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Mini-Review: Artificial Catecholamine Receptors in Aqueous Media

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Mini-Review: Artificial Catecholamine Receptors in Aqueous Media

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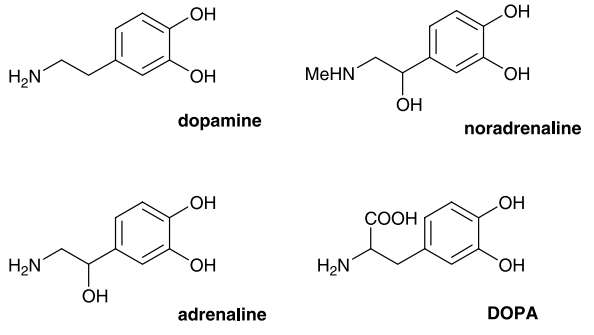
The literature on artificial receptors that recognize catecholamines in aqueous solution is reviewed. Although the substrates offer a number of potential sites for molecular recognition, the solvent constrains the range of possible pair-wise interactions that can be utilized. As a result, the dual goal of strong binding and high selectivity has yet to be attained by any artificial receptor design.

Keywords: Molecular recognition; Receptor design; Catecholamine; Water; Selectivity

INTRODUCTION

The catecholamines comprise a family of neurotransmitters characterized by an *ortho*-dihydroxy substituted phenylethylamine skeleton; contained within this class of biologically relevant compounds are *dopamine*, *adrenaline* (epinephrine), and *noradrenaline* (norepinephrine), as well as their biogenic precursor *L-DOPA*. In mammals, their levels are associated with a number of diseases such as Parkinson's disease, Menkes' disease, as well as phaeochromocytoma [1].



Analyses that are selective, sensitive, and convenient are thus important for both diagnostic and therapeutic purposes. To these ends, a diverse range of technology has been developed over the past two decades, including high-resolution chromatography, electro-analytic methods, sol-gel/micelle associated receptors [2,3], and solid-state sensors. While these approaches each have their strengths, a non-intrusive, real-time sensing scheme in biological media remains wanting. Artificial receptors that are able to function in aqueous media have been perceived as a potential solution, and the field has witnessed steady and sustained growth over the past decade. The design of receptors is also of interest in and of itself for the design of artificial signal transduction systems. This review summarizes the challenges faced and reviews the achievements attained, in the hopes that this will lead to new research directions. This is a focused review where we consider only discrete supramolecular entities that bind at least one catecholamine member in water or 1:1 methanol:water.

Water is a challenging environment for molecular recognition for two reasons: (i) only a limited arsenal of molecular interactions is useful, and (ii) it imposes peculiar solubility requirements. Because water has a high dielectric constant, charge-charge interactions are screened and their influence lowered considerably; by being a capable hydrogen-bond donor/acceptor, water also competes strongly for hydrogen-bonding sites on both host and guest, reducing the effectiveness of hydrogen bonding as a molecular recognition element. Artificial receptors are usually

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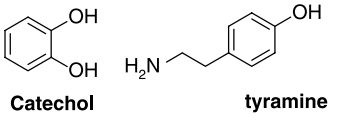
large organic molecules with limited solubility in an aqueous medium; particular functional groups need to be installed to confer the necessary solubility. These additional functional groups may interfere with the envisaged host-guest binding, and can also translate into a substantially more difficult synthesis from the outset.

Yet independent of the medium, specific recognition of a catecholamine is also a challenge in its own right, as the receptor must be capable of discriminating between a diverse group of competitors. Catecholamines have a number of features amenable to intermolecular association; these are summarized in Fig. 1. Yet other bio-molecules often share one or more functionalities that are present in catecholamines: amino acids, for example, contain a primary amine which can interfere with an iminium formation scheme, and *cis*-diols (e.g., galactose/fructose) can interfere with a boronic acid based catechol binding schemes. A selection of competitors



that share functional groups and/or shape similarities as shown above.

