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L-Arginine bearing an anthrylmethyl group: fluorescent molecular NAND logic gate with H^+ and ATP as inputs

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Abstract—A novel L-arginine derivative was synthesized and its interactions with ATP in aqueous solutions were demonstrated by fluorescence, UV–vis, and ^{1}H NMR spectroscopy. A two-input NAND logic gate was presented on the basis of this single molecule.
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Molecular analogs of electronic devices have attracted research interest in recent years and have potential applications in a chemical computer.[1] As one of molecular devices, fluorescent logic gates play a pivotal role in molecular computation because they are detectable as a single molecule and can simultaneously treat multiple inputs.[2] Within the past decade, many fluorescent logic gates showing NOT, AND, OR, XOR, NAND, INHIBIT operations, and combinational logic circuits incorporating single logic gates have been reported.[3,4] Among all the logic gates, the particularly important one is NAND gate, which is considered to be a universal gate since every other gate function can be generated by successive implementation of NAND gates.[5] However, to our knowledge, relatively few fluorescent molecular NAND logic gates have been reported.[6]

Recently, much attention has been focused on the interactions of L-arginine residue with ATP and the important roles of L-arginine in F_1F_0-ATPase.[7,8] In our previous papers,[9] we reported the molecular recognition of L-arginine with ATP through hydrogen bonding and electrostatic interactions and the L-arginine conformation changes during the process. Despite its well-studied biological functions and activities, it appeared to us that no work has been reported on the modification of L-arginine with fluorophores as a potential logic gate with ATP input. On the basis of the structural motif of the L-arginine-ATP adduct, we have designed a novel compound **1** in which an anthrylmethyl group was appended to the amino nitrogen atom of L-arginine. The anthracene moiety was coupled with L-arginine to serve as a fluorophore as well as to involve the π–π stacking with the adenine fragment of ATP. We expected that **1** could bind and sense ATP efficiently in aqueous solutions and a potential logic operation of **1** could be established.

The synthesis of compound **1** was carried out by condensing 9-anthradehyde with L-arginine in the presence of ethanol, followed by reduction with $NaBH_4$ (Scheme 1), yield 72%. Then **1** was dissolved in ethanol and precipitated as a light yellowish hydrochloride salt: **1**·2HCl.[10]

Figure 1 demonstrates the emission intensity changes ($\lambda_{em} = 418$ nm) of **1** and its ATP adduct in aqueous solutions in the pH range 2.0–12.0. Free ligand **1** shows typical photo-induced electron transfer (PET) processes with quenched fluorescence in basic solutions and the revival of fluorescence in neutral and acidic solutions. When the amine group of **1** is proton-free in basic solutions, there is a thermodynamically favorable PET from the amino lone pair to the excited fluorophore (anthracene unit) that induces fluorescence quenching. Upon protonation in neutral and acidic solutions, the amino

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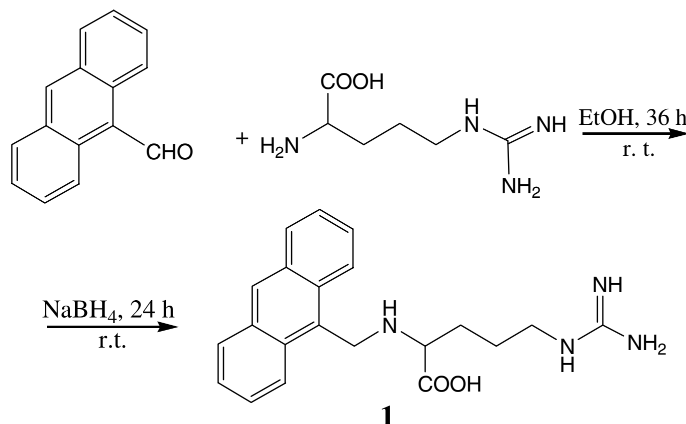


Scheme 1. Synthesis of compound **1**.

