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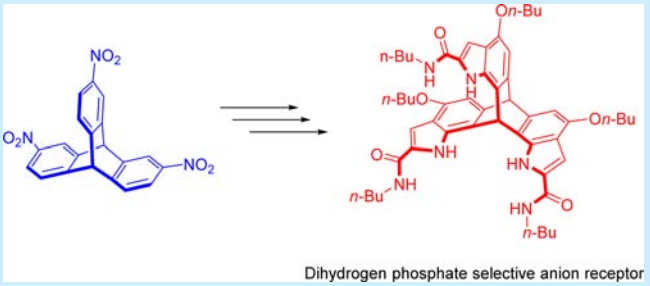
Synthesis, Structure, and Complexation Properties of a C_3-Symmetrical Triptycene-Based Anion Receptor: Selectivity for Dihydrogen Phosphate

Jarosław M. Granda,* Jakub Grabowski, and Janusz Jurczak*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting Information

ABSTRACT: A new anion binding motif based on triptycene core has been synthesized from 2,7,14-trinitrotriptycene. Its well-defined binding pocket allowed for the selective recognition and sensing of dihydrogen phosphate in DMSO-d_6 + 0.5% H_2O.



Interest in anion recognition has long been motivated by applications in anion sensors,[1] responsive gels,[2] extraction and separation of anions,[3] transmembrane transport,[4] anion-driven supramolecular architectonics,[5] and catalysis.[6] Among the biologically active anions, phosphates are particularly important, forming part of various genetic information and energy carrying molecules, e.g., RNA, DNA, ATP, etc. Elevated phosphate concentrations are also related to chronic kidney disease and hyperphosphatemia.[7] In addition, phosphates are major constituents present in anthropogenic pollutants (e.g., artificial fertilizers, detergents, etc.). Phosphate accumulation in water reservoirs leads to their eutrophication as a consequence of blue and green algal blooms.[8] In this spirit, designing receptors able to selectively bind phosphates poses a particular challenge for synthetic and supramolecular chemists.

The existing charged receptors for phosphates often suffer from poor selectivity over other anions, while selective neutral receptors work mainly in nondemanding solvents, e.g., Katayev and co-workers recently described a sapphyrin-based phosphate receptor, for which they report low selectivity between dihydrogen phosphate (K_{ass} > 10000) and acetate (K_{ass} = 3500) in DMSO-d_6 + 0.5% H_2O.[9] We demonstrated also diindolylmethane-based receptor binding dihydrogen phosphate in methanol mixtures. However, it exhibited poor selectivity over other anions.[10] For thorough review on dihydrogen phosphate recognition and binding see ref 8.

The common strategy for designing a selective anion receptor involves the rational deployment of hydrogen bond donors on an appropriate scaffold allowing for multiple cooperative interactions with a selected guest. While the method is simple in concept, precise control of binding pocket geometry is not trivial in this case. In this regard, we envisioned that introducing pyrrole rings to a triptycene skeleton would give a scorpionate-like anion receptor **1** with a well-defined binding pocket (Figure 1).

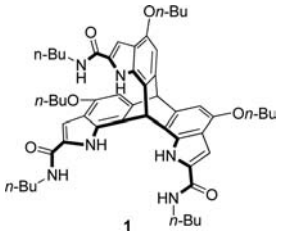


Figure 1. Triptycene-based receptor **1** studied in this work.

We opted to use a triptycene skeleton owing to its interesting structural properties, including its unique paddle wheel shape and rigid structure. This building block has recently found many applications in catalysis,[11] in the synthesis of porous materials,[12] and in supramolecular chemistry.[13] However, heterocyclic NHs are also excellent hydrogen bond donors, successfully used in the construction of various anion receptors.[14] However, most anion receptors studied to date are characterized by two-dimensional structure and conformational liability. Additionally, there is a limited number of C_3-symmetrical molecules in comparison to C_2 systems.[15] In many cases, the preparation of C_3 molecules is hampered by a lack of regioselectivity in the key reaction used in their synthesis. Therefore, there is a need to devise new structural motifs of receptors as well as new methodology for their synthesis. These facts prompted us to synthesize and study the structure of anion receptor **1**. Receptor **1** was synthesized in five steps, starting from 2,7,14-trinitrotriptycene (**2**) described by Chen[16] (Scheme 1).

In the first step, hydrogenation (H_2, Pd/C) of trinitrotriptycene **2** yielded proper triamine, which was diazotizated with sodium nitrite, followed by decomposition to give triphenolder-

