Structural Effects on the Stability of Some Hydrogen-Bonded Complexes with Nucleobases

Lianhe Yu[a] and Hans-Jörg Schneider*[a]

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The effect that additional groups flanking the hydrogen bond donor/acceptor arrays have on the association constants (K_a) of complexes of chloroform-soluble thymine and adenine derivatives has been investigated by NMR shift titration. Constants for thymine and 2,6-diaminoacyl pyridine derivatives, in which the acyl group bears either $(CH_2)_nR$ or some other substituent, vary greatly. The peak value of K_a = 1130 M^{-1} occurs for n = 2 and R = phenyl. Computer modeling with CHARMm suggests that this is due to a weak additional stabilization by a C–H-π interaction; in line with this the complex shows small upfield NMR shifts for the terminal methyl groups. Four other receptors were prepared which could, in principle, form hydrogen bonds with all donor/acceptor sites of adenine; NMR titrations, however, showed very low complexation energies, probably due to deviations from the ideal hydrogen bond geometry necessary to form stronger complexes.

Introduction

Hydrogen-bonds are key factors through which a biological system "recognizes" another system on a molecular level.[1] Association of nucleobases with synthetic ligands by specific hydrogen-bonding has been a longstanding focus of supramolecular chemistry.[2][3] The predictability of the underlying binding free energies (ΔG_{cplx}) of association between hydrogen bond donors **D** and acceptors **A** (on the basis of empirically derived free energy increments ΔG[4]) was significantly improved after the discovery of secondary interactions which can either stabilize such associations, if the partial charges flanking the donor or acceptor atom are opposite to those of the complexed system (as in **DD-AA** or **DDD-AAA** homo-combinations) or destabilize (as in the case of hetero-combinations like **DA-AD**, **DAD-ADA** etc.).[5] The more recent quantification of ΔG_{cplx} with two additive increments,[6] one for the primary hydrogen bond the other for the secondary interaction, is in line with experimental results from a impressive series of such host-guest complexes.[7] Relatively little, however, is known about the consequence of deviations from ideal hydrogen bond geometries on the stability of these complexes. The present paper addresses this question, with an emphasis on conformational aspects which have not received much attention until now. A recent publication[8] has already shown that the complexation energies are significantly lowered by bulky groups flanking the interacting hydrogen bonds. In the present work, firstly variations of binding constants K of thymine, which was made soluble in chloroform by attaching an n-butyl substituent, with acyl derivatives of 2,6-diaminopyridine, in which the RCO− side chain structure was varied (including phenyl groups for possible additional binding effects), are described, secondly, the first attempts to complex a chloroform adenine derivative simultaneously at the Watson−Crick and the Hoogsteen pairing sites, using bis(imidazolone) derivatives, are described. These could offer the necessary **AD** combinations for hydrogen bonding, but have, to the best of our knowledge, not yet been explored for nucleobase complexation.

[a] FR Organische Chemie, Universität des Saarlandes, D-66041 Saarbrücken, Germany

Results and Discussion

The synthesis of the new compounds from commercially available starting materials is straightforward, and described in the Experimental Section. Complexation for the host-guest complexes **1** and *N*-butylthymine (**2**), **4** and 9-ethyladenine (**5**), as well as the self association of **4a** and **6**, were studied by ^{1}H-NMR titrations, using protocols described earlier.[9] In all cases the NH shifts showed the largest change, of up to 7 ppm in the dilution experiments with **4a** and **6,** and 4.8 ppm with the host-guest pairs. In some cases other NMR signals, such as 6-CH, 5-CH_3 and CH_3 in a butyl substituent, in a thymine derivative could also be used, and showed satisfactory agreement with the constants derived from the NH shift titration. For all complexes a 1:1 stoichiometry was established using Job-Plots,[10] in line with the observed good fit to a 1:1 model in the titrations (Figure 1). Dilution experiments with the compounds **4a** showed self-association constant below 8 M^{-1} (see Figure 2); this ensured that at the concentrations used during the NMR titration self association did not interfere with the host-guest complex formation. Due to the smaller number of possible hydrogen bonds the monomer **6** showed a self-association constant of only 2 M^{-1}. Intramolecular association between the imidazolone units in ligands **4a** to **4d** is excluded on the basis of the observed N−H shift, which is always 4.2 ± 0.1 ppm in $CDCl_3$; intermolecular assocation

