Accepted Manuscript

A novel C_{3v}-symmetric molecular clip with tris(diamide) recognition sites on trindane platform for $H_2PO_4^-$ recognition

Gi-Dong Kim, Shilpa Bothra, Suban K Sahoo, Heung-Jin Choi

PII: S0040-4039(18)30369-1
DOI: https://doi.org/10.1016/j.tetlet.2018.03.055
Reference: TETL 49824

To appear in: *Tetrahedron Letters*

Received Date: 14 February 2018
Accepted Date: 19 March 2018

Please cite this article as: Kim, G-D., Bothra, S., Sahoo, S.K., Choi, H-J., A novel C_{3v}-symmetric molecular clip with tris(diamide) recognition sites on trindane platform for $H_2PO_4^-$ recognition, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.03.055

A novel C_{3v}-symmetric molecular clip with tris(diamide) recognition sites on trindane platform for $H_2PO_4^-$ recognition

Gi-Dong Kim[a], Shilpa Bothra[b], Suban K Sahoo[b] and Heung-Jin Choi[a,*]

[a] *Department of Applied Chemistry, Kyungpook National University, Daegu, 41566, Korea.*

[b] *Department of Applied Chemistry, SV National Institute of Technology, Surat-395007, Gujarat, India.*

Abstract

To avoid the deprotonation events occurred in the receptor upon recognition of basic anions, a novel C_{3v}-symmetric anion receptor **2** with two amide groups appended in each arm was designed and synthesized by using the trindane tricarboxylic acid as tripodal molecular framework. The anion recognition ability by **2** was examined by ^{1}H NMR titration study in DMSO-d_6, which revealed that the addition of $H_2PO_4^-$ guests caused substantial downfield shifts of the amide-NH protons peaks due to the formation of a host-guest complex in 1:1 binding stoichiometry with the estimated binding constant (K_a) of 244 M^{-1}. No noticeable binding of **2** was observed with other tested anions such as F^-, Cl^-, Br^-, I^-, NO_3^- and HSO_4^- under similar conditions.

Keywords: C_{3v} symmetric anion receptor; Trindane; $H_2PO_4^-$ recognition; ^{1}H NMR.

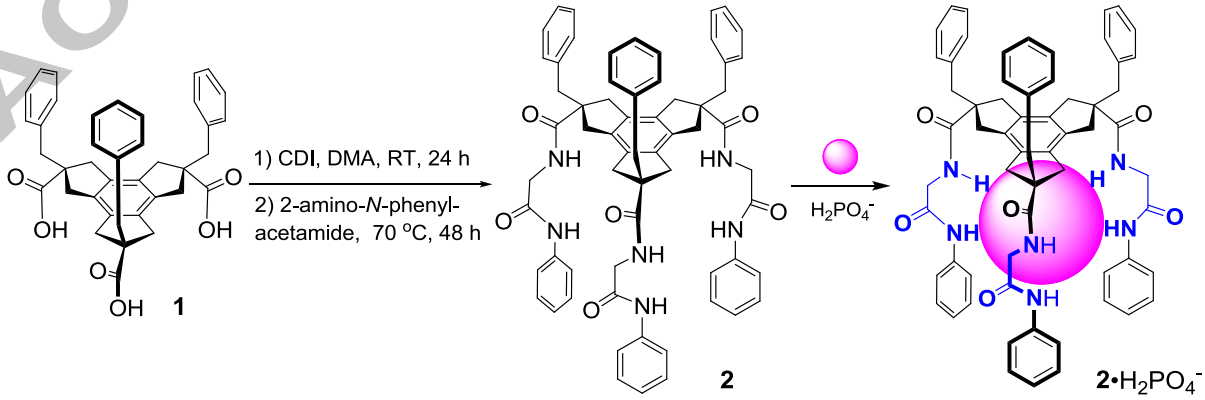
*Corresponding author: Tel.: +82 (53) 950 5582; fax: +82 (53) 950 6594; e-mail address: choihj@knu.ac.kr (H.-J. Choi).

