Improved Binding of Adenine by a Synthetic Receptor

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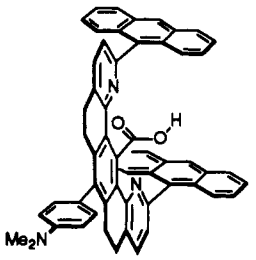
Summary: A new synthesis of molecular tweezers of type **1** is more efficient and general, and allows access to **3**, a receptor whose structure is closer to being optimized for adenine binding. Receptor **3** binds adenine in chloroform with $K_{assoc} > 10^5$ M^{-1}.

We have recently described the synthesis of "molecular tweezer" **1**, a new type of synthetic receptor in which a carboxylic acid is held within an aromatic cleft.[1,2] In chloroform-*d*, **1** was found to bind 9-propyladenine tightly[2] and with reasonable selectivity over other nucleotide bases.[3] In spite of these appealing properties, **1** was not regarded as an optimized receptor for two reasons: (1) its spacer was not fully oxidized, thereby allowing for a substantial amount of twist, which reduces $\pi-\pi$ overlap between host and guest, and (2) it forms only two out of five possible hydrogen bonds to 9-substituted adenines. We have addressed the first issue and report herein that fully oxidized molecular tweezer **3** binds 9-propyladenine (**4**) substantially stronger than does **2**, an analogue of **1**. We also report the curious observation that the anthracene chromophores contribute to the complex stability (i.e. 2.5–4 kcal mol^{-1}) only when the adenine guest is held in the cleft by hydrogen bonding.



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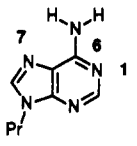

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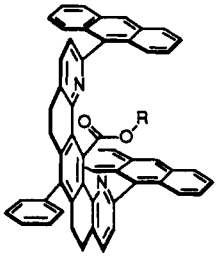
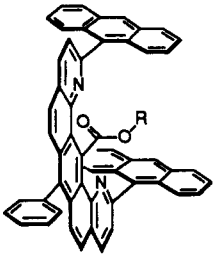


2 : R = H
10 : R = CH_3



3 : R = H
12 : R = CH_3

The synthetic route to **1** was lengthy and lacked generality.[2] Additionally, it necessitated the incorporation of a pendant (dimethylamino)phenyl substituent whose reactivity frustrated attempts to fully oxidize the spacer unit. For these reasons a more efficient and general synthesis has been developed to **2** and **3**. The new synthesis began with 5,6,7,8-tetrahydro-2-quinolone which was treated with phosphous oxychloride to afford chloride **5** in 90% yield (Scheme I). Benzylic oxidation[4] was accomplished by

