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New Rebek imide-type receptors for adenine featuring acetylene-linked π-stacking platforms†

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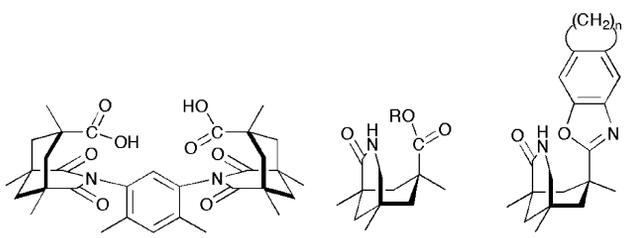
Rebek imide-type molecular clefts with π-stacking platforms attached to the imide scaffold by an acetylene linker have been prepared by Sonogashira cross-coupling. In the solid state, a novel dimerisation mode for this class of imide receptors was found by crystal structure analysis, whereas efficient 1 : 1 complexation with 9-ethyladenine was observed in $CDCl_3$ solution.

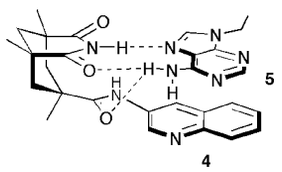
By modification of Kemp's triacid, Rebek and co-workers developed a variety of powerful achiral and chiral molecular clefts for the recognition of small H-bonding molecules and metal ions (*e.g.* **1**).[1] Some of these derivatives (*e.g.* **2a** and **3a**) have been used as chiral auxiliaries to control the stereochemical outcome of various reactions, such as radical additions, allylations, annulations and enolate alkylations.[2] Other applications include the catalytic enantioselective protonation of prochiral enolates using the optically active clefts as chiral proton sources[3] and enantioselective intramolecular [2 + 2]-photocycloadditions in supramolecular complexes formed by **2b** and **3b**.[4]



1 **2a** R = 2-naphthyl **2b** R = 3-CHO-phenyl **3a** n = 0 **3b** n = 4

The majority of the known Rebek imide receptors[5] feature an aromatic, π-stacking platform attached by ester or amide linkers to the imide scaffold. In a few cases, this platform is directly linked to the imide by a heterocyclic ring formed by condensation of the carboxyl group.[2–4] Restricted rotation about the ester and amide bonds may lead to different receptor conformations and, ultimately, to host–guest complexes with different interaction geometries and strengths. In addition, amide linkers can directly contribute to the binding process as shown in Fig. 1 for the complex of Rebek imide **4** with 9-ethyladenine (**5**), for which a bifurcated hydrogen bond involving the basic amide carbonyl group was proposed.[5]

As part of our investigations of the interaction preferences of adenine in complexes formed by Rebek imide receptors,[6] we became interested in introducing an acetylenic linker between the aromatic platform and imide scaffold. Such a spacer would allow free rotation of the platform to adopt the best possible geometry for interactions with bound adenine derivatives.



5 **4**

Fig. 1 Bifurcated H-bond proposed for the complex of Rebek imide receptor **4** with 9-ethyladenine (**5**).

Furthermore, the absence of H-bonding sites in the linker would enable a more precise determination of the energetic contributions of imide recognition and π-stacking.

The formation of the new receptors **6** and **7** required the synthesis of the novel alkyne **8**. After a variety of protocols for the introduction of the ethynyl residue in the sterically encumbered site close to the protected imide moiety failed, a five-step synthesis starting from Kemp's triacid was finally successful (*Scheme 1*).‡ The imide–acid chloride **9**, obtained from the triacid by a known procedure,[2a] was selectively reduced with $LiAlH(^tBuO)_3$ to the primary alcohol that was subsequently oxidised to aldehyde **10** with PCC. The direct conversion of **9** to aldehyde **10** by other methods failed. Protection of the imide moiety by PMBCl afforded **11** in 85% yield. Alkyne **8** was obtained from aldehyde **11** under mild conditions in a Horner–Wadsworth–Emmons-type reaction using dimethyl-1-diazo-2-oxopropylphosphonate (**12**).[7] Attempts to perform this reaction with unprotected **10** failed, likely due to unfavourable electronic effects caused by the deprotonation of the neighboring imide N–H in the basic solution. Sonogashira cross-couplings of **8** with 3-bromoquinoline or 8-iodo-9-propyladenine afforded compounds **13** (75%) and **14** (90%), respectively. Finally, removal of the imide-protecting group with CAN provided the two targeted receptors **6** (72%) and **7** (88%).

