Artificial Allosteric Receptors for Nucleotide Bases and Alkali-Metal Cations

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Received April 26, 1993

Abstract: New allosteric thymine receptors, 2,6-diamidopyridine derivatives tethered to an anthracene ring by a polyoxyethylene chain, were synthesized. In these receptors, binding of 1-butylthymine was enhanced by a factor of 4–6 by recognition of sodium cations, and the changes in the electron density of the anthracene ring were found to have influence on the allosterism by through-space interaction. The anthracene-linked diamidopyridines represent a rationally designed new class of artificial allosteric receptors.

Introduction

Multiple ligand-binding sites that conjugate to each other to regulate the reactivity of enzymes are seen in many natural proteins.[1] This remarkable feature of enzymatic catalysis, the so-called *allosteric effect*, has inspired investigations into furnishing model systems, from which several artificial allosteric receptors have been synthesized.[2] To the best of our knowledge, however, no such receptors for nucleotide bases have been reported.[3] As part of our program aimed at the development of multifunctional artificial receptors for biologically important species[4,5] such as alkali-metal cations, nucleoside bases, etc., we sought to construct allosteric receptors for these species. Here we present the synthesis and allosteric behavior of rationally designed new receptors for sodium cations and thymine derivatives.

Molecular Design and Synthesis

The design of the receptors **1** was based on the hydrogen-bonding complementarity between 1-butylthymine (**3**) and 2,6-diamidopyridine,[6] which was tethered to an anthracene ring by a polyoxyethylene chain. We expected that recognition of alkali-metal cations by the polyoxyethylene chain might cause **1** to exist as a "scorpion"-like conformation (**1**·**3**·Na^+), which would place the anthracene ring directly above the bound **3** (as judged by CPK molecular model) to add an additional binding force from aromatic π-stacking interaction (i.e., positive allosteric effect) (Schemes I and II).[7]

The receptors were synthesized from three components, i.e., 2,6-diacetamido-4-pyridone, polyoxyethylene, and anthracene derivatives. For the synthesis of **1a**, **1b**, and **6**, bromoanthracene derivatives were coupled with acetylenic alcohol by palladium/copper-catalyzed cross-coupling reaction to give anthracene derivatives bearing acetylene and alcohol groups, followed by connection with polyoxyethylene chains and the pyridone. On the other hand, **1c** and **2** were prepared by the reversed reaction sequences. Other compounds were commercially available or easily synthesized (Scheme III).

Results and Discussion

Treatment of **1a** (14.3 mM, in $CDCl_3$) with 1-butylthymine (**3**, 1.0 equiv) revealed the formation of a triple-hydrogen-bonded complex **1a**·**3** in the ^1H NMR spectrum. The NH protons on both **1a** and **3** were shifted downfield by 2.29 and 2.97 ppm, respectively. On the other hand, only negligible changes were observed for other resonances. Subsequent addition of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate dihydrate (Na-TFPB·$2H_2O$, 3.0 equiv to **1a**) to the solution resulted in a split in the polyoxyethylene resonances, indicating that the sodium cations were bound to the polyoxyethylene groups, and upfield shifts (0.07–0.20 ppm) were observed in the **1a** acetyl-Me, H^a, H^b, H^c, and thymine-Me, reflecting the *increased probability* of the close approach of the anthracene ring to the hydrogen-bonded site (Figure 1), as depicted in Scheme I. Unfortunately, little changes in its UV and fluorescence spectra were observed upon the addition. This is partly because the probability of the existence as the expected comformation is not so high and partly because the concentration of the complex is very low under the conditions employed for the measurement, more than 10^2-fold dilute compared to that for NMR experiments. Formation of the 1:1:1 complex (**1a**·**3**·Na^+) was confirmed by Job's plots[8] that contained a maximum at a mole ratio of 0.5 in each case (Figure 2). The association constants (K) between **1a** and **3** of 1150 ± 100 and

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(7) The diameter of the cavity made of the polyoxyethylene chain in the conformation was estimated to be ca. 0.25 nm on the basis of the CPK model, which was bigger than that of 15-crown-5 but smaller than that of 18-crown-6.

