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Assessment of intermolecular N—H···F and N—H···Cl hydrogen bonding in stabilising hetero- and homodimers in solution

Yan-Hua Liu[a], Xiao-Na Xu[a], Xin Zhao[a]* and Zhan-Ting Li[a,b]*

[a]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P.R. China;* [b]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P.R. China*

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This paper describes the first assessment of intermolecular weak N—H···F and N—H···Cl hydrogen bonding in stabilising hetero- and homodimers in solution. Aromatic amide and urea monomers have been designed and synthesised. The association constants of the heterodimers formed by two complementary monomers and the homodimers formed by self-complementary monomers have been determined by using ^{1}H titration and dilution experiments. The results show that both N—H···F and N—H···Cl hydrogen bonds are able to stabilise the corresponding dimers to a measurable extent, even though the stability of the dimers is generally low.

Keywords: supramolecule; hydrogen bond; fluorine acceptor; chlorine acceptor; dimerisation

Introduction

Hydrogen bonding is the most versatile non-covalent force in supramolecular chemistry (*1*). For amide derivatives, it is well known that O and N atoms are strong hydrogen-bonding acceptors (*2*). Although F atom has the highest electronegativity and the electronegative of Cl atom is also substantially higher than that of H atom, it had been generally deemed that, different from the F^- and Cl^- anions that are very strong hydrogen-bonding acceptors, both F and Cl atoms in organic compounds are very weak hydrogen-bonding acceptors (*3–5*). For F atom, this phenomenon had been attributed to its low polarisability and tightly contracted lone pairs (*5*), whereas, for Cl atom, the increased van der Waals radius and decreased electron cloud density make it more difficult to engage in hydrogen bonding with amide or hydroxyl derivatives (*6*). Searches of crystal structures from the Cambridge Structural Database showed that only in the absence of a better acceptor can such hydrogen bonds be formed (*6*, *7*).

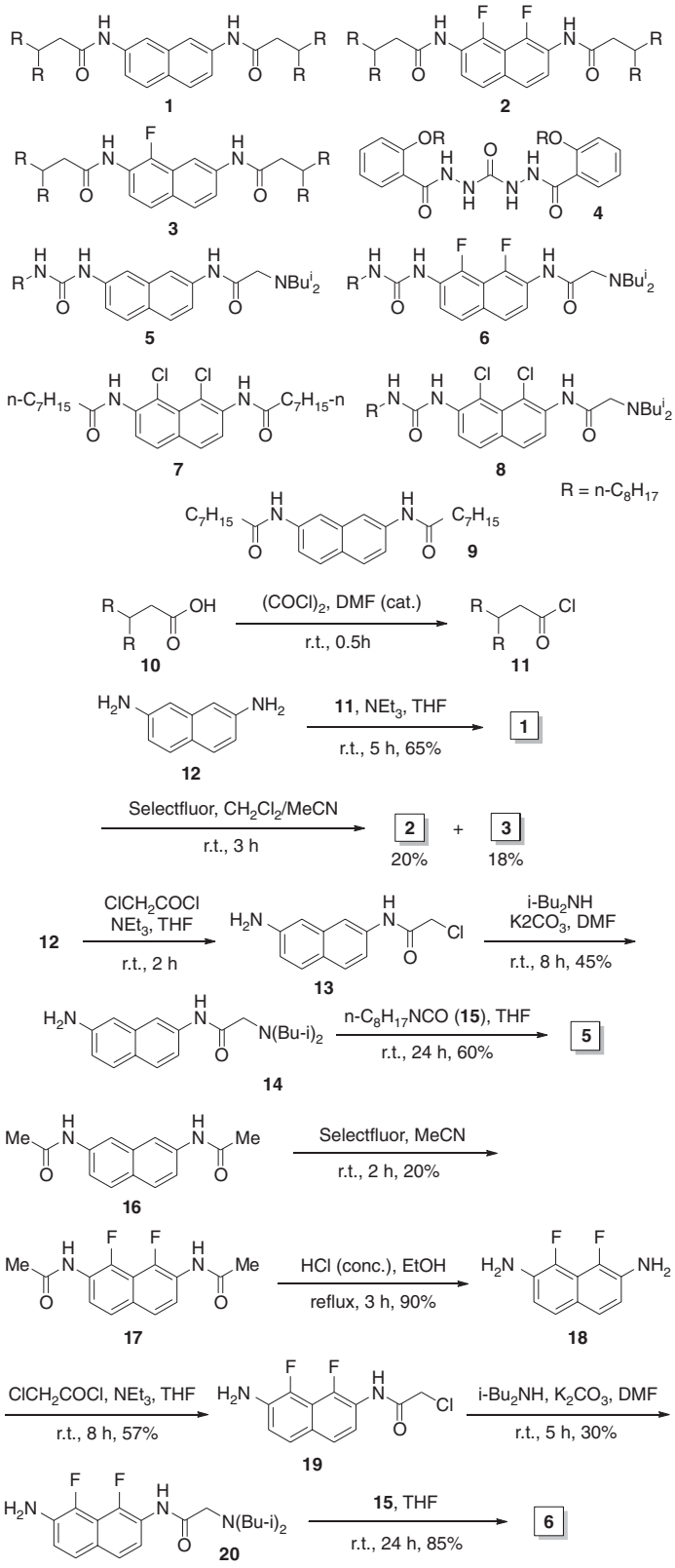
We previously established that aromatic amides can form intramolecular five- and six-membered N—H···F hydrogen bonding (*8*). We also found that, when the strong intermolecular N—H···O=C hydrogen bonding is suppressed by introducing large steric group(s) or additional intramolecular hydrogen bonding, both five and six-membered intramolecular N—H···Cl hydrogen bonding can be formed by aromatic amides (*9*). Given the increasing importance of weak hydrogen bonds in crystal engineering (*10*), chemical biology and drug design (*11*), we became interested in exploiting if intermolecular N—H···F and N—H···Cl hydrogen bonds can enhance the stability of dimeric supramolecules in solution. To the best of our knowledge, no studies were reported to assess the contribution of these two intermolecular hydrogen bonds in stabilising supramolecular systems, even though they have been proposed in solution and observed in crystal structures (*12*, *13*). In this paper, we describe the evaluation of the stability of a series of new heterodimers in organic solvents which reveals that both N—H···F and N—H···Cl intermolecular hydrogen bonds exist in solution and stabilise the heterodimers to a measurable extent.

