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Amphoteric Homotropic Allosteric Association between a Hexakis-Urea Receptor and Dihydrogen Phosphate

Seiya Kondo[+], Junya Masuda[+], Tomoki Komiyama, Nobuhiro Yasuda, Hikaru Takaya,* Masamichi Yamanaka*

Abstract: Conformationally flexible hexakis-urea **1** was synthesized efficiently by condensing hexakis(aminomethyl)benzene with 4-nitrophenyl-(3,5-di-*tert*-butylphenyl)carbamate. The hexakis-urea **1** is unexpectedly soluble in organic solvents of low polarity due to intramolecular hydrogen bonding. The hexakis-urea **1** recognizes chloride, bromide, and acetate in a 1:2 host–guest ratio and in a positive allosteric manner in $CDCl_3$. The ability of **1** to recognize dihydrogen phosphate is a unique outcome, and the structure of the associated complex, which structure contains four dihydrogen phosphate ions, was clarified by single-crystal X-ray structural analysis. However, in solution, a complex with three dihydrogen phosphate ions was identified. The dihydrogen phosphate association in $CDCl_3$ proceeds in an amphoteric allosteric manner; in a positive allosteric manner ($K_1 < K_2$) in the first step and a negative allosteric manner ($K_2 > K_3$) in the subsequent step.

Allosteric cooperativity is important for realizing complex biological processes.[1] For example, the positive homotropic allosteric association between four oxygen molecules and hemoglobin enables the efficient binding and release of molecular oxygen at appropriate organs.[2] Protein structural dynamics is the key to realizing allosteric association in nature.[3] Inspired by nature, much attention has been paid to creating artificial allosteric systems, especially for allosteric receptors.[4,5] The flexible conformational alteration of a receptor is the key to achieving allosteric recognition of guest molecules.[5,6] On the other hand, pre-organization[7] is a typical strategy used to design artificial receptors with high affinities and selectivities. Accordingly, the development of an artificial allosteric receptor that satisfies these contradictory requirements of flexibility and rigidity remains a challenging subject in supramolecular chemistry.

A hexa-substituted benzene bearing flexible methylene linkers is a soft framework with changeable and conformational flexibly; for example, the six substituents can be alternately oriented above and below the plane of the benzene ring (the *ababab* conformation), or they can all be oriented in the same direction (the *aaaaaa* conformation) (Figure 1). In the absence of interactions between substituents, the *ababab* conformation is the thermodynamically most stable; this conformation has separate cavities for guest recognition. By introducing appropriate hydrogen–bonding substituents, the *aaaaaa* conformation can become more favorable than the *ababab* conformation through the formation of intramolecular hydrogen bonds.[8] The *aaaaaa* conformation of a hexa-substituted benzene is a rigid and pre-organized conformation; consequently, hexa-substituted benzenes with appropriate hydrogen–bonding functional groups are expected to be adequate allosteric receptor structures.

Ideal positive allosteric cooperativity accompanying guest recognition occurs through the dynamic conformational transformation of the *aaaaaa* conformation into the *ababab* conformation. With this in mind, we selected ureido as a hydrogen–bonding functional group for incorporation onto the hexa-substituted benzene framework. The ureido group has been used as an anion receptor,[9] in organocatalysis,[10] as components of supramolecular polymers,[11] and in capsular assembly.[12] Some allosteric receptors have been developed for anions by appropriately arranging multiple ureido groups.[13] In this paper, we report a highly symmetrical and conformationally flexible hexakis-urea **1** as an allosteric receptor for anions; **1** recognizes typical anions in 1:2 host–guest ratios in a positive homotropic allosteric manner. Furthermore, **1** recognizes dihydrogen phosphate in a 1:3 host–guest ratio with a unique amphoteric homotropic allosteric manner; i.e., a positive allosteric manner ($K_1 < K_2$) in the first step and negative allosteric manner ($K_2 > K_3$) in the subsequent step. Single crystal X-ray analyses revealed the flexible conformations of hexakis-urea **1** and the structures of its guest-associated complexes.