Scheme I

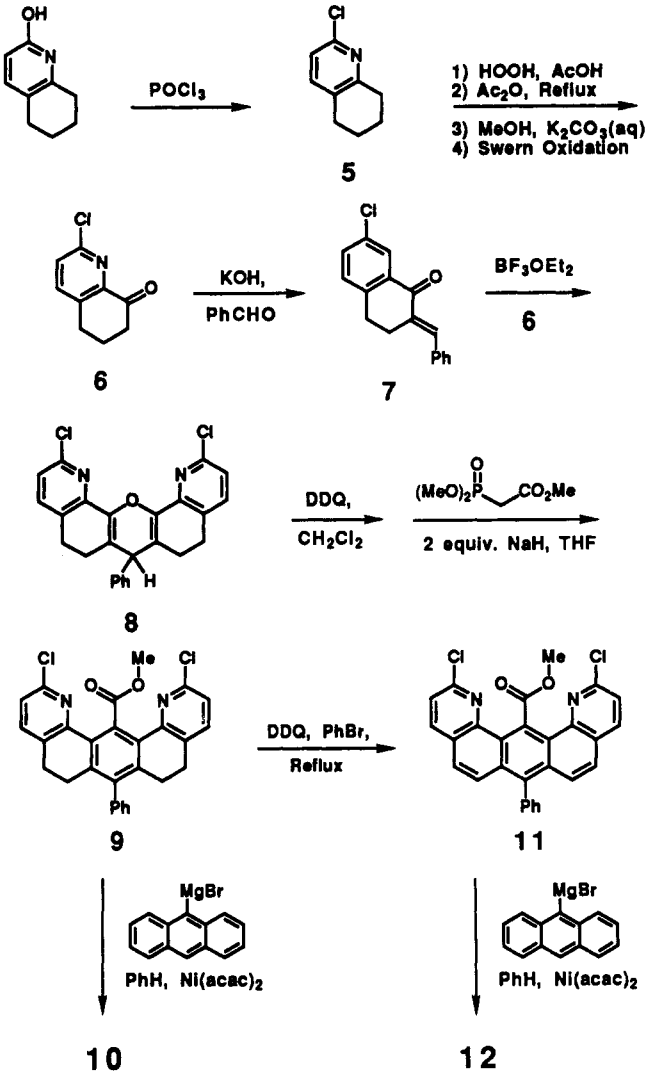


Table I. Complexation Data from the UV–Visible Titration of 2, 3, and 13 with 9-Propyladenine in Chloroform-*d* at 298 K[a]

compd	λ_{max}, nm	$\Delta\epsilon$	$-\Delta G°$, kcal mol^{-1}	K_{assoc}, m^{-1}
13				<10[b]
2	386	2110	5.7	14 000[c]
3	406	2160	6.9	120 000[c]

[a] For **2**, [host] ≈ 4×10^{-5} M, [4] ≈ (4–30) × 10^{-6} M. For **3**, [host] = 5×10^{-6} M, [4]] ≈ (5–60) × 10^{-6} M. Data up to 80–90% saturation was used. [b] Based on negligible shift in ^1H NMR of anthracene protons of **13** (4×10^{-4} M) in the presence of 5×10^{-3} M **4**. [c] Using the method described in ref 2. Based on triplicate runs, the values are good to ±20% for **2** and ±15% for **3**.

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(1) Chen, C.-W.; Whitlock, H. W. *J. Am. Chem. Soc.* **1978**, *100*, 4921–4922.
(2) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054–8055.
(3) Zimmerman, S. C.; Wu, W.; Zeng, Z., manuscript in preparation.

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conversion to the *N*-oxide, treatment with acetic anhydride, hydrolysis, and Swern oxidation[5] to produce chloroquinolone **6** in 65% overall yield. Treatment of **6** with benzaldehyde and potassium hydroxide in aqueous methanol afforded benzylidene **7** in 72% yield. Coupling of the benzylidene with **6** in boron trifluoride etherate produced pyran **8**, which was oxidized with DDQ and condensed with trimethyl phosphonoacetate and sodium hydride in THF to produce dichloride **9** in 37% yield (three steps).[2,6]

As a late intermediate in the synthesis, dichloride **9** could be coupled with a variety of complexing chromophores. For example, reaction of **9** with 9-anthrylmagnesium bromide in refluxing benzene produced ester **10**.[7] Most importantly, **9** provided access to **3**. Thus, oxidation of **9** with DDQ in refluxing bromobenzene afforded the fully aromatic spacer **11** in 41% yield. Dichloride **11** was coupled with 9-anthrylmagnesium bromide in refluxing benzene to afford ester **12** in 45% yield along with the monoaddition product (46% yield). Treatment of **10** and **12** with boron trichloride in methylene chloride afforded the corresponding molecular tweezers **2** and **3** in 50% and 67% yields, respectively.

Two interesting features noticed in the ^{1}H NMR spectrum of esters **10** and **12** may bear on the complexation efficiencies of the corresponding carboxylic acids (**2** and **3**). First, in the ^{1}H NMR spectrum of **12** doubling (1:1) of the proton resonances was observed for the anthracene rings of ester **12**, while all other protons resonated normally. This atropisomerism most likely reflects slow rotation of the methyl ester and the anthracene rings on the NMR time scale. This property is not seen in **10**, suggesting that **10** is more flexible than **12**, thereby allowing free rotation of one or both of the groups. Of course, slow rotation with isochronous protons cannot be ruled out. The second interesting aspect of the ^{1}H NMR spectra relates to the large upfield chemical shifts of the methyl ester resonances. The methyl esters in **10** and **12** resonate at δ = 1.71 ppm and δ = 1.42 ppm, respectively. These values represent upfield chemical shifts of 2.37 ppm (**10**) and 3.16 ppm (**12**) relative to the corresponding dichloride precursors **9** and **11**. The larger upfield shift in **12** suggests that it has a smaller inter-anthracene separation and/or a reduced twist in its spacer leading to higher shielding of the methyl protons (vide infra).

