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Fluorescent Sensing of Triphosphate Nucleotides via Anthracene Derivatives

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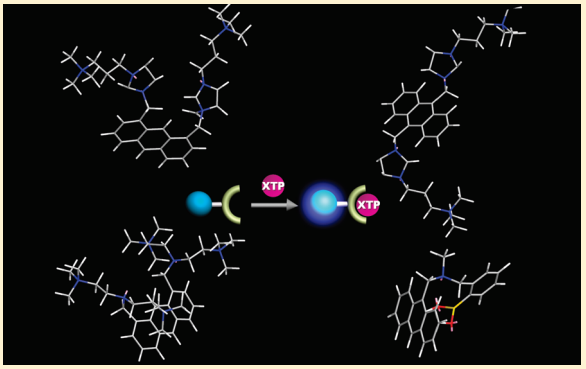
Supporting Information

ABSTRACT: A nucleotide is composed of a nucleobase, a five-carbon sugar, and phosphate groups. Recognition of these three sites can provide useful information for the development of selective fluorescent receptors for a specific nucleotide. In this paper, anthracene derivatives with two imidazolium groups at the 1,8- and 9,10-positions, quaternary ammonium groups, or the boronic acid group were examined for the recognition of nucleotides, such as ATP, GTP, CTP, TTP, UTP, ADP, and AMP, via fluorescence changes. The anthracene group provides the interaction between the bases of the nucleotides. The imidazolium and quaternary ammonium groups induce hydrogen bonding interactions with the phosphate groups of the nucleotides. The boronic acid group can interact with the ribose of the nucleotides.



INTRODUCTION

The recognition and sensing of nucleotides is an active area of research due to their biological significance.[1] For example, ATP is a universal energy source and an extracellular signaling mediator in many biological processes.[2] ATP can also serve as a phosphate donor in kinase-catalyzed protein phosphorylation, and the extracellular ATP released from the cell membrane mediates many cell-to-cell signals in a wide range of physiological and pathological conditions.[3] GTP is involved in RNA synthesis and the citric acid cycle and acts as an energy source for protein synthesis.[4] UTP serves as a donor for energy transduction in organisms and as a control element in metabolic processes through its participation in enzymatic reactions, such as the many glycosylation processes that are catalyzed by glycosyltransferases.[5] Thymidine nucleotides, including thymidine-monophosphate (TMP), -diphosphate (TDP), and -triphosphate (TTP), which are synthesized from thymidine in vivo, are essential building blocks in DNA replication and cell division.[6]

Although several highly sensitive and selective methods are currently available for their determination, including high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), enzyme-based methods, chromatography, mass spectrometry, and electrochemical methods, there are still some problems due to the operation of sophisticated chromatographic instrumentation or a combination of the procedure and its quantitative reproducibility. Sensors based on the analyte-induced changes in fluorescence are particularly attractive due to their simplicity and in vivo/in vitro imaging.[7] Accordingly, the development of fluorescent and colorimetric chemosensors for their detection has attracted significant attention over the past few years. Many fluorescent chemosensors have been designed for ATP,[8] GTP,[9] TTP,[10] UTP,[11] etc. Among them, our contributions of GTP[9a] and ATP[8a] utilizing imidazolium derivatives are included, in which imidazolium groups[12] can induce ionic hydrogen bonding interactions between the imidazolium $(C-H)^+$ and phosphate groups.

A nucleotide is composed of a nucleobase, a five-carbon sugar, and phosphate groups. Recognition of these three sites can provide useful information in the development of selective fluorescent receptors for a specific nucleotide. In this paper, anthracene derivatives bearing two imidazolium groups at the 1,8- and 9,10-positions (**1** and **2**), quaternary ammonium groups (**3**), or boronic acid group (**4**) (Figure 1) have been studied for the recognition of nucleotides, such as ATP, GTP, CTP, TTP, UTP, ADP, and AMP, via fluorescence changes. The anthracene group provides the interaction between the bases of nucleotides. The imidazolium and quaternary ammonium groups induce hydrogen bonding with the phosphate groups of nucleotides. The boronic acid group can interact with the ribose of the nucleotides examined. The fluorescent changes in these compounds with various nucleotides were examined carefully.

