DOI: 10.1002/ejoc.200800589

On the Importance of the Nature of Hydrogen Bond Donors in Multiple Hydrogen Bond Systems[‡]

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Keywords: Association constant / Hydrogen bond / Isothermal titration calorimetry (ITC) / NMR titration / Supramolecular chemistry

Association constants for the reaction between a fourfold hydrogen bond receptor **4** possessing an AADA hydrogen bond pattern and several complementary partners **5**–**7** with DDAD and DDA patterns have been determined by NMR titration and by isothermal titration calorimetry (ITC). A variation of one donor site in the DDAD pattern resulted in the following, surprising sequence of stability of the complexes: K_{Ass}(**6**, X = NHCOR) > K_{Ass}(**7**, X = H) > K_{Ass}(**5**, X = NHR). The synthesis of a well soluble DDAD receptor, the amidopyridylurea **6b** with a triethylene glycol chain, is described.

Introduction

The hydrogen bond is one of the most important interactions for molecular recognition in supramolecular chemistry.[1] Besides a decent binding energy, which may vary from a few kJ mol^{-1} to more than 100 kJ mol^{-1}, the hydrogen bond possesses directionality and reversibility. Thus by combination of several hydrogen bonds, patterns are generated that can bind only to respective complementary partners. Such pairs of patterns are of central importance in the DNA double helix but also in many other recognition events. The more hydrogen bonds a motif combines the stronger is the binding and the higher is the selectivity in the complex formation.[2]

Therefore, quadruple hydrogen bond motifs have been investigated during the last decade. By permutation, ten patterns of donors D and acceptors A can be generated of which two are self-complementary. The first system AADD (**1**) was described 1997 and due to the self-complementarity it forms a homodimer **1·1**.[3] The first heterodimer of non-selfcomplementary quadruple hydrogen bond motifs was the DAAD·ADDA complex **2a·3** that we published in 1998 (Figure 1).[4]

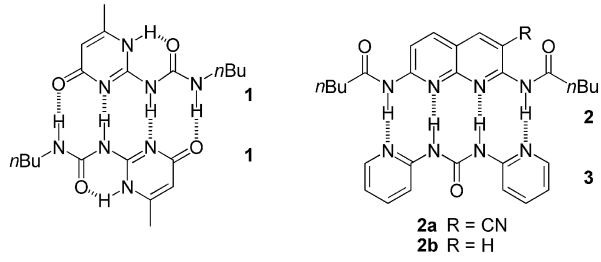

Figure 1. Homodimer and heterodimer held together by four hydrogen bonds. Left: AADD receptor **1** was the first self-complementary quadruple hydrogen bond motif, which forms a very stable homodimer **1·1**. Right: The first heterodimer formed by non self-complementary quadruple hydrogen bonds was **2a·3**.

At first glance, all complexes with four hydrogen bonds should exhibit binding constants of similar magnitude but already for three parallel and antiparallel hydrogen bonds it was shown that secondary interactions,[5] i.e. parallel or antiparallel dipoles, drastically alter the binding constant (e.g. K_{Ass}(DDD·AAA)[6] = 5.0·10^5 M^{-1} and K_{Ass}(DAD·ADA)[7] = 960 M^{-1}).

This alteration is also found in complexes, which are bound by four hydrogen bonds. For instance, the two possible self-complementary binding motifs possess different numbers of attractive and repulsive secondary interactions. Consequently, for the dimeric complex $(AADD)_2$, the association constant K_{Ass} was determined to be 3.6·10^6 M^{-1} but for the $(ADAD)_2$ complex the association constant K_{Ass} was smaller by one order of magnitude: 4.5·10^5 M^{-1}.[3b]

After having synthesized the DAAD·ADDA pair **2a·3**, we tried to obtain a second type of heterodimer: the AADA·DDAD pairs **4·5** and **4·6a**.[8] As already noticed for some derivatives of the building blocks of the DAAD·ADDA pair **2a·3**, the building blocks of

[‡] Multiple Hydrogen Bonds, 5. Part 4: Ref.[4b]

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AADA·DDAD showed limited solubilities in apolar organic solvents.[8] This is not surprising because molecules which contain hydrogen-bond donor and acceptor positions are able to undergo a number of attractive interactions among themselves: hydrogen bonds, flat packing and ππ-stacking interactions. For the AADA motif **4**, we increased the solubility by introducing a xylyl unit that is oriented perpendicular to the plane of the heterocycle due to steric interactions thus hampering crystallization.