Results and discussion

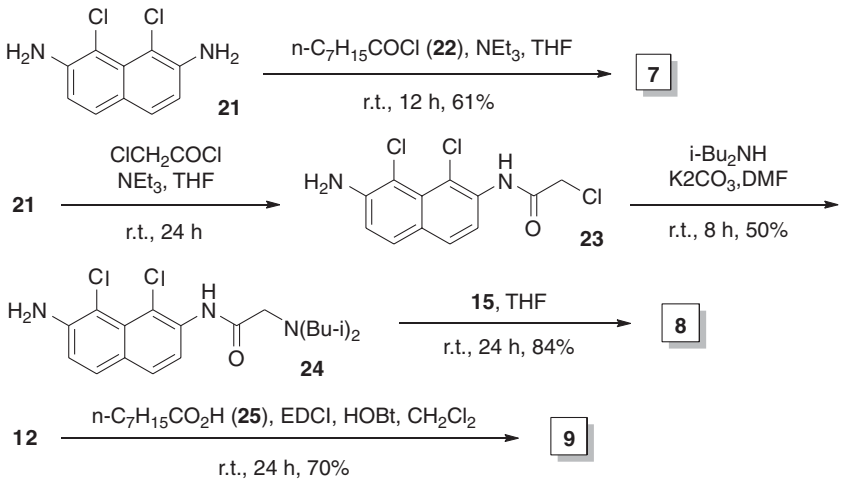
Compounds **1**–**9** were prepared to investigate the contribution of intermolecular N—H···F and N—H···Cl hydrogen bonding in stabilising N—H···O hydrogen-bonded heterodimers of aromatic amide and urea derivatives. It was expected that the intermolecular N—H···F and N—H···Cl hydrogen bonding, if any, would be quite weaker. Thus, in order to make it possible to quantitatively evaluate their contribution, fluorine- and chlorine-free analogues were designed, which were expected to form heterodimers of low stability and, for all the compounds, long aliphatic chains were introduced to provide solubility in organic solvents of low polarity.

The synthetic routes for compounds **1**–**3**, **5** and **6** are provided in Scheme 1. For the preparation of **1**, acid **10** (*14*) was first converted into acyl chloride **11**, which was then treated with diamine **12** (*15*) to afford **1** in 65% yield. Further treatment of **1** with Selectfluor (*16*) in the mixture

*Corresponding author. Email: xzhao@mail.sioc.ac.cn; ztli@mail.sioc.ac.cn



Scheme 1. Synthesis of compounds **1**–**3**, **5** and **6**.



Scheme 2. Synthesis of compounds **7**–**9**.

of acetonitrile and dichloromethane afforded **2** and **3** in 20% and 18% yields, respectively. For the synthesis of compound **5**, compound **13** was first prepared from the reaction of **12** and chloroacetyl chloride and then treated with di(iso-butyl)amine to produce **14**, which further reacted with *n*-octyl isocyanate **15** in tetrahydrofuran (THF) to afford **5**. Then, diamide **16** (*17*) was treated with Selectfluor in acetonitrile to produce **17** in 20% yield. Compound **17** was further converted into **18** in refluxed hydrochloric acid. The obtained diamine **18** reacted with chloroacetyl chloride to give **19** in 57% yield. Treatment of **19** with di(iso-butyl)amine in dimethylformamide (DMF) afforded **20** in 30% yield. Compound **20** further reacted with **10** to give **6** in 85% yield.

Compound **7** was prepared from the reaction of **21** (*18*) and **22** in 61% yield (Scheme 2). Starting from **21**, compound **8** was prepared through three-step reactions, while compound **9** was prepared from the coupling reaction of **12** with **25**. Compound **4** was prepared according to a previously reported method (*19*).

The binding between compounds **1** and **4** in $CDCl_3$ was then investigated by ^{1}H NMR titration experiments. Adding 7.5 equiv. of **4** to the solution of **1** (10 mM) in $CDCl_3$ caused the NH signal of **1** to shift downfield by 0.59 ppm (Supporting Information, Figure S1). By fitting a 1:1 binding motif for the change of the chemical shift of this signal (*19*, *20*), we derived an association constant (K_a) of 5.5 ± 0.51 M^{-1} for heterodimer **1**·**4** (Supporting Information, Figure S2). With a mixture of $CDCl_3$ and C_6D_6 (1:4) as the solvent, adding 6.8 equiv. of **4** to the solution of **1** could cause the NH signal of the latter to shift downfield by 1.56 ppm, and a K_a of 19.3 ± 1.8 M^{-1} was derived from titration experiments (Supporting Information, Figures S3 and S4). The intramolecular six-membered N—H···O hydrogen bonding and the rigid planarity of the backbone of **4** had been established previously (*19*). Thus, it is reasonable to propose that the two compounds formed a doubly hydrogen-bonded dimer (Chart 1).

^{1}H and ^{19}F NMR titrations were then performed for **2** (10 mM) by **4** in $CDCl_3$. Adding 6.3 equiv. of **4** caused the NH signal of **2** to shift downfield by 0.12 ppm and the F signal in the ^{19}F spectrum to shift downfield by 0.43 ppm (Supporting Information, Figures S5 and S7). From the ^{1}H NMR titration data, the K_a of the 1:1 complex **2**·**4** was determined to be 11.2 ± 1.1 M^{-1} (Supporting Information, Figure S6). Because the intramolecular five-membered N—H···F hydrogen bonding has been well established (*8*, *9*), the two compounds should form a heterodimer through four intermolecular hydrogen bonds (Chart 1), that is, two N—H···O and two N—H···F hydrogen bonds. In the mixture of $CDCl_3$ and C_6D_6 (1:4, v/v), similar downfield shifting was also observed in the ^{1}H and ^{19}F NMR spectra (Supporting Information, Figures S8 and S10), and the K_a of the heterodimer was determined to be 25.8 ± 2.1 M^{-1} (Supporting Information, Figure S9). Both values of dimer **2**·**4** are notably higher than the corresponding values of dimer **1**·**4**, indicating that the intermolecular N—H···F hydrogen bonding should exist in both solvents to stabilise the heterodimer to a measurable extent.

^{1}H NMR titrations were then conducted for compound **3** (10 mM) by **4** in $CDCl_3$. It was observed that 10.6 equiv. of **4** could cause the NH signal of **1** to shift downfield by 0.14 ppm (Supporting Information, Figure S11). From the titration experiments, a K_a of 8.2 ± 1.4 M^{-1} was derived for their 1:1 complex **3**·**4** (Supporting Information, Figure S12), which was higher than that of dimer **1**·**4**, but lower than that of dimer **2**·**4**. The ^{19}F signal of **3** was also found to shift downfield by 0.30 ppm in the presence of 10.6 equiv. of **4** (Supporting Information, Figure S13). This observation further supported that the two com-

