

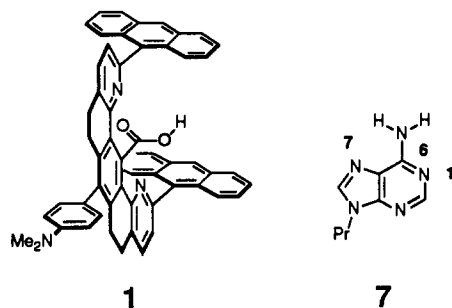
A Rigid Molecular Tweezer with an Active Site Carboxylic Acid: An Exceptionally Efficient Receptor for Adenine in an Organic Solvent[†]

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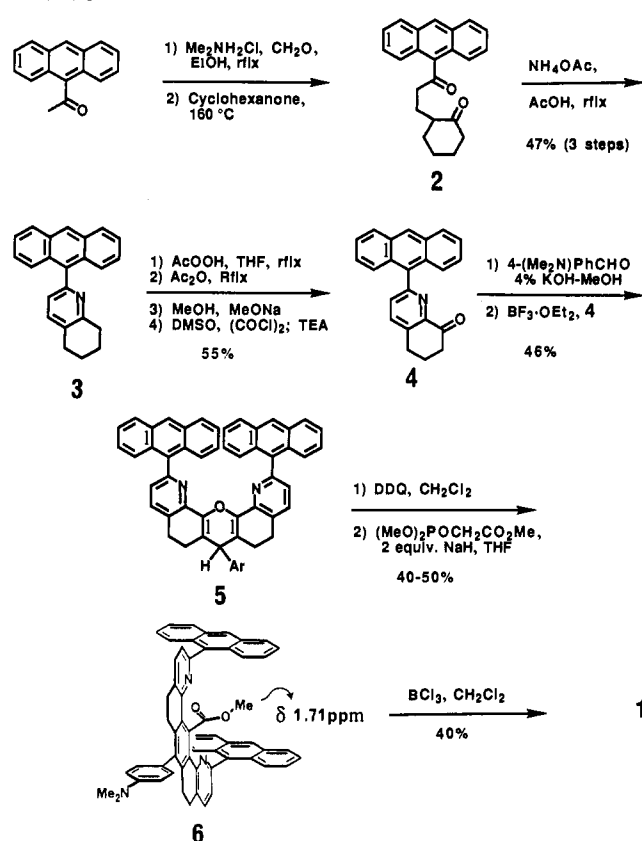
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Substantial progress has been made toward the development of synthetic receptors that utilize hydrogen bonding as a force in complexation. These receptors can be divided into two classes: those that contain a nearly planar array of multiple hydrogen bond donor and acceptor groups² 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 *nonmacrocylic* receptor (molecular tweezer **1**) wherein a binding site is created by the convergence



of two aromatic surfaces and a carboxylic acid.^{6,7} These cleft-like receptors retain the exceptional complexation power of the na-

Scheme I



phthalenophanes, but can bind much larger guests such as the nucleotide base adenine.

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 hydroxylation¹² and Swern oxidation¹³ 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-propyladenine¹⁴ (**7**) in chloroform-*d* was monitored by ¹H 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

(8) Maxwell, C. E. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 305.

(9) Gill, N. S.; James, K. B.; Lions, F.; Potts, K. T. *J. Am. Chem. Soc.* **1952**, *74*, 4923-4928.

(10) All new compounds gave correct elemental analysis and/or high resolution mass spectral data and had ¹H NMR and IR spectra that were in accord with the assigned structures. Molecular tweezer **1** analyzed correctly as a fractional solvate of methylene chloride.

(11) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* **1985**, *50*, 2407-2412. See also: Bell, T. W.; Rothenberger, S. D. *Tetrahedron Lett.* **1987**, *28*, 4817-4820.

(12) Cf.: Thummel, R. P. In *Pyridine and Its Derivatives*; Newkome, G. R., Ed.; The Chemistry of Heterocyclic Compounds; Wiley: New York, 1984; Vol. 14, Part 5, Chapter 2.

(13) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.

(14) We warmly thank Prof. Nelson J. Leonard for a generous sample of 9-propyladenine.

(15) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563-5566.

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(2) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673-3674. Kelley, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549-6551.

(3) (a) Rebek, J., Jr.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738-6739. (b) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *Ibid.* **1987**, *109*, 2426-2431. (c) Rebek, J., Jr. *Science* **1987**, *235*, 1478-1484. (d) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 5033-5035. (e) Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Parris, K.; Williams, K.; Rebek, J., Jr. *Ibid.* **1989**, *111*, 1082-1090. (f) Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *Ibid.* **1989**, *111*, 1090-1094. (g) Hamilton, A. D.; Van Engen, D. *Ibid.* **1987**, *109*, 5035-5036. (h) Goswami, S.; Hamilton, A. D.; Van Engen, D. *Ibid.* **1989**, *111*, 3425-3426.

(4) For other systems, see: Aarts, V. M. L. J.; van Staveren, C. J.; Grootenhuis, P. D. J.; van Eerden, J.; Kruse, L.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1986**, *108*, 5035-5036. Kilburn, J. D.; Mackenzie, A. R.; Still, W. C. *Ibid.* **1988**, *110*, 1307-1308. Pant, N.; Hamilton, A. D. *Ibid.* **1988**, *110*, 2002-2003. Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787-5789. Ebmeyer, F.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 79-81.

