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Recognition of caffeine by a water-soluble acyclic phane compound

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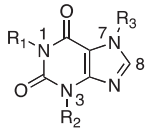
ABSTRACT

Caffeine (1,3,7-trimethylxanthine) is a chemical substance associated with everyday human life. In order to recognize caffeine in water, six water-soluble acyclic phane compounds composed of three aromatic rings were examined as artificial receptors. ^{1}H NMR titration experiments revealed that 6,6′-[1,3-phenylenebis(carbonylimino)]bis-1,3-naphthalenedisulfonate had the highest binding ability for caffeine, with a binding constant (K_b) of 127±5 M^{-1} at 300 K. While this phane compound also formed a complex with theophylline (1,3-dimethylxanthine) at around half the value of the binding constant for caffeine (K_b=64±4 M^{-1}), it showed weak or little complexation for adenosine, guanosine, inosine, and their 5′-phosphates (sodium salts of adenylic acid, guanylic acid, and inosinic acid).

1. Introduction

Caffeine is a stimulant drug, which is consumed daily by many people around the world. It is found widely in coffee, teas, and soft drinks, as well as in chocolate and cocoa.[1,2] Caffeine is also a familiar bitter substance, which gives a fascinating taste to these foods and beverages. However, it is reported that, although the moderate daily intake (≤400 mg) does not cause any adverse effects for healthy adults, its consumption should be kept lower for pregnant women and children.[3]



Caffeine ($R_1 = R_2 = R_3 = Me$)
Theophylline ($R_1 = R_2 = Me$, $R_3 = H$)
Theobromine ($R_1 = H$, $R_2 = R_3 = Me$)

Thus, since caffeine is a chemical substance associated with everyday human life, artificial caffeine receptors have been studied as challenging targets by supramolecular chemists in the last 13 years. Most of the previous research studies addressed the molecular recognition of caffeine in comparatively low polar organic solvents.[4–10] There have not been many studies on recognition in water. This is probably because, in organic solvents, effective use of hydrogen bonds between polar groups, such as XH/Y systems, where 'X' and 'Y' represent atoms with high electronegativity, e.g., oxygen or nitrogen atoms, as a major binding force facilitates the more refined molecular design of the receptors. Chemical sensors and chromatographic technologies are the most typical applications for receptor molecules. However, in such cases, caffeine is often in aqueous sample solutions. Therefore, an even greater effort is essential to develop artificial receptors for recognizing caffeine in water. In order to achieve complexation in water, use of van der Waals and CH/π interactions are effective,[11] because hydrogen bonds involving XH groups in water weaken in many cases of complexation between organic compounds with simple structures. It is well known that caffeine forms complexes with polyphenolic compounds in water,[12–16] in which van der Waals and CH/π interactions appear to play a significant role. Recently, it was demonstrated that caffeine concentration could be estimated from the change in the fluorescence emission intensity using water-soluble pyrene derivatives and acridine orange.[17,18] Crego-Calama et al. used zinc complexes of porphyrin derivatives of aromatics as caffeine receptors.[19] These systems attained more stable complexation by adding a coordination bond between the central metal in the porphyrin compound and the lone-pair electrons of the caffeine

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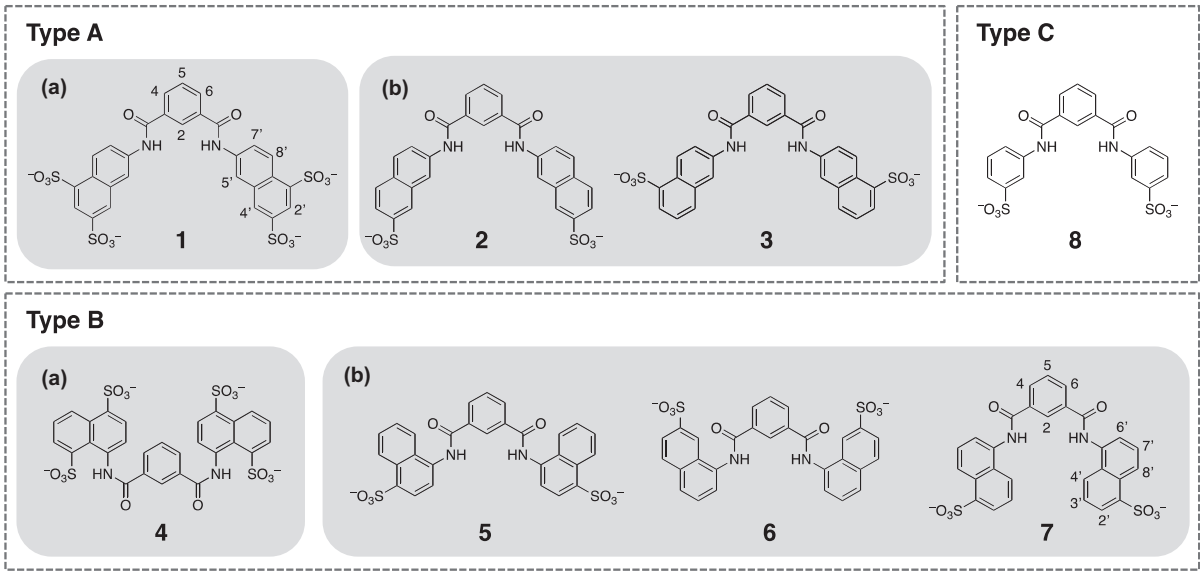

