Synthesis and Structure of Molecular Tweezers Containing Active Site Functionality

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Abstract: A series of molecules has been synthesized in which a functional group is buried inside an aromatic binding cleft. These novel compounds, called "molecular tweezers", have a methyl ester (6a, 7-9a, 10a), a carboxylic acid (6b, 9b, 10b, 45), or a nitrile (50) in their clefts. Molecular tweezer 21 has a metal ligand, an annelated terpyridine, oriented toward the binding cleft. The structures of 7-10 have been determined either by X-ray analysis or by molecular modeling techniques and were found to contain different inter-anthracene (acridine) distances and varying degrees of twist in their spacers. As precursors to nucleotide base receptors, these molecules represent four discrete steps toward the development of an optimized receptor for adenine.

Previous reports from this laboratory1 have described the synthesis, structure, and complexation chemistry of a class of host molecules, called molecular tweezers2 (e.g. 1). The critical structural element of these cleft-like receptors is the tetra-hydrodibenzo[c,h]acidine spacer, which holds the two acridine rings in an enforced syn orientation with a ca. 7-Å interchromophore separation. As such, receptor 1 efficiently binds π-deficient guests in organic solvents by forming π-sandwich complexes.

In order to increase the molecular tweezers “stickiness”3 for π-neutral guests, we have sought to incorporate a functional group that might hydrogen bond to the guest. Preliminary studies have shown that spacers 2-5, containing bay region ester groups, can be efficiently synthesized.4 X-ray crystal analysis of 3 and 5 showed them to have very different structural features and therefore disparate potentials for the construction of a guest sticky molecular tweezer. In a preliminary report we described the synthesis of 6b, an efficient receptor of adenine, which is based on spacer 4.5 Herein we present full details of this synthesis of 6 along with a new, more efficient, and general synthesis. Also reported are synthetic and structural studies of molecular tweezers based on spacers 2, 3, and 5 and molecular tweezers with either a nitrile (50) or a terpyridine ligand (21) oriented toward the binding cleft. In the following paper full details of the complexation chemistry of molecular tweezer 6b are described and a comparative binding study with adenine receptors 9b and 10b is given.

Results and Discussion

Design. The design of the new receptors has as its starting point our earlier molecular tweezers (e.g. 1) which were known to bind efficiently π-deficient aromatic guests through the formation of π-sandwich complexes. Although these receptors contain a weakly basic nitrogen atom oriented toward the binding cleft, we sought a functional group that could engage in two or more hydrogen bonds and thus increase the binding affinity and selectivity for π-neutral guests. A carboxylic acid was chosen as a suitable group.6 Even though carboxylic acids can dimerize in nonpolar apotic media,7 self-association would be hindered since the group would be buried deep within an aromatic cleft (see Figure 1). The new spacer design raised several important structural concerns. The previous dibenzo[c,h]acidine spacer was known to have a C-2 to C-12 distance of 7.24 Å8 so that chromophores attached at these positions would be held just slightly further apart than the presumed optimum of 6.8 Å. If a functional group were attached to the central atom of the bay region, it was expected that the C-2 to C-12 distance would increase and the spacer might distort as a result of the introduction of severe peri-interactions.9 For this reason, it was important to determine the C-2 to C-12 distances and the relative orientations of the carboxylic acid and the complexing chromophores in these new molecular tweezers. A model study showed that spacer 3 could be efficiently syn-

Figure 1. Schematic representation of a molecular tweezer with a carboxylic acid at the central bay-region position of the spacer unit. The guest is an aromatic compound capable of forming one or more hydrogen bonds to the carboxylic acid.

Scheme 1

(a) Synthesis of 6a: A Molecular Tweezer with an Active Site Ester. Our previously described synthesis of 6a was begun with 9-acetylanthracene which was converted into its Mannich base 11 with use of standard conditions (Scheme I). Refluxing 11 in 3 equiv of cyclohexanone afforded 1,5-diketone 12, and this was reacted with ammonium acetate in refluxing acetic acid to afford the C-2 to C-12 distance of 7.5 Å. Although the addition of cupric acetate gave 13 in higher yield, the reaction proved to be more difficult to work up on a very large scale. Oxidation of the benzylic position in 13 was effected by refluxing with benzaldehyde in acetic anhydride. Treatment of benzylidene (14) could be obtained in 69% yield, but its ozonolysis was problematic in that competitive oxidation of the anthracene ring occurred.

Rather than pursuing alternative methods for oxidatively cleaving the arylidene in 14, a four-step lateral oxidation was applied to 13. Toward this end, 13 was converted into its N-oxide (15) with peracetic acid, and this was refluxed in acetic anhydride to afford the benzylic acetate 16 (Scheme II). Hydrolysis to quinolinol 17 followed by Swern oxidation afforded quinolone 18 in 55% yield for the four steps. Treatment of 18 with 4-(dimethylamino)benzaldehyde and base afforded the corresponding arylidene 19 in 85% yield. This particular aldehyde was used since it gave the best yield in the subsequent coupling reaction with 18 in boron trifluoride etherate.

Surprisingly, the boron trifluoride etherate mediated coupling reaction produced pyran 20 in 72% yield, rather than the expected pyrylium salt. The production of 20 proved to be helpful since the intermediate pyrylium salts in the synthesis of the earlier molecular tweezers (e.g. 1) could not be isolated, while 20 could be purified readily by chromatography. Treatment of 20 with DDQ effected its conversion to the pyrylium salt, which was directly condensed with trimethyl phosphonoacetate in the presence of 2 equiv of sodium hydride.

This remarkable reaction, which has been discussed in detail, produced molecular tweezer 6a in 40–50% yields. The corresponding carboxylic acid 6b was obtained in 40% yield by treatment of 6a with boron trichloride. Although 6b proved to be an efficient receptor for adenine, it was anticipated that the fully oxidized spacer would provide an even more suitable disposition of the complexing functionality. Unfortunately, oxidation of the spacer in 6a with DDQ was unsuccessful due to competitive oxidation of the (dimethylamino)phenyl substituent. Other attempted oxidations also proved to be unsuccessful. The problem was overcome by application of an improved synthesis (vide infra).

Beyond the higher efficiency and generality of the approach, it provides access to the fully oxidized molecular tweezer 10. Thus, DDQ oxidation of 38 in refluxing bromobenzene afforded dichloride 40 in 41% yield. Reaction of 40 with 9-anthrylmagnesium bromide in the presence of nickel(II) acetonylacetate produced 10a in ca. 45% yield along with the mono-coupled product in 46% yield.