As complementary DDAD motifs, the pyridylureas **5** and **6a** were synthesized and their association with receptor **4** was investigated in chloroform. While the amino-substituted pyridylurea **5** was sufficiently soluble in chloroform for a standard NMR titration, the acylated derivative **6a** was not. Nevertheless, a binding constant could be determined for the pair **4·6a** by inverse titration.[8]

In 2004, Quinn and Zimmerman[9] determined the association constant for the complexes **4·7a** and **4·7b**,[10] which are bound by only three N–H···N hydrogen bonds. To their surprise, they found association constants larger than the association constant for the complex **4·5**[8] in which four hydrogen bonds can be formed (Figure 2).

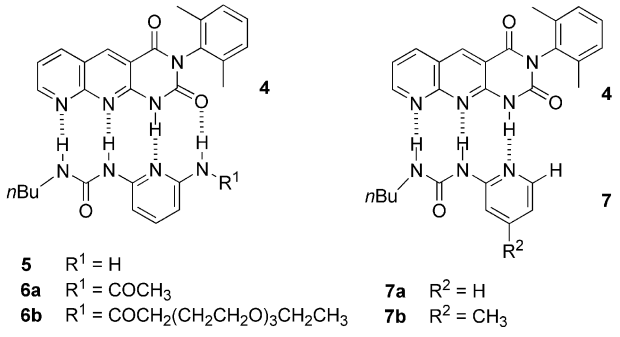


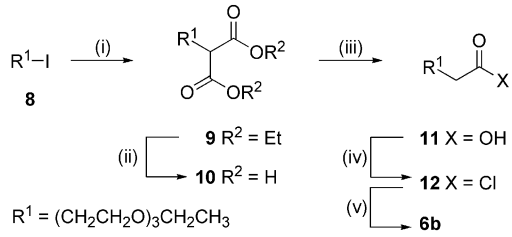
Figure 2. Comparison of heterodimer complexes with AADA receptor **4**. Left: In **5** and **6**, the hydrogen bond pattern is – in comparison to **7** – enlarged to DDAD by an additional NH substituent, allowing four hydrogen bonds in the heterodimer. Right: **4** binds to a DDA receptor **7** forming three hydrogen bonds if C–H···O is not considered to be a hydrogen bond.

Zimmerman and Quinn performed an X-ray analysis of the complex **4·7b** and studied its geometrical structure.[9] They recognized an inward curvature of the AADA counterpart **4**. Such a curvature is caused by the fact that aromatic C–N bonds are shorter than aromatic C–C bonds and by repulsion between the carbonyl groups and the coplanar pyridine ring. An inward curvature of at least one partner in a heterodimer bound by four hydrogen bonds causes longer bond lengths for the inner hydrogen bonds. With a longer hydrogen bond being weaker than a shorter one, Quinn and Zimmerman explain the smaller association constant found for **4·5** when compared with **4·7**. Additionally, they discuss an attractive interaction between the α-hydrogen atom of the pyridine ring of **7** and the carbonyl group of **4**.

However, this reasonable explanation fails to explain the value of K_{Ass}(**4·6a**) = 590 M^{-1} which we published in 2002,[8] and this discrepancy had not been discussed yet.[9]

Results and Discussion

Although association constants should not depend on the method by which they were determined, we wanted to perform a titration of **4** with **6** comparable to the measurements for the other pairs **4** with **7** and **4** with **5**, respectively. But for this enterprise, **6** had to be well soluble in chloroform. Therefore, we synthesized the derivative **6b** (Scheme 1) in which the acetyl group in the amide part of **6a** is substituted by an acyl moiety that was derived from a triethylene glycol ether.



Scheme 1. Synthesis of the soluble DDAD counterpart **6b**: (i) diethyl malonate, EtONa/EtOH, reflux 18 h, 92%; (ii) KOH/H_2O, room temp. 24 h, 99%; (iii) 170 °C, 30 min, quant.; (iv) $(COCl)_2$/DMF, room temp. 18 h, quant.; (v) **5**/NEt_3, 0 °C 1 h, room temp. 48 h, 91%.

The respective acid **11** was synthesized by a malonic ester synthesis, starting from commercially available triethylene glycol monoethyl ether. Tosylation[11] and exchange of the tosylate by iodide gave **8**.[12] Then diethyl malonate was alkylated with **8**, giving the ester **9** in 92% yield. Saponification of ester **9** afforded the diacid **10** in almost quantitative yield (99%), and heating to 170 °C for 30 min afforded quantitative decarboxylation to monoacid **11**. Reaction with oxalyl dichloride activated the acid and the resulting acid chloride **12** was then coupled with the amino-substituted pyridylurea **5** giving a new DDAD domain **6b** in 91% yield. As desired, the triethylene glycol chain provided **6b** with a very good solubility in chloroform thus allowing comparison to the other systems under identical NMR titration conditions.