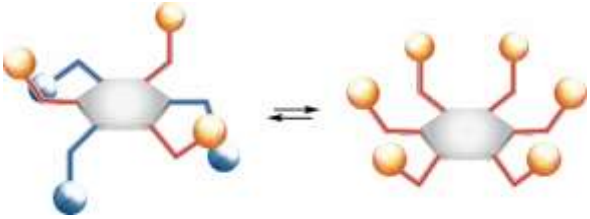

Figure 1. Schematic representation of the flexible conformation conversion of a hexa-substituted benzene: the *ababab* conformation (left) and the *aaaaaa* conformation (right).

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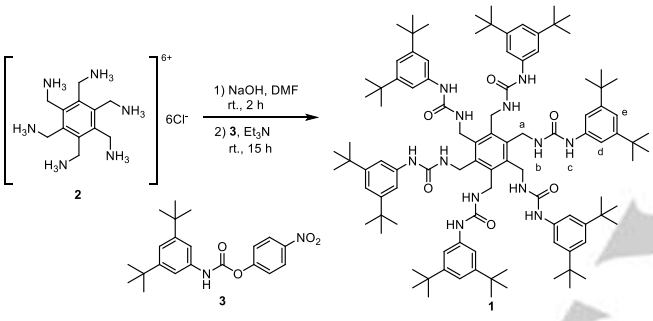
Hexakis-urea **1**, which bears six ureido groups bonded to the core benzene ring through methylene linkers, was designed as a receptor molecule for anions. The methylene groups of **1** play important roles in term of realizing flexible conformational conversion (Figure 1). The ureido groups in **1** are all oriented in the same direction in a non-polar organic solvent, which is due to intramolecular hydrogen bonding.[8] Hexakis-urea **1** is efficiently synthesized from hexakis(aminomethyl)benzene hexahydrochloride **2**[14], which was *in-situ* converted into hexakis(aminomethyl)benzene, the free-base form, by the reaction of appropriate amount of sodium hydroxide, followed by condensation with 4-nitrophenyl-(3,5-di-*tert*-butylphenyl)carbamate (**3**) to afford **1** (Scheme 1). To our delight, the desired hexakis-urea **1** was isolated in 80% yield, and no partially reacted by-products (pentakis-urea, tetrakis-urea, *etc*.) were detected. The structure of **1** was confirmed by NMR spectroscopy and mass spectrometry (MS) (Supporting Information).



Scheme 1. Synthesis of hexakis-urea **1**.

Ureidos are generally poorly soluble in organic solvents, especially organic solvents of low polarity, such as chloroform and benzene, if the hydrogen bond donors and acceptors cannot be saturated intramolecularly as in the receptor described here.[15] Their poor solubilities are obstacles that prevent their applications as supramolecular receptors. However, somewhat unexpectedly, **1** was found to be extremely soluble in organic solvents (Table S1); it was highly soluble in halogenated solvents, with its saturation concentrations in dichloromethane, chloroform, and 1,1,2,2-tetrachloroethane determined to be 11 mM, 19 mM and 60 mM, respectively. The saturation concentrations of **1** in non-polar toluene and benzene are 4 mM and 7 mM, respectively, while the solubility of **1** in polar DMSO, in which higher solubility was expected, is low, at 2.5 mM. The ^{1}H-NMR spectra of **1** in DMSO-d_6 and $CDCl_3$ are significantly different (Figures 2 and S1). The NH proton (H^b) signal of the ureido moieties in $CDCl_3$ appear down field (9.36 ppm) compared to the shift in DMSO-d_6 (6.49 ppm). The methylene protons (H^a) are split into two signals in $CDCl_3$, while they appear as a broad singlet in DMSO-d_6. These spectral differences are ascribable to conformational differences in the two solvents. The ureido moieties of **1** can freely change their orientations in DMSO-d_6, while their orientations are more rigid in $CDCl_3$ as a result of intramolecular hydrogen bonding between ureido groups. In the latter conformation, the polar ureido groups are positioned inwards and the less polar *tert*-butyl groups are positioned outwards. Solvation between the *tert*-butyl groups and organic solvents of low polarity results in the high solubility of hexakis-urea **1** in these solvents. Variable-concentration ^{1}H NMR spectra in $CDCl_3$ indicated that **1** exists in a discrete monomeric form through intramolecular hydrogen bonding (Figure S2).