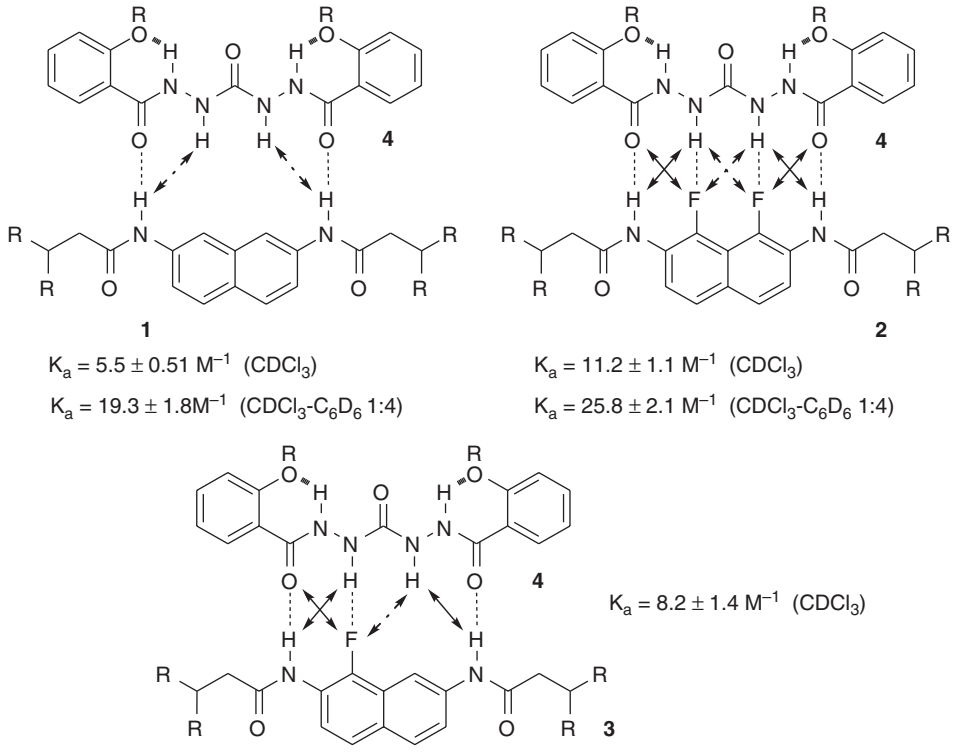


Chart 1. Binding patterns of heterodimers **1**·**4**, **2**·**4** and **3**·**4** and the possible secondary electrostatic interactions, marked by solid arrows for repulsion and dotted arrows for attraction.

pounds formed a complex through three intermolecular hydrogen bonds, that is, two N—H···O hydrogen bonds and one N—H···F hydrogen bond (Chart 1).

The earlier results show that intermolecular N—H···F hydrogen bonding does exist in chloroform or its mixture with a solvent of lower polarity, but is quite weak. Thus, we may propose that the intermolecular N—H···O and N—H···F hydrogen bonds stabilised each other.

The fact that the intermolecular N—H···F hydrogen bonding is weak should be mainly attributed to the intrinsic weakness of fluorine in organic molecules. However, for dimers **2**·**4** and **3**·**4**, secondary electrostatic interactions might also play an important role (*21*). Compared with dimer **1**·**4**, dimer **2**·**4** may produce two more electrostatic repulsions between F and O atoms and two more electrostatic attractions between F and H atoms (Chart 1). Corey–Pauling–Koltun (CPK) space-filling modelling for the planar conformations of the two compounds revealed that the electrostatic repulsion between the larger F and O atoms should be larger than the electrostatic attraction between the F and smaller H atoms, and thus the secondary interactions as a whole were unfavourable for the stability of the dimers.

To get deeper insight into the intermolecular N—H···F hydrogen bonding, urea derivatives **5** and **6** were also prepared and investigated. The ^{1}H NMR dilution experiments for control **5** in $CDCl_3$ were first performed. Reducing the concentration from 37 to 0.2 mM caused the signals of H-a and H-b to shift upfield by 0.67 and 0.99 ppm, whereas the signal of H-c did not show observable shifting (Supporting Information, Figure S14). These results indicated that H-c was not engaged in intermolecular hydrogen bonding due to its formation of intramolecular N—H···N hydrogen bonding with the amino group. This intramolecular hydrogen bonding was also evidenced by the fact that the signal of H-c appeared in the downfield area (9.55 ppm) related to that of the NH signal of **1** (7.25 ppm, 10 mM). By fitting the data of H-a and H-b to a 1:1 binding pattern, we obtained the same K_a of $8.6 \pm 0.53\ M^{-1}$ for its homodimer (Supporting Information, Figure S15), which may exist in two different forms, that is, **5**·**5** and **5**·**5**′, depending on the relative orientation of the two molecules (Chart 2). The ^{1}H NMR dilution experiments of **5** were also preformed in C_6D_6. Decreasing the concentration from 35 M to 0.2 mM caused the signals of H-a and H-b to shift upfield by 2.53 and 2.84 ppm, respectively (Supporting Information, Figure S16). From both sets of titration data, a K_a of about $50.7 \pm 6.2\ M^{-1}$ was obtained (Supporting Information, Figure S17). The signal of H-c was almost not shifted (9.48 ppm), again indicating that it was only involved with intramolecular hydrogen bonding.

We then performed ^{1}H and ^{19}F NMR dilution experiments, from 35 to 0.2 mM, for compound **6** in

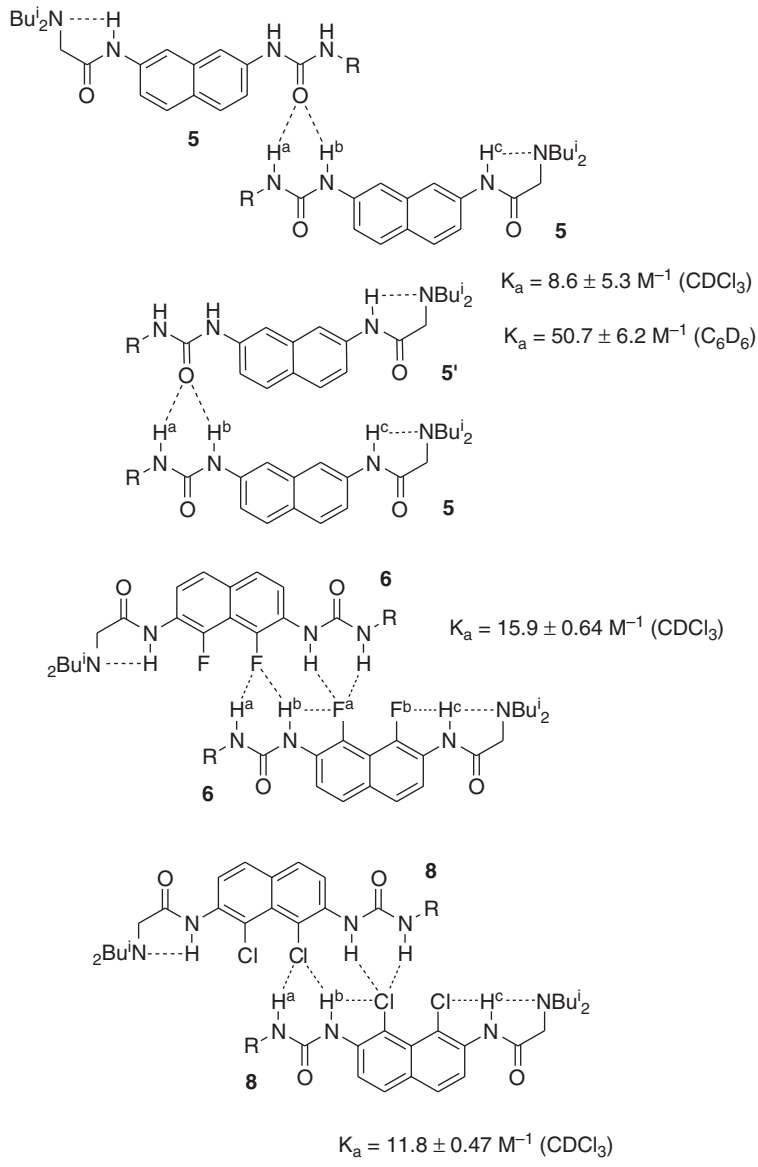


Chart 2. Self-binding patterns of compounds **5**, **6** and **8**.

