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Comparative Probe for Stacking Interactions in Simple A:T Base Pair Mimics

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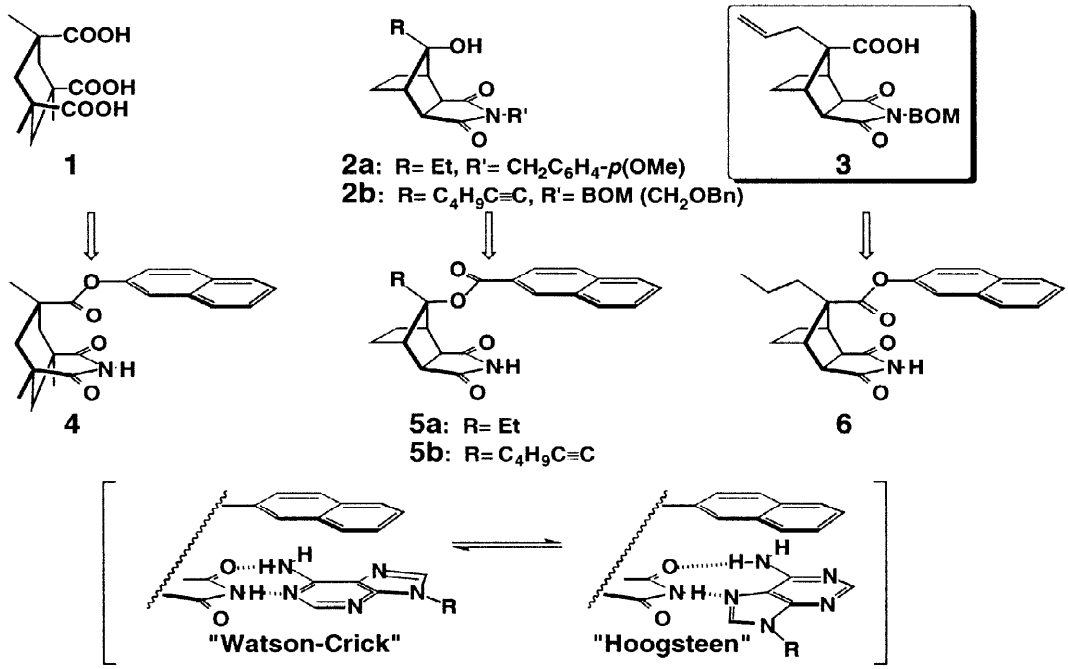
Abstract: The design and synthesis of a new scaffold for the assembly of receptor models, soluble in organic solvent, is described. It was converted into a simple receptor for 9-butyladenine and compared to other isosteric AT base pair mimics. The results support the Sanders and Hunter π-stacking model.

The design and synthesis of novel organic scaffolds have become an important area of organic chemistry. Some of these scaffolds, which are typically used for the assembly of abiotic receptors for molecular recognition studies,[1] can also be used for assembling catalysts,[2] chiral auxiliaries,[3] chiral proton sources,[4] sensors,[5] carriers,[6] replicators,[7] even combinatorial peptidomimetic libraries.[8] Basic to all these applications is the ability of an organic scaffold to preorganize functional groups in three-dimensional space.

Among the various scaffolds used to date, Kemp's triacid **1** has been used for a wide range of applications[9] by virtue of its molecular U-turn functionality (Scheme 1). Since 1996, we have been reporting on the use of hydroxyimide scaffolds **2** for the modular assembly of abiotic receptors.[10,11] These isosteres of Kemp's imide acid derivative are very easy to functionalize (via the "R" group in **2**) and can be prepared in multigram scale.



Scheme 1.

