Synthesis and Selective Recognition of Dihydrogen Phosphate by Urea-Anthraquinone

Seungwon Jeon,* Duck Hee Park, Hyo Kyoung Lee, Jin Young Park, Sung Ok Kang, and Kye Chun Nam*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
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A neutral ligand is synthesized and studied for the binding properties with anions by electrochemical methods. The binding of 1,8-bis[(N'-phenylureido)ethyloxy]anthraquinone (BPUA) with $H_2PO_4^-$ makes cathodic shift of its electrochemical potentials and red shift of absorption band. This novel neutral anion receptor BPUA binds anions through hydrogen bonding and show high selectivity with $H_2PO_4^-$ over $CH_3CO_2^-$, Cl^-, and HSO_4^-. The selectivity of $H_2PO_4^-$ over $CH_3CO_2^-$, Cl^-, and HSO_4^- may be attributed to the stronger hydrogen bonding with urea moiety and also with anthraquinone moiety of BPUA receptor, and also the higher complementarity of the cavity of BPUA for tetrahedral $H_2PO_4^-$.

Key Words : Receptor, Urea-anthraquinone, Dihydrogen phosphate ion, Binding

Introduction

In comparison with the variety of host molecules as cation receptors, the investigation of selective receptors for anions is still less.[1] Especially in nature sulfate and phosphate binding proteins are very important receptors for the active transport systems in the cell, and prove selectivities of more than 10^5 for binding sulfate over phosphate and phosphate over sulfate, respectively.[2] Selective complexation of anions is more demanding than that of cations in the view of the higher free energies of solvation of anions and the pH dependence of anion complexation.[3] Neutral ferrocene receptors,[4-7] thiouronium receptors,[8] neutral bisthiourea or bisurea hosts,[9-12] and porphyrin receptors[13] were investigated for selective recognition of $H_2PO_4^-$ anion. A selective complexation of Cl^-, Br^- or I^- can be achieved by the neutral urea receptors derived from the lower rim of calix[4]arene,[14] and three urea groups at the lower rim of calix[6]arene are well suited for complexation of tricarboxylate.[15] The urea moiety is a powerful donor of hydrogen bond as recently shown in the complexation of dicarboxylate anion.[16] Recently, calix-quinones and -nitros as redox-switchable calixarenes have been synthesized and studied for electrochemistry and ionic binding.[17-21] A redox-switchable receptor is a compound capable of forming a complex with a given substrate in such a way that the thermodynamic stability of the complex is determined by the oxidation state of the receptor. The quinone moieties of ester derived calix[4]quinones were known to hydrogen bonding with proton of NH_4^+. The anthraquinone moiety has proved to be the most versatile and useful redox-active group in chemical and biological systems.[22-24] Crown ether derivatives containing anthraquinone moiety were studied for cation binding-redox coupling.[25] These compounds must possess a redox-active subunit and a well-defined binding site. We recently reported the synthesis and anion binding of urea-functionalized calix[4]diquinone,[20,21] and also the synthesis and the cation binding of diester-anthraquinone.[26]

In this paper we report the binding properties of urea-anthraquinone toward $H_2PO_4^-$ against some anions such as $CH_3CO_2^-$, Cl^-, HSO_4^-, and NO_3^-. The binding study was conducted with electrochemical and spectroscopic methods.

Experimental Section

Synthesis.

1,8-Bis(cyanomethyloxy)-9,10-anthraquinone (2): A 1,8-dihydroxyanthraquinone (0.1 g, 0.4 mmol), potassium carbonate (0.3 g, 2.2 mmol), and bromoacetonitrile (0.3 mL, 4.3 mmol) in acetone (125 mL) was stirred and heated under reflux for 1 day. The cooled mixture was filtered and the solvent was removed. The crude product was further purified by column chromatography (eluents $CHCl_3$: *n*-hexane : ethylacetate = 6 : 3 : 3) to give 65 mg (50%) of **(2)**. ^{1}H NMR ($CDCl_3$) δ 8.1 (d, H, ArH), 7.8 (t, H, ArH), 7.5 (d, H, ArH), 5.0 (s, 2H, -OCH_2-).

