported method.[8f] Theoretical calculation was performed with Gaussian 98 software on a Pentium III 866 computer.[31]

***N′,N′*-(2-Octyloxybenzoyl) Carbonic Dihydrazide (1).** To a solution of 2-octyloxybenzoic acid **3**[16b] (0.52 g, 2.10 mmol), carbohydrazide **4** (0.09 g, 1.00 mmol), and 1-hydroxybenzotriazole hydrate (HOBT) (0.32 g, 2.30 mmol) in dichloromethane−water (30 mL, 2:1) cooled in an ice-bath was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.35 g, 2.30 mmol) with stirring. The mixture was stirred for 1 h at 0 °C and then for 12 h at room temperature. Dichloromethane (20 mL) was added, and the organic phase was washed with aqueous hydrochloric acid (2 N, 20 mL), saturated sodium bicarbonate solution (20 mL), water (20 mL), and brine (20 mL), and was dried over sodium sulfate. Upon removal of the solvent, the resulting residue was purified by column chromatography (CH_2Cl_2/EtOH 60:1) to afford compound **1** (0.32 g, 60%) as a colorless crystal. Mp 108−109 °C. ^{1}H NMR ($CDCl_3$): δ 9.99 (d, 2H), 8.48 (br, 2H), 8.16 (d, d, 2H), 7.45−7.40 (m, 2H), 7.03 (t, 2H), 6.94 (d, 2H), 4.11 (t, 4H), 1.95−1.88 (m, 4H), 1.47−1.25 (m, 20H), 0.85 (t, 6H). IR (KBr): 3333, 3180, 2926, 1629, 1479, 1233, 753 cm^{-1}. ESI-MS: *m*/*z* 355 [M^+ + H]. Anal. Calcd for $C_{31}H_{46}O_5N_4$: C, 67.11; H, 8.37; N, 10.09. Found: C, 67.40; H, 7.99; N, 10.27.

Cyclohexane-1,1-dicarboxylic Acid Diethyl Ester (7). Diethyl malonate **5** (24.0 g, 0.15 mol), 1,5-dibromoalkane **6** (34.5 g, 0.15 mol), and sodium ethanolate (20.0 g, 0.33 mol) were reacted in dry ethanol (150 mL) and worked up as described in the literature.[32] After workup and column chromatography (petroleum ether (60−90 °C)/AcOEt 10:1), the title compound was obtained as a colorless oil (18.0 g, 53%). ^{1}H NMR ($CDCl_3$): δ 9.53 (s, 2H), 9.17 (s, 2H), 7.79 (d, J = 6.4 Hz, 4H), 6.72 (d, J = 6.4 Hz, 4H), 3.88 (t, J = 5.9 Hz, 4H), 2.06 (s, 4H), 1.77−1.70 (m, 4H), 1.51 (s, 4H), 1.44−1.27 (m, 38H), 0.88 (t, J = 5.9 Hz, 6H). EI-MS: *m*/*z* 228 [M^+].

Cyclohexane-1,1-dicarbonyl Chloride (8). Compound **7** was first hydrolyzed with sodium hydroxide in hot water to cyclohexane-1,1-dicarboxylic acid as described in the literature.[33] The diacid was then treated with excessive thionyl chloride under reflux for 6 h. After the solvent was removed under reduced pressure, compound **8** was obtained as an oil, which was used for the next step without further purification.

4-Dodecyloxybenzoic Acid Hydrazide (10). A suspension of 4-dodecyloxybenzoic acid methyl ester **9**[34] (3.00 g, 9.40 mmol) and hydrazine monohydrate (5.00 g) in methanol (50 mL) was heated under reflux for 10 h and then cooled to room temperature. The precipitate formed was filtered, washed with water thoroughly, and then recrystallized from ethyl acetate to afford compound **10** as colorless solid (2.80 g, 93%). Mp 94−96 °C. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, J = 8.6 Hz, 2H), 7.27 (br, 1H), 6.93 (d, J = 8.6 Hz, 2H), 4.00 (t, J = 6.5 Hz, 2H), 3.05 (br, 2H), 1.80 (q, J = 7.2 Hz, 2H), 1.46−1.27 (m, 18H), 0.89 (t, J = 6.4 Hz, 3H). EI-MS: *m*/*z* 320 [M^+]. Anal. Calcd for $C_{19}H_{32}O_2N_2$: C, 71.19; H, 10.08; N, 8.84. Found: C, 71.19; H, 9.88; N, 8.63.