Anions are ubiquitous and well known to play important roles in a wide array of chemical, biological and environmental processes [1,2]. Among the various bioactive anions, the phosphates are the most important anions due to their key roles in various information processing, energy storage, and signal transduction [3]. It is a component of adenosine triphosphate (ATP), a fundamental energy source in living things and is deeply involved in DNA duplication and transcription [4]. Phosphate ions are widely employed in the fertilizers which is considered as the main nutrients of plants and animals [5,6]. Excessive level of phosphate ions causes detrimental effect to the environment and can lead to eutrophication causing disruption of aquatic life cycles [7,8]. Hence, the detection and recognition of phosphate ions concentration in the soil and aqueous samples are of great significance for the controlling and guarding against the eutrophication and human disease occurrence [9]. Also, determining phosphate ions concentrations in body fluids can help to diagnose various health problems such as hyperparathyroidism, vitamin D deficiency and Fanconi syndrome [5].

The advancement of the host-guest chemistry in the recent few decades led to the development of numerous molecular receptors for the selective recognition and sensing of target anionic guest. Most of the reported neutral receptors possess groups like amide, urea, thiourea, imidazole, indole, amine, pyrrole and sulphonamide moieties with hydrogen bond donor functionalities whereas the cationic receptors are derived from ammonium, guanidium, quinolinium, phosphonium protonated quinoxaline salts, with electrostatic interaction between the anionic guest and cationic receptors [10,11]. However, the factors like high hydration energy and versatile geometry of anions have created several challenges to develop suitable receptor for the selective recognition of target anion. For example, the recognition of hydrogen phosphate may be interfered with the most basic anions like fluoride which can deprotonate the hydrogen bond donor functionalities of the receptor. Therefore, there is a search of new receptor which can selectively recognize the bioactive hydrogen phosphate

anion without any interference from the other anions. In designing new receptor for hydrogen phosphate, efforts are made to develop multi-dimensional molecular scaffolds possessing adequate flexibility and preorganized structure with a suitable cavity to accommodate the tetrahedral shaped anion through multiple hydrogen binding sites. Various multifunctional anion receptors with linear, dipodal and tripodal structures are reported for the selective recognition of hydrogen phosphate. Among the various multi-dimensional molecular scaffolds, much emphasis have been given to develop preorganized C_{3v} symmetric tripodal receptors with multiple binding sites, increase binding dimension because the tripodal conformation has the ability to form spheroidal cavity to encapsulate anions of perfect fitting [12,13].

Our group have demonstrated various C_{3v}-symmetric anionic receptor for $H_2PO_4^-$ containing urea/thiourea group at each lower feet of trindane framework that shows a moderate binding affinity toward an anionic guest and also deprotonated upon excess addition of fluoride anion [14-17]. Continuing our research in the development of the structurally modified anion receptor based on C_{3v}-symmetric trindane framework with a preorganized anion binding cavity, herein, a new tripodal anion receptor **2** possessing tris(diamide) recognition sites on trindane platform was synthesized (**Scheme 1**) and its anion recognition ability was examined by ^{1}H NMR in DMSO-d_6.



Scheme 1. Synthesis of the C_{3v}-symmetric anion receptor **2**.

The C_{3v} trindane-tricarboxylic acid **1**, *cis,cis,cis*-2,5,8-tribenzyltrindane-2,5,8-tricarboxylic acid was prepared by following our reported method, hydrolyzing trindane tricarboxylate ester. [14, 17, 19] The known diamide podal moiety, 2-amino-*N*-phenylacetamide is prepared from readily available compounds. Boc-Gly-OH and aniline was coupled via activation of carboxylic acid with *N*,*N*'-carbonyldiimidazole (CDI) in DMA to yield Boc-2-amino-*N*-phenylacetate, which was treated with trifluoroacetic acid to deprotect Boc group to give 2-amino-*N*-phenylacetamide in high yield. [SI]