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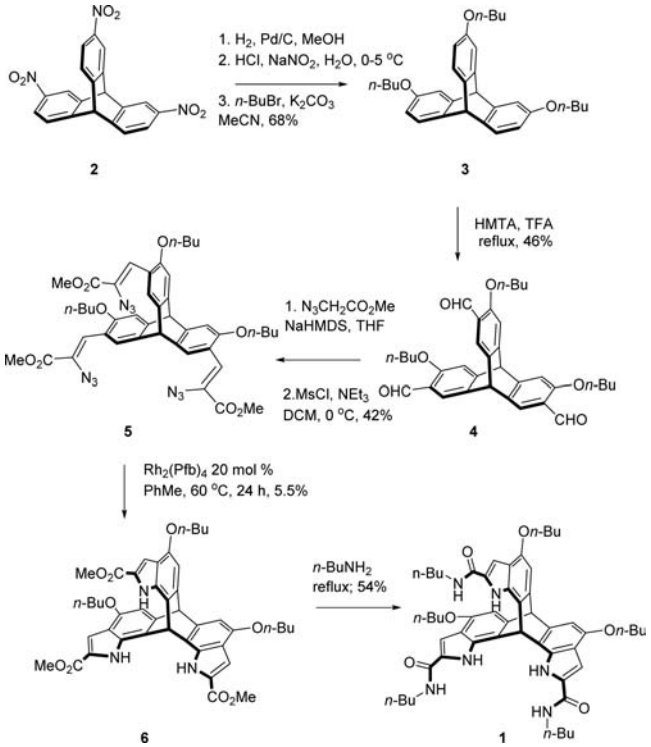
Scheme 1. Synthesis of Triptycene-Based Anion Receptor 1



ivative (not isolated due to poor solubility), which was alkylated with *n*-butyl bromide to give derivative **3**.[17] Derivative **4** was obtained by Duff formylation using urotropine combined with trifluoroacetic acid.[13a] The trialdehyde **4** was then subjected to aldol condensation with methyl azidoacetate, giving intermediate triazidotrialcohol, which was immediately treated with methanesulfonyl chloride in the presence of trietlhyl amine to afford trivinyl-intermediate **5**. The indole rings were constructed by a catalytic variant of the Hemetsberger−Knittel[18] reaction, using rhodium perfluorobutyrate dimer[19] as a catalyst.[20] Three consecutive reactions take place in such a step, and closing of the next indole ring may become more unfavorable; therefore, yield of 5.5% is reasonable. In the final step, the amide functionalities were introduced by reaction of compound **6** with *n*-butyl amine, under reflux.

The structure of the receptor **1** was confirmed by NMR and MS experiments. ^{1}H NMR spectrum analysis confirmed the C_3-symmetry of compound **1**. Interestingly, the bridge proton located in the anion binding pocket exhibits a chemical shift of δ = 7.29 ppm and is shifted about 1.65 ppm downfield from the second bridge proton (δ = 5.64), as a result of the ring current of pyrrole rings. Figure 2 shows the energy minimized structure of anion receptor **1** obtained from DFT/M06-2X/6-31+G* level of theory. Similarly, as for other anion receptors based on indole-2-carboxylic acid,[21] free receptor **1** prefers *anti* conformation of indole NH vs amide NH, which is in agreement with data obtained from a 2D NOESY NMR experiment. Molecular orbital analysis shows a HOMO−LUMO gap $\Delta E_{HOMO-LUMO}$ = 5.9 eV as well as some delocalization through bridgehead carbon atoms (for molecular orbitals see the Supporting Information).

The binding properties of receptor **1** were investigated in DMSO-d_6 + 0.5% H_2O by titration under ^{1}H NMR control or by titration under fluorescence control (Table 1). Receptor **1** shows moderate affinity toward basic carboxylate anion, which may be explained in terms of the binding pocket not offering a good fit to

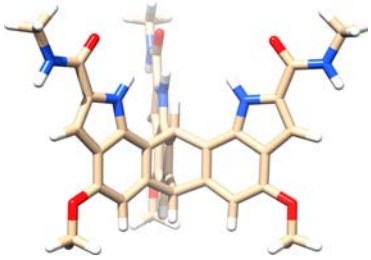


Figure 2. Lowest energy structure of receptor **1** obtained from DFT/M06-2X/6-31+G* level of theory. For simplicity *n*-butyl groups have been replaced by methyl groups.

Table 1. Binding Properties of Receptor 1

entry	anion	K_{ass} [M^{-1}]^a	K_{ass} [M^{-1}]^b	ΔG_{ass} [kJ·M^{-1}]^a	ΔG_{ass} [kJ·M^{-1}]^b
1	AcO^-	1047	1417	−17.5	−18.0
2	$PhCOO^-$	102	211	−11.7	−13.3
3	$H_2PO_4^-$	*d*	67608		−27.5
4	Cl^-	*c*	*c*		
5	Br^-	*c*	*c*		
5	NO_3^-	*c*	*c*		
6	HSO_4^-	*c*	*c*		

^{a}Obtained from titration under ^{1}H NMR control in DMSO-d_6 + 0.5% H_2O at 303 K model of binding 1/1. ^{b}Obtained from titration under fluorescence control in DMSO + 0.5% H_2O at 298 K model of binding 1/1. ^{c}Change in receptor fluorescence or chemical shift of receptor protons was not observed. ^{d}Complex binding equilibria.

carboxylates. Titration of receptor **1** with dihydrogen phosphate anions revealed a slow binding equilibrium on the NMR time scale and a composite binding equilibrium (Figure 3).