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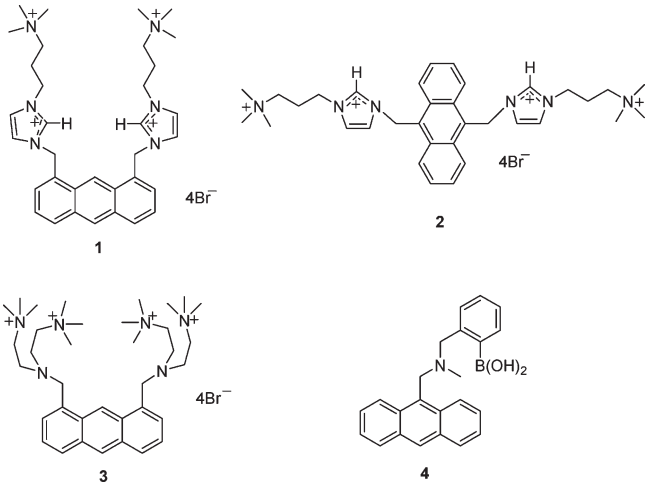


Figure 1. Structures of compounds **1**−**4**.

RESULTS AND DISCUSSION

Synthesis. For the synthesis of the 9,10-bis(imidazolium) anthracene derivative **2**, 9,10-bis(imidazolylmethyl)anthracene **5** was obtained from 9,10-bis(bromomethyl)anthracene using the reported procedure.[13] Compound **5** was then reacted with (3-bromopropyl)trimethyl ammonium bromide to give compound **2** after recrystallization from acetonitrile−methanol (1:1) in 65% yield (Scheme 1). For the synthesis of compound **3**, 1,8-anthracenedimethanamine **6** was first obtained from 1,8-anthracenedimethanol in a 53% yield using the reported procedure.[14] Treating this diamino anthracene **6** with (2-bromoethyl)trimethyl ammonium bromide in CH_2Cl_2-*i*PrOH gave tetraammonium anthracene **3** in a 81% yield (Scheme 1). Compounds **1**[9a] and **4**[15] were synthesized using the reported procedures.

*Binding Study for Compounds **1** and **2***. Previously, compound **1** (3 μM) was reported to show a large fluorescent quenching effect with GTP and a smaller fluorescent enhancement with ATP at pH 7.4 (10 mM HEPES).[9a] The association constants for GTP and ATP were reported to be 8.7×10^4 and 1.5×10^4 M^{-1}, respectively.[9a] In addition, the interactions of the nucleic bases with the middle ring of the anthracene moiety of compound **1** with a T-shape along with ionic hydrogen bonding interactions between the imidazolium/ammonium moieties and phosphate groups were proposed based on ^{1}H NMR experiments and theoretical calculations. In a previous study, GTP, ATP, ADP, and AMP along with simple anions were examined. In the present study, CTP, TTP, and UTP were also examined (Figure 2). CTP and TTP induced small increases in fluorescence, and a slight fluorescent quenching effect was observed with UTP, as shown Figure 3.

On the other hand, the 9,10-isomer **2** displayed different fluorescent changes with the nucleotides, particularly with ATP. As shown in Figure 4, the addition of TTP, CTP, and UTP (100 equiv) induced fluorescent enhancements to compound **2** (1 μM) at pH 7.4 (10 mM HEPES). As in the case of the 1,8-isomer **1**, GTP induced a significant fluorescent quenching effect. The main difference between the 1,8-isomer **1** and 9,10-isomer **2** is that compound **2** displayed a fluorescent quenching effect with ATP. There were also relatively smaller fluorescent quenching effects with ADP and AMP (Figure 4).