The tripodal receptor **2** possessing three diamide-podants on trindane platform was synthesized first by treating with CDI to form the active intermediate acylimidazole, which then react with the amine nucleophile, 2-amino-*N*-phenylacetamide at 70 ºC for 48 hours. To complete the reaction on the threefold multi-reaction sites, the reaction condition was optimized for reaction period, temperature and dryness of solvent and reagents. The carbonyl activating reagent CDI was chosen because of sterically small imidazole moiety and easy removal of imidazole byproduct from the amide bond formation. In optimizing process other polar and bulky active ester intermediates from carbodiimide type reagents hindered to block the second and third attacks of the amine nucleophiles by intramolecular hydrogen bonding interaction. It was apparent that the reaction condition require unusually high temperature to overcome the interaction between carbonyl activating intermediate and the amine nucleophile with bulky and polar functional groups. The moderate yield of the receptor **2** was still due to laborious separation from the mono- and di-substituted incomplete products which have similar structure and chemical properties. The ^{1}H NMR spectrum **2** revealed the disappearance of –COOH protons peak of **1** at δ 12.47 and the appearance of two amide protons peaks at δ 9.95 and δ 8.23 ppm. Also, the C_{3v}-symmetry conformation of the trindane derivative **2** was confirmed from the two sets of doublets at δ 3.08 and 2.78 ppm with the

coupling constant of ^{2}J = 15.5 Hz assigned for the two diastereotopic benzylic protons and a singlet for the methylene groups of benzyl groups at 2.96 ppm. In ^{13}C NMR, the peaks for the two carbonyl groups present in **2** were observed at δ 175.8 and 167.9 ppm. These results along with the mass data confirmed the formation of tris(diamide) based anion receptor **2**. The possible 3D structure of the receptor **2** was proposed through the DFT calculations in the gas phase by using the B3LYP/6-31* method. As shown in Figure 1, the three appended arms of **2** are interconnected by multiple intrastand hydrogen bonding which provides a C_{3v}-symmetry structure and also not appreciable conformation adjustment is required in **2** to accommodate the perfect fit anions. The molecular electrostatic map (MEP) of **2** reveals that the most positive region located in blue color was observed over the amide protons, which are expected to encapsulate the perfect fit anion by forming the hydrogen bonds.

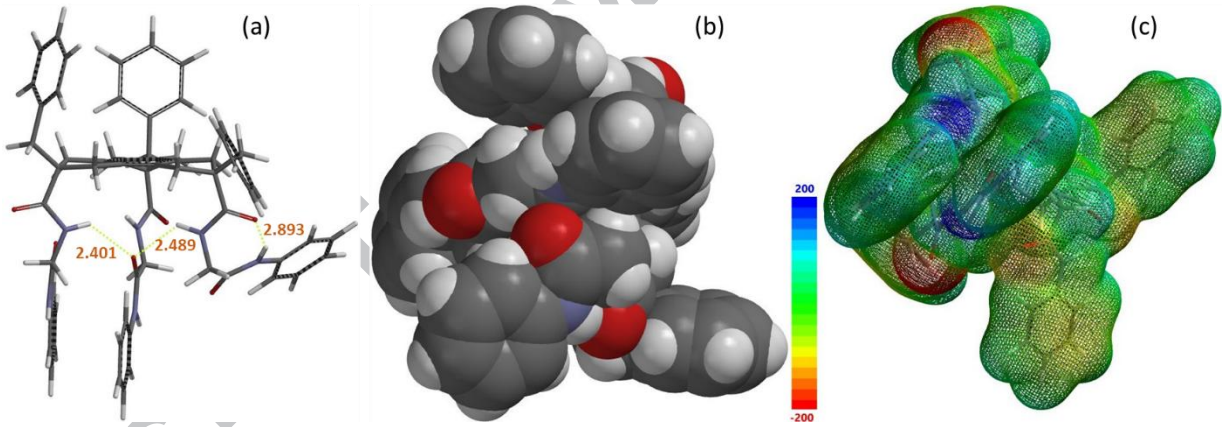


Figure 1. DFT computed structure of the receptor **2**: (a) tube model showing the intrastand hydrogen bonding (Å), (b) space filling model showing the compactness of the three appended arms, and (c) molecular electrostatic map (MEP).