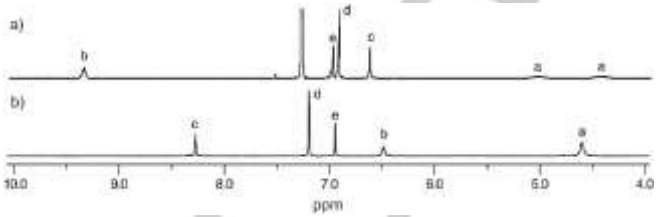


Figure 2. ^{1}H NMR spectra of **1** in a) $CDCl_3$, b) DMSO-d_6.

The intramolecularly hydrogen-bonded monomeric structure of hexakis-urea **1** was finally confirmed by single crystal X-ray analysis of a crystal prepared by the slow diffusion of cyclohexane to a $CHCl_3$ solution of **1** (**1-CHCl$_3$**) (Table S2). As shown in Figures 3a and S3, all of the ureido groups are locked by intramolecular hydrogen bonding and are aligned in the same direction to form the *aaaaaa* conformation and a bowl-shaped structure with appreciable interior space for cyclohexane encapsulation (Figure S4). The hydrogen bonds in this assembly show different lengths at the bottom of the core benzene–ring (H^b) and the mouth of the bowl (H^c), with average distances of 1.90 and 2.32 Å, respectively; the latter is substantially longer than the common value of an inter-ureido hydrogen bond (~2.00 Å). The molecular packing structure of **1-CHCl$_3$** shows no intermolecular hydrogen bonds (Figure S4e) and all ureido groups participate in the intramolecular hydrogen-bonded assembly. These results are in good agreement with the ^{1}H NMR spectrum of **1** in $CDCl_3$. Note that a chiral ureido-group conformation is formed in the crystalline phase, in which all ureido groups are directed in a left-handed manner as viewed from the bowl mouth; the C_2 crystal space group of **1** is in agreement with the observed chiral separation (Figure S4f). Such spontaneous chiral crystallization of achiral molecule has been well known phenomenon where the achiral organic molecules are assembled in an enantioselective manner through hydrogen bonding, π-π, or C-H-π interactions, giving a mixture of chiral crystal.[16] Unfortunately, we could not succeeded X-ray crystallographic analysis of the crystal of **1** possessing an opposite right-handed chirality.

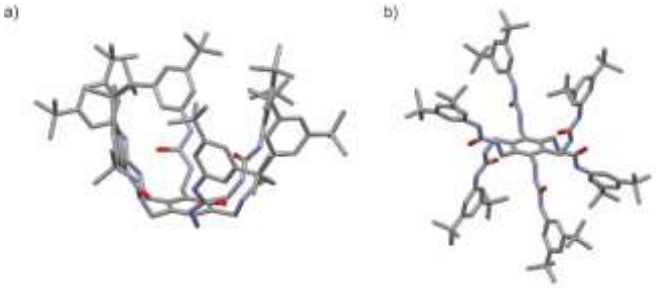


Figure 3. X-ray crystal structures of a) **1-CHCl$_3$** (the *aaaaaa* conformation from $CHCl_3$ and cyclohexane), b) **1-DMSO** (the *ababab* conformation from DMSO). All the solvated molecules are omitted for clarify.

