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The AAAA·DDDD Hydrogen Bond Dimer. Synthesis of a Soluble Sulfurane as AAAA Domain and Generation of a DDDD Counterpart*,†

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Sulfurane **5b** with solubility enhancing substituents has been synthesized to be used as an AAAA recognition site in quadruple hydrogen bond heterodimers. A complementary DDDD partner [**4b** + H^+] has been generated from a DDAD domain **4b** by protonation. The association constant for the heterodimer complex formation has been determined by NMR titration in chloroform.

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Introduction

The hydrogen bond is one of the most important interactions in supramolecular chemistry.[1] While a single hydrogen bond possesses a binding enthalpy between a few and several hundred kJ mol^{-1}, the cooperation of several hydrogen bonds[2] leads to strongly bound complexes, the DNA double helix being the most prominent example. In contrast to many other intermolecular forces, hydrogen bonds possess a directionality and thus hydrogen bond binding motifs are characterized by the number and the orientation of the hydrogen bond donors and acceptors.

Quadruple hydrogen bond motifs† have only been studied in the past decade. By alteration of hydrogen bond donors (D) and acceptors (A) it is possible to construct 10 different patterns of hydrogen bond motifs. Two of these patterns (AADD and ADAD) are self-complementary; hence they form homodimers $(AADD)_2$ and $(ADAD)_2$. The first example of a quadruple hydrogen bonded homodimer was published in 1997.[6]

The eight remaining patterns of quadruple hydrogen bond motifs are non-self-complementary and, therefore, they form four different heterodimer pairs. In 1998, we published the first DAAD·ADDA heterodimers (**1a**·**2**),[7] followed in 2002 by a second pattern, the AADA·DDAD heterodimer (**3**·**4a**) (see Fig. 1).[8]

It was shown for dimers that are held together by three hydrogen bonds in close proximity‡ (= three primary interactions) that secondary interactions[9] between neighbouring hydrogen bonds contribute considerably to the binding energy in those dimers. The influence of a secondary interaction to the binding energy is either stabilizing or destabilizing depending on the

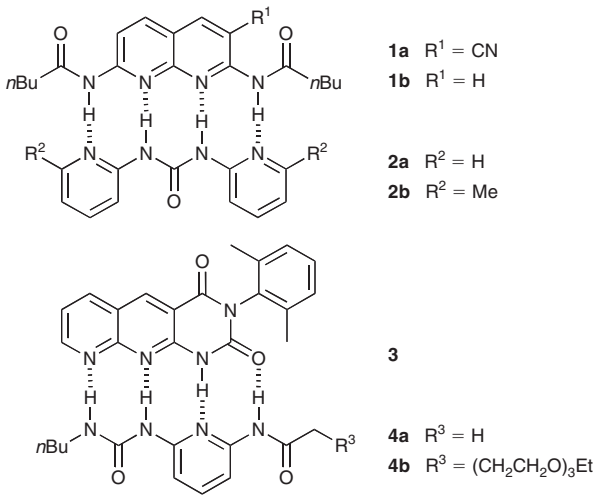

Fig. 1. Non-self-complementary quadruple hydrogen bond patterns forming heterodimers. Top: DAAD·ADDA (**1**·**2**) and bottom: AADA·DDAD (**3**·**4**).

*Dedicated to Professor Dr Christoph Rüchardt on the occasion of his 80th birthday.

†Multiple hydrogen bonds 6. Part 5: ref. [17].

‡In this work, only those multiple hydrogen bonding patterns are discussed in which the hydrogen bonds are in close proximity to each other and separated by not more than one atom. For our studies we consider a suitable DDDD counterpart a molecule that fulfills the following criteria: (a) It needs to be soluble in chloroform, so that we can perform a NMR titration and can compare our results to our previous work. (b) The molecule should not be too flexible. In particular, intramolecular hydrogen bonds should be avoided because these must be broken in order to form a complex using the binding motif. Therefore, ureas such as triuret or its derivatives are not suitable for our work.[3] (c) The DDDD domain must match the AAAA pattern in curvature and distance. Therefore, multiple urea units[3,4] or pattern in which the NH units are separated by more than one atom[5] are not suitable although they contain four or more NH units.