(c) Synthesis of 21: A Molecular Tweezer with a Metal Binding Site. The well-precedented conversion of pyrylium salts, pyrans, and 1,5-diketones to pyridines made an obvious precursor to an annelated terpyridine ligand. In the event, treatment of 20 with ammonium acetate afforded 21 in 54% yield. Terpyridine has a rich complexation chemistry and Thummel has shown that the annelated terpyridine spacer in 21 is a better ligand for ruthenium trichloride than terpyridine itself. Thus, the vacant coordination site of a metal might converge on the binding cleft thereby increasing the binding affinity of a coordinating aromatic guest. The development of catalytic systems based on 21 can be envisaged as well.

(d) Synthesis of Highly Twisted Molecular Tweezers 7 and 8 with Active Site Esters. The synthesis of 7 and 8 proved to be quite straightforward (Scheme IV). As previously described, dibromide 41 was obtained in 6 steps from bromobenzene and succinic anhydride. At low temperature 41 underwent bromide–lithium exchange with 2 equiv of n-butyllithium and the resulting diion smoothly added to 2,7-dimethoxy-10-(2-methoxyethoxy)-9-acridone (42). Treatment of the addition product with acid afforded molecular tweezer 7 in 65% yield. Alternatively,
dibromide 41 was oxidized with DDQ to produce the fully unsaturated spacer 43, which underwent bromide-lithium exchange and addition to 42 to afford molecular tweezer 8 in 50% yield. Although this expeditious (7 step) route to 7 proceeded in only 8% overall yield, gram quantities of 7 could be obtained readily.

Conversion of ester 7 to the corresponding carboxylic acid proved troublesome. Boron trichloride, which was successful in converting ester 6a into acid 6b, converted 7 primarily into ketone 44, with only a small amount of a product which was tentatively identified as the carboxylic acid 45 (Scheme V). The \( ^1H \) NMR spectrum of this material in CDCl\(_3\) contained broad resonances, indicating the presence of a zwitterion and/or a mixture of aggregates. The IR spectrum was consistent with the presence of a zwitterion, and the \( ^1H \) NMR spectrum in basic DMSO-\( d_6 \) contained sharp resonances that were consistent with the carboxylate salt of 45. Two higher yielding routes to 45 were developed. In the first, the ester in 7 was hydrolyzed in 84% yield with sodium cyanide in DMSO. The second route involved conversion of methyl ester 41 into the corresponding methoxyethoxymethyl (MEM) ester (Scheme VI). Remarkably, it was found that the hindered ester in 41 could be converted into acid 46 in 82% yield by treatment with lithium triethylborohydride. The mechanism of this reaction has not been investigated, and to our knowledge this is the first example of an ester hydrolysis by this powerful reducing agent. Esterification of 46 with (methoxyethoxy)methyl chloride afforded ester 47 which underwent lithium–bromide exchange, addition to 42, and hydrolysis to form 45 in 33% yield.

In order to avoid proton transfer and/or hydrogen bonding to the acridine nitrogen, efforts were made to attach anthracene chromophores to dibromide 41. In the first approach, 41 was subjected to lithium–bromide exchange and then treated with cerium trichloride followed by anthrone (Scheme VII). Although the unstable molecular tweezer 48 was obtained in 60% yield, the reaction proved to be irreproducible. The second approach involved conversion of dibromide 41 into the corresponding diiodide 49 (62%). Subsequent coupling with 9-anthrylmagnesium bromide with catalytic nickel(II) acetonylacetate afforded 48 as a mixture with the monoaddition product. The relatively high instability of 48 precluded its isolation in pure form. In related molecular tweezers it has been found that this instability results from oxidation of the anthracene moieties and can be greatly inhibited by substitution in the 10-position.\(^{23}\) Thus, substituted analogues of 48 have the potential for increased stability and might be suitable precursors to the corresponding carboxylic acids.

(e) Synthesis of Molecular Tweezer 50 with an Active Site Nitrile. The generality of the approach in Scheme IV was demonstrated by the synthesis of molecular tweezer 50 which contains a nitrile in the cleft. As shown in Scheme VIII, pyrylium salt

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(23) Zeng, Z. Unpublished results.
Scheme IV

1) n-BuLi, THF
-78 °C

2) 42

3) EtOH, HCl

Scheme V

Acr = 9-(2,7-dimethoxycoridinyl)

Scheme VI

1) n-BuLi, THF
-78 °C

2) 42

3) EtOH, HCl
and base to afford nitrile 52. Treatment of 52 with n-butyllithium effected lithium–bromide exchange and coupling with acridone 42 afforded molecular tweezer 50 in 65% yield. Despite its steric hindrance, conversion of the nitrile in 50 to amides, amidines, and related functionality can be envisaged.

In summary, molecular tweezers containing active site esters (69, 79a, 10a), carboxylic acids (6b, 9b, 10b, 45), nitriles (50c), and a terpyridine spacer (21) have been synthesized. Although the overall (unoptimized) yields are modest, the synthetic sequences that have been developed are short and readily allow >500-mg quantities of the molecular tweezers to be obtained.

**Structure of Molecular Tweezers 7-10.** The X-ray structure of molecular tweezer 1 showed it to possess a nearly perfect cofacial orientation of the acridine rings with a 6.8-Å separation, features which were regarded as most desirable for sandwich complexation of aromatic guests (see Figure 2). However, as noted previously, a larger interchromophore separation may not necessitate a sacrifice of complexation efficiency since rotations around the aryl-aryl bonds have the effect of reducing the interchromophore separation. This ability of these receptors to self-adjust their cleft dimensions makes the “molecular tweezer” moniker apropos. As seen in Figure 3, an arbitrarily chosen interchromophore distance of 7.8 Å (at maximum separation) can close to the presumed optimum of 6.8 Å by 30° rotations about the spacer–chromophore bonds. Of course, a reduced overlap between the chromophores accompanies these rotations.

In the new molecular tweezers (e.g. 6) it was assumed that the optimum conformation for binding complementary guests would have the carboxylic acid and the two anthracene chromophores in nearly parallel planes with an ca. 3.4-Å separation between adjacent planes. However, a model study showed the presence of the bay region functional group could markedly increase the C-2 to C-12 distance and cause the spacer to distort from planarity into a helical shape. Thus, it was important to determine not only the ground-state conformations of molecular tweezers 7-10, but also the degree to which their inherent flexibilities might allow access to conformations suitable for complexation. These issues were addressed through a combination of X-ray structural analysis and molecular modeling.