In a second set of measurements, we determined the association constants between AADA receptor **4** and the complementary DDAD domains **5**–**7a** also by isothermal titration calorimetry (ITC). Table 1 displays all NMR and ITC data.

Table 1. Association constants K_{Ass} and thermodynamic data for the complexes of **4** with **5**–**7a**. K_{Ass} have been determined by NMR titration and by isothermal titration calorimetry, the thermodynamic data have been calculated from the ITC measurements.

	4·5	**4·6a**	**4·6b**	**4·7a**
K_{Ass}(NMR) [M^{-1}]	120[8]	590[8]	872	393[9]
K_{Ass}(ITC) [M^{-1}]	400	613	1120	645
ΔH [kJ mol^{-1}]	–11.1	–16.4	–1.61	–23.6
ΔS [J mol^{-1} K^{-1}]	–25.4	–42.4	8.56	–66.2

By comparing the association constants of Table 1, it becomes obvious that "less is not more".[9] Only the amino-substituted pyridylurea **5** shows a smaller binding constant

to **4** than hydrogen-substituted **7a**, which forms only three hydrogen bonds (if the C–H···O interaction is not considered to be a hydrogen bond) in a complex with **4**. The acylated (aminopyridyl)ureas **6a** and **6b** both exhibit distinctly larger binding constants than **7**.[9]

Although the complex **4·5** contains four hydrogen bonds like **4·6**, it possesses a smaller association constant. The difference between **5** and **6** is the amine or the amide group in the DDAD pattern, respectively. This finding reveals that the association in hydrogen-bonded complexes is stronger when an amide is used as a donor group instead of an amine. Hence, to get strong association the use of amides as donor groups is recommended.

The large influence of the nature of the hydrogen-bond donor on the magnitude of association constants is found in other systems, too. The acidity of the N–H group seems to be crucial. A closer look at the K_{Ass} values for the DAAD·ADDA systems **2a·3** and **2b·3** reveals that the latter one is bound less strongly: K_{Ass}(**2a·3**) = 2000 M^{-1} [4]; K_{Ass}(**2b·3**) = 1200 M^{-1}.[15] The DAAD receptors differ in their substitution pattern. In 3-position, **2a** carries a cyano group whereas **2b** is unsubstituted. It seems that the electron-withdrawing effect of the cyano group is favorable for a stronger binding. Presumably, the cyano group acidifies the N–H unit in 2-position and thus strengthens its hydrogen bond.

Secondly, the amine 2,7-bis(butylamino)naphthyridine **13** binds much weaker to **3** than the amides **2** [K_{Ass}(**13·3**) = 36 M^{-1}], (Figure 3). Naphthyridine **13** was synthesized by the reaction of known[13,14] dichloronaphthyridine **14** with *n*-butylamine in 68% yield (Scheme 2). Also in this example, the N–H donor in the amides **2** is more acidic than the amine N–H atoms in **13**, and thus larger binding constants have been found for the more acidic amide system than for the amine.

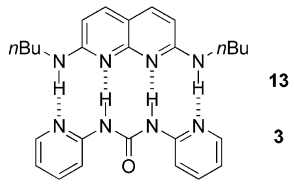
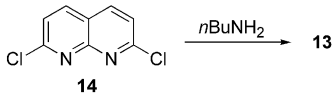


Figure 3. DAAD·ADDA complex in which the DAAD counterpart **13** contains amino groups as donors. Although this complex is bound by four hydrogen bonds its association constant is only K_{Ass}(**13·3**) = 36 M^{-1}.



Scheme 2. Synthesis of the DAAD counterpart **13**, which provides amino groups as hydrogen-bond donors. Reaction conditions: 78 °C, 18 h, 68%.

These results do not contradict the curvature effect. On the contrary, the binding constants (see Table 1) are smaller than one can expect for a system bound by four hydrogen bonds. For instance the DAAD·ADDA systems **2·3** possess binding constants larger than $K_{Ass} = 10^3$ M^{-1} [4,15] although the number of positive and negative secondary interactions is the same in a DAAD·ADDA and an AADA·DDAD pair. Schneider's increments[16] to estimate the association constants for hydrogen bonded complexes were successful to predict[4] the association constant K_{Ass} for **2a·3**. The smaller values for AADA·DDAD can therefore be due to the curvature although **2** for instance also possesses short aromatic C–N bonds.

