Adrenaline Recognition in Water

Oliver Molt, Daniel Rübeling, Gerhard Schäfer, and Thomas Schrader*[a]

Abstract: Host molecule **1** displays a high affinity in water towards catecholamines and especially related structures such as β-blockers with extended aromatic π-faces (up to $7\times10^{3}\,\text{M}^{-1}$ for each single complexation step or $5\times10^{7}\,\text{M}^{-2}$ for both steps). The amphiphilic structural design leads to an extensive self-association of host molecules through their aromatic flanks. Above a cmc (critical micelle concentration) of $3\times10^{-4}\,\text{M}$, host **1** forms micelles that produce a favorable microenvironment for hydrophobic interactions with the included guest molecules. Electrostatic attraction of the ammonium alcohol by the phosphonate anions is thus combined with hydrophobic contributions between the aromatic moieties. Ionic hydrogen bonds with polar OH or NH groups of the guest enforce the non-covalent interactions, and finally lead to increased specificity. Both its affinity and its selectivity towards adrenergic receptor substrates are greatly enhanced if the receptor molecule **1** is transferred from water into a lipid monolayer. Catecholamines and β-blockers lead to drastically different effects at concentrations approaching the micromolar regime. Especially β-blockers with minute structural changes can be easily distinguished from each other. In both cases, extensive hydrophobic interactions with a self-associated and/or self-organized microenvironment are largely responsible for the observed high efficiency and specificity.

Keywords: adrenergic receptor · beta-blockers · hydrophobic effect · molecular recognition · monolayers

Introduction

Adrenaline is the lead compound of a whole class of catecholamine neurotransmitters and mediates signal transduction across cell membranes.[1] It is a small, highly polar molecule, which is bound very shortly and efficiently by its natural receptor. This recognition eventually leads to a conformational change within the transmembrane helices of the receptor and in turn triggers the activation of the G protein on the cytosolic side of the membrane.[2] A deep binding pocket is needed to provide a sufficiently hydrophobic environment for complete desolvation of the charged hormone. It is flanked by several polar amino acid residues, which are specifically engaged in electrostatic and hydrogen bond interactions with their polar guest.[3] Artificial receptor molecules, which are designed to mimick this binding mode for adrenaline without the 40 kD protein, must find a way to create both the hydrophobic microenvironment and an array of convergent binding sites for efficient interaction with the guests' functional groups.

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Results and Discussion

State of the art: Most artificial catecholamine receptor molecules are not biomimetic at all; recently bipyridinium/gold nanoparticle arrays,[4] phenyl boronates,[5] and pyrazole-containing cryptands have been developed.[6] Bioorganic approaches include RNA aptamers[7] or copper-containing redox enzymes.[8] In the past years, our group has presented several successive generations of adrenaline binders based on a general recognition motif for amino alcohols, which features xylylene bisphosphonate dianions.[9] The hydrophobic contribution comes mainly from macrocyclic cavities with nonpolar walls, which carried the amino alcohol recognition element at the bottom and a catechol-affinity moiety at the top.[10] Thus, adrenaline derivatives and β-blockers have been included in polar organic solvents, in one case with 50% water.[11] However, never was biomimetic adrenaline recognition achieved by bisphosphonates in pure water. Recently, we found that flat receptor molecules for bisamidinium drugs with optimized proportions are able to carry two guest molecules at the same time.[12] By extensive stacking interactions, they maximize the hydrophobic attractions and simultaneously create a good environment for strong Coulomb interactions. The affinity for bisamidines is comparable to that of DNA, which binds them in a 1:1 complex of $K_a=10^{6}\,\text{M}^{-1}$ in its minor groove. It appears that nature often uses this effective combination of powerful salt bridges and

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hydrophobic forces for efficient recognition of small highly polar substrates (e.g., sugar-binding proteins).[13] Would it be possible to bind two adrenaline molecules by a bisphosphonate-based receptor? We decided to optimize the catechole recognition elements and to improve the pre-organization of our macrocyclic receptor cavities. This was indeed realized by the use of tolane spacers for the walls,[14] and by the introduction of a second bisphosphonate moiety in the top part instead of the former aromatic diamide. It stretches the whole macrocyle by repulsion of its four negatively-charged phosphonate anions, and ensures superior interactions with the catechol by ionic hydrogen bonds.[15]

Modeling: Modeling experiments confirmed the expected stiffness of the macrocyclic skeleton; the host alone is calculated in the shape of a twisted rectangle with linear, stiff sidewalls (Figure 1). In a subsequent molecular dynamics calculation only the bridging *p*-xylylene bisphosphonates showed some mobility. The four phosphonate monoanions are all pointing towards the solvent, away from each other. In order to receive guest molecules, only a small amount of energy is needed to produce an open conformation.[16]

The results from Monte-Carlo simulations for such complexes with adrenaline were especially intriguing; the 2:1 complex was indeed calculated to be the most stable one, with a well defined geometry. Each bisphosphonate moiety receives the amino alcohol of one guest in a chelate fashion, and additionally forms hydrogen bonds with the catechole of the other guest. If the second guest molecule was oriented parallel to the first one at the beginning of the calculation, it would always rotate inside the complex, until it finally reached the antiparallel orientation; this ternary complex was reproducibly found as that unique conformation, which was by far the lowest in energy (Figure 2). Subsequent molecular dynamics calculations came to the same result, moreover, host and guest are still mobile enough in the complex for a favorable entropy balance.[17]