(a) Structure of Spacers 2-5. The structures of spacers 3 and 5 have been determined by X-ray analysis. The structure of spacer 2 can be inferred from that of molecular tweezer 7, whose X-ray structure has been determined (vide infra). No direct structural information is available for 4, despite the fact that its related molecular tweezer, acid 6, is the most thoroughly studied receptor. Therefore, molecular modeling techniques were used to determine the structure of 4, after their accuracy was tested by comparison with the X-ray data of 3 and 5. It was assumed in these calculations that the esters and their corresponding carboxylic acids will have very similar structures.

The PC Model program was used for the calculations and was found to reproduce the bond distances and angles of the X-ray data remarkably well, while somewhat larger differences were found in dihedral angles (data not shown). Since small differences in bond and dihedral angles can accumulate to produce large overall differences between the calculated and X-ray conformations, it is preferable to focus on those structural parameters that give the molecular tweezers their gross structure. These parameters include the C-2 to C-12 distance which defines the maximum interchromophore separation in the molecular tweezers and the spacer twist angle which largely determines the extent of interchromophore overlap. Finally, the dihedral angle between the ester group and the spacer will affect how well the guest is able to hydrogen bond to the corresponding carboxylic acid.

As seen in Table I, the calculated C-2 to C-12 distances agree extremely well (<2%) with the corresponding X-ray data. Larger differences are seen in the comparisons between the spacer–ester dihedral angles, but the agreement is still quite good (<9%). The amount of twist in the spacers is reproduced well for 2, but only partially for 3, while the calculated structure for spacer 5 is substantially more planar than seen in the X-ray structure. Overall, the calculated structures are in good agreement with the X-ray data.

The ease with which the ester groups can rotate from their optimum conformation was determined with use of the dihedral driver function with Δ increments and geometry optimization. The resulting data (Figure 4) contain two interesting features. The rotation of the ester group in spacers 3-5 led to a discontinuity in energy due a new local minima whose structure could be described as crescent shaped. These conformations were not seen in any of the X-ray structures and are not expected to play any significant role since they are of much higher energy than the helical conformation. It can also be seen from Figure 4 that some flexibility is present in the spacers since rotations of ±20° from the optimum ester dihedral angle in 2 and 3 and ±30° from the optimum in 4 and 5 cost less than 2 kcal mol⁻¹ in energy.

Table I. Comparison of Conformations in Spacer Units 2-5

<table>
<thead>
<tr>
<th>spacer</th>
<th>methoda</th>
<th>C-2 to C-12 distance, Å</th>
<th>spacer twist angle, deg</th>
<th>ester to spacer dihedral angle, deg</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>A</td>
<td>8.29</td>
<td>36</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>8.21</td>
<td>35</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>8.20</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>4 (7)</td>
<td>B</td>
<td>8.20</td>
<td>19</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>7.66</td>
<td>22</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>7.63</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>7.62</td>
<td>11</td>
<td>78</td>
</tr>
</tbody>
</table>

aMethod A: PC Model calculation. Method B: X-ray crystal structure.

Table II. Upfield 'H NMR Chemical Shift (ppm) of Methyl Esters in Molecular Tweezers 7-10 and 48

<table>
<thead>
<tr>
<th>molecular tweez</th>
<th>chemical shift of methyl ester</th>
<th>chemical shift of methyl ester</th>
<th>Δδ, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>2.72</td>
<td>41</td>
<td>3.91</td>
</tr>
<tr>
<td>8</td>
<td>2.72</td>
<td>41</td>
<td>3.91</td>
</tr>
<tr>
<td>9</td>
<td>2.73</td>
<td>43</td>
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<tr>
<td>10</td>
<td>1.71</td>
<td>30</td>
<td>4.62</td>
</tr>
</tbody>
</table>

The upfield chemical shift of the methyl ester in 7 and 48 are identical.
Dihedral driver calculations for the anthracene to spacer bond again indicate a moderate degree of flexibility. The preferred dihedral angle of ca. 90° can be changed by ±20° in 7 and 8, ±30° in 9, and ±40° in 10 with less than a 2 kcal mol⁻¹ cost in energy. However, this flexibility is insufficient to allow molecular tweezers 7 and 8 to organize their binding clefts for simultaneous hydrogen bonding and π-sandwich complexation. The acridine rings in these systems can close to within only 7.7 Å and there is minimal overlap between the chromophores. In contrast, 9 and 10 are sufficiently flexible to allow their anthracene rings and ester group to occupy parallel planes separated by the presumed optimum of 3.4 Å between adjacent planes (i.e. inter-anthracene separation of 6.8 Å) with only a minimum energy investment.

In summary, it has been found that the C-2 to C-12 distances range from 8.2 to 7.5 Å and increase in the order 10 < 9 < 8 < 7. Additionally, the lowest energy conformations of the spacers are nonplanar with helical twists of between 40° and 2° from end-to-end. This means that the degree of chromophore overlap
tweezers to act as receptors for nucleotide bases is the subject of an optimized binding cleft. The ability of some of these molecular complexes aromatic compounds with complementary hydrogen-bonding arrays. X-ray analysis, combined with simple molecular mechanics calculations, suggests that these four molecules have regular variations in structure that represent discrete steps toward the ester-to-spacer bond and around the aryl-aryl bonds is relatively flat within 20–40° of the optimum, suggesting that molecular tweezers 7–10 have a moderate degree of flexibility.

Conclusions

Expeditious routes have been developed for the synthesis of novel compounds wherein a functional group is “buried” within an aromatic cleft. Four of these compounds contain ester groups that can be converted into carboxylic acids and might be expected to increase in the order 7 < 8 < 9 < 10. Molecular mechanics calculations suggest that the potential barrier for rotations around the ester-to-spacer bond and around the aryl-aryl bonds is relatively flat within 20–40° of the optimum, suggesting that molecular tweezers 7–10 have a moderate degree of flexibility.

