Tetrahedron 70 (2014) 7893–7899

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Positive allosteric binding behavior of pyrene-appended triazole-modified thiacalix[4]arene-based fluorescent receptors

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ARTICLE INFO

Article history:
Received 26 July 2014
Received in revised form 26 August 2014
Accepted 28 August 2014
Available online 6 September 2014

Keywords:
Thiacalix[4]arene
1,3-*alternate* conformation
Pyrenyl-appended triazole
Urea
Allosteric effect

ABSTRACT

The novel heteroditopic receptors **5a~c** have been synthesized, which bear a thiacalix[4]arene in the 1,3-*alternate* conformation. Two urea moieties possessing various aryl groups with either electron-donating or -withdrawing groups at their *p*-positions function as anion-binding sites. At the opposite side of the cavity are two pyrene-appended triazole rings, which act as cation-binding sites. The binding property of receptor **5c** was investigated by means of ^{1}H NMR and UV–vis spectroscopy and by fluorescence titration experiments in the presence of various transition metal cations and anions in CH_2Cl_2–DMSO (10:1, v/v) solution. Interestingly, it was found that receptor **5c** possessing two *p*-nitrophenyl ureido moieties, most efficiently complexes in the urea cavity or bistriazoles; the plausible allosteric effect of receptor **5c** was also investigated.

1. Introduction

The investigation of macrocycles such as calix[*n*]arenes[1], which are attractive building blocks for creating host systems capable of selectively recognizing cation, anion or neutral molecules has become an active area of research in supramolecular chemistry. Thiacalix[4]arenes[2,3], which are sulfur-bridged analogs of calix[4]arenes are excellent scaffolds and have been utilized in chemosensors, supramolecular self-assemblies and the catalytic activity of enzymes. A large number of enzymes have allosteric sites to control catalytic activity by stabilizing the active conformation. Many systems based on thiacalix[4]arenes are capable of host–guest interactions and involve conformational changes caused by the allosteric binding[4] of metal cations, and these relate to the maintenance of the essential material balance necessary for life. Anions also have been widely employed in biological, environmental and industrial processes.[5] The development of anion selective sensors[6] based on calix[*n*]arenes has received a considerable amount of attention in the area of supramolecular chemistry. Calix[*n*]arene urea derivatives are extremely prominent and are efficient for anion complexations via the N–H protons due to the formation of hydrogen bonds.[7,8] Click chemistry[9] is one of the most useful and widely employed reactions in synthetic chemistry. In particular, the Cu(I)-catalyzed azide–alkyne cycloaddition reaction is a highly versatile method, which can be performed in high yield under very mild conditions. The 1,4-disubstituted-1,2,3-triazole products can act as relatively stable functional groups as covalent linkers or as ligands for metal cations, and have been utilized in the fields of drug discovery and materials science. Recently, many calix[*n*]arene derivatives bearing 1,4-disubstituted-1,2,3-triazoles as linking groups have been developed and investigated.[10]

Chung[11] and co-workers reported a fluorescent chemosensor bearing a calix[4]arene in a 1,3-*alternate* conformation, which contains two anthracene-appended triazole rings and the crown-ether moiety.[11a] This receptor exhibited a negative allosteric effect between the Pb^{2+} and K^+ ions in common organic solvents. Moreover, they also reported that a homobinuclear ditopic fluorescent chemosensor bearing a 1,3-*alternate* calix[4]arene, which contained two anthracene-appended triazole rings and two phenylenaminones at the opposite sides of the calix[4]arene cavity.[11d] This receptor exhibited a positive allosteric effect between 2 equiv of Ag^+ ion in common organic solvents. However, investigations concerning the appearance of allosteric effects in analogs based on thiacalix[4]arenes/metal cations/anions has not yet been reported. Herein, we have independently designed a heterodimeric system[12] based on a thiacalix[4]arene having two different