1,8-Bis(2-aminoethyloxy)-9,10-dihydroxyanthracene (4): A 15 mL of 1 M BH_3/THF solution was added to 0.5 g (1.6 mmol) of (**2**) under nitrogen atmosphere and refluxed for 2 hrs. The solvent was removed and the residue treated with 10 mL of 2 M HCl and refluxed for 1 hr. After cooling down to room temperature, 10% KOH solution was added until the solution became basic and extracted with $CHCl_3$. After the solvent was removed, the product was triturated to give 0.37 g (70%) of (**4**). ^{1}H NMR ($CDCl_3$) δ 7.14 (t, 2H, ArH, J = 7.8 Hz), 6.89 (d, 2H, ArH, J = 7.8 Hz), 6.74 (d, 2H, ArH, J = 7.8 Hz), 4.03 (t, 4H, -OCH_2-, J = 5.2 Hz), 3.98 and 3.95 (two s, 4H, $ArCH_2Ar$), 3.14 (t, 4H, -CH_2N-, J = 5.2 Hz), 1.92 (br s, 4H, NH_2).

1,8-Bis[(N'-phenylureido)ethyloxy]-9,10-dihydroxyanthracene (5): To 0.1 g (0.3 mmol) of compound (**4**) in methylene chloride (10 mL), 0.07 g (0.6 mmol) phenylisocyanate was added and refluxed for 1 hr under the nitrogen atmosphere. After the solvent was removed, the residue triturated with *n*-hexane to give 0.11 g (65%) of (**5**). ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 2H, -NH, J = 7.8 Hz), 7.39 (d, 4H, ArH, J = 7.8 Hz), 7.18 (m, 6H, ArH), 6.88 (m, 6H, ArH), 6.44 (t, 2H, -NH, J = 5.6 Hz), 4.06 (t, 4H, -OCH_2-, J = 5.5 Hz), 3.93 and

3.88 (two s, 4H, $ArCH_2Ar$), 3.54 (q, 4H, $-CH_2N-$, J = 5.6 Hz); ^{13}C NMR (DMSO-d_6) δ 155.4 (-NHCONH-), 155.3, 140.2, 136.9, 128.5, 126.6, 123.6, 121.1, 119.7, 117.7, and 108.9 (Ar), 67.2 ($-OCH_2-$), 34.6 and 21.4 ($ArCH_2Ar$); FAB MS *m/z* 537.1 (M^+, Calcd 536.6).

1,8-Bis[(N'-phenylureido)ethyloxy]anthraquinone (6) (BPUA): To 0.5 g (0.88 mmol) of compound (**5**) in DMSO (30 mL), 0.2 g (0.2 mmol) chromium(VI) oxide and a little of celite were added. The mixture was reacted in the 80 °C for 1 day. After cooling down to room temperature, it was extracted with $CHCl_3$ and 2 N HCl. The crude product was further purified by column chromatography (acetone : *n*-hexane = 1 : 1) to give 0.27 g (50-60%) of (**6**). ^1H NMR (DMSO-d_6) δ 8.54 (s, 2H, -NH), 7.66, 7.42, and 7.35 (d, 8H, ArH), 7.49, 7.18, and 6.87 (t, 8H, ArH), 6.45 (t, 2H, -NH), 4.20 (m, 4H, $-CH_2N-$), and 3.56 (m, 4H, $-OCH_2-$).

Reagents. As a supporting electrolyte, tetrabutylammonium hexafluorophosphate (Bu_4NPF_6) was used as received from Fluka. Anhydrous dimethylsulfoxide (DMSO), tetrahydrofurane (THF), and acetonitrile (CH_3CN) were used as received from Aldrich. All anions [tetrabutylammonium salts Bu_4NX (X = Cl^-, Br^-, I^-, ClO_4^-, $CH_3CO_2^-$, $H_2PO_4^-$, HSO_4^-, CN^-)] were used as received from Aldrich or Fluka. These were added to urea-anthraquinone solution with a microsyringe, after preparing 0.2 M anion solution in DMSO and CH_3CN.