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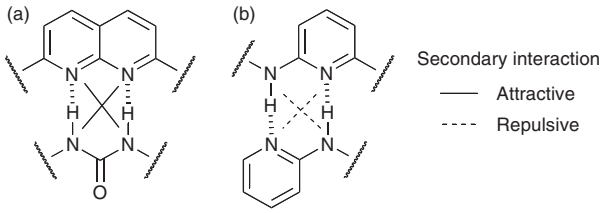


Fig. 2. (a) Parallel arrangement (DD·AA) of hydrogen bonds results in attractive secondary interactions. (b) Antiparallel arrangement (DA·AD) results in repulsive secondary interactions.

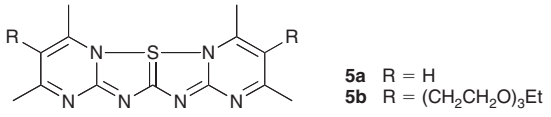


Fig. 3. Sulfurane **5** with four hydrogen bond acceptor groups next to each other (AAAA pattern). The substituents in **5b** have been introduced to provide the molecule with a good solubility in chloroform.

arrangement of the hydrogen bonds. In the case of a parallel arrangement DD·AA (see Fig. 2a), there is a positive contribution, and for an antiparallel one DA·AD (see Fig. 2b), there is a negative contribution to the binding energy.

The following ranges of association constants for complexes with three hydrogen bonds illustrate the effect of secondary interactions. Three primary and four attractive secondary hydrogen bonds result in K_{Ass}(DDD·AAA) of 10^5–$10^6\ M^{-1}$, while three primary and four repulsive secondary interactions give K_{Ass}(DAD·ADA) of 10^2–$10^3\ M^{-1}$.[10]

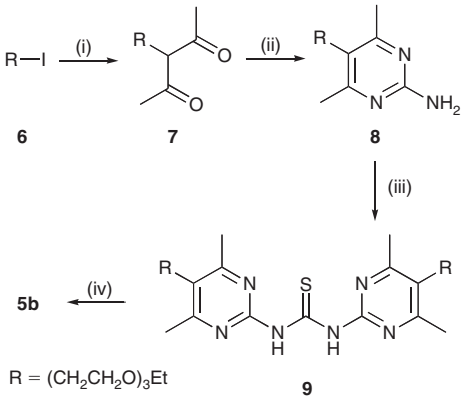
This finding must also be considered for dimers with four hydrogen bonds. For instance, the two possible self-complementary binding motifs (AADD and ADAD) possess different numbers of attractive and repulsive secondary interactions along with the four primary interactions. Consequently, for the dimeric complex $(AADD)_2$,[11] the association constant was determined to be $K_{Ass} > 3.6 \times 10^6\ M^{-1}$, but for the $(ADAD)_2$ complex the association constant was smaller by one order of magnitude: $K_{Ass} > 2.0 \times 10^5\ M^{-1}$.[12]

In addition to four primary interactions, the AAAA·DDDD dimer has only attractive secondary interactions and should, therefore, be the most stable dimer with four hydrogen bonds. Hence, a molecule with four hydrogen bond acceptor groups (AAAA) and another molecule with four hydrogen bond donor groups (DDDD) are needed.

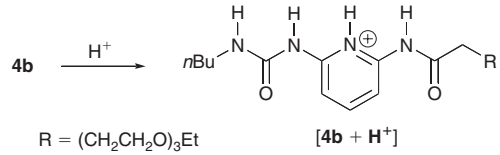
Results and Discussion

An example of a molecule with four acceptor groups next to each other is sulfurane **5a** (see Fig. 3), which was published by Akiba and coworkers[13] in 1996. But because of its poor solubility in chloroform it was inapplicable for our purpose. We wanted to study the association constants of the counterparts in chloroform to be able to compare the results to previous studies. Therefore, we decided to synthesize a related sulfurane **5b** with polyether substituents, which should improve its solubility.

The synthesis of **5b** started with the tosylation[14] of commercially available triethylene glycol monoethyl ether. Exchange of the tosylate by iodide gave iodide **6**.[15] Pentane-2,4-dione was alkylated with iodide **6** (see Scheme 1) to give the diketone[¶] **7** in



Scheme 1. Synthesis of the sulfurane **5b**: (i) KO^{t}Bu, pentane-2,4-dione; (ii) HN=C(NH$_2$)$_2$; (iii) (a) 2 × **8**, (b) NaHCO$_3$, CSCl$_2$; (iv) (a) SO$_2$Cl$_2$, (b) NaHCO$_3$.



