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Phospinate selective hosts and importance of C-H hydrogen bonding for affinity modulation toward anion guests

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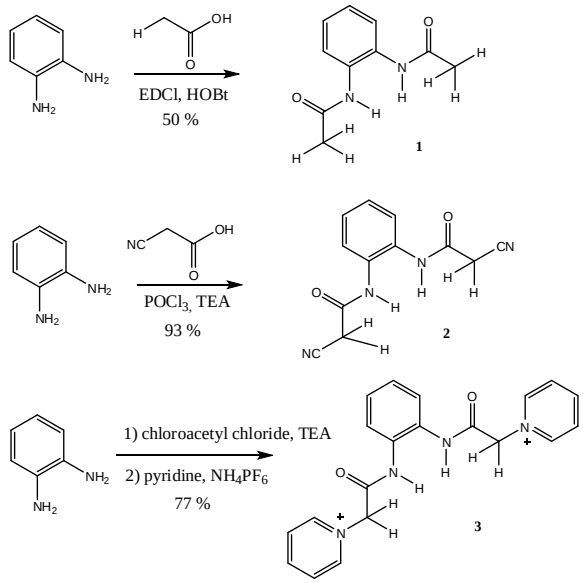
ABSTRACT

Even though phosphinate and its analogs are very important guests in nature, the artificial receptors which are capable of selective recognition of phosphinate are rare. Here, we report a series of acetate and phosphinate selective hosts (**1**, **2** and **3**) which utilize amide N-H and aliphatic C-H groups as hydrogen bonding donors. In this series of receptors, even though the amide N-H hydrogen bonding element was found to be the most significant, by varying the polarity of C-H group, the magnitude of recognition could be modulated considerably. The affinities of host **3** against all the tested anion guests showed significantly higher affinities compared with those of hosts **1** and **2**, and this could be attributed to the difference of C-H group polarities among the receptors **1**, **2** and **3**. C_α-H hydrogen in host **3** is the most highly polarized by the charged pyridinium group. Therefore, it is the strongest host in this series of hosts. From the experiments shown here, we demonstrated the importance of C-H hydrogen bonding element as a decisive modulating moiety for anionic recognition.

As an attempt to study anion receptors having weak C-H hydrogen bonds, we have reported various new anion receptors with C-H hydrogen bonds.[1] Among them, we reported phosphinate selective receptors, which utilized amide N-H, pyrrole N-H and vinyl C-H as hydrogen bond donors.[2] In these receptors, the strength of association constants could be controlled by the polarity of vinyl C-H. The receptors for phosphinate have been rarely reported even though phosphinates are related with antifolates[3] and used for preventing and/or treating metabolic diseases such as obesity, NASH (nonalcoholic steatohepatitis), hypercholesterolemia and hyperlipidemia. They are also associated with conditions such as atherosclerosis, coronary heart disease, impaired glucose tolerance, metabolic syndrome X and diabetes.[4] In this work, we have designed and synthesized receptors **1**, **2** and **3** to develop new anion receptors selective for phosphinate. These receptors utilize both amide N-H and alpha C-H (C_α-H) to the carbonyl group. Since the difference of three receptors (**1**, **2** and **3**) is due to the substituent group variation attached to the alpha carbon (C_α) to the carbonyl group, the strength of association depends mainly on the polarity of C_α-H bond. Receptor **2** has cyano group at the C_α position. Since this group is an electron withdrawing group, enhanced molecular recognition toward anion guest was expected. Receptor **3** has positively charged pyridinium at the C_α position. Therefore, the highest binding constant was expected. The binding phenomena of these receptors were monitored by ^{1}H NMR and fluorescence spectra.

For the synthesis of receptors **1** and **2**, 1,2-phenylenediamine was reacted with acetic acid or cyanoacetic acid. For the synthesis of receptor **3**, the product from the reaction between 1,2-phenylenediamine and chloroacetyl chloride was reacted further with pyridine (Scheme 1).