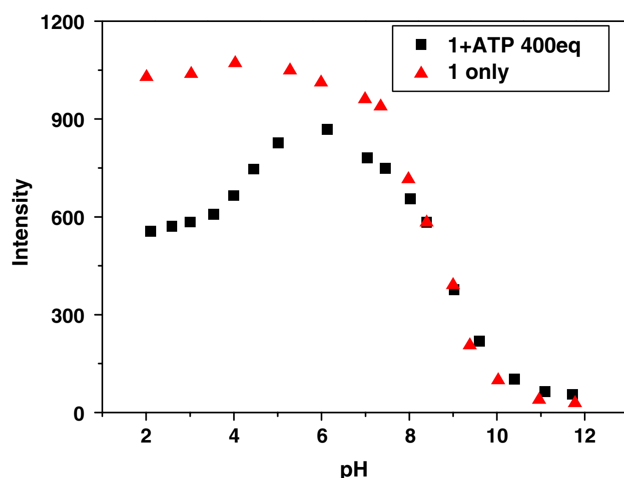


Figure 1. PH dependence of the fluorescence emission peaks at 418 nm of compound **1** ($\lambda_{ex} = 368$ nm): in the absence of ATP (▲); in the presence of 400-fold ATP excess (■).

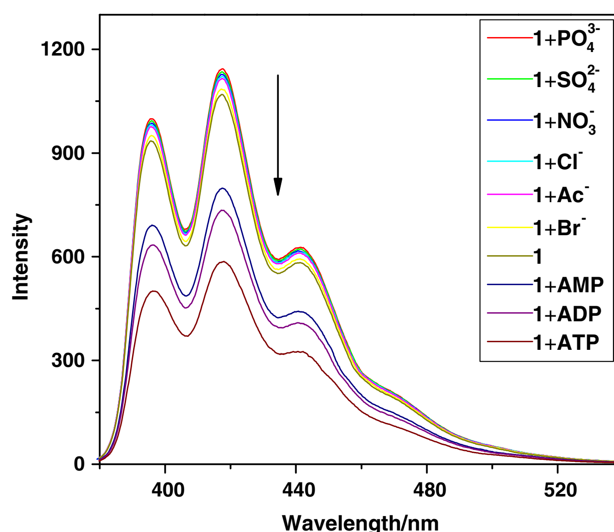


Figure 2. Fluorescence spectra of receptor **1** in the presence of sodium salt of several guests in H_2O. [receptor] = 1.0×10^{-5} M, [guest] = 4.0×10^{-3} M. Excitation wavelength: 368 nm.

lone pair is engaged and the PET process is inhibited, resulting in an increase in emission intensity.[11] Comparing the fluorescence emission titration curves of **1** and its ATP adduct (Fig. 1), the most interesting feature in this system is the quenching induced by the addition of ATP at pH values below 4.0. This quenching effect might be ascribed to the PET or energy transfer from ATP to the photo-excited anthracene unit favored by π–π stacking interactions between the anthracene moiety and the adenine fragment.[11b]

Figure 2 shows the anion-induced fluorescence spectra changes of **1** (1.0×10^{-5} M) in aqueous solutions at pH 3.0. Compound **1** displays a chelation-enhanced fluorescence quenching (CHEQ) effect for ATP, even though **1** also displays relatively small CHEQ effects for ADP and AMP. Almost no fluorescent changes are observed in the cases of PO_4^{3-}, SO_4^{2-}, NO_3^-, Cl^-, CH_3COO^-, and Br^-, even at high concentration up to 400 equiv each. It is suggested that the hydrogen bonding, electrostatic and π–π stacking interactions contribute to the formation of a stable adduct between **1** and ATP (Fig. 3). The largest quenching in fluorescence intensity upon ATP addition was demonstrated probably due to the better stacking interactions between the anthracene unit and the adenine part. ^{1}H NMR studies provide unambiguous evidence for the π–π stacking interactions (Fig. 4). Complexation is accompanied by upfield shifts of the ^{1}H NMR signals of the adenine fragment of ATP and the anthracene unit of **1**, suggesting the presence of π–π stacking interactions between them.