Instrumentation. The voltammetric measurements were accomplished with three electrodes potentiostat [Bioanalytical Systems (BAS 100B/W)]. A Ag/AgCl electrode supplied by BAS was used as a reference electrode. A platinum-wire electrode was used as an auxiliary electrode. A glassy carbon electrode of 3.0 mm diameter was used as a working electrode, and its surface was highly polished with alumina paste prior to each experiment. All reported potentials were with respect to a Ag/AgCl electrode at room temperature under an argon atmosphere. Absorption spectra were obtained from Jasco V-530 spectrophotometer which the optical path length is 10 mm.

Results and Discussion

Electrochemical properties. The synthetic procedure of BPUA is drawn in Figure 1. The electrochemical properties of BPUA were investigated in DMSO using cyclic voltammetry with Bu_4NPF_6 as a supporting electrolyte under an argon atmosphere. Cyclic voltammograms (CVs) of BPUA in the absence of $H_2PO_4^-$ anion are shown in Figure 2. According to CVs, BPUA gives the first quasi-reversible wave (the cathodic peak potential at -0.697 V and the corresponding anodic peak potential at -0.184 V) followed by the second wave at more negative potential (-1.280 V) with irreversible (Fig. 2a). The reduction current of second wave is unusually high value when compared with first wave, because catalytic reduction may occur due to the regeneration of radical anion from the reaction of reduced-dianion and quinone. The first reduction potential (-0.697 V)

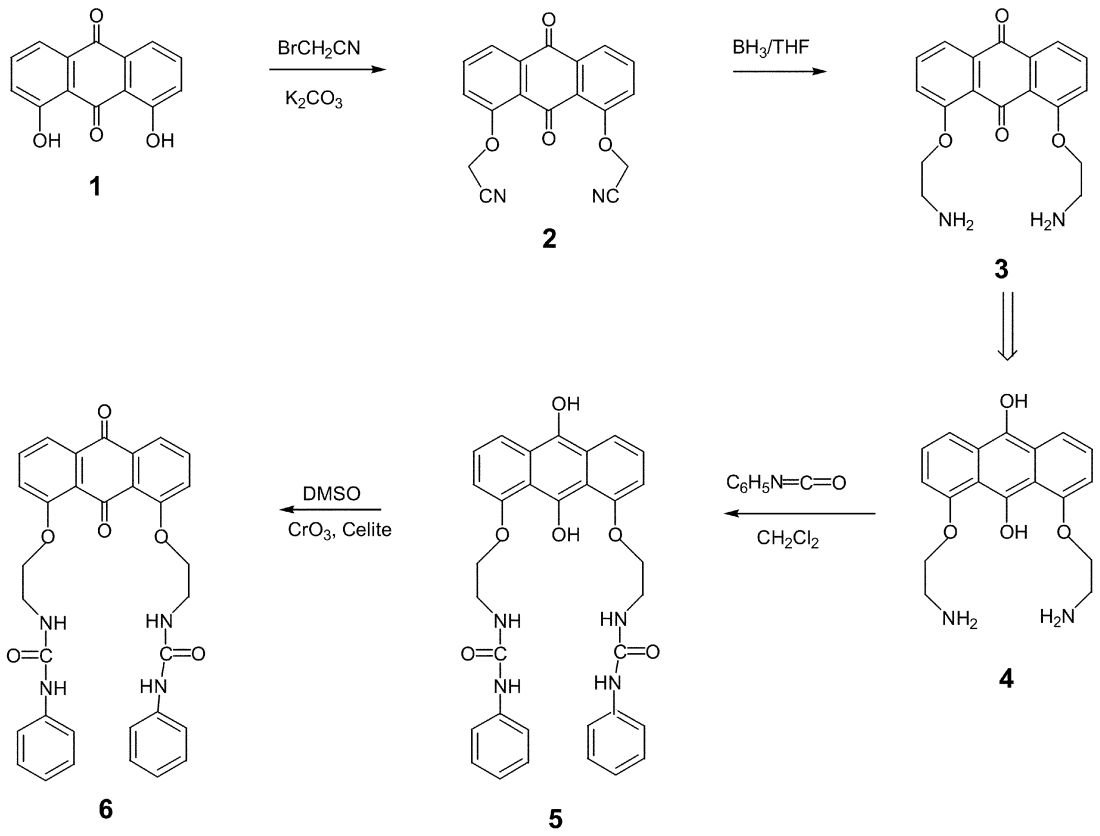

Figure 1. Synthesis of 1,8-bis[(N'-phenylureido)ethyloxy]anthraquinone (BPUA).