Scheme 1. Synthetic procedure for anion receptors **1**, **2** and **3**.

The ability of receptor **3** to recognize dimethyl phosphinate was studied by standard ^{1}H NMR titration experiments in DMSO-d_6 using a constant host concentration (2 mM) and increasing concentrations of dimethyl phosphinate. The addition of tetrabutylammonium dimethyl phosphinate salt to the solution of receptor **3** in DMSO-d_6 resulted in a downfield shift of amide N-H, and C_α-H peaks. For example, amide N-H peak moved from 10.10 ppm to 12.24 ppm and C_α-H peak moved from 5.62 ppm to 5.91 ppm (Figure 1). The stoichiometry between receptor **3** and

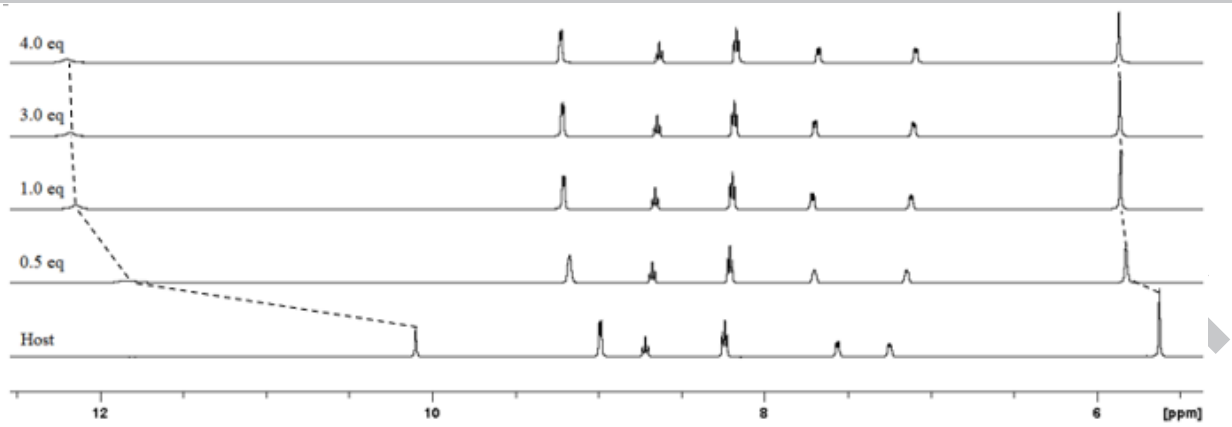


Figure 1. ^{1}H NMR spectra of 2 mM DMSO-d_6 solution of receptor **3** with increasing amounts tetrabutylammonium dimethyl phosphinate

dimethyl phosphinate was determined to be 1:1 using ^{1}H NMR Job plot in DMSO-d_6 (Figure 2)

Analysis of chemical shift utilizing EQNMR[5] gave the association constant. The association constant calculated was 6.6 × 10^{3} M^{-1} from ^{1}H NMR titration, respectively.

Receptor **2** showed lower association constant for dimethyl phosphinate than that of receptor **3** as expected. For example, the association constant between receptor **2** and dimethyl phosphinate calculated was 1.3 × 10^{2} from ^{1}H NMR titration. The affinity of receptor **2** and **3** for the anion can be attributed to N-H and C_α-H hydrogen bond and the lower association of receptor **2** can be explained with lower polarity of C_α-H bond. However, in the case of receptor **1**, only N-H bond was clear to participate in the binding event. Since the contribution of C_α-H was very small, it was not obvious whether this bond is involved (Figure 3). Only N-H bond was clearly found to participate in the binding event. Therefore, receptor **1** had the weakest affinity for the dimethyl phosphinate. These results indicate that the strength of association of dimethyl phosphinate depends on the polarity of C_α-H bonds in these receptors