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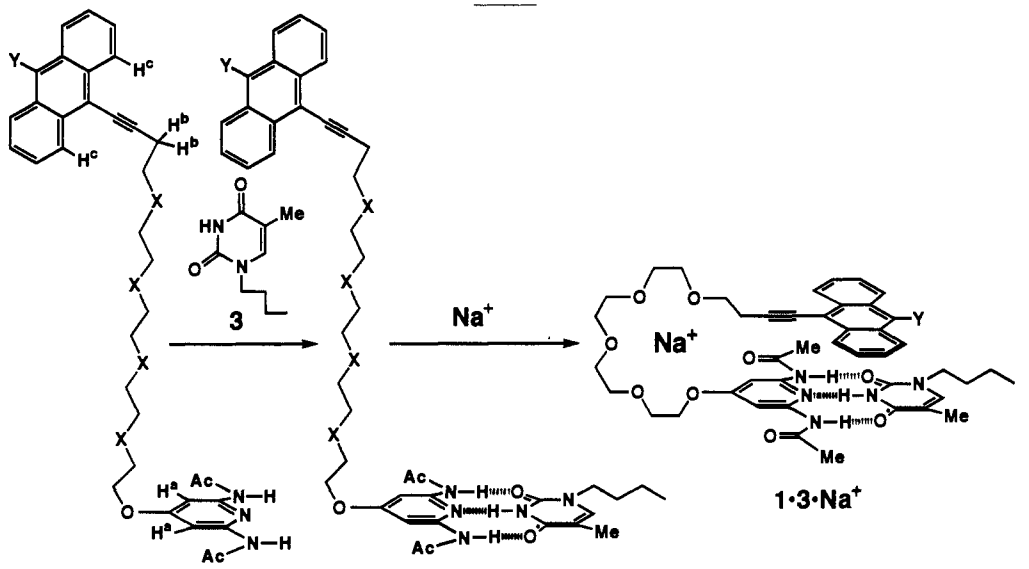
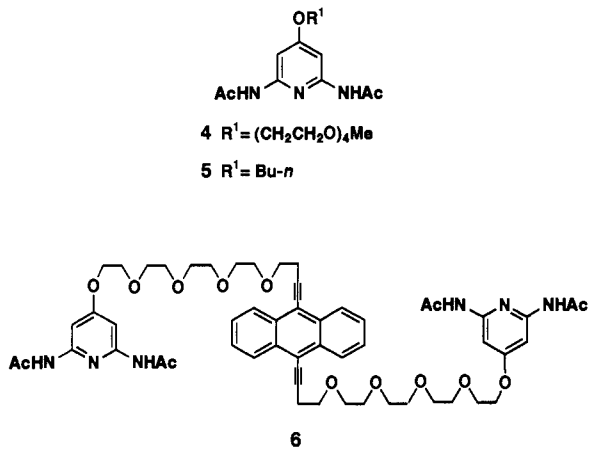
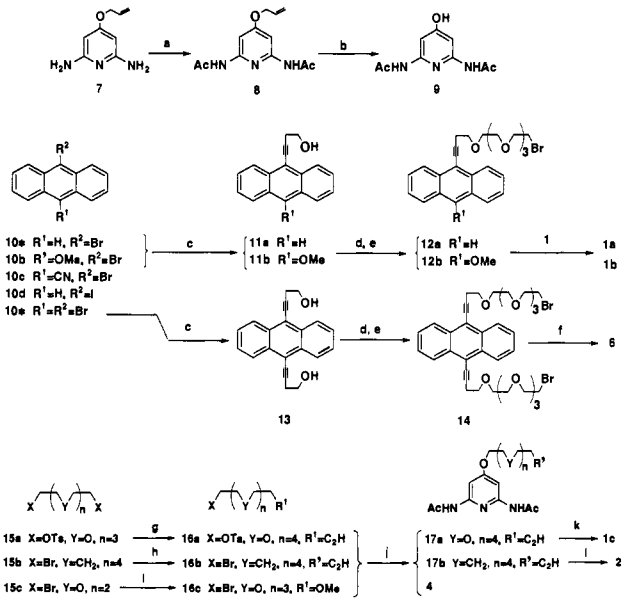
Scheme I



Scheme II



Scheme III[a]



[a] (a) AcCl, $CHCl_3$, Et_3N; (b) $(Ph_3P)_3RhCl$, DABCO, EtOH, H_2O, CH_3CN; (c) 3-butyn-1-ol, $(Ph_3P)_2PdCl_2$, CuI, *n*-Bu_2NH or Et_2NH; (d) *n*-BuLi, dioxane; (e) tetraethylene glycol dibromide, HMPA; (f) *t*-BuOK, **9**, diglyme, HMPA; (g) 3-butyn-1-ol, NaH, DMF; (h) NaC_2H, xylene; (i) ethylene glycol monomethyl ether, NaH, DMF; (j) *t*-BuOK, **9**, DMF; (k) **10c**, $(Ph_3P)_2PdCl_2$, CuI, Et_3N; (l) **10d**, $(Ph_3P)_2PdCl_2$, CuI, *n*-Bu_2NH.

7100 ± 800 M^{-1} were determined by the Foster–Fyfe analysis[9] for the salt-free and the sodium-containing solutions, respectively, by monitoring the chemical shifts of the **1a** NH protons as a function of **3** concentration. Binding of 1-butylthymine was enhanced by a factor of ca. 6 in the presence of the sodium cations.

Changes in the electron density of the anthracene ring were found to have influence on the association constants.[10] Thus, *K* values for the association of **1b** and **1c** with **3** in the absence of Na^+ were similar to that for the association of **1a**, while increased but different *K* values were obtained in the presence of Na^+. These results clearly indicated that there is a through-space interaction between the anthracene ring and the hydrogen-bonded thymine derivative. As expected, **2**, the corresponding alkyl analogue of **1a**, showed neither sodium cation-induced upfield shifts nor allosteric effect under the same conditions employed for **1** (Figure 3).

It was found, however, that the aromatic π-stacking interaction was not the only major additional binding factor contributing to the positive allosteric effect. Thus, **4**, the corresponding anthracene-free receptor, revealed the increased association constant upon addition of Na^+. Although it may be difficult to determine all the factors contributing to this increment, it is anticipated that binding of Na^+ by the polyoxyethylene groups is essential. Indeed, little increment in *K* values between **5** and **3** was observed in the presence of 1 equiv of 15-crown-5 and Na^+ (Figure 3). This result excludes the possibility that the increment observed for **4** is caused by an ionic strength effect.