Scheme 2. Altering a hydrogen bond acceptor group into a hydrogen bond donor group by using anhydrous *p*-toluenesulfonic acid: Generation of cation [**4b** + **H**$^+$], which has a DDDD pattern.

47% yield. Condensation of **7** with the free guanidine base gave **8** in 40% yield. Reaction of two equivalents of **8** with thiophosgene in the presence of sodium bicarbonate afforded thiourea **9** in 80% yield. Thiourea **9** quickly forms yellow by-products. Therefore, crude **9** was mixed with sulfuryl chloride and neutralization with sodium bicarbonate gave the target sulfurane **5b** in 85% yield.

As desired, the polyether substituents provided **5b** with a very good solubility in chloroform, which now allows the use of **5b** as the AAAA counterpart in respective binding experiments.

A suitable[3–5]‡ DDDD counterpart for quadruple hydrogen bond recognition experiments, which is sufficiently soluble in chloroform, has not been synthesized until now. By using a handy trick we can change a hydrogen bond acceptor group into a hydrogen bond donor group. Just by using an equimolar amount of Brønsted acid, an acceptor group can be turned into a donor group. The idea of switching between a donor and acceptor is not new and has been used previously for similar recognition events.[16] Therefore, a molecule, which has three donor and one acceptor positions, was needed. In a previous work, we published access to amidopyridine urea **4b**, which possesses the DDAD pattern and is very highly soluble in chloroform.[17] Adding acid (i.e., anhydrous *p*-toluenesulfonic acid) to a solution of **4b** in chloroform should turn the hydrogen bond pattern from DDAD to the desired DDDD pattern (see Scheme 2).

The reaction of **5b** with [**4b** + **H**$^+$] (see Fig. 4) should give the desired heterodimer AAAA·DDDD (**5b**·[**4b** + **H**$^+$]).

When sulfurane **5b** was titrated in chloroform with its counterpart [**4b** + **H**$^+$], the NMR data showed a gradual shift of the signals of the starting materials to those of the complex. This proves that **5b** retains its tetracyclic structure during the titration with the resulting complex being in equilibrium with

[¶] **7a** = keto form (60%), **7b** = enol form (40%).

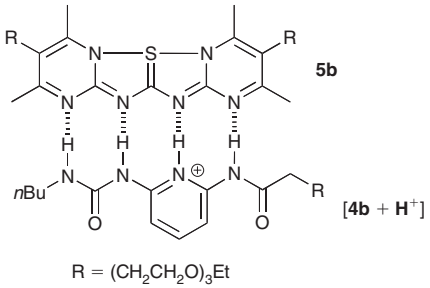


Fig. 4. Formation of the heterodimer AAAA·DDDD (**5b**·[**4b** + **H**$^+$]) with four hydrogen bonds and six attractive secondary interactions.

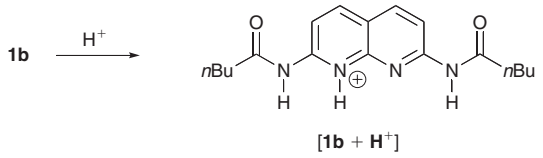
the starting materials.[§] The association constant of the heterodimer **5b**·[**4b** + **H**$^+$] was determined to be $K_{Ass} = 525\ M^{-1}$. Estimation of the association constant for an AAAA·DDDD heterodimer such as **5b**·[**4b** + **H**$^+$], which is bound by four hydrogen bonds (four primary interactions) and has six attractive secondary interactions, gives an association constant of $K_{Ass} = 3.9 \times 10^8\ M^{-1}$.[18] The association constant we determined for this complex is surprisingly low.