Cyclohexane-1,1-dicarboxylic Acid *N′,N′*-Di(2-octyloxybenzoyl)-hydrazide (2). To a stirred solution of compound **10** (1.76 g, 5.50 mmol) and triethylamine (1.00 mL, 10.0 mmol) in chloroform (50 mL) was added dropwise a solution of compound **8** (0.57 g, 2.74 mmol) in chloroform (10 mL) over 30 min at room temperature. Stirring was continued for 24 h at room temperature. The solution was then washed with dilute hydrochloric acid (2 N), water, and was dried over sodium sulfate. After removal of the solvent, the resulting residue was purified by column chromatography (CH_2Cl_2/EtOH 60:1) to afford compound **2** as a colorless solid (1.42 g, 67%). Mp 186−188 °C. ^{1}H NMR ($CDCl_3$): δ 9.53 (s, 2H), 9.17 (s, 2H), 7.79 (d, 4H), 6.72 (d, 4H), 3.88 (t, 4H), 2.06 (s, 4H), 1.77−1.70 (m, 4H), 1.51 (s, 4H), 1.44−1.27 (m, 38H), 0.88 (t, 6H). ESI-MS: *m*/*z* 777 [M + H]$^+$. IR (KBr): 3269, 2924, 1669, 1608, 1499, 1256, 844 cm^{-1}. Anal. Calcd for $C_{46}H_{72}O_6N_4$: C, 71.08; H, 9.36; N, 7.21. Found: C, 71.03; H, 9.04; N, 6.96.

Pyridine-2-carboxylic Acid Hydrazide (14). This compound was prepared as a white solid (95%) from pyridine-2-carboxylic acid methyl ester **13** and hydrazine according to the procedure described for **10**. Mp 102−103 °C [lit.[35] 101 °C]. ^{1}H NMR ($CDCl_3$): 9.03 (br, 1H), 8.56−8.53 (m, 1H), 8.17−8.14 (m, 1H), 7.87−7.82 (m, 1H), 7.45−7.41 (m, 1H), 4.09 (br, 2H). EI-MS: *m*/*z* 138 [M + H]$^+$.

Cyclohexane-1,1-dicarboxylic Acid *N′,N′*-Di(pyridine-2-carbonyl)dihydrazide (11). This compound was prepared as a white solid (72%) from the reaction of diacyl chloride **8** and hydrazide **14** according to the procedure described for compound **2**. Mp 210−212 °C. ^{1}H NMR ($CDCl_3$): δ 9.89 (d, J = 3.0 Hz, 2H), 9.37 (d, J = 3.0 Hz, 2H), 8.55−8.59 (m, 2H), 8.14−8.10 (m, 2H), 7.87−7.81 (m, 2H), 7.48−7.44 (m, 2H), 2.20−2.16 (m, 4H), 1.64−1.62 (m, 4H), 1.48−1.40 (m, 2H). EI-MS: *m*/*z* 411 [M^+ + H]. IR (KBr): 3332, 3162, 2945, 1701, 1652, 1507, 749 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_6O_4$: C, 58.52; H, 5.41; N, 20.48. Found: C, 58.43; H, 5.40; N, 20.26.

2-Octyloxybenzoic Acid Hydrazide (16). This compound was prepared as a white solid (98%) from the reaction of 2-octyloxybenzoic acid methyl ester **15**[28c] with hydrazine according to the procedure described for **10**. Mp 76 °C. ^{1}H NMR ($CDCl_3$): δ 9.06 (s, 1H), 8.21 (d, d, J = 7.8 Hz, 2.1 Hz, 1H), 7.43 (t, d, J = 7.7 Hz, 1.8 Hz, 1H), 7.07 (t, d, J = 8.7 Hz, 0.9 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 4.12 (t, J = 6.6 Hz, 2H), 3.90 (br, 2H), 1.91−1.84 (m, 2H), 1.50−1.26 (m, 10H), 0.87 (t, J = 6.9 Hz, 3H). EI-MS: *m*/*z* 265 [M^+ + H].