Fig. 1. Acyclic phane compounds of caffeine receptor candidates.

nitrogen in addition to the van der Waals and CH/π interactions between the porphyrin skeleton and the caffeine molecule. However, when these metal complex type receptors are applied to chemical sensors or chromatographic technologies, ion exchange may occur between the central metal ion in the porphyrin compound and the other metal ions in the sample solutions.[20]

In this study, in order to find new aromatic-type receptor structures that can recognize caffeine in water, the complexation between water-soluble acyclic phane compounds and caffeine was investigated. Acyclic aromatic structures are found in natural compounds forming complexes with caffeine, for example, tea polyphenols.[12–15,21] Here, we present the binding abilities of six phane compounds for caffeine. Furthermore, complexation of these compounds with other well-known methylxanthine derivatives, nucleosides, and nucleotides with purine skeletons is described.

2. Results and discussion

As shown in Fig. 1, the acyclic phane compounds composed of three aromatic rings were prepared as caffeine receptor candidates. The space surrounded by these aromatic rings is expected to provide a suitable environment for binding caffeine, because more intermolecular interactions, i.e., van der Waals and CH/π interactions, can be obtained in the space. While both types A (**1**,[22] **2**,[23] and **3**[23]) and B (**4**,[22] **5**,[23] **6**,[23] and **7**) are constructed from one benzene ring and two naphthalene rings, these two types differ in the positions of the amide groups on the naphthalene skeletons. In each group, there are type (a) with four sulfonate groups and type (b) with two sulfonate groups. Compound **8**[22] with three benzene rings was added as type C. However, type A-(b) compounds (**2** and **3**) did not have enough water solubility to perform the binding experiments. Therefore, only six compounds (**1** and **4**–**8**) were examined in this study.

The binding abilities of these phane compounds for caffeine were evaluated by the binding constants obtained from ^{1}H NMR titration experiments in deuterium oxide buffered at pD 7.0 by phosphate,[24] where the concentration of the phane compounds was increased from 0.00 to 5.00 mM against a constant concentration of caffeine (1.00 mM).[25] Fig. 2 shows ^{1}H NMR chemical shift changes ($\Delta\delta$) in each proton of caffeine against the total concentration of the phane compounds. All the ^{1}H NMR signals of caffeine shifted upfield. The chemical shift changes by adding compound **1** were the largest. All Job plots of these complexations showed a maximum at 0.5 mol fraction (Fig. 3).[26] Therefore, the stoichiometric ratios in the complexes were revealed to be 1:1. The binding constants of **1** and **4**–**8** for caffeine were calculated by the application of the 1:1 binding model to the titration plots in Fig. 2. As shown in Table 1, the binding constants were obtained as the mean values of the binding constants calculated from the chemical shift changes of four ^{1}H NMR signals of caffeine. The binding constant of **1** gave the largest value (127±5 M^{-1}), which is similar to the binding constant between caffeine and epigallocatechin-3-*O*-gallate, a well-known green tea catechin.[15] The binding constants of the other phane compounds **4**–**8** resulted in smaller values (20–30 M^{-1}).

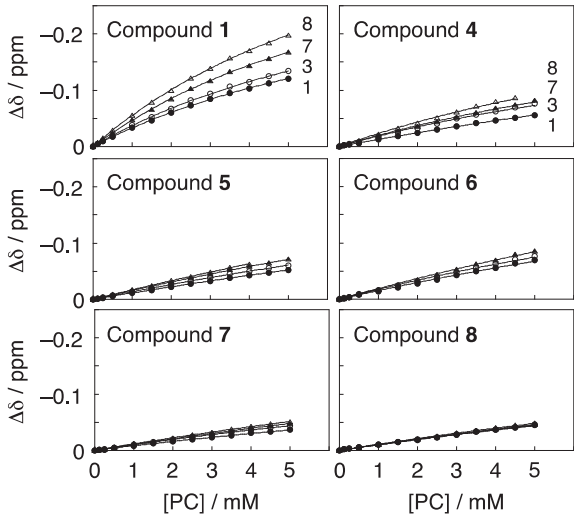

Fig. 2. ^{1}H NMR chemical shift changes ($\Delta\delta$) in caffeine with increasing concentrations of phane compounds (PC) **1** and **4**–**8** in D_2O at 300 K. [PC] is total concentration of the phane compound. The numbers in the graphs identify the protons of caffeine according to the proton-attached carbon number or the methyl group-attached nitrogen number.

Similar binding studies were performed for theophylline, an analog of caffeine. Theophylline is the most common bronchodilator and is found in tea leaves and drinks.[27,28] As shown in Fig. 4, the largest chemical shift changes in the theophylline protons in