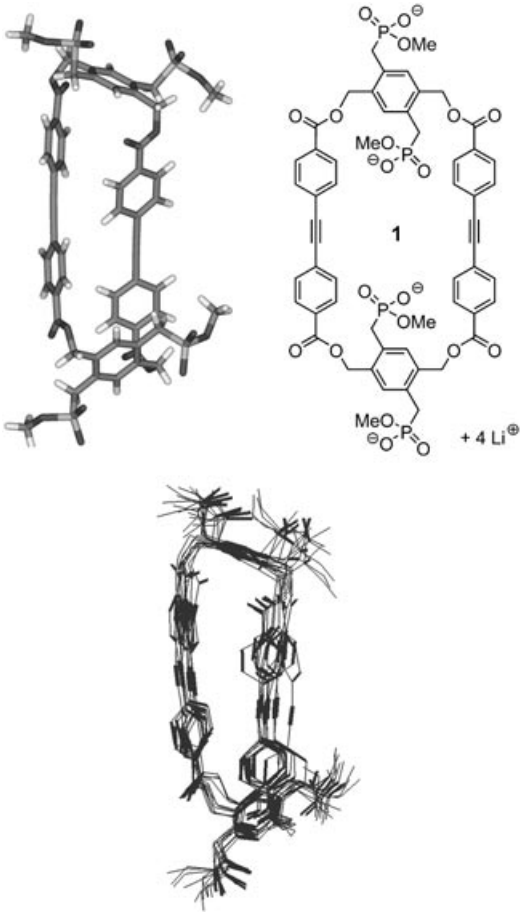


Figure 1. Monte-Carlo simulation (MacroModel 7.0, Amber*, water, 3000 steps) and subsequent molecular dynamics calculation of the free host **1** in water (10 ps, 25 °C, no constraints).

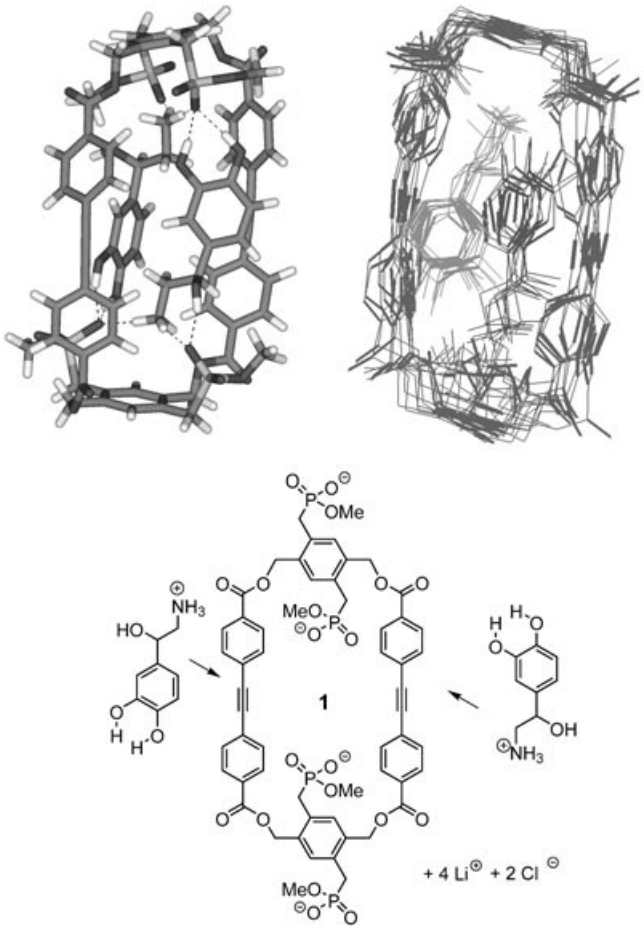


Figure 2. The new receptor molecule **1** with two bisphosphonate moieties and the result of a Monte-Carlo simulation of the 2:1 binding mode with noradrenaline (MacroModel 7.2, Amber*, 3000 steps, water). Top right: subsequent molecular dynamics calculation (10 ps, 25 °C).

Synthesis: A modular approach reduces the synthesis to the alternating connection of two building blocks. The tolane sidewall can be prepared by two successive Sonogashira couplings,[18] whereas the phosphonate-modified *p*-xylylene dibromide is accessible by sequentiel NBS (N-bromosuccinimide)-bromination and the Arbuzov reaction. Although the rectangle can be synthesized in one step by a four component reaction, yields remain low, because a byproduct, presumably the double-sized macrocycle, is also formed. We therefore chose the esterification of two monoprotected

tolane carboxylic acids with the xylylene dibromide head group to afford the U-shaped precursor. After deprotection, cyclization with Cs_2CO_3 (cesium effect) followed.[19] Final mild dealkylation with LiBr furnishes the desired receptor molecule in a 16% overall yield (Figure 3).[20] The lithium tetraphosphonate is soluble in polar media such as methanol and water.