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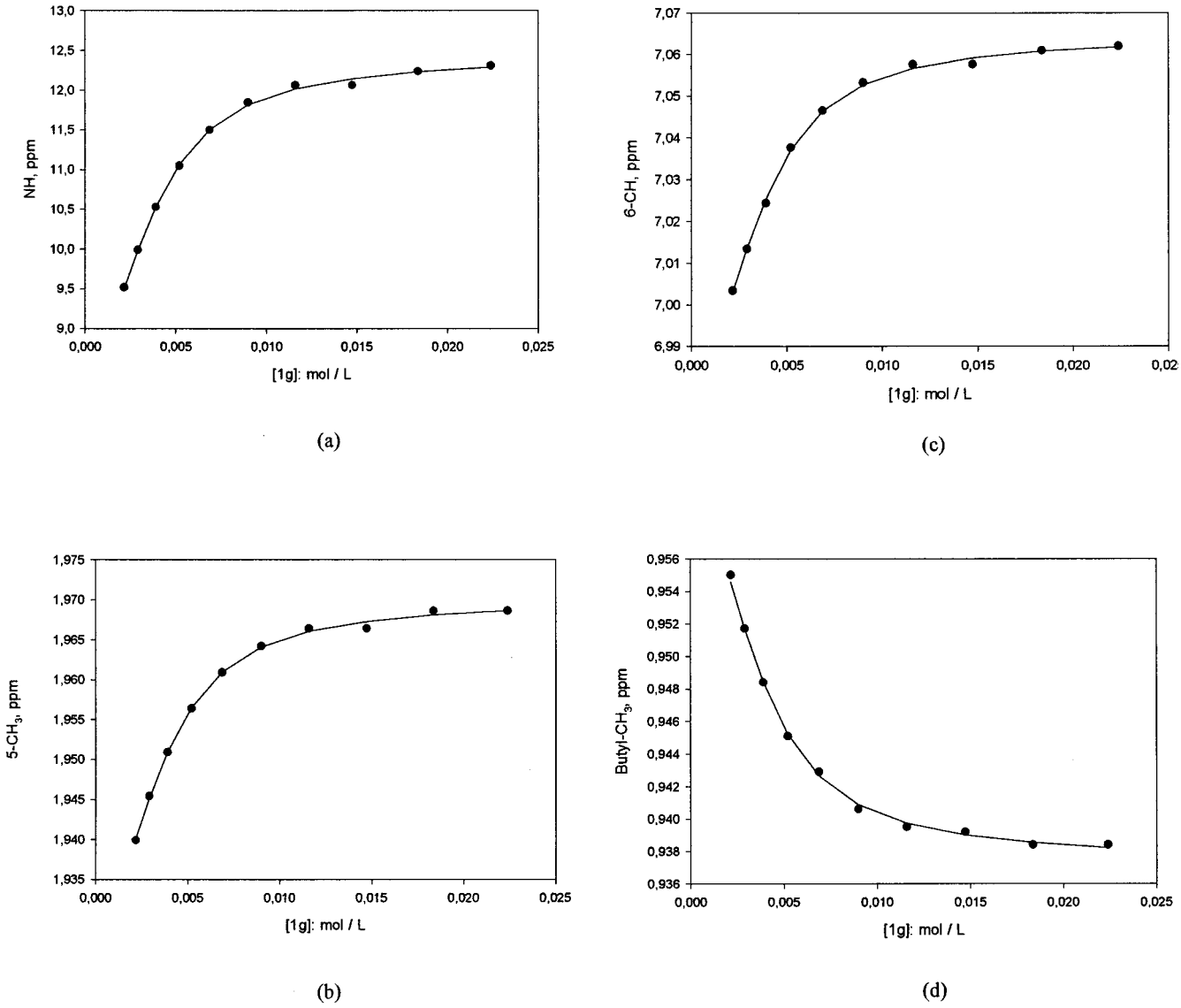


Figure 1. NMR titration with nonlinear least-square curve fitting for complex **1g−2** based on four different protons of butylthymine; solvent: $CDCl_3$; a) NH signal, b) 5-CH_3 signal, c) 6-CH signal, d) CH_3 signal of butyl group

with these compounds always leading to shifts of 7 ppm or lower.

DAD-ADA Complexes with a Thymine Derivative

As shown in Scheme 1, thymine has hydrogen bonding sites in an **ADA** array, which in principle can be recognized by receptors with an **DAD** array through triple hydrogen-bonded complexation (**DAD-ADA**). Substituents in bis-(acylamino)pyridine strongly affect the association constants of complexes as well as the chemically induced shift of the observed protons in complexes (Table 1). Large association constants were observed for the complexes **1a−2** (1025 M^{-1}), **1g−2** (1130 M^{-1}) and **1h−2** (560 M^{-1}). The simple 2,6-diaminopyridine (**3**) forms 1:1 complexes with N^1-butylthymine (**2**) with $K = 72\ M^{-1}$ only, in line with the much smaller acidity of the $-NH_2$ protons in comparison to −NHCOR protons.

Steric hindrance by substituents (R) in **1** has a dramatic influence on the association constants. If the size of R = CH_3 was increased to R = n-C_3H_7 the association constant decreased by > 50% (compare $K = 1025\ M^{-1}$ for **1a−2** and $K = 400\ M^{-1}$ in **1b−2**); for **1c** with R = $(CH_3)_3C$, the NMR titration indicated that only very weak hydrogen-bonded complexes are formed ($K < 8\ M^{-1}$, CIS < 0.1 ppm). As indicated earlier,[8] the associations are very sensitive to steric hindrance by side groups.

Interestingly, comparison of the association constants of **1e−2**, **1f−2**, **1g−2**, **1h−2** shows, at first sight, unexpected variations, as these ligands differ only in the number n of the CH_2 groups between a terminal phenyl and the amide function. The phenyl groups were introduced with the hope