While this obstacle could be overcome by a multi-topic recognition scheme, it remains difficult to distinguish between members of the catecholamine family, as they are not only chemically similar, but also have a conformationally flexible backbone which obscures shape-selectivities. Molecular recognition of catecholamines is a pH-dependent process because of the multiple protonation states: Fig. 2 illustrates the speciation for dopamine as a function of pH. Ionizable groups on the receptor must match the guest's protonation state, and be suitably soluble at that pH. An additional complication comes from the

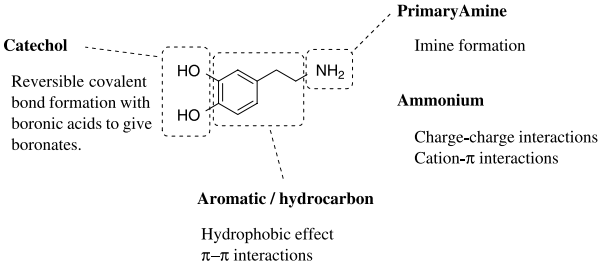


FIGURE 1 Features of catecholamines amenable for molecular recognition.

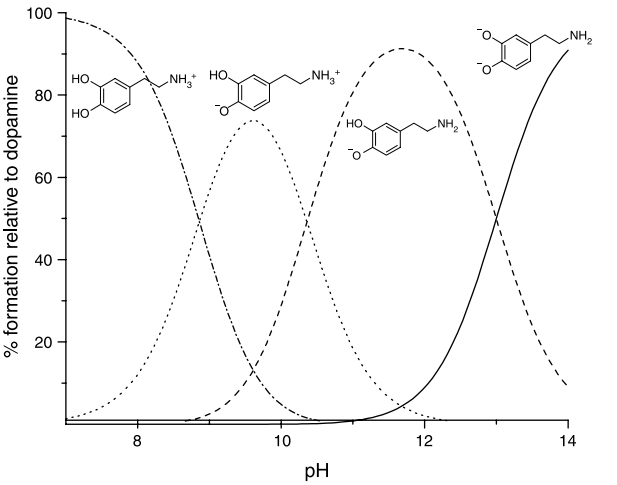
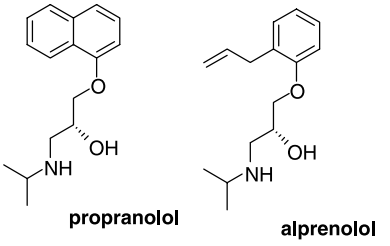


FIGURE 2 Protonation states for dopamine. pK_a values were determined by Larmarque to be 8.86, 10.36, and 13.0, respectively. It should be noted that the removal of acidic phenolic proton on the catechol moiety to produce a zwitterions occurs at a more acidic pH than the deprotonation of the ammonium [4].



ease of air oxidation of catechols in basic solutions—for practical applications, the receptors should function in neutral or slightly acidic solutions.

SUMMARY OF BINDING DATA AND SELECTIVITY

The molecular receptors that have been synthesized and characterized can be roughly classified into three categories based on their design architecture [5]:

i) Pre-organized host with hydrophobic cavity but no specific catecholamine directed functionality (**1**–**8**);
ii) Open structures with multi-topic, complementary interactions for the catechol and amine functionalities (**9**–**15**); and
iii) Macrocyclic structures that integrate complementary interactions with a pre-organized host (**16**–**23**).

Before examining the unique characteristics of the individual systems we summarize the reported binding data and selectivities to illustrate the performance attained in an overall sense. The receptors described in this review generally form

discrete 1:1 complexes with different catecholamines, the molecularity determined by Job plot analyses or ESI-MS. The association constant (K_{ass}) describes the extent of the equilibrium in Eq. (1), and may be evaluated by a number of conventional titration techniques [6]. Table I summarizes K_{ass} values as reported in the literature, whereas Fig. 3 summarizes binding constants for guests as *selectivities*, normalized to the most tightly bound catecholamine (Eq. (2)). A selectivity value above unity indicates that the competing guest is bound more tightly by the receptor than any of the catecholamines examined.

$$\text{Host} + \text{Guest} \overset{K_{ass}}{\rightleftharpoons} \text{Host}\cdot\text{Guest}$$

$$K_{ass} = \frac{[\text{Host}\cdot\text{Guest}]}{[\text{Host}][\text{Guest}]} \quad (1)$$

$$\text{Selectivity} = \frac{K_{guest}}{K_{catecholamine}} \quad (2)$$

Taken together, Table I and Fig. 3 show that although there is a wide range in complex stability, this is not translated into high selectivity by any receptor.