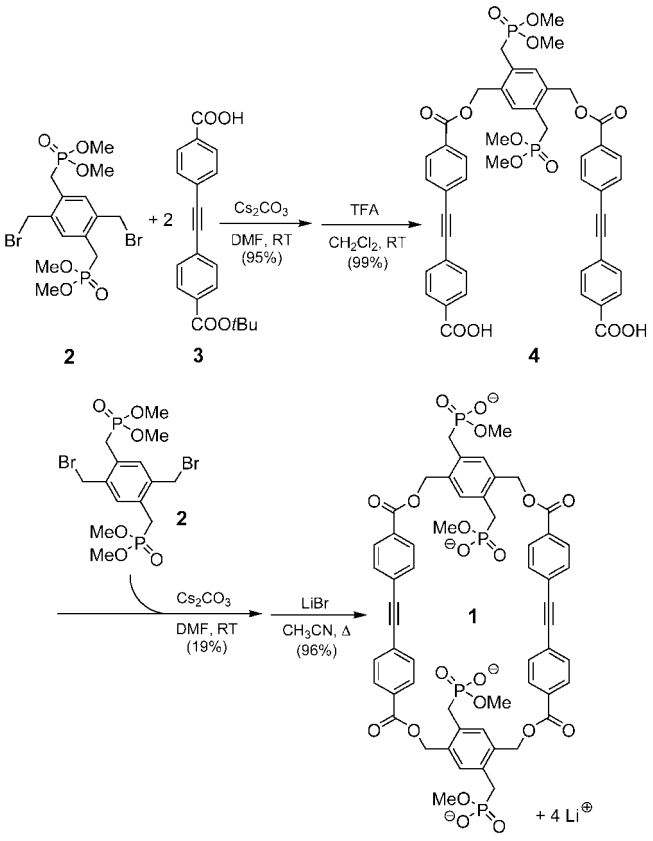


Figure 3. Sequential synthesis of macrocycle **1** from xylylene bisphosphonate **2** and tolane building blocks **3**.

Self association: Contrary to expectations, the NMR signals remained sharp only in methanolic solution, and pure water produced extremely broad "mountains". Although a relatively low value of 130 M^{-1} was determined for the self-association constant by dilution titration, the aggregates are thermally stable up to 90 °C. Since shifts occurred mainly in the tolane region, the host molecules probably aggregate through their stiff unpolar aromatic sidewalls forming vesicle-like structures with a hydrophobic interior. The results from modeling experiments suggest a relatively dense packing of receptor molecules in their thermodynamically most stable twisted form, with close contacts between their tolane sidewalls. In these structures, hydrophobic cavities between neighbouring host molecules offer enough room for the potential insertion of guest molecules, which are too large to be accomodated within the macrocycle's cavity. These intermolecular cavities may explain the extraordinary affinity of the self-associated receptor molecule **1** for unpolar β-blockers (see Figure 4). Surface tension measurements on a Langmuir film balance prove the formation of micelles above a cmc (critical micelle concentration) of 3×10^{-4} M (Figure 4 top). Evidently, host **1** lowers the surface pressure or increases the surface tension. We tentatively explain this unusual behaviour by the concentration of negatively-charged phosphonates at the air/water interface, which leads to an ion-pair reinforced hydrogen-bond network.

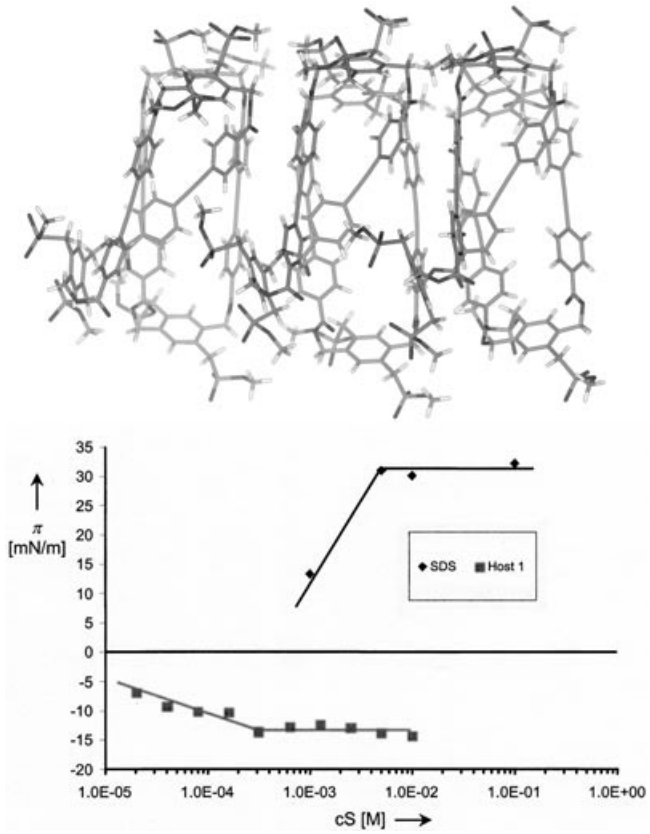


Figure 4. Top: molecular mechanics calculation of a hexameric host aggregate (MacroModel 7.2, water, 3000 steps). Note the similarity to lipid bilayers with polar headgroups and nonpolar vertical ethinylaryl chains. Bottom: surface pressure π [mN m^{-1}] plotted against surfactant concentration c_S [M] at 25 °C.