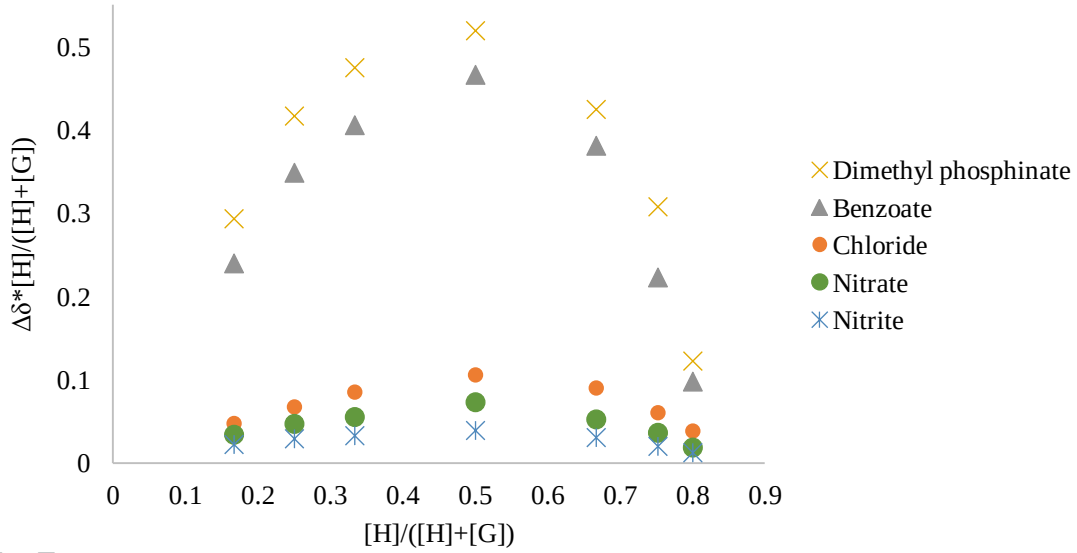


Figure 2. Job plots of receptor **3** with tetrabutylammonium anion salts obtained by ^{1}H NMR spectroscopy

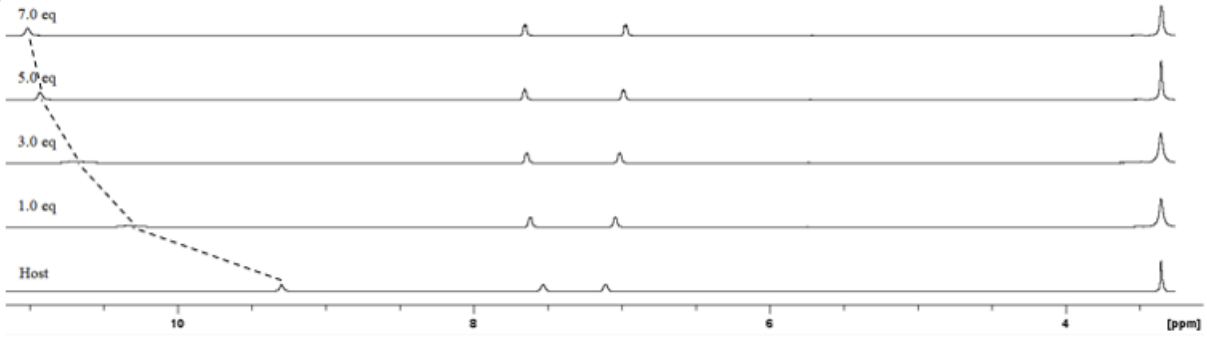
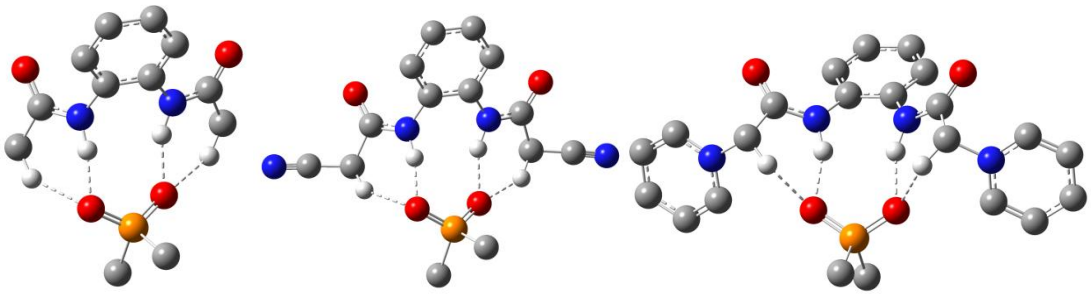