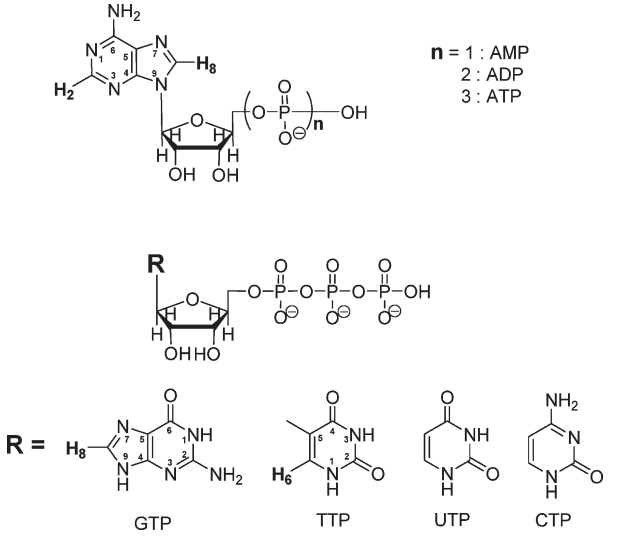
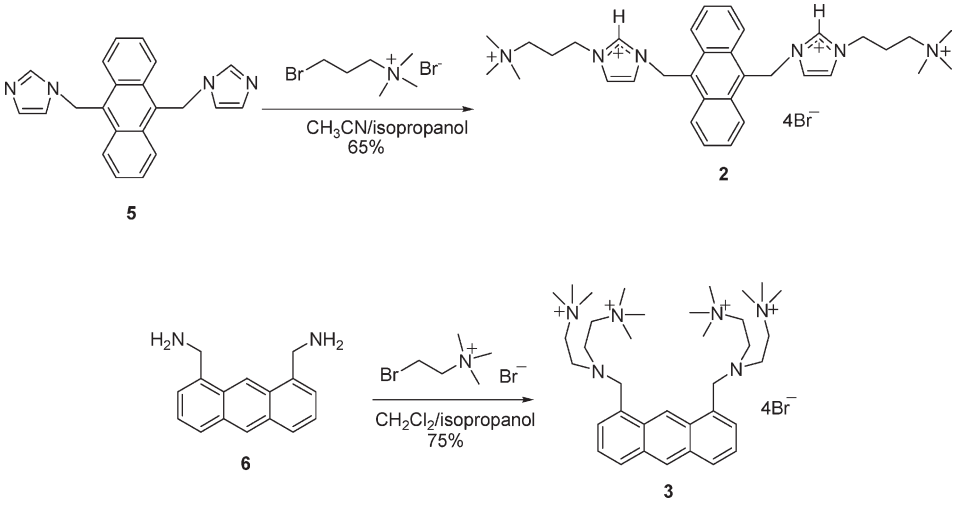


Figure 2. Structure of various nucleotides.

Scheme 1. Synthesis of Compounds 2 and 3



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As shown in Figure 5, although the fluorescent quenching effect was larger for GTP than ATP, the binding affinity was tighter for ATP. The larger quenching effect is due to guanine, which is an efficient quencher.[9a] From fluorescent titrations, the association constants for ATP and GTP (Figure 5) were calculated to be 5.1×10^4 and 2.4×10^4 M^{-1} (errors <10%), respectively.[16]

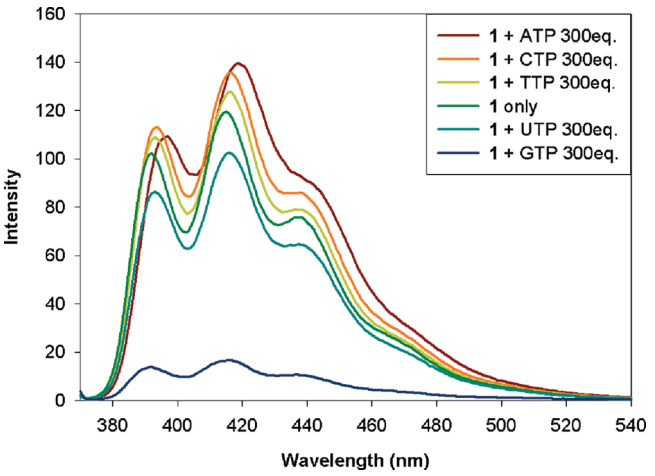

Figure 3. Fluorescent emission changes of **1** (3 μM) upon addition of sodium salts of ATP, CTP, GTP, TTP, and UTP (300 equiv) at pH 7.4

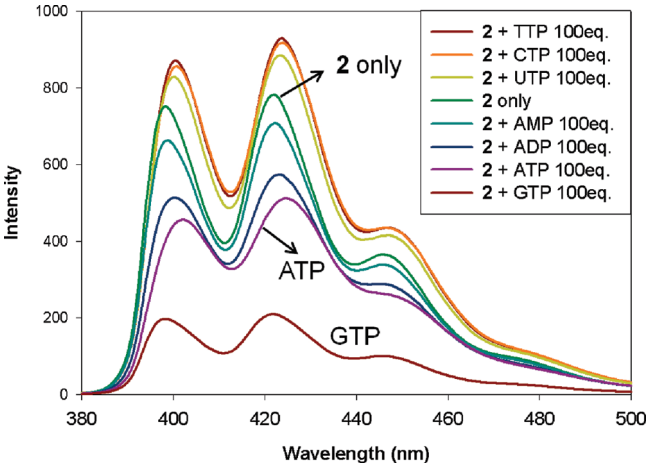

Figure 4. Fluorescent emission changes of **2** (1 μM) upon addition of sodium salts of AMP, ADP, ATP, CTP, GTP, TTP, and UTP (100 equiv) at pH 7.4 (10 mM HEPES) (excitation at 373 nm).