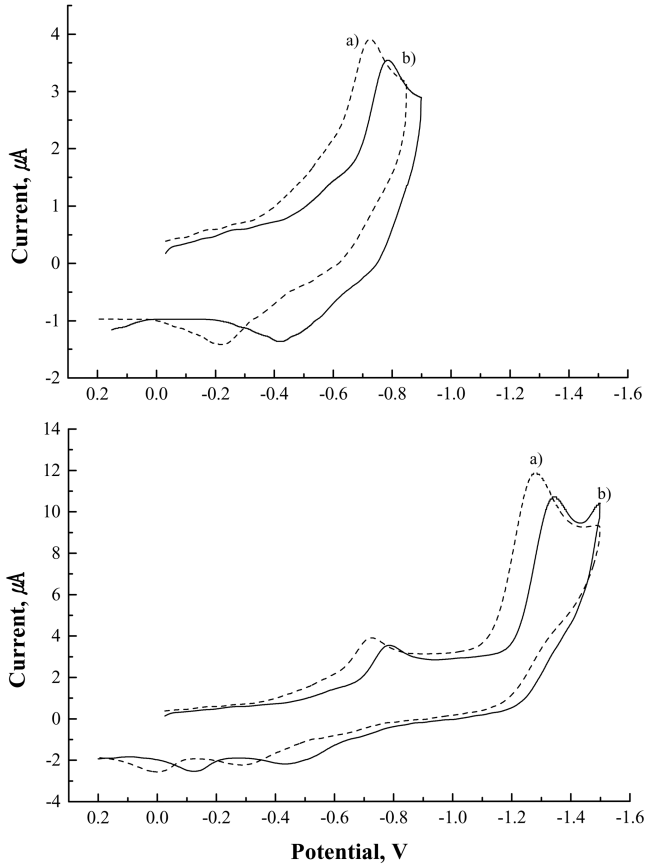

Figure 2. Cyclic Voltammograms of BPUA in the absence (a) and presence (b) of $H_2PO_4^-$.

of the synthesized BPUA is more positive than those of diester-anthraquinone (-1.022 V), 1,8-dihydroxyanthraquinone (-0.890 V) and anthraquinone (-1.040 V).[26] It is well known that the reduction waves correspond to the formation of radical anion and dianion, respectively. The amide moieties of BPUA act mainly as a binding site of anion, and the quinone moieties of BPUA constitute a redox active center as well as a binding site. The anion recognition properties of the receptors can be studied by electrochemical methods. When stoichiometric equivalents of anion guests are added to the electrochemical solutions of BPUA, the first reduction potential of BPUA will be expected to shift negative value. Cyclic voltammograms of BPUA in the presence of 10 equivalents of $H_2PO_4^-$ are also shown in Figure 2b. Cyclic voltammograms are recorded after progressively adding stoichiometric equivalents of anion guests to the electrochemical solutions. Large cathodic perturbations of the reduction wave for BPUA are observed on additions of $H_2PO_4^-$ as anion guests. The addition of excess $H_2PO_4^-$ causes an 80 mV cathodic shift in the first reduction peak. This large cathodic shift suggests a strong stabilization of BPUA in the presence of $H_2PO_4^-$. A stabilization of the complex results from hydrogen bondings between urea moieties of BPUA and oxygen of $H_2PO_4^-$, and quinone moiety of BPUA and hydrogen of $H_2PO_4^-$. Meanwhile, the oxygen moiety of reduced quinone isn't easily protonated by