In order to understand this finding we wanted to check the strategy of altering a hydrogen bond pattern by protonation. First, an NMR titration of sulfurane **5b** with unprotonated **4b** was carried out. The AAAA and the DDAD partners may form hydrogen bonds in two ways. They either form the dimer as expected but with one repulsive A–A interaction in addition to three attractive D–A hydrogen bonds, or the two domains only coordinate by two hydrogen bonds, i.e., the DD end of **4b** coordinates to an AA part of **5b**. Thus, the association constant for **5b**·**4b** should be much smaller than that of **5b**·[**4b** + **H**$^+$]. The effect we measured was even stronger than expected. In the NMR titration experiment for **5b**·**4b**, no change of the NMR shifts of the amide protons could be observed. This means that the association constant for complex **5b**·**4b** in the absence of protons is determined to be $K_{Ass} < 1\ M^{-1}$. This finding is surprising because the possible formation of two or three hydrogen bonds should lead at least to a weak association for complex **5b**·**4b**.

To verify that the change of an acceptor group into a donor group by addition of Brønsted acid is successful and really leads to an altered motif of quadruple hydrogen bonds we expanded our study to another heterodimer pair (for three hydrogen bonds, see ref. [16a]).

For heterodimers DDAD·AADA, association constants are available from our previous work.[8,17] If one could generate one partner of a DDAD·AADA complex by protonation and react it with a corresponding counterpart in a NMR titration, the resulting association constant can be compared with other known association constants for DDAD·AADA complexes. If an association constant was found to be in the same order of magnitude as the known association constants, the assumption that a binding motif can be switched by protonation would be proven.

For such an experiment, we chose to generate the DDAD counterpart from the DAAD domain **1b**, which was synthesized according to a procedure by Zimmerman and coworkers.[19] Compound **1b** was then protonated with anhydrous *p*-toluenesulfonic acid to generate [**1b** + **H**$^+$], which has a DDAD pattern (see Scheme 3).



Scheme 3. Generation of the DDAD domain [**1b** + **H**$^+$] by protonation of **1b** with anhydrous *p*-toluenesulfonic acid.

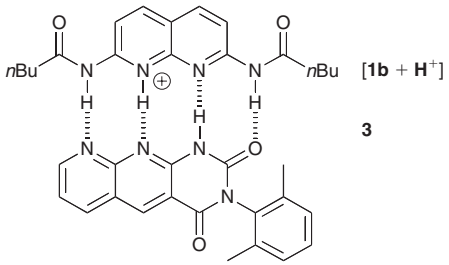


Fig. 5. Formation of heterodimer DDAD·AADA ([**1b** + **H**$^+$]·**3**) with one counterpart being protonated.

Table 1. Association constants, K_{Ass}, for heterodimers determined by NMR titration

Heterodimer	K_{Ass} [M^{-1}]
5b·[**4b** + **H**$^+$]	525
5b·**4b**	<1
[**1b** + **H**$^+$]·**3**	442
4b·**3**	872

The AADA counterpart **3** was obtained following a synthesis of Brammer et al.[8] Reaction of [**1b** + **H**$^+$] with counterpart **3** (see Fig. 5) should give the heterodimer DDAD·AADA ([**1b** + **H**$^+$]·**3**).

By NMR titration, the association constant for the heterodimer [**1b** + **H**$^+$]·**3** was determined to be $K_{Ass} = 442\ M^{-1}$. This association constant is in the order of magnitude found for related DDAD·AADA pairs: K_{Ass}(DDAD·AADA) = 10^2–$10^3\ M^{-1}$. For instance, the association constant for the DDAD·AADA complex **4b**·**3** was determined to be $K_{Ass} = 872\ M^{-1}$.[8,17] All association constants of importance for this work are summarized in Table 1.

Although the experiment discussed above showed that the strategy of altering a binding site by using an acid is successful, it still remains to explain the surprisingly low association constant found for the **5b**·[**4b** + **H**$^+$] complex.

Which reasons have been found previously that are responsible for a decrease in binding of complexes bound by hydrogen bonds? Several factors have been identified and four of them shall be discussed here: (i) pre-organization; (ii) steric hindrance; (iii) substitution by ethylene glycol chains; and (iv) basicity of the hydrogen bond acceptors:

(i) It is known from X-ray analyses and other studies that pyridine ureas such as **4** form intramolecular hydrogen bonds.[7,20] These bonds must be broken in order to form the heterodimeric

[§]As reported in ref. [13], sulfuranes are not stable when they are reacted with strong electrophiles. Therefore, it must be taken into account that protonation also could destroy the sulfurane. However, the methylation of a sulfurane is an irreversible reaction, the protonation a reversible one. Furthermore, decomposition by methylation primarily occurs with unsymmetrically substituted sulfuranes, and during the course of our titrations no decomposition was observed.