$CDCl_3$. As expected, the signal, appearing at 9.80 ppm, of H-c did not shift, indicating that it also only formed intramolecular hydrogen bonding (Supporting Information, Figure S18). In contrast, the signals of H-a and H-b were shifted upfield by 0.74 and 0.62 ppm, respectively. From the titration data, a K_a of 15.9 ± 0.64 M^{-1} was obtained for the 1:1 complex **6**·**6** (Supporting Information, Figure S19). Upon diluting the solution from 35 to 0.2 mM, the signal of F-a in the ^{19}F NMR shifted upfield by 1.36 ppm (Supporting Information, Figure S20). In contrast, the signal of F-b slightly shifted downfield by 0.05 ppm. These results indicated that F-a formed intermolecular F···H—N hydrogen bonding to lead to the formation of a homodimer, but F-b did not. The slight upfield shifting of F-b at high concentrations may be attributed to the shielding effect of the naphthalene ring of another molecule of the dimer. Considering the ^1H NMR observation, the results supported that the homodimer of **6** might be stabilised by bifurcated F···H—N hydrogen bonding of F-a (Chart 2).

We then investigated the possibility of the Cl atoms of **7** and **8** to form intermolecular Cl···H—N hydrogen bonding. The ^1H NMR spectrum of the 1:1 solution of **7** and **4** (5 mM) in $CDCl_3$ was first recorded (Supporting Information, Figure S21). Compared with the corresponding signal in the ^1H NMR spectrum of pure **7** of the identical concentration, the NH signal of **7** in the mixture did not shift, suggesting that no intermolecular hydrogen bonding was formed between this N*H* atom and the carbonyl O atom of **4**, which also excluded the possibility of the intermolecular Cl···H—N hydrogen bonding and

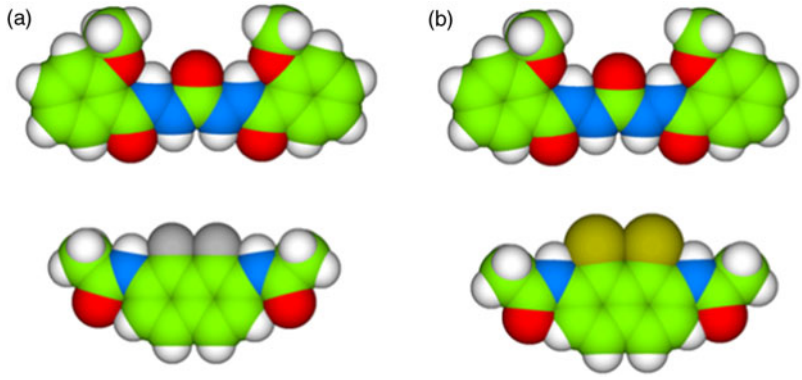


Figure 1. CPK modelling of compounds (a) **4** versus **2** and (b) **4** versus **7**.

the DAAD-ADDA (D: hydrogen-bonding donor, A: hydrogen-bonding acceptor) quadruple hydrogen-bonding heterodimer **4·7**. CPK modelling showed that (Figure 1), due to the large van der Waals radius of the Cl atom, electrostatic repulsion would occur between it and the carbonyl O atom before intermolecular hydrogen bonding could be formed. Thus, such DAAD-ADDA-styled binding could not take place. The H-a signal of **4** in the mixture shifted downfield by 0.05 ppm, indicating that it formed weak intermolecular hydrogen bonding with the carbonyl O atom of **7** (Chart 3). The ^{1}H NMR spectrum of the 1:1 (5 mM) mixture of **9** and **4** in $CDCl_3$ was also recorded (Supporting Information, Figure S22). Compared with the corresponding signals of the pure samples, the signals of NH of **9** and H-a of **4** both shifted downfield by 0.05 ppm, suggesting that both NH atoms were involved in intermolecular hydrogen bonding by forming heterodimers **4·9** and **4·9′** (Chart 3).

Finally, the self-binding of compound **8** was studied in $CDCl_3$ by ^{1}H NMR dilution experiments (Supporting Information, Figure S23). Diluting the solution from 50 to 0.2 mM did not lead to any shifting for the signal of H-c, supporting that this N*H* atom was also only engaged in intramolecular hydrogen bonding. Upon dilution, the signals of H-a and H-b were shifted upfield by 0.98 and 0.30 ppm, respectively. From both sets of data, a K_a of 11.8 ± 0.47 M^{-1} was obtained for homodimer **8·8** by fitting the data to a 1:1 binding mode (Supporting Information, Figure S24). This value was lower than that of dimer **6·6**, but higher than that of **5·5**, suggesting that intermolecular weak Cl···H—N hydrogen bonding could exist at high concentrations. Considering that the Cl atom is weaker than the F atom as

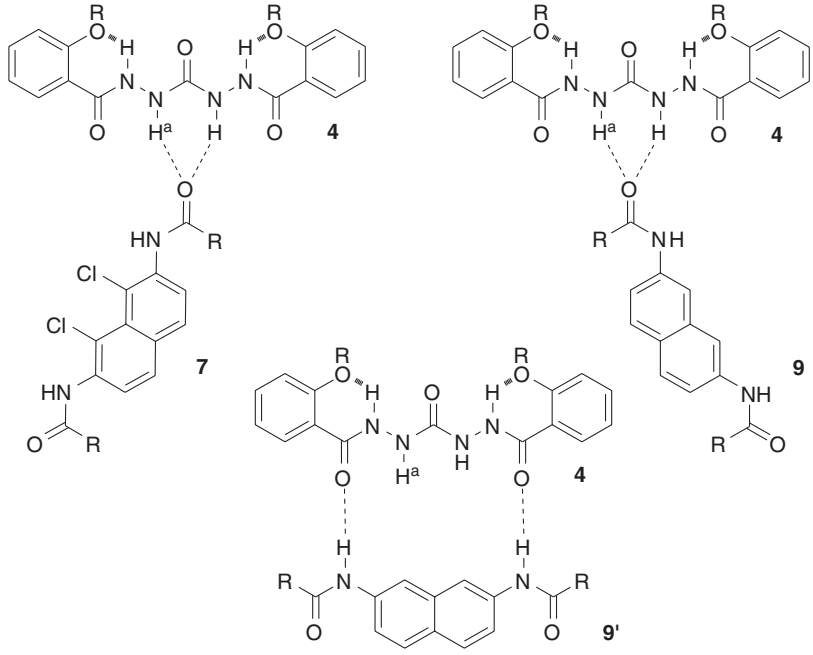


Chart 3. Proposed binding patterns between compounds **4**, **7** and **9**.

a hydrogen-bonding acceptor and has a larger van der Waals radium, we conjecture that only the Cl atom adjacent to the urea unit was engaged in the intermolecular hydrogen bonding (Chart 2) to form a binding motif similar to that of **6**.

Conclusion

We have for the first time assessed the contribution of intermolecular F···H—N and Cl···H—N hydrogen bonding in stabilising dimers formed by aromatic amide and urea derivatives. It is revealed that, although the two hydrogen bonds are very weak in solution, they can be formed when strong intermolecular O···H—N hydrogen bonding is present. Generally, the intermolecular F···H—N hydrogen bonding is stronger than the intermolecular Cl···H—N hydrogen bonding, which is consistent with the relative stability of the two intramolecular ones. Because both F···H—N and Cl···H—N hydrogen bonds are very weak, it should be cautious to propose them for supramolecular systems in solvents of even low polarity.