The addition of ATP (Figure 6, Table 1) and GTP (see Table 1 and Supporting Information Figure S1) to a 2 mM solution of compound **2** at pD 7.4 in D_2O caused a significant upfield shift in the aromatic protons of the anthracene moiety of compound **2** in addition to the H-2 and H-8 of ATP (−0.205 and −0.209, respectively), H-8 of GTP (−0.239), and the anomeric protons. Similar chemical shifts of hydrogen in positions 2 and 7, 3 and 6, and 4 and 5 of anthracene suggest additional interactions of the nucleic bases with the anthracene moiety of compound **2** in a T-shape H−π interaction.[9a] On the other hand, TTP induced relatively smaller downfield shifts of the aromatic of the anthracene moiety and benzylic methylene hydrogen atoms (see Table 1 and Supporting Information Figure S2). H-6 of TTP and the anomeric proton displayed an upfield shift (−0.263 and −0.215, respectively).

Binding Study for Compound ***3***. Figure 7a shows the fluorescent changes in compound **3** (6 μM) upon the addition of various anions, such as $H_2PO_4^-$, F^-, Cl^-, Br^-, I^-, HSO_4^-, $CH_3CO_2^-$, and pyrophosphate (PPi) (300 equiv) at pH 9.0 (50 mM CHES). Among these simple anions, compound **3** exhibited selective fluorescent enhancement with pyrophosphate. Figure 7b explains the fluorescent changes in compound **3** upon the addition of PPi, ATP, CTP, GTP, TTP, and UTP. Compound **3** displayed relatively large fluorescent enhancement with ATP and CTP. On the other hand, a significant fluorescent quenching effect was observed with GTP. As shown in Figure 7b, there were no significant changes upon the addition of TTP and UTP. Compound **3** also displayed smaller fluorescent enhancements with ADP and AMP (Figure S3, Supporting Information).

From the fluorescent titrations, the association constants of ATP, GTP, ADP, CTP, and pyrophosphate were 7.7×10^3, 4.1×10^3, 2.3×10^3, 2.0×10^3, and 8.0×10^2 M^{-1} (errors <10%), respectively.[16] The selectivity for ATP is approximately 2 and 4 times that for GTP and CTP, respectively. Figure 8 shows the fluorescent enhancements with ATP and CTP as well as the fluorescent quenching effect with GTP. On the other hand, there were no significant fluorescent changes upon the addition of TTP

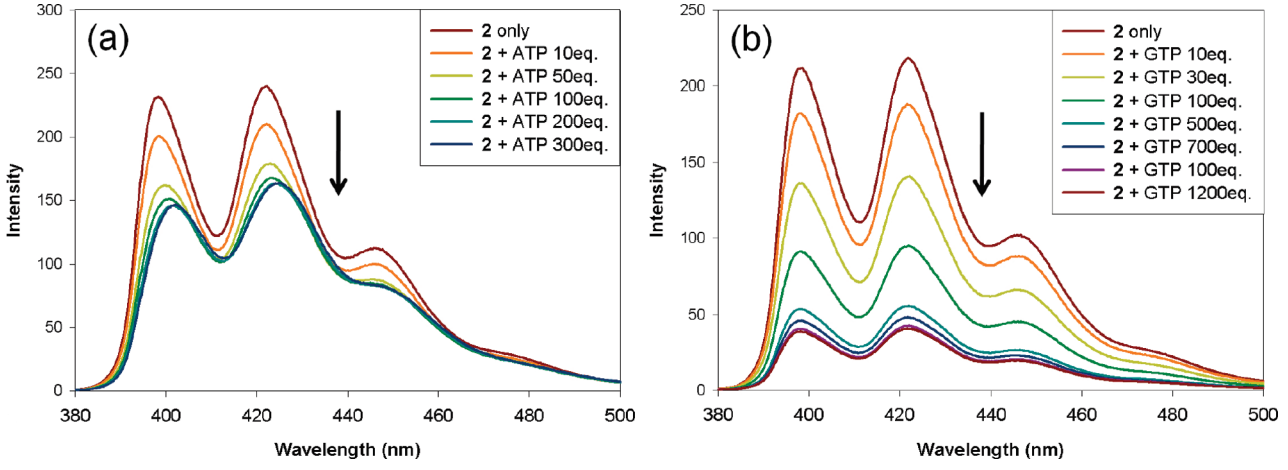

Figure 5. Fluorescent titrations of **2** (1 μM) upon addition of sodium salt of ATP (a) and GTP (b) at pH 7.4 (10 mM HEPES) (excitation at 367 nm).