complex. Also, in its protonated form, an intramolecular hydrogen bond is possible in [**4b** + H^+] between the protonated pyridine nitrogen atom and one of the carbonyl groups. (ii) In sulfurane **5b**, methyl groups are attached in the α-position of the outer pyrimidine rings. They repulse the hydrogen-bonded partner. The effect of methyl groups in the α-positions of dipyridyl urea **2b** upon complex formation with naphthyridine **1a** has been studied[7,21] and a decrease in K_{Ass} of more than one order of magnitude has been determined. (iii) In the course of our investigation, Meijer and coworkers published[22] that ethylene glycol chains may reduce binding constants. (iv) The drawing of complex **5b**·[**4b** + H^+] in Fig. 4 suggests that the DDAD moiety is protonated in the DDDD·AAAA complex. But a protonation of the AAAA structure is also conceivable. Such a protonation would also be productive for the formation of a heterodimer because a resulting AADA structure of [**5b** + H^+] would match the DDAD pattern of **4b**. However, a much smaller association constant would be expected for [**5b** + H^+]·**4b** because a DDAD·AADA heterodimer would have four repulsive secondary hydrogen bond interactions. Whereas all dipoles are parallel in a DDDD·AAAA arrangement (four primary interactions and six attractive secondary interactions), the two attractive secondary interactions in a DDAD·AADA heterodimer are outnumbered by four repulsive ones, which leads to a total of four primary and two repulsive secondary interactions. (v) In principle, a protonation of **5b** could also lead to a cleavage of a S–N bond and thus to the formation of an AADA structure, which would be much less favourable in a dimer formation. However, from the NMR data it is obvious that the sulfurane remains in its tetracyclic structure in the presence of protonated **4b** (see above).

Conclusions

By substitution with triethylene glycol chains, a chloroform-soluble quadruple hydrogen bond acceptor AAAA **5b** has been made available. A complementary quadruple hydrogen bond donor DDDD [**4b** + H^+] was generated from a DDAD precursor by protonation. The binding constant K_{Ass} was determined by NMR titration in deuterated chloroform but is not yet satisfying. In order to increase the binding, several structural changes can be suggested such as the removal of the methyl substituents of sulfurane **5b** and a variation of the ethylene glycol part. A further increase can be expected with a less flexible counterpart DDAD, and finally the protonation of DDAD **4b** may be facilitated by increasing the basicity of the pyridine unit, for instance by a 4-dimethylamino substitution.

Experimental

General Procedures

The following chemicals were obtained commercially and used without further purification: guanidine hydrochloride (Fluka), pentane-2,4-dione (Fluka), potassium *tert*-butoxide (Acros), sulfuryl chloride (Merck), thiophosgene (Acros), and triethylene glycol monoethyl ether (Merck). Iodide **6** was obtained from the reaction of sodium iodide with triethylene glycol monoethyl ether *p*-tosylate.[15] This tosylate was prepared according to a preparation published by Le Mest and coworkers.[14] Compound **4b** was synthesized by a procedure described by us in an earlier work.[17] Compound **1b** was obtained according to a procedure described by Zimmerman and coworkers,[19] and **3** was obtained according to a procedure described by Brammer et al.[8] Anhydrous ethanol was obtained by refluxing with sodium and diethyl phthalate (1 h) followed by distillation. Anhydrous dichloromethane (DCM) was obtained by refluxing with calcium hydride (1 h) followed by distillation. Anhydrous tetrahydrofuran (THF) was obtained by refluxing it with lithium aluminium hydride and triphenylmethane (1 h) followed by distillation. Column chromatography was carried out with silica gel (Macherey–Nagel).

