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H-Bonded complexes of adenine with Rebek imide receptors are stabilised by cation–π interactions and destabilised by stacking with perfluoroaromatics†

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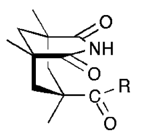
A series of Rebek imide receptors with naphthalene or heteroaromatic platforms attached by amide or ester linkers have been prepared from the corresponding acyl chloride or anhydride; the X-ray crystal structure of the receptor-derived anhydride reveals a supramolecular H-bonded helix formation in the crystal; the complexes of adenine bound to the receptors by Hoogsteen H-bonding are found to be stabilised by stacking with a methylquinolinium ion, but destabilised by stacking with a perfluorinated naphthalene.

Cation–π interactions, initially discovered by Stauffer and Dougherty in molecular recognition studies with synthetic receptors,[1] are increasingly identified as a major force in structural biology.[2] Kool *et al*. have simultaneously demonstrated that fluorinated aromatics can elegantly substitute as isosteres for natural nucleobases when incorporated into duplex DNA.[3] These and other experimental developments,[4] as well as those in theory,[5] have initiated our interest in quantifying the propensity of adenine to undergo cation–π interactions and stacking interactions with fluorinated aromatics using Rebek imides as versatile receptors.[6] We have already shown that adenine prefers Hoogsteen over Watson–Crick H-bonding to these receptors in solution and in the solid state;[7] questions remain as to the consequences of π–π-stacking electrostatics on base-paired structure and orientation.[8] To initiate these studies we have prepared the Rebek imide derivatives **1a–i** (Table 1) and investigated their association with 9-ethyladenine (**2**) in $CDCl_3$ and in crystals.



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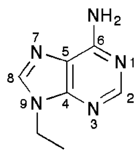

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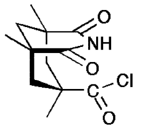

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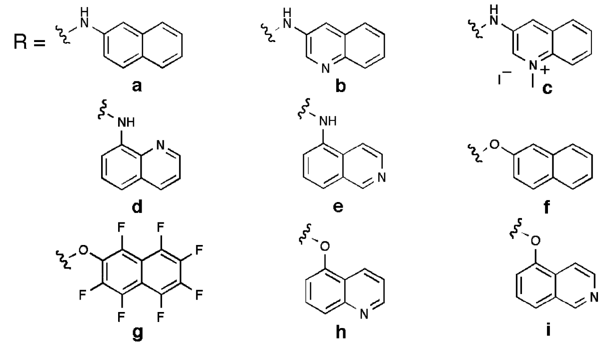
Receptors **1a–i** were prepared by reacting the imide acid chloride derivative of Kemp's triacid **3**[9] with the corresponding aromatic amines or alcohols. Alternatively, **1a,b,d** could be prepared in comparable yields by acylation of the amines with the notably stable anhydride **4** that was obtained in 73% yield by coupling **3** with its imide carboxylic acid precursor (see ESI† for details). In the solid state, anhydride **4**, a novel supramolecular synthon, displays a remarkable helical self-assembly, mediated by the H-bonding recognition pattern of the imide ring (Fig. 1).‡

^{1}H NMR binding titrations (295 K) were undertaken to determine the stability (K_a/M^{-1}; $-\Delta G°$/kJ mol^{-1}) of the complexes formed in $CDCl_3$ (and, when required for solubility reasons, in $(CDCl_2)_2$) and van't Hoff analysis yielded the thermodynamic quantities $\Delta H°$ and $\Delta S°$ (Table 2).[10] Binding data are corrected for the dimerisation constants of the imides (K_d/M^{-1}) that were assessed in ^{1}H NMR dilution experiments (see ESI†). In most cases, the K_d values were negligible (between 2 and 12 M^{-1}) and did not lead to significant changes in the corrected association constants K_a. 1:1 Binding stoichiometries were ascertained by Job plot analysis. In all ^{1}H NMR experiments, the complexation-induced downfield shift of the imide N–H proton in the Rebek imide receptor was monitored and evaluated (see ESI†). The complexation of the naphthyl receptors **1a** and **1f** with 9-ethyladenine (**2**) had previously been reported by Rebek *et al.*;[6c,d] data obtained in this work (as a control) are in good agreement with those of the previous study. NOE experiments showed for most complexes the previously observed[7] slight preference (between 60:40 and 80:20) for Hoogsteen over Watson–Crick H-bonding association.