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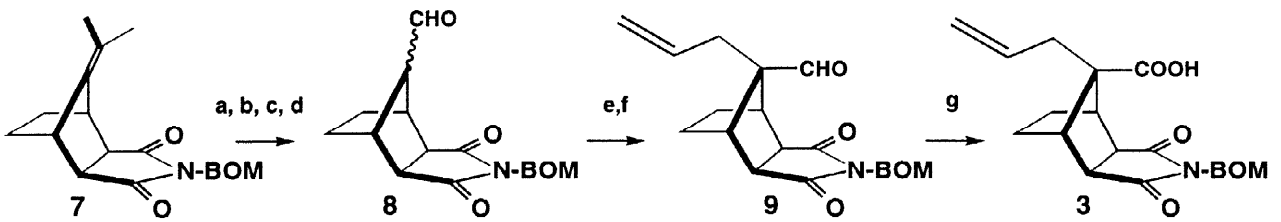
To test the hydroxyimide convergence, simple receptors of 9-butyladenine, inspired by Rebek's AT base pair mimics[12], were assembled from scaffold **2**. For instance, receptor **5a**, prepared from 2-naphthoic acid and **2a**, was subjected to NMR titration with 9-butyladenine (9-BuA) in $CDCl_3$ and gave evidence of both Watson-Crick and Hoogsteen complexes (Scheme 1). The association constant (K_a) for **5a** was 184 M^{-1} which is twice as high as the value reported for the Kemp's triacid counterpart **4**.[10a] However, receptors **5a** and **4** differ in both the orientation of the aryl ester linkage and the conformational restrictions imposed by the two different scaffolds. In order to minimize conformational disparities between scaffold **2** in an "inverted ester" analog, we have synthesized the imide acid scaffold **3** and wish to report the binding properties of the corresponding 9-BuA receptor **6**. Imide acid **3** was chosen for its structural analogy to hydroxyimide **2** which enforces a functional handle to be *cis* to the imide. The acid group in **3**, once esterified with an aromatic alcohol would generate receptors that are essentially identical to those derived from scaffold **2** except for the orientation of the ester linkage.

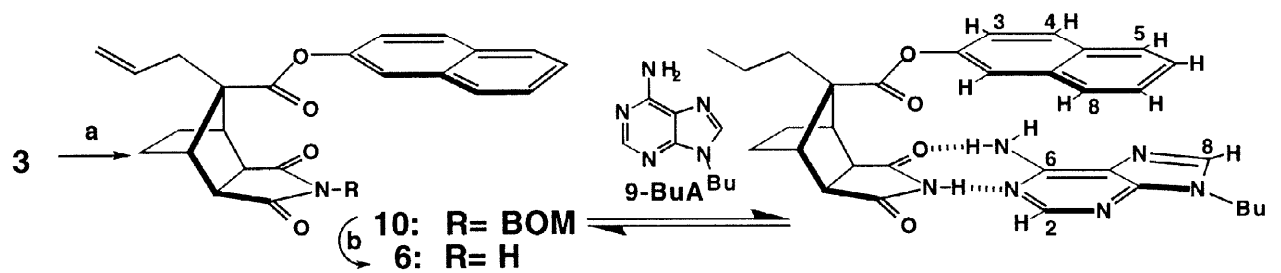
Retrosynthetic analysis suggested a simple route starting from the previously described tricyclic adduct **7**, obtained *via* a Diels-Alder reaction under thermodynamic conditions[10] (Scheme 2).



Scheme 2. a) O_3/CH_2Cl_2 -78°, then Me_2S, 100%; b) n-BuLi/2-(dimethoxyphosphoryl)-1,3-dithiane, THF, -78°, 62%; c) Et_3SiH/TFA, CH_2Cl_2, rt, 95%; d) $HgCl_2/HgO$, 80% CH_3CN-H_2O, reflux, 95%; e) KH, allyl bromide, THF, 41%; f) xylene reflux, 4 days, 75%; g) $NaClO_2$, aq $NaHPO_4$, t-BuOH/H_2O, 68%.

The ozonolysis product of **7** was transformed to the corresponding ketenedithioacetal by a Horner-Emmons reaction, followed by reduction to the dithioacetal and hydrolysis to afford aldehyde **8**. O-alkylation of aldehyde **8** with allyl bromide followed by Claisen rearrangement of the resulting allyl enol ether afforded a single allyl aldehyde **9**. The relative stereochemistry of the quaternary allyl aldehyde **9** was established by nOe experiments. For instance, irradiation of the CH_2 of the allyl group revealed a 6.8% nOe to the two *exo* hydrogens of the ethano bridge of the bicyclo[2.2.1]heptane skeleton. Lindgren oxidation of **9** afforded the desired tricyclic scaffold **3**.

The simple naphthyl-bearing receptor **6** was then prepared by converting **3** into its acid chloride followed by esterification with the potassium alkoxide of 2-naphthol to give the N-protected "inverted" naphthoyl ester **10** (Scheme 3). Large upfield shifts in the NMR spectrum of the naphthylated adduct **10** provided further evidence for the desired stereochemistry at the quaternary allyl ester center (i.e. naphthoylation of **3** caused 0.27 and a 0.22 ppm upfield shifts of the N-CH_2 and O-CH_2-Ph signals of the BOM protecting group in **10**, respectively). Removal of the imide protecting group by hydrogenolysis followed by ammonolysis ($H_2/Pd(OH)_2$-C in EtOH then NH_3 in THF)[13] provided the "inverted" ester receptor **6**. This deprotection was unoptimized as we have shown the sequence to proceed in high yields in related systems.