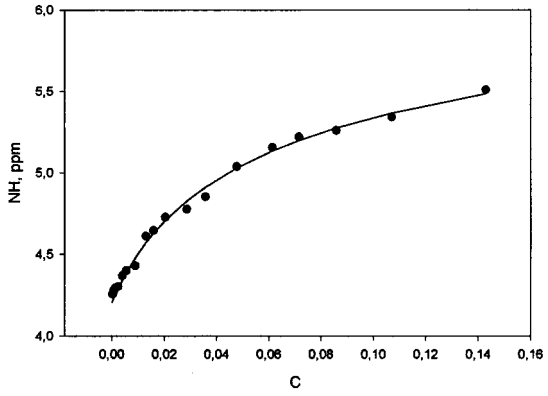
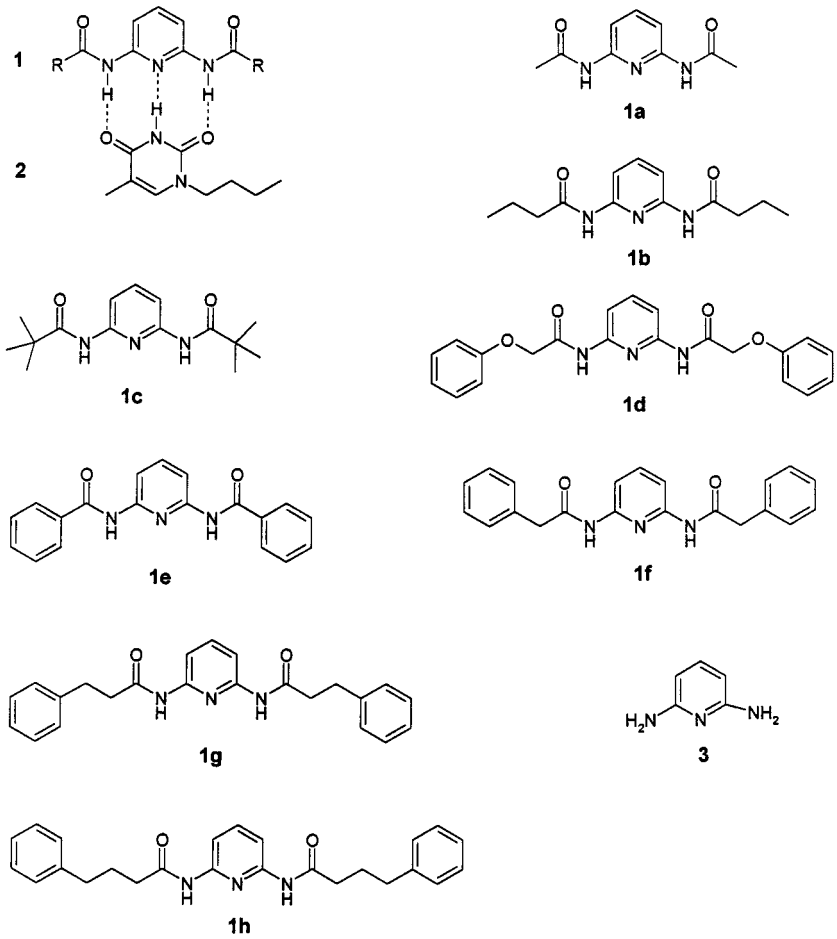


Figure 2. Self-association of **4a**; least-square curve fitting of NMR shifts in a dilution experiment

distance between the thymine butyl methyl protons and the phenyl surface is 3.0 Å, while the closest distance between the protons of 5-CH_3 in thymine and phenyl surface receptor is 3.3 Å. These distances are not too far from the sum of the van der Waals radii of phenyl groups and the hydrogen atom (1.7 + 1.2 Å), considering the uncertainty of the corresponding potentials in the applied force field. Similar orientations are seen in the simulated structure of complex **1h−2** (Figure 3d). The presence of stabilizing C−H-π interactions in complex **1g−2** is supported experimentally by the observed upfield NMR shift of methyl protons, which varies between $\Delta\delta_{max} = -0.02$ for thymine butyl methyl protons and $\Delta\delta_{max} = 0.04$ for 5-methyl protons in thymine; the size of the shielding effect is necessarily small, as a result of time averaging with the other, more distant, CH_3 protons and the loose contact between phenyl and alkyl groups.



Scheme 1. Structures of receptors for thymine

of finding additional interactions with the nucleobase. With $n = 2$, i.e. with receptor **1g**, one observes the largest affinity, with both $n = 3$ and $n = 0$ or 1 we find a decrease of K_a values. These observations can be understood with the help of computer-aided molecular modeling studies. Figure 3 shows the energy-minimized structures for the complexes between **1** and **2** using the CHARMm force field.[11] Intermolecular C−H-π interactions[12] were observed for complexes **1g−2** and **1h−2**: In **1g−2** (Figure 3c), the closest

Possible AD-DA Complexes with Adenine

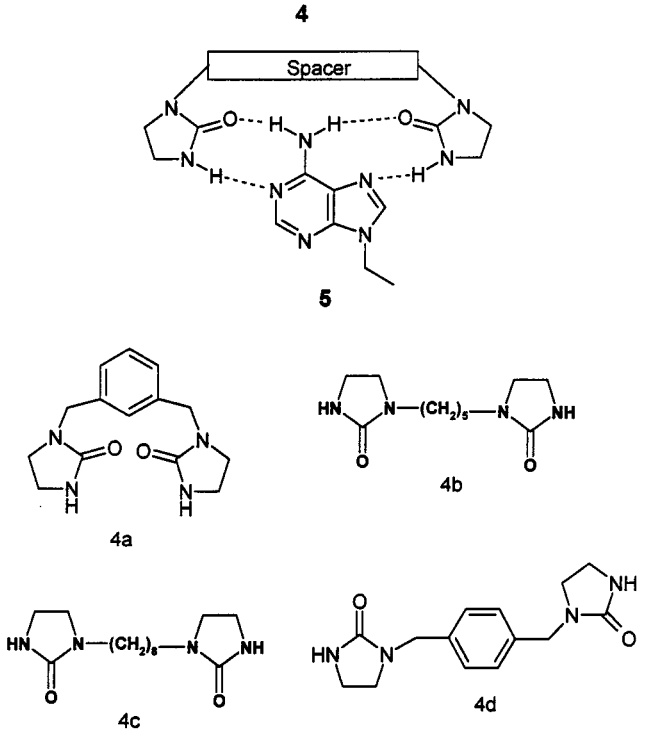
The four receptor structures **4a−4d** offer **DA** and **AD** binding sites, which with a suitable spacer between could make use of both Watson−Crick and Hoogsteen hydrogen bonding (Scheme 2). Figure 4 shows a CHARMm-optimized structure of the complex of receptor **4a** and 9-ethyladenine. In order to avoid self-association of the receptors **4**, NH peaks in the host molecules were monitored during