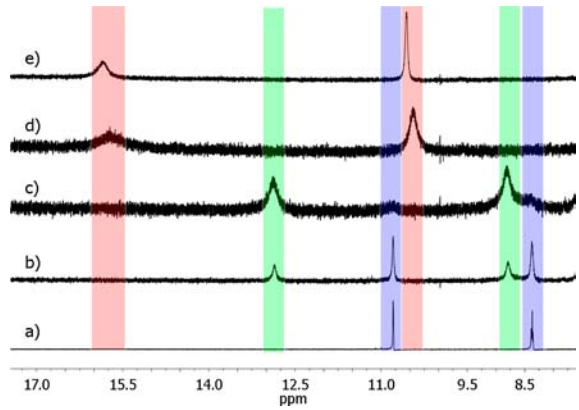


Figure 3. ^{1}H NMR titration of compound **1** in DMSO-d_6 + 0.5% H_2O. (a) Free receptor amide and indole NHs; (b) 0.5 equiv of $TBAH_2PO_4$; (c) 1.0 equiv of $TBAH_2PO_4$; (d) 5.1 equiv of $TBAH_2PO_4$; (e) 1.0 equiv of $TBAH_2PO_4$ + 1.0 equiv of TBAOH.

Addition of the first equivalent of anion causes the disappearance of receptor **1** signals with the simultaneous appearance of complex with dihydrogen phosphate anion. Further increase of anion concentration leads to a similar event of this kind: namely, disappearance of signals of this complex and formation of a new set of signals in the NMR spectrum. The rationale for this fact is that bound dihydrogen phosphate with receptor **1** has increased acidity to such extent that the unbound dihydrogen phosphate is able to deprotonate it. A similar

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property of dihydrogen phosphate has been described by Gale and co-workers.[22]

Upon addition of the anions the bridgehead hydrogen atom inside anion binding pocket also exhibited chemical shift changes, which probably is a consequence of hydrogen bond formation with anion.

However, the binding constant for dihydrogen phosphate anion was obtained by titration under fluorescence control. Addition of this anion to solution of receptor **1** caused fluorescence quenching, and this anion was bound with high affinity K_{ass} = 67 608 M^{-1}. Figure 4 shows an example of titration of receptor **1** with dihydrogen phosphate anion.

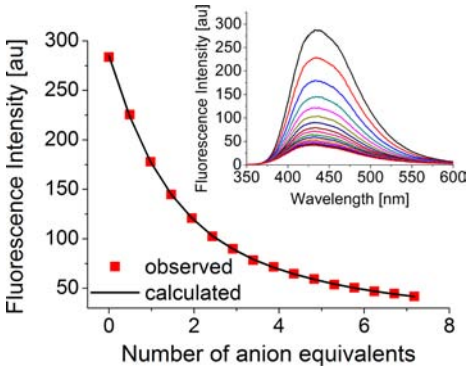

Figure 4. Changes in fluorescence at 430 nm upon addition of dihydrogen phosphate anion in DMSO + 0.5% H_2O with excitation of 310 nm. Inset shows fluorescence spectra.

Quite the opposite, anions such as chloride, bromide, nitrate, and hydrogen sulfate were not bound by receptor **1**. Addition of these anions to solution of receptor **1** did not cause any chemical shift change. These results are in agreement with those obtained from titration under fluorescence control.

Figure 5 shows the structure of receptor **1** with dihydrogen phosphate obtained from DFT calculations. The anion is placed

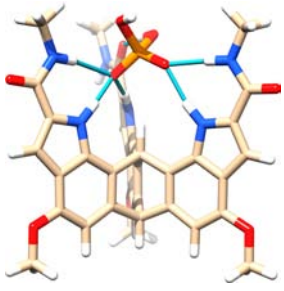

Figure 5. DFT calculated structure of **1**·$H_2PO_4^-$ (M06-2X/6-31+G*). The indole NH···$H_2PO_4^-$ distance is 1.80−1.82 Å; the amide distance NH···$H_2PO_4^-$ is 1.90−2.21 Å. For simplicity *n*-butyl groups have been replaced by methyl groups.

centrally inside the binding pocket and is bound by five hydrogen bond donors, three indole NHs and two amide NHs. There is also a hydrogen bond between the carbonyl group of receptor and the hydroxyl group of anion. The lengths of the hydrogen bonds are 1.80−2.21 Å.

In conclusion, we have developed a new synthetic pathway leading to C_3-symmetric triptycene derivatives having fused pyrrole rings, starting from readily available 2,7,14-trinitrotriptycene. In the key step, the indole rings were closed using a Hemetsberger−Knittel procedure. Investigation of receptor **1** binding properties in DMSO-d_6 + 0.5% H_2O showed excellent selectivity toward dihydrogen phosphate anion, which was bound 50 times more strongly than acetate. We believe that this new C_3-symmetrical platform may be useful for construction of a new class of anion receptors, molecular machines, as well as materials having aromatic rings fused to a triptycene skeleton.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03066.

Synthetic procedures, copies of NMR spectra, computational details, NMR, and fluorescence titration details (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jaroslaw.granda@icho.edu.pl.
*E-mail: janusz.jurczak@icho.edu.pl.

Notes

The authors declare no competing financial interest.

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