Binding experiments: Addition of catecholamines to the new receptor molecule resulted in large upfield shifts of the guest molecules, especially in the aromatic region. Job plots indicate a clean 2:1-stoichiometry, as expected from the modeling studies (see Figure 5 and Table 1).[21]

We performed NMR titrations with increasing amounts of host compound and obtained smooth binding curves.[22] They allowed an excellent fit in accordance with the determined complex stoichiometry by nonlinear regression, with standard deviations in the range of 2–10%. No cooperativity could be found in any case, that is, both guest molecules are bound independent of each other with exactly the same binding constant. Therefore, for ease of comparison we always use the 1:1 association constants for each single binding step in [M^{-1}] (Table 2); the overall 2:1 association constants are also given in [M^{-2}]. When we increased the solvent polarity from pure methanol over methanol/water (1:1) to pure water, a remarkable dependence of the 1:1 binding

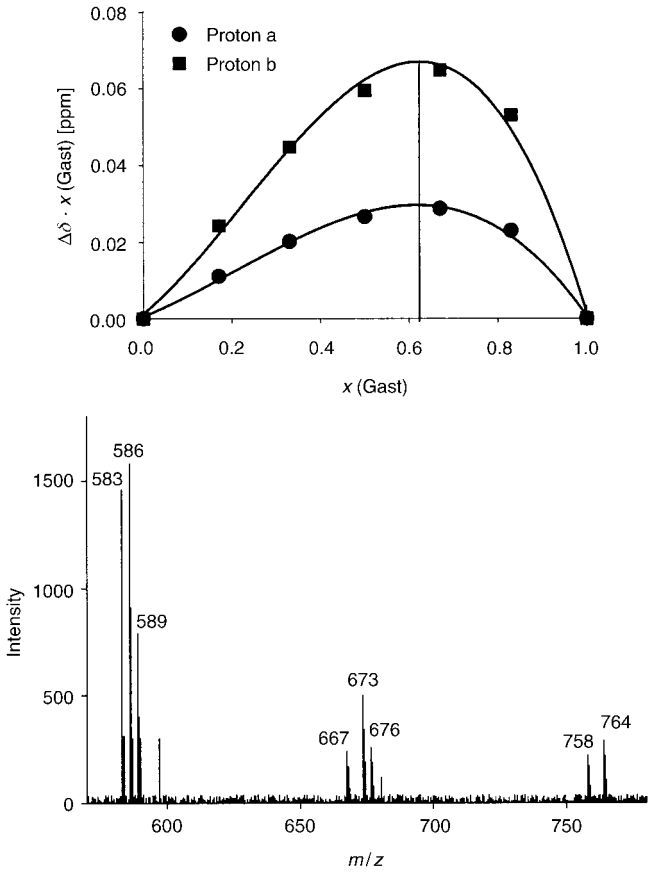


Figure 5. Top: job plot for complex formation between host **1** and noradrenaline **6** in [D_4]MeOH (proton a: C**H**$_2$-NH$_3$Cl, proton b: -C**H**(OH)-); bottom: ESI-MS spectrum for the same complexation with strong molecular ion peaks for the free host, as well as its 1:1 and 2:1 complex with noradrenaline (from methanol).

Table 1. ESI-MS data for the complex formation betwen host **1** and noradrenaline **6** in [D_4]MeOH. Peak values shown for 1:1 and 2:1 complex wih noradrenaline (from methanol).

Species	*m/z* Found	Assignment	*m/z* Calculated
free host **1**	583.1126	$[\mathbf{1}^{4-}+2H^+]^{2-}$	583.0923
	586.1119	$[\mathbf{1}^{4-}+H^++Li^+]^{2-}$	586.0964
	589.1172	$[\mathbf{1}^{4-}+2Li^+]^{2-}$	589.1005
1:1 complex	667.6610	$[\mathbf{1}^{4-}+NA^++H^+]^{2-}]$	667.6293
	673.6583	$[\mathbf{1}^{4-}+NA^++2Li^+-H^+]^{2-}]$	673.6374
	676.6658	$[\mathbf{1}^{4-}+NA^++3Li^+-2H^+]^{2-}]$	676.6415
2:1 complex	758.2089	$[\mathbf{1}^{4-}+2NA^++2Li^+-2H^+]^{2-}]$	758.1744
	764.2065	$[\mathbf{1}^{4-}+2NA^++4Li^+-4H^+]^{2-}]$	764.1826

constant was revealed for noradrenaline **6**. Whereas it amounts to 4000 M^{-1} in MeOD, it drops to ~700 M^{-1} in MeOD/D_2O (1:1); however, transition to pure water again leads to a marked increase up to 1200 M^{-1}! In the same order, the NMR shifts of the guest molecules are also falling and rising, both in the aromatic region (hydrophobic interactions), and in the amino alcohol moiety (electrostatic interactions) (in each case from 0.2 ppm in MeOD over 0.05 ppm in MeOD/D_2O to 0.3 ppm in pure D_2O).[23] We explain this unusual behavior with the observed aggregation of host molecules, which takes place only in pure water. Evidently, under these circumstances the host creates an increasingly hydrophobic microenvironment for the approaching guest, which facilitates the docking/inclusion of even two catecholamine molecules at the same time. Well-defined host–guest complexes with aggregated receptor species have been observed earlier with macrocyclic amphiphilic host compounds.[24]