Table 1. Association constants (K_a), complexation-induced shift (CIS) and association energies (ΔG) of hydrogen-bonded complexes between **1** and **2** (solvent: $CDCl_3$)

Host (obsd. compd.)	Guest (added)	K_a [M^{-1}]	ΔG [kJ/mol][b,c]	CIS [ppm]
1a	**2**[a]	1025	−17.2	2.90
2	**1b**	NH: 440	−14.8	4.76
		6-CH: 443		0.11
		5-CH_3: 310		0.052
2	**1c**	NH: < 10	< −5	< 0.1
2	**1d**	NH: 5.7	−4.3	2.22
2	**1e**	NH:55	−9.9	2.30
2	**1f**	NH: 350	−14.3	4.66
		6-CH: 331		0.15
		5-CH_3: 265		0.095
2	**1g**	NH: 1035	−17.4	4.57
		6-CH: 1207		0.098
		5-CH_3: 1149		0.047
		Bu-CH_3: 1113		−0.027
2	**1h**	NH: 583	−15.7	4.795
		6-CH: 625		0.094
		5-CH_3: 475		0.026
		Bu-CH_3: 573		0.015
3	**2**	NH: 72	−10.6	1.25

[a] Due to solubility problem, compound **1a** can only be treated as observed compounds. − [b] ΔG derived from the average of the different K_a values for the same complex. − [c] Titration were conducted at 298 ± 5 K; errors in K ≤ 10%; in ΔG < 0.5 kJ/mol, in CIS ± 0.005 ppm.

the NMR titration upon addition of 9-ethyladenine (**5**). The self-association constant for 9-ethyladenine (**5**) in [D]-chloroform has been reported to be very small (K_D = 3.1 M^{-1}),[13] and so dimerization of **5** can be neglected. Due to the limited solubility of **4d** in chloroform it was impossible



Scheme 2. Structures of receptors for adenine

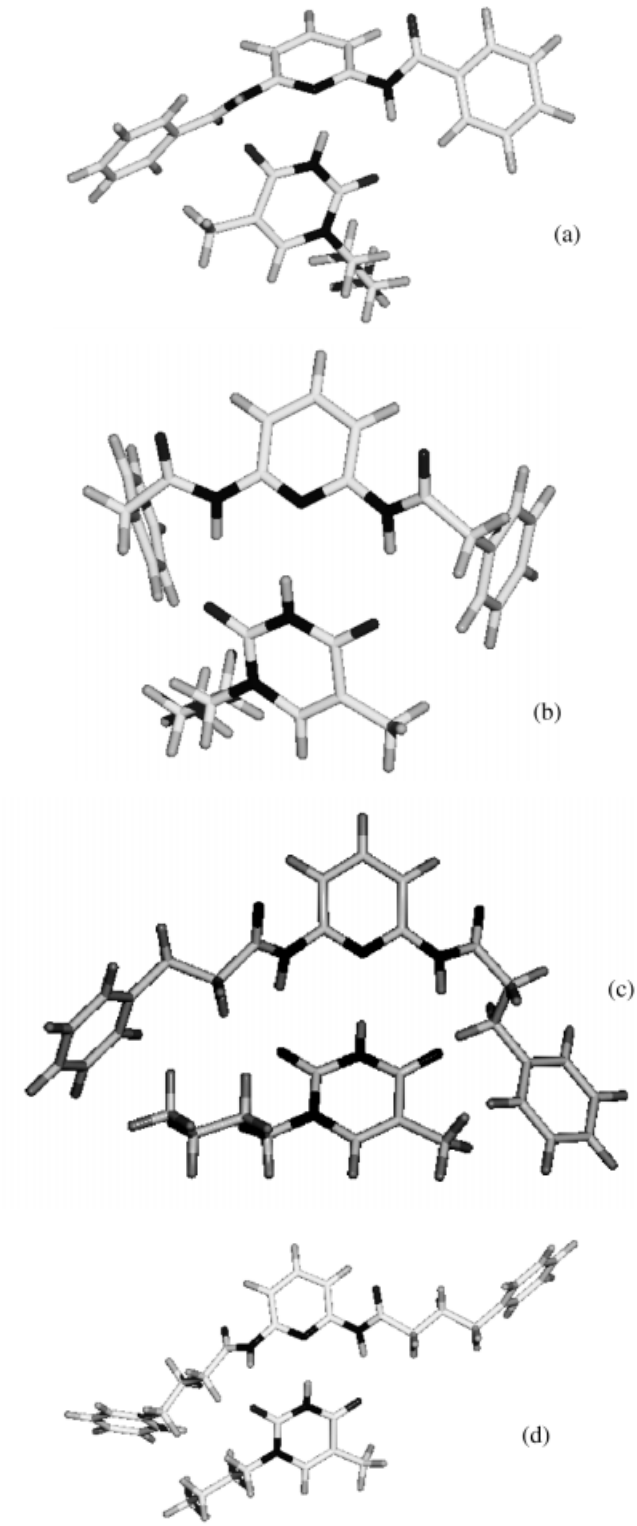
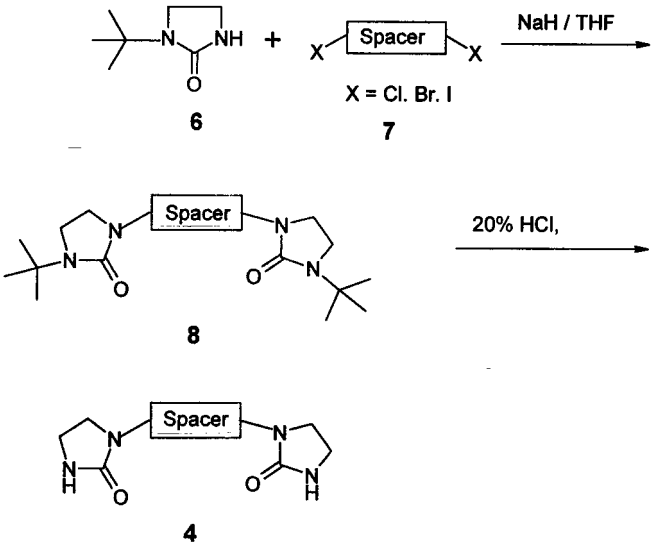