Experimental section

Compound 1

A solution of acid **10** (0.40 g, 1.30 mmol) and DMF (0.05 mL) in oxalyl chloride (0.5 mL, 5.8 mmol) was stirred for 0.5 h and then concentrated *in vacuo* to give **11** as an oil. The acyl chloride was dissolved in THF (5 mL) and the solution was added to a solution of compound **12** (0.10 g, 0.60 mmol) and $N(CH_2CH_3)_3$ (0.2 mL, 1.40 mmol) in THF (30 mL). After stirring for 5 h, the solution was concentrated with a rotavapor. The resulting residue was triturated with dichloromethane (50 mL). The solution was washed with diluted hydrochloric acid (0.5 N, 10 mL × 2), water (20 mL) and brine (25 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting crude product was subjected to column chromatography (petroleum ether:AcOEt, 3:1) to give compound **1** as a white solid (0.30 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.71 (d, $J = 8.8$ Hz, 2H), 7.47 (d, $J = 7.8$ Hz, 2H), 2.30 (d, $J = 6.8$ Hz, 4H), 2.11–1.90 (m, 2H), 1.47–1.13 (m, 56H), 0.86 (t, $J = 6.7$ Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 135.9, 134.0, 128.1, 127.8, 119.6, 116.8, 42.9, 35.5, 33.9, 31.9, 30.1, 29.7, 29.4, 26.7, 22.7, 14.1. MS (MALDI-TOF): *m*/*z* 719.4 $[M + H]^+$. HR-MS (MALDI-FT): calcd for $C_{48}H_{83}N_2O_2$: 719.6449 $[M + H]^+$. Found: 719.6457.

Compounds 2 *and* 3

To a solution of compound **1** (0.20 g, 0.30 mmol) in acetonitrile (40 mL) and dichloromethane (80 mL) was added selectfluor (0.90 g, 1.10 mmol). The solution was stirred for 3 h and then concentrated. The resulting residue was dissolved in dichloromethane (100 mL) again and the solution was washed with water (50 mL × 3) and brine (50 mL) and dried over sodium sulfate. After the solvent was removed, the resulting residue was subjected to column chromatography (CH_2Cl_2) to give compounds **2** (42 mg, 20%) and **3** (37 mg, 18%) as waxy solids. Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27–8.00 (m, 2H), 7.78 (s, 2H), 7.31 (d, $J = 9.0$ Hz, 2H), 2.41 (d, $J = 6.9$ Hz, 4H), 2.12–1.87 (m, 2H), 1.58–1.15 (m, 56H), 0.87 (t, $J = 6.7$ kHz, 12H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −138.3 (s, 1F). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 146.7, 146.5, 144.0, 143.9, 128.9, 123.2, 120.7, 113.0, 42.8, 35.6, 33.9, 31.9, 30.0, 29.6, 29.4, 26.7, 22.7, 14.1. MS (MALDI-TOF): *m*/*z* 755.6 $[M + H]^+$. HR-MS (MALDI-FT): calcd for $C_{48}H_{81}F_2N_2O_2$ $[M + H]^+$: 755.6261. Found: 755.6274. Compound **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42–8.22 (m, 2H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.60–7.34 (m, 4H), 2.35 (dd, $J_1 = 14.3$ Hz, $J_2 = 6.8$ Hz, 4H), 2.01 (s, 2H), 1.46–1.11 (m, 56H), 0.86 (t, $J = 6.1$ Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.0, 148.8, 146.3, 136.2, 128.1, 123.2, 120.1, 108.8, 42.8, 35.73, 35.63, 34.0, 32.1, 30.1, 29.8, 29.5, 26.8, 22.8, 14.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ: −140.1 (s, 1F). MS (MALDI-TOF): *m*/*z* 737.4 $[M + H]^+$. HR-MS (MALDI-FT): calcd for $C_{48}H_{82}F_1N_2O_2$ $[M + H]^+$: 737.6355. Found: 737.6364.

Compound 14

To a solution of compound **12** (0.10 g, 0.60 mmol) and NEt_3 (0.09 mL, 0.6 mmol) in THF (40 mL) was added chloroactyl chloride (0.05 mL, 0.6 mmol). The solution was stirred for 2 h and then concentrated with a rotavapor. The resulting residue was triturated with dichloromethane (20 mL) and the solution was washed with water (10 mL × 3) and brine (10 mL) and dried over sodium sulfate. The solution was then concentrated *in vacuo* to afford **13**. The crude product was not further purified and dissolved in DMF (5 mL). To the solution were added potassium carbonate (0.30 g, 2.20 mmol) and di(iso-butyl)amine (0.22 mL, 1.30 mmol), and the solution was stirred for 8 h and then concentrated under reduced pressure. The resulting residue was triturated with dichloromethane (200 mL). The solution was washed with water (100 mL × 3) and brine (100 mL) and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the resulting slurry was subjected to column chromatography (petroleum ether:AcOEt, 4:1) to afford compound **14** as a white solid (93 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.08 (s, 1H), 7.61 (dd, $J_1 = 16.4$ Hz, $J_2 = 8.6$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 1H), 6.95 (s, 1H), 6.91–6.77 (m, 1H), 3.87 (s, 2H), 3.16 (s, 2H), 2.27 (d, $J = 7.1$ Hz, 4H), 1.84 (dt, $J_1 = 13.3$ Hz, $J_2 = 6.7$ Hz, 2H),

0.98 (d, $J = 6.5$ Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 144.8, 135.7, 135.6, 128.9, 128.7, 125.0, 117.2, 115.7, 113.6, 108.4, 64.3, 60.7, 26.3, 21.0. MS (ESI): *m/z* 328.4 $[M + H]^+$. HR-MS (ESI): calcd for $C_{20}H_{30}N_3O$ $[M + H]^+$: 328.2383. Found: 328.2395.

Compound 5

To a solution of compound **14** (45 mg, 0.10 mmol) in THF (5 mL) was added *n*-octyl isocyanate **15** (0.04 mL, 0.20 mmol). The solution was stirred for 24 h and then concentrated with a rotavapor. The resulting residue was dissolved in dichloromethane (5 mL). The solution was washed with saturated sodium bicarbonate solution (3 mL × 2), water (3 mL) and brine (3 mL) and dried over sodium sulfate. Upon removal of the solvent, the resulting slurry was subject to column chromatography (petroleum ether: AcOEt, 3:1) to give compound **5** as a white solid (40 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.10 (s, 1H), 7.72 (dd, $J_1 = 16.5$ Hz, $J_2 = 7.8$ Hz, 3H), 7.47 (d, $J = 8.5$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 6.68 (s, 1H), 4.99 (s, 1H), 3.25 (dd, $J_1 = 13.3$ Hz, $J_2 = 6.7$ Hz, 2H), 3.17 (s, 2H), 2.29 (d, $J = 7.2$ Hz, 4H), 1.95–1.75 (m, 2H), 1.57–1.42 (m, 2H), 1.38–1.11 (s, 10H), 0.99 (d, $J = 6.5$ Hz, 12H), 0.85 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 156.3, 137.5, 135.6, 134.8, 128.8, 128.7, 127.4, 120.0, 117.9 115.8, 115.3, 64.4, 60.7, 40.5, 31.9, 30.3, 29.8, 29.4, 27.1, 26.4, 22.8, 21.2, 14.2. MS (ESI): *m/z* 483.7 $[M + H]^+$. HR-MS (ESI): calcd for $C_{29}H_{47}N_4O_2$ $[M + H]^+$: 483.3694. Found: 483.3697.