Experimental Section

General Methods. The following solvents were freshly distilled prior to use: tetrahydrofuran (THF) from sodium benzophene keyl, methanol (CH₃OH) from magnesium turnings, methylene chloride (CH₂Cl₂) from calcium hydride, dimethylformamide (DMF), predried over 4 Å molecular sieves, from barium oxide. Dimethyl sulfoxide (DMSO) and triethylamine were distilled over calcium hydride and stored under a nitrogen atmosphere. All other solvents and reagents were of reagent grade quality and used without further purification. Analytical TLC was performed on 0.2 mm silica 60 coated plastic sheets (EM Science) with F-254 indicator. Flash chromatography was performed on Merck 40-63 µm silica gel. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

1H and 13C NMR spectra were recorded on a General Electric QE-300 instrument unless otherwise stated. Spectra were obtained in chloroform-d. Chemical shifts are reported in parts per million (ppm) with TMS as an internal reference, and coupling constants are reported in hertz (Hz). Infrared spectra were recorded on a Perkin-Elmer 1320 spectrometer. Mass spectra were obtained on a Finnigan-MAT-731 spectrometer. Elemental analyses were performed at the University of Illinois School of Chemical Sciences. Some molecular tweezers were found to remain small quantities of the recrystallization/precipitation solvent as evidenced by the 1H NMR and elemental analysis. The elemental analysis is reported for the partial solvate which best fit the combustion data. The X-ray analysis data were collected on an Enraf-Nonius CAD4 automated x-axis diffractometer and analyzed with SHELXS-86.

1-(9-Anthracenyl)-3-(dimethylamino)-1-propanone (11). To a mixture of 50.0 g (0.23 mol) of 9-acetylanthracene, 9.0 g (0.1 mol) of paraform-aldehyde, 24.5 g (0.3 mol) of dimethylamination chloride, and 100 mL of 95% ethanol was added 1.2 mL of concentrated aqueous HCl and the solution was heated to reflux for 32 h. The reaction was cooled to room temperature and partitioned between 250 mL of 2 N HCl and 300 mL of ether. The ether layer was washed once with 100 mL of 2 N HCl. The combined aqueous layers were cooled to 0 °C, basified with solid sodium carbonate, and extracted with 10% 2-propanol-chloroform. The solution was heated to reflux for 32 h. The reaction was cooled to room temperature and partitioned between 250 mL of 2 N HCl and 300 mL of ether. The ether layer was washed once with 100 mL of 2 N HCl. The combined aqueous layers were cooled to 0 °C, basified with solid sodium carbonate, and extracted with 10% 2-propanol-chloroform. The organic layer was dried over Na₂SO₄ and concentrated to give 48.8 g (78%) of 11 as a colorless oil which was judged to be >95% pure by 1H NMR: 1H NMR δ 8.48 (s, 1 H, H-10'), 8.03 (d, J₉₋₁₀ = 9.7, 2 H, H-4', H-5'), 7.85 (d, J₁₂₋₁₃ = 9.3, 2 H, H-1', H-2'), 7.51–7.46 (m, 4 H, H-2/, H-3', H-6', H-7'), 3.24 (t, J = 7.2, 2 H, NCH₂), 2.90 (t, J = 7.2, 2 H, COCH₂), 2.28 (s, 6 H, NCH₃); 13C NMR δ 209.29, 131.02, 128.74, 128.23, 126.94, 126.71, 125.47, 124.39, 53.86, 45.49, 44.58; MS (EI, 70 eV), m/z (relative intensity) 277 (M⁺, 12); exact mass calced for C₁₉H₁₉NO m/z 277.14662, found 277.14712.

1-(9-Anthracenyl)-3-(2-oxo-1-cyclohexyl)-1-propanone (12). A solution of 48.8 g (0.17 mol) of 11 and 51.8 g (0.46 mol) of cyclohexanone was heated to reflux for 20 min. The remaining cyclohexanone was
Figure 5. Side (A) and top (B) view of the X-ray structure of 7. Note: View B is a different perspective form that of the calculated structures in Figure 6.

Figure 6. Top view of the calculated minimum energy conformation of 7 (A), 8 (B), 9a (C), and 10a (D) (see text for details).
removed at reduced pressure to afford 58.1 g (100%) of 12 as a colorless oil which was judged to be >95% pure by 1H NMR: 1H NMR δ 8.44 (1, H-H, H'-5), 8.00 (d, J = 8.4, 2, H-H', H'-5), 7.63-7.56 (3, m, H-H', H'-4, H'-5), 7.47-7.20 (5, m, 5, H-H', H'-3, H'-4, H'-5, H'-6), 7.35-7.19 (2, m, 1, H-H', H'-6), 3.21-3.02 (2, m, 2, H-H', H'-5), 1.97-1.79 (2, m, H-H, H'), 1.34-1.28 (4, t, J = 7.0, 2, H-H'), 0.83 (d, J = 8.4, 2, H-H', H'-5), 0.81 (s, 3, H, 1, H-H', 1, H-H'), 0.72 (d, J = 7.0, 2, H-H', H'-5), 0.62 (d, J = 7.0, 2, H-H', H'-5).

2-(9-Anthracenyl)-5,6,7,8-tetrahydroquinoline (13). To a solution of 25.0 g (76 mmol) of diketone 12 in 150 mL of acetic acid was added 17.5 g (0.23 mol) of ammonium acetate. The reaction mixture was heated to reflux for 24 h, cooled to 0°C, and made basic with a 20% aqueous solution of NaOH. After extraction with chloroform, the organic layers were washed with a saturated aqueous sodium bicarbonate solution, dried over Na2SO4, filtered, and concentrated at reduced pressure. The reaction was quenched by the addition of anhydrous methanol (45 mL) and 2,6-di-tert-butyl-4-methylphenol (0.16 g). The reaction mixture was stirred at 75°C for 3.5 h, cooled, dissolved in chloroform, and washed with 10% aqueous potassium carbonate solution. The organic layer was dried over MgSO4 and filtered, and the solvent was removed by reduced pressure. The residue was purified by flash chromatography (1:4 EtOAc-chloroform) to yield 600 mg (85%) of 13 as a red-orange powder: 1H NMR δ 8.48 (1, H-H, H'-5), 8.41 (d, J = 8.1, 2, H-H', H'-5), 8.34 (d, J = 8.1, 2, H-H', H'-5), 7.99-7.90 (4, m, 4, H-H', H'-2, H'-3), 7.81-7.62 (4, m, 4, H-H', H'-2, H'-3), 7.63-7.35 (5, m, 5, H-H', H'-2, H'-3, H'-4, H'-5, H'-6), 7.36-7.17 (2, m, 2, H-H', H'-5), 3.08 (t, J = 7.0, 2, H-H', H'-5), 2.84 (m, 4, H-H', H'-5), 2.79 (m, 4, H-H', H'-5), 2.57 (m, 2, H-H', H'-5), 2.46 (m, 2, H-H', H'-5), 2.26-2.02 (m, 2, H-H', H'-5), 1.65 (s, 3, H, 1, H-H', 1, H-H'), 1.09-1.00 (m, 3, H, 2, H-H', 2, H-H'), 0.98 (s, 3, H, 1, H-H', 1, H-H').