Complexation studies were performed in chloroform or chloroform-*d* and were monitored by UV–visible or ^{1}H NMR spectroscopy. Self-association of **2** and **3** at the concentrations used (ca. 5×10^{-6} M) was considered to be unlikely since both compounds obeyed Beer's law up to a concentration of 3×10^{-5} M. The self-association constant for 9-ethyladenine is small, $K_{dimer} = 3.1$ M^{-1}, so that dimerization of **4** can be considered to be negligible under the conditions employed.[8] As was found with **1**, the ^{1}H NMR spectrum of **2** in chloroform-*d* changed upon addition of 9-propyladenine (**4**) in a manner consistent with the formation of a hydrogen bonded and π-stacked complex. While this complex was in fast exchange with it components, the **3·4** complex showed extremely broad

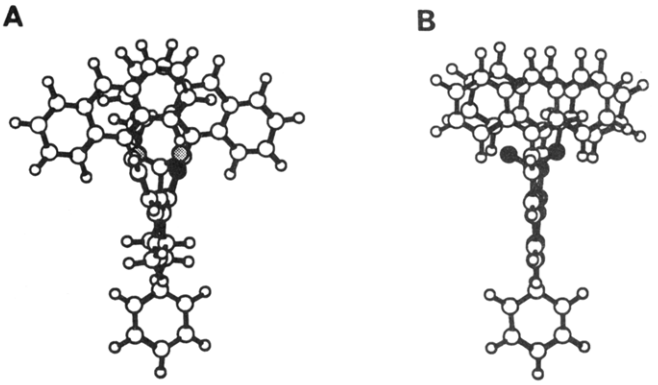


Figure 1. View of the calculated ground-state conformation for **10** (A) and **12** (B) looking along the aromatic spacer.

anthracene resonances throughout the titration, indicating slow exchange on the ^{1}H NMR time scale. This finding, combined with the high stability of the complex, made UV–visible spectroscopy the method of choice for determining binding constants.

The results of the binding studies appear in Table I. The affinity of molecular tweezer **2** for **4** is quite high, K_{assoc} = 14 000 M^{-1}, and that of receptor **3** for **4** is exceptionally high, K_{assoc} = 120 000 M^{-1}.[9] The importance of the anthracene rings to the stability of both complexes is evidenced by the fact that in chloroform-*d* butyric acid and benzoic acid bind 9-ethyladenine with association constants of 160 and 700 M^{-1}, respectively.[10–13] Thus, the contribution to complex stability made by the aromatic clefts in **2** and **3** is ca. 2.5 and 4.0 kcal mol^{-1}, respectively. The difference between **2** and **3** most likely reflects the greater degree of organization in the latter receptor. Shown in Figure 1 are the calculated low energy conformations of **10** and **12**.[14] Although the inter-anthracene distance in **12** is not significantly smaller than in **10** (7.52 vs 7.66 Å), there is a marked decrease in the degree of spacer twist, leading to a cleft which is closer to being optimized for adenine complexation. The larger twist in **10** reflects its ability to alleviate the severe peri-interactions between the ester and nitrogen atoms,[6] which were absent in our earlier system.[15]

The role of the anthracene rings in the complexation has not been established, although they stabilize the complex by 2.5–4 kcal mol^{-1}. This value might represent the polarization and dispersion forces operating between two

(4) Cf: Thummel, R. P. In *Pyridine and Its Derivatives*; Newkome, G. R., Ed.; Advances in Heterocyclic Chemistry; Wiley: New York, 1984; Vol. 15, Part 5, Chapter 2.

(5) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.

(6) Zimmerman, S. C. *Tetrahedron Lett.* **1988**, 983–986.