The anion recognition ability of the tris(diamide) receptor **2** (4 mM) was investigated by the ^{1}H NMR method by adding ten equivalents of various *n*-tetrabutylammonium (TBA) anions (TBAX, where X = F^-, Cl^-, Br^-, I^-, NO_3^- , HSO_4^- and $H_2PO_4^-$) in DMSO-d_6. As shown in Figure 2, there is no noticeable shift in the ^{1}H NMR spectrum of **2** was observed in the presence of anions such as F^-, Cl^-, Br^-, I^-, NO_3^- and HSO_4^- due to the very weak interaction

with the receptor **2**. However, the amide protons peaks of **2** at δ 9.95 and δ 8.23 ppm were broadened and shifted to downfield region respectively to δ 10.91 and δ 9.13 ppm in the presence of $H_2PO_4^-$ anion. Also, a slight downfield shift of the peak at δ 7.59 ppm of the aromatic protons closer to the amide groups was observed. The selective affinity of **2** towards $H_2PO_4^-$ anion may be attributed to the tetrahedral geometry that fitted well within the tripodal cavity created by the tris(diamide) arms. Also, the downfield shift of the amide protons peaks of **2** indicate the formation of a host-guest complex with the $H_2PO_4^-$ anion among the other tested anions through multiple hydrogen bonding interactions.

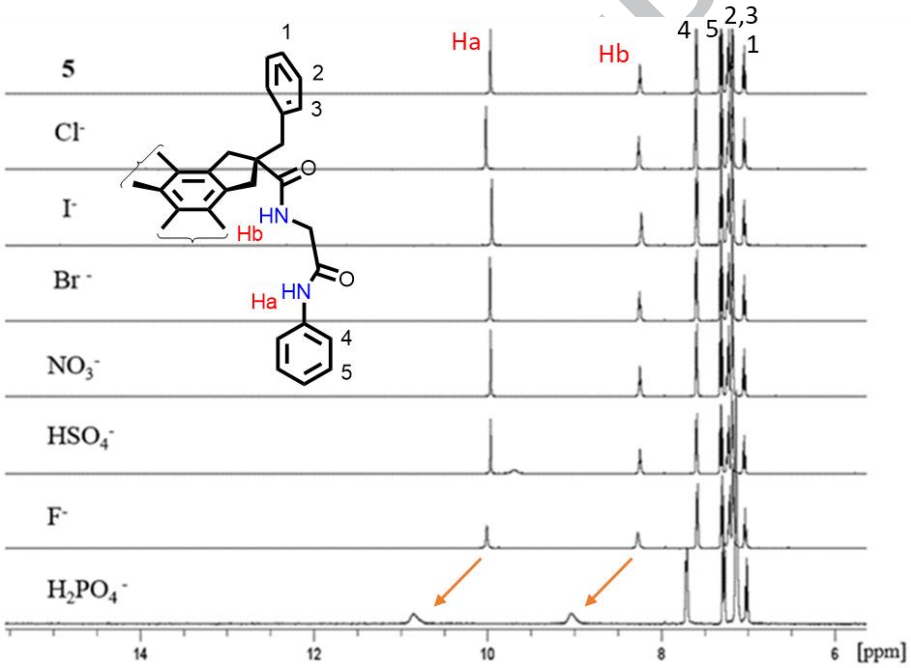


Figure 2. Partial ^{1}H NMR spectral changes of a DMSO-d_6 solution of **2** (4 mM) upon addition of ten equivalents of different anions.