2-(9-Anthracenyl)-6,7,8-trihydroquinoline 1-Oxide (15). To a stirred solution of 7.0 g (22.6 mmol) of 13 in 80 mL of THF was added slowly 8.5 mL (45.2 mmol) of 35% peracetic acid. The reaction was refluxed for 5 h, cooled to room temperature, dried with chloroform, and washed with 4 N KOH. The aqueous layer was extracted once with chloroform. The combined organic layers were dried over Na2SO4 and concentrated at reduced pressure. The reaction was quenched by the addition of 10 mL of trimethyl phosphonoacetate was added to a suspension of 24 mg of Na2SO4, filtered, and concentrated at reduced pressure. Flash chromatography (19 EtOAc-CH2Cl2) afforded 150 mg (72%) of unstable pyran, which was judged to be 90% pure by 1H NMR: 1H NMR δ 8.19 (1, H-H, H'-5), 8.18 (d, J = 8.1, 2, H-H', H'-5), 8.15 (d, J = 7.0, 2, H-H', H'-5), 7.99-7.90 (4, m, 4, H-H', H'-2, H'-3), 7.80-7.71 (4, m, 4, H-H', H'-2, H'-3), 7.63-7.17 (2, m, 2, H-H', H'-5), 3.08 (t, J = 7.0, 2, H-H', H'-5), 2.84 (m, 4, H-H', H'-5), 2.79 (m, 4, H-H', H'-5), 2.57 (m, 2, H-H', H'-5), 2.46 (m, 2, H-H', H'-5), 2.26-2.02 (m, 2, H-H', H'-5), 1.65 (s, 3, H, 1, H-H', 1, H-H'), 1.09-1.00 (m, 3, H, 2, H-H', 2, H-H'), 0.98 (s, 3, H, 1, H-H', 1, H-H').
8.03 (d, J = 8.5, 4 H, H-4', H-5'), 7.69-7.63 (m, 6 H, H-4, H-3', H-6'), 7.45-7.40 (m, 4 H, H-2', H-7'); 7.27 (d, J = 8.3, 2 H, H-2'), 7.18-7.17 (m, 6 H, H-3, H-1', H-8'), 6.85 (d, J = 8.3, 2 H, H-3'); 3.05 (s, 6 H, NMe3), 2.81 (t, J = 3.4, 4 H, H-5), 2.75 (t, J = 3.4, 4 H, H-6); MS (FD, -4 kV), m/z (relative intensity) 277 (M', 100), 225 (M', 5), 181 (M', 10), 170 (M', 15), 159 (M', 20), 147 (M', 30), 123 (M', 100), 119 (M', 55), 75 (M', 55), 57 (M', 55). Anal. Caled. for C42H40BrN6O: C, 58.57; H, 4.47; N, 5.19; Br, 29.42. Found: C, 58.55; H, 4.46; N, 5.18; Br, 29.41.

2-Chloro-5,6,7,8-tetrahydroquinoline (32). A mixture of 48.1 mL (0.52 mol) of POCl3 and 25.6 g (0.17 mol) of 5,6,7,8-tetrahydroquinoline was heated to 100-102 °C; 'H NMR δ 7.32 (t, J = 7.8, 2 H, H-7); 'C NMR δ 139.07, 138.67, 138.64, 138.30, 137.65, 137.29, 136.69, 135.97, 121.36, 37.83. Anal. Caled. for C20H15ClN3O: C, 58.87; H, 3.94; N, 7.37; Cl, 19.87. Found: C, 58.84; H, 3.98; N, 7.34; Cl, 19.90.

2-Chloro-5,6,7,8-tetrahydroquinoline N-Oxide (33). With use of the procedure described for 32, 30 g of 32 afforded a white solid: mp 150-151 °C; 'H NMR δ 7.59 (d, J = 8.3, 1 H, H-4), 7.05 (d, J = 8.3, 1 H, H-3), 6.35 (t, J = 7.8, 2 H, H-7), 2.87 (t, J = 6.0, 2 H, H-5), 1.87 (m, 2 H, H-6); 'C NMR δ 139.07, 139.06, 138.99, 138.84, 138.64, 138.63, 138.62, 138.30, 137.65, 137.29, 136.69, 37.83. Anal. Caled. for C20H14ClN3O2: C, 56.39; H, 3.48; N, 6.73; Cl, 17.93. Found: C, 56.36; H, 3.48; N, 6.69; Cl, 17.90.

2-Chloro-5,6,7,8-tetrahydroquinoline N-oxide (34). A solution of 7.20 g (0.037 mol) of 32 in 50 mL of CH30H and 25 mL of 10% Na2SO4 was stirred at room temperature overnight. The mixture was filtered and the filtered oil was dissolved into cold 2 N sodium hydroxide to neutralize the acid and was extracted with ether. The organic layer was dried over MgSO4 and the solvent was removed under reduced pressure, the residue was purified by flash chromatography (EtOAc) to afford 5.77 g (78%) of 34 as a light yellow oil: 'H NMR δ 7.89-7.83 (m, 2 H, H-2, H-3), 7.19 (d, J = 8.3, 1 H, H-8), 6.84 (d, J = 8.3, 1 H, H-7); MS (EI, 70 eV), m/z (relative intensity) 277 (M', 100), 226 (M', 56), 225 (M', 55), 170 (M', 20), 159 (M', 35), 147 (M', 50), 136 (M', 100), 119 (M', 100), 75 (M', 100), 57 (M', 100). Anal. Caled. for C19H14ClN3O: C, 59.2; H, 3.94; N, 6.73; Cl, 17.90. Found: C, 59.1; H, 3.92; N, 6.68; Cl, 17.89.