The crystal structure of **6**, obtained by X-ray diffraction analysis, contains two symmetry-independent molecules.§ Two conformationally equivalent molecules arrange in a local pseudo-twofold symmetry, forming two H-bonds between the cyclic imide N–H protons and the basic nitrogen atoms of the quinoline rings (Fig. 2). The dimer is further stabilised by

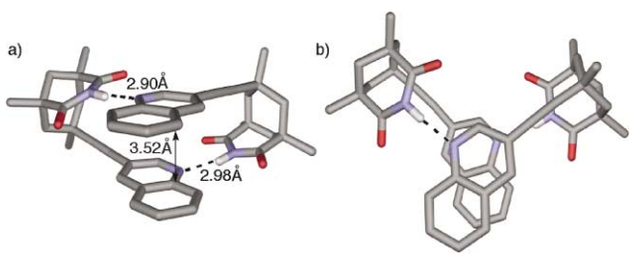


Fig. 2 Crystal structure of **6**: a) the dimer viewed along the *a* axis; b) π-stacking interaction between the quinoline rings viewed along the *c* axis.

† Electronic supplementary information (ESI) available: synthetic protocols, binding studies and Job plot analysis. See http://www.rsc.org/suppdata/ob/b4/b404311a/.

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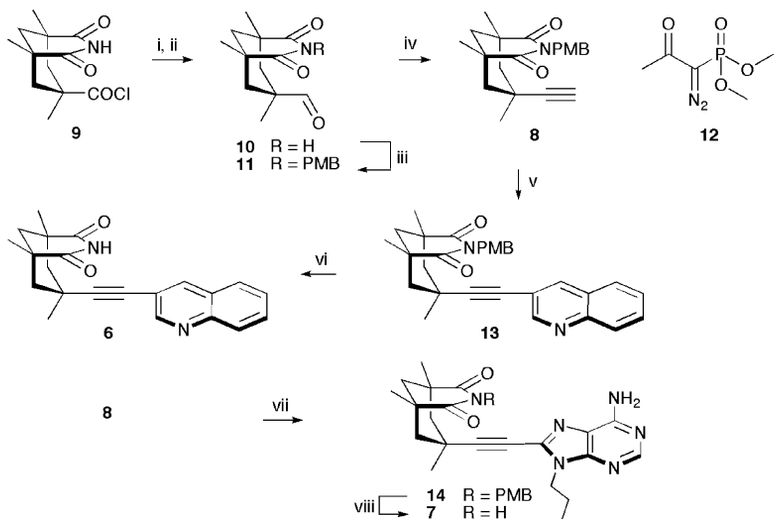
Table 1 Association constants K_a and thermodynamic parameters describing the 1 : 1 binding of **4**[a] and **6** to **5** in $CDCl_3$ (295 K)[b]

Complex	K_a/M^{-1} [b]	$-\Delta G°$/kJ mol^{-1}	$-\Delta H°$/kJ mol^{-1}	$-\Delta S°$/e.u.
4·5	182 ± 7	12.8	38.9	23.0
6·5	121 ± 4	11.7	27.9	14.1

[a] Data for **4** taken from ref. 6*b*. [b] Uncertainty in K_a estimated from duplicate or triplicate runs; values corrected for imide dimerisation.



Scheme 1 Synthesis of compounds **6** and **13b**. *Reagents and conditions:* i, $LiAlH(^tBuO)_3$, THF, 0 °C, 98%; ii, PCC, CH_2Cl_2, r.t., 84%; iii, PMBCl, NaH, NaI (cat), DMF, 0 °C ⟶ r.t., 85%; iv, **12**, K_2CO_3, MeOH, 0 °C ⟶ r.t., 68%; v, 3-Bromoquinoline, $[Pd(PPh_3)_2Cl_2]$, CuI, $^iPr_2NH$, THF, 50 °C, 75%; vi, CAN, CH_3CN/H_2O (10 : 1), r.t., 72%; vii, 8-Iodo-9-propyladenine, $[Pd(PPh_3)_2Cl_2]$, CuI, $^iPr_2NH$, THF, 50 °C, 90%; viii, CAN, CH_3CN/H_2O (10 : 1), r.t., 88%. PCC = pyridinium chlorochromate; PMBCl = *p*-methoxybenzyl chloride; CAN = cerium ammonium nitrate.