The opposite orientation of both guest molecules inside the tight complex is strongly supported by NOESY (Nuclear Overhauser and Exchange Spectroscopy) measurements. Contrary to the NOE (Nuclear Overhauser Effect) effects in noradrenaline, those of the host–guest complex are all positive, which indicates a decelerated rotation.[25] One additional NOE occurs between proton **a** and **e** of the guest. Since the distance is much too large for an intramolecular NOE (4.5 Å), this must be an intermolecular crosspeak between the two bound guest molecules. A short distance of 2.5 Å is indeed found in the 2:1 complex structure, but only if both guest molecules are oriented antiparallel to each other (Figure 6). Another indication for the formation of stable 2:1 complexes is found in the ESI-MS (electrospray ionisation mass spectrometry) spectrum, which produces a strong molecular ion peak for this preferred stoichiometry, in addition to a strong peak corresponding to the 1:1 complex. Interestingly enough, the analysis of both complex ion peak series reveals that in each guest, up to two protons are replaced by lithium cations. These must be two acidic phenolic hydrogen atoms, which will be bound to the phosphonates by strong lithium chelate salt bridges. Thus, experi-

Table 2. Binding constants [$K_{a\,(1:1)}$ and $K_{a\,(2:1)}$] as well as $\Delta\delta_{sat}$ values in complexes between host **1** and various guest molecules by NMR titrations in D_2O at 27 °C. For each guest, up to five independent CH proton signals were evaluated. For details, see Supporting Information.

No.	Guest molecules[a]	$K_{a\,(1:1)}$ [M^{-1}][b]	$K_{a\,(2:1)}$ [M^{-2}][b]	$\Delta\delta_{sat}$ [ppm][c]	Stoichiometry[d]
5	serotonin	1620 M^{-1} ± 4%	2.6×10^6 M^{-2} ± 4%	0.59	2:1
6	noradrenaline	1250 M^{-1} ± 6%	1.5×10^6 M^{-2} ± 6%	0.20	2:1
7	adrenaline	1230 M^{-1} ± 4%	1.5×10^6 M^{-2} ± 4%.	0.26	2:1
8	dopamine	870 M^{-1} ± 4%	7.6×10^5 M^{-2} ± 4%	0.33	2:1
9	acetylcholine	530 M^{-1} ± 25%	2.8×10^5 M^{-2} ± 25%	0.07	2:1
10	ethanolamine	< 1	< 1	–	–
11	catechole	< 1	< 1	–	–
12	alprenolol	7100 M^{-1} ± 8%	4.9×10^7 M^{-2} ± 8%	1.10	2:1
13	propranolol	4290 M^{-1} ± 11%	$1.8\cdot10^7$ M^{-2} ± 11%	0.93	2:1
14	atenolol	830 M^{-1} ± 8%	$6.7\cdot10^5$ M^{-2} ± 8%	1.71	2:1
15	2-phenylethylamine	1500 M^{-1} ± 2%	–	0.89	1:1
16	L-tyrosine methyl ester	130 M^{-1} ± 47%	–	0.19	1:1
17	glycine	< 1	< 1	–	–
18	GABA	< 1	< 1	–	–
19	D-glucose	< 1	< 1	–	–

[a] As hydrochloride salts. [b] Errors are calculated as standard deviations from the nonlinear regression. [c] Largest shifts from selected CH protons. [d] From job plots and curve-fitting of the titration curves.

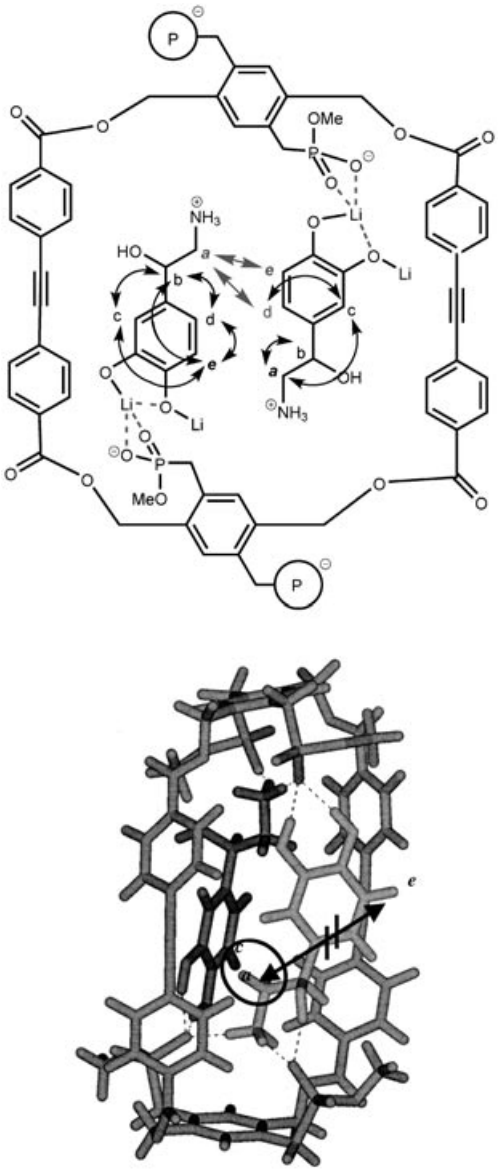


Figure 6. Top: schematic drawing of the complex with intermolecular NOE crosspeaks between the two noradrenaline guest molecules and the additional lithium salt bridges between catechole and phosphonates. Bottom: the arrow indicates protons ***a*** and ***e*** of the noradrenaline guest, which produce a crosspeak only in the complex. The intermolecular distance betweeen ***a*** and ***e*** is much smaller (circle) than the intramolecular (arrow). All NOE's in the complex are positive, strong and reciprocal.

mental evidence has been found for the expected phosphonate–catechol interaction in the complex.