2-Chloro-5,6,7,8-tetrahydroquinoline N-oxide (35). With use of the procedure described for 26, 30 g of 34 was converted into a crude product that was purified by flash chromatography (1:2 EtOAc-petroleum ether) to produce 3.33 g (98%) of 35 as a colorless oil: 'H NMR δ 7.59-7.52 (m, 2 H, H-2, H-3), 7.26 (m, 2 H, H-5), 2.87 (t, J = 6.0, 2 H, H-5); 'C NMR δ 140.98, 139.94, 139.82, 138.63, 138.62, 138.59, 138.30, 137.64, 137.29, 136.69, 135.89, 135.65, 135.58, 135.54, 135.20, 134.99, 134.95, 134.92, 134.85, 134.79, 128.85, 128.33. Anal. Caled. for C19H13ClN3O: C, 59.2; H, 3.94; N, 6.73; Cl, 17.90. Found: C, 59.2; H, 3.92; N, 6.71; Cl, 17.89.
Methyl 2,12-dibromo-7-phenyl-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylate (38). A mixture of 3.25 mmol) of sodium hydride and 1.2 g (6.6 mmol) of trimethyl phosphonoacetate in 400 mL of dry THF was allowed to stir overnight. The suspension was filtered and the filtrate was extracted with petroleum ether-CH2Cl2 (1:1, 20 mL). The residue was purified by flash chromatography (CH2Cl2) to afford 157 mg (93%) of 38 as a yellow solid: mp > 300 °C; 1H NMR δ 8.38 (s, 2 H, H-10'), 7.92 (d, 4 H, H-3', H-4', H-5'), 7.46-7.41 (m, 3 H, H-3', H-4', H-5'), 7.34 (dd, J3,4 = 7.9, 2 H, H-4, H-10), 3.91 (s, 3 H, OCH3); MS (El, 70 eV), m/z 607.98 (M+, 30), 605.96 (M-, 27), 521.88 (M-, HOCH3, 25), 519.86 (M-, HOCH3, 93), 390.74 (M-, HOCH3, 33), 272.70 (M-, HOCH3, 100), 172.63 (M-, HOCH3, 100). Anal. Calcd for C28H16Br2O2: C, 58.37; H, 3.50; N, 3.77. Found: C, 57.76; H, 3.75; N, 3.81.

Methyl 2,12-Dibromo-7-phenyl-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylate (38). A mixture of 60.0 g (52.5 mmol) of 2-chloro-5,6,7,8-tetrahydro-8-quinolone and 8.5 g (35 mmol) of DDQ was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was extracted with petroleum ether-CH2Cl2 (1:1, 50 mL). The residue was purified by flash chromatography (CH2Cl2) to afford 724 mg (78%) of 38 as a white solid: mp > 300 °C; 1H NMR δ 8.38 (s, 2 H, H-10'), 7.92 (d, 4 H, H-3', H-4', H-5'), 7.46-7.41 (m, 3 H, H-3', H-4', H-5'), 7.34 (dd, J3,4 = 7.9, 2 H, H-4, H-10), 3.91 (s, 3 H, OCH3); MS (El, 70 eV), m/z 607.98 (M+, 30), 605.96 (M-, 27), 521.88 (M-, HOCH3, 25), 519.86 (M-, HOCH3, 93), 390.74 (M-, HOCH3, 33), 272.70 (M-, HOCH3, 100), 172.63 (M-, HOCH3, 100). Anal. Calcd for C28H16Br2O2: C, 58.37; H, 3.50; N, 3.77. Found: C, 57.76; H, 3.75; N, 3.81.

Methyl 2,12-Dibromo-7-phenyl-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylate (40). A mixture of 453 mmg of 38 and 21.1 g (112.7 mmol) of DDQ was refluxed under nitrogen in bromobenzene for 20 h. The mixture was allowed to cool to room temperature and passed through a dry column of silica gel, eluting with CH2Cl2. The fractions containing product were combined and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH2Cl2) to afford 183 mg (41%) of 40 as a yellow powder: mp > 300 °C; 1H NMR δ 8.12 (d, J3,4 = 8.4, 2 H, H-10), 7.64-7.59 (m, 9 H, H-3, H-4, H-10, H-11), 7.36-7.30 (m, 3 H, H-3, H-4, H-5), 4.08 (s, 3 H, OCH3); MS (El, 70 eV), m/z 576.07 (M+, 100), 574.05 (M-, 138), 486.07 (M-, HOCH3, 59), 368.99 (M-, HOCH3, 33), 270.89 (M-, HOCH3, 100), 170.82 (M-, HOCH3, 100). Anal. Calcd for C28H16Br2O2: C, 58.37; H, 3.50; N, 3.77. Found: C, 57.76; H, 3.75; N, 3.81.

Methyl 2,12-Bis-(9-anthryl)-7-phenyl-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylate (41). A mixture of 6.10 g (25 mmol) of 7-bromo-1-tetralone and 7.91 g (35 mmol) of 7-bromo-2-benzylidene-2-bromo-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylate (38) was added in one portion to this thick white slurry. The reaction mixture was refluxed for 4 h, cooled to room temperature, quenched with 1 N aqueous HCl, extracted with CH2Cl2, and dried over Na2SO4. The solvent was removed at reduced pressure. The residue was purified by flash chromatography (CH2Cl2) to afford 0.66 g (21%) of 38 as a white solid: mp > 280 °C; 1H NMR δ 7.45 (m, 3 H, H-3', H-4', H-5'), 7.33 (ABq, 4 H, H-3, H-4, H-10, H-11), 7.13 (dd, J8,9 = 8.0, J8,9 = 1.3, 2 H, H-2', H-6'), 3.14 (s, 3 H, CO2CH3), 2.69 (m, 4 H, H-6, H-8), 2.55 (m, 4 H, H-5, H-9); MS (El, 70 eV), m/z (relative intensity) 576 (18), 576 (31), 574 (17); exact mass calcd for C59H33Br2O2 m/z 793.9984, found 793.9983. Anal. Calcd: C, 58.37; H, 3.50; N, 3.77. Found: C, 57.82; H, 3.50; N, 3.77.