Compound 17

To a solution of compound **16** (2.50 g, 10.0 mmol) in acetonitrile (100 mL) was added Selectfluor (14.2 g, 40.0 mmol). The solution was stirred for 2 h and then concentrated. The resulting slurry was dissolved in ethyl acetate (200 mL). After workup, the resulting residue was subjected to column chromatography (petroleum ether: AcOEt, 2:1) to give compound **17** as a white solid (0.58 g, 20%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 2H), 8.05–7.84 (m, 2H), 7.71 (d, $J = 8.9$ Hz, 2H), 2.14 (s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6): δ −131.0. ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.8, 147.6, 147.5, 145.0, 144.9, 129.5, 123.4, 123.3, 122.9, 113.3, 23.4. MS (ESI): *m/z* 278 $[M]^+$. HR-MS (ESI): calcd for $C_{14}H_{12}N_2O_2F_2$: 278.0867. Found: 278.0868.

Compound 18

To a suspension of compound **17** (0.25 g, 0.90 mmol) in water (15 mL) and ethanol (30 mL) was added concentrated hydrochloric acid (15 mL). The mixture was heated under reflux for 3 h, cooled to room temperature and neutralised with saturated sodium bicarbonate solution. The mixture was then concentrated with a rotavapor, and the resulting slurry was triturated with ethyl acetate (100 mL). The organic phase was washed with water (50 mL × 3) and brine (50 mL) and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting crude product was subjected to column chromatography (petroleum ether:CH_2Cl_2, 1:1) to give compound **18** as a grey solid (0.16 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, $J = 8.7$ Hz, 2H), 6.78 (dt, $J_1 = 8.3$ Hz, $J_2 = 4.0$ Hz, 1H), 3.86 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −147.4. ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.3, 140.8, 131.5, 124.3, 115.8, 115.4. MS (ESI): *m/z* 195.1 $[M + H]^+$. HR-MS (ESI): calcd for $C_{10}H_9N_2F_2$ $[M + H]^+$: 195.0728. Found: 195.0730.

Compound 19

To a solution of compound **18** (0.11 g, 0.60 mmol) and NEt_3 (0.08 mL, 0.60 mmol) in THF (40 mL) was added a solution of chloroacetyl chloride (0.042 mL, 0.60 mmol) in THF (5 mL) in 30 min. The solution was stirred for 8 h and then concentrated with a rotavapor. The resulting residue was dissolved in dichloromethane (20 mL), and the solution was washed with water (10 mL × 3) and brine (10 mL) and dried over sodium sulfate. After the solvent was removed, the resulting crude product was subjected to column chromatography (CH_2Cl_2:petroleum ether, 2:1) to give compound **19** as a white solid (82 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.15 (dd, $J_1 = 8.8$ Hz, $J_2 = 7.0$ Hz, 1H), 7.49 (d, $J = 9.0$ Hz, 1H), 7.42 (d, $J = 8.7$ Hz, 1H), 6.99 (t, $J = 8.3$ Hz, 1H), 4.25 (s, 2H), 3.97 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −138.35 (d, $J = 52.7$ Hz, 1F), −145.74 (d, $J = 52.2$ Hz, 1F). ^{13}C NMR (101 MHz, DMSO-d_6): δ 165.2, 146.9, 144.4, 141.5, 139.1, 134.0, 133.9, 125.4, 123.9, 123.5, 122.1, 122.0, 119.3, 118.1, 114.2, 43.1. MS (ESI): *m/z* 270 $[M]^+$. HR-MS (ESI): calcd for $C_{12}H_9N_2OF_2Cl$ $[M]^+$: 270.0371. Found: 270.0370.

Compound 20

A suspension of **19** (60 mg, 0.20 mmol), potassium carbonate (0.10 g, 0.70 mmol) and di(iso-butyl)amine (0.40 mL, 0.20 mmol) in DMF (3 mL) was stirred for 5 h and then concentrated under reduced pressure. The resulting residue was triturated with dichloromethane (5 mL), and the organic phase was washed with water (3 mL × 3) and brine (3 mL), and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the resulting slurry was subjected to column chromatography (petroleum ether:AcOEt, 6:1) to give compound **20** as a white solid (24.2 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.46–8.33 (m, 1H), 7.47 (d, $J = 8.9$ Hz,

1H), 7.40 (d, $J = 8.6$ Hz, 1H), 6.95 (t, $J = 8.3$ Hz, 1H), 3.95 (s, 2H), 3.20 (s, 2H), 2.28 (d, $J = 7.2$ Hz, 4H), 1.83 (dt, $J_1 = 13.4$ Hz, $J_2 = 6.8$ Hz, 2H), 0.99 (d, $J = 6.5$ Hz, 12H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −140.3 (d, $J = 54.3$ Hz, 1F), −146.4 (d, $J = 53.4$ Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.5, 145.5, 143.5, 141.6, 131.5, 131.4, 126.6, 124.0, 123.8, 123.6, 118.4, 116.9, 114.6, 64.7, 61.2, 26.4, 21.1. MS (ESI): *m/z* 364.4 $[M + H]^+$. HR-MS (ESI): calcd for $C_{20}H_{28}N_3OF_2$ $[M + H]^+$: 364.2195. Found: 364.2189.

Compound 6

To a solution of compound **20** (20 mg, 0.05 mmol) in THF was added *n*-octyl isocyanate (0.05 mL, 0.30 mmol). The solution was stirred for 24 h and then concentrated *in vacuo*. The resulting slurry was dissolved in dichloromethane (3 mL), and the solution was washed with saturated sodium bicarbonate solution (2 mL), water (2 mL × 2) and brine (2 mL) and dried over sodium sulfate. Upon concentration under reduced pressure, the resulting residue was subjected to column chromatography (petroleum ether:AcOEt, 4:1) to give compound **6** as a white solid (24.3 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.41–8.31 (m, 1H), 8.15 (dd, $J_1 = 8.9$ Hz, $J_2 = 7.3$ Hz, 1H), 7.44 (t, $J = 10.4$ Hz, 2H), 6.91 (d, $J = 2.9$ Hz, 1H), 5.19 (s, 1H), 3.28 (dd, $J_1 = 12.9$ Hz, $J_2 = 7.0$ Hz, 2H), 3.23 (s, 2H), 2.31 (d, $J = 7.2$ Hz, 4H), 1.85 (dt, $J_1 = 13.5$ Hz, $J_2 = 6.7$ Hz, 2H), 1.60–1.47 (m, 2H), 1.26 (d, $J = 8.2$ Hz, 10H), 0.99 (d, $J = 6.6$ Hz, 12H), 0.87 (t, $J = 6.8$ Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −137.0 (d, $J = 57.9$ Hz, 1F), −139.2 (d, $J = 55.9$ Hz, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 155.5, 146.4, 145.5, 144.4, 143.5, 128.1, 125.1, 123.4, 123.2, 122.5, 122.4, 120.6, 118.9, 113.3, 77.3, 77.0, 76.8, 64.5, 60.9, 40.3, 31.8, 30.1, 29.7, 29.3, 26.9, 26.3, 22.6, 20.9, 14.1. MS (ESI): *m/z* 519.7 $[M + H].^+$ HR-MS (ESI): calcd for $C_{29}H_{45}N_4O_2F_2$ $[M + H]^+$: 519.3505. Found: 519.3500.