The ^{1}H NMR titration of **2** (4 mM) was performed by successive addition of incremental addition of *n*-tetrabutylammonium dihydrogen phosphate (TBA•H_2PO_4) in DMSO-d_6 (Figure 3a). Similar titrations were also performed with some non-selective anions to check the changes in the tris(diamide) protons peaks with the successive increasing

concentrations of the anions like F^-, HSO_4^-, Br^- and NO_3^- (Fig. 3b). The results shown in Figure 3 indicate that upon addition of $H_2PO_4^-$ to **2** solution resulted in a significant downfield shift for both amide-NH peaks without any appreciable shift in the other protons peaks. It may be expected that the receptor **2** retained the C_{3v} symmetry and the interactions of amide-NH groups of the receptor with $H_2PO_4^-$ in solution formed the host-guest complex. The complexation-induced shift of the amide-NH NMR signals were fitted by using a nonlinear least squares regression program WinEQNMR [18], which gave the best fit for a 1:1 binding model with the estimated binding constant (K_a) of 244 M^{-1}.

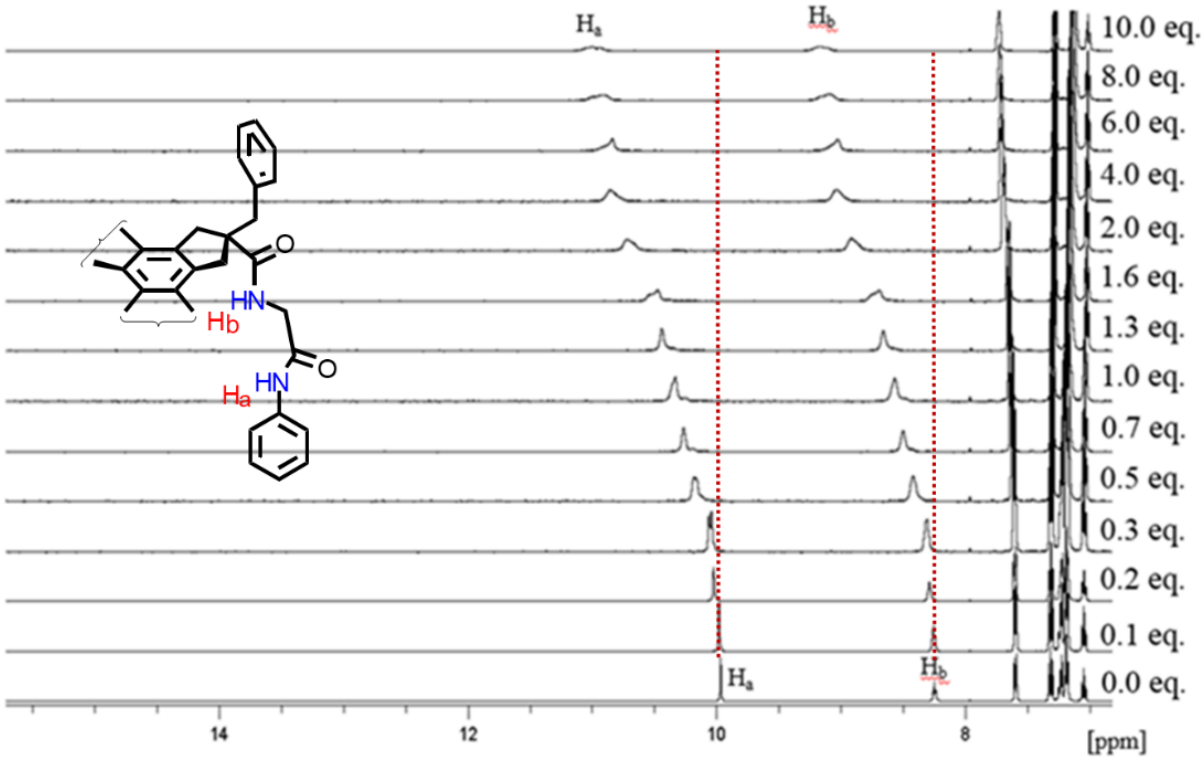


Figure 3a. Partial ^1H NMR spectral changes of a DMSO-d_6 solution of **2** (4 mM) upon addition of TBA•H_2PO_4.