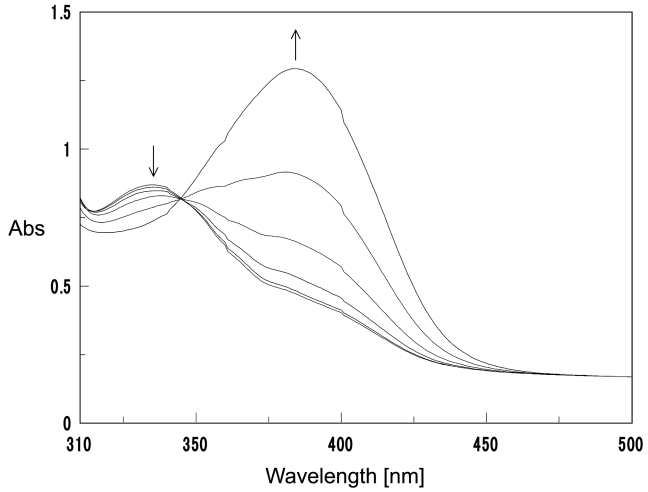

Figure 3. UV/vis spectra for $H_2PO_4^-$ (0, 1, 2, 4, 6, 10 eq) binding of urea-anthraquinone in DMSO.

the proton of $H_2PO_4^-$ ($pK_a = 7.8$ in H_2O). Likewise, the addition of excess $CH_3CO_2^-$ anion to the electrochemical DMSO solutions of BPUA receptor also resulted in an 78 mV cathodic shift in the first reduction peak, and it seems to be a stabilization of BPUA in the presence of $CH_3CO_2^-$. A 63 mV cathodic shift to ten equivalents addition of $H_2PO_4^-$ and 53 mV to ten equivalents addition of CH_3COO^- are observed in the second reduction potential. However, any shift is not observed by the addition of HSO_4^-, NO_3^- and Cl^-. It suggests that BPUA can bind with anions (HSO_4^-, NO_3^- and Cl^-) very weakly. Meanwhile, no shift of the first reduction potential of unsubstituted anthraquinone such as 1,8-dihydroxyanthraquinone and anthraquinone in the presence $H_2PO_4^-$ or CH_3COO^- was observed, and this result indicates that their anions seem to be no bound to the quinone moiety.

Spectroscopic properties. Figure 3 shows absorption spectra of BPUA in DMSO in the absence and presence of $H_2PO_4^-$. The result of spectroscopic experiments provides some evidence on binding property. The maximum wavelength (λ_{max}) of BPUA is 333 nm in DMSO solvent. The λ_{max} shifts to long wavelength in the presence of $H_2PO_4^-$ in DMSO. After successive addition of $H_2PO_4^-$ (0, 1, 2, 4, 6, 10 eq) to the DMSO solution of BPUA, the peak of 333 nm decreased and new peak of 384 nm increased with an isosbestic point of 347 nm which demonstrates the absence of any long-lived intermediates. The above result indicates that BPUA can bind with $H_2PO_4^-$ in DMSO. The wavelength shift value through the binding between BPUA and $H_2PO_4^-$ is 51 nm which suggests strong binding in DMSO having high dielectric constant ($\varepsilon = 47$). However, although successive addition of CH_3COO^- as strong base to the DMSO solution of BPUA, there is very small change (< 2 nm) of the maximum wavelength. This result indicates that BPUA seems to bind with CH_3COO^- in DMSO very weakly. It is well known that basicity of CH_3COO^- is higher than that of $H_2PO_4^-$, and they are strong bases. So the binding between BPUA and $H_2PO_4^-$ isn't an acid-base reaction but the anion

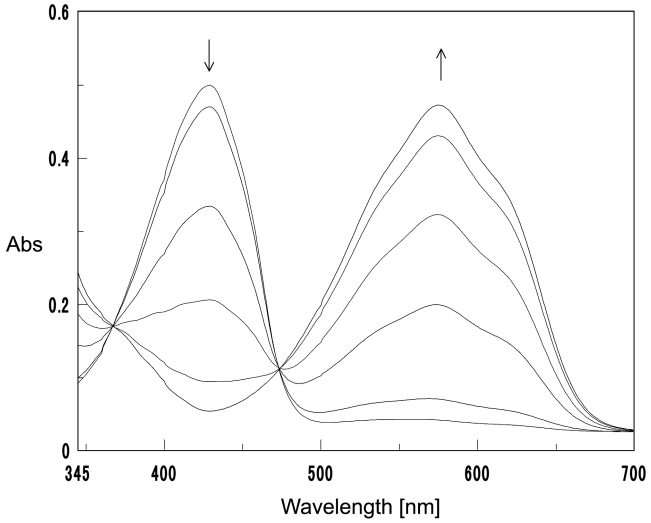

Figure 4. UV/vis spectra for $H_2PO_4^-$ (0, 1, 2, 4, 6, 10 eq) binding of 1,8-dihydroxyanthraquinone in DMSO.