10.1002/chem.201904241

COMMUNICATION

In marked contrast, the single crystals of **1** formed from the DMSO solution are significantly different (Figures 3b and S5, Table S3). The *ababab* conformation of **1-DMSO** reveals six ureido groups that are alternately positioned on opposite side of the plane of the benzene ring. In the crystalline phase, two pairs of ureido groups are intermolecularly hydrogen bonded to afford a ladder-like conformation; the remaining ureido pairs are intramolecularly hydrogen bonded to tightly maintain the *ababab* conformation (Figure S6). No molecule is encapsulated in the *ababab* conformer of **1-DMSO** in the crystal phase, despite the presence of cavity spaces of sufficient size.

The anion recognition properties of **1** in $CDCl_3$ were examined by acquiring and analyzing the ^{1}H NMR spectra of mixtures of **1** and tetrabutylammonium (TBA^+) salts. The chemical shifts of the protons in **1** changed upon addition of the chloride (Cl^-), bromide (Br^-), and acetate (CH_3COO^-) salts of TBA (Figure S7), while the addition of the corresponding hexafluorophosphate (PF_6^-), perchlorate (ClO_4^-), and iodide (I^-) did not result in any changes in these chemical shifts (Figure S8). A Job plot constructed by the ^{1}H NMR titration of **1** and TBACl revealed a 1:2 (**1**:Cl^-) complex stoichiometry (Figures S9 and S10). Electrospray ionization Fourier-transform ion cyclotron resonance MS (ESI FT-ICR MS)[17] of a mixture of **1** and TBACl revealed a peak at *m/z* = 855.5481 that corresponds to the $[\mathbf{1}\cdot 2Cl]^{2-}$ (Figure S11). Association constants in $CDCl_3$ were determined by nonlinear least-squares regression from the ^{1}H NMR-titrated concentrations of **1** and the chloride-bound complexes. The association constants obtained in this manner are K_1 = 21 M^{-1} for the 1:1 complex and K_2 = 230 M^{-1} for the 1:2 complex (from the 1:1 complex), with a cooperativity factor[18] ($\alpha_{12} = 4K_2/K_1$) of 44 (Table 1, and Figures S12 and S13). Positive allosteric associations with **1** were also found for the bromide (K_1 = 42 M^{-1}; K_2 = 390 M^{-1}; α_{12} = 37) and acetate (K_1 = 490 M^{-1}; K_2 = 5800 M^{-1}; α_{12} = 47) (Table 1 and Figures S14–S17).

Table 1. Association constants of **1** with anions in $CDCl_3$ and DMSO-d_6, and their cooperativity factors.[a]

anion	solvent	K_1 (M^{-1})	K_2 (M^{-1})	α_{12}[b]	K_3 (M^{-1})	α_{23}[c]
Cl^-	$CDCl_3$	21	230	44	-	-
Br^-	$CDCl_3$	42	390	37	-	-
AcO^-	$CDCl_3$	490	5800	47	-	-
$H_2PO_4^-$	$CDCl_3$	83	1300	63	6	0.005
Cl^-	DMSO-d_6	140	150	4.3	-	-
$H_2PO_4^-$	DMSO-d_6	2100	1900	3.6	-	-

[a] Association constants measured by ^{1}H NMR titration. Uncertainties are less than 15%. All anions were used as TBA salts. [b] $\alpha_{12} = 4K_2/K_1$. [c] $\alpha_{23} = K_3/K_2$.

The association dynamics of chloride, bromide, and acetate with **1** were fast in the chemical shift time scale; hence the ^{1}H NMR spectra of these mixtures are averaged. In contrast, the ^{1}H NMR spectrum of a mixture of **1** and dihydrogen phosphate ($H_2PO_4^-$) showed two sets of signals assigned to the association complex and free **1** (Figure 4a), which means that the association and dissociation of dihydrogen phosphate with **1** are sufficiently slower than the NMR timescale.