These experiments underline that also in multiple hydrogen bonded systems, the strength of a hydrogen bond strongly depends on the nature of the donor. The observation that Schneider's rule of thumb[16] gives useful values in many cases probably results from the fact that the increments to a large extent have been derived from similar hydrogen bonds like amides or ureas.

Table 1 also shows interesting results when the ITC data are evaluated. All ITC values are larger than the constants determined by NMR spectroscopy. But such a deviation is not unreasonable. The NMR values have been determined from the change of the shifts of the protons involved in the hydrogen bonds. Thus, all changes are only caused by hydrogen bonds involving the specific proton analyzed. In contrast, the isothermal titration calorimetry is a calorimetric method that summarizes all interactions of the reaction partners, regardless whether hydrogen bonds or other intermolecular forces cause the interactions.[17] Therefore, the ITC values need to be larger than the NMR values because all other interactions are added on top of the hydrogen bonds. Although the error on the determination of association constants is at least 20%, additional information can be retrieved from the data. The difference of the association constants determined by NMR or ITC is largest for the amino-substituted pyridylurea **5**. This suggests that the hydrogen bonds are only a part of the interactions determined by ITC.

ITC also allows to analyze the enthalpic and entropic contributions ΔH and ΔS to the free enthalpy of complexation, reflected in the K_{Ass} values (see Table 1). All complexes show a negative reaction enthalpy ΔH but for complex **4·6b**, ΔH is almost zero. In contrast, the entropic contribution ΔS for this pair is positive while all other complexes show negative reaction entropies ΔS. The association constants K_{Ass} (or respectively the free reaction enthalpies) are all of comparable magnitude; thus an enthalpy-entropy compensation exists. Nevertheless, the question must be asked how the different behaviour of complex **4·6b** can be rationalized. The polyether chain is the obvious difference between **6b** and the other receptors **5**, **6a** and **7a**. Presumably, the polyether chain oxygen atoms interact with the hydrogen-bond donors in **6b**. When the complex **4·6b** is formed, these interactions have to be interrupted resulting in a smaller gain of enthalpy ΔH if compared to **4·5**, **4·6a** or **4·7a**. But simultaneously, the polyether chain is not bound any longer to the hydrogen-bond acceptors in **6b** and the additional degrees of conformational freedom create a positive reaction entropy ΔS.

Conclusions

The fact that we found a range of association constants for complexes that are bound by four hydrogen bonds in the same arrangement (AADA·DDAD, see Table 1) urges us to pay greater attention to the nature of the hydrogen-bond donors and acceptors, in addition to number, pattern, and shape of the counterparts. In particular, it is important to notice whether the donor group is an amine or an amide.

Experimental Section

General Remarks: The following chemicals were obtained commercially and used without further purification: *n*-butylamine (Fluka), diethyl malonate (Merck), oxalyl chloride (Fluka), triethylene glycol monoethyl ether (Fluka), chloroform (Acros) HPLC grade. **4**, **5** and **6a** were obtained according to a procedure described.[8] **7** was synthesized according to a preparation described by Boehmer.[18] Iodide **8** was obtained from the reaction of sodium iodide with triethylene glycol monoethyl ether *p*-tosylate.[11] This tosylate was prepared according to a preparation published by Le Mest.[11] **14** was obtained according to the literature: 2-amino-7-hydroxynaphthyridine was synthesized according to a procedure published by Stuk[13] and this was converted by a preparation of Newkome[14] to 2,7-dihydroxynaphthyridine and after chlorination to **14**. Anhydrous ethanol was obtained by refluxing with sodium and diethyl phthalate (1 h) followed by distillation. Anhydrous dichloromethane was obtained by refluxing with calcium hydride (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 AM 300, DRX 500 or AV 600 instruments. Assignments are supported by COSY, HSQC and HMBC. IR spectra were recorded with a Perkin–Elmer Paragon 1000 spectrometer. Mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230 spectrometer. ESI mass spectra were recorded with an Applied Biosystems Mariner Spectrometry Workstation. Elemental analyses were carried out with a EuroEA 3000 Elemental Analyzer from Euro Vector. Gas-chromatographic studies were carried out with an Agilent Gas Chromatograph 6890N, column: Optima, 1/30 m. Calorimetric studies were performed with a MicroCal VP-ITC-Microcalorimeter; 2.0 mM solution of **4** in HPLC-grade $CHCl_3$ was filled into the cell. Then, 40 mM solutions of **5**, **6** or **7** in $CHCl_3$ were added slowly, and the calorimetric changes were recorded and analyzed by the MicroCal software. NMR titrations were carried out with a Bruker DRX 500 instrument at 25 °C adding **5**, **6** or **7** slowly to a 13.8 mM solution of **4** in $CDCl_3$ while recording the changes in the resonances of the amide protons of **4**.