Figure 3. Quanta/CHARMm-minimized structures for the complexes of **1e−2** (a), **1f−2**(b), **1g−2** (c), **1h−2** (d)

to conduct NMR titrations with this host in $CDCl_3$. The binding studies showed that receptors with both rigid (**4a**) and flexible spacers (**4b**,**4c**) have low binding constants with 9-ethyladenine (Table 2). We attribute these poor binding properties to an unfavorable hydrogen bond geometry. The

simulations with CHARMm suggest that the bonds are either too long (e.g. 4 Å between the adenine N^1 atom and one imidazolone NH), or have the hydrogens bent out too much, with D−H−A angles of up to 80°.



Scheme 3. Synthetic scheme for receptors **4**

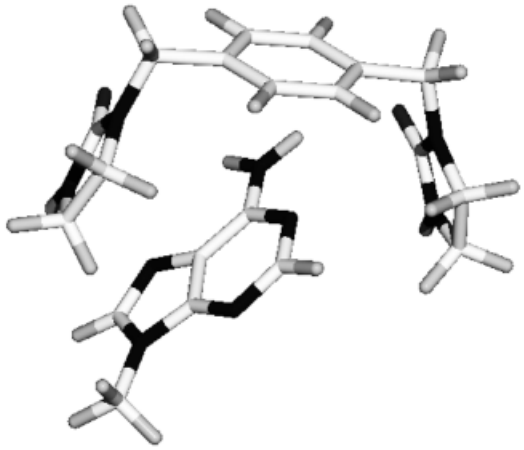


Figure 4. CHARMm-optimized structure of the complex of receptor **4a** and 9-ethyladenine

Table 2. Association constants of complexes between **4** and **5**; see footnotes to Table 1

Host (obsd. compd.)	Guest (added)	K_a [M^{-1}]	ΔG [kJ/mol]	CIS [ppm]
4a	**5**	11	−5.9	1.397
4b	**5**	4.9	−3.9	1.390
4c	**5**	6.6	−4.7	1.280

Experimental Section

General: ^{1}H NMR and ^{13}C NMR: Bruker AM-400 system at 400 and 100 MHz, respectively, chemical shifts are reported in ppm downfield from internal TMS. − M.p.: Gallenkamp Melting Point Apparatus; uncorrected values. − NMR titrations: $CDCl_3$ (99.8% D content), the solvent was dried with 4-Å molecular sieves before use, least-squares fit of the titration curves usually between 20 and 80% complexation performed as described earlier[9] using Sigmaplot 5.0 (Jandel Scientific). THF was purified before use (by refluxing with sodium/benzophenone) and distilled immediately before use. Dichloromethane was refluxed with phosphorus pentoxide and distilled; triethylamine was dried with potassium hydroxide prior to use. All other solvents and reagents were of reagent-grade quality and used without further purification. *N*^{1}-butylthymine (**2**) and 9-ethyladenine (**5**) were prepared by alkylation of thymine and adenine according to ref.[14][15]

General Procedure for the Preparation of 2,6-Diaminopyridine *N,N′*-Diacyl Derivatives 1a−1h:[16] A solution of the corresponding acid chloride (10 mmol) in dry dichloromethane (10 mL) was added dropwise to an ice-cooled mixture of 2,6-diaminopyridine (5 mmol) and dry triethylamine (10 mmol) in dry dichloromethane (30 mL). The reaction mixture was stirred overnight at room temp.; then the reaction was quenched with 20 mL of water, the organic layer separated, washed with both an aqueous solution of sodium bicarbonate (20 mL, 5%) and with water, dried with magnesium sulfate and concentrated under reduced pressure. The crude products were recrystallized from solvents as indicated.

2,6-Bis(acetylamino)pyridine (1a): Recrystallized from chloroform, colorless crystals, yield: 82%, m.p. 205−206°C. − ^{1}H NMR ($CDCl_3$): δ = 7.879 (d, *J* = 7.9 Hz, 2 H, Py-H^{3,5}), 7.700 (t, *J* = 7.9 Hz, 1 H, Py-H^4), 7.616 (s, br., 2 H, NH), 2.197 (s, 6 H, CH_3). − $C_9H_{11}N_3O_2$ (193.09): calcd. C 55.96, H 5.70, N 21.76; found C 56.14, H 5.80, N 21.37.

2,6-Bis(butyrylamino)pyridine (1b): Recrystallized from chloroform/petroleum ether, colorless plates, yield: 76%, m.p. 111−112°C. − ^{1}H NMR ($CDCl_3$): δ = 7.901 (d, *J* = 7.9 Hz, 2 H, Py-H^{3,5}), 7.653 (t, *J* = 7.9 Hz, 1 H, Py-H^4), 7.350 (s, br., 2 H, NH), 2.335 (t, *J* = 7.5 Hz, 4 H, $COCH_2$), 1.730 (sext, *J* = 7.6 Hz, 4 H, CH_2), 0.979 (t, *J* = 7.6, 6 H, CH_3). − ^{13}C NMR: δ = 171.5 (CO), 149.5 (Py-C^{2,6}), 140.5 (Py-C^{3,5}), 109.3 (Py-C^4), 39.4 (CH_2CO), 18.6 (CH_2), 13.5 (CH_3). − $C_{13}H_{19}N_3O_2$ (249.15): calcd. C 62.65, H 7.63, N 16.87; found C 62.36, H 7.62, N 16.78.