Group 1: Pre-organized Hosts Based on the Hydrophobic Effect

Anionic Cyclophanes 1–5

Cyclophanes **1** and **2**, described by Inoue and coworkers in 1997, were the first hosts reported to bind dopamine in water [7]. To simplify structural elucidation of the host-guest complexes, the cyclophanes **3**–**5** which have a more limited range of conformations were invesitigated subsequently [8]. In both studies, the association constants (K_{ass}) were determined by NMR titration at pD = 8.0. The selection of pD is partially governed by the insolubility of the hosts at more acidic pH; it should be noted that at this pD, the catechol functionality is deprotonated to a small extent

TABLE I Binding constants for catecholamine recognition by receptors[†]

Receptor	K_{ass} for Dopamine/M^{-1}	K_{ass} for Adrenaline/M^{-1}	K_{ass} for Noradrenaline/M^{-1}	K_{ass} for L-DOPA/M^{-1}	Conditions for K_{ass} Determination	Ref
1	20	–	–	–	NMR Titration; pD adjusted to 8.0 by Na_2CO_3	7
2	Forms insoluble 1:2 **2**:dop complex	–	–	–	See **1**	7
3	23 ± 2	–	–	–	See **1**	8
4	20 ± 2	–	–	–	See **1**	8
5	16 ± 2	–	–	–	See **1**	8
6	43200 ± 6800	–	–	–	Competition (by NMR), relative to absolute K_{ass} determined by UV–Vis.	9
7	71000 ± 6000	–	–	–	Fluorescence titration (50 mM NaOAc, pH 4.74)	10
8	Quenches fluorescence somewhat; not quantified.	–	–	–	Fluorescence quenching of Me_2DAP^+ in 100 mM NaCl, buffered with phosphate to pH 7.0.	11
9	5720 ± 572	5050 ± 505	–	–	Fluorescence titration in 50% MeOH, 50 mM HEPES buffer to pH 7.4.	12
10	7300 ± 730	5750 ± 575	–	–	See **9**	12
11	–	–	–	1600	Fluorescence titration in 100 mM MOPS buffered to pH 7.2 No error estimates provided.	13
12	3400 ± 680	5000 ± 1000	5300 ± 1300	–	Fluorescence titration, 100 mM $Na_2S_2O_3$, 50 mM HEPES, 20 mM NaCl, pH = 7.0, 37°C.	14
13	230 ± 28	200 ± 24	340 ± 41	*nb*	NMR titration; 100 mM phosphate buffered to pH 7. Values agree with UV–Vis competition experiments.	15
14	630 ± 76	550 ± 66	690 ± 83	590 ± 71	See **13**.	15
15	180 ± 22	190 ± 23	190 ± 23	*nb*	See **13**	15
16	1200	–	–	–	Potentiometric titrations, values of K_{eff} at pH 7.4. Values confirmed by UV–Vis titration.	4
17	759	–	–	–	See **16**	4
18	2.4×10^5	–	–	–	See **16**	4
19	246 ± 93	153 ± 21	215 ± 26	–	NMR titration in 50% MeOH	16
20	142 ± 20	21 ± 36	136 ± 14	–	See **19**	17
21	870 ± 35	1230 ± 74	1250 ± 75	–	NMR titration at 27°C. K_{ass} cited are for 1:1 binding.	18
22	161 ± 26	<1	67 ± 7	–	NMR Titration	19
23	178 ± 27	<1	74 ± 8	–	See **23**	19
RNA-aptamer	6.25×10^5	–	3.63×10^5	1.88×10^5	Equilibrium filtration [20]; K_{ass} for noradrenaline by competition experiment	21

[†] Unless otherwise stated, values of K_{ass} were determined at room temperature. Uncertainty in K_{ass} derived from original reports.