Figure 3. ^{1}H NMR spectra of 2 mM DMSO-d_6 solution of receptor **1** with increasing amounts tetrabutylammonium dimethyl phosphinate



Host 1 **Host 2** **Host 3**

Figure 4. Optimized geometries of phosphinate complexes with host **1**, **2**, and **3**. Note that the structures were optimized in the gas phase.

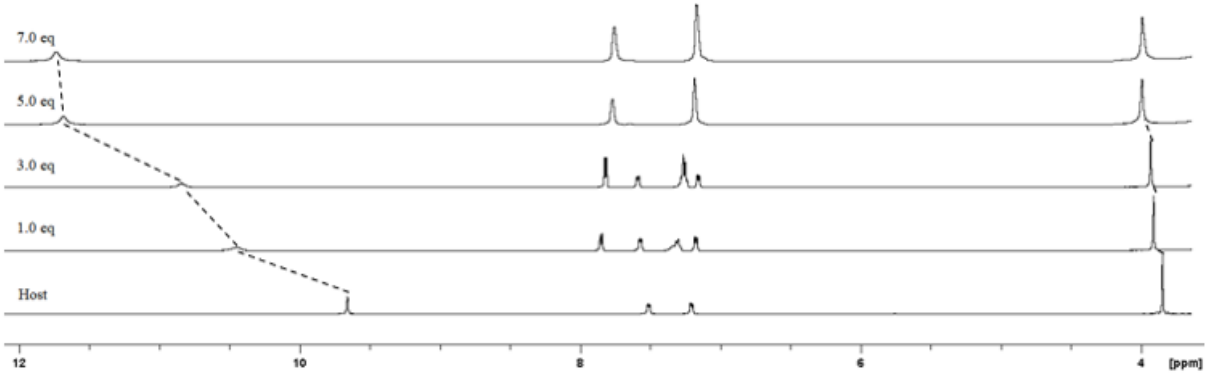


Figure 5. ^{1}H NMR spectra of 2 mM DMSO-d_6 solution of receptor **3** with increasing amounts tetrabutylammonium benzoate

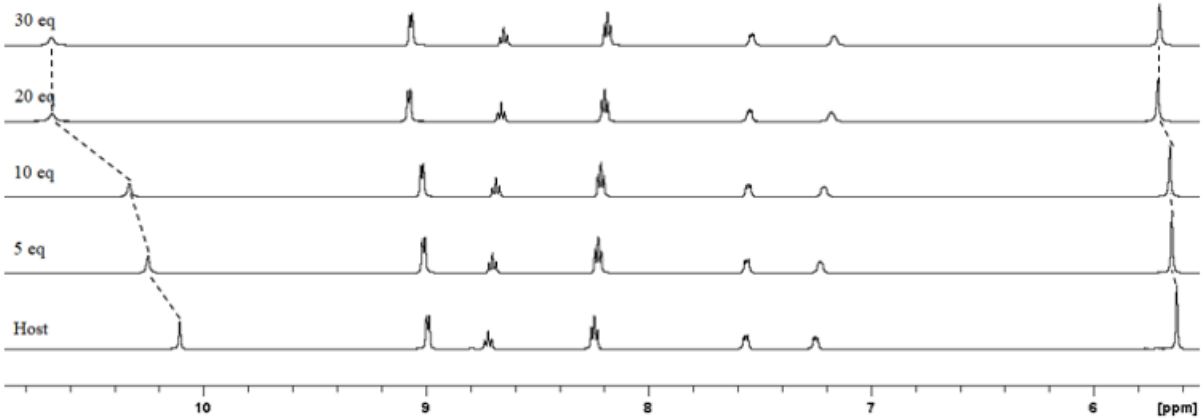


Figure 6. ^{1}H NMR spectra of 2 mM DMSO-d_6 solution of receptor **3** with increasing amounts tetrabutylammonium nitrite