2,6-Bis(*tert*-butyrylamino)pyridine (1c): Recrystallized from ethyl acetate/petroleum ether, colorless solid, yield: 78%, m.p. 246−249°C (decomp.). − ^{1}H NMR ($CDCl_3$): δ = 11.83 (s, br., 2 H, NH), 8.281 (t, *J* = 8.3 Hz, 2 H, Py-H^{3,5}), 7.960 (t, *J* = 8.3 Hz, 1 H, Py-H^4), 1.469 (s, 18 H, CH_3). − ^{13}C NMR: δ = 182.2 (CO), 145.7 (Py-C^{2,6}), 139.2 (Py-C^{3,5}), 109.2 (Py-C^4), 40.9 [C(CH_3)], 26.8 (CH_3). − $C_{15}H_{23}N_3O_2$ (277.18): calcd. C 64.94, H 8.30, N 15.16; found C 64.97, H 7.55, N 15.09.

2,6-Bis(phenoxyacetylamino)pyridine (1d): Recrystallized from ethanol, yield: 80%, colorless crystals, m.p. 144−145.5°C. − ^{1}H NMR ($CDCl_3$): δ = 8.675 (s, br., 2 H, NH), 7.994 (d, *J* = 8.0 Hz, 2 H, Py-H^{3,5}), 7.710 (t, *J* = 8.0 Hz, 1 H, Py-H^4), 7.312 (t, *J* = 8.0 Hz, 4 H, Ph-H^{3,5}), 7.030 (t, *J* = 7.5 Hz, 2 H, Ph-H^4), 6.975 (t, *J* = 8.8 Hz, 4 H, Ph-H^{2,6}), 4.567 (s, 4 H, OCH_2). − ^{13}C NMR: δ = 166.6 (CO), 157.2 (Ph-C^1), 148.9 (Py-C^{2,6}), 140.7 (Py-C^{3,5}), 129.8, 122.5, 115.1(Ph-C$^{2-6}$), 110.2(Py-C^4), 67.9 (OCH_2). − $C_{19}H_{15}N_3O_4$ (349.11): calcd. C 60.48, H 3.98, N 11.14; found C 60.45, H 3.83, N 10.93.

2,6- Bis(benzoacetylamino)pyridine (1e): Recrystallized from ethanol, yield: 76%, colorless plates, m.p. 176−178°C. − ^{1}H NMR ($CDCl_3$): δ = 8.330 (s, br., 2 H, NH), 8.072 (d, *J* = 8.0 Hz, 2 H, Py-H^{3,5}), 7.863 (d, *J* = 8.0 Hz, 4 H, Ph-H^{2,6}), 7.746 (t, *J* = 8.0 Hz,

1 H, Py-H^4), 7.526 (t, J = 7.5 Hz, 2 H, Ph-H^4), 7.448 (t, J = 7.5 Hz, 4 H, Ph-H^{3,5}). − ^{13}C NMR: δ = 165.4 (CO), 149.8 (Py-C^{2,6}), 140.8 (Py-C^{3,5}), 134.3, 132.2, 128.8, 127.1 (Ph-C), 109.9 (Py-C^4). − $C_{19}H_{15}N_3O_2$ (317.12): calcd. C 71.92, H 4.73, N 13.25; found C 71.71, H 5.00, N 13.10

2,6-Bis(phenylacetylamino)pyridine (1f): Recrystallized from ethanol, yield: 74%, colorless crystals, m.p. 134−136°C. − ^{1}H NMR ($CDCl_3$): δ = 7.866 (d, J = 8.0 Hz, 2 H, Py-H^{3,5}), 7.807 (s, br., 2 H, NH), 7.580 (t, J = 8.0 Hz, 1 H, Py-H^4), 7.364 (t, J = 7.5 Hz, 4 H, Ph-H^{3,5}), 7.316 (d, J = 7.5 Hz, 4 H, Ph-H^{2,6}), 7.268 (t, J = 7.9 Hz, 2 H, Ph-H^4), 3.584 (s, 4 H, CH_2). − ^{13}C NMR: δ = 169.2 (CO), 149.2 (Py-C^{2,6}), 140.5 (Py-C^{3,5}), 133.9, 129.2, 128.9, 127.4 (Ph-C), 109.5 (Py-C^4), 44.5 (CH_2). − $C_{21}H_{19}N_3O_2$ (345.15): calcd. C 73.04, H 5.51, N 12.17; found C 73.76, H 5.56, N 11.94.

2,6-Bis(3-phenylpropionylamino)pyridine (1g): Recrystallized from dichloromethane/petroleum ether, colorless plates, yield: 72%, m.p. 130−131°C. − ^{1}H NMR ($CDCl_3$): δ = 7.831 (d, J = 8.0 Hz, 2 H, Py-H^{3,5}), 7.722 (s, br., 2 H, NH), 7.552 (t, J = 8.0 Hz, 1 H, Py-H^4), 7.247−7.139 (m, 10 H, Ph-H), 2.987 (t, J = 8.0 Hz, 4 H, $COCH_2$), 2.577 (t, J = 8.0 Hz, 4 H, CH2). − ^{13}C NMR: δ = 170.6 (CO), 149.4 (Py-C^{2,6}), 140 (Py-C^{3,5}).5, 140.3, 128.5, 128.1, 126.3 (Ph-C), 109.5 (Py-C^4), 38.9 (CH_2CO), 31.0 (CH_2). − $C_{23}H_{23}N_3O_2$ (373.18): calcd. C 73.99, H 6.17, N 11.26; found C 73.82, H 6.85, N 11.20.