complexation of urea-anthraquinone with $H_2PO_4^-$. Confirmed experiments were performed using 1,8-dihydroxyanthraquinone as an acid compound. Figure 4 shows absorption spectra of 1,8-dihydroxyanthraquinone in DMSO in the absence and presence of $H_2PO_4^-$. The shift of λ_{max} of 1,8-dihydroxyanthraquinone was observed in the presence of $H_2PO_4^-$ or CH_3COO^-. After successive addition of $H_2PO_4^-$ (0, 1, 2, 4, 6, 10 eq) to the DMSO solution of 1,8-dihydroxyanthraquinone, the peak of 428 nm decreased and new peak of 575 nm increased with isosbestic points of 367 and 473 nm. The above result indicates that the binding between 1,8-dihydroxyanthraquinone and $H_2PO_4^-$ or CH_3COO^- is an acid-base reaction. Meanwhile, the wavelength shift value through the binding between BPUA and $H_2PO_4^-$ is only 10 nm which suggests weak binding in THF ($\varepsilon = 7.6$). This result demonstrates that the binding extent of host-guest can depend on a dielectric constant.

Based on the electrochemical and spectroscopic results, the tetrahedral $H_2PO_4^-$ coordinates to the amide moieties of BPUA and also weakly binds to quinone moiety by hydrogen bonding. Interestingly a selectivity for $H_2PO_4^-$ was observed for urea-functionalized anthraquinone receptor. The influence of the hydrogen bond of quinone moiety with $H_2PO_4^-$ is very clear according to the electrochemical potential shift and spectroscopic wavelength shift. The addition of anions to BPUA solutions resulted in cathodic shifts of the quinone/semiquinone redox couple with the relative magnitudes following the order $H_2PO_4^-$ > $CH_3CO_2^-$ > HSO_4^-, NO_3^-, Cl^-. The binding constant of the tetrahedral dihydrogen phosphate anion is larger than that of the tetrahedral hydrogen sulfate. The results obtained from electrochemical measurements are similar to those obtained from spectroscopic studies. This novel neutral anion receptor BPUA binds anion through hydrogen bonding and shows high selectivity with $H_2PO_4^-$ over $CH_3CO_2^-$, Cl^-, HSO_4^-. The good selectivity of $H_2PO_4^-$ over $CH_3CO_2^-$, Cl^-, HSO_4^- may be attributed to the stronger hydrogen bonding with urea moieties and also with quinone moiety of BPUA, and also the higher complementarity of the cavity of BPUA for $H_2PO_4^-$. Finally, the effect of $H_2PO_4^-$ binding to BPUA may be stronger than other anions employed, and the reason is ascribed to the geometric effect of anion structure.

In conclusion, we have synthesized a new class of neutral ligands which are able to bind anions through hydrogen bonding. Urea-functionalized anthraquinone is more easily reduced than anthraquinone due to urea moieties of BPUA. Especially the binding effect of $H_2PO_4^-$ to BPUA may be stronger than other anions employed, because of the intermolecular powerful hydrogen bonding between the quinone moiety of BPUA and $H_2PO_4^-$ as a hydrogen donor together the hydrogen bonding the urea moieties of BPUA and $H_2PO_4^-$ as a hydrogen acceptor, and the cavity of BPUA. Thus this novel BPUA receptor not only forms thermodynamically very stable complexes with $H_2PO_4^-$ but can also electrochemically sense these anion guests *via* substantial cathodic perturbation and wavelength shift effects. These anion receptors exhibit high selectivities for $H_2PO_4^-$ guest. The use of these receptors as carriers for anion transport of tetrahedral anions, specially such as $H_2PO_4^-$, in membranes and as anion receptors in ion selective electrodes for anion sensing are currently in progress.

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