To understand more precisely how the binding events happened, we studied the binding poses with computer simulations using density functional theory. Initial geometries for phosphinate complexes were set utilizing the information from experimental spectra. All the calculations have been performed with Gaussian 09 suite of programs.[6] We have used popular hybrid B3LYP functional[7] with extensive basis sets of 6-311G(d,p). All the geometries were fully optimized without any constraints and later confirmed to be at the local minima in energy hypersurface by second derivative calculations with respect to coordinate. Solvation effects were considered with polarizable continuum model (PCM)[8] using dielectric constant of DMSO. Partial charges were evaluated using natural population analysis scheme.[9] For geometry inspection, GaussView5.0 was used. For host **1**, the modelled structure might not be accurate since the participation of C_α-H hydrogen in the binding event is not clear from NMR experiments. There could be some intervention of solvent molecules (DMSO). Since the structures are optimized in the gas phase, in all modelled structures, C_α-H hydrogens seemed to play roles in molecular recognition events. The optimized geometries are shown in Figure 4. The average distance between C_α-H hydrogen and complexed phosphinate oxygen are 2.249, 2.187 and 2.098 Å, for host **1**, **2** and **3**, respectively. Therefore, it seems clear that as the polarity of C_α-H gets higher, the hydrogen bonding distance (C_α-H---O-phosphinate) becomes shorter, and the interaction between them gets stronger.

This is also consistent with calculated binding energy. In DMSO solvent as well as in gas phase, host **3** has the highest affinity toward phosphinate. The binding energies were calculated using various models. Starting from mere electronic energy, basis set superposition error correction was considered, and thermal free energy was also considered. Finally, solvent effect was also considered using polarization continuum model approximation. The calculated relative complexation energies are summarized in Table 1. As shown in Table 1, in every model, host **3** has the highest affinity toward phosphinate, consistent with experimental findings.

Phenyl phosphinate and diphenyl phosphinate gave similar results with dimethyl phosphinate except that they showed lower association constants than dimethyl phosphinate for the receptors **1**, **2** and **3**.

^{1}H NMR titration of receptor **3** with benzoate in DMSO-d_6 showed downfield shift of amide N-H, and C_α-H peaks. For example, amide N-H peak moved from 10.10 ppm to 12.51 ppm and C_α-H peak moved from 5.62 ppm to 5.82 ppm (Figure 5), which suggests formation of hydrogen bonds

Table 1. The calculated complexation energies of phosphinate with three hosts (**1**, **2** and **3**)

	ΔE	ΔE_{BSSEC}	ΔG_{BSSEC}	ΔG_{DMSO}
Host 1	-43.3	-35.1	-23.3	-7.9
Host 2	-56.9	-49.1	-36.1	-11.0
Host 3	-184.0	-175.3	-159.3	-129.9

ΔE is electronic energy. ΔE_{BSSEC} is electronic energy with basis set superposition error correction (BSSEC). ΔG_{BSSEC} is Gibbs free energy after thermal correction to ΔE_{BSSEC} ΔG_{DMSO} denotes binding energy in DMSO solution using polarizable continuum (PCM) model. Units are in kcal/mol.