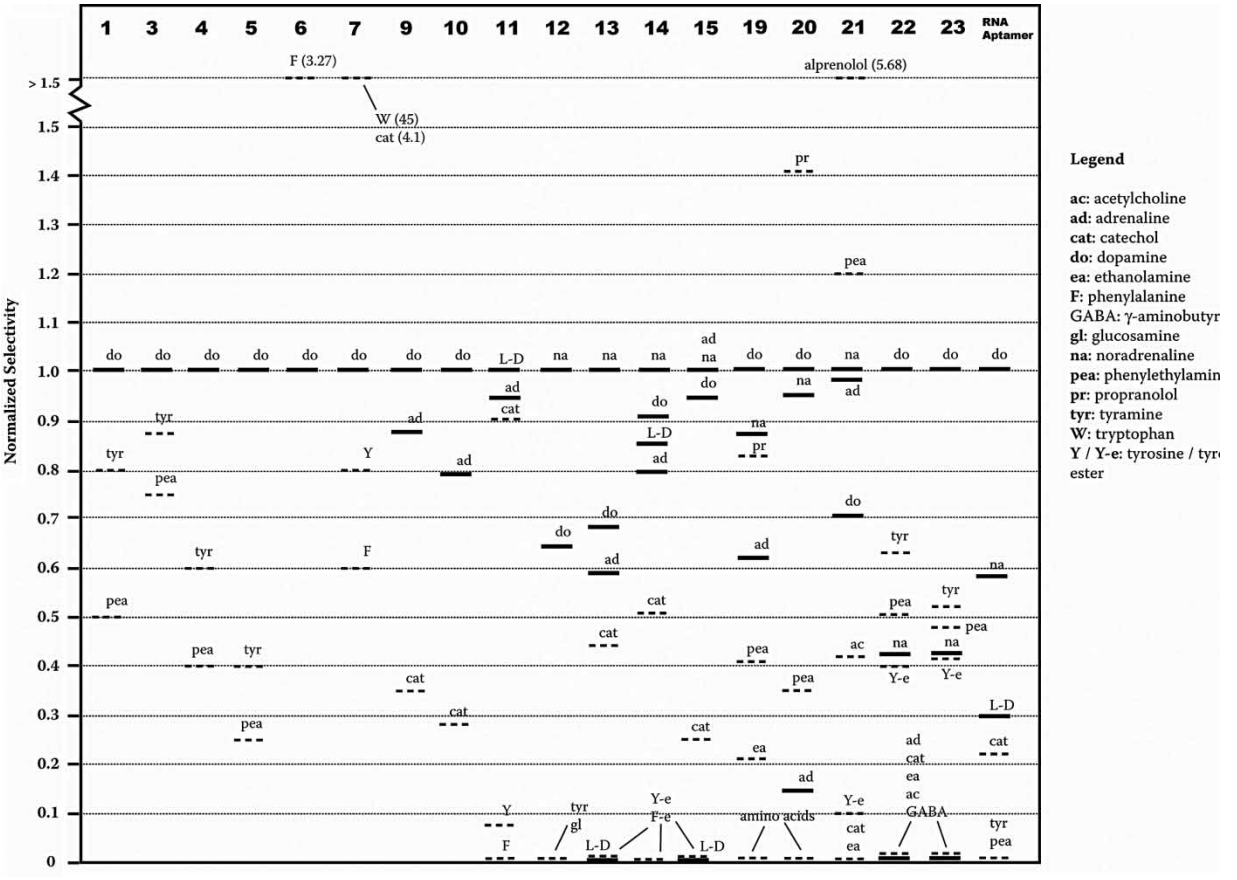
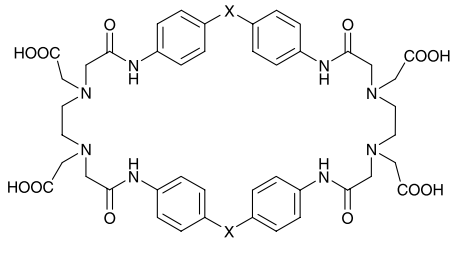
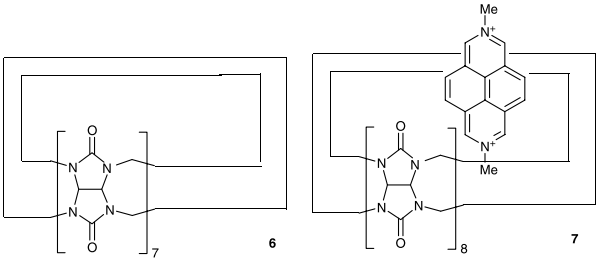


FIGURE 3 Selectivities of catecholamine receptors. Selectivity for **9** determined in 50% MeOH.

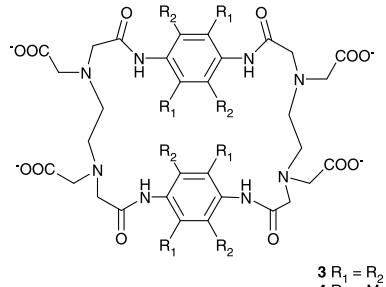
(see Fig. 1), and the interaction is hence of the host with a composite mixture. The binding is modest, and the hosts—despite steric differences—offer little distinction between structurally similar phenethylamines. At higher concentrations of dopamine, precipitation occurred; the solid was determined by ^{1}H NMR in DMSO-d_6 to be the corresponding 1:2 complex of **2** with dopamine.