The natural adrenergic receptor (as its synthetic models) binds only one adrenaline guest molecule at a time. A host capable of binding two guest molecules simultaneously has a much higher efficiency. The relative amount of bound noradrenaline in a 2:1 complex with $K_a = 1200\,\text{M}^{-1}$ corresponds to that in a 1:1 complex with $K_a = 2500\,\text{M}^{-1}$; this is true at least up to a host/guest ratio of 1:1. For alprenolol with $K_a = 7000\,\text{M}^{-1}$ in the 2:1 complex this even compares with a K_a value of $\sim 14000\,\text{M}^{-1}$ in the 1:1 complex.[26] The affinity of our new host for adrenaline derivatives in water places it among the most efficient binders kown to date.[27] However, it is much more selective than most other synthetic receptors (see below).

Selectivity: A total of 14 neurotransmitters or structurally closely related guest molecules were titrated with the new host. All catecholamines **6**–**8** gave an excellent 2:1 fit and similar association constants in the range of 900–1300 M^{-1}. The β-blockers alprenolol **12** and propranolol **13** bind especially tightly with 4000 and 7000 M^{-1}, respectively, probably because the extended aromatic rest is capable of optimizing its hydrophobic interactions with the nonpolar surrounding in the aggregates (Figure 7). In this case, a terminal polar group is detrimental for efficient binding, as atenolol only reaches a moderate affinity towards **1**. Binding experiments with **1** in aqueous NaCl (10 mM) demonstrate that electrostatic attraction is important, but strongly supported by hydrophobic interactions, and the K_a value for alprenolol decreases only slightly from 7100 to 2600 M^{-1}.

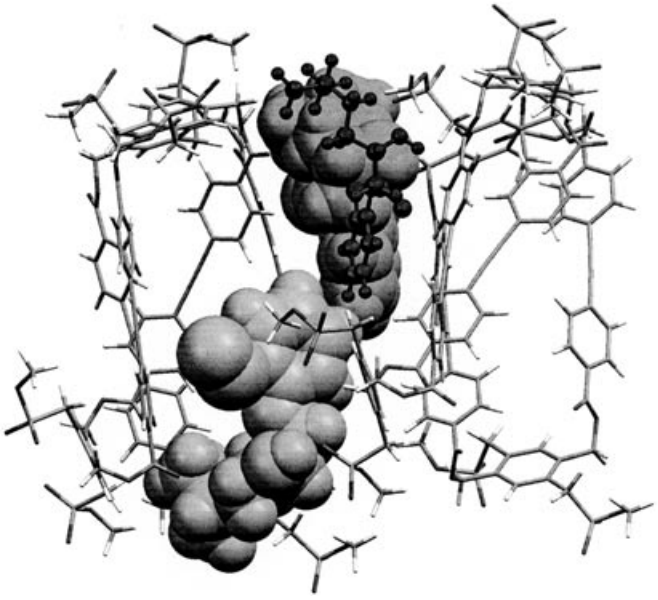


Figure 7. Energy-minimized structure illustrating the efficient inclusion of three alprenolol molecules into a tetrameric host aggregate (MacroModel 7.2, water, 1000 steps).

For effective recognition, electrostatic interactions and the hydrophobic effect are essential. Evidence for this is provided by cutting the catcholamine skeleton into two halves. Neither ethanolamine **10** (ion pairing) nor catechol **11** (hydrophobic attraction) alone show any affinity for the new host. Likewise, the amino acid neurotransmitters glycine **17** and GABA **18** are not bound by the receptor molecule. Even with an ester-protected carboxylate and free ammonium cation complexes with amino acids (e.g., **16**) reach K_a values of only one tenth of those for catecholamines. Accordingly, the new host requires a guest structure with a slim amino alcohol on one end and an aromatic group on the

other end, preferably with polar substituents. These conditions are also met by serotonin **5**, which again binds very well. Polar substituents with hydrophobic faces alone are not sufficient for complexation: no binding occurs with free glucose, although it fits into the cavity of **1**. Small aromatic amines such as phenethylamine **15** are recognized, but only in the form of a 1:1 complex. Large upfield shifts (0.9 ppm) clearly indicate their complete inclusion in the host's cavity (See Scheme 1).