Table 2. Association constants (M^{-1}) of receptors **1**, **2** and **3** with various anions in DMSO

Anion	**1**	**2**	**3**
CH_3COO^-	1070	2333	*DP
$C_6H_5COO^-$	387	763	5438
$(CH_3)_2POO^-$	964	1321	6671
$(C_6H_5)HPOO^-$	209	239	2788
$(C_6H_5)_2POO^-$	353	975	4188
NO_2^-	*NB	NB	841
NO_3^-	NB	NB	215
Cl^-	NB	NB	448
Br^-	NB	NB	67

The numbers in the parenthesis are association constant from fluorescence titration. *DP: deprotonation, *NB: nonbinding

The stoichiometry between receptor **3** and benzoate was determined to be 1:1 (Figure 2). The association constant calculated from ^{1}H NMR titration was 5.4×10^3 M^{-1}. Unfortunately, only deprotonation was observed from ^{1}H NMR titration of receptor **3** with acetate in DMSO-d_6. Similar behaviors were observed with receptors **1** and **2**. Receptors **1** and **2** showed lower association constants for carboxylate than those of receptor **3** and only N-H bond participated in the binding event for the receptor **1**. These results indicate that the strength of association of carboxylate also depends on the polarity of C_α-H bonds with these receptors

The complexation abilities of receptor **3** to nitrite was also measured by standard ^{1}H NMR titration experiments in DMSO-d_6 using a constant host concentration (2 mM) and increasing concentrations of nirtite anions. The addition of tetrabutylammonium nirtite salts to the solution of receptor **3** in DMSO-d_6 resulted in downfield shifts of amide N-H peak and C_α-H peak. For example, addition of tetrabutylammonium nitrite moved amide N-H from 10.10 to 10.72 ppm and C_α-H from 5.62 to 5.74 ppm (Figure 5a). The downfield shifts of these protons indicate the presence of a hydrogen bond interaction between these hydrogens and nitrite ion.

The stoichiometry between receptor **3** and nitrite was determined to be 1:1 using ^{1}H NMR Job plot in DMSO-d_6 (Fig. 2). The association constants for nitrite calculated were 8.4×10^2 from ^{1}H NMR titration. The less polar nitrate gave lower association constant for the receptor **3** as expected. The association constants of nitrate for the receptor **3** turned out to be 2.0×10^2 from ^{1}H NMR titration. Receptor **1** and **2** did not show any affinities for the nitrite and nitrate and no shift of C_α-H peak was observed. Chloride and bromide showed quite similar behaviors like nitrate and nitrite.

The receptor **3** showed somewhat noisy fluorescence spectrum due to low fluorescent phenyl moiety. The excitation and emission wavelength were 250 and 460 nm respectively. However, the intensity of emission spectrum from 60 μM solution of the receptor **3** gradually increased as the concentration of tetrabutylammonium dimethyl phosphinate was increased (1 - 10 equiv), which also indicates the association between the receptor **3** and dimethyl phosphinate. As fluorescence titration spectra of these receptors are noisy due to low fluorescent phenyl moiety, we did not calculate association constants from the fluorescence titration spectrum. However, they showed consistent association phenomena between these receptors and anions.(see supporting information). All calculated binding constants for these anions are summarized in Table 2.

One notable trend is the difference between aliphatic anion guests and aromatic anion guests. For example, acetate has higher binding affinity compared with that of benzoate regardless of hosts used. And for phosphinate series, dimethylphosphinate has the highest binding affinity among the phosphinate guests. This could be attributed to the electron delocalization of negative charge into aromatic moieties. And this was also confirmed by partial charges obtained from natural population analysis. For acetate, the partial charge of oxygen is -0.792 and for benzoacetate, -0.770. Therefore, the oxygens of benzoate are slightly less negative compare with those of acetate. For dimethylphosphinate, the partial charge is -1.156, while for $(C_6H_5)_2POO^-$ and $(C_6H_5)HPOO^-$, -1.146 and -1.137, respectively. Again, the oxygen charges of aromatic guests are less negative, resulting in lower binding energies, as shown in Table 2.