Cyclohexane-1,1-dicarboxylic Acid *N′,N′*-Di(2-octyloxycarbonylbenzoyl)dihydrazide (12). This compound was prepared as a white solid in 55% yield from **8** and **16** according to the procedure described for compound **1**. Mp 136−137 °C. ^{1}H NMR ($CDCl_3$): δ 10.66 (d, J =

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6.6 Hz, 2H), 9.57 (d, J = 6.0 Hz, 2H), 8.19 (d,d, J = 8.1 Hz, 1.5 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.06 (t, J = 8.1 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 4 Hz), 2.18 (t, J = 5.4 Hz, 4H), 2.03−1.98 (m, 4H), 1.66 (s, 4H), 1.54−1.27 (m, 22H), 0.86 (t, J = 6.9 Hz, 6H). IR (KBr): 3368, 2926, 1701, 1658, 1625, 1469, 1232, 755 cm^{-1}. ESI-MS: m/z 665 [M^+ + H]. Anal. Calcd for $C_{28}H_{56}N_4O_6$: C, 68.63; H, 8.51; N, 8.43. Found: C, 68.75; H, 8.56; N, 8.46.

***N′,N′*-(2-Fluorobenzoyl) Carbonic Dihydrazide (17).** This compound was prepared as a white solid (75%) from the reaction of **4** and **18** according to the procedure described for compound **1**. Mp 190−191 °C. ^{1}H NMR ($CDCl_3$): δ 8.82 (d, J = 11.4 Hz, 2H), 8.36 (s, 2H), 8.00 (t, J = 7.8 Hz, 2H), 7.50−7.43 (m, 2H), 7.20 (t, J = 7.5 Hz, 2H), 7.11−7.04 (m, 2H). EI-MS: m/z 334 [M^+]. IR (KBr): 3321, 1661, 1479, 1274, 758 cm^{-1}. Anal. Calcd for $C_{15}H_{12}F_2N_4O_3$: C, 53.89; H, 3.63; N, 16.76. Found: C, 53.80; H, 3.67; N, 17.13.

2-Fluoroisophthalic Acid (21). A suspension of 2-fluoro-*m*-xylene **20** (0.50 g, 4.00 mmol), cetyltrimethylammonium bromide (0.10 g), and potassium permanganate (2.50 g, 16.0 mmol) in water (25 mL) was heated under reflux for 3 h. The mixture was cooled to room temperature, and the solid was filtered off and washed with water (10 mL). The filtrate was acidified with concentrated hydrochloric acid to pH = 5. The resulting precipitate was filtered, washed with water (3 × 10 mL), and dried to give the title compound as a white solid (0.30 g, 41%). Mp > 250 °C. ^{1}H NMR (DMSO-d_6): δ 13.49 (br, 2H), 8.04 (t, J = 6.9 Hz, 2H), 7.38 (t, J = 8.4 Hz, 1H). EI-MS: m/z 184 [M^+]. Anal. Calcd for $C_8H_5FO_4$: C, 52.18; H, 2.74. Found: C, 52.26; H, 3.08.

2-Fluoroisophthalic Acid Monooctyl Ester (22). To a solution of compound **21** (0.73 g, 3.80 mmol) and *n*-octanol (5 mL) in THF (20 mL) was added dropwise concentrated H_2SO_4 (0.3 mL) under stirring at room temperature. The solution was heated under reflux for 24 h and then cooled to room temperature. Dichloromethane (50 mL) was added, and the organic phase was washed with water (3 × 30 mL), brine (30 mL), and was then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give an oily residue, which was purified by column chromatography (CH_2Cl_2/EtOH 20:1). The title compound was obtained as a white solid (0.57 g, 49%). Mp 92−93 °C. ^{1}H NMR ($CDCl_3$): δ 8.20−8.15 (m, 2H), 7.32 (t, J = 7.8 Hz, 1H), 4.36 (t, J = 6.9 Hz, 2H), 1.80−1.75 (m, 2H), 1.44−1.28 (m, 10H), 0.87 (t, J = 6.3 Hz, 3H). EI-MS: m/z 296 [M^+]. Anal. Calcd for $C_{16}H_{21}FO_4$: C, 64.84; H, 7.16. Found: C, 64.80; H, 7.29.

***N′,N′*-(3-Octyloxycarbonyl-2-fluorobenzoyl) Carbonic Dihydrazide (19).** This compound was prepared as a white solid (78%) from the reaction of compounds **8** and **22** following the procedure described above for preparing **1**. Mp 122−123 °C. ^{1}H NMR ($CDCl_3$): δ 9.11 (d, J = 9.6 Hz, 2H), 8.69 (s, 2H), 8.10−8.04 (m, 2H), 7.96−7.91 (m, 2H), 7.18 (t, J = 7.5 Hz, 2H), 4.25 (t, J = 6.9 Hz, 4H), 1.73−1.64 (m, 4H), 1.40−1.26 (m, 20H), 0.86 (t, J = 6.6 Hz, 6H). ESI-MS: m/z 669.3 [M^+ + Na]. Anal. Calcd for $C_{33}H_{44}F_2N_4O_7$: C, 61.27; H, 6.87; N, 8.66. Found: C, 61.35; H, 6.92; N, 8.71.

