Towards Synthetic Adrenaline Receptors—Shape-Selective Adrenaline Recognition in Water**

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Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 68th birthday

Abstract: In spite of their key role in signal transduction, the mechanism of action of adrenergic receptors is still poorly understood. We have imitated the postulated binding pattern of the large membrane protein with a small, rationally designed synthetic host molecule. Experimental evidence is presented for the simultaneous operation of electrostatic attraction, hydrogen bonds, π stacking, and hydrophobic interactions. By virtue of this combination of weak attractive forces, adrenaline derivatives in water are bound with high shape selectivity for the slim dopamine skeleton. We think that these findings support the postulated cooperative interplay of noncovalent interactions in the natural receptors. In addition, they provide access to a new type of adrenaline sensor. This may be the first step towards an artificial signal-transduction system.

Keywords: dopamines · epinephrine · hormones · molecular recognition · receptors

Introduction

G-protein-coupled receptors (GPCRs) are probably the most intensively investigated among all receptor groups. 60% of all commercially available drugs interact with GPCRs, with a world market volume of 84 billion USD in 1995. Adrenergic receptors make up one of the major classes in the GPCR family.[1] They are expressed throughout the human body, and are involved in vital signal transduction processes from the extracellular environment across the cell membrane into the cytosol. For medical treatment, the adrenergic receptor antagonists are most interesting, because they can suppress pathological symptoms by blocking the binding sites of the respective receptors. A well-known example is propranolol, which is a β-blocker and treats hypertension.[2] β-Adrenergic receptors are important targets for therapeutic agonists and antagonists in treatment of heart failure or asthma.[3] The use of selective α-1A-adrenoceptor antagonists is an efficacious way to treat benign prostatic hyperplasia.[4] Today adrenergic receptors are still hot topics for pharmaceutical research. The medical treatment of chronic heart failure has undergone a remarkable transition in the past ten years. The approach has changed to a more long-term, reparative strategy, which relies on treatment with β-adrenergic blocking agents. β-Blockers have, in fact, become the most extensively studied class of agents in the treatment of congestive heart failure.[5] Despite recent advances in the crystallization of membrane-bound proteins,[6] no crystal structure of any adrenergic receptor has been resolved to date. Homology modeling of similar G-protein coupled receptors and site-directed mutagenesis experiments have provided quite detailed pictures of tertiary structures, but they still remain somewhat speculative. Thus, the exact mechanism of adrenaline and antagonist recognition remains unknown. In addition, the signal transduction path from the initial adrenaline binding across the membrane into the interior of the cell resulting in G-protein activation has not been fully elucidated to date. We think that by synthesizing small model receptors, chemists can learn from nature about the efficient interplay of noncovalent interactions, necessary for efficiency and selectivity in molecular recognition. Such a small model receptor could allow a systematic study of the influence of certain noncovalent interactions on the overall binding enthalpy. It could also shed new light on the specific combination of noncovalent interactions present in natural receptors. In our case, the design of an efficient adrenaline sensor would also open the path for the design of an artificial signal transduction system.

In the past decade, the flourishing development of supramolecular chemistry combined with the pharmaceutical interest in catecholamines inspired many groups to design artificial host molecules for this important class of com-