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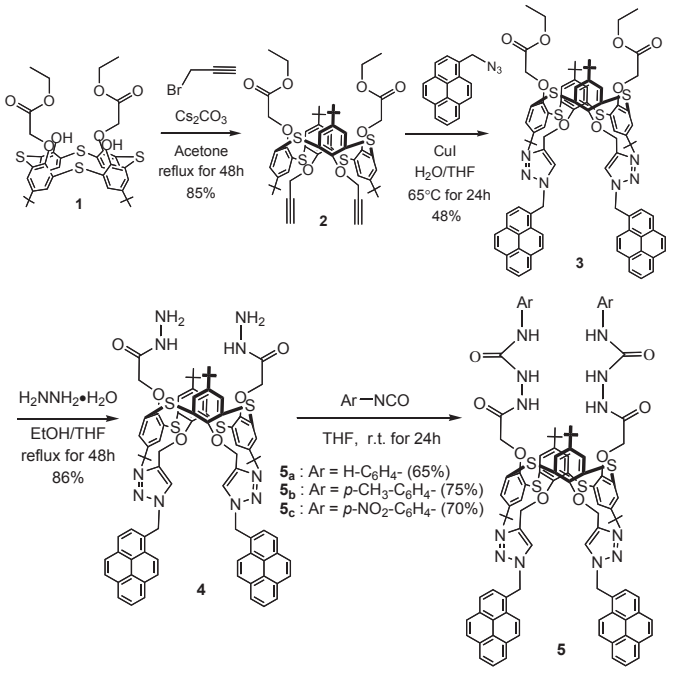
http://dx.doi.org/10.1016/j.tet.2014.08.068
0040-4020/

side arms. Specifically, we have incorporated two ureas moieties, which link various phenyl groups substituted with the electron-donating or -withdrawing groups at the *p*-positions and two pyrene-appended triazole rings at the opposite side of thiacalix[4]arene cavity. We built up the hypothesis that the heterodimeric system, which is controlled by the complexation of the opposite side arms with Cl^- and Ag^+ ions, exhibits an effective positive allosteric effect.

2. Results and discussion

2.1. Synthesis

O-Alkylation of *distal*-1 was carried out with 10 equiv of propargyl bromide in the presence of 10 equiv of Cs_2CO_3 according to the reported procedure to afford the desired 1,3-*alternate*-2 in 85% yield.[12] A Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of 1,3-*alternate*-2 with 4 equiv of 1-azidomethylpyrene via Click chemistry was carried out according to the reported procedure, and afforded the 1,2,3-triazole thiacalix[4]arene 1,3-*alternate*-3 in 48% yield. The hydrazinolysis of 1,3-*alternate*-3 was carried out with a large excess of hydrazine hydrate to afford the desired 1,3-*alternate*-4 in 86% yield. The condensation of 1,3-*alternate*-4 with 4 equiv of the appropriate isocyanate in THF furnished the receptors $\mathbf{5_{a\sim c}}$ in good yield (Scheme 1). In general, the ^1H NMR spectra of receptors $\mathbf{5_{a\sim c}}$ in $CDCl_3$–DMSO (10:1, v/v) exhibited the characteristics of a 1,3-*alternate* canformation, *viz* two singlets (18H each) for the *tert*-butyl protons, one singlet (4H) for OCH_2CO protons, one singlet (4H) for OCH_2–triazole protons, two singlets (4H each) for aromatic protons, two singlets (2H each) for four urea NH protons and one singlet (2H) for triazole–*H* protons. Moreover, a concentration dependence of the ^1H NMR chemical shifts of the ureido protons in receptor $\mathbf{5_c}$ was not observed (Figure S13). This result suggests that receptor $\mathbf{5_c}$ has a strong intramolecular hydrogen bond between the two ureas moieties.



Scheme 1. Synthesis of receptors 1,3-*alternate*-$\mathbf{5_{a\sim c}}$.