π-stacking of the quinoline rings. This unusual geometry differs from the solid-state structures of other known Rebek imide dimers in which recognition is mediated by the complementary hydrogen-bonding imides.[6a] On the other hand, this observation confirms what Rebek and co-workers had predicted by analysis of dimerisation data of **4** in $CDCl_3$ solution.[5b]

In the solid state and in solution, Rebek imide **7** with an adenine platform forms a dimer with a very high dimerisation constant $K_{dim} \geq 10^4$ measured in $CDCl_3$ at 295 K. The X-ray structure of **7** shows two independent pairs of molecules related by a centre of symmetry forming Watson–Crick H-bonds between the adenine rings and the imide moieties (Fig. 3),§ although the N–H ··· O interaction (N ··· O distances 3.02/3.55 Å) is rather weak. One of the two dimers (shown in Fig. 3) forms H-bonds to neighboring adenines *via* their Hoogsteen faces, while the other dimer is anchored to heavily disordered $CHCl_3$ molecules.

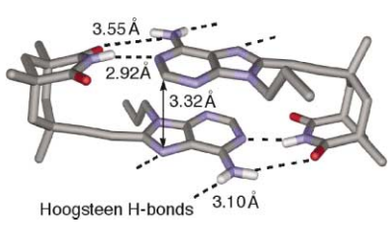


Fig. 3 Crystal structure of **7**: one of the two symmetrically independent dimers is shown. Dimerisation occurs *via* Watson–Crick H-bonding and adenine π-stacking; neighboring adenines in one plane interact *via* Hoogsteen H-bonding.

The complexation between receptor **6** and 9-ethyladenine (**5**) was studied by ^{1}H-NMR binding titrations ($CDCl_3$, 295 K), which afforded the strength of the association (K_a [M^{-1}], $-\Delta G°$ [kJ mol^{-1}]).[8] The thermodynamic parameters ($\Delta H°$, $\Delta S°$) were ascertained by van't Hoff plots, while Job plot analysis confirmed the 1 : 1 binding stoichiometry (see ESI †). Although the 9-ethyladenine complex of **6** is less stable than the complex of its amide analogue **4** ($\Delta\Delta G°$ = 1.1 kJ mol^{-1}, Table 1), the results confirm the efficiency of the alkyne-linked quinoline in π-stacking with the nucleobase. The difference in affinity can be largely attributed to the lack of bifurcated H-bonds (Fig. 1) in complex **6·5**. The substantial bonding contributions of H-bond donor–acceptor centres in the linker are also illustrated by the difference in the dimerisation constants: self-association of receptor **6** (K_{dim}(**6**) = 36 ± 4) is much less effective than that of **4** (K_{dim}(**4**) = 131 ± 39). In the absence of H-bonding interactions with the linker, the overall binding free enthalpy of **6·5** ($-\Delta G°$ = 11.7 kJ mol^{-1}) can be easily separated into its component terms. The imide–adenine H-bonding[9] is worth 8.3 kJ mol^{-1} while the aromatic stacking between the alkynated quinoline and bound adenine provides 3.4 kJ mol^{-1}.

In summary, Rebek imide receptors with acetylene-linked π-stacking platforms eliminate undesirable H-bonding contributions from previously used ester and amide linkers to adenine complexation, thereby allowing a more accurate separation of the energetics of imide H-bonding and π-stacking. Alkyne **8** is a versatile partner for cross-coupling reactions, and we will report on the properties of a larger family of new Rebek imide receptors with different acetylene-linked π-stacking platforms in due course.

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Notes and references

‡ *Selected experimental protocols (see also ESI): Preparation of* **8**. To a solution of **12** (4.47 g, 23.2 mmol) in dry MeOH (47 ml) under N_2 at 0 °C, oven-dried K_2CO_3 (3.86 g, 27.9 mmol) was added and the yellow suspension stirred for 1 h. A solution of **11** (4.0 g, 11.6 mmol) in dry THF (52 ml) was added dropwise and the resulting suspension stirred for 2 h at 0 °C and for 12 h at r.t. The mixture was concentrated *in vacuo*, the residue dissolved in Et_2O and the solution washed with 5% aq. $NaHCO_3$, dried (Na_2SO_4) and concentrated. Flash chromatography (FC, SiO_2; CH_2Cl_2) afforded **8** (2.67 g, 68%) as a white solid, mp 118 °C; ν_{max}(neat)/cm^{-1} 3276*m*, 2966*w*, 2935*w*, 2362*w*, 2336*w*, 1718*m*, 1671*s*,