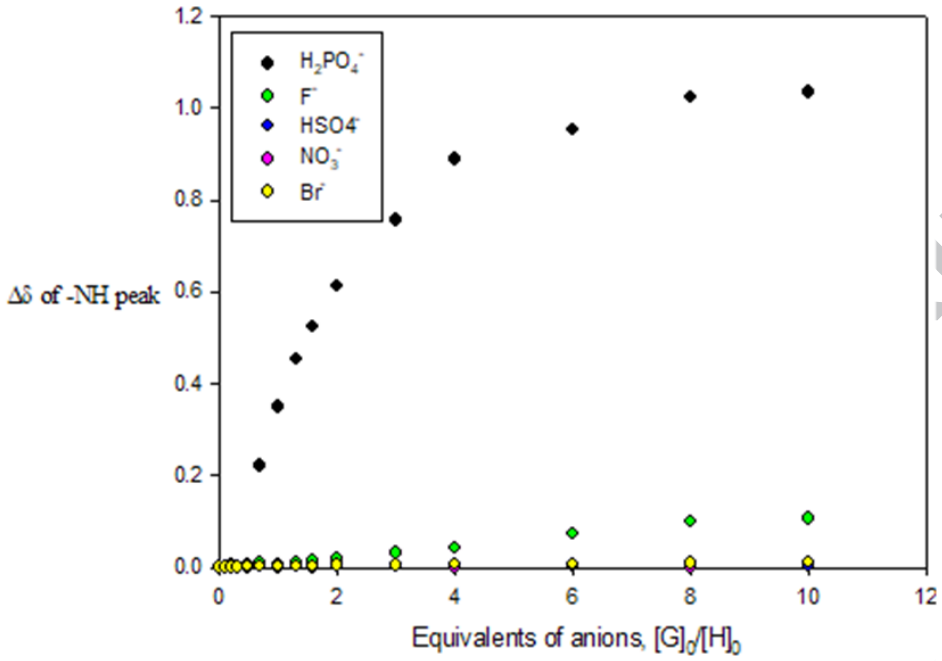


Figure 3b. NMR titration curves of tris(diamide) receptor **2** with TBA salts of anionic guests in DMSO-d_6 at 25 ^{o}C ($[H]_o$ = 4.0 mM, $[G]_o$ = 40.0 mM; axis: CIS of the amide proton). (♦, $H_2PO_4^-$; ♦, F^-; ♦, HSO_4^-; ♦, Br^-; ♦, NO_3^-).

Based on the experimental evidences, the interactions of **2** with $H_2PO_4^-$ was further evaluated by density functional theory (DFT) calculations. The different 3D views of the optimized structure of the **2**•$H_2PO_4^-$ complex are shown in Figure 4. The estimated binding energy for $H_2PO_4^-$ was 21.29 kcal/mol to form the host-guest complex, where the host arrange its three appended arm to a perfect C_{3v} symmetry in order to encapsulate the $H_2PO_4^-$ anion. As shown in Figure 4a, the $H_2PO_4^-$ anion is wrapped within the tripodal cavity of **2** *via* six NH···O hydrogen bonds (1.799–2.154 Å). Three of the four oxygen atoms present in $H_2PO_4^-$ anion are held by the six amide-NH groups present in the receptor **2**. The MEP calculation of **2**•$H_2PO_4^-$ complex revealed an internal change transfer between the $H_2PO_4^-$ anion and the receptor **2**, which resulted in the decrease in receptor **2** band gap ($\Delta E = E_{LUMO}$-

E_{HOMO}) from 6.71 eV to 4.79 eV upon formation of **2**•$H_2PO_4^-$ complex.