Compound 7

To a solution of *n*-octanoic acid (0.30 mL, 1.90 mmol) and DMF (0.05 mL) in THF (10 mL) was added oxalyl chloride (1.0 mL, 11.6 mmol). After stirring for 0.5 h, the solution was concentrated under reduced pressure. The resulting octanoyl chloride **22** was dissolved in THF (15 mL) and the solution was added to a solution of compound **21** (0.20 g, 0.90 mmol) and NEt_3 (0.30 mL, 2.20 mmol) in THF (15 mL). After stirring for 12 h, the solution was concentrated with a rotavapor. The resulting residue was dissolved in dichloromethane (10 mL), and the solution was washed with saturated sodium bicarbonate solution (5 mL × 2), water (5 mL × 3) and brine (5 mL) and dried over sodium sulfate. After removal of the solvent under reduced pressure, the resulting crude product was purified by column chromatography (petroleum ether: AcOEt, 4:1) to give compound **7** as a white solid (0.26 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, $J = 8.9$ Hz, 2H), 8.07 (s, 2H), 7.72 (d, $J = 9.0$ Hz, 2H), 2.50 (t, $J = 7.5$ Hz, 2H), 1.85–1.72 (m, 2H), 1.49–1.23 (m, 8H), 0.89 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 136.0, 130.1, 128.7, 127.4, 120.2, 116.2, 38.43, 31.8, 29.3, 29.2, 25.7, 22.8, 14.23. MS (MALDI-FT): *m/z* 479.2 $[M + H]^+$. HR-MS (MALDI-FT): calcd for $C_{26}H_{37}N_2O_2Cl_2$ $[M + H]^+$: 479.2227. Found: 479.2230.

Compound 24

To a solution of compound **21** (0.30 g, 1.30 mmol) and NEt_3 (0.40 g, 2.80 mmol) in THF (40 mL) was added chloroacetyl chloride (0.12 mL, 1.60 mmol). The solution was stirred for 24 h and then concentrated under reduced pressure. The resulting residue was dissolved in dichloromethane (20 mL), and the solution was washed with saturated sodium bicarbonate solution (10 mL × 2), water (10mL × 2) and brine (10 mL) and dried over sodium sulfate. After concentration, compound **23** was obtained, which, without further purification, was dissolved in DMF (5 mL). To the solution were added di(iso-butyl)amine (1.00 mL, 5.70 mmol) and sodium carbonate (0.37 g, 2.60 mmol). The mixture was stirred for 8 h and then concentrated under reduced pressure. The resulting slurry was triturated with dichloromethane (10 mL), and the solution was washed with water (5 mL × 3) and brine (5 mL) and dried over sodium sulfate. Upon removal of the solvent with a rotavapor, the resulting crude product was purified by column chromatography (petroleum ether:AcOEt, 5:1) to give compound **24** as a white solid (0.26 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.45 (d, $J = 8.9$ Hz, 1H), 7.60 (d, $J = 8.9$ Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 1H), 4.52 (s, 2H), 3.24 (s, 2H), 2.30 (d, $J = 7.1$ Hz, 4H), 1.86 (dt, $J_1 = 13.4$ Hz, $J_2 = 6.7$ Hz, 2H), 0.99 (d, $J = 6.6$ Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 143.8, 135.8, 128.8, 128.6, 128.5, 127.3, 117.1, 117.0, 115.3, 109.4, 64.7, 61.6, 26.5, 21.3. MS (ESI): *m/z* 396.4 $[M + H]^+$. HR-MS (ESI): calcd. for $C_{20}H_{28}N_3Cl_2O$ $[M + H]^+$: 396.1604. Found: 396.1611.

Compound 8

To a solution of compound **24** (0.10 g, 0.30 mmol) in THF (5 mL) was added *n*-octyl isocyanate (0.05 mL, 0.30 mmol). The solution was stirred for 24 h and then concentrated under reduced pressure. The resulting slurry was dissolved in dichloromethane (5 mL). After workup, the solvent was removed and the resulting residue was subjected to column chromatography (petroleum ether:

AcOEt, 2:1) to give compound **8** as a white solid (0.12 m, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.36 (d, $J = 8.9$ Hz, 1H), 8.22 (d, $J = 8.9$ Hz, 1H), 7.63–7.46 (m, 2H), 7.41 (s, 1H), 5.51 (s, 1H), 3.40–3.16 (m, 4H), 2.31 (d, $J = 7.1$ Hz, 4H), 1.87 (dt, $J_1 = 13.1$ Hz, $J_2 = 6.6$ Hz, 2H), 1.54 (d, $J = 6.8$ Hz, 2H), 1.25 (s, 10H), 0.99 (d, $J = 6.5$ Hz, 12H), 0.86 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 155.5, 137.4, 135.0, 129.2, 128.3, 128.0, 127.3, 120.5, 119.2, 117.1, 115.3, 64.6, 61.4, 40.5, 31.9, 30.2, 29.4, 29.3, 27.1, 26.5, 22.7, 21.2, 14.2. MS (ESI): *m/z* 551.5 $[M + H]^+$. HR-MS (ESI): calcd for $C_{29}H_{45}N_4O_2Cl_2$ $[M + H]^+$: 551.2914. Found: 551.2921.

Compound 9

To a mixture of compound **12** (0.50 g, 3.20 mmol) and *n*-octanoic acid (1.3 mL, 8.23 mmol) in dichloromethane (20 mL) were added *N*-hydroxybenzotrizole (0.85 mg, 6.30 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.89 g, 9.80 mmol). The solution was stirred for 24 h and then dichloromethane (20 mL) was added. The solution was washed with diluted hydrochloric acid (1 N, 20 mL), saturated sodium bicarbonate solution (20 mL), water (20 mL × 2) and brine (20 mL) and dried over sodium sulfate. After the solvent was removed under reduced pressure, the resulting residue was subjected to column chromatography (petroleum ether:AcOEt, 3:1) to afford compound **9** as a white solid (0.91 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H), 7.72 (d, $J = 8.7$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.27 (s, 2H), 2.41 (t, $J = 7.6$ Hz, 4H), 1.84–1.69 (m, 4H), 1.31 (t, $J = 22.6$ Hz, 16H), 0.89 (t, $J = 6.8$ Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 136.4, 134.5, 128.5, 126.5, 119.1, 116.1, 46.0, 38.0, 31.8, 29.3, 25.81, 22.8, 14.2. MS (MALDI-FT): *m/z* 411.3 $[M + H]^+$. HR-MS (MALDI-FT): calcd for $C_{26}H_{39}N_2O_2$ $[M + H]^+$: 411.3006. Found: 411.3013.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplemental data