2,6-Bis(3-phenylpropionylamino)pyridine (1h): Recrystallized from dichloromethane/petroleum ether, colorless plates, yield: 65%, m.p. 140.5−142°C. − ^{1}H NMR ($CDCl_3$): δ = 7.879 (d, J = 8.0 Hz, 2 H, Py-H^{3,5}), 7.653 (t, J = 8.0 Hz, 1 H, Py-H^4), 7.640 (s, br., 2 H, NH), 7.286−7.154 (m, 10 H, Ph-H), 2.677 (t, J = 7.1 Hz, 4 H, CH_2CO), 2.332 (t, J = 7.1 Hz, 4 H, CH_2), 2.031 (sept, J = 7.5 Hz, 4 H, CH_2). − ^{13}C NMR: δ = 171.1(CO), 149.4 (Py-C^{2,6}), 141.1, 140.7, 128.4, 126.0 (Ph-C), 109.4 (Py-C^4), 36.7 (CH_2CO), 34.9 (CH_2), 26.5 (CH_2). − $C_{25}H_{27}N_3O_2$ (401.21): calcd. C 74.81, H 6.73, N 10.47; found C 74.14, H 6.62, N 10.37.

1-*tert*-Butylimidazolidin-2-one (6): Preparation as described in ref.[17] − ^{1}H NMR ($CDCl_3$): δ = 4.749 (s, br., 1 H, NH), 3.441 (t, J = 7.5 Hz, 4 H, NCH_2CH_2N), 3.296 (t, J = 7.5 Hz, 2 H, NCH_2CH_2N). − $C_7H_{14}N_2O$ (142.11): C 59.15, H 9,86, N 19.72; found C 59.09, H 9.46, N 19.41.

General Procedure for Preparation of the Bis(1-*tert*-butylimidazolidin-2-one) Derivatives 8: 1-*tert*-Butylimidazolin-2-one (**6**; 10 mmol) was added to a stirred suspension of sodium hydride (60% in mineral oil; 23 mmol) in dry THF (40 mL) at room temp. under nitrogen. After 30 min at room temp., 10 mmol of α,α-dibromo-*m*-xylene (for **8a**), 1,5-diiodopentane (for **8b**), 1,8-diiododoctane (for **8c**) and α,α-dichloro-*p*-xylene (for **8d**) in dry THF (5 mL) was added dropwise, and the reaction mixture was stirred overnight at room temp. Most of the solvents were removed and ice-cold water (30 mL) was added, the precipated solids were collected by filtration, washed with water, dried, and recrystallized from solvents as indicated below.

8a: Recrystallized from dichloromethane/petroleum ether, yield: 78%, colorless powder, m.p. 93−94°C. − ^{1}H NMR ($CDCl_3$): δ = 7.273 (t, J = 7.1 Hz, 1 H, Ph-H^6), 7.160 (d, J = 7.1 Hz, 3 H, Ph-H^{2,4,6}), 4.303 (s, 4 H, CH_2), 3.295 (t, J = 8.0 Hz, 4 H, NCH_2CH_2N), 3.054 (t, J = 8.0 Hz, 4 H, NCH_2CH_2N), 1.395 (s, 18 H, CH_3). − ^{13}C NMR: δ = 161.3 (CO), 137.9, 128.7, 127.8, 127.0 (Ph-C), 53.1 (CH_2), 48.3 [$C(CH_3)_3$], 42.0 (NCH_2CH_2N), 40.6 (NCH_2CH_2N), 27.5 (CH_3). − $C_{22}H_{34}N_4O_2$ (386.27): calcd. C 68.39, H 8.81, N 14.51; found C 68.45, H 8.72, N 14.35.

8b: Recrystallized from dichloromethane/petroleum ether, yield: 49%, colorless crystals, m.p. 63−64°C. − ^{1}H NMR ($CDCl_3$): δ = 3.288 (t, J = 8.0 Hz,4 H, NCH_2), 3.170 (t, J = 7.5 Hz, 4 H, NCH_2CH_2N), 3.115 (t, J = 7.6 Hz, 4 H, NCH_2CH_2N), 1.532−1.478 (m, 4 H, CH_2), 1.305 (s, 2 H, CH_2), 1.289 (s, 18 H, CH_3). − ^{13}C NMR: δ = 161.4 (CO), 52.7 [$C(CH_3)_3$], 43.7 (NCH_2), 42.1 (NCH_2CH_2N), 40.6 (NCH_2CH_2N), 27.4 (CH_2), 27.3 (CH_2), 26.9 (CH_3). − $C_{19}H_{36}N_4O_2$ (352.28): calcd. C 64.77, H 10.23, N 15.91; found C 64.66, H 9.61, N 16.26.

8c: Recrystallized from dichloromethane/petroleum ether, yield: 48%, slightly yellow solid, m.p. 57−59°C. − ^{1}H NMR ($CDCl_3$): δ = 3.291 (t, J = 8.0 Hz, 4 H, NCH_2), 3.178 (t, J = 7.6 Hz, 4 H, NCH_2CH_2N), 3.096 (t, J = 7.6 Hz, 4 H, NCH_2CH_2N), 1.513−1.431 (m, 8 H, CH_2), 1.345 (s, 18 H, CH_3), 1.315−1.255 (m, 4 H, CH_2). − ^{13}C NMR: δ = 161.7 (CO), 52.4 [$C(CH_3)_3$], 43.2 (NCH_2), 42.0 (NCH_2CH_2N), 40.7 (NCH_2CH_2N), 27.3 (CH_2), 27.2 (CH_2), 26.8 (CH_2), 23.8 (CH_3). − $C_{22}H_{42}N_4O_2$ (394.33): calcd. C 67.00, H 10.66, N 14.21; found C 66.72, H 10.11, N 13.97.