***N*-Butyl-*N*′-[6-(5,8,11-trioxatridecanoylamino)-2-pyridyl]urea (6b):** Compound **5**[8] (1.25 g, 6.00 mmol) and triethylamine (832 μL, 6.00 mmol) were dissolved in anhydrous dichloromethane (50 mL). Under N_2 atmosphere and 0 °C, **12** (1.19 g, 5.00 mmol) was slowly added and the mixture was stirred at 0 °C for 1 h. After warming up to room temperature, the reaction mixture was allowed to stir for 48 h. Water (25 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried with magnesium sulfate, and the solvent was evaporated to dryness. Column chromatography (silica gel, ethyl acetate, R_f = 0.28) yielded **6b** as a colorless oil (1.87 g, 91% yield). ^{1}H NMR[19] (500 MHz, $CDCl_3$, 25 °C): δ = 0.95 (t, ^3J = 7.4 Hz, 3 H, 4′-CH_3), 1.18 (t, ^3J = 7.0 Hz, 3 H, 13′′-CH_3), 1.41 (sext, ^3J = 7.4 Hz, 2 H, 3′-CH_2), 1.61 (quint, ^3J = 7.4 Hz, 2 H, 2′-CH_2), 2.00 (quint, ^3J = 6.9 Hz, 2 H, 3′′-CH_2), 2.54 (t, ^3J = 6.9 Hz, 2 H, 2′′-CH_2), 3.37 (td, ^3J = 7.4, ^3J = 6.1 Hz, 2 H, 1′-CH_2), 3.51 (q, ^3J = 7.0 Hz, 2 H, 12′′-CH_2), 3.58 (t, ^3J = 6.9 Hz, 2 H, 4′′-CH_2), 3.56–3.67 (m, 8 H, 6′′-CH_2, 7′′-CH_2, 9′′-CH_2, 10′′-CH_2), 6.51 (m, 1 H, Ar-4-*H*), 7.55 (m, 2 H, Ar-5-*H*, Ar-3-*H*), 8.00 (br. s, 1 H, Ar-N*H*), 8.41 (br. s, 1 H, Ar-N*H*), 8.82 (br. s, 1 H, N*H*) ppm. ^{13}C NMR[19] (125.8 MHz, $CDCl_3$, 25 °C): δ = 13.9 (q, 4-*C*H$_3$), 15.1 (q, 13′′-*C*H$_3$), 20.3 (t, 3-*C*H$_2$), 25.5 (t, 2-*C*H$_2$), 32.3 (t, 1-*C*H$_2$), 34.5 (t, 3′′-*C*H$_2$), 39.8 (t, 2′′-*C*H$_2$), 66.7 (t, 4′′-*C*H$_2$), 69.8 (t, 12′′-*C*H$_2$), 70.1 (t, 6′′-*C*H$_2$), 70.1 (t, 7′′-*C*H$_2$), 70.4 (t, 9′′-*C*H$_2$), 70.5 (t, 10′′-*C*H$_2$), 105.9 (d, Ar-3-*C*), 106.8 (d, Ar-5-*C*), 140.3 (d, Ar-4-*C*), 148.8 (s, Ar-2-*C*), 151.7 (s, NH*C*ON), 155.5 (s, Ar-6-*C*), 171.5 (s, NH*CO*CH$_2$) ppm. IR (KBr): $\tilde{\nu}$ = 3261, 2958, 2871, 1676, 1594, 1545, 1449, 1348, 1255, 1158, 1112, 801 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 410 (13) [M]$^+$, 220 (35) [M – $C_{10}H_{22}O_3$]$^+$, 204 (65) [M – $C_{10}H_{16}N_4O$]$^+$, 177 (100) [M – $C_{13}H_{28}O_3$]$^+$. MS (CI, isobutane): *m*/*z* (%) = 411 (9) [M + H]$^+$, 338 (31) [M – $C_4H_{10}N$]$^+$, 74 (100) [M – $C_{16}H_{24}N_4O_4$]$^+$. MS (ESI, $CHCl_3$): *m*/*z* (%) = 843 (3) [M_2 + Na]$^+$, 433 (100) [M + Na]$^+$. $C_{20}H_{34}N_4O_5$ (410.51): calcd. C 58.52, H 8.35, N 13.65; found C 58.30, H 8.59, N 13.38.