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References

(1) (a) Ajayaghosh, A.; George, S.J.; Schenning, A.P.H.J. *Top. Curr. Chem.* **2005**, 258, 83–118; (b) Scarso, A.; Rebek, J., Jr. *Top. Curr. Chem.* **2006**, *265*, 1–46; (c) Zhao, X.; Li, Z.-T. *Chem. Commun.* **2010**, *46*, 1601–1616; (d) Gonzalez-Rodriguez, D.; Schenning, A.P.H.J. *Chem. Mater.* **2011**, *23*, 310–325; (e) Yuan, L.; Zhang, P.; Feng, W.; Gong, B. *Curr. Org. Chem.* **2011**, *15*, 1250–1265; (f) Yang, Y.; Chu, W.-J.; Liu, J.-W.; Chen, C.-F. *Curr. Org. Chem.* **2011**, *15*, 1302–1313; (g) Li, S.-L.; Xiao, T.; Lin, C.; Wang, L. *Chem. Soc. Rev.* **2012**, *41*, 5950–5968; (h) Fu, H.; Liu, Y.; Zeng, H. *Chem. Commun.* **2013**, *49*, 4127–4144; (i) Zhang, X.; Zeng, Q.; Wang, C. *RSC Adv.* **2013**, *3*, 11351–11366; (j) Yang, S.K.; Zimmerman, S.C. *Israel J. Chem.* **2013**, *53*, 511–520; (k) Li, X.; Fang, Y.; Deng, P.; Hu, J.; Li, T.; Feng, W.; Yuan, L. *Org. Lett.* **2011**, *13*, 4628–4631; (l) Xu, J.-F.; Chen, Y.-Z.; Wu, D.; Wu, L.-Z.; Tung, C.-H.; Yang, Q.-Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 9738–9742; (m) Yan, X.; Jiang, B.; Cook, T.R.; Zhang, Y.; Li, J.; Yu, Y.; Huang, F.; Yang, H.-B.; Stang, P.J. *J. Am. Chem. Soc.* **2013**, *135*, 16813–16816; (n) Peng, H.-Q.; Xu, J.-F.; Chen, Y.-Z.; Wu, L.-Z.; Tung, C.-H.; Yang, Q.-Z. *Chem. Commun.* **2014**, *50*, 1334–1337.

(2) (a) Zimmerman, S.C.; Corbin, P.S. *Struct. Bond.* **2000**, *96*, 63–94; (b) Parra, R.D.; Zeng, H.; Zhu, J.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem. Eur. J.* **2001**, *7*, 4352–4357; (c) Sijbesma, R.P.; Meijer, E.W. *Chem. Commun.* **2003**, 5–16; (d) Huc, I. Eur. *J. Org. Chem.* **2004**, 17–29; (e) Zhang, D.-W.; Zhao, X.; Hou, J.-L.; Li, Z.-T. *Chem. Rev.* **2012**, *112*, 5271–5316.

(3) Pauling, L. *The Nature of the Chemical Bond*; 3rd ed. Cornell University Press: Ithaca, NY, 1960.

(4) Desiraju, G.R.; Steiner, T. *The Weak Hydrogen Bond: In Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999.

(5) Dunitz, J.D. *ChemBioChem* **2004**, *5*, 614–621.

(6) Sony, S.M.M.; Ponnuswamy, M.N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1766–1772.

(7) (a) Shimoni, L.; Glusker, J.P. *Struct. Chem.* **1994**, *5*, 383–397; (b) Howard, J.A.K.; Roy, V.J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613–12622; (c) Dunitz, D. K.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 89–98.

(8) (a) Li, C.; Ren, S.-F.; Hou, J.-L.; Yi, H.-P.; Zhu, S.-Z.; Jiang, X.-K.; Li, Z.-T. *Angew. Chem. Int. Ed.* **2005**, *44*, 5725–5729; (b) Zhu, Y.-Y.; Wu, J.; Li, C.; Zhu, J.; Hou, J.-L.; Li, C.-Z.; Jiang, X.-K.; Li, Z.-T. *Cryst. Growth Des.* **2007**, *7*, 1490–1496; (c) Li, C.; Zhu, Y.-Y.; Yi, H.-P.; Li, C.-Z.; Jiang, X.-K.; Li, Z.-T. Li, *Chem. Eur. J.* **2007**, *13*, 9990–9998.

(9) (a) Zhu, Y.-Y.; Yi, H.-P.; Li, C.; Jiang, X.-K.; Li, Z.-T. *Cryst. Growth Des.* **2008**, *8*, 1294–1300; (b) Wang, D.-Y.; Wang, J.-L.; Zhang, D.-W.; Li, Z.-T. *Sci. China Chem.* **2012**, *55*, 2018–2026.

(10) (a) Marjo, C.E.; Bishop, R.; Craig, D.C.; Scudder, M.L. *Eur. J. Org. Chem.* **2001**, 863–873; (b) Rahman, A.N.M.M.; Bishop, R.; Craig, D.C.; Scudder, M.L. *Eur. J. Org. Chem.* **2003**, 72–81; (c) Desiraju, G.R. *Chem. Commun.* **2005**, 2995–3001.

(11) (a) Calhorda, M.J. *Chem. Commun.* **2000**, 801–809; (b) Sándorfy, C. *J. Mol. Struct.* **2004**, *708*, 3–5; (c) Gao, D.; Zhan, C.-G. *Proteins Struct. Funct. Bioinf.* **2006**, *62*, 99–110; (d) Takahashi, O.; Kohno, Y.; Nishio, M. *Chem. Rev.* **2010**, *110*, 6049–6076; (e) Scheiner, S. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13860–13872.

(12) (a) Raja, R.; Thomas, J.M.; Jones, M.D.; Johnson, B.F.G.; Vaughan, D.E.W. *J. Am. Chem. Soc.* **2003**, *125*, 14982–14983; (b) Scerba, M.T.; Leavitt, C.M.; Diener, M.E.; DeBlase, A.F.; Guasco, T.L.; Siegler, M.A.; Bair, N.; Johnson, M.A.; Lectka, T. *J. Org. Chem.* **2011**, *76*, 7975–7984.

(13) Brancatelli, G.; Drommi, D.; Bruno, G.; Faraone, F. *Acta Crystallogr. E* **2010**, *66*, m1368.
(14) Elbl-Weiser, K.; Krieger, C.; Staab, H.A. *Eur. J. Org. Chem.* **2000**, 327–333.
(15) Himeno, S.; Imagawa, H.; Inoue, M.; Nagahama, M.; Nakano, M.; Nishizawa, M.; Oda, M.; Sakurai, J.; Setsu, K.; Shibutani, M.; Watanabe, N.; Yabiku, K.; Yamamoto, H. *J. Med. Chem.* **2013**, *56*, 381–385.
(16) Singh, R.P.; Shreeve, J.M. *Acc. Chem. Res.* **2004**, *37*, 31–44.
(17) Schmitt, P.; Zimmerman, S.C. *J. Am. Chem. Soc.* **1995**, *117*, 10769–10770.
(18) Bell, F.; Gibson, J.A.; Wilson, R.D.J. *J. Chem. Soc.* **1956**, *40*, 2335–2340.
(19) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128–15139.
(20) Conners, K.A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.
(21) Jorgensen, W.L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008–2010.