1610*m*, 1600*s*, 1509*s*, 1468*m*, 1450*m*, 1432*m*, 1375*s*, 1292*s*; δ_H(300 MHz, $CDCl_3$) 7.34 (2 H, d, *J* 9.0), 6.8 (2 H, d, *J* 9.0), 4.74 (2 H, s), 3.77 (3 H, s), 2.16 (2 H, d, *J* 14.1), 1.94 (1 H, d, *J* 13.2), 1.84 (1 H, s), 1.32–1.23 (12 H); δ_C(75 MHz, $CDCl_3$) 176.56, 158.53, 130.55, 129.44, 113.53, 88.61, 69.43, 55.22, 48.07, 43.03, 42.86, 40.33, 33.17, 30.32, 26.1; HR-FT-MALDI-MS (DHB) calcd for $C_{21}H_{25}NO_3Na^+$ ([*M* + Na]$^+$): 362.1727; found: 326.1726; EA calcd for $C_{21}H_{25}NO_3$ (339.43): C 74.31, H 7.42, N 4.13; found: C 74.34; H 7.62, N 4.04%. *Preparation of* **13**: Alkyne **8** (0.63 g, 1.85 mmol) and 3-bromoquinoline (0.25 ml, 1.83 mmol) were added to a pressure-resistant Schlenk flask, previously dried and evacuated by N_2-pump cycles. THF (15 ml) was added, the solution degassed by three freeze–pump–thaw cycles and [$Pd(PPh_3)_2Cl_2$] (64.4 mg, 5 mol%), CuI (35 mg, 10 mol%) and $^iPr_2NH$ (5 ml) were added under N_2. The mixture was degassed by four freeze–pump–thaw cycles and stirred at 50 °C for 18 h. Upon cooling to r.t., Et_2O was added and the ammonium salt precipitated. The solution was filtered and concentrated to dryness. FC (SiO_2; CH_2Cl_2/Et_2O 10 : 0.1) afforded **13** (0.64 g, 75%) as a white solid, mp 146–147 °C; ν_{max}(neat)/cm^{-1} 2969*w*, 2933*w*, 1717*w*, 1667*s*, 1608*w*, 1513*s*, 1462*w*, 1378*w*, 1294*m*, 1250*s*, 1162*s*; δ_H(300 MHz, $CDCl_3$) 8.84 (1 H, d, *J* 1.8), 8.16 (1 H, d, *J* 1.8), 8.06 (1 H, d, *J* 8.4), 7.74 (1 H, d, *J* 8.1), 7.66 (1 H, ddd, *J* 8.4, 7.8, 1.2), 7.51 (1 H, td, *J* 8.1, 7.8), 7.14 (2 H, d, *J* 8.4), 6.72 (2 H, d, *J* 8.4), 4.64 (2 H, s), 3.70 (3 H, s), 2.31 (2 H, d, *J* 12.6), 1.92 (1 H, d, *J* 13.5), 1.40–1.24 (12 H, m); δ_C(75 MHz, $CDCl_3$) 177.04, 165.40, 158.85, 152.41, 146.91, 138.61, 130.31, 130.14, 130.00, 129.58, 127.78, 127.44, 117.37, 113.85, 97.78, 55.38, 48.24, 43.09, 42.96, 40.59, 33.37, 31.56, 26.30; HR-FT-MALDI-MS (DHB) calcd for $C_{30}H_{31}N_2O_3^+$ (*M*H$^+$): 467.2329; found: 467.2326; EA calcd for $C_{30}H_{30}N_2O_3$ (466.58): C 77.23, H 6.48, N 6.00; found: C 76.94; H 6.65, N 5.99%.

§ *Crystal data*. Compound **6**, $C_{22}H_{22}N_2O_2$, *M* = 346.43, monoclinic, space group $P2_1/a$, *a* = 14.9171(2), *b* = 12.9531(2), *c* = 19.9159(3) Å, β = 107.7345(8)°, *V* = 3665.33(9) Å^3, *T* = 172 K, *Z* = 8, μ = 0.081 mm^{-1}, 9409 reflections collected, R_1 = 0.0485 based on $F[I > 2\sigma(I)]$, $wR(F^2)$ = 0.1541 (all data). Compound **7**, $2(C_{21}H_{26}N_{16}O_2)\cdot 0.5(CHCl_3)$, *M* = 848.13, triclinic, space group $P\bar{1}$, *a* = 7.6166(3), *b* = 16.8616(8), *c* = 17.8082(7) Å, α = 88.088(3)°, β = 81.177(3)°, γ = 77.664(2)°, *V* = 2207.8(2) Å^3, *T* = 100 K, *Z* = 2, μ = 0.170 mm^{-1}, 6757 reflections collected, R_1 = 0.0843 based on $F[I > 2\sigma(I)]$, $wR(F^2)$ = 0.2353 (all data). CCDC reference numbers 234432 and 234433. See http://www.rsc.org/suppdata/ob/b4/b404311a/ for crystallographic data in .cif or other electronic format.

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