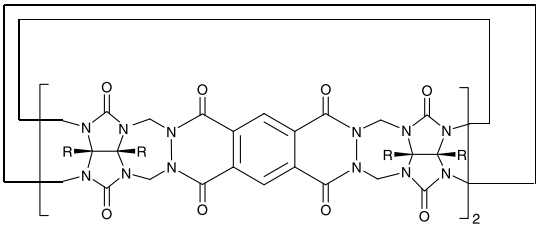
1 X = O
2 X = CH_2



6 **7**



3 $R_1 = R_2 = H$
4 $R_1 = Me$, $R_2 = H$
5 $R_1 = R_2 = Me$



8 R = COOH

Cucurbiturils 6, 7, 8

Cucurbit[*n*]urils (CB[*n*]) are a series of macrocyclic methylene-bridged glycoluril oligomers where *n* designates the number of glycoluril units. The family of compounds is water-soluble, and shows strong and selective interactions with ammonium cations through a combination of ion-dipole interactions, hydrogen bonds, and the hydrophobic effect [22]. While the well-investigated CB[6] shows no binding to the catecholamine family, Isaacs and co-workers recently (2005) reported that **6** (CB[7]) displays strong ($K_{ass} = 4.32 \times 10^4\,M^{-1}$) binding towards dopamine [9]. However, the large, symmetric cavity prefers bulkier guests to the relatively slim dopamine skeleton: **6** will bind a wide array of ammonium ions, with the highest K_{ass} for adamantylamine standing at a staggering $4.3 \times 10^{12}\,M^{-1}$. The receptor clearly has no specific selectivity for catecholamines.

Concurrently, Kaifer and co-workers reported that CB[8] (**7**) forms a stable inclusion complex with 2,7-dimethyldiazapyrenium (1:1 complex with K_{ass} of $9 \times 10^5\,M^{-1}$) with an enhancement of fluorescence [10]. This increase in fluorescence is quenched by addition of a suitable guest; while this effect is not quantified in the paper, it is noted that the quenching is much more pronounced with catechol than dopamine.

A subsequent report from the Isaacs group describes compound **8**, a CB[6] analogue where a flatter cavity (Fig. 4) is obtained by introducing benzene rings at opposing faces. This receptor shows similar binding towards dopamine as **6** [11]. As expected, the combination of cavity shape and hydrophobic effect favor the large surface area, size-matched guests (such as tryptophan) over dopamine.

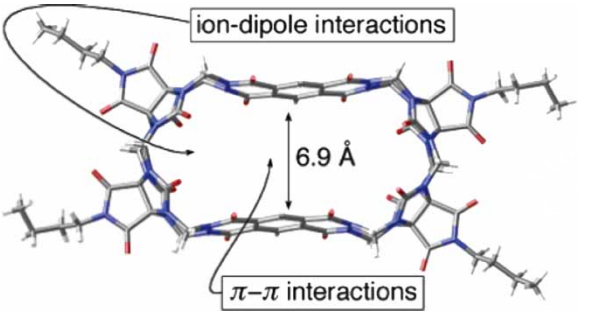
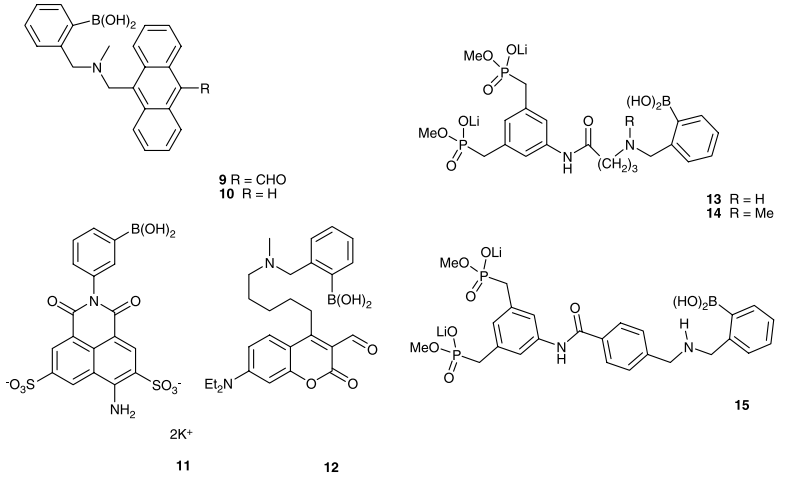


FIGURE 4 Molecular interactions of **8** with dopamine. Figure adapted from reference [11] with permission.

