Pergamon

Tetrahedron Letters 39 (1998) 5735–5738

TETRAHEDRON LETTERS

Heterodimers for molecular recognition by fourfold hydrogen bonds

Ulrich Lüning* and Christine Kühl
Institut für Organische Chemie, Olshausenstr. 40, D-24098 Kiel, Germany

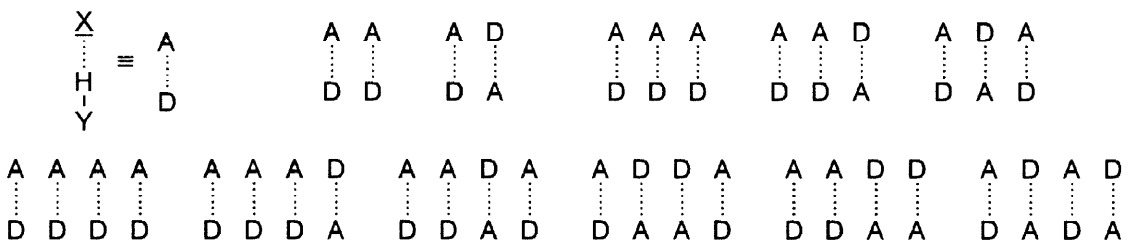
Received 15 May 1998; accepted 5 June 1998

Abstract

DAAD hydrogen bond donor (D) and acceptor (A) arrays **1** were synthesized and the recognition of the complementary ADDA substrates **2** and heterodimer formation by four hydrogen bonds was measured by ^{1}H NMR titrations. The binding energy of a sterically not crowded dimer is in accordance with the value calculated from increments.

Keywords: supramolecular chemistry; hydrogen bonds; molecular recognition; azaheterocycles.

Intermolecular interactions, especially hydrogen bonds between atoms X with a free electron pair and Y with an acidic hydrogen atom, are the bases of many processes of supramolecular chemistry and molecular recognition [1-9]. The strength of these interactions depends on the number of the hydrogen bonds. With an increasing number of hydrogen bonds the molecular recognition becomes more and more specific because more combinations of hydrogen bond donors (D) and acceptors (A) will become possible.



Only two dimers are possible with two hydrogen bonds while three hydrogen bonds give three [10] and four hydrogen bonds will already give six possible combinations. Some of these dimers are homodimers, i.e. they recognize and bind themselves (AD, ADAD, AADD) but for an *aimed* molecular recognition, especially for the construction of supramolecular structures, heterodimers are necessary.

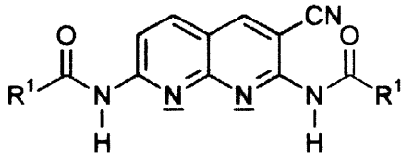
In the literature not many dimers containing four neighboring hydrogen bonds have been described [11-15]. All these structures are homodimer. Here we describe heterodimers which are bound by four hydrogen bonds (side by side linear four point recognition).

Fax: +49-431-880-1558, e-mail: luening@oc.uni-kiel.de

0040-4039/98/$19.00
PII: S0040-4039(98)01200-3

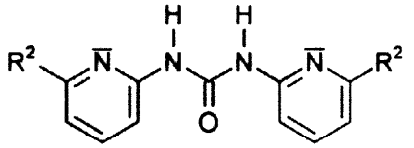
As DAAD-units 2,7-bis(acylamino)-1,8-naphthyridines **1** were chosen, as complementary units the literature known di- and monopyridyl ureas **2** and **3** [16-20] and 6-amino-2-pyridyl ureas **4**[1] were used. The synthesis of the naphthyridine receptors **1**[2] starting from 2,6-diamino-3-formylpyridine **5** [21] is summarized in Scheme 1.