In conclusion, Phosphinate and its analogous guests are very important in nature. Since phosphinate-selective artificial receptors are rare, we have developed acetate and phosphinate selective hosts based on the hydrogen bonding interaction using amide N-H and aliphatic C-H groups (hosts **1**, **2** and **3**). Since C_α-H hydrogen in host **3** is the most highly polarized by the charged pyridinium group, it is the strongest host in this series of hosts. Amide N-H hydrogen bonding element was the most significant one in anion recognition. However, by varying the polarity of C_α-H group, the magnitude of interaction energy was changed considerably. Host **3** showed one order of magnitude higher affinities for most anion guests studied in this work compared to those of host **1**. This could be attributed to the difference of polarities between C_α-H groups in host **1** and **3**. In case of receptor **3**, the charge-assisted C-H hydrogen bonding interactions were very crucial. Therefore, we report here the importance of C_α-H hydrogen bonding element as a decisive modulating moiety for anionic recognition.

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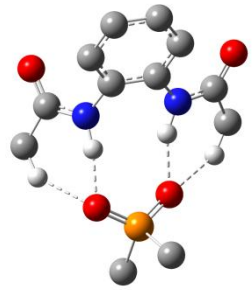
References

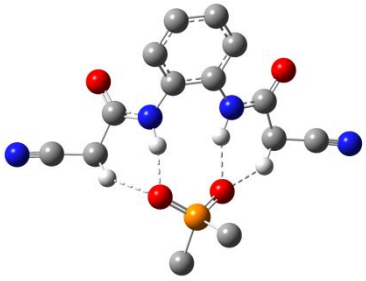
1. (a) Choi, Y.; Kang, J. J. Incl. Phenom. Macrocycl. Chem. **2014**, 79, 95-102; (b) Shi, G.; Gadhe, C. G.; Park, S. W.; Kim, K.S.; Kang, J.; Seema, H.; Singh, N. J.; Cho, S. J. Organic Letters, **2014**, 16, 334-337; (c) Pandian, T. S.; Srinivasadesikan, V.; Lin, M. C.; Kang, J. Tetrahedron, **2015**, 71, 7782-7788; (d) Pandian, T. S.; Kang, J. Tetrahedron Letters, **2015**, 56(28), 4191-4194; (e) Pandian, T. S.; Srinivasadesikan, V.; Lin, M.C.; Kang, J. Tetrahedron, **2015**, 71, 8350-8356; (f) Choi, Y.; Kim, T.; Jang, S.; Kang, J. New Journal of Chemistry, **2016**, 40, 794-802; (g) Jo, J.; Putika, R.; Lin, M. C.; Kang, J. Tetrahedron Letters, **2016**, 57, 3208-3214
2. Sohn. D. H.; Park, J. I.; Cho, S. J.; Kang J. Tetrahedron, **2017**, 73, 212-221
3. Yang, Y.; Coward, J. K. *J. Org. Chem.* **2007**, 72(15), 5748-5758
4. Erion, M. D.; Jiang, H.; Boyer, S. H. PCT Int. Appl. WO 2006128056 A2 20061130, 2006.
5. Hynes M.J. *J. Chem Soc Dalton Trans*. **1993**, 311-312
6. Frisch MJ, Trucks GW, Schlegel HB, et al. Gaussian 09, Revision E.01.Wallingford CT: Gaussian, Inc.; 2009
7. Lee C, Yang W, Parr RG. *Phys. Rev. B.* **1988**, 37, 785-789
8. Chipman DM. Reaction field treatment of charge penetration. *J. Chem. Phys*. **2000**, 112, 5558-5565
9. Reed AE, Weinstock RB, Weinhold F. J. Chem. Phys. **1985**, 83, 7

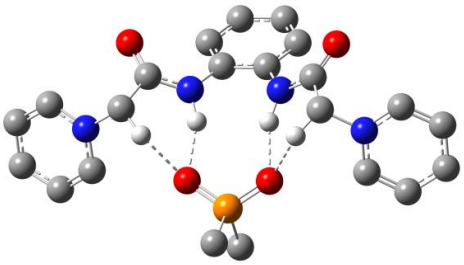
Highlights

- Phosphinate selective anion receptor
- Control of recognition by varying C-H polarity
- Importance of C-H hydrogen bonding

Graphical Abstract







Host 1 **Host 2**

Host 3