Diethyl 2-(3,6,9-Trioxaundecyl)malonate (9): Under N_2 atmosphere sodium (1.77 g, 77.0 mmol) was carefully dissolved in 200 mL of anhydrous ethanol to give a sodium ethanolate solution. To this solution, a mixture of **8** (22.2 g, 77.0 mmol) and diethyl malonate (12.5 g, 78.0 mmol) was added dropwise under N_2 atmosphere and heated at reflux for 18 h. After cooling and evaporation of the solvent, the residue was dissolved in water (50 mL). The mixture was acidified with concentrated hydrochloric acid (pH 1) and extracted with dichloromethane (5 × 50 mL). The combined organic layer was dried with magnesium sulfate and the solvent was removed. Column chromatography [silica gel, cyclohexane/ethyl acetate (1:1), R_f = 0.22] yielded **9** as a colorless oil (22.7 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.21 (t, ^3J = 7.0 Hz, 3 H, 11′-H), 1.27 (t, ^3J = 7.2 Hz, 6 H, COOCH$_2$CH_3), 2.18 (td, ^3J = 6.1, ^3J = 7.3 Hz, 2 H, 1′-H), 3.53 (t, ^3J = 6.1 Hz, 1 H, 2′-H), 3.52 (t, ^3J = 7.3 Hz, 2 H, CH), 3.53 (q, ^3J = 7.0 Hz, 2 H, 10′-H), 3.56–3.65 (m, 4 H, 4′-H, 5′-H), 3.62–3.66 (m, 4 H, 7′-H, 8′-H), 4.193 (dq, ^2J = 10.6, ^3J = 7.2 Hz, 2 H, COO-CH_aH$_b$-CH$_3$), 4.195 (dq, ^2J = 10.6, ^3J = 7.2 Hz, 2 H, COO-CH$_a$$H_b$-CH$_3$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ = 14.0 (q, COO-CH$_2$*C*H$_3$), 15.1 (q, 11′-*C*), 28.7 (t, 1′-*C*), 48.9 (d, *C*H), 61.3 (t, COO-*C*H$_2$-CH$_3$), 66.6 (t, 10′-*C*), 68.3 (t, 2′-*C*), 69.8 (t, 4′-*C*), 70.2 (t, 5′-*C*), 70.5 (t, 7′-*C*), 70.6 (t, 8′-*C*), 169.3 (s, *C*=O) ppm. IR (film): $\tilde{\nu}$ = 3444, 2977, 2869, 1732, 1446, 1370, 1258, 1112, 1028 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 187 (80) [M – $C_6H_{13}O_3$]$^+$, 160 (85) [M – $C_7H_{12}O_4$]$^+$, 159 (69) [M – $C_8H_{17}O_3$]$^+$, 117 (100) [M – $C_9H_{15}O_5$]$^+$, 73 (94) [M – $C_{11}H_{19}O_6$]$^+$. MS (CI, isobutane): *m*/*z* (%) = 321 (31) [M + H]$^+$, 187 (100) [M – $C_6H_{13}O_3$]$^+$, 117 (54) [M – $C_9H_{15}O_5$]$^+$. MS (ESI, $CHCl_3$): *m*/*z* (%) = 343 (100) [M + Na]$^+$. $C_{15}H_{28}O_7$ (320.40): calcd. C 56.23, H 8.81; found C 56.25, H 8.92. GC (Optima, 1/30 m, temp. program:[20] 70$_5$–*10*–250$_{20}$): t_{ret} = 17.8 min, purity: 99%.

2-(3,6,9-Trioxaundecyl)malonic Acid (10): Compound **9** (13.6 g, 42.5 mmol) was dissolved in 2 M potassium hydroxide solution (100 mL) and was stirred at room temperature for 24 h. The mixture was washed with diethyl ether (50 mL) and acidified with concentrated hydrochloric acid (pH 1). Then for 5 h, the mixture was extracted continuously with diethyl ether. The organic extract was dried with magnesium sulfate and the solvent was evaporated. Column chromatography [silica gel, dichloromethane/ethanol (4:1), R_f = 0.11] yielded **10** as a colorless oil (11.1 g, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, ^3J = 7.0 Hz, 3 H, 11′-H), 2.25 (td, ^3J = 6.0, ^3J = 6.0 Hz, 2 H, 1′-H), 3.55 (q, ^3J = 7.0 Hz, 2 H, 10′-H), 3.54–3.59 (m, 3 H, CH, 2′-H), 3.59–3.64 (m, 4 H, 4′-H, 5′-H), 3.65–3.68 (m, 4 H, 7′-H, 8′-H), 10.42 (br. s, 2 H, OH) ppm.