Figure 5 explains the fluorescence titration of **1** with ATP in aqueous solutions at pH 3.0. The intensity of the emission peaks decreased with the increase in ATP concentration. Figure 6 shows the changes in the UV–vis absorption spectra of **1** in the presence of different concentrations of ATP in aqueous solutions at pH 3.0. With increasing ATP concentration, **1** shows a decrease in the absorption corresponding to the anthracene moiety. Changes of absorbance ($1/\Delta A$) can be formulated as a function of 1/[ATP] using the Benesi–Hildebrand method (inset of Fig. 6).[12] The association constant k_a was 3.49×10^2 M^{-1} and the fit constant was 0.9991.

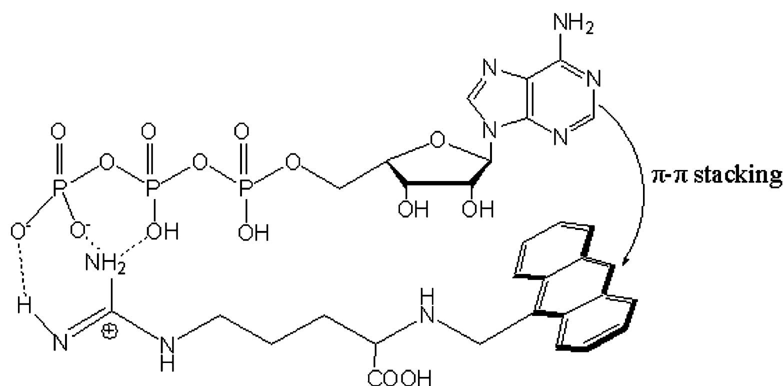


Figure 3. Schematic representation of the proposed hydrogen bonding, electrostatic and π–π stacking interactions between **1** and ATP.

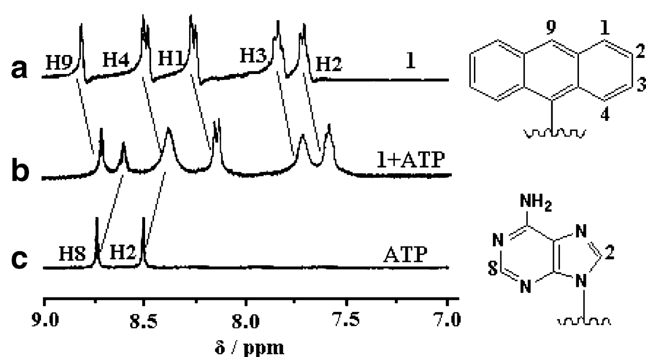


Figure 4. Partial NMR (D_2O–CD_3OD = 1:1, 45 °C) spectra of (a) host **1** (8.0×10^{-3} M), (b) **1** + ATP (1:1 molar ratio), and (c) ATP at pD 2.0.

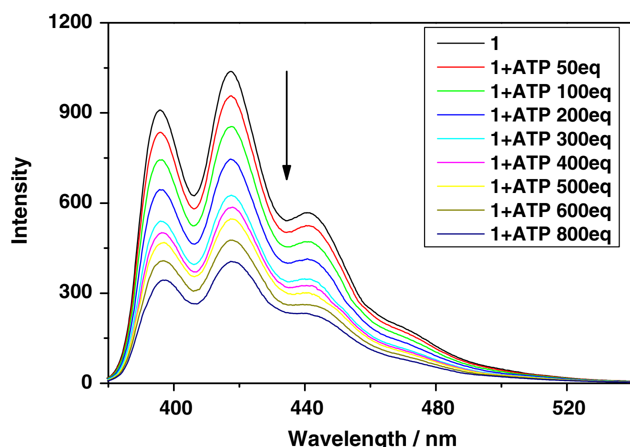


Figure 5. Changes in fluorescence spectra of **1** (1.0×10^{-5} M) with gradual addition of ATP in aqueous solution (pH 3.0): [ATP] = 0–8.0×10^{-3} M; λ_{ex} = 368 nm.