(9) (a) Foster, R.; Fyfe, C. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1969**, *4*, 1–89. (b) The *K* value is comparable to that reported for 4-alkoxy-2,6-diamidopyridines: Hamilton, A. D.; Little, D. *J. Chem. Soc., Chem. Commun.* **1990**, 297–300.

(10) These effects, however, cannot clearly be explained in terms of simple donor–acceptor interactions: Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 9701–9702 and references therein.

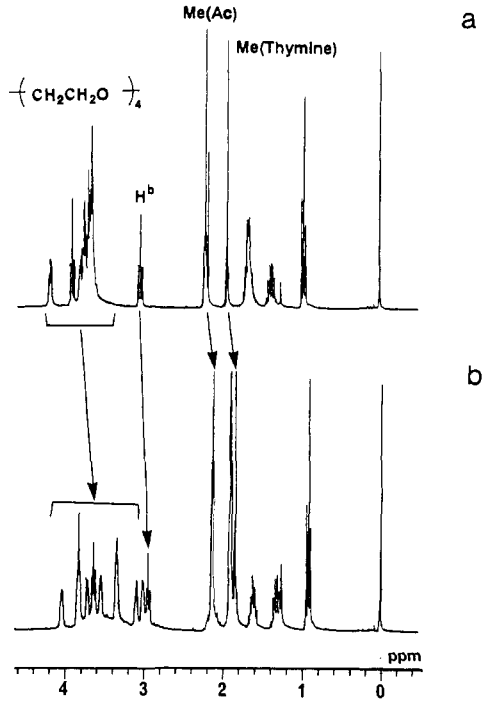


Figure 1. ^1H NMR spectra (270 MHz) of **1a** + **3** in $CDCl_3$ (a, top) before addition of NaTFPB and (b, bottom) after the addition.

Allosteric behavior of the bifunctional receptor **6** was examined. The receptor formed 1:2 complexes with 1-butylthymine (**3**), as judged by a Job's plot. After NaTFPB (2 equiv to **6**) was added to the complex, larger upfield shifts (0.21–0.33 ppm) in the receptor were observed owing to the diamagnetic anisotropy when compared to that of **1a**, indicating that as more binding units are incorporated, the stronger complexes are formed (Scheme IV).[9b,11] This result has implications in construction of supramolecular assemblies by hydrogen bonds and the aromatic π-stacking interaction resembling the DNA structure.

Conclusion

We developed the first artificial allosteric receptor for alkali-metal cations and nucleotide bases. In these receptors, binding of 1-butylthymine was enhanced by a factor of 4–6 by recognition of sodium cations. This increment of the binding constant was found to be governed by not only the aromatic π-stacking interaction of the anthracene ring but also some kind of electric interaction of the complexed cations. Although the allosterism in the present system is not remarkably high (an energy difference of $\sim$1 kcal/mol), the anthracene-linked diamidopyridines represent a rationally designed new class of artificial allosteric receptors. We are currently extending this approach to other nucleotide bases and to self-assembly of the corresponding bifunctional substrates as well as synchronizing this function with our other multifunctional artificial receptors.

Experimental Section

Instrumentation. ^1H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively. Mass spectra were recorded at 70 eV, in the electron-impact mode. Melting points are uncorrected.

Materials. The starting materials were all commercially available, and **7**,[12] **10b**,[13] **10d**,[14] and **15b**[15] were prepared according to literature procedures.

Methods for the Evaluation of Stoichiometry and Association Constants. The stoichiometry of the complex was determined on the basis of Job's plot[8] (Figure 2) by ^1H NMR. The K values were determined by monitoring the chemical shifts of the **1** NH protons as a function of **3** concentration (**1**, 0.5 mM; NaTFPB·$2H_2O$, 0.5 mM; **3**, 4.3–14.0 mM).[9]

4-(Allyloxy)-2,6-diacetamidopyridine (8). To a $CHCl_3$–Et_3N (120 + 3 mL) mixed solution of 4-(allyloxy)-2,6-diaminopyridine (**7**)[12] (948 mg, 5.74 mmol) was added acetyl chloride (1803 mg, 23 mmol) dropwise at −15 °C, and the reaction mixture was stirred at that temperature for 5.5 h. After removal of the solvent, the residue was extracted with EtOAc to give **8**: yield = 94% (1345 mg); oil; IR (neat) 3276, 1679, 1618, 1585, 1440, 1241, 1166, 1045, 997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 6 H), 4.57–4.61 (m, 2 H), 5.28–5.46 (m, 2 H), 5.93–6.07 (m, 1 H), 7.53 (br s, 2 H), 8.25 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.83, 69.15, 96.48, 110.51, 132.07, 160.50; MS m/e (relative intensity) 249 (M^+, 12%).