In summary we have found a host molecule that binds catecholamines and especially related structures, such as β-blockers with extended aromatic π-faces with high affinity in water. A combination of electrostatic attraction of the ammonium alcohol and hydrophobic contributions in the aromatic moiety are essential. Ionic hydrogen bonds with polar OH or NH groups of the guest enforce the non-covalent interactions and finally lead to increased specificity.[28] Interestingly, the aggregation of host molecules through their aromatic flanks seems to produce a favorable microenvironment for hydrophobic interactions with the included guest molecules. These observations prompted us to incorporate the new receptor molecule into a monolayer of stearic acid at the air/water interface.[29]

Langmuir film balance: Despite its highly charged tetraanionic nature, the new host molecule is amphiphilic enough to produce a marked linear increase in the pressure/area (π-A) diagram of stearic acid on a Langmuir film balance; this indicates the embedding process.[30] Contrary to former experiments with a less polar macrocyclic bisphosphonate, the picture of a connected Brewster angle microscope remained smooth without any appearance of patches.[31] Large arrays or domains of the self-aggregating host molecules seem to be avoided, probably because of self-repulsion among the surrounding negative charges. Latest bioanalytical results show that even the natural adrenergic receptors only form dimeric structures.[32] With only a 0.4 equivalent of receptor per stearic acid, a highly sensitive doped monolayer evolves, which distinguishes not only between catecholamines and β-blockers as such, but also between structurally related compounds of the same class.[33] Moderate increases in the π-A isotherm [1–3 Å^2/molecule] are characteristic of catecholamine binding; this is similar to observations from macrocyclic and tweezer-type bisphosphonate receptors examined before (Figure 8, Table 3). Negative controls revealed that

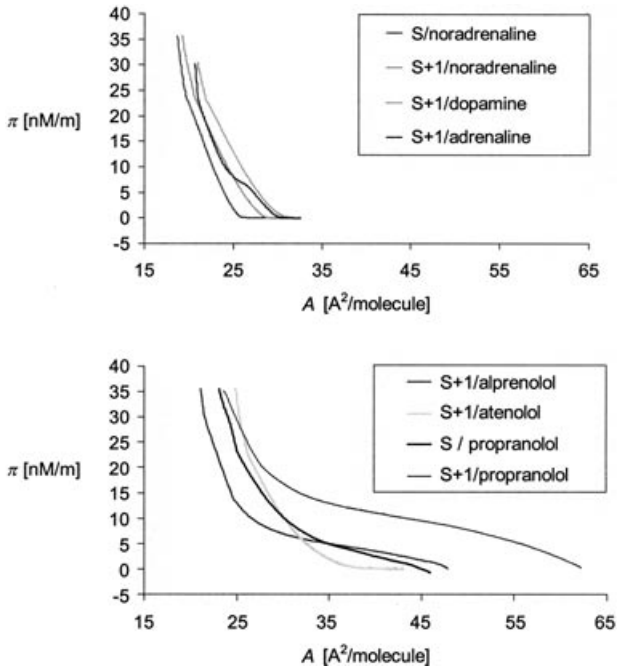
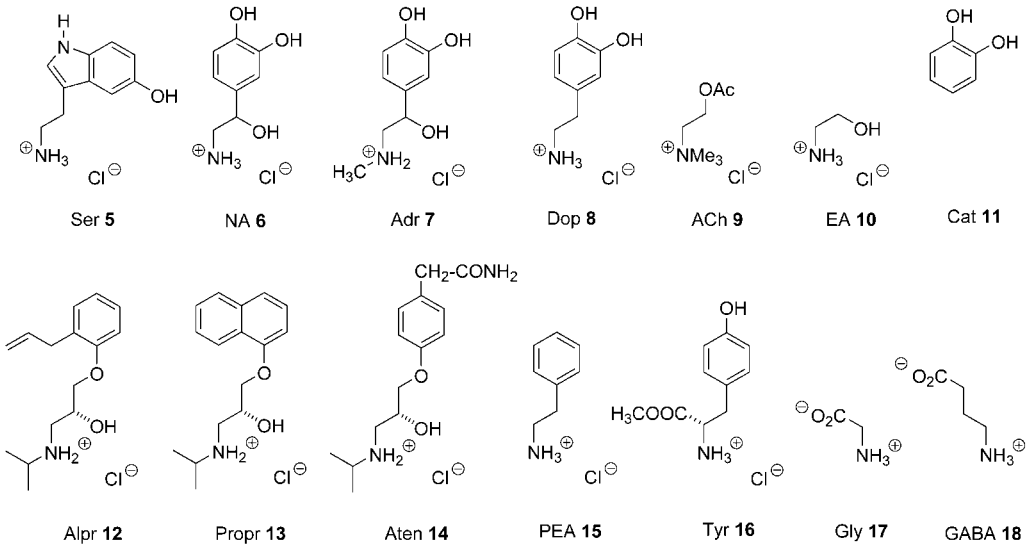


Figure 8. Top: pressure-area-isotherms of stearic acid (S) and receptor **1** in monolayer over water with noradrenaline (NA), adrenaline (Adr) and dopamine (Dop). Reference: pure stearic acid over noradrenaline. Bottom: pressure-area-isotherms of stearic acid (S) and receptor **1** in monolayer over water, with alprenolol (Alp), atenolol (Aten) and propranolol (Prop). Reference: pure stearic acid over propranolol.



Scheme 1. Guest molecules for host **1**, tested in solution and at the air/water interface.

Table 3. A_0 and ΔA_0 values of stearic acid monolayers with embedded receptor **1** over different subphases. A_0 = apparent total area of one stearic acid molecule in the liquid condensed phase; $\Delta A_0 = A_0$ (monolayer with **1** over guest soln.) A_0 (monolayer with **1** over water), that is, net influence of the guest. Monolayer: 0.2 equiv. of receptor molecule **1** per stearic acid molecule; guest molecules at 10^{-4} M.