The logic characteristics of NAND gate **1** in aqueous solutions were established by the observation of the fluorescence spectra under four inputs conditions (Fig. 7a). The truth table for a two input NAND gate is shown in Figure 7b, in which H^+ concentration ($input_1$) is $10^{-6.0}$ M (low, binary 0) or $10^{-2.0}$ M (high, 1) and ATP concentration ($input_2$) is 0 M (low, 0) or 2.0×10^{-2} M (high, 1). Herein we regard a fluorescence intensity of 600 as the threshold value, the output = 0 when the intensity of the emission peak at 418 nm is low (<600), whereas the output = 1 when the intensity of the emission peak at 418 nm is high (>600). Thus a strong fluorescence signal is observed when either H^+ or ATP alone is present at high enough concentrations. In contrast, a significant fluorescence quenching occurs when both H^+ and ATP are simultaneously present. Namely, only when $input_1 = 1$ and $input_2 = 1$ does the output = 0. This resulting pattern mimics the function of an electronic NAND gate with a low output state occurring only in the presence of two inputs. Besides, the quantum yields of compound **1** have been measured to be 0.624, 0.640, 0.602, and 0.209 under four inputs conditions, respectively, using anthracene in deoxygenated ethanol as standard ($\Phi_{fs} = 0.27$).[13] The fluorescence quantum yields (Φ_f) at output = 1 are about 3 times higher than that at output = 0.

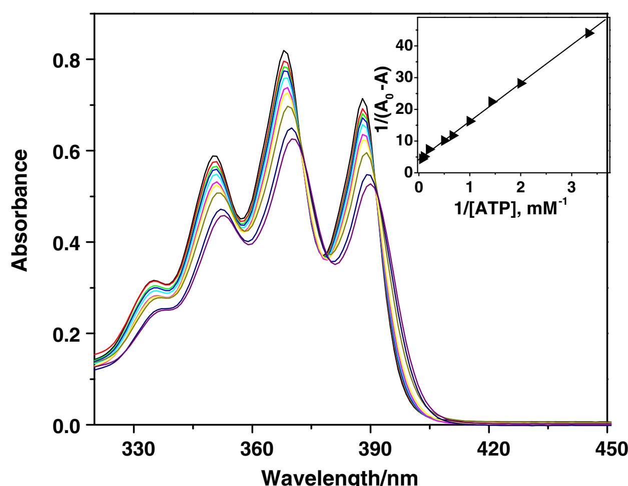
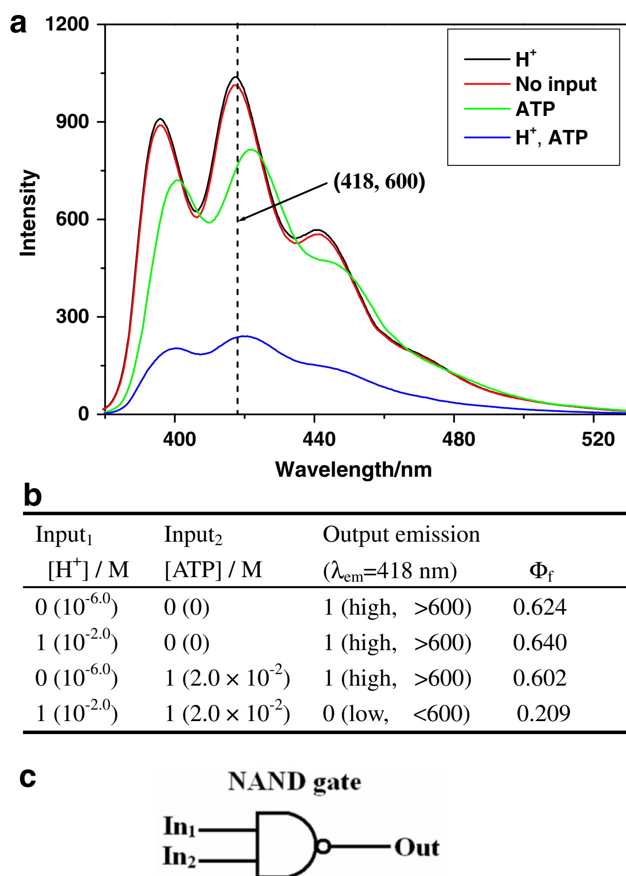