2,6-Diacetamido-4-pyridone (9). A CH_3CN–H_2O–EtOH (8 + 8 + 8 mL) mixed solution of **8** (776 mg, 3.1 mmol), $(Ph_3P)_3RhCl$ (173 mg, 0.19 mmol), and triethylenediamine (28 mg, 0.25 mmol) was heated at 70 °C for 16 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 10:1) to give **9**: yield = 87% (568 mg); mp 235.1–241.0 °C; IR (KBr) 3200, 3110, 1672, 1589, 1535, 1469, 1429, 1384, 1222, 1189, 1160, 985, 837 cm^{-1}; ^1H NMR (CD_3OD) δ 2.17 (br s, 6 H), 7.28 (br s, 2 H); ^{13}C NMR (D_2O) δ 24.27, 99.12, 145.17, 174.99; MS m/e (relative intensity) 209 (M^+, 30%). Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.29; N, 20.08. Found: C, 51.53; H, 5.19; N, 19.88.

9-(4-Hydroxybut-1-ynyl)anthracene (11a). To an n-Bu_2NH solution (16 mL) of 9-bromoanthracene (**10a**) (514 mg, 2 mmol), $(PPh_3)_2PdCl_2$ (14 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol) was added 3-butyn-1-ol (322 mg, 4.8 mmol), and the reaction mixture was heated at 95 °C for 12 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 3:1) to give **11a**: yield = 70% (344 mg); mp 109–111 °C; IR (KBr) 3291, 3048, 2883, 2212, 1357, 1049, 889, 734, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (t, J = 6.1 Hz, 1 H), 3.05 (t, J = 6.1 Hz, 2 H), 4.03 (q, J = 6.1 Hz, 2 H), 7.46–7.59 (m, 4 H), 8.00 (d, J = 7.9 Hz, 2 H), 8.40 (s, 1 H), 8.53 (dd, J = 7.9, 1.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.63, 61.57, 79.11, 97.87, 117.52, 125.63, 126.52, 126.70, 127.26, 128.68, 131.19, 132.74; MS m/e (relative intensity) 246 (M^+, 100%). Anal. Calcd for $C_{18}H_{14}O$: C, 87.70; H, 5.72. Found: C, 87.60; H, 5.48.

9-(16-Bromo-5,8,11,14-tetraoxahexadec-1-ynyl)anthracene (12a). To a dioxane solution (80 mL) of **11a** (2467 mg, 10 mmol) was added an n-hexane solution of n-BuLi (11 mmol) dropwise at 5 °C. The reaction mixture was allowed to warm to room temperature; then to the solution was added a hexamethylphosphoric triamide (HMPA) solution (16 mL) of tetraethylene glycol dibromide (8000 mg, 25 mmol) in one portion. The reaction mixture was heated at 100 °C for an additional 18 h. After removal of the solvent, the residue was extracted with ether. The extract was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 2:1) to give **12a**: yield = 46% (2205 mg); oil; IR (neat) 3052, 2871, 2212, 1440, 1357, 1112, 740, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.06 (t, J = 6.7 Hz, 2 H), 3.43 (t, J = 6.7 Hz, 2 H), 3.62–3.79 (m, 14 H), 3.92 (t, J = 6.7 Hz, 2 H), 7.48–7.56 (m, 4 H), 7.99 (d, J = 7.9 Hz, 2 H), 8.39 (s, 1 H), 8.55 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.58, 30.31, 78.22, 98.42, 117.96, 125.58, 126.33, 126.88, 126.94, 128.60, 131.20, 132.68; MS m/e (relative intensity) 486 (M^+, 7%).

Receptor 1a. An HMPA solution (1 mL) of **9** (20.9 mg, 0.1 mmol) and potassium *tert*-butoxide (13.4 mg, 0.12 mmol) was stirred at room temperature for 1 h; then to the solution was added a diethylene glycol dimethyl ether (diglyme) solution (0.5 mL) of **12a** (48.5 mg, 0.1 mmol), and the reaction mixture was heated at 150 °C for 24 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **1a**: yield = 39% (23.8 mg); oil; IR (neat) 2923, 1689, 1585, 1438, 1243, 1105, 997, 847, 741, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 6 H), 3.04 (t, J = 6.7 Hz, 2 H), 3.63–3.78 (m, 14 H), 3.89 (t, J = 6.7 Hz, 2 H), 4.14 (t, J = 4.3 Hz, 2 H), 7.43–7.54 (m, 8 H), 7.96 (d, J = 7.9 Hz, 2 H), 8.35 (s, 1 H), 8.53 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.50, 24.63, 67.85, 69.17, 69.83, 70.46, 70.54, 70.60, 70.82, 78.16, 96.23, 98.44, 117.90, 125.52, 126.27, 126.82, 126.86, 128.54, 131.12, 132.62, 150.55, 168.50, 168.64.

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(12) Markees, D. G.; Dewey, V. C.; Kidder, G. W. *J. Med. Chem.* **1968**, *11*, 126–129.
(13) Meyer, K. H.; Schlösser, H. *Justus Liebigs Ann. Chem.* **1920**, *420*, 126–133.
(14) Suzuki, H.; Kondo, A.; Inouye, M.; Ogawa, T. *Synthesis* **1986**, 121–122.
(15) Chuit, P. *Helv. Chim. Acta* **1926**, *9*, 268–272.