DAAD:



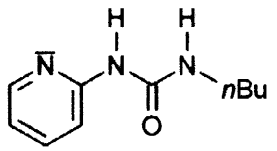
1a: R^1 = *n*Bu
1b: R^1 = *t*Bu

ADDA:



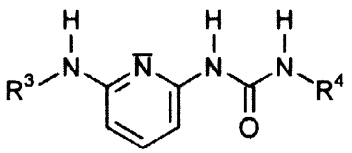
2a: R^2 = H
2b: R^2 = Me

ADD:



3

DADD:



4a: R^3 = H, R^4 = *c*Hex
4b: R^3 = H, R^4 = *n*Bu
4c: R^3 = Ac, R^4 = *n*Bu

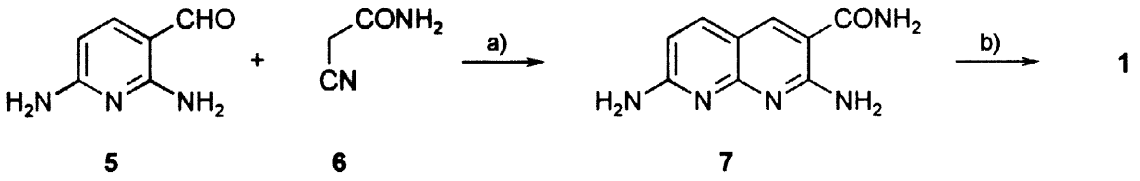
The formation of heterodimers between **1** and **2** was investigated by ^{1}H NMR spectroscopy in $CDCl_3$ (500 MHz) at 295 K. The association constants K_{ass} for the formation of 1 : 1 complexes were calculated from the changes of the chemical shifts of the NH protons of **1**. For comparison the dimer formation between **1** and the ADD unit **3**, as well as the dimer formation between **1** and the non complementary DADD unit **4b** were measured. Table 1 summarizes these data. The reaction enthalpies ΔG were determined from the association constants K_{ass} and are compared with the reaction enthalpies calculated from increments (ΔG_c) [22]. The increment for a hydrogen bond is 7.9 kJmol^{-1}, a secondary [23] repulsive or attractive electrostatic interaction is ± 2.9 kJmol^{-1}. As *X*-ray analyses, NMR and IR spectroscopy show [24], **2**, **3** and **4** are able to form intramolecular hydrogen bonds. Therefore in the calculations of ΔG_c', 7.9 kJmol^{-1} were taken into account for the cleavage of the intramolecular hydrogen bond.

K_{ass} were determined from titrations at at least seven different ratios followed by non-linear least squares curve fitting [25] (R > 0.99). The formation of strong hydrogen bonds between **1a** and **2a** (K_{ass} = 2000 M^{-1}) could also be followed by IR in solution [IR($CHCl_3$): **2a**: $\tilde{\nu}_{NH}$(free):

---

1 From 2,6-diaminopyridine and isocyanates in toluene: **4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.2-2.1 (m, 10 H), 3.7-3.9 (m, 1 H), 4.30 (br. s, 2 H), 6.06 (d, 8.0 Hz, 1 H), 6.13 (d, 8.0 Hz, 1 H), 7.32 (t, 8.0 Hz, 1 H), 7.89 (br. s, 1 H, N*H*), 9.15 (d, 7.6 Hz, 1 H, N*H*). **4b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (t, 7.1 Hz, 3H), 1.3-1.7 (m, 4H), 3.37 (m_c, 2H), 4.32 (br. s, 2H) 6.06 (d, 8.0 Hz, 1 H), 6.13 (d, 7.7 Hz, 1 H), 7.33 (m_c, 1 H), 8.01 (br. s, 1 H, N*H*), 9.14 (m_c, 1 H, N*H*). **4c**: ^{1}H NMR (200 MHz, [D_6]-DMSO): δ = 0.89 (t, 7.1 Hz, 3 H), 1.2-1.5 (m, 4 H), 2.10 (s, 3 H), 3.19 (m_c, 2 H), 6.76 (d, 7.9 Hz, 1 H), 7.40 (d, 7.9 Hz, 1 H), 7.58 (t, 8.0 Hz, 1 H), 8.68 (m_c, 1 H, N*H*), 9.09 (br. s, 1 H, N*H*), 10.23 (br. s, 1 H, N*H*).

2 **1a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, 7.4 Hz, 3 H), 0.97 (t, 7.4 Hz, 3 H), 1.45 (sext., 7.5 Hz, 2 H), 1.46 (sext., 7.5 Hz, 2 H), 1.75 (quint., 7.4 Hz, 2 H), 1.78 (quint., 7.4 Hz, 2 H), 2.49 (t, 7.5 Hz, 2 H), 2.69 (t, 7.5 Hz, 2 H), 8.15 (br. s, 1H, NH_a), 8.18 (d, 8.9 Hz, 1 H), 8.35 (br. s, 1 H, NH_b), 8.49 (s, 1 H), 8.59 (d, 8.9 Hz, 1 H). **1b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 1.40 (s, 9 H), 8.16 (br. s, 1 H, NH_a), 8.22 (d, 8.9 Hz, 1 H), 8.47 (br. s, 1 H, NH_b), 8.52 (s, 1 H), 8.62 (d, 8.9 Hz, 1 H).