^{1}H and ^{13}C NMR spectra were recorded with Bruker DRX 500 or AV 600 instruments. Assignments are supported by correlation spectroscopy, heteronuclear single-quantum correlation, and heteronuclear multiple bond correlation experiments. Pym is used as an abbreviation for pyrimidine to assign the NMR signals to the molecule. Melting points were recorded with Electrothermal Melting Point Apparatus, Fa. Electrothermal Engineering Ltd and have not been corrected. Elemental analyses were carried out with a EuroEA 3000 Elemental Analyzer from Euro Vector. IR spectra were recorded with a Perkin–Elmer Paragon 1000 spectrometer. Mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230 spectrometer. Electrospray ionization (ESI) mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation. Gas chromatography (GC) studies were carried out with Agilent Gas Chromatograph 6890N, column: Optima 1/30 m. The temperature program used for the GC was as follows: isothermal heating for 5 min at 70°C, heating with 10°C min^{-1} until 250°C, and then isothermal heating at 250°C for an additional 20 min. NMR titrations were carried out with the Bruker DRX 500 instrument at 25°C. One counterpart was successively added to a solution of the other in deuterated chloroform ($CDCl_3$) while recording the changes in chemical shift of the amide protons. The resulting data was analyzed by a non-linear regression thus determining the association constant K_{Ass} and the maximum of the change in chemical shift $\Delta\delta_{max}$. The protonated counterparts [**4b** + H^+] and [**1b** + H^+] were generated by combining stoichiometric amounts of anhydrous *p*-toluenesulfonic acid with **4b** or **1b**, respectively, in $CDCl_3$. Anhydrous *p*-toluensulfonic acid was obtained from *p*-toluenesulfonic acid monohydrate after heating for 1 h at 100°C at 1 mbar.

*3,9-Bis(3,6,9-trioxaundecyl)-2,4,8,10-tetramethyl-6λ4-pyrimido-[1,2:2,3]-[1,2,4]thiadiazolo-[1,5:1,5][1,2,4] thiadiazolo-[2,3:1,2]-pyrimidine (**5b**)*

To a solution of **9** (max. 1.83 g, 3.00 mmol) in anhydrous DCM (50 mL) was added sulfuryl chloride (250 μL, 3.10 mmol) and the solution was stirred at room temperature (RT) for 24 h. Sodium bicarbonate (260 mg, 3.10 mmol) was added and the mixture was stirred for another 18 h. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, DCM/ethanol (19/1), R_f 0.16). The product was recrystallized from diethyl ether and was obtained as a colourless solid (1.55 g, 85% yield). Mp 167–168°C. (Found C 57.17, H 7.86, N 13.79, S 5.15. Calcd for $C_{29}H_{46}N_6O_6S$: C 57.40, H 7.64, N 13.85, S 5.28%.) ν_{max} (KBr)/cm^{-1} 3448, 2991, 2866, 1590, 1535, 1505, 1438, 1376, 1326, 1255, 1112, 1255, 791, 572. δ_H (500 MHz, $CDCl_3$, 25°C) 1.18 (6H, t, ^3J 7.0, 11-CH_3), 2.57 (6H, s, 6-Pym-CH_3), 2.71 (6H, s, 4-Pym-CH_3), 2.90 (4H, t, ^3J 6.9, 2-CH_2), 3.49 (4H, q, ^3J 7.0, 10-CH_2), 3.52–3.56 (4H, m, 1-CH_2), 3.57–3.62 (16H, m, –OCH_2–). δ_C (125.8 MHz, $CDCl_3$, 25°C) 15.1 (q, 11-CH_3), 17.3 (q, 4-Pym-CH_3), 23.6 (q, 6-Pym-CH_3), 28.1 (t, 1-CH_2), 66.6 (t, 10-CH_2), 69.8 (t, 2-CH_2), 70.0 (t, –OCH_2–), 70.5 (t, –OCH_2–), 70.6 (t, –OCH_2–), 70.7 (t, –OCH_2–), 118.8 (s, 5-Pym-C), 154.6 (s, 4-Pym-C), 158.5 (s, 2-Pym-C), 170.3 (s, C=S), 170.4 (s, 6-Pym-C). *m*/*z* (EI, 70 eV) 577 (1%)

$[M - C_2H_5]^+$, 136 (100). *m/z* (CI, isobutane) 326 (16%), 284 (100) $[M - (C_8H_{17}O_2)_2]^+$, 135 (85). *m/z* (ESI, $CHCl_3$) 1235 (5%) $[M_2 + Na]^+$, 629 (100) $[M + Na]^+$, 607 (15) $[M + H]^+$.