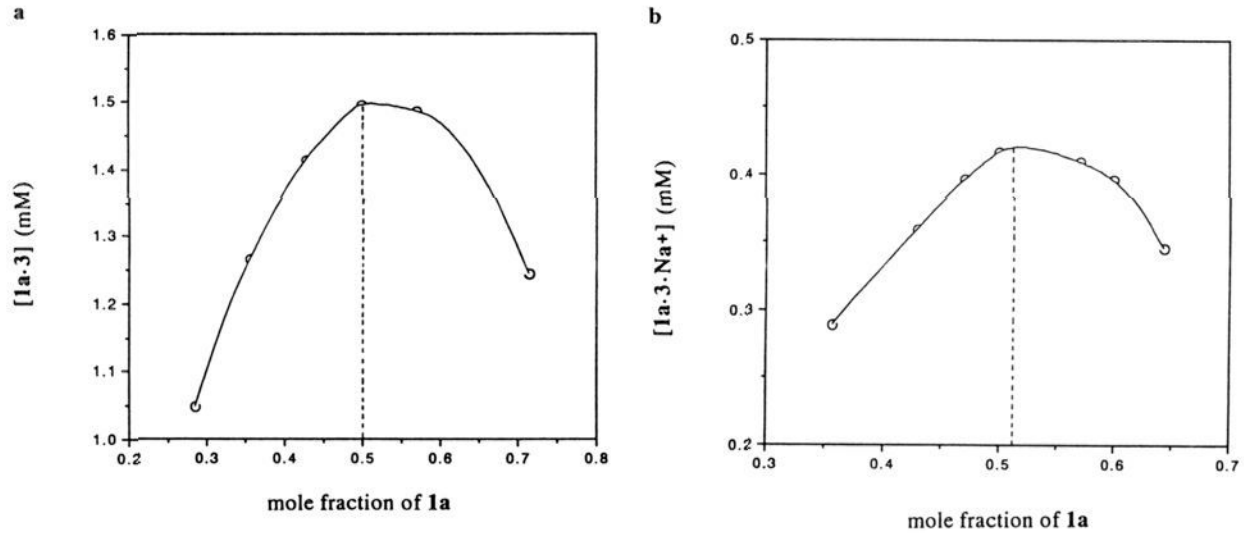


Figure 2. Job plot: (a) **1a** (5 mM) + **3** (5 mM); (b) **1a** (5 mM; including 3 equiv of **3**) + NaTFPB (5 mM).

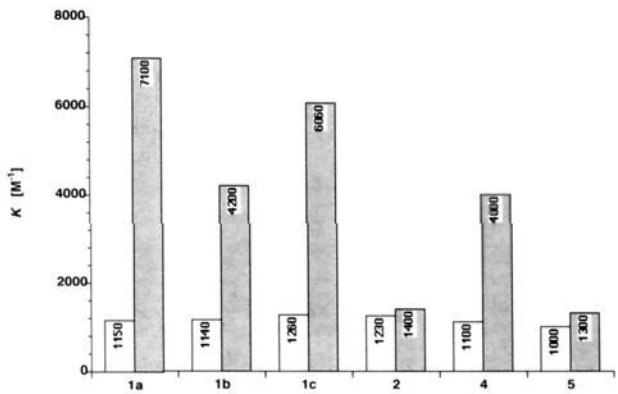
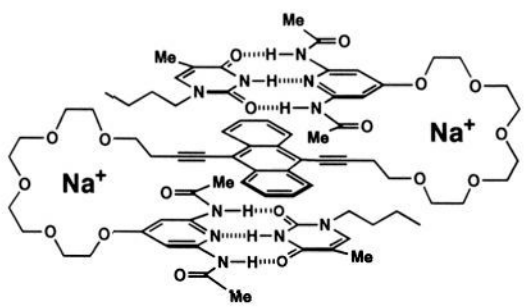


Figure 3. Constants (K) for the association of **1a**, **1b**, **1c**, **2**, **4**, and **5** with **3** in the absence (white column) and presence (dotted column) of NaTFPB. In the case of **5**, 1 equiv of 15-crown-5 was present. For details, see Experimental Section.

Scheme IV



6·3·Na⁺

9-(4-Hydroxybut-1-ynyl)-10-methoxyanthracene (11b). To an n-Bu_2NH solution (15 mL) of 9-bromo-10-methoxyanthracene (**10b**)[13] (287 mg, 1 mmol), $(PPh_3)_2PdCl_2$ (7.0 mg, 0.01 mmol), and CuI (0.95 mg, 0.005 mmol) was added 3-butyn-1-ol (201 mg, 3.0 mmol), and the reaction mixture was heated at 95 °C for 15 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 3:1) to give **11b**: yield = 91% (252 mg); oil; IR (KBr) 3187, 2927, 1618, 1432, 1377, 1080, 1049, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.03 (t, J = 6.1 Hz, 2 H), 4.02 (t, J = 6.1 Hz, 2 H), 4.14 (s, 3 H), 7.50–7.57 (m, 4 H), 8.29 (d, J = 7.3 Hz, 2 H), 8.54 (d, J = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.63, 61.59, 63.49, 79.01, 97.04, 113.58, 122.65, 125.54, 126.66, 127.10, 133.65; MS m/e (relative intensity) 276 (M^+, 64%), 261 (M^+ – Me, 35%).