Table 1 Rebek-type receptors for 9-ethyladenine (**2**)



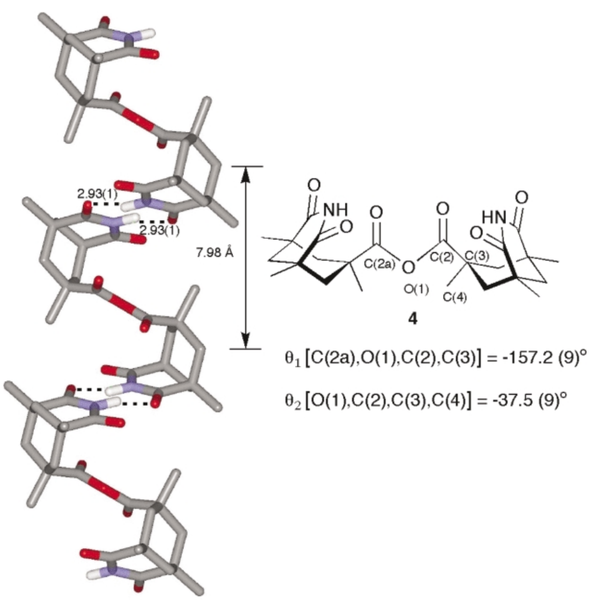


Fig. 1 Supramolecular helix formed by anhydride **4** in the crystal.

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† Electronic supplementary information (ESI) available: Protocols for the synthesis of **1a–i**; description of ^{1}H NMR binding titrations, determination of dimerisation constants, van't Hoff analysis and Job plot analysis; crystal structure data for complexes **1c·2**, **1d·2** and **4**. See http://www.rsc.org/suppdata/cc/b3/b314353h/

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The following results were obtained: (i) the host·guest complexes formed by receptors with amide linkers to the aromatic platform are generally more stable than those formed by receptors with ester linkers, as had been previously observed by Rebek *et al.*[6b]

(ii) The complexes of quinoline derivatives **1b** and **1d** are significantly more stable ($\Delta\Delta G° = 1.1–1.9$ kJ mol^{-1}) than the complex of isoquinoline derivative **1e**, pointing to an influence of the orientation of the heterocyclic platform on the efficiency of the stacking with the parallel-bound adenine derivative. Experimental data for more complexes are required before a meaningful assessment of the contributions of dipole–dipole interactions, polarisability,[11] and changes in molecular electrostatic potential to the observed binding differences can be made.

(iii) Adenine clearly prefers (by $\Delta\Delta G° = 2.5$ kJ mol^{-1}) stacking with an electron-rich naphthalene (in **1f**) over the stacking with a perfluorinated naphthalene (in **1g**) of opposite quadrupole moment.[12] This result parallels those that are found in DNA-like duplexes containing perfluoroaromatics[13a,b] and provides a clear incentive for a systematic fluorine scan on the binding affinity by sequentially introducing one or more fluorine atoms at different positions into the π-stacking platform.

(iv) Since the methylquinolinium receptor **1c** is insoluble in $CDCl_3$, its binding capacity was evaluated in the better solvent $(CDCl_2)_2$, where the overall association strength is reduced (complex **1b·2** in $CHCl_3$: $-\Delta G° = 12.8$ kJ mol^{-1}; in $(CDCl_2)_2$: -10.6 kJ mol^{-1}). In $(CDCl_2)_2$, the complex of the methylquinolinium receptor **1c** is 2.4 kJ mol^{-1} more stable than the complex of the corresponding neutral quinoline receptor **1b**, clearly demonstrating that adenine undergoes favourable cation–π interactions with heterocyclic onium ions.[12]

The favourable effects of additional cation–π interactions also become apparent from crystallographic studies, although we are well aware that caution is advised in interpreting binding geometries in the solid state due to crystal packing effects (Fig. 2). In complex **1d·2** adenine is bound in the Hoogsteen mode, whereas it adopts the reversed Hoogsteen mode in complex **1c·2**.‡ However, while the quinoline moiety in **1d·2** turns away from the adenine ring, largely avoiding π-stacking interactions, the methylquinolinium ring of **1c** adopts an orientation that ensures significant overlap with the cofacial adenine chromophore. The onium nitrogen atom is located above the C(5)–C(6) bond of adenine. Theoretical calculations will be required to explain the orientational preference of the chromophores in the two complexes. We shall continue exploiting versatile Rebek imides and related receptors in our attempts to quantify the strength and geometry of intermolecular aromatic interactions involving nucleobases.