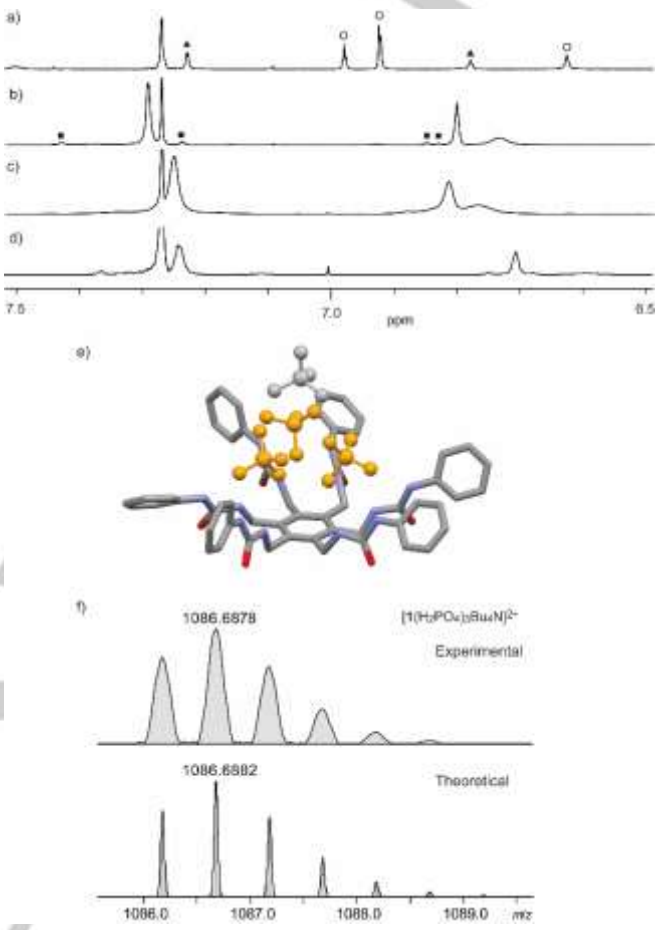


Figure 4. ^{1}H NMR spectra of **1** and $TBAH_2PO_4$ in $CDCl_3$ a) **1** (1.0 mM) + $TBAH_2PO_4$ (2.0 equiv.), b) **1** (3.0 mM) + $TBAH_2PO_4$ (3.8 equiv.), c) **1** (10.0 mM) + $TBAH_2PO_4$ (2.9 equiv.), d) **1** (10.0 mM) + $TBAH_2PO_4$ (31.2 equiv.). The typical signals of the free **1**, 1:2 complex ($\mathbf{1}\cdot 2H_2PO_4^-$), and 1:1 complex ($\mathbf{1}\cdot H_2PO_4^-$) are marked with ○, ▲, and ■, respectively. e) X-ray crystal structures of **1** + dihydrogen phosphate ($\mathbf{1}\cdot 4H_2PO_4^-$). The *tert*-butyl groups are omitted for clarify. f) ESI FT-ICR MS of 1:3 complex ($\mathbf{1}\cdot 3H_2PO_4^-$).

ESI FT-ICR MS of a mixture of **1** and $TBAH_2PO_4$ indicated the formation of a 1:2 complex (**1**:$H_2PO_4^-$), and a molecular ion peak corresponding to $[\mathbf{1}\cdot 2H_2PO_4]^{2-}$ was detected at *m/z* = 917.0532 (calcd. 917.0603) (Figure S18). The association constant ($K_{12} = K_1 \times K_2$) was calculated to be 1.07×10^5 M^{-2} by integrating the ratio of the complex ($\mathbf{1}\cdot 2H_2PO_4^-$) to free **1** (Figure 4a). The ^{1}H NMR spectrum of a mixture of **1** (3.0 mM) and $TBAH_2PO_4$ (11.4 mM) shows two sets of signals (Figure 4b); one set is readily assigned to the 1:2 complex of **1** and dihydrogen phosphate ($\mathbf{1}\cdot 2H_2PO_4^-$). The other set of signals are assigned to the 1:1 complex of **1** and dihydrogen phosphate ($\mathbf{1}\cdot H_2PO_4^-$) because the signals appear to be of lower symmetry than those of the 1:2 complex; the ureido moieties of the 1:1 complex ($\mathbf{1}\cdot H_2PO_4^-$) are magnetically non-equivalent. The existence of the 1:1 complex ($\mathbf{1}\cdot H_2PO_4^-$) was also confirmed by an ESI FT-ICR MS peak at *m/z* = 1737.1428 that corresponds to the $[\mathbf{1}\cdot H_2PO_4]^-$ molecular ion in addition to the