^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ = 14.6 (q, 11′-*C*), 29.2 (t, 1′-*C*), 48.3 (d, *C*H), 66.8 (t, 10′-*C*), 68.2 (t, 2′-*C*), 69.8 (t, 4′-*C*), 69.8 (t, 5′-*C*), 69.8 (t, 7′-*C*), 70.2 (t, 8′-*C*), 173.1 (s, *C*=O) ppm. IR (film): $\tilde{\nu}$ = 3439, 2879, 1728, 1350, 1248, 1180, 1099, 946 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 117 (19) $[M - C_5H_7O_5]^+$, 88 (100) $[M - C_7H_{12}O_5]^+$. MS (CI, isobutane): *m*/*z* (%) = 265 (2) $[M + H]^+$, 221 (6) $[M - CO_2 + H]^+$, 117 (100) $[M - C_5H_7O_5]^+$. $C_{10}H_{20}O_7$ (264.27) calcd. C 49.99, H 7.63. $C_{10}H_{20}O_7 \cdot 0.5EtOH \cdot 0.2H_2O$: calcd. C 49.54, H 8.11 found C 49.45, H 8.13. GC (Optima, 1/30 m, temp. program:[20] 70_5–*10*–250_{20}): t_{ret} = 14.3 min, purity: 97%.

5,8,11-Trioxatridecanoic Acid (11): 10 (6.61 g, 25.0 mmol) was heated to 170 °C for 30 min. Column chromatography [silica gel, dichloromethane/ethanol (19:1), R_f = 0.26] yielded **11** as a colorless oil (5.51 g, 100% yield). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, ^3J = 7.0 Hz, 3 H, 13-H), 1.92 (tt, ^3J = 7.2, ^3J = 6.1 Hz, 2 H, 3-H), 2.45 (t, ^3J = 7.2 Hz, 2 H, 2-H), 3.53 (t, ^3J = 6.1 Hz, 2 H, 4-H), 3.55 (q, ^3J = 7.0 Hz, 2 H, 12-H), 3.58–3.63 (m, 4 H, 6-H, 7-H), 3.63–3.67 (m, 4 H, 9-H, 10-H), 8.51 (br. s, 1 H, OH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 25 °C): δ = 15.0 (q, 13-*C*), 24.8 (t, 3-*C*), 31.0 (t, 2-*C*), 66.6 (t, 12-*C*), 69.8 (t, 4-*C*), 70.1 (t, 6-*C*), 70.1 (t, 7-*C*), 70.5 (t, 9-*C*), 70.5 (t, 10-*C*), 178.1 (s, 1-*C*) ppm. IR (film): $\tilde{\nu}$ = 3448, 2871, 1719, 1350, 1250, 1109, 948 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 202 (1) $[M - H_2O]^+$, 161 (7) $[M - C_2H_3O_2]^+$, 117 (100) $[M - C_4H_7O_3]^+$, 87 (100) $[M - C_6H_{13}O_3]^+$. MS (CI, isobutane): *m*/*z* (%) = 221 (5) $[M + H]^+$, 203 (7) $[M - OH]^+$, 161 (1) $[M - C_2H_3O_2]^+$, 117 (100) $[M - C_4H_7O_3]^+$. $C_{10}H_{20}O_5$ (220.26) calcd. C 54.53, H 9.15. $C_{10}H_{20}O_5 \cdot 0.5H_2O$: calcd. C 54.30, H 9.53; found C 54.13, H 9.52. GC (Optima, 1/30 m, temp. program:[20] 70_5–*10*–250_{20}): t_{ret} = 14.2 min, purity: 95%.