Scheme 3. a) $SOCl_2$, THF/ 2-naphthol and KH, 40%; b) $H_2/Pd(OH)_2$-C in EtOH, NH_3/THF, 17%.

^{1}H-NMR titration of a $CDCl_3$ solution of receptor **6** with 9-BuA resulted in anticipated complexation-induced-shifts of both host and guest protons[14] (Table 1). After addition of 9 equivalents of guest, saturation had reached 88% and the imide in **6** had shifted downfield from 7.72 to 11.89 ppm[15], a clear indication of two-point hydrogen bonding to the guest. This was corroborated by downfield shifts of the 6-amino hydrogens of 9-BuA. In addition, upfield shifts of the naphthyl protons were indicative of stacking interactions between the host and the purine nucleus of the guest. Corresponding upfield shifts of the carbon-bound protons of 9-butyladenine were also observed.

Table 1. Complexation-Induced Shifts (CIS) From the Titration of Host **6** with 9-BuA.[a]

Hydrogen(s)	CIS (ppm)
Host **6**:	
imide NH	+ 4.17
H3-H4 (naphthoyl)	– 0.08
H5-H8 (naphthoyl)	– 0.20
9-BuA:	
6-amino	+ 0.82[b]
H2	– 0.17[b]
H8	– 0.29[b]
N-CH_2 (butyl side-chain)	– 0.15[b]

[a] At 88% saturation, from addition of 9 equivalents of 9-BuA. b Comparing the chemical shift of pure 9-BuA and the solution containing the highest **6**:9-BuA ratio (4:1).

Quantitative treatment of the titration data with HOSTEST[16] gave an excellent fit to the 1:1 binding isotherm (R^2>99.99) and revealed an association constant[17] $K_a = 42\ M^{-1}$ which is one quarter of the value reported for receptor **5a**.[10a] Monte Carlo conformational analyses[18] on receptors **5a** and **6** suggest that the relative geometry of the naphthyl ring with respect to the imide plane is similar for both compounds, despite the fact that the naphthyl ring in **6** is coplanar with the ester plane whereas it is twisted in **5a**. The energy potential for deviating from their respective global minima is shallow. Thus, we cannot invoke clear steric/conformational arguments to account for the difference in binding between this pair of receptors. This presents an interesting opportunity to probe the effect of the two ester linkages on the π-stacking properties of the aryl ring toward the H-bonded 9-BuA guest. The comparative analysis of **5a** and **6** is also simplified since their ester linkages, as opposed to the amide linkages found in many other abiotic receptor assemblies, are much less likely to participate in bifurcated hydrogen bonding to the 6-NH_2 of the 9-BuA guest, which can complicate the analysis of the binding interactions.[9e]

In receptor **6**, the ether oxygen of the naphthyl ester will be a weak electron donor and increase the donor character of the aromatic ring. In contrast, the ester linker in **5a/5b** will be an important electron-withdrawing group *via* conjugation of the ester carbonyl with the naphthyl ring.

Entropic solvophobic effects cannot account for the different binding properties of **5a** and **6** since the comparative analysis was done in chloroform.[19] Likewise, the van der Waals interactions in the two complexes cannot explain the results since the π-overlap in the two host-guest complexes will be very similar. However, the binding results of **5a** and **6** with 9-BuA are in agreemeent with the electrostatic model for π-stacking interactions popularized by Sanders and Hunter.[20,21] The model, which is primarily electrostatic, is based on the attractive interactions between π-electrons of one ring and the σ-framework of the other ring, which can outweigh unfavorable contributions such as π-π repulsion of the two rings. Accordingly, 9-BuA which is a π-rich guest, will prefer to stack to the host whose naphthyl ring is the most π-poor, in a face-to-face geometry. Due to the π-polarization of the carbonyl group in **5a**, the naphthyl ring will be relatively electron poor and, as a result of reduced π-π repulsion of the rings, translates into stronger π-stacking between host and guest. With receptor **6**, the ester group will increase the π-π repulsion component *via* a small π-donation into the naphthyl ring, which accounts for the difference in K_a.

Thus, a short synthetic route to imide acid **3** has been developed and its application to a simple abiotic receptor **6** for 9-BuA has been demonstrated. Comparing the binding results of **6** to other isosteric AT base pair mimics allowed for an isolated study of the effect of the electronic nature of the receptors' aryl surface on the binding of 9-BuA. The results, which are in agreement with the Sanders and Hunter model for π-stacking, provide a rationale for the advantageous use of hydroxyimides such as **2** for the modular assembly of abiotic receptor models and other molecular devices.

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