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pounds. However, most of these structures were monotopic, that is, they recognized only one typical functional group of their guest. Thus, the ammonium group was bound by crown ethers[7] or ester crowns.[8] Certain cyclopeptides are able to distinguish between the enantiomeric forms of noradrenaline.[9] Zinc porphyrin tweezers[10] and xylylene bisphosphonates[11] offer the advantage of selectivity for amino alcohols. Most of these artificial receptors have been developed primarily for dopamine recognition, and in some cases dopamine selectivity has been found: a pyrazole-containing podand imitates the crown ether environment around the guest;[12] a homooxacalix[3]arene triether was incorporated into liquid membranes with a PVC matrix, which then showed a dopamine-selective change in their membrane potential,[13] and template recognition was achieved with dopamine in organic–inorganic hybrid films prepared by a sol–gel process.[14] Monotopic catechol recognition was achieved either with an aza crown, which forms hydrogen bonds to the catechol hydroxyls,[9] or with bipyridinium moieties, which exert a π-stacking attraction on the electron-rich catechol ring.[15] Combined with a peptide tether this has been exploited for enantioselective dopamine recognition.[16] Some of these simple binding motifs have been combined with powerful analytical methods: crown ethers have found applications in capillary zone electrophoresis,[17] phenylboronates are used for electrochemical detection of catecholamines,[18] and ω-mercapto poly(ethylene glycol) SAMs (self-assembled monolayers) on gold electrodes can quantify the dopamine content in the blood serum.[19] Interdigitated array microelectrodes have also been used as electrochemical sensors for catecholamines.[20] In recent years, several ditopic receptor structures have been developed, which again focus on ammonium and catechol binding for efficient dopamine recognition: (aza)crowns bind the ammonium functionality by means of hydrogen bonds.[21] For catechol recognition a whole arsenal of different binding motifs has been developed, ranging from protonated azacrowns for hydrogen bonds with the phenolic oxygens[22] to macrotricyclic hydrophobic cavities that include the anionic catechol ring at higher pH values.[23] π–π Interactions with quinones,[23] hydrogen bonds to phosphonate anions[24] as well as kinetically fast, reversible covalent bonds to boronic acids[25] are alternatives for efficient catechol recognition. Even nonpolar cavities supported by peripheral carboxylates for nonspecific Coulombic attraction have been used for the construction of ditopic dopamine hosts.[26] Finally, a bioorganic approach generates dopamine-selective RNA aptamers by in vitro selection.[27] However, none of the above-mentioned synthetic receptor molecules is specific for catechol amino alcohols, and most are far from a biomimetic recognition pattern.

Our own previous work began with the discovery that in highly polar organic solution *m*- and *p*-xylylene bisphosphonates bind to 1,2- and 1,3-amino alcohols one order of magnitude tighter than to ordinary primary and secondary amines.[5a] Attachment of aromatic arms on the remaining phosphonate ester functionality led to second-generation receptor molecules, which showed a modest increase in binding energy with catecholamines as a result of π–π interactions.[5b] The next step was the imitation of the deep aromatic cleft in the natural adrenoceptor by a hydrophobic macrocycle with peripheral phosphonates for an induced-fit process (Figure 1).[28] In **1**, the catechol ring is indeed buried in the macrocyclic hydrophobic cavity. Unfortunately, this new host undergoes strong self-association in water and cannot distinguish between amino acids and adrenaline derivatives.

Results and Discussion

To make the fourth generation of biomimetic artificial adrenaline receptor molecules we followed a new concept: in order to maximize van der Waals interactions and hydrophobic forces, we developed a macrocyclic system with integral phosphonate moieties (Scheme 1). Their incorporation into the macrocyclic framework should favor a complex geometry in which all binding sites of the receptor surround the adrenaline molecule. Thus, close contacts lead to strong electrostatic attraction and ideal hydrogen bonds, and also help desolvation in water. Additional hydrogen bonding sites for the catechol hydroxy groups and a potential sandwich-type arrangement for catechol recognition by π stacking were further features of this new host design. The result was recently published as the first shape-selective adrenaline host molecule, which mimics the natural receptor and binds adrenaline derivatives in water.[29]

In receptor **2a**, the amino alcohol can be bound by the *p*-xylylene bisphosphonate moiety, whereas the catechol ring is flanked by two electron-poor nitroarenes, supported by the isophthalamide head group for hydrogen bonds to the phenolic hydroxy groups. This is close to the picture that