8d: Recrystallized from chloroform/petroleum ether, yield: 88%, colorless plates, m.p., 162−164°C. − ^{1}H NMR ($CDCl_3$): δ = 7.217 (s, 4 H, Ar-H), 4.301 (s, 4 H, CH_2), 3.293 (t, J = 7.6 Hz, 4 H, NCH_2CH_2N), 3.063 (t, J = 7.6 Hz, 4 H, NCH_2CH_2N), 1.377 (s, 18 H, CH_3). − ^{13}C NMR: δ = 161.3 (CO), 136.6 (Ph-C^{1,4}), 128.3 (Ph-C^{2,3,5,6}), 53.1 [$C(CH_3)_3$], 48.1 (CH_2), 41.9 (NCH_2CH_2N), 40.7 (NCH_2CH_2N), 27.5(CH_3). − $C_{22}H_{34}N_4O_2$ (386.27): calcd. C 68.39, H 8.81, N 14.51; found C 68.59, H 8.83, N 14.39.

General Procedure for Preparation of Bis[α,α′-bis(2-oxoimidazolidin-1-yl)] Derivatives 4:[18] **8** (5 mmol) was suspended in 15% aqueous HCl (10 mL) and the mixture heated to 80°C for 7−10 h. The clear solution was neutralized to pH = 7−8 with 4N NaOH while cooling in an ice bath, then the mixture was extracted with chloroform (3 × 30 mL), the organic phase dried with $MgSO_4$, concentrated under reduced pressure and the residue recrystallized from solvents as indicated.

4a: Recrystallized from chloroform/petroleum ether, yield: 56%, colorless crystals, m.p. 189−191°C. − ^{1}H NMR ($CDCl_3$): δ = 7.304 (t, J = 7.1 Hz, 1 H, Ph-H^5), 7.192 (d, J = 7.1 Hz, 3 H, Ph-H^{2,4,6}), 5.509 (s, br., 2 H, NH), 4.361 (s, 4 H, CH_2), 3.424 (t, J = 8.4 Hz, 4 H, NCH_2CH_2N), 3.305 (t, J = 8.4 Hz, NCH_2CH_2N). − ^{13}C NMR: δ = 162.8 (CO), 137.6, 128.9, 127.4, 127.0 (Ph-C), 47.6 (CH_2), 44.7 (NCH_2CH_2N), 38.1 (NCH_2CH_2N). − $C_{14}H_{18}N_4O_2$ (274.14): calcd. C 61.31, H 6.57, N 20.44; found C 60.90, H 6.58, N 20.67.

4b: Recrystallized from dichloromethane/petroleum ether, yield: 47%, colorless solid, m.p. 135−137°C. − ^{1}H NMR ($CDCl_3$): δ = 4.228 (s, br., 2 H, NH), 3.433−3.389 (m, 8 H, NCH_2CH_2N), 3.188 (t, J = 7.5 Hz, 4 H, NCH_2), 1.585−1.521 (m, 4 H, CH_2), 1.384−1.322 (m, 2 H, CH_2). − ^{13}C NMR: δ = 163.0 (CO), 44.9 (NCH_2), 43.2 (NCH_2CH_2N), 38.2 (NCH_2NCH_2), 27.1 (CH_2), 23.7 (CH_2). − $C_{11}H_{20}N_4O_2$ (240.16): calcd. C 55.00, H 8.33, N 23.33; found C 55.29, H 8.07, N 22.67.

4c: Recrystallized from dichloromethane/petroleum ether, yield: 63%, slightly yellow solid, m.p. 127−129°C. − ^{1}H NMR ($CDCl_3$): δ = 4.256 (s, br., 2 H, NH), 3.431−3.402 (m, 8 H, NCH_2CH_2N), 3.170 (t, 4 H, J = 7.1, NCH_2), 1.516−1.482 (m, 4 H, CH_2), 1.316−1.310 (m, 8 H, CH_2). − ^{13}C NMR: δ = 163.1 (CO), 44.9 (NCH_2), 43.4(NCH_2NCH_2N), 38.2(NCH_2CH_2N), 29.1 (CH_2), 27.5(CH_2), 26.6(CH_2). − $C_{14}H_{26}N_4O_2$ (282.20): calcd. C 59.57, H 9.22, N 19.86; found C 59.88, H 8.79, N 19.54.

4d: Recrystallized from DMSO, yield: 49%, colorless solid, m.p. 280°C (decomp.). − ^{1}H NMR ([D_6]DMSO): δ = 7.190 (s, 4 H, Ar-H), 4.420 (s, 4 H, CH_2), 3.267 (t, J = 7.6 Hz, 4 H, NCH_2CH_2N), 3.052 (t, J = 7.6 Hz, NCH_2CH_2N). − ^{13}C NMR: δ = 163.5 (CO),

137.4 (Ph-$C^{1,4}$), 129.2 (Ph-$C^{2,3,5,6}$), 53.5 (CH_2), 42.2 (NCH_2CH_2N), 41.0 (NCH_2CH_2N). − $C_{14}H_{18}N_4O_2$ (274.14): calcd. C 61.31, H 6.57, N 20.44; found C 60.79, H 6.49, N 19.77.

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