9-(16-Bromo-5,8,11,14-tetraoxahexadec-1-ynyl)-10-methoxyanthracene (12b). To a dioxane solution (50 mL) of **11b** (365 mg, 1.3 mmol) was added a hexane solution of n-BuLi (1.4 mmol) dropwise at 5 °C. The reaction mixture was allowed to warm to room temperature; then to the solution was added an HMPA solution (2 mL) of tetraethylene glycol dibromide (1056 mg, 3.3 mmol) in one portion. The reaction mixture was heated at 90 °C for 13 h. After removal of the solvent, the residue was extracted with ether. The extract was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 2:1) to give **12b**: yield = 41% (277 mg); oil; IR (neat) 3062, 2867, 2223, 1377, 1113, 1084, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.04 (t, J = 6.7 Hz, 2 H), 3.45 (t, J = 6.7 Hz, 2 H), 3.63–3.79 (m, 14 H), 3.91 (t, J = 6.7 Hz, 2 H), 4.15 (s, 3 H), 7.50–7.56 (m, 4 H), 8.28 (d, J = 6.7 Hz, 2 H), 8.55 (d, J = 6.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.50, 30.27, 63.38, 69.91, 70.46, 70.52, 70.64, 71.13, 78.06, 97.53, 113.94, 122.49, 124.19, 125.42, 126.43, 127.20, 133.51, 152.51; MS m/e (relative intensity) 514 (M^+, 63%).

Receptor 1b. An HMPA solution (1 mL) of **9** (26 mg, 0.13 mmol) and potassium *tert*-butoxide (16 mg, 0.14 mmol) was stirred at room temperature for 30 min; then to the solution was added a diglyme solution (4 mL) of **12b** (65 mg, 0.13 mmol). The reaction mixture was heated at 100 °C for 12 h. After removal of the solvent, the residue was extracted with ether. The extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **1b**: yield = 53% (43 mg); oil; IR (neat) 2898, 1683, 1585, 1436, 1245, 1083, 995, 846, 775, 673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 6 H), 3.03 (t, J = 6.7 Hz, 2 H), 3.64–3.89 (m, 16 H), 4.14 (s, 3 H), 4.16 (t, J = 3.7 Hz, 2 H), 7.48–7.56 (m, 8 H), 8.30 (d, J = 6.8 Hz, 2 H), 8.55 (d, J = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.56, 24.83, 63.45, 67.97, 69.25, 69.95, 70.54, 70.64, 70.70, 70.94, 78.08, 96.23, 97.61, 114.06, 122.53, 124.25, 125.48, 126.47, 127.30, 133.57, 150.39, 152.53, 168.42, 168.68.

9,10-Bis(4-hydroxybut-1-ynyl)anthracene (13). To an Et_2NH solution (80 mL) of 9,10-dibromoanthracene (**10e**) (3360 mg, 10 mmol), $(PPh_3)_2PdCl_2$ (140 mg, 0.2 mmol), and CuI (19 mg, 0.1 mmol) was added 3-butyn-1-ol (4200 mg, 60 mmol), and the reaction mixture was heated at 65 °C for 20 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 1:1) to give **13**: yield = 71% (2230 mg); IR (KBr) 3268, 2881, 2213, 1434, 1396, 1037, 759, 640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.05 (t, J = 6.7 Hz, 4 H), 4.04 (t, J = 6.7 Hz, 4 H), 7.58 (dd, J = 6.7, 3.1 Hz, 4 H), 8.57 (dd, J = 6.7, 3.1 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 24.71, 61.52, 99.41, 126.66, 127.18; MS m/e (relative intensity) 314 (M^+, 100%).

9,10-Bis(16-bromo-5,8,11,14-tetraoxahexadec-1-ynyl)anthracene (14). To a dioxane solution (140 mL) of **13** (1553 mg, 4.87 mmol) was added an n-hexane solution of n-BuLi (10.7 mmol) dropwise at 5 °C. The reaction mixture was allowed to warm to room temperature; then to the solution was added an HMPA solution (7.8 mL) of tetraethylene glycol dibromide (9400 mg, 30 mmol) in one portion. The reaction mixture was heated at 90 °C for 12 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 1:1) to give **14**: yield = 25% (962 mg); oil; IR (neat) 2867, 2215, 1619, 1519, 1396, 1128, 769, 644 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 3.05 (t, J = 6.7 Hz, 4 H), 3.44 (t, J = 6.1 Hz, 4 H), 3.62–3.78 (m, 28 H), 3.91 (t, J = 6.7 Hz, 4 H), 7.56 (dd, J = 6.7, 3.1 Hz, 4 H), 8.56 (dd, J = 6.7, 3.1 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.66, 30.31, 69.83, 70.54, 70.60, 70.70, 70.76, 71.21, 78.42, 99.83, 110.45, 126.47, 127.26, 132.17.

Bifunctional Receptor 6. An HMPA solution (1 mL) of **9** (86 mg, 0.41 mmol) and potassium *tert*-butoxide (51 mg, 0.45 mmol) was stirred at room temperature for 4 h; then to the solution was added a diglyme solution (2.5 mL) of **14** (156 mg, 0.20 mmol). The reaction mixture was heated at 90 °C for 19 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **6**: yield = 9% (19.4 mg); oil; IR (neat) 3290, 2875, 1697, 1618, 1439, 1242, 1109, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 12 H), 3.03 (t, J = 6.7 Hz, 4 H), 3.62–3.80 (m, 28 H), 3.89 (t, J = 6.7 Hz, 4 H), 4.15 (t, J = 4.3 Hz, 4 H), 7.46 (br s, 4 H), 7.54 (dd, J = 6.7, 3.1 Hz, 4 H), 7.76 (br s, 4 H), 8.53 (dd, J = 6.7, 3.1 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.62, 24.75, 67.91, 69.21, 69.79, 70.52, 70.60, 70.66, 70.70, 70.88, 78.36, 96.23, 99.85, 126.45, 127.24, 132.11, 150.49, 168.56.