1-Octyl-3-(4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidin-2-yl)urea (24). A suspension of 2-amino-3*H*-pyrido[2,3-*d*]pyrimidin-4-one[36] (2.00 g, 12.4 mmol) and *n*-octyl isocyanate (2.0 mL, 12.4 mmol) in THF (200 mL) was stirred under reflux for 6 days, and the solvent was then removed under reduced pressure. The resulting residue was washed thoroughly with petroleum ether (30−60 °C) and then purified by column chromatography (MeOH/CH_2Cl_2 1:25) to afford **19** as a white solid (0.50 g, 14%). Mp 173−175 °C. ^{1}H NMR (DMSO-d_6): δ 11.20 (s, 1H), 9.76 (s, 1H), 8.78 (s, 1H), 8.33 (s, 1H), 7.69 (s, 1H), 7.22−7.24 (m, 1H), 3.17−3.20 (m, 2H), 1.42−1.44 (m, 2H), 1.22−1.27 (m, 10H), 0.82 (t, J = 5.5 Hz, 3H). FAB-MS: m/z 318 [M^+ + H]. Anal. Calcd for $C_{16}H_{23}N_5O_2$: C, 60.55; H, 7.30; N, 22.07. Found: C, 60.35; H, 7.21; N, 21.88.

1-(6-Methyl-4-oxo-1,4-dihydropyrimidin-2-yl)-3-octylurea (25). A suspension of 2-amino-4-hydroxy-6-methylpyrimidine (0.50 g, 0.40 mmol) and *n*-octyl isocyanate (0.62 g, 0.40 mmol) in THF (120 mL) was heated at 90 °C for 48 h. The solvent was then removed, and the resulting residue was washed thoroughly with cooled ether to give a solid, which was subjected to flash chromatography (CH_2Cl_2/MeOH 10:1) to afford compound **25** (1.08 g, 97%) as a white solid. Mp 171−173 °C. ^{1}H NMR: δ 13.14 (s, 1H), 11.85 (s, 1H), 10.13 (s, 1H), 5.81 (s, 1H), 3.20−3.26 (m, 2H), 2.22 (s, 3H), 1.54−1.61 (m, 2H), 1.25−1.30 (m, 10H), 0.86 (t, J = 6.6 Hz, 3H). EI-MS: m/z 280 [M^+]. Anal. Calcd for $C_{14}H_{24}N_4O_2$: C, 59.98; H, 8.63; N, 19.98. Found: C, 59.84; H, 8.60; N, 19.97.

^{1}H NMR Binding Studies. All ^{1}H NMR binding studies were carried out at 25 °C. $CDCl_3$ used in binding studies was passed though a short column of dry, activated basic alumina prior to use. Volumetric flasks and syringes used in preparing solutions were washed with dried dichloromethane and dried in a vacuum before use. Samples (usually 0.6 mL) were prepared from stock solutions, transferred to the NMR tubes, and diluted accordingly with syringes. For one series, usually 13−20 samples were prepared, and binding constants reported typically are averages of two experiments, which were obtained by fitting chemical shift change data to 1:1 binding isotherms with standard nonlinear curve-fitting procedures.[17] The nonlinear equations were derived from mass-balance equations and the relationship between the concentrations of free and complexed samples and the weighted chemical shifts under the condition of rapid exchange.[17] The data were obtained with 400 or 600 MHz (for samples of dilute concentration) spectrometers.

X-ray Data. Compound **1** was crystallized from chloroform by slow evaporation of solvent at room temperature. Crystal size, 0.423 × 0.347 × 0.128 mm; space group, *P*-1 (triclinic); unit cell dimensions, a = 9.3928(13) Å, b = 9.5527(14) Å, c = 18.941(3) Å, α = 76.966(3)°, β = 78.834(3)°, γ = 74.785(3)°; volume, 1581.3(4) (Å)^3.

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Supporting Information Available: (Partial) 2D-NOESY spectra (400 MHz) of heterodimers **1·2**, **1·11**, **1·12**, **19·2**, **19·11**, **19·12**, **1·23**, and **19·23** in $CDCl_3$, scheme of the thermodynamic cycle for the calculation of the binding constant of complex **23·25**, and X-ray crystallographic data for **1** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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