Methyl 2,12-Bis-(9-anthryl)-7-phenyl-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylate (41). A solution of 21.9 mg (0.029 mmol) of 10a in 60 mL of CH2Cl2 cooled to 0 °C was added 2.9 mg of boron trifluoride in hexane (1.0 M). The solution was refluxed under nitrogen overnight. The mixture was cooled to room temperature, diluted with CH2Cl2, vigorously washed with saturated NaHCO3, dried over Na2SO4, filtered, and concentrated at reduced pressure. The residue was purified by flash chromatography (CH2Cl2) to afford 257 mg (73%) of 41 as a yellow solid. Flash chromatography (CH2Cl2) afforded 137 mg (50%) of 9b as yellow powder: 1H NMR δ 8.51 (s, 2 H, H-10), 8.05 (d, J8,9 = 8.5, H-5', H-5), 7.68-7.64 (m, 6 H, H-4, H-10, H-3', H-3'), 7.52-7.47 (m, 7 H, H-2', H-7', H-9', H-13'), 7.31-7.28 (m, 4 H, H-11), 7.20-7.17 (m, 4 H, H-5'), H-6), 3.86 (s, 3 H, CO2CH3); MS (FAB) 767 (M + H); exact mass calcd for C59H45Br2O2 m/z 767.2698, found 767.2690.

2,12-Bis-(9-anthryl)-7-phenyl-5,6,7,8-tetrahydro-1,13-diazabenzeno-[a]janthracene-14-carboxylic Acid (9b). To a solution of 282 mg (0.37 mmol) of ester 9a in 50 mL of CH2Cl2 cooled to 0 °C was added 3.7 mmol of boron trifluoride in hexane (1.0 M). The solution was refluxed under nitrogen overnight. The mixture was cooled to room temperature, diluted with CH2Cl2, vigorously washed with saturated NaHCO3, dried over Na2SO4, filtered, and concentrated at reduced pressure. The residue was purified by flash chromatography (CH2Cl2) to afford 257 mg (73%) of 41 as a yellow solid.
CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure, and the residue was flash chromatographed (5% CH₂OH-CH₂Cl₂) to afford 2.74 g (78%) of 42 as a yellow solid: mp 116–118 °C; IR (KBr) 1599 cm⁻¹; 1H NMR 8.79 (d, J₁,₂ = 6.6 Hz, H-1, H-3), 7.79 (s, 4 H, H-6, H-8), 7.59 (t, J₂,₃ = 6.9 Hz, H-2'), 7.43 (d, J₁,₃ = 8.2 Hz, H-2, H-6'), 3.81 (t, 2 H, J₁,₂ = 8.2 Hz, H-2, H-6'), 3.81 (t, J₁,₂ = 8.2 Hz, H-3, H-4'), 7.47–7.50 (m, 3 H, H-3', H-4', H-5'), 7.42 (dd, J₁₁,₁₂ = 2.4 Hz, H-2, H-3', 6.7), 7.39 (J₁₂,₁₃ = 7.6 Hz, H-2, H-3, H-11), 7.33 (d, J₁₁,₁₂ = 7.5 Hz, 2 H, H-2', H-6'), 7.11 (dd, J₁₂,₁₃ = 7.6 Hz, H-2, H-4'), 6.99 (J₁₂,₁₃ = 2.4 Hz, H-1', H-1'), 7.31 (s, 12 H, OCH₃), 2.67 (t, J₁₁,₁₂ = 6.0 Hz, 2 H, H-4'), 4.09 (m, 6 H, 2-CH₂-CH₂-); MS (FAB, Xe) 887 (M* + H); exact mass calced for C₆₀H₄₃N₂O₆: m/z 887.31209, found 887.31120.

2.12-Dibromo-7-phenylbenz[a]anthracene-14-carboxylic Acid (45). To a solution of 166 mg (0.29 mmol) of 41 in 5 mL of THF cooled to −78 °C was added 1.72 mL (1.90 mmol) of n-butyllithium in hexane at −78 °C and the solution was stirred for 0.5 h. To the mixture in 50 mL of dry THF was added 1.9 mL (1.90 mmol) of diethylcyanomethylphosphonate. The mixture was stirred for 1 h at room temperature and the mixture was quenched with cold water and acidified with a mixture of 1N aqueous HCl and 1N aqueous NaOH. The mixture was stirred with CH₂Cl₂, the organic layer was dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (3% EtOAc-CH₂Cl₂) to afford 105.5 mg (51%) of 46 as a white solid: 1H NMR 8.78 (d, 2 H, H-1, H-3), 7.46–7.40 (m, 3 H, H-3', H-4', H-5'), 7.34 (d, J₁₂,₁₃ = 8.0 Hz, 2 H, H-3, H-11), 7.16 (d, J₁₂,₁₃ = 7.3 Hz, 2 H, H-2', H-6'), 7.12 (d, J₁₂,₁₃ = 8.2 Hz, H-4', H-10), 2.61 (t, J₁₁,₁₂ = 6.0 Hz, 2 H, H-4', H-10), 1.26 (t, J₁₁,₁₂ = 6.8 Hz, H-3, H-3'), 7.88 (d, J₁₁,₁₂ = 7.3 Hz, 2 H, H-2', H-6'), 7.47 (d, J₁₂,₁₃ = 7.1 Hz, 2 H, H-2', H-6'), 6.95 (J₁₂,₁₃ = 2.4 Hz, H-1', H-1'), 3.71 (s, 12 H, OCH₃), 1.96 (m, 6 H, 2-CH₂-CH₂-); MS (FAB, Xe) 887 (M* + H); exact mass calced for C₆₀H₄₃N₂O₆: m/z 887.31209, found 887.31120.

2.12-Dibromo-7-phenyl-5,6,8,9-tetrahydrodibenz[a]anthracene-14-carboxylate (46). To a solution of 101 mmol (0.18 mmol) of 41 in 5 mL of THF at 0 °C was added 0.88 mL (0.85 mmol) of a solution of lithium diethylhydridoborohydride in 50 mL of dry THF and the mixture was stirred for 0.5 h at room temperature. The reaction was quenched with cold water and a mixture of 1 N aqueous sodium hydroxide and 1 N of 30% aqueous hydrogen peroxide. After being stirred for 0.5 h, the mixture was acidified with 1 N aqueous HCl solution and extracted with ether. The ethereal solution was dried over MgSO₄ and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (3% EtOAc-CH₂Cl₂) to afford 81.0 mg (82%) of 46 as a white solid: 1H NMR 8.70 (s, 2 H, H-1, H-3), 7.46–7.40 (m, 3 H, H-3', H-4', H-5'), 7.34 (d, J₁₂,₁₃ = 8.0 Hz, 2 H, H-3, H-11), 7.16 (d, J₁₂,₁₃ = 7.3 Hz, 2 H, H-2', H-6'), 7.12 (d, J₁₂,₁₃ = 8.2 Hz, H-4', H-10), 2.61 (t, J₁₁,₁₂ = 6.0 Hz, 2 H, H-4', H-10), 1.26 (t, J₁₁,₁₂ = 6.8 Hz, H-3, H-3'), 7.88 (d, J₁₁,₁₂ = 7.3 Hz, 2 H, H-2', H-6'), 7.47 (d, J₁₂,₁₃ = 7.1 Hz, 2 H, H-2', H-6'), 6.95 (J₁₂,₁₃ = 2.4 Hz, H-1', H-1'), 3.71 (s, 12 H, OCH₃), 1.96 (m, 6 H, 2-CH₂-CH₂-); MS (FAB, Xe) 887 (M* + H); exact mass calced for C₆₀H₄₃N₂O₆: m/z 887.31209, found 887.31120.