*3-Acetyl-6,9,12-trioxatetradecan-2-one (**7**)*

To a suspension of potassium *tert*-butoxide (14.6 g, 130 mmol) in THF (100 mL) was added a solution of pentane-2,4-dione (13.0 g, 130 mmol) in THF (50 mL) at 0°C. To this mixture was added a solution of **6**, (18.6 g, 64.0 mmol) in THF (50 mL). The reaction mixture was then heated to reflux for 18 h. After cooling, the mixture was acidified with 1 N hydrochloric acid (pH 1) and diluted with diethyl ether (200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried with magnesium sulfate and the solvent was removed under vacuum. Column chromatography (silica gel, cyclohexane/ethyl acetate (1/1), R_f 0.22) yielded **7** as a colourless oil (8.10 g, 47% yield). (Found C 59.56, H 9.52. Calcd for $C_{13}H_{24}O_5 \cdot 0.1H_2O$: C 59.56, H 9.31%.) ν_{max} (film)/cm^{-1} 3519, 2868, 1725, 1698, 1605, 1423, 1358, 1283, 1248, 1115, 848. δ_H (500 MHz, $CDCl_3$, 25°C) 1.15 (3H, t, ^3J 7.0, 14-CH_3), 2.13 [1.2H, dt, ^3J 6.9, ^3J 5.9, 4-CH_2 (**7a**†)], 2.17 [2.4H, s, 1-CH_3, 3-C–$COCH_3$ (**7b**†)], 2.22 [3.6H, s, 1-CH_3, 3-CH–$COCH_3$ (**7a**)], 2.55 [0.8H, t, ^3J 7.3, 4-CH_2 (**7b**)], 3.46 [1.2H, t, ^3J 5.9, 5-CH_2 (**7a**)], 3.47 [0.8H, t, ^3J 7.3, 5-CH_2 (**7b**)], 3.53 (2H, q, ^3J 7.0, 13-CH_2), 3.57–3.67 (8H, m, –OCH_2–), 3.86 [0.6H, t, ^3J 6.9, 3-CH (**7a**)]. Signal for the enol proton could not be observed. δ_C (125.8 MHz, $CDCl_3$, 25°C) 15.0 (q, 14-CH_3), 23.0 [q, 1-CH_3, 3-C–$COCH_3$ (**7b**)], 27.8 [t, 4-CH_2 (**7b**)], 28.2 [t, 4-CH_2 (**7a**)], 29.3 [q, 1-CH_3, 3-CH–$COCH_3$ (**7a**)], 65.4 [d, 3-CH (**7a**)], 66.5 (t, 13-CH_2), 68.5 [t, 5-CH_2 (**7a**)], 68.6 [t, 5-CH_2 (**7b**)], 69.6 (t, –OCH_2–), 70.0 (t, –OCH_2–), 70.3 (t, –OCH_2–), 70.5 (t, –OCH_2–), 106.6 [s, 3-C (**7b**)], 191.6 [s, C=O (**7b**)], 204.1 [s, C=O (**7a**)]. *m/z* (EI, 70 eV) 260 (2%) $[M]^+$, 161 (6), 127 (63), 85 (100), 73 (85). *m/z* (CI, isobutane) 261 (23%) $[M + H]^+$, 127 (40). *m/z* (ESI, $CHCl_3$) 283 (100%) $[M + Na]^+$. GC $t_{ret} = 15.5$ min, purity: 96%.