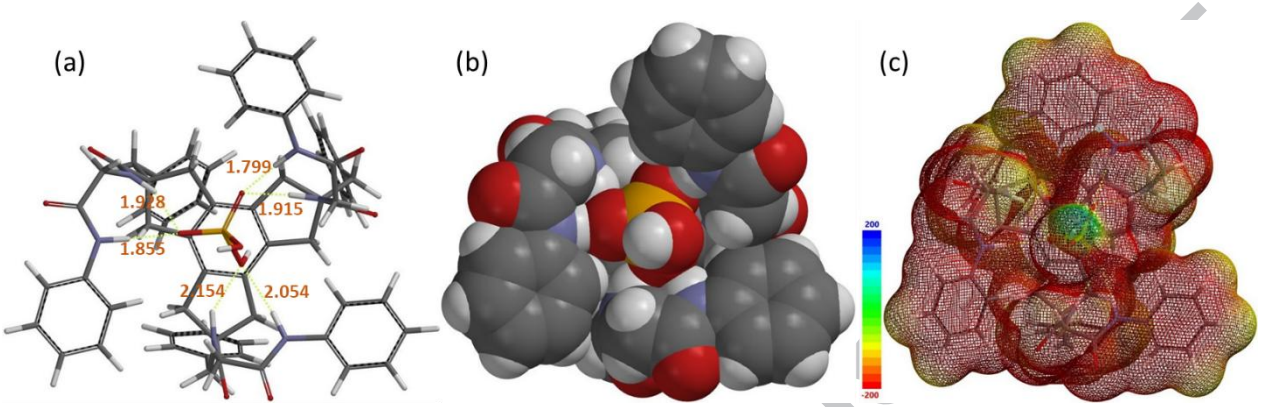


Figure 4. DFT computed structure of **2**•$H_2PO_4^-$ complex: (a) tube model showing the hydrogen bonding (Å) between **2** and $H_2PO_4^-$, (b) space filling model showing the compactness during the encapsulation of $H_2PO_4^-$ by the three appended arms, and (c) the molecular electrostatic map (MEP).

In conclusion, a new C_{3v} symmetrical anion receptor **2** was synthesized from the trindane tripodal platform possessing six amide-NH groups to recognize the anionic guests. This tris(diamide) receptor **2** is structurally analogous to the numerous anion receptors reported with the urea/thiourea recognition unit, but the inherent selectivity towards the bioactive $H_2PO_4^-$ anion and silent towards the other oxo-anions and basic halides makes the receptor **2** unique. The flexibility of the tris(diamide) arms in **2** provides a perfect tripodal cavity to encapsulate the $H_2PO_4^-$ anion *via* six NH···O hydrogen bonds. The present research outcomes will accelerate many more research on developing new multi-dimensional anion receptors by using the tris(diamide) arms in different tripodal platform with varying flexibility. Also, the selective recognition of **2** towards $H_2PO_4^-$ anion will gives new direction for the designing of optically active receptors to detect $H_2PO_4^-$ anion, and to study its extraction and transport properties.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2017R1D1A1B03032108).

Supplementary data

Supplementary data associated with this article can be found, in the online version,