Scheme 1. Synthesis of the naphthyridine receptors **1**. Reaction conditions and yields:
a) 20 eq. **6**, 4 eq. piperidine, dry EtOH, N_2, 3.5 h reflux, 62%
b) 2.5 - 3 eq. NEt_3, 4 eq. R^1COCl, dry pyridine, 2 h reflux; R^1 = *n*Bu, 62%; R^1 = *t*Bu, 43%.

3431 cm^{-1}, $\tilde{\nu}_{NH}$(intramolecular): 3150 cm^{-1} (broad), **1a**: $\tilde{\nu}_{NH}$(free): 3402 cm^{-1}, **1a · 2a**: $\tilde{\nu}_{NH}$(bound): 3212 cm^{-1} (broad)]. A NOESY spectrum showed the interaction between the 6-H-atoms in **2a** and all butyl-H atoms and the NH protons in 2- and 7-position of the naphthyridine **1a**.

For the other heterodimers with complementary units **1 · 2** and **1 · 3** the maximum changes in chemical shifts were smaller. This can be due to steric interactions between the substituents R^1 and R^2. But also in a dimer **1a · 3**, statistically only 50% of the NH protons of **1a** are bound in a hydrogen bond. This is reflected in $\Delta\delta_{max}$ values between 2 and 2.5 ppm.

If the intramolecular hydrogen bonds in **2** or **3** are taken into account, the increments [22] predict the strength of the hydrogen bonds in the sterically not strained dimer. If the steric hindrance is increased by larger substituents R^1 and R^2 not only the constant for the dimerization K_{ass} diminishes drastically (for **1b · 2b** only 16 M^{-1} are found). Also the maximum change of the chemical shifts $\Delta\delta_{max}$ drops from >4 to <1 ppm.

The heterodimers presented here with fourfold hydrogen bonds represent promissing templates for molecular recognition. In comparison with triple hydrogen bonds as for instance in nucleic acids the specificity of a molecular recognition is increased by the fourth hydrogen bond because only one of ten possible partners is complementary.

The 6-amino-2- pyridyl ureas **4** contain a DADD hydrogen bond donor and acceptor array instead of the complementary ADDA pattern which is necessary for the binding of **1**. They are *not* complementary to the bisaminonaphthyridines **1**. If **4b** binds to **1a** such dimer formation will

Table 1.
Formation of heterodimers between DAAD-naphthyridines **1** and molecules with three (**3**) or four (**2**, **4**) hydrogen bond donors and acceptors. Non-linear least squares curve fitting of the titration data gave the maximum chemical shift of the amide-protons $\Delta\delta_{max}$ (NH) and the association constant K_{ass} [a]. $\Delta\Delta G_c$ is the difference between the free enthalpy ΔG calculated from K_{ass} and ΔG_c calculated from increments [22].

			$\Delta\delta_{max}$		K_{Ass}	ΔG	ΔG_c	$\Delta\Delta G_c$
	R^1	R^2	NH_a	NH_b	[M^{-1}]	[kJmol^{-1}]	[kJmol^{-1}]	[kJmol^{-1}]
1a · 2a	*n*Bu	H	4.4	3.7	2000	-18.6	-17.9	-0.7
1a · 2b	*n*Bu	Me	3.0	2.4	160	-12.4	-17.9	5.5
1a · 3	*n*Bu	–	2.2	2.5	40	-9.0	-15.8	6.8
1b · 2a	*t*Bu	H	1.0	1.5	37	-8.9	-17.9	9.0
1b · 2b	*t*Bu	Me	0.8	0.2	16	-6.8	-17.9	11.1
1a · 4b	*n*Bu	–	1.7	2.1	31	-8.4	-15.8	7.4

a) [**1**] = 3-7 mM, the reaction partner was added in steps at 295 K until 15-30 equivalents were reached. Estimated error: <20%. A self association of **1** was not observed in the concentration range of the NMR titrations.

only be bound by three bridges: DAAD · DDAD. Therefore the association constant K_{ass} is only 31 M^{-1}, comparable to **1a** · **3**.