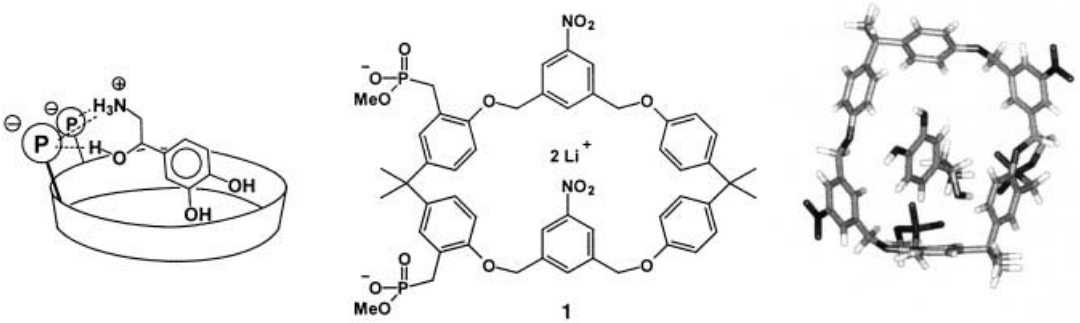

Figure 1. Macrocyclic host **1** with a hydrophobic cavity and peripheral phosphonates for ditopic recognition of adrenaline derivatives; left: schematic design; center: Lewis structure; right: conformational minimum calculated with Cerius² molecular simulations, force field: Dreiding 2.21.

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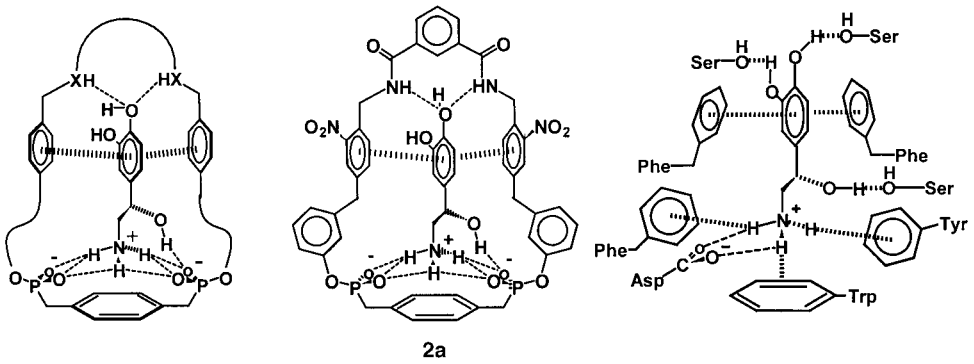


Scheme 1. Multipoint binding of adrenaline derivatives by biomimetic adrenaline host **2a** with integral phosphonates. Left: schematic illustration of the planned interactions; middle: proposed binding mode; right: natural binding pattern of noradrenaline in the β-adrenergic receptor.

emerged from site-directed mutagenesis studies, molecular modeling, and electron-diffraction experiments for the natural example.[30] There, the ammonium functionality is bound by electrostatic interactions and hydrogen bonds to an aspartate, enforced by π–cation interactions with surrounding aromatic amino acid residues. The catechol ring is buried in a deep cleft between two phenylalanine residues. The aliphatic as well as both phenolic hydroxy groups are each hydrogen-bonded to a serine OH (Scheme 1).

In force-field calculations (MacroModel 7.0, Amber*) minimum energy structures were found, which correspond to the postulated arrangement in Scheme 1. High binding enthalpies result from the combination of electrostatic interactions, hydrogen bonds, and van der Waals attraction. We carried out Monte Carlo simulations in water (3000 steps), followed by a molecular dynamics run at ambient temperature for 10 ps. The resulting optimized complex geometries are depicted in Figure 2. In the complex, noradrenaline fits snugly into the cavity formed by the macrocyclic host. However, a relatively high degree of flexibility is still maintained, as demonstrated by the stacked plot of 10 snapshots from the molecular dynamics calculations. Whitesides and others have shown that benzylic bonds especially contain a lot of torsional entropy, resulting from the unhindered rotation around these bonds.[31] Our macrocycle possesses eight benzylic bonds, which might reduce the degree of preorientation, but on the other hand facilitate an induced-fit process.