Group 2: Complementary Hosts Based on Boronic Acid Binding

This class of receptors (**9**–**15**), reminiscent of earlier catecholamine selective transporters in organic solvents developed by B.D. Smith and collaborators in the mid-1990's [23], utilize the reversible covalent bond formed between boronic acids and catechols as a specific recognition element. This complexation is pH dependent as the competing equilibria of the boronate species occurs near physiological pH. Amongst this class of compounds, compound **11** is distinct from the others in that it is not an ortho-(aminomethyl) boronic acid, and hence would show different speciation at near neutral pH than the other structures in this class.



Fluorescent Boronic Acid Receptors

A primary feature of receptors **9**–**12** reported independently by several groups in 2004–2005, is that they incorporate a fluorescent platform, which allows facile determination of their binding affinity and is a

step towards convenient optical sensors [24]. While **11** and **12** are reported to bind various catecholamines with K_{ass} on the order of 10^3 in water [13,14], **9** and **10** were reported to be binders of similar strength in 50% MeOH [12]. The absence of reported values in water is speculated to be attributed to poor water solubility of **9** and **10**. Despite **9** having an additional aldehyde which should be able to interact with the primary amine through reversible iminium formation, **9** and **10** show almost identical binding (within experimental error) to dopamine (primary amine) and adrenaline (secondary amine). The geometry of the aldehyde may thus require further optimization.

Compound **11**, an example of a tritopic receptor for L-DOPA (Fig. 5), binds with comparable strength to catechol. This indicates that the contribution from the ammonium-sulfonate interaction is modest, and serves to illustrate the effective charge-screening by water.

Among these, compound **12** reported by Secor and Glass is best characterized, but a complete elucidation of selectivities is not yet reported. While the receptor does not bind with simple amines [14], the expected binding of the receptor to the parent catechol was not evaluated. It was shown that D-glucosamine, with all the hydroxyl groups in *trans* configuration to one another, does not bind well to the receptor. For practical applications [14], it is also necessary to show that the receptor is selective against *cis*-diols (e.g., fructose), which are known to bind to boronic acids with high affinities. The absence of an isobestic point in the UV–vis titration data, suggests that the host-guest complex is not a simple two-state equilibrium, and further experiments may provide insight to the mechanism of binding.

Phosphonate-Boronate Receptors

The acyclic phosphonate-boronate compounds **13**–**15** reported in 2005 by Schrader and co-workers [15] are

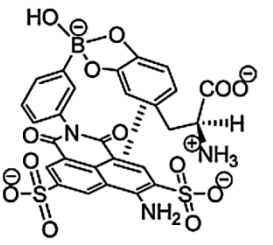


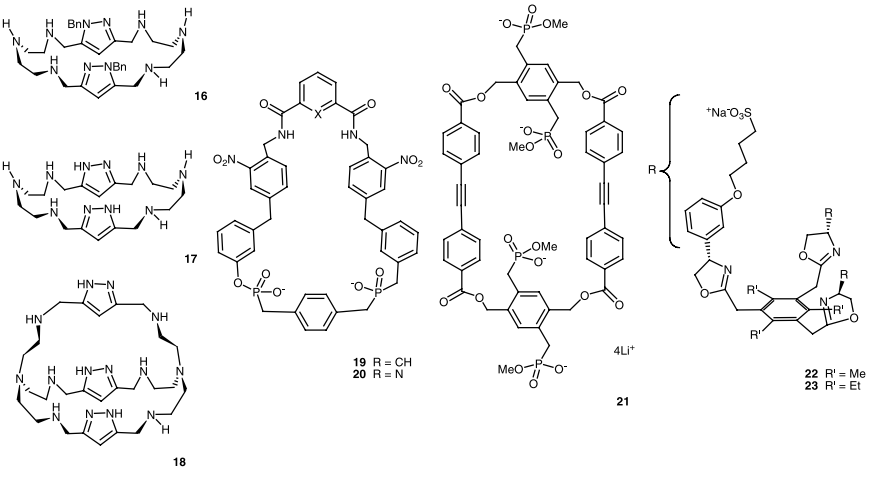
FIGURE 5 Three-point recognition between **11** and L-DOPA. Figure adapted from reference [13] with permission.