2.2. Binding studies

Upon addition of Cl^- ion (0–20 μM) to a solution of receptor $\mathbf{5_c}$ (1.0 μM), Figure S19 shows that both the monomer and excimer emissions of the pyrene units gradually decrease. A Job's plot binding between receptor $\mathbf{5_c}$ and Cl^- ion reveals a 1:1 stoichiometry (Figure S20), while the association constant (K_a value) for the complexation with Cl^- ion by receptor $\mathbf{5_c}$ was determined to be 42,500±2975 M^{-1} as determined by the fluorescence titration experiment in CH_2Cl_2–DMSO (10:1, v/v) (Figure S21 and Table 1). Moreover, K_a values between the receptors $\mathbf{5_{a\sim b}}$ and Cl^- ion were determined by analyzing fluorescence titration experiments, respectively (Figures S15–S18 and Table 1). These results suggest that the association constants depend on the electron-donating/withdrawing groups located at the *p*-position. In the presence of the electron-withdrawing group NO_2 (receptor $\mathbf{5_c}$), the K_a value was greater than that for the unsubstituted receptor (receptor $\mathbf{5_a}$). In contrast, in the case of receptor $\mathbf{5_b}$, with the electron-donating Me group, there was a general decrease in the K_a value for the complexation with Cl^- ion in comparison to the case in the unsubstituted receptor $\mathbf{5_a}$. Therefore, the introduction of electron-withdrawing groups at the *p*-position appears to increase the acidity of the urea protons, and hence enhance the anion-binding ability through hydrogen-bonding interactions. The K_a value of receptor $\mathbf{5_c}$ with the electron-withdrawing NO_2 group at the *p*-position was the best out of all the K_a values between receptors $\mathbf{5_{a\sim c}}$ and Cl^- ion. From the above, we can say that the receptor $\mathbf{5_c}$, with the electron-withdrawing NO_2 group at the *p*-position, has the most effective recognition ability toward selected anions of the systems screened herein. Given this, complexation studies of receptor $\mathbf{5_c}$ toward targeting various transition metal cations and anions were carried out using ^1H NMR and UV–vis spectroscopy and by fluorescence titration experiments.

Table 1
Association constants[a] of receptor $\mathbf{5_{a\sim c}}$ with Cl^- ion[b]

Host	$\mathbf{5_a}$	$\mathbf{5_b}$	$\mathbf{5_c}$
R	H	*p*-CH_3	*p*-NO_2
K_a [M^{-1}]	6250±438	3000±210	42,500±2975

[a] Measured in CH_2Cl_2–DMSO (10:1, v/v) at 27 °C by fluorescence titration experiments (Figures S15–S21); host concentration was 1.0 μM.
[b] Guests used: Bu_4NCl.

The UV–vis absorption spectra of receptor $\mathbf{5_c}$ (1.0 μM) were recorded in the presence of various anions (20 equiv) in CH_2Cl_2–DMSO (10:1, v/v) as shown in Figure S14. The receptor $\mathbf{5_c}$ (1.0 μM) exhibits an absorption band at 347 nm in the UV–vis absorption spectra in the absence of anions. Interestingly, significant changes moving to a longer wavelength in absorption spectra were observed in the presence of F^-, AcO^-, $PhCOO^-$ or $H_2PO_4^-$ with a color change from colorless to dark yellow by the naked eye, respectively. These results suggest that the quinoid structure was formed by the deprotonation of the urea NH groups in the *p*-nitrophenyl ureido moiety. Fig. 1 reveals the fluorescence intensity changes of the monomer (393 nm) and excimer (486 nm) emissions for receptor $\mathbf{5_c}$ in the presence of various anions. Receptor $\mathbf{5_c}$ exhibited a decrease in intensity of both the monomer and excimer emissions with various anions. Upon addition of Cl^- ion to a solution of receptor $\mathbf{5_c}$, the decrease of intensity of the monomer emission is presumably caused by a photo-induced electron transfer (PET) mechanism, which operates from the oxygen of the urea moiety, which complexes with the Cl^- ion via hydrogen bonding to the pyrene moieties. By contrast, upon addition of F^-, AcO^-, $PhCOO^-$ or $H_2PO_4^-$ ions to a solution of receptor $\mathbf{5_c}$, the