2,6-Diacetamido-4-(1,4,7,10,13-pentaoxaheptadec-16-ynyl)pyridine (17a). To a DMF solution (6.5 mL) of NaH (124 mg, 5.2 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added 3-butyn-1-ol (328 mg, 4.68 mmol) at 0 °C, and the reaction mixture was stirred at that temperature for 1 h. Then to the reaction mixture was added tetraethylene glycol bis(4-toluenesulfonate) (**15a**) (1960 mg, 3.9 mmol), and the reaction mixture was stirred at room temperature for an additional 14 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (alumina; eluent, hexane–EtOAc = 1:1) to give a mixture of 3,6,9,12-tetraoxahexadec-15-yn-1-ol 4-toluenesulfonate (**16a**), 5,8,11,14,17-pentaoxaheneicosa-1,20-diyne, and tetraethylene glycol bis-(4-toluenesulfonate) (930 mg). This reaction mixture was used for the next reaction without further purification. A DMF solution (4 mL) of **9** (84 mg, 0.4 mmol) and potassium *tert*-butoxide (54 mg, 0.48 mmol) was stirred at room temperature for 1 h. Then to this solution was added the mixture described above (930 mg), and the reaction mixture was heated at 100 °C for 13 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **17a**: yield = 44% (based on **9**) (77 mg); oil; IR (neat) 3253, 2875, 2119, 1955, 1693, 1618, 1436, 1108, 997, 950, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98 (t, J = 2.4 Hz, 1 H), 2.17 (s, 6 H), 2.44–2.51 (m, 2 H), 3.59–3.72 (m, 14 H), 3.86 (t, J = 4.9 Hz, 2 H), 4.21 (t, J = 4.9 Hz, 2 H), 7.51 (br s, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.74, 24.53, 67.79, 69.17, 69.25, 69.29, 69.33, 70.20, 70.42, 70.52, 70.80, 81.25, 96.17, 150.67, 168.38, 168.91; MS m/e (relative intensity) 437 (M^+, 2.2%).

9-Bromo-10-cyanoanthracene (10c). A CS_2 suspension (80 mL) of 9-bromoanthracene (**10a**) (3220 mg, 12.5 mmol) and anhydrous aluminum chloride (3333 mg, 25 mmol) was stirred at room temperature for 1 h; then a CS_2 solution (50 mL) of BrCN (1589 mg, 15 mmol) was added to the reaction mixture at that temperature dropwise over a 1-h period. After the completion of the addition, the reaction mixture was refluxed at 60 °C for 37 h. The reaction mixture was filtered, and the resulting precipitate was washed with $CHCl_3$. The combined filtrate was evaporated and chromatographed (silica gel; eluent, hexane–EtOAc = 20:1) to give **10c**: yield = 20% (709 mg); IR (KBr) 2214, 1645, 1091, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67–7.79 (m, 4 H), 8.45 (dd, J = 1.8, 7.9 Hz, 2 H), 8.60 (dd, J = 1.8, 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 106.46, 117.01, 125.87, 128.15, 128.76, 129.26, 130.17, 130.40, 133.49; MS m/e (relative intensity) 282 (M^+, 14%).

Receptor 1c. A Et_3N solution (5 mL) of **10c** (49 mg, 0.17 mmol), **17a** (50 mg, 0.12 mmol), $(PPh_3)_2PdCl_2$ (1.2 mg, 1.7×10^{-3} mmol), and CuI (0.16 mg, 8.7×10^{-4} mmol) was heated at 90 °C for 14 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **1c**: yield = 30% (22 mg); oil; IR (neat) 2875, 2212, 1683, 1585, 1438, 1245, 1110, 997, 848, 767, 642 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 6 H), 3.08 (t, J = 6.7 Hz, 2 H), 3.64–3.84 (m, 14 H), 3.93 (t, J = 6.7 Hz, 2 H), 4.16 (t, J = 4.9 Hz, 2 H), 7.45 (br s, 2 H), 7.60–7.74 (m, 6 H), 8.40 (d, J = 7.9 Hz, 2 H), 8.62 (d, J = 7.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.74, 24.85, 67.93, 69.27, 69.45, 70.58, 70.72, 70.94, 96.17, 103.63, 105.23, 117.36, 125.65, 127.10, 127.81, 128.98, 131.67, 132.72, 150.41, 168.46, 168.58.

