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# Recent advances in molecular recognition in water: artificial receptors and supramolecular catalysis

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## 1. Introduction

Molecular recognition by artificial receptors has now expanded to a huge part of supramolecular chemistry. A number of targets for selective binding have been dramatically increased in recent decades because of better understanding how non-covalent interactions work, how strong are these interactions and how to arrange them in space to achieve affinity and selectivity for target species. If we compare the binding efficiency of existing synthetic receptors with natural receptors, natural ones are still well ahead. However, natural protein–ligand interactions are still full of mystery. Thus, we have a problem with many parameters from 'bottom' and 'top' sides and it does not matter if we design a host for a guest, or a guest for a host. We should not forget that a molecular

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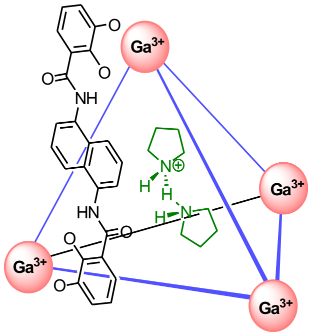
recognition in natural systems involves not only two players—‘host’ and ‘guest’—rather than three ‘host’, ‘guest’, and ‘water’. Whitesides in 2005 wrote in his review about the problem of designing ligands to bind tightly to proteins: “one should perhaps simplify the question, and ask - What is the difficulty? - to which the short answer would be - water”.[1] As one will see below in this review, water plays almost a major role in determining the energy of binding processes. However, speaking about energetical contributions of different parameters of host, guest, and water we may come to the conclusion that ‘it is a problem that has the feeling of swatting mosquitoes: kill one, and so many remain that it seems to make no difference’.[1] Hence, to understand molecular recognition in water, the ‘bottom-up’ approach looks rather feasible. In this review, we focus on artificial receptors that were specifically designed or studied to bind guests in an aqueous solution. In the last part of the review we discuss receptors that are able not only to bind in water but also to perform supramolecular synthesis or catalysis. The collected literature was published between 2008 and 2013. For earlier work we refer the reader to the first review ‘Supramolecular Chemistry in Water’, published in 2007 by Oshovsky, Reinhoudt, and Verboom.[2] The herein presented literature is structured according to the type of guests, for which artificial hosts were designed. Under ‘artificial host’ or ‘receptor’, we understand a molecule that binds guests through non-covalent interactions and usually provides a multivalent coordination, namely a combination of several non-covalent interactions. We also include examples, in which in addition to non-covalent interactions metal–guest coordination is present. Molecular transport by artificial hosts is not included because this topic was recently reviewed by Gale.[3] Several publications touching recognition in aqueous medium have been recently appeared; they include recognition of phosphates,[4,5] amines,[6] catecholamines,[7] ion-pairs,[8] sugars,[9–11,5] general anion binding,[12–14] recognition by cucurbiturils,[15,16] recognition by water-soluble container molecules,[17,18] and binding mechanisms in supramolecular chemistry.[19]

## 2. Receptors for amines and ammonium ions

Recognition of ammonium ions attracts a considerable attention in supramolecular chemistry because a number of amines take specific function in living systems. The range of targets for selective binding and sensing by artificial receptors remains during the last 10 years essentially the same. The group of interest involves acetylcholine and its derivatives, protonated aliphatic amines, amine-rich peptides, biogenic amines, i.e., the products of decarboxylation of amino acids. Späth and König published a comprehensive review[6] on recognition of amines and ammonium ions and we refer the reader to this article for more information. Our particular attention is focused on receptors that bind ammonium ions in an aqueous solution. Recognition of ammonium ions in a classical sense is usually associated with ammonium-crown ether- or amine-transition metal complexes. These complexes are sufficiently strong in water but often lack selectivity between the members of the desired raw of amines. From the recent literature, a shift to molecular capsules as receptors for ammonium ions is clearly seen. Such receptors provide additional hydrophobic interactions with the alkyl residues of amines and possess high binding constants in water due to shielding of a guest from the polar environment.

A nice example of a molecular cage that binds ammonium ions in water was provided by Bergman and Raymond, who investigated the properties of a water-soluble self-assembled supramolecular host **1**.[20] This host can encapsulate proton-bound homodimers of *N*-alkylaziridines, azetidines, pyrrolidines, and piperidines. The encapsulation process of a protonated dimer was discovered after the analysis of $^1$H NMR spectrum of the host with *N*-methylpyrrolidine. The stability of the formed complexes is high and less than 1 equiv of *N*-methylpyrrolidine used in the reaction with the host still leads to the formation of the protonated homodimer complex (**1**·Guest). Heterodimer complexes were also formed and were detected by standard analytical techniques. Complexation of a mixture of *N*-methylpyrrolidine and *N*-isopropylaziridine with the host leads to a complex with two different molecules inside the cavity of the host, as revealed from $^1$H NMR spectra. The origin of this interesting selectivity is unclear and apparently, more data should be gathered to understand selectivity rules for this host. Quantum chemical calculations were conducted to assess the energetic contribution of the binding. These calculations predicted that the formation of proton-bound amine homodimers are highly enthalpically favorable, when compared with the solvent adducts of protonated amines.



**1•Guest**

Rebek and co-workers took another strategy to access binding in water, namely they have functionalized a cavitand with carboxylate groups. Three-wall cavitands **2** and **3** bind even larger guests[21] than the previously described four-wall analogue.[22] The new receptors bind bulky aliphatic and aromatic amines in chloroform saturated with $D_2O$. However, water-soluble cavitand **3** binds only 1-adamantanol. Only this guest correctly fills the hydrophobic cavity of the host and stabilizes the folded conformation in water, which is formed by intramolecular hydrogen bonds. As inferred from $^1$H NMR measurements, the signals of guests shift upfield upon encapsulation, aggregates of hosts are broken, and signals become sharper. As an alternative strategy to confer the solubility in water over a wide pH range, it was suggested to functionalize the cavitand with PEG groups (**4**).[23] The previously reported cavitand soluble in organic solutions was shown to bind different ammonium cations in chloroform saturated with water. New cavitand **4** was soluble at millimolar range in $D_2O$ at pD 1–12. The NMR spectrum of the host is rather broad, but becomes sharp after addition of 2-adamantane amine or other guests. The signals of guests appear in the far upfield region because of the large anisotropy imparted by the eight aromatic rings. Binding constants for the investigated amines were in the range of $10–10^2$ $M^{-1}$, as inferred from the NMR spectra. Interestingly, the host did not bind long chain aliphatic amines except dodecylsulfate. Thermodynamic data of the binding of 2-aminoadamantane suggests an entropically favorable binding: $\Delta S$=55 $mol^{-1}K^{-1}$, $\Delta H$=20 kJ $mol^{-1}$. This fact was explained in terms of solvent release upon the encapsulation process. The authors also postulated that the enthalpic penalty on the binding event originates from a greater ion pair separation of the guest complex. The host–guest structure is rather rigid because it is kinetically stabilized through intramolecular H-bonds present in the host structure. With the help of EXSY experiments it was possible to obtain a barrier of 17.6 kcal $mol^{-1}$ for the dissociation process of guests from the cavity of the host.