A Rigid Molecular Tweezer with an Active Site Carboxylic Acid: An Exceptionally Efficient Receptor for Adenine in an Organic Solvent†

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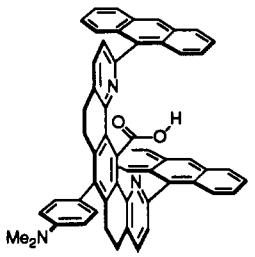
Substantial progress has been made toward the development of synthetic receptors that utilize hydrogen bonding as a force in complexation. These receptors can be divided into two classes: those that contain a nearly planar array of multiple hydrogen bond donor and acceptor groups[2] and those that provide fewer hydrogen-bonding interactions but contribute a *single* π-stacking surface.[3,4] An exception is Whitlock's naphthalenophane wherein two π-stacking interactions and a hydrogen bond accepting (dimethylamino)pyridine (DMAP) unit conspire to produce remarkably high affinities for 4-nitrophenol.[5a,b] In many of these systems, important questions regarding the origin of complex stability remain to be answered. For example, does the high affinity in the naphthalenophanes result from the very precise steric match between the cavity and the guest molecule?[5c] In this communication we report a *nonmacrocyclic* receptor (molecular tweezer **1**) wherein a binding site is created by the convergence



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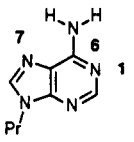

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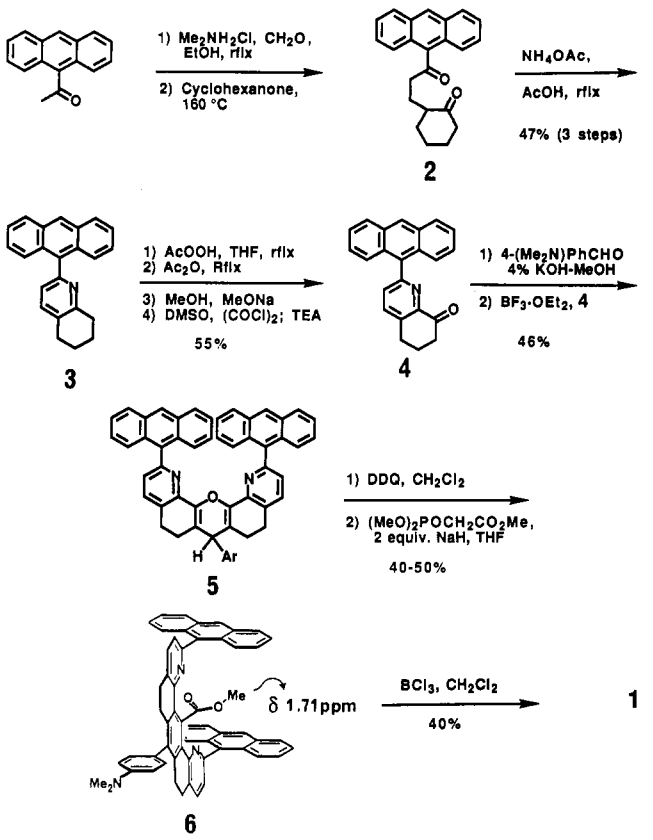
of two aromatic surfaces and a carboxylic acid.[6,7] These cleft-like receptors retain the exceptional complexation power of the naphthalenophanes, but can bind much larger guests such as the nucleotide base adenine.

Scheme I



Molecular tweezer **1** was designed by using previously reported synthetic and structural information.[6] The synthesis began with conversion of 9-acetylanthracene into its Mannich base,[8] reaction with neat cyclohexanone,[9] and treatment with ammonium acetate to produce tetrahydroquinoline **3** (Scheme I).[10,11] Lateral hydroxylation[12] and Swern oxidation[13] produced **4**, which was converted to **6**.[6b] Evidence that the carboxylic functionality is buried in the aromatic cleft was the large (2.3 ppm) upfield shift of the methyl resonance of the ester in **6** relative to a model compound lacking the anthracene units. Receptor **1** was obtained in 40% yield by treatment of **6** with boron trichloride in dichloromethane.

Titration of **1** with 9-propyladenine[14] (**7**) in chloroform-*d* was monitored by ^{1}H NMR, following the upfield shift of the H-4 and H-10 resonance of the anthracene moiety and H-2 of the (dimethylamino)phenyl substituent in **1**. The binding was strong enough that >99% of the titration curve could be accessed. Dissociation constants and complexation shifts ($\Delta\delta_{max}$) were determined by curve fitting the titration data using the method of Wilcox and Cowart,[15] as previously described.[6c] Due to uncertainties in fitting sharply curved binding isotherms, the data were also linearized by using the Higuchi method.[16] The $\Delta\delta_{max}$ values

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(1) NSF Presidential Young Investigator Awardee, American Cancer Society Junior Faculty Awardee.