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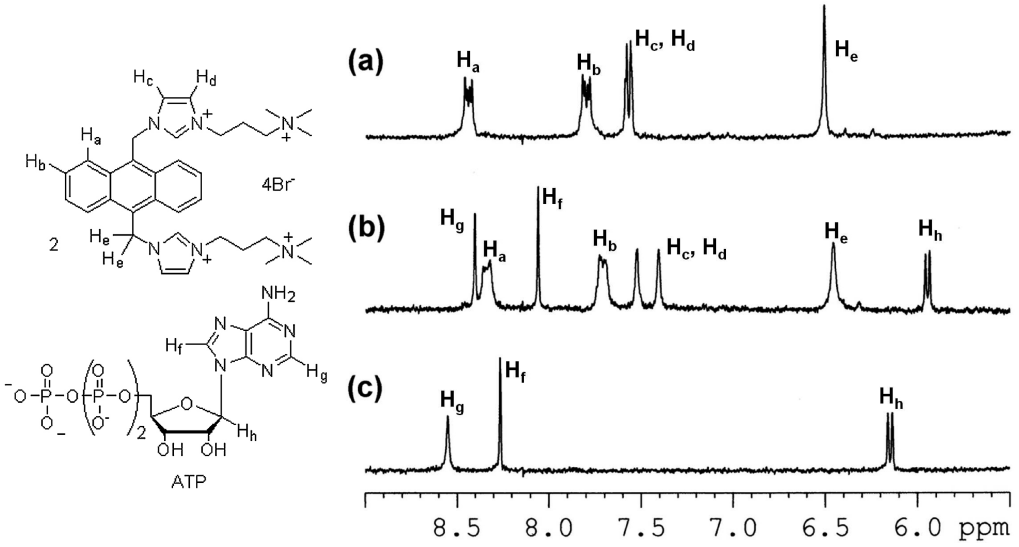

Figure 6. Partial NMR spectra for (a) host **2** (2 mM), (b) **2** + ATP (1.1 equiv), and (c) ATP at pD 7.4.

Table 1. Changes in ^{1}H NMR Chemical Shifts ($\Delta\delta$) of Aromatic Protons and Benzylic Protons in 2 with ATP, GTP, and TTP at pD 7.4

guest	H_a	H_b	H_c	H_d	H_e
ATP	−0.103	−0.091	−0.011	−0.153	−0.052
GTP	−0.100	−0.082	−0.031	−0.068	−0.044
TTP	0.043	0.027	0.057	0.042	0.071

and UTP. Compounds **1** and **3** differ by the binding unit for the recognition of phosphate groups. Both compounds showed similar trends for the binding affinity toward nucleotides. The relatively small fluorescent enhancement of compound **3** with PPi can be attributed to the interaction of PPi with the benzylic nitrogen on compound **3**, which can block the photoinduced electron transfer process from benzylic nitrogen to the anthracene moiety.[17]

Binding Study for Compound ***4***. Boronic acids have high affinities for substances that contain vicinal diol groups (e.g., carbohydrates). Consequently, they have been used in novel boronic acid-based fluorescent chemosensors for carbohydrates.[18] Indeed, there is an example of boronic acid derivative, which was used as a fluorescent sensing system for ATP.[8c] Finally, anthracene-boronic acid derivative **4** was examined using ATP, ADP, AMP, GTP, CTP, TTP, UTP, and PPi at pH 7.4 (10 mM HEPES). As shown in Figure 9, AMP, ADP, and ATP displayed large fluorescent enhancements and PPi, CTP, UTP, and TTP showed small fluorescent enhancements. However, the addition of GTP induced a fluorescent quenching effect. These results suggest that recognition of the ribose moiety by boronic acid can be an important way of selectively recognizing nucleotides. The association constants for ATP, ADP, AMP, and GTP were 5.2×10^3, 4.8×10^3, 1.3×10^4, and 6.2×10^3 M^{-1} (errors <10%), respectively (Figure S4, Supporting Information).[16]

Binding Modes for Compounds ***1***−***4***. To justify the H−π interactions conjectured from the NMR spectra, the ONIOM calculations were carried out as done in our previous study for **1**.[9a] The direct interaction parts (the base of ATP/GTP/AMP