2,6-Diacetamido-4-(1-oxaheptadec-16-ynyl)pyridine (17b). To a DMF solution (2.5 mL) of 1,14-dibromotetradecane (**15b**)[15] (394 mg, 1.1 mmol) was added a xylene suspension of sodium acetylide (1.43 mmol), and the reaction mixture was stirred at room temperature for 21 h. After removal of the solvent, the residue was extracted with CH_2Cl_2, and the extract was evaporated. The residue was a mixture of 1,14-dibromotetradecane, 16-bromohexadec-1-yne (**16b**), and octadeca-1,17-diyne (335 mg). This reaction mixture was used for the next reaction without further purification. A DMF solution (2 mL) of **9** (63 mg, 0.3 mmol) and potassium *tert*-butoxide (16 mg, 0.14 mmol) was stirred at room temperature for 1 h. Then to this solution was added a DMF–HMPA mixed solution (5 + 0.3 mL) of the mixture described above (335 mg), and the reaction mixture was heated at 100 °C for an additional 24 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **17b**: yield = 55% (based on **9**) (71 mg); IR (neat) 3268, 2921, 2850, 2117, 1668, 1585, 1429, 1245, 1166, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27–1.56 (m, 24 H), 1.74–1.80 (m, 2 H), 1.94 (m, 2 H), 2.18 (s, 6 H), 4.04 (t, J = 6.1 Hz, 2 H), 7.49 (br s, 4 H); ^{13}C NMR ($CDCl_3$) δ 18.37, 24.63, 25.87, 28.49, 28.74, 28.88, 29.08, 29.30, 29.48, 29.52, 29.57, 68.05, 68.54, 84.81, 96.29, 150.55, 168.74, 168.99; MS m/e (relative intensity) 429 (M^+, 7%).

Receptor 2. An n-Bu_2NH solution (2 mL) of **10d**[14] (24 mg, 0.08 mmol), **17b** (23 mg, 0.05 mmol), $(PPh_3)_2PdCl_2$ (0.56 mg, 5.3×10^{-4} mmol), and CuI (0.076 mg, 2.6×10^{-4} mmol) was heated at 100 °C for 16 h. After removal of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1; followed by alumina; eluent, CH_2Cl_2; then ODS reversed-phase silica gel; eluent, MeOH) to give **2**: yield = 8% (2.7 mg); oil; IR (neat) 2925, 1676, 1583, 1442, 1241, 1164, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26–1.80 (m, 24 H), 2.17 (s, 6 H), 2.76 (t, J = 6.7 Hz, 2 H), 4.03 (t, J = 6.7 Hz, 2 H), 7.47–7.57 (m, 8 H), 7.99 (d, J = 7.3 Hz, 2 H), 8.37 (s, 1 H), 8.56 (d, J = 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.21, 24.88, 25.93, 28.94, 29.20, 29.28, 29.36, 29.57, 29.61, 29.65, 29.69, 68.68, 96.23, 125.56, 126.21, 126.60, 127.00, 127.08, 128.60, 131.27, 132.67, 150.23, 168.50.

2,6-Diacetamido-4-(1,4,7,10,13-pentaoxatetradecyl)pyridine (4). To a DMF suspension (2 mL) of NaH (68.6 mg, 2.9 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added ethylene glycol monomethyl ether (198 mg, 2.6 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. Triethylene glycol dibromide (**15c**) (552 mg, 2 mmol) was added at room temperature. The mixture was stirred at that temperature for 12 h. After removal of the solvent, the residue was extracted with $CHCl_3$, and the extract was evaporated. The residue was a mixture of 1-bromo-3,6,9,12-tetraoxatridecane (**16c**), pentaethylene glycol dimethyl ether, and triethylene glycol dibromide (400 mg). This reaction mixture was used for the next reaction without further purification. A DMF solution (3 mL) of **9** (105 mg, 0.5 mmol) and potassium *tert*-butoxide (66 mg, 0.55 mmol) was stirred at room temperature for 1 h; then to this reaction mixture was added a DMF solution (5 mL) of the mixture described above (400 mg). The reaction mixture was heated at 100 °C for 4 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH_2Cl_2–MeOH = 20:1) to give **4**: yield = 19% (based on **9**) (38 mg); oil; IR (neat) 3234, 2877, 1687, 1585, 1439, 1244, 1105, 849, 553 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 6 H), 3.37 (s, 3 H), 3.53–3.57 (m, 2 H), 3.62–3.73 (m, 10 H), 3.84 (t, J = 4.9 Hz, 2 H), 4.19 (t, J = 4.9 Hz, 2 H), 7.51 (br s, 2 H), 7.88 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.67, 58.96, 64.13, 67.91, 69.23, 70.46, 70.58, 70.88, 70.91, 96.25, 150.59, 168.54, 168.68.

2,6-Diacetamido-4-(*n*-butoxy)pyridine (5). To a $CHCl_3$–Et_3N (120 + 3 mL) mixed solution of 4-(*n*-butoxy)-2,6-diaminopyridine[12] (1853.6 mg, 10 mmol) was added acetyl chloride (3925 mg, 50 mmol) dropwise at −15 °C, and the reaction mixture was stirred at that temperature for 7 h. After removal of the solvent, the residue was extracted with EtOAc. The extract was evaporated and chromatographed (silica gel; eluent, EtOAc) to give **5**: yield = 25% (668 mg); oil; IR (neat) 3278, 2960, 1679, 1621, 1585, 1245, 1166, 1045, 997, 848 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3 H), 1.40–1.54 (m, 2 H), 1.71–1.81 (m, 2 H), 4.04 (t, J = 6.1 Hz, 2 H), 7.50 (br s, 2 H), 7.55 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.68, 19.03, 24.51, 30.84, 68.20, 96.35, 150.63, 168.91; MS m/e (relative intensity) 265 (M^+, 45%).