The information stored in a fourfold hydrogen bond array can be increased even further when unsymmetrical donor-acceptor-arrays are used instead of the symmetrical ADDA · DAAD system presented here (AAAD · DDDA or AADA · DDAD). While DAAD and ADDA units can be bound in two orientations due to their symmetry (e.g. **1**: with the cyano group 'left' or 'right'), a DDAD or AADA system has only one possible orientation in a complex. With **4a-c** DDAD receptors already exist.

Acknowledgements:
We thank Dr. C. Wolff and Dipl.-Chem. G. Kohlmeyer-Yilmaz for their help in NMR spectroscopy.

[1] Lehn J-M. Supramolecular Chemistry, Weinheim: VCH, 1995.
[2] Voegel J J, Benner S A. J. Am. Chem. Soc. 1994;116:6929-6930.
[3] Murray T J, Zimmerman S C. Tetrahedron Lett. 1995;36:7627-7630, and ref. cited.
[4] MacGillivray L R, Atwood J L. Nature 1997;389:469-472.
[5] Tokunaga Y, Rudkevich D M, Rebek J Jr. Angew. Chem. 1997;109:2770-2773; Angew. Chem. Int. Ed. Engl. 1997;36:2656-2659, and ref. cited.
[6] Vreekamp R H, van Duynhoven J P M, Hubert M, Verboom W, Reinhoudt D N. Angew. Chem. 1996;108:1306-1309; Angew. Chem. Int. Ed. Engl. 1996;35:1215-1218.
[7] Whitesides G M, Simanek E E, Mathias J P, Seto C T, Chin D N, Mammen M, Gordon D M. Acc. Chem. Res. 1995;27:37-44.
[8] Ghadiri M R, Granja J R, Milligan R A, McRee D E, Khazanovich N. Nature 1993;366:324.
[9] Kelly T R, Bridger G J, Zhao C. J. Am. Chem. Soc. 1990;112:8024-8034.
[10] For a systematic variation: [3]; of nucleobases see [2].
[11] Griffin R J, Lowe P R. J. Chem. Soc. Perkin Trans 1 1992;1811-1819.
[12] Sijbesma R P, Beijer F H, Brunsveld L, Folmer B J B, Hirschberg J H K K, Lange R F M, Lowe J K L, Meijer E W. Science 1997;278:1601-1604.
[13] Beijer F H, Kooijman H, Spek A L, Sijbesma R P, Meijer E W. Angew. Chem. 1998;110:79-82, Angew. Chem. Int. Ed. Engl. 1998;37:75-78.
[14] Ducharme Y, Wuest J D. J. Org. Chem. 1988;53:5787-5789.
[15] Other ADAD systems exclusively form polymere structures, e.g: Garcia-Tellado F, Geib S J, Goswami S, Hamilton A D. J. Am. Chem. Soc. 1991;113:9265-9269.
[16] **2a**: Camps R, Arch. Pharm. (Weinheim Ger.) 1902;240,350.
[17] **2a**: Beilsteins Handbuch der Organischen Chemie, 4. Aufl., 3. und 4. Ergänzungswerk, Bd. 22, S. 3896, Berlin: Springer Verlag 1979.
[18] **2b**: Clemo G R, Fox B W, Raper R. J Chem. Soc. 1954;2693-2701.
[19] **3**: Boehmer J W. Recl. Trav. Chim. Pays-Bas 1936;55, 379.
[20] **3**: Beilsteins Handbuch der Organischen Chemie, 4. Aufl., 3. und 4. Ergänzungswerk, Bd. 22, S. 3894, Berlin: Springer Verlag 1979.
[21] Fenlon E E, Murray T J, Baloga M H, Zimmerman S C. J. Org. Chem. 1993;58:6625-6628.
[22] Sartorius J, Schneider H-J. Chem. Eur. J. 1996;2:1446-1552.
[23] Jorgensen W L, Pranata J. J. Am. Chem. Soc. 1990;112:2008-2010.
[24] Kühl C. Dissertation in preparation, Universität Kiel 1998.
[25] Connors K A. Binding Constants. New York: Wiley 1987.