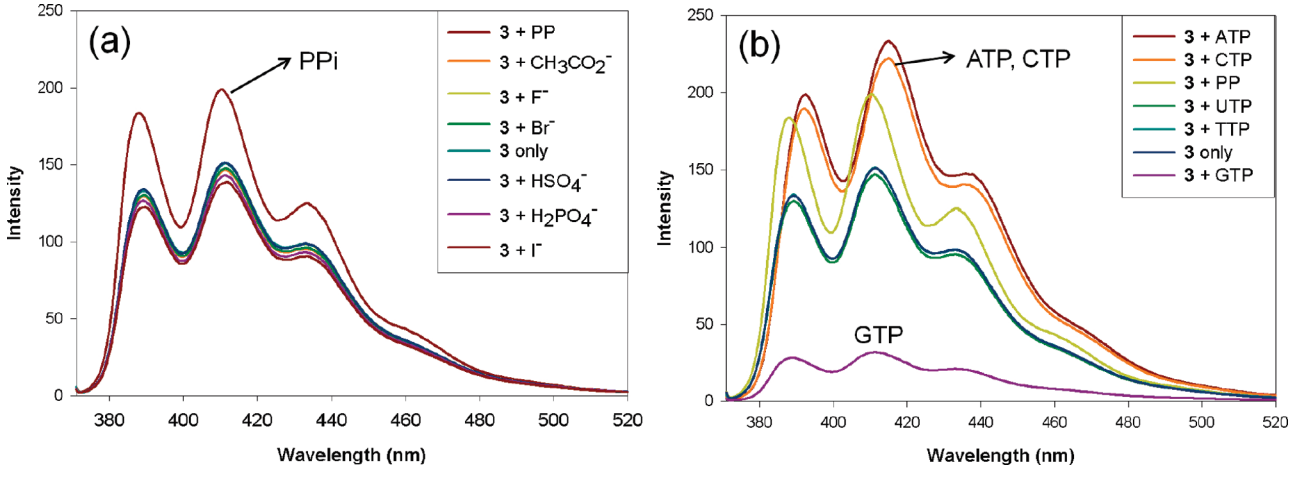

Figure 7. (a) Fluorescent emission changes of **3** (6 μM) upon addition of tetrabutylammonium salt of $CH_3CO_2^-$, HSO_4^-, I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$, and pyrophosphate (PPi) (300 equiv) at pH 9.0 (50 mM CHES) and (b) fluorescent emission changes of **1** (6 μM) upon addition of sodium salt of PPi, ATP, CTP, GTP, TTP, and UTP (300 equiv) at pH 9.0 (50 mM CHES) (excitation at 367 nm).

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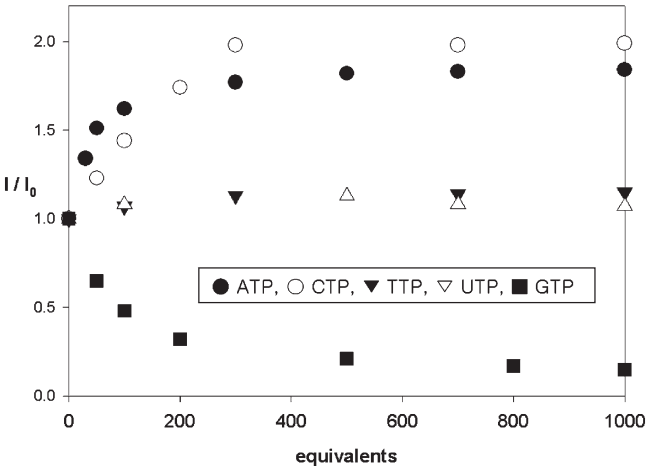

Figure 8. Relative fluorescence emission responses of **3** (3 μM) to the nucleoside triphosphate concentrations at pH 9.0 (50 mM CHES) (excitation at 367 nm).

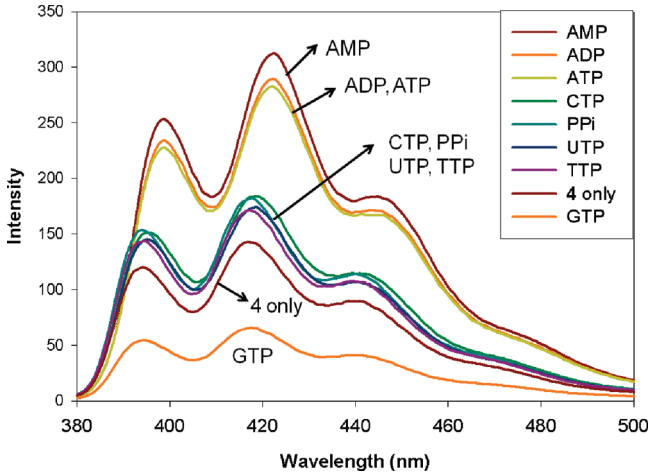

Figure 9. Fluorescent emission changes of **4** (3 μM) upon addition of sodium salt of PPi, ATP, ADP, AMP, CTP, GTP, TTP, and UTP (100 equiv) at pH 7.4 (10 mM HEPES) (excitation at 367 nm).