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Table 2 Association constants K_a and thermodynamic parameters describing the 1:1 binding of **1a–i** to **2** in $CDCl_3$ (295 K)[a]

Complex	K_a[b]/M^{-1}	$-\Delta G°$/ kJ mol^{-1}	$\Delta\delta_{sat}$[c]/ ppm	$-\Delta H°$/ kJ mol^{-1}	$-\Delta S°$/cal K^{-1} mol^{-1}
1a·2	167 ± 4	12.5	5.7	26.3	11.7
1b·2	182 ± 7	12.8	3.9	38.9[e]	23.0
1b·2[d]	75 ± 1	10.6	5.7	25.5[e]	12.6
1c·2[d]	205 ± 20	13.0	5.6	25.1	10.5
1d·2	136 ± 5	12.0	5.5	32.2	16.5
1e·2	86 ± 3	10.9	5.0	28.9	15.3
1f·2	69 ± 1	10.4	5.9	23.8	11.2
1g·2	26 ± 1	7.9	6.3	26.3	14.5
1h·2	57 ± 1	9.9	5.9	25.5	13.3
1i·2[d]	29 ± 2	8.2	6.4	23.0	11.9

[a] Uncertainty in K_a estimated from duplicate or triplicate runs. [b] Values corrected for imide dimerisation. [c] Downfield shift of the imide N–H proton at saturation binding. [d] In $(CDCl_2)_2$. [e] Nonlinear van't Hoff plots above 303 K.

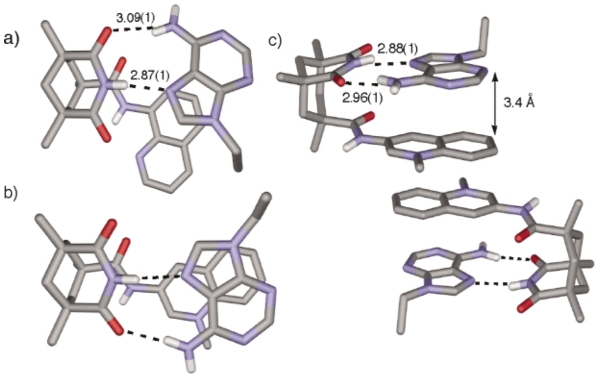

Fig. 2 (a) Top view of complex **1d·2** in the crystal structure. (b) Top view of complex **1c·2** in the crystal structure. (c) Cation–π and heterocyclic π–π stacking in the crystal of **1c·2**.

Notes and references

‡ *Crystal data*: Compound **4**, $C_{24}H_{32}N_2O_7\cdot CH_2Cl_2$, $M = 545.44$, monoclinic, space group $C2/c$, $a = 15.631(8)$, $b = 16.523(11)$, $c = 11.782(6)$ Å, $\beta = 114.05(4)°$, $V = 2779(3)$ Å^3, $T = 293$ K, $Z = 4$, $\mu = 2.479$ mm^{-1}, 1278 reflections collected, $R_1 = 0.0834$ based on $F\ [I > 2\sigma(I)]$, $wR_2(F^2) = 0.2555$ (all data). Complex **1d·2**, $C_{21}H_{23}N_3O_3\cdot C_7H_9N_5$, $M = 528.62$, triclinic, space group $P\bar{1}$, $a = 8.097(4)$, $b = 9.350(5)$, $c = 18.786(9)$ Å, $\alpha = 76.19(3)$, $\beta = 78.45(3)$, $\gamma = 85.08(3)°$, $V = 1352.0(12)$ Å^3, $T = 293$ K, $Z = 2$, $\mu = 0.715$ mm^{-1}, 2768 reflections collected, $R_1 = 0.0436$ based on $F\ [I > 2\sigma(I)]$, $wR_2(F^2) = 0.1322$ (all data). Complex **1c·2**, $C_{22}H_{26}IN_3O_3\cdot C_7H_9N_5\cdot H_2O$, $M = 688.57$, triclinic, space group $P\bar{1}$, $a = 8.578(2)$, $b = 12.724(3)$, $c = 15.621(3)$ Å, $\alpha = 109.03(3)$, $\beta = 95.46(3)$, $\gamma = 102.40(3)°$, $V = 1548.8(6)$ Å^3, $T = 293$ K, $Z = 2$, $\mu = 1.081$ mm^{-1}, 2457 reflections collected, $R_1 = 0.0514$ based on $F\ [I > 2\sigma(I)]$, $wR_2(F^2) = 0.1251$ (all data). CCDC 224117–224119. See http://www.rsc.org/suppdata/cc/b3/b314353h/ for crystallographic data in CIF or other electronic format.

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