Monolayer	Subphase	A_0 [Å^2/molecule]	ΔA_0 [Å^2/molecule]
stearic acid	Water	20.5	–
stearic acid + **1**	Water	21.5	1
stearic acid	noradrenaline (~catecholamines)	21.5	0
stearic acid + **1**	(*R*/*S*)-noradrenaline	23.5	2
stearic acid + **1**	(*R*/*S*)-adrenaline	22.5	1
stearic acid + **1**	dopamine	24.5	3
stearic acid	propranolol (~β-blockers)	27.5	0
stearic acid + **1**	(*R*/*S*)-alprenolol	23.5	−4
stearic acid + **1**	(*R*/*S*)-atenolol	29.0	1.5
stearic acid + **1**	(*R*)-propranolol	32.5	5

in all cases no interaction takes place between the guest molecules and the stearic acid monolayer itself. By contrast, all β-blockers examined in our study drastically expanded the pure monolayer by ~6 Å^2 per molecule. Subinjection of the antihypertensives produced very distinct additional changes in the π-A diagram, which demonstrate the exquisite selectivity and high affinity of the immobilized receptor molecules for structurally related β-blockers. Atenolol, propranolol, and alprenolol differ only in the substitution pattern of their terminal phenoxy aromatic group. Atenolol leads to a moderate increase in π-A, whereas propranolol dramatically expands the monolayer especially in the liquid phase [=5 Å^2/molecule]. Alprenolol finally leads to a strong negative π-A shift of 4 Å^2/molecule.

We explain this divergent behavior with a model, developed earlier for amphiphilic water-soluble host molecules. Since guest molecules are subinjected into the aqueous phase, they are bound by solvated receptor molecules close to the monolayer. The host molecules' negative charges become neutralized in part and their lipophilicity increases. This in turn leads to reincorporation of the whole complex into the monolayer and explains the moderate increases observed with the three catecholamines; these correspond to their similar binding constants in water (Table 2). β-Blockers lack the polar catechol moiety leading to a nonpolar aromatic headgroup; this makes them much more amphiphilic and explains their tendency to insert the hydrophobic heads into the lipid monolayer. Incorporation of the receptor molecule into the monolayer leads to a moderate additional increase in π-A, which corresponds to its moderate binding constant. Propranolol, on the other hand, provides an expanded π-face for more efficient stacking interactions with the receptor, and seems to form loose hydrophobic aggregates in the lower pressure region, which are only dissolved as the pressure increases. The smaller and compact alprenolol finally binds so tightly to the host, that its complex is drawn from the monolayer back into the aqueous subphase. Since large π-A changes can still be detected far below 10^{-4} M^{-1}, a rough estimation of the respective binding constants at the air/water interface leads to K_a values which must clearly surpass 10^5 M^{-1} and might be used for new β-blocker sensoring devices.[34] Thus, the new microenvironment in the monolayer leads to high selectivity for minute structural changes in the analytes.[35] A complete list of changes in the π/A diagrams induced by various related guest molecules is summarized in Table 3 (see also Figure 9.

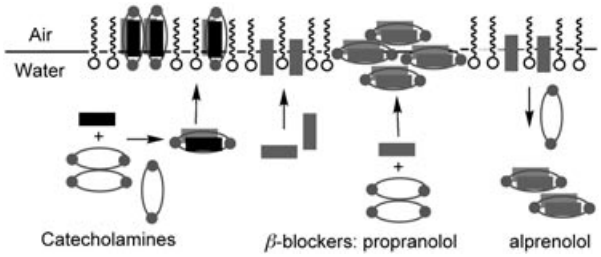


Figure 9. Proposed binding modes for catecholamines and β-blockers within the monolayer.

Conclusion

We conclude that the transfer of receptor molecule **1** from water to the altered microenvironment within a monolayer greatly enhances both its affinity and its selectivity towards adrenergic receptor substrates. Catecholamines and β-blockers lead to drastically different effects at concentrations approaching the micromolar regime. Especially β-blockers with minute structural changes can be easily distinguished from each other. In both cases, extensive hydrophobic interactions with a self-associated and/or self-organized microenvironment are largely responsible for the observed high efficiency and specificity. In the future we intend to incorporate the new macrocyclic receptor molecules into alternating layers of receptor and ammonium-stabilized gold nanoparticles attached to an ITO (indium tin oxide) electrode for electrochemical detection of catecholamine derivatives and β-blockers (Figure 10).[36]

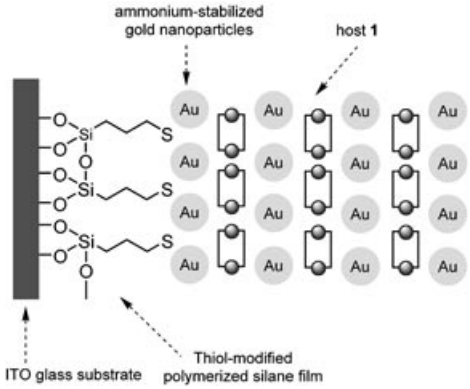


Figure 10. Schematic illustration of the new proposed array of alternating layers composed of receptor molecules **1** and cationic gold nanoparticles on ITO.

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