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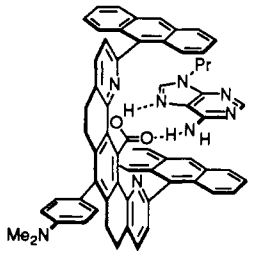
from both analyses were identical, and the association constants agreed within 13%. The association constant thus obtained, K_{assoc} = 25 000 ± 6000 M^{-1}, is the largest reported to date for a complex between a synthetic receptor and a nucleic acid base.[17]

The importance of the carboxylic acid in the complexation is evidenced by the negligible effect that ca. 0.02 M 9-propyladenine has on the ^1H NMR chemical shifts of a 4.5 × 10^{-3} M solution of ester **6**. Lancelot has shown that butyric acid binds 9-ethyladenine in chloroform-*d* (K_{assoc} = 160 M^{-1}) by forming simultaneous hydrogen bonds to N-1 and N-6 and to N-6 and N-7, the former favored by a 2.8:1 ratio.[18] Thus, it is tempting to ascribe



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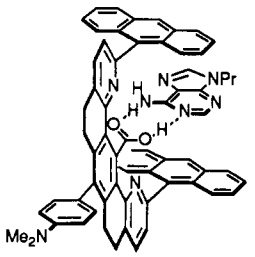

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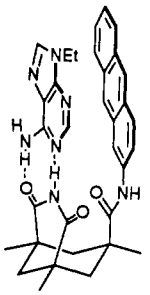
the high affinity of **1** for 9-propyladenine to the formation of complexes such as **8** and **9**. The complexation shifts in both host and guest are compatible with the presence of both of these complexes.[17]

While the factors contributing to the stability of the complex remain to be determined, comparison with known receptors is informative. Rebek's receptor **10** uses two hydrogen bonds and a single π-stacking interaction to complex 9-ethyladenine with an association constant of 440 M^{-1}.[3c-f,19] It can be concluded that the second stacking interaction provided by **1** increases its K_{assoc} by approximately 60-fold. More importantly, it has been shown that "π-sandwiching" and hydrogen bonding to a *single* edge of adenine can result in exceptional binding affinity. High



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binding affinity in other systems requires simultaneous hydrogen bonding to N-1, N-6 (two sites), and N-7.[3c-f,h] Since N-7 and one N-6 site are inaccessible in double-stranded RNA and DNA, the molecular tweezer strategy may better allow for selective binding to these macromolecules. This problem and the complexation of mononucleotides in protic solvents represent challenges toward which our current efforts are directed.

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(17) Binding study at 298 K. Individual association constants (K_{assoc}) were calculated for each of the three proton resonances monitored in **1**. The nine values obtained from three runs were averaged. $\Delta\delta_{max}$ values for **1** (all upfield shifts): anthracene H-10, 0.60 ppm; anthracene H-4, 0.52 ppm; (dimethylamino)phenyl H-2, 21 Hz. Other protons became obscured during the titration. A 1 × 10^{-3} M solution of 9-propyladenine containing 4 × 10^{-4} M **1** showed the following upfield shifts ($\Delta\delta$): H-2, 0.16 ppm; 4-NH_2, 0.40 ppm; H-8, 0.40 ppm; 9-CH_2, 0.07 ppm.

(18) Determined by ^1H NMR at 303 K: Lancelot, G. *J. Am. Chem. Soc.* **1977**, *99*, 7037–7042.

(19) A related receptor containing two Kemp triacid units uses four hydrogen bonds and one stacking interaction to complex 9-ethyladenine with K_{assoc} = 11 000 M^{-1} (30% $CD_3CN/CDCl_3$, 25 °C), ref 3c-f.

Orderly Functional Group Dyads. Recognition of Biotin and Adenine Derivatives by a New Synthetic Host[1]

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The catalytic effects of enzymes and the specificity of biogenic receptors illustrate the remarkable properties of properly ordered functional group arrays. The development of general approaches to orderly functional group arrays is an important challenge to the synthetic organic chemist. We describe here a generalizable approach to chiral functional group dyads. The method is illustrated by the preparation of **1** and **2**, chiral molecules wherein two carboxylic acids may intersect at an angle of approximately 120°. The functional groups of these molecules are well-arranged for binding to several guests, including biotin and adenine derivatives, through formation of four hydrogen bonds. Host **1** binds to 9-ethyladenine (**3**) in THF-d_8. Control experiments suggest that **3** interacts with the host through the use of N7 and *both* hydrogen atoms at N6. In $CDCl_3$, host **2** binds very effectively to 9-ethyladenine, to biotin methyl ester (**4**), and to several other guests.

Triple ribonucleic acid helix formation and protein–nucleic acid interactions take advantage of the ability of the adenine base to form four hydrogen bonds (H-bonds).[3] Two H-bonds may be made to N6 and N7 (as in the Hoogsteen nucleic acid dimers), while at the same time another two H-bonds may be made to N6 and N1 (as in the Watson–Crick dimer).[4,5] Cyclic urea derivatives such as biotin methyl ester (**4**) also present two potential sites for hydrogen bond formation. Modeling studies suggested that a single molecule may bind to both sides of adenine or biotin provided that the host molecule contain two properly arranged carboxylic acids that intersect at about a 120° angle.[6,7] The

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