and the anthracene) were described by the MP2/6-31G* level of theory and the others by the semiempirical PM3 level. Similar to our previous study, water molecules have been used to stabilize the negatively charged phosphates. The calculated structures were shown in Figure 10. Similar to the interactions between **1** and ATP/GTP, the T-shape H$-\pi$ interactions between the base of ATP/GTP/AMP and the anthracene moiety of compounds **2**$-$**4** can be clearly seen in the complexes of **2**-ATP, **2**-GTP, **3**-ATP, and **4**-AMP. In addition to the H$-\pi$ interaction, it is believed that the electrostatic interactions between the positively charged moieties of **2**$-$**3** (the $(C-H)^+$ of imidazolium moiety, hydrogen atoms of the alkyl chains, and the $(N-H)^+$ of the protonated amine) and the phosphates of ATP/GTP have a significant contribution. On the other hand, in compound **4**, the boron atom binds to the oxygen atoms of the ribose moiety, and the water interacts with the oxygen atoms of the phosphate through the H-bonds where the H$\cdots$O distances were calculated in the range of 1.7$-$2.0 Å. The closest C$-$H distances in the H$-\pi$ interactions for **2**-ATP, **2**-GTP, **3**-ATP, and **4**-AMP were calculated to be 2.389, 2.668, 3.461, and 2.495 Å, respectively. The structural features of **2**-ATP, **2**-GTP, **3**-ATP, and **4**-AMP were very similar to those of **1**-ATP and **1**-GTP in our previous report.

In conclusion, anthracene derivatives bearing two imidazolium groups at the 1,8- and 9,10-positions (**1** and **2**), quaternary ammonium groups (**3**), or boronic acid group (**4**) were studied for their ability to recognize nucleotides such as ATP, GTP, CTP, TTP, UTP, ADP, and AMP via fluorescence changes. The anthracene group provides the interaction between the bases of the nucleotides. The imidazolium and quaternary ammonium groups induce hydrogen bonding interactions with the phosphate groups of the nucleotides. The boronic acid group can interact with the ribose group of the nucleotides examined. Compound **1** showed the tightest binding with GTP with a fluorescent quenching effect, and moderate fluorescent enhancement was observed with ATP. The 9,10-isomer **2** also displayed a large fluorescent quenching effect with GTP, but ATP induced a fluorescent quenching effect with a higher association constant. Compound **3** showed fluorescent enhancements with ATP and CTP, whereas it showed a large fluorescent quenching effect with GTP, with moderate selectivity for ATP over the other nucleotides. Finally, boronic acid derivative **4** displayed large fluorescent enhancements with AMP, ADP, and ATP as well as a fluorescent quenching effect with GTP with a moderate selectivity for AMP compared to the other nucleotides (Figure S5, Supporting Information). A nucleotide is composed of a nucleobase, a five-carbon sugar, and a phosphate groups. Recognition of these three sites can provide useful information for the development of selective fluorescent receptors for a specific nucleotide. Compounds **1**$-$**4** have potential use as fluorescent chemosensors for nucleotides. This study provides important information for the design of new fluorescent chemosensors for nucleotides.

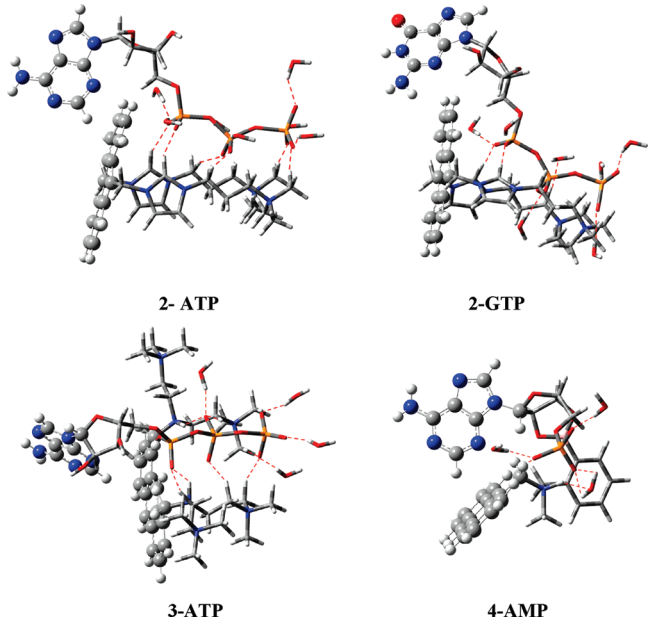

Figure 10. Calculated structures representing the binding modes **2**-ATP, **2**-GTP, **3**-ATP, and **4**-AMP. The ball-and-stick type represents the groups for which high-level (MP2/6-31G*) theory was used in the calculations, while the cylinder type represents low-level (semiempirical PM3) theory. The red lines show the H-bond length less than 2.0 Å.