5,8,11-Trioxatridecanoyl Chloride (12): Under N_2 atmosphere **11** (2.20 g, 10.0 mmol) and DMF (0.5 mL) were dissolved in anhydrous dichloromethane (50 mL). Oxalyl dichloride (1.72 mL, 20.0 mmol) was slowly added and the mixture was stirred at room temperature for 18 h. Removal of the solvent yielded the crude product **12**, which was used without further purification (2.39 g, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.22 (t, ^3J = 7.0 Hz, 3 H, 13-H), 1.97 (tt, ^3J = 7.2, ^3J = 5.9 Hz, 2 H, 3-H), 3.03 (t, ^3J = 7.2 Hz, 2 H, 2-H), 3.52 (t, ^3J = 5.9 Hz, 2 H, 4-H), 3.54 (q, ^3J = 7.0 Hz, 2 H, 12-H), 3.58–3.68 (m, 8 H, 6-H, 7-H, 9-H, 10-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 15.0 (q, 13-*C*), 25.1 (t, 3-*C*), 43.9 (t, 2-*C*), 66.5 (t, 12-*C*), 68.8 (t, 4-*C*), 69.7 (t, 6-*C*), 70.1 (t, 7-*C*), 70.4 (t, 9-*C*), 70.6 (t, 10-*C*), 173.7 (t, 1-*C*) ppm. IR (film): $\tilde{\nu}$ = 2973, 2923, 2869 1802, 1444, 1350, 1247, 1115, 961 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 151 (12) $[M(^{37}Cl) - C_4H_9O_2]^+$, 149 (33) $[M(^{35}Cl) - C_4H_9O_2]^+$, 72 (100) $[M - C_6H_{11}ClO_3]^+$. MS (CI, isobutane): *m*/*z* (%) = 241 (4) $[M(^{37}Cl)]^+$, 239 (13) $[M(^{35}Cl)]^+$, 117 (100) $[M - C_4H_6ClO_2]^+$. MS (ESI, $CHCl_3$): *m*/*z* (%) = 261 (100) $[M + Na]^+$.

2,7-Bis(butylamino)-1,8-naphthyridine (13): Under N_2 atmosphere 2,7-dichloro-1,8-naphthyridine (**14**, 4.00 g, 20.0 mmol) was dissolved in *n*-butylamine (65 mL) and heated at 78 °C for 18 h. After cooling, the solvent was removed and the residue was dissolved in dichloromethane (25 mL) and water (25 mL). After separation of the layers, the aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic layer was dried with magnesium sulfate, and the solvent was evaporated to dryness. Column chromatography (silica gel, ethyl acetate, R_f = 0.13) yielded **13** as yellow crystals (3.71 g, 68% yield); m.p. 87–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.94 (t, ^3J = 7.0 Hz, 6 H, 4-CH_3), 1.40 (sext, ^3J = 7.0 Hz, 4 H, 3-CH_2), 1.61 (quint, ^3J = 7.0 Hz, 4 H, 2-CH_2), 3.44 (dt, ^3J = 5.7, ^3J = 7.0 Hz, 4 H, 1-CH_2), 4.84 (br. t, ^3J = 5.7 Hz, 2 H, N*H*), 6.33 (d, ^3J = 8.6 Hz, 2 H, Ar-3-*H*, Ar-6-*H*), 7.55 (d, ^3J = 8.6 Hz, 2 H, Ar-4-*H*, Ar-5-*H*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 13.8 (q, 4-*C*H$_3$), 20.1 (t, 3-*C*H$_2$), 31.7 (t, 2-*C*H$_2$), 41.5 (t, 1-*C*H$_2$), 105.3 (d, Ar-3-*C*, Ar-6-*C*), 110.5 (s, Ar-8a-*C*), 137.0 (d, Ar-4-*C*, Ar-5-*C*), 157.2 (s, Ar-4a-*C*), 159.6 (s, Ar-2-*C*, Ar-7-*C*) ppm. IR (KBr): $\tilde{\nu}$ = 3355, 3226, 2952, 2926, 2869, 1604, 1578, 1536, 1458, 1368, 1342, 1142, 966, 797, 728 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 272 (43) $[M]^+$, 243 (100) $[M - C_2H_5]^+$, 229 (66) $[M - C_3H_7]^+$. MS (CI, isobutane): *m*/*z* (%) = 273 (100) $[M + H]^+$. MS (ESI, $CHCl_3$): *m*/*z* (%) = 545 (15) $[M_2 + H]^+$, 273 (100) $[M + H]^+$. $C_{16}H_{24}N_4$ (272.39): calcd. C 70.55, H 8.88, N 20.57; found C 70.35, H 8.97, N 20.66.

Acknowledgments

The support of the Deutsche Forschungsgemeinschaft (DFG) (Lu 378/15) is greatfully acknowledged.

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[19] The hydrogen atoms in the polyether chain are tagged with a double quote (e.g. 13′′-CH_3).
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Received: June 18, 2008
Published Online: November 5, 2008