10.1002/chem.201904241

molecular ion peak of the 1:2 complex (Figure S19). The association constant K_2 was calculated to be 1300 M^{-1} from the integration ratio of the 1:1 to the 1:2 complex (Table 1). Finally, the association constant K_1 and the cooperativity factor α_{12} were calculated to be 83 M^{-1} and 63, respectively (Table 1).

We proposed the following mechanism to account for the observed positive allosteric recognition (Figure 5). In organic solvents of low polarity, such as $CDCl_3$, **1** is present in the *aaaaaa* conformation with all ureido groups directed in the same manner through intramolecular hydrogen bonding. The conformation of hexakis-urea **1** changes from the *aaaaaa* conformation to the alternating *ababab* conformation in the presence of a strongly-associative anion, capable of disrupting the intramolecular hydrogen bonding in **1**. Two independent anion recognition sites are formed in the *ababab* conformation, which results in strong positive allosteric cooperativity.

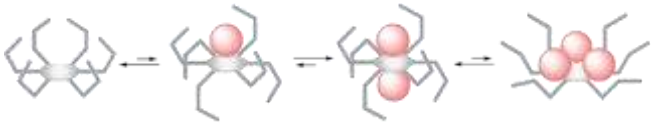


Figure 5. Schematic representation of guest recognition in hexakis-urea **1** accompanied by a conformational change.

Intramolecular hydrogen bonding in hexakis-urea **1** must play an important role in the expression of allosteric cooperativity. Accordingly, the ability of **1** to recognize anions in DMSO solution, in which intramolecular hydrogen bonds are difficult to form, was examined. DMSO-d_6 solutions of **1** were titrated using TBACl and $TBAH_2PO_4$. In both cases, the equilibrium dynamics were faster than the NMR timescale; therefore, the ^{1}H NMR spectra of these mixtures were averaged. The association constants were determined by nonlinear least-squares regression by calculating the concentrations of **1** and the anion-bound complexes. In DMSO-d_6, **1** and the anions also associated in 1:2 host–guest ratios, with moderate association constants for chloride (K_1 = 140 M^{-1}; K_2 = 150 M^{-1}; α_{12} = 4.3) and dihydrogen phosphate (K_1 = 2100 M^{-1}; K_2 = 1900 M^{-1}; α_{12} = 3.6) (Table 1 and Figures S20–S23). The total association constants ($K_1 \times K_2$) were greater in DMSO-d_6 than in $CDCl_3$ for both chloride and dihydrogen phosphate, probably because energy is required to break the intramolecular hydrogen bonds and associate the anion in $CDCl_3$.

In order to determine the structures of **1** associated with guest anions, single crystals of **1** in the presence of a large excess of $TBAH_2PO_4$ were prepared; X-ray diffractometry showed that the host-guest complex has an unexpected 1:4 structural ratio (Figures 4e and S24, Table S4).[19] The X-ray structure of **1-4H_2PO_4** clearly reveals that guest $H_2PO_4^-$ molecules are bound to **1** through intermolecular hydrogen bonds between the ureido N-H and the oxygen atoms of $H_2PO_4^-$ (Figure S25). Four $H_2PO_4^-$ molecules are encapsulated in **1** in the crystal phase, in which a pyramidal assembly of $H_2PO_4^-$ is formed and the three basal $H_2PO_4^-$ molecules are clipped by ureido groups through intermolecular N-H···O=P/O(H)-P hydrogen bonding (Figure S25a,b). It is noteworthy that the ureido-group orientations in **1-4H_2PO_4** clearly different from those of the cyclohexane-encapsulated **1-$CHCl_3$**. No intramolecular hydrogen bonds are formed between the ureido groups, and all ureido C=O groups are directed outside.