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EXPERIMENTAL SECTION

Compound 2. To a solution of **5**[13] (200 mg, 0.59 mmol) in acetonitrile−*i*PrOH (1:1, v/v) (50 mL) was added (3-bromopropyl)-trimethyl ammonium bromide (616 mg, 2.36 mmol). The resulting solution was refluxed for 20 h. After cooling the solution, the precipitate was filtered and washed with cold acetonitrile several times. After recrystallization with acetonitrile−methanol (1:1), pale yellow solid was obtained in 61% yield (330 mg): mp 220−224 °C; ^{1}H NMR (CD_3OD, 250 MHz) δ 8.98 (s, 2H), 8.57 (dd, 4H, J = 7.1 Hz and 3.2 Hz), 7.72−7.80 (m, 8H), 8.59 (s, 4H), 4.30 (t, 4H, 7.2 Hz), 3.46−3.58 (m, 8H), 3.18 (s, 18H); ^{13}C NMR (CD_3OD) δ 137.4, 132.5, 129.3, 127.4, 125.5, 124.5, 124.0, 79.5, 63.9, 53.8, 27.1, 25.1; HRMS (FAB) m/z = 781.1437 $[M + H - Br]^+$, calcd for $C_{34}H_{49}Br_3N_6^+$ = 777.1485 and 780.4966.

Compound 3. 1,8-Anthracenedimethanamine **6** was obtained in 53% yield from 1,8-anthracenedimethanol following the published procedure.[6] To a solution of 1,8-anthracenedimethanamine **6** (60 mg, 0.254 mmol) in CH_2Cl_2−*i*PrOH (1:1, v/v) (25 mL) was added (2-bromoethyl)trimethyl ammonium bromide (251 mg, 1.02 mmol). The resulting solution was refluxed for 20 h. After cooling the solution, the precipitate was filtered and washed with CH_2Cl_2 and cold acetonitrile several times. Analytically pure **3** was obtained in 81% yield (201 mg): mp 239−242 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.29 (brs, 2H), 8.79 (s, 1H), 8.76 (s, 1H), 8.21 (dd, 2H, J = 6.9 Hz and 2.7 Hz), 7.76 (m, 4H), 7.62 (m, 4H), 6.25 (s, 4H), 4.38 (t, 4H, J = 7.2 Hz), 3.52 (m, 4H), 3.19 (s, 18H), 2.47 (m, 4H); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ 131.2, 130.3, 129.4, 128.8, 128.2, 127.9, 125.3, 118.6, 64.6, 55.1, 53.1, 52.4; MS (ESI) m/z = 978.3 $[M + H]^+$, calcd for $C_{36}H_{66}Br_5N_6$ = 977.1. Anal. Calcd for $C_{36}H_{66}Br_9N_6^{3-}$: C, 33.21; H, 5.11; N, 6.45. Found: C, 33.36; H, 5.14; N, 6.28.

Preparation of Fluorometric Anion Titration Solutions. Stock solutions (1 mM) of the sodium salts of $H_2PO_4^-$, HSO_4^-, $CH_3CO_2^-$, F^-, Cl^-, Br^-, I^-, and pyrophosphate in double distilled water and sodium salts of ATP, ADP, AMP, CTP, GTP, TTP, and UTP in adequate buffer solution were prepared. Stock solution of compounds (0.1 mM) was also prepared in adequate buffer solution. Test solutions were prepared by placing 4−40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each anion stock, and diluting the solution to 4 mL with buffer solution.

Calculation Methods. Geometry optimizations of **2**-ATP, **2**-GTP, **3**-ATP, and **4**-AMP complexes including water molecules near each oxygen atom of the triphosphate group of the ATP/GTP/AMP were carried out using ONIOM (MP2/6-31G* calculations for the anthracene moiety and nucleic base and PM3 calculations for the remaining part) using a suite of Gaussian 03 programs.[19]

ASSOCIATED CONTENT

Supporting Information. Fluorescent spectra and ^{1}H and ^{13}C NMR spectra of compounds **2** and **3** are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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