*2-Amino-4,6-dimethyl-5-(3,6,9-trioxaundecyl)-pyrimidine (**8**)*

Under a N_2 atmosphere, sodium (920 mg, 40.0 mmol) was carefully dissolved in 100 mL of anhydrous ethanol to give a sodium ethanolate solution. To this solution was added guanidine hydrochloride (3.82 g, 40.0 mmol), and the mixture was stirred for 15 min at RT, the solid was filtered off and the solvent was evaporated. The residue was dissolved in THF (100 mL), **7** (7.72 g, 29.7 mmol) was added, and the solution was heated to reflux for 18 h. After cooling, the solvent was evaporated and the residue was dissolved in DCM (50 mL) and water (50 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic extracts were dried with magnesium sulfate and the solvent was removed under vacuum. Column chromatography (silica gel, DCM/ethanol (9/1), R_f 0.24) yielded **8** as a colourless solid (3.30 g, 40% yield). Mp 34.3–34.8°C. (Found C 59.28, H 9.18, N 14.89. Calcd for $C_{14}H_{25}N_3O_3$: C 59.34, H 8.89, N 14.83%.) ν_{max} (KBr)/cm^{-1} 3346, 3192, 2869, 1637, 1561, 1466, 1388, 1240, 1111, 798, 559. δ_H (500 MHz, $CDCl_3$, 25°C) 1.16 (3 H, t, ^3J 7.0, 11-CH_3), 2.30 (6H, s, 4-Pym-CH_3, 6-Pym-CH_3), 2.77 (2H, t, ^3J 7.5, 2-CH_2), 3.46 (2H, t, ^3J 7.5, 1-CH_2), 3.47 (2H, q, ^3J 7.0, 10-CH_2), 3.54–3.64 (8H, m, –OCH_2–), 5.19 (2H, br s, NH_2). δ_C (125.8 MHz, $CDCl_3$, 25°C) 15.0 (q, 11-CH_3), 21.8 (q, 4-Pym-CH_3, 6-Pym-CH_3), 28.0 (t, 1-CH_2), 66.5 (t, 10-CH_2), 69.7 (t, 2-CH_2), 70.0 (t, –OCH_2–), 70.3 (t, –OCH_2–), 70.5 (t, –OCH_2–), 70.6 (t, –OCH_2–), 117.3 (s, 5-Pym-C), 160.7 (s, 2-Pym-C), 166.2 (s, 4-Pym-C, 6-Pym-C). *m/z* (EI, 70 eV) 283 (2%) $[M]^+$, 254 (6), 150 (99), 136 (100). *m/z* (CI, isobutane) 284 (100%) $[M + H]^+$, 136 (17). *m/z* (ESI, $CHCl_3$) 306 (8%) $[M + Na]^+$, 284 (100) $[M + H]^+$.

*N,N′-Bis[4,6-dimethyl-5-(3,6,9-trioxaundecyl)-pyrimidin-2-yl]thiourea (**9**)*

To a suspension of sodium bicarbonate (1.07 g, 12.7 mmol) and **8** (3.00 g, 10.6 mmol) in acetonitrile (50 mL) was added thiophosgene (383 µL, 5.00 mmol) and the mixture was heated to reflux for 18 h. After cooling, the solvent was evaporated and the residue was purified by column chromatography (silica gel, DCM/ethanol (19/1), $R_f = 0.31$). Compound **9** was obtained as a yellow oil (2.43 g, 80% yield). ν_{max} (KBr)/cm^{-1} 3422, 2961, 2867, 1580, 1540, 1438, 1370, 1295, 1112, 791. δ_H (600 MHz, $CDCl_3$, 25°C) 1.19 (6H, t, ^3J 7.0, 11-CH_3), 2.53 (12H, s, 4-Pym-CH_3, 6-Pym-CH_3), 2.92 (4H, t, ^3J 6.7, 1-CH_2), 3.51 (4H, q, ^3J 7.0, 10-CH_2), 3.55–3.64 (20H, m, –OCH_2–), 8.64 (1H, br s, NH), 13.75 (1H, br s, NH). δ_C (150.9 MHz, $CDCl_3$, 25°C) 15.1 (q, 11-CH_3), 22.3 (q, 4-Pym-CH_3, 6-Pym-CH_3), 28.6 (t, 1-CH_2), 66.6 (t, 10-CH_2), 69.6 (t, 2-CH_2), 69.8 (t, –OCH_2–), 70.5 (t, –OCH_2–), 70.7 (t, –OCH_2–), 70.7 (t, –OCH_2–), 166.8 (br s, 4-Pym-C, 6-Pym-C), 177.8 (s, C=S). Signals for 2-Pym-C and 5-Pym-C could not be observed. *m/z* (EI, 70 eV) 457 (18%), 136 (100). *m/z* (CI, isobutane) 326 (16%), 284 (100), 135 (85). *m/z* (ESI, $CHCl_3$) 631 (100%) $[M + Na]^+$, 609 (30) $[M + H]^+$. (Found 631.3239. Calcd for $C_{29}H_{48}N_6O_6SNa^+$: 631.3254 (2.4 ppm); Found 632.3346. Calcd for $C_{28}{}^{13}CH_{48}N_6O_6SNa^+$: 632.3287 (9.3 ppm).)

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