We conclude that the $H_2PO_4^-$ at the fourth vertex only binds in the crystal phase because this $H_2PO_4^-$ is bound only to the three basal $H_2PO_4^-$ units through three hydrogen bonds without interacting with any ureido group (Figure S25a and S25f). The 1:4 association in the crystal phase, and the 1:3 association in the gas and solution phases, as confirmed by MS and NMR experiments, can be rationalized by considering the substantial stabilization associated with TBA crystal packing, where three TBA molecules cap the aperture of the urea cage to the hold $H_2PO_4^-$ assembly (Figure S25c–e). ESI FT-ICR MS of a mixture of **1** and excess $TBAH_2PO_4$ indicates the formation of a 1:3 complex (**1**:$H_2PO_4^-$), with a molecular ion peak corresponding to $[\mathbf{1}\cdot 3H_2PO_4\cdot Bu_4N]^{2-}$ detected at *m*/*z* = 1086.6878 (calcd. 1086.6871) (Figure 4f). The addition of excess $TBAH_2PO_4$ to a 1.0 mM $CDCl_3$ solution of **1** showed identical ^{1}H NMR signals to that of the 1:2 host-guest complex described above. When a highly concentrated solution of **1** in $CDCl_3$ (10 mM) was titrated with $TBAH_2PO_4$, changes in the signals suggestive of the formation of a 1:3 complex were observed (Figure 4c,d). The association constant K_3 obtained for this complex by nonlinear least-squares regression was found to be 6 M^{-1} (from the 1:2 complex) (Table 1 and Figures S26 and S27). The cooperativity factor ($\alpha_{23} = K_3/K_2$) of 0.019 is indicative of a negative allosteric association in going from the 1:2 complex to the 1:3 complex. Thus, the association of hexakis-urea **1** with dihydrogen phosphate in $CDCl_3$ occurs in an amphoteric allosteric manner; the formation of the 1:2 complex from the 1:1 complex progresses in a positive allosteric manner, while the formation of the 1:3 complex from the 1:2 complex proceeds in a negative allosteric manner. To the best of our knowledge, this is the first example of an amphoteric homotropic allosteric association of guest molecule.

In conclusion, we synthesized hexakis-urea **1** in satisfactory yield. Despite having six polar ureido groups, **1** is extremely soluble in organic solvents of low polarity. Solid-state structures were determined by single crystal X-ray analyses. Hexakis-urea **1** is an anion receptor and typically two anionic molecules associated with **1**; these associations in $CDCl_3$ proceed in a positive allosteric manner due to a dynamic alteration in conformation. Furthermore, **1** associates dihydrogen phosphate in a 1:3 host-guest ratio, and this associations proceeds in an unprecedented amphoteric allosteric manner ($K_1 < K_2$, $K_2 > K_3$) (Figure 5).

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Keywords: allosteric cooperativity • anion recognition • host-guest system • hydrogen bonding • receptors

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Entry for the Table of Contents

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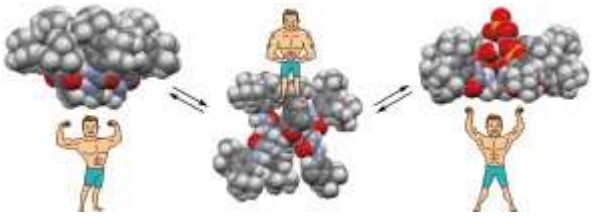

Conformationally flexible hexakis-urea **1** is an allosteric receptor for anions; it recognizes chloride, bromide, and acetate in a 1:2 host-guest ratio in a positive allosteric manner. On the other hand, dihydrogen phosphate is recognized by **1** in a 1:3 host-guest ratio in a unique amphoteric allosteric manner.

S. Kondo, J. Masuda, T. Komiyama, N. Yasuda, H. Takaya, M. Yamanaka**

Page No. – Page No.

Amphoteric Homotropic Allosteric Association between a Hexakis-Urea Receptor and Dihydrogen Phosphate