(7) The conditions for this coupling reaction have not been optimized so the yield is low. The dibromide corresponding to **9** has been found to couple with 9-anthrylmagnesium bromide in a 73% yield, but this dibromide is more difficult to obtain: Zeng, Z., unpublished results.

(8) Kyogoku, Y.; Lord, R. C.; Rich, A. *Proc. Natl. Acad. Sci., U.S.A.* **1967**, *57*, 250–257.

(9) The K_{assoc} for **2·4** is less than that reported for the **1·4** complex (K_{assoc} = 25 000 ± 6000 M^{-1}). Although the difference is close to the error limits, it may reflect the change in conditions under which the binding studies were performed. Thus, K_{assoc} for the **1·4** complex as determined by the UV method (K_{assoc} 12 000 M^{-1}) is nearly identical with that for the **2·4** complex. Association constants have previously been found to change with the method (conditions) used: Foster, R. *Organic Charge-Transfer Complexes*; Academic: New York, 1969; pp 157–160.

(10) Lancelot, G. *J. Am. Chem. Soc.* **1977**, *99*, 7037–7042.

(11) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055–8057.

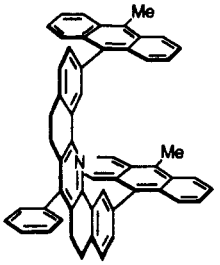
(12) (a) Other receptors combining hydrogen bonding and π-sandwiching: Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 4071–4073. Echavarren, A.; Galán, A.; Lehn, J.-M.; Mendoza, J. *Ibid.* **1989**, *111*, 4994–4995. (b) Related receptors: Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255 and references therein.

(13) Butyric acid is a more appropriate model for the carboxylic acid in **1–3** than is benzoic acid: Wu, W., unpublished results.

(14) Using PC Model from Serena Software, Bloomington, IN. This package contains the MMX force field, which is derived from the MM2 force field and the pi-VESCF routines of MMP1 (MM2 and MMP1 were developed by N. L. Allinger). We have found this software to effectively reproduce the X-ray structures of molecular tweezers and spacer units obtained in these laboratories.

(15) Zimmerman, S. C.; Mrksich, M.; Baloga, M. *J. Am. Chem. Soc.* **1989**, *111*, 8528–8530.

highly polarizable anthracene rings and an adenine chromophore. However, it was found that dianthryl molecular tweezer **13** shows no affinity for **4** in chloroform-*d* (K_{assoc} < 10 M^{-1}).[16] This striking result suggests that the benefit from π-stacking is felt only when the adenine is held proximate to the anthracenes through hydrogen bonding.[17]



13

Alternatively, the aromatic cleft may serve to desolvate the carboxylic acid. In either case, placing a carboxylic acid deep within an aromatic cleft markedly enhances its complexation efficiency. The flexibility of the synthesis described herein should allow the incorporation of addition hydrogen bonding functionalities resulting in receptors with even higher affinities for adenine. In a more general vein, our results suggest that the stability of hydrogen-bonded complexes can be dramatically increased by surrounding the appropriate functionality with an aromatic cleft.

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(16) In other studies we have found **13** to bind π-deficient guests (e.g. 2,4,5,7-tetranitrofluorenone) as tightly as did the analogous acridine based molecular tweezers (ref 15).

(17) In a similar system, this type of cooperativity has been attributed to a "spatio-temporal hypothesis": Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7120–7121.

A General Preparation of Highly Functionalized Zinc and Copper Organometallics at the α-Position to an Oxygen

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Summary: α-Bromoalkyl acetates **2**, which are readily prepared by the addition of acetyl bromide to aldehydes, insert zinc under mild conditions affording, after the addition of CuCN·2LiCl, polyfunctional α-acetoxy copper reagents of type **1**. Their reactivity toward various organic electrophiles is described.