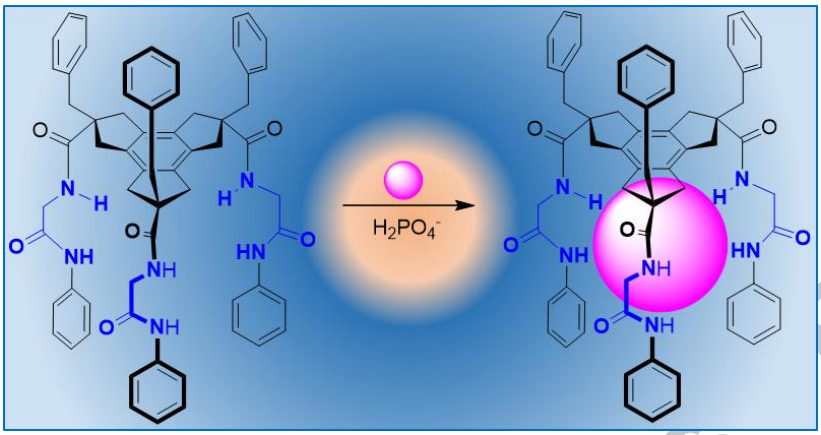
References

1. P.A. Gale, C.C. Tong, C.J. Haynes, O. Adeosun, D.E. Gross, E. Karnas, E.M. Sedenberg, R. Quesada, J.L. Sessler, *J. Am. Chem. Soc.*, 2010, 132, 3240-3241.
2. C.-H. Lee, H. Miyaji, D.-W. Yoon, J.L. Sessler, *Chem. Commun.*, 2008, 24-34.
3. I.A. Azath, P. Suresh, K. Pitchumani, Sensors and Actuators B Chem., 2011, 155, 909-914.
4. T. Tabary, L.-Y. Ju, J.H. Cohen, *J. Immunol. Methods*, 1992, 156, 55-60.
5. Z. Zou, J. Han, A. Jang, P.L. Bishop, C.H. Ahn, *Biosens. Bioelectron.*, 2007, 22, 1902-1907.
6. R. Liang, M. Liu, L. Wu, Reactive and Functional Polymers, 2007, 67, 769-779.
7. J. Penuelas, B. Poulter, J. Sardans, P. Ciais, M. Van Der Velde, L. Bopp, O. Boucher, Y. Godderis, P. Hinsinger, J. Llusia, *Nat. Commun.*, 2013, 4, 2934.
8. L.S.B. Upadhyay, N. Verma, *Biosens. Bioelectron.*, 2015, 68, 611-616.
9. X. Jia, D. Chen, L. Bin, H. Lu, R. Zhang, Y. Zheng, *Sci. Rep.*, 2016, 6, 27728.
10. S. Sen, M. Mukherjee, K. Chakrabarty, I. Hauli, S.K. Mukhopadhyay, P. Chattopadhyay, *Org. Biomol. Chem.*, 2013, 11, 1537-1544.
11. N. Kaur, G. Kaur, U.A. Fegade, A. Singh, S.K. Sahoo, A.S. Kuwar, N. Singh, *TrAC*

Analyt. Chem., 2017, 95, 86-109.

12. R. Dutta, P. Ghosh, *Chem. Commun.*, 2014, 50, 10538-10554.
13. R. Dutta, P. Ghosh, *Chem. Commun.*, 2015, 51, 9070-9084.
14. H.-J. Choi, Y.S. Park, S.H. Yun, H.-S. Kim, C.S. Cho, K. Ko, K.H. Ahn, *Org. Lett*., 2002, 4, 795-798.
15. Y.S. Park, S.-H. Bang, H.-J. Choi, *Tetrahedron Lett.*, 2013, 54, 6708-6711.
16. S.K. Sahoo, G.-D. Kim, H.-J. Choi, *J. Photochem. Photobiol. C Photochem. Rev.*, 2016, 27, 30-53.
17. W. Kim, S.K. Sahoo, G.-D. Kim, H.-J. Choi, *Tetrahedron*, 2015, 71, 8111-8116.
18. M.J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311-312.
19. W. Kim, S. K. Sahoo, G.-D. Kim, H.-J. Choi, *RSC Adv.*, 2016, 6, 7872-7878.

Graphical Abstract



Highlights

- A novel tripodal C_{3v}-symmetric anion receptor **2** with two amide groups appended in each arm of trindane tricarboxylic acid was synthesized.
- The anion recognition ability by **2** was examined by ^{1}H NMR in DMSO-d_6.
- Addition of $H_2PO_4^-$ guests caused substantial downfield shifts of the amide-NH protons peaks of **2**.
- Receptor **2** formed a host-guest complex with $H_2PO_4^-$ in 1:1 binding stoichiometry with the estimated binding constant (K_a) of 244 M^{-1} in DMSO-d_6.