2.12-Dibromo-7-phenyl-5,6,8,9-tetrahydrodibenz[a]anthracene-14-carboxylate (44). To a stirred slurry of 367 mg (14.9 mmol) of 41 in 4 mL of THF at 0 °C was added 1.9 mL (2.3 mmol) of a solution of lithium diethylhydridoborohydride in 50 mL of dry THF and the solution was stirred for 0.5 h at room temperature. The mixture was quenched with cold water and acidified with a mixture of 1 N aqueous HCl and 1N aqueous NaOH. The mixture was stirred with CH₂Cl₂, the organic layer was dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ and the solution was transferred via canula to a solution of 240.2 mg (0.7 mmol) of 3,4-Me₂-N-butyramine in 50 mL of dry THF at −78 °C. To the mixture in 50 mL of 30% aqueous NaOH solution and extracted with ether. The ethereal solution was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (5% EtOAc-CH₂Cl₂) to afford 254 mg (82%) of 47 as a white powder: 'H NMR (sodium salt 4%-EtOAc) 8.03 (d, J₁₂,₁₃ = 7.1 Hz, H-2', H-6'), 7.81 (d, J₁₂,₁₃ = 7.1 Hz, H-2', H-6'), 7.70 (d, J₁₂,₁₃ = 7.1 Hz, H-2', H-6'), 6.99 (J₁₂,₁₃ = 2.4 Hz, H-1', H-1'), 7.45–7.42 (m, 3 H, H-3', H-4', H-5'), 7.38–7.35 (m, 7 H, H-3, H-4, H-5, H-6', H-7', H-8), 7.20 (d, J₁₂,₁₃ = 7.5 Hz, 2 H, H-2', H-6'), 7.03 (d, J₁₂,₁₃ = 7.6 Hz, H-2', H-6'), 6.89 (J₁₂,₁₃ = 2.4 Hz, H-1', H-1'), 3.71 (s, 12 H, OCH₃), 2.61 (t, J₁₁,₁₂ = 6.0 Hz, 2 H, H-4', H-10), 2.45 (t, J₁₁,₁₂ = 6.4 Hz, 4 H, H-6, H-8), 3.20 (t, J₁₁,₁₂ = 5.8 Hz, H-4', H-10), 2.60 (t, J₁₁,₁₂ = 5.6 Hz, H-3, H-3'), 1.96 (m, 6 H, 2-CH₂-CH₂-); MS (FAB, Xe) 867 (M* + H); exact mass calced for C₆₀H₄₃N₂O₆: m/z 867.31209, found 867.31120.
mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (1:3 CH₂Cl₂–petroleum ether) to afford 743.3 mg (83%) of 52 as a light yellow solid: mp > 244 °C. 1H NMR 8.48 (d, J5,6 = 1.5, 2 H, H-1, H-3), 7.48-7.51 (m, 5 H, H-3, H-11, H-3', H-4', H-5'), 7.16-7.12 (m, 4 H, H-4, H-10, H-2', H-6'). 2.62 (t, J5,6 = 6.6, 4 H, H-10, H-8), 2.43 (t, J5,6 = 6.6, 4 H, H-5, H-9); 13C NMR 8.143, 138.7, 138.1, 137.3, 131.4, 131.0, 130.7, 128.7, 127.9, 120.2, 120.1, 104.0, 28.7, 27.5; MS (EI, 70 eV), m/z (relative intensity) 539 (4), 541 (7), 543 (3); MS (FAB, Xe) exact mass calced for C₅₉H₃₈BrNO₇ m/z 856.3316, found 856.3310.

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Complexation of Nucleotide Bases by Molecular Tweezers with Active Site Carboxylic Acids: Effects of Microenvironment

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Abstract: In chloroform-d molecular tweezer 1 forms a 1:1 complex (Job plot) with 9-propyladenine (4). Changes in the UV-visible absorption spectrum of 1 upon addition of 4 and the changes 1 and 4 induce in each other's 1H NMR spectrum are consistent with those of a complex comprised of hydrogen bonds and π-stacking interactions. The microenvironment around the carboxylic acid group in 1 markedly alters its complexation behavior relative to a simple carboxylic acid such as butyric acid (Lancelot, J. Am. Chem. Soc. 1977, 99, 7037-7042). The association constants for the 1-4 and butyric acid-5 complexes are 25 000 M⁻¹ (298 K) and 160 M⁻¹ (303 K), respectively. Butyric acid prefers a type 1 hydrogen bonding pattern while 1 adopts a type 7 pattern. The nucleotide base selectivities follow the order G > C > A > U for butyric acid and A > G >> C > U for 1. The presence of proton solvents markedly decreases the strength of the complex between 1 and 4. Two analogues of 1 have also been studied, molecular tweezer 2 and 3. Both lack the dimethylamino substituent found in 1, while 3 has a spacer unit that is fully oxidized. The association constants for the 2-4 and 3-4 complexes are 14 000 and 120 000 M⁻¹, respectively.

Nonequivalen interactions are of fundamental importance to all biological processes. This has inspired the study of host–guest chemistry whose goals include the development of artificial enzymes and the understanding of complexation phenomena.1 While the small, usually nonpeptidic, organic hosts bear little resemblance to natural "receptors" such as enzymes and antibodies, they have several distinct advantages. They provide a more manageable degree of structural complexity. Furthermore, hosts with different functional group orientations, varying degrees of flexibility, and modified electronic properties can be synthesized and compared. Additionally, synthetic receptors are often soluble in several solvents, and because these molecules are constructed of covalent bonds they maintain their structural integrity in a wide range of media. Well-chosen changes in structure and solvent provide invaluable insights into molecular recognition phenomena.

Our interest in this area has been with receptors, called "molecular tweezers,"2 which complex aromatic guests through π-sandwiching3 and, more recently, through π-sandwiching com-