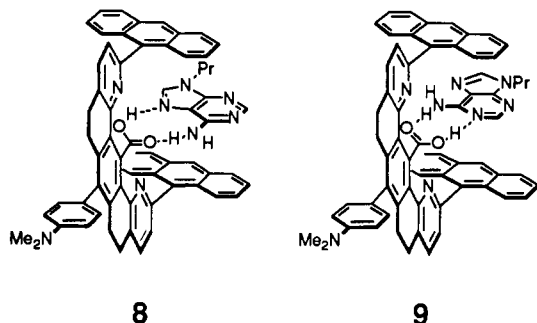
(5) (a) Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7120-7121. (b) Sheridan, R. E.; Whitlock, H. W., Jr. *Ibid.* **1988**, *110*, 4071-4073. (c) Haeg, M. E.; Whitlock, B. J.; Whitlock, H. W., Jr. *Ibid.* **1989**, *111*, 692-696.

(6) For our previous studies of molecular tweezers, see: (a) Zimmerman, S. C.; VanZyl, C. M. *J. Am. Chem. Soc.* **1987**, *109*, 7894-7896. (b) Zimmerman, S. C. *Tetrahedron Lett.* **1988**, *29*, 983-986. (c) Zimmerman, S. C.; VanZyl, C. M.; Hamilton, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1373-1381.

(7) For related molecular tweezers, see: Chen, C.-W.; Whitlock, H. W. *J. Am. Chem. Soc.* **1978**, *100*, 4921-4922. Wilcox, C. S.; Greer, L. M.; Lynch, V. *Ibid.* **1987**, *109*, 1865-1867.

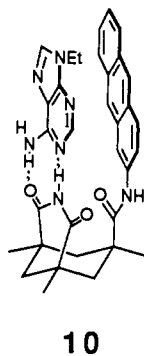
from both analyses were identical, and the association constants agreed within 13%. The association constant thus obtained, $K_{\text{assoc}} = 25000 \pm 6000 \text{ M}^{-1}$, is the largest reported to date for a complex between a synthetic receptor and a nucleic acid base.¹⁷

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 $4.5 \times 10^{-3} \text{ M}$ solution of ester **6**. Lancelot has shown that butyric acid binds 9-ethyladenine in chloroform-*d* ($K_{\text{assoc}} = 160 \text{ M}^{-1}$) 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



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



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

(16) Nakano, M.; Nakano, N. I.; Higuchi, T. *J. Phys. Chem.* **1967**, *71*, 3954-3959. For a discussion of the use of this method, see: Connors, K. A. *Binding Constants*; Wiley: New York, 1987; p 197.

(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. $\Delta\delta_{\text{max}}$ 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 $1 \times 10^{-3} \text{ M}$ solution of 9-propyladenine containing $4 \times 10^{-4} \text{ M}$ **1** showed the following upfield shifts ($\Delta\delta$): H-2, 0.16 ppm; 4-NH₂, 0.40 ppm; H-8, 0.40 ppm; 9-CH₂, 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 $K_{\text{assoc}} = 11000 \text{ M}^{-1}$ (30% CD₃CN/CDCl₃, 25 °C), ref 3c-f.

toward which our current efforts are directed.

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Orderly Functional Group Dyads. Recognition of Biotin and Adenine Derivatives by a New Synthetic Host¹

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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*₆. Control experiments suggest that **3** interacts with the host through the use of N7 and *both* hydrogen atoms at N6. In CDCl₃, 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

(1) Part 10 in a series on the Chemistry of Synthetic Receptors and Functional Group Arrays. Part 9: Wilcox, C. S.; Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Lynch, V. In *Proceedings of the 5th International Symposium on Inclusion Phenomena*; Atwood, J., Ed.; Plenum Press: New York, 1989.

(2) Fellow of the Alfred P. Sloan Foundation, 1988-1990.

(3) (a) Seeman, N. C.; Rosenberg, J. M.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 804-808. (b) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984; Chapter 18.

(4) Hoogsteen, K. In *Molecular Associations in Biology*; Pullman, B., Ed.; Academic: New York, 1968; pp 21-38.

(5) Watson, J. D.; Crick, F. H. C. *Nature (London)* **1953**, *171*, 737.

(6) (a) A diimide that binds strongly to adenine derivatives in chloroform has been described: Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090-1094. (b) A macrocyclic diamide that binds 9-butyladenine in chloroform by simultaneous Watson-Crick-Hoogsteen motifs has been developed: Goswami, S.; Van Engen, D.; Hamilton, A. D. *J. Am. Chem. Soc.* **1989**, *111*, 3425-3426. (We thank Prof. Hamilton for making available a preprint of this manuscript.)

(7) Several crescentic or macrocyclic hosts containing convergent hydrogen bonding sites have been described. Recent contributions include the following: Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. Kilburn, J. D.; MacKenzie, A. R.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 1307. Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. Rebek, J., Jr. *J. Mol. Recognition* **1988**, *1*, 1-8. Osterberg, C. E.; Arif, A. M.; Richmond, T. G. *J. Am. Chem. Soc.* **1988**, *110*, 6903.