Lithium organometallics at the α-position to oxygen have proven to be very useful intermediates in organic syntheses.[1] However, their high reactivity and the methods used for their preparation precludes the presence of most functional groups in these compounds. We report herein a new general preparation of highly functionalized zinc and copper organometallics of type **1**. Thus, the α-bromoalkyl acetates **2**, prepared by the addition of acetyl bromide to aldehydes **3** (CH_3COBr (1.5 equiv), $ZnCl_2$ catalyst, CH_2Cl_2, 25 °C, 2 h; 85–90%)[2,3] were found to react

(1) (a) Beak, P.; McKinnie, B. G. *J. Am. Chem. Soc.* **1977**, *99*, 5213. (b) Beak, P.; Carter, L. G. *J. Org. Chem.* **1981**, *46*, 2363. (c) Beak, P.; Baillargeon, M.; Carter, L. G. *J. Org. Chem.* **1978**, *43*, 4255. (d) Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512. (e) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1290. (f) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (g) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (h) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900. (i) Hoppe, D.; Brönneke, A. *Synthesis* **1982**, 1045. (j) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822. (k) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3163, 3165. (l) Lehmann, R.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 745. (m) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1985**, *50*, 4655. (n) Sawyer, J. S.; Kucerovy, A.; MacDonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. (o) McDougal, P. G.; Rico, J. G.; VanDerveer, D. *J. Org. Chem.* **1986**, *51*, 4492. (p) Shiner, C. S.; Tsunoda, T.; Goodman, B. A.; Ingham, S.; Lee, S.; Vorndam, P. E. *J. Am. Chem. Soc.* **1989**, *111*, 1381. (q) Rychnovsky, S. D.; Mickus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011. (r) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982. (s) Knochel, P.; Chou, T.-S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202.

(2) (a) Kyburz, R.; Schaltegger, H.; Neuenschwander, M. *Helv. Chim. Acta* **1971**, *54*, 1037. (b) Neuenschwander, M.; Iseli, R. *Helv. Chim. Acta* **1977**, *60*, 1061. (c) Bigler, P.; Mühle, H.; Neuenschwander, M. *Synthesis* 1978, 593. (d) Neuenschwander, M.; Bigler, P.; Christen, K.; Iseli, R.; Kyburz, R.; Mühle, H. *Helv. Chim. Acta* **1978**, *61*, 2047.

(3) Typical procedure: preparation of an organozinc reagent derived from an α-(bromoalkyl) acetate and its reaction with an allylic bromide; (a) **Preparation of (1-Acetoxy-2-methylpropyl)zinc Bromide.** A three-necked, 25-mL flask equipped with an argon inlet, a stirring bar, a low-temperature thermometer, and an addition funnel was charged under argon with zinc dust (Aldrich, 325 mesh; 1 g, 15 mmol), 2 mL of dry DMSO, and 2 mL of dry THF. The mixture was cooled to 0 °C, and 1-bromo-2-methylpropyl acetate (**2**; R = i-Pr, 1.95 g, 10 mmol) in 5 mL of THF prepared as described above was added dropwise within 10 min. The reaction mixture was warmed to 8–10 °C and stirred at this temperature overnight (10 h) leading to an almost quantitative formation of the corresponding zinc organometallic as indicated by GLC analysis of a hydrolyzed reaction aliquot. (b) **Preparation of Ethyl 4-Acetoxy-5-methyl-2-methylenehexanoate (13).** The THF solution of (1-acetoxy-2-methylpropyl)zinc bromide (10 mmol) prepared as described above was added via syringe at −78 °C to a suspension of LiCl (0.7 g, 16 mmol) and CuCN (0.72 g, 8 mmol) in 3 mL of THF. A solution of ethyl α-(bromomethyl)acrylate (0.97 g, 5 mmol) in 3 mL of THF was added, and the reaction mixture was warmed to 0 °C. The reaction was completed after 0.5 h as shown by GLC analysis. The reaction mixture was then diluted with 50 mL of ether and poured in 25 mL of a saturated NH_4Cl solution. The organic and aqueous layers were separated, and the aqueous layer was extracted twice with 25 mL of ether. The combined organic phase was successively washed with H_2O (2 × 20 mL) and brine (10 mL). After drying over $MgSO_4$ and filtration, the solvent was evaporated and the crude oil was purified by flash chromatography (solvent: hexane/ether 20–10:1), yielding 1.08 g (95%) of the analytically pure product **13** (purity >99% by GLC analysis).

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