Figure 6. Effect of ATP concentrations (0–1.5×10^{-2} M) on absorption spectra of **1** (1.0×10^{-4} M) in aqueous solution. Inset shows the plot of $1/\Delta A_{368\,nm}$ as a function of 1/[ATP] (Benesi–Hildebrand plot).

In conclusion, we have shown that a novel L-arginine derivative **1** can selectively bind and sense ATP in acidic aqueous solutions and a two-input NAND logic gate was presented on the basis of this single molecule. Further work is presently being performed in order to



Input$_1$ [H$^+$] / M	Input$_2$ [ATP] / M	Output emission (λ_{em}=418 nm)	Φ_f
0 ($10^{-6.0}$)	0 (0)	1 (high, >600)	0.624
1 ($10^{-2.0}$)	0 (0)	1 (high, >600)	0.640
0 ($10^{-6.0}$)	1 (2.0×10^{-2})	1 (high, >600)	0.602
1 ($10^{-2.0}$)	1 (2.0×10^{-2})	0 (low, <600)	0.209

Figure 7. (a) Changes in fluorescence spectra (excitation at 368 nm) of **1** (1.0×10^{-5} M) for the NAND gate in the absence and presence of 2.0×10^{-2} M ATP at pH 2.0 or 6.0 in aqueous solutions, (b) truth table, and (c) NAND logic scheme.

obtain related fluorescent molecular devices with logic operations.

Acknowledgement

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10. General procedure for the synthesis of compound **1**: L-Arginine (0.9 g, 5 mmol) and 9-anthraldehyde (1.1 g, 5 mmol) were dissolved in 50 mL of ethanol and reacted for 36 h at room temperature. Then $NaBH_4$ (1.0 g, 25 mmol) was added portionwise and the resulting solution was stirred at room temperature for 24 h. Ethanol was distilled off under reduced pressure, and then the residue was treated with 50 mL of water and stirred for 2 h. After filtration and recrystallization from EtOH, the colorless sheet crystals were obtained in a 72% yield. Mp: 200–202 °C; MS (ESI): 365.2 $[M+H]^+$. Compound **1** (0.4 g, 1.1 mmol) was dissolved in ethanol and precipitated as a yellow hydrochloride salt: **1**·2HCl. Mp: 249–251 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ: 8.51 (d, 2H, $J = 8.8$ Hz), 8.46 (s, 1H), 8.02 (d, 2H, $J = 8.4$ Hz), 7.57–7.53 (m, 2H), 7.49–7.45 (m, 2H), 4.69 (dd, 2H, $J = 12.4$ Hz), 3.38 (t, 1H, $J = 5.6$ Hz), 3.17–3.09 (m, 2H), 1.70–1.65 (m, 4H); ^{13}C NMR (CD_3OD) δ: 179.4, 157.5, 132.7, 131.0, 130.0, 128.6, 126.3, 125.7, 125.0, 63.5, 44.6, 40.3, 30.6, 26.1; Anal. Calcd for $C_{21}H_{26}N_4O_2Cl_2$: C, 57.67; H, 5.99; N, 12.81. Found: C, 57.24; H, 6.15; N, 12.55.
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