conceptually derived from their earlier macrocyclic phosphonates (*vide infra*). Compounds **13** to **15** share the same boronic acid recognition element as **9**–**12**, but possess an additional bisphosphonate recognition elements, the latter with hydrogen-bonding pattern specific for amino alcohols. Among the members of the series, the receptors differ in the spacer flexibility (**13** vs. **14**/**15**) and Lewis basicity of amine (2^0 vs. 3^0 in **14** and **15**, respectively). The binding constants reported are much lower than the other boronate based receptors [15] (Table I); this may be due to the use of phosphate buffers in assays, which competes for boronate binding, or self-association of receptor. The suite of compounds discriminates well against non-catechol species, but expected selectivity amongst catecholamines (based on preference of bisphosphonates to bind amino alcohols over simple amines) was not found. These were applied in a competitive assay scheme (with Alizarin Red) to quantify total amount of catecholamines in bodily fluids with excellent selectivity.

Group 3: Pre-organized Hosts with Integrated Complementary Functionality

Macrocyclic Polyamines 16–18

In 2001, Navarro's group reported the macrocyclic and macrocyclic polyamines **16**–**18** and the investigation of their acid-base chemistry [4].



At physiological pH, an equilibrium mixture exists, where between two to four of the amines are protonated; these ammonium ions are then able to interact with the catechol oxygens [4]. The effective binding constants are larger than expected from simple electrostatic considerations, and the macrobicyclic polyamine binds dopamine with a micromolar K_d, a binding strength second only to the RNA-aptamer discussed below.

In the presence of cupric ions, these compounds exist as a pH- and concentration-dependent equilibrium mixture of various protonated and Cu^{++}-chelating species. At pH 7 and 2:1 Cu^{++}:macrocycle, **16** and **17** forms an exclusive species containing two cupric ions, whereas macrobiscyclic **18** forms a mono-protonated, bis-cupric species [4]. Strong metal-ligand interactions between the copper-bound species with catecholates results in exceptionally stable complexes (log $K_{ass} = 8.9$ for Cu_2**16**), i.e., up to three orders of magnitude stronger binding than the parent compounds on their own [4]. This series of compound highlights the usefulness of the underutilized metal-ligand interaction as anchoring elements in catecholamine recognition [25].

Bisphosphonate Cyclophanes

Concurrently, the Schrader group reported macrocyclic biphosphonates in which the cyclophane structure was expected to provide a suitable cavity [16,17]. Receptors **19** and **20** are similar to **13**–**15** in that bisphosphonates are used as recognition elements; they differ in that the bisphophonates are integrated within a cyclophane, which serves to structurally pre-organize the receptor. These macrocycles are noteworthy in that they are designed to be asymmetric to fit the catecholamines: the catechol functional group was expected to be able to interact with the amide protons on the opposing side. Synthetically, this presents additional challenges to be surmounted, and the compounds are available in 12 steps with a total of 1.3% yield [16]. Conformations of the free host were characterized by NOE spectroscopy. Disappointingly, both receptors self-associate strongly in pure water, and useful association constants can be determined only in 50% MeOH. The binding constants are modest, similar to that of the non-pre-organized **15**. As with **13**–**15**, preference for amino alcohol was expected [26] but not found. An unexpected feature of this pair of heterocycles is that they do not bind amino acid esters at all, and this is not well understood.

Elongated Bisphophonate Macrocycle 21

Compound **21** is a remarkable receptor in that it was rationally designed to form a 1:2 complex with catecholamines in water, and was confirmed to be such experimentally by Schrader and co-workers in 2004 [18]. The solution structure of the resultant 1:2 receptor: adrenaline complex was elucidated with NOE spectroscopy [18]. No cooperativity between binding of guests is found; that is, the binding of the guests is independent of one another. The macrocycle binds all catecholamines with similar strength; it also binds other dopamine receptor agonists (β-blockers). In many cases, the association constant increases with the hydrophobic surface area of the guest, as the hydrophobic effect would predict.

Amphiphilic Tripodes

Ahn *et al.* [19] recently reported a pair of amphiphilic benzene tripodal structures **22** and **23** which bind selected catecholamines with modest strength. Steric gearing on benzene ring provides a pre-organized binding pocket, and solubility was conferred by strategically placed sulfonate groups on the other end of the elongated receptor (Fig. 6). The receptor recognizes ammonium on catecholamines by a combination of cation-π interactions and hydrogen-bonding. Hydrophobic effects were leveraged to match the carbon skeleton, allowing **22**/**23** to differentiate other small ammonium guests. However, since the receptors have no specific interactions with the catechol moiety, they do not differentiate between the various phenethylamines. These structures are note-worthy in that (i) they are open structures that attain the preorganization typical of macrocyclic hosts through steric gearing of different degrees [27], and that (ii) the cavity size allows it to uniquely discriminate between primary and secondary ammonium cations, as well as subtle changes of the carbon skeleton. The latter allows the receptor to clearly differentiate between, e.g., dopamine and adrenaline.

RNA-Aptamer

To set these rationale designs in context, we conclude with a discussion of a RNA-aptamer, reported in 1997 [21], that was selected and amplified using

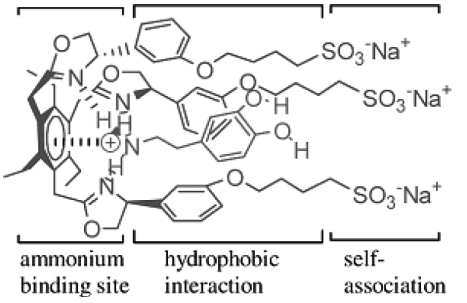


FIGURE 6 Molecular interactions of **22**/**23** with catecholamines. Figure adapted from reference [19] with permission.

biochemical techniques. Following a Darwinian approach, Mannironi *et al* used *in vitro* selection of RNA (SELEX) [28] to obtain a 57 nucleotide (nt) RNA-aptamer with micromolar binding affinity to dopamine. *In vitro* selection begins with a random sequence of RNA (whose single stranded nature allows it to adopt various 3-dimensional shapes), and PCR to amplify sequences that were able to bind to a dopamine-agarose affinity column. The process is repeated with ever more stringent binding requirements until an aptamer that is selective for dopamine is selected and isolated from an initial pool of 3.4×10^{14} different RNA molecules. The resulting aptamer shows excellent selectivity *and* sensitivity. While the fragile nature of RNA prevents this from being of practical commercial use, and the inherently random nature of the experiment (together with difficulties in structural elucidation) leads to no clear chemical insights, this is worth mentioning because it provides optimism that selectivity and sensitivity with relatively small molecules is a legitimate goal.

SUMMARY AND PERSPECTIVE

In this review, we articulated the challenges imposed by the guest and the media, and proceeded to discuss how these challenges were met in each particular case. It is fair to state that, with the exception of the RNA aptamer, no one artificial host is yet both strongly binding and highly selective towards catecholamines. What can we learn from the collective state-of-the-art that can help future designs? What needs to be done to parlay the growing fundamental understanding into feasible technologies, such as sensors?

In the considerations of complex stability, **18** and the cucurbiturils are head-and-shoulders above the others. This seems to suggest that a preorganized host which effectively maximizes the hydrophobic interaction is necessary. It is not known whether other water-soluble, preorganized hosts, such as cyclodextrins or large sulfonated calixarenes are able to interact with catecholamines with similar affinity. The strong affinity towards the cationic Cu_2 **16** suggests metal-ligand interaction as an synthetically accessible alternative to strict preorganization.

The hydrophobic effect in itself is inherently selective only for surface area of the guest, and selectivity must necessarily come from shape and chemical complementarity, preferably with several weak interactions acting in unison. With these criteria, and the example of **7**, a possible future direction is to design stable *binary complexes* as host; a well-chosen host assures the system has adequate solubility and an adequate hydrophobic effect in operation, whereas the included guest can be used to select for the correct functionality and steric requirement. The included guest, like that in **7**, can have additional optical properties; this converts the chemical binding into an optical signal, which is desirable for convenient sensing purposes. This modular design also promises more facile synthesis, which in turn means a larger suite of potential systems to evaluate.

Complementing rational design are strategies that stem from a combinatorial approach. Solid-phase supported combinatorial libraries have generated impressive examples of small molecule receptors, and may hold promise to future generations of catecholamine binders. The dynamic combinatorial approach has shown itself to be capable of generating unexpected structures that recognize substrates in water with both strong binding and high selectivity [29]; while a full analysis is beyond the scope of this paper, further development of the concept could lead to structures highly selective for not only catecholamines in general, but for a particular member within the class [30]. We anticipate continued development within this field in upcoming years.

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