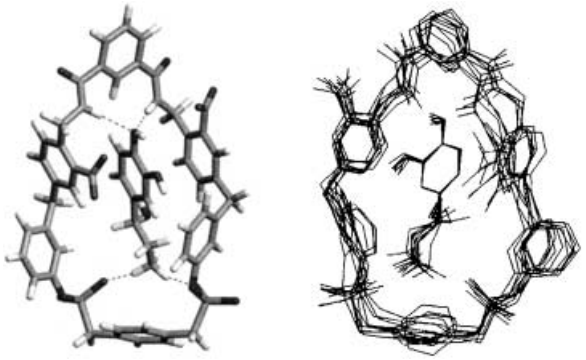
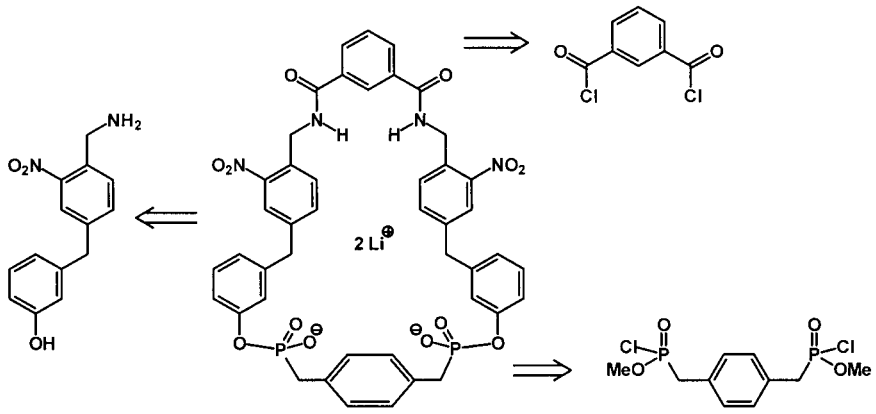


Figure 2. Left: Optimized complex geometry according to Monte Carlo simulations in water for the inclusion of noradrenaline inside the cavity of macrocyclic host **2a**. Right: Superimposed snapshots of the subsequent molecular dynamics calculation.

Synthesis: The encouraging modeling results prompted us to develop a modular, highly convergent synthesis for **2a**, which allows for the simple construction of structural analogues. Two synthetic cuts lead to three smaller building blocks, namely an activated *p*-xylylene bisphosphonate, a functionalized diphenylmethane and an isophthaloyl derivative (Scheme 2). We decided to begin with the diphenylmethane centerpiece, attach two of them to the bisphosphonate, and finally close the macrocyclic ring by a double amidation with isophthaloyl dichloride.

The main synthetic challenge of the whole pathway resides in the highly and asymmetrically functionalized diphenylmethane derivative. This unit has been a favorite structural key element in artificial receptor molecules for years.[32] It combines a relatively high degree of preorganization (owing to the absence of multiple torsional degrees of freedom) with the potential to create an electron-rich environment in its concave inner sphere, fine-tuned by appropriate substituents

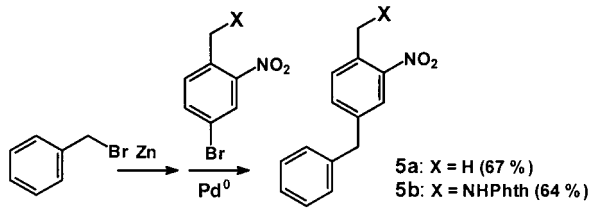


Scheme 2. Retrosynthetic analysis of macrocyclic host **2a**: three building blocks open the path to a flexible modular synthesis with many variations.

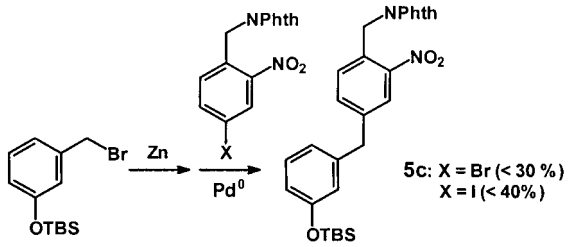
on its phenyl rings.[33] However, most of the open-chain or macrocyclic hosts based on this moiety were restricted to symmetric geometries because the general route to diphenylmethane derivatives employs the double attack of formaldehyde on two electron-rich arenes.[34] Consequently, most of the published synthetic receptor molecules that carry a diphenylmethane unit show only small selectivity for unsymmetrical or even chiral substrates. To improve their recognition pattern, the regioselective introduction of specific binding sites on the diphenylmethane skeleton would be beneficial. Few synthetic pathways exist that lead to unsymmetrical diphenylmethanes: one of them is an acid-catalyzed Friedel–Crafts alkylation of an electron-poor benzyl alcohol with another arene.[35] However, many benzyl alcohols polymerize under strongly acidic conditions, and the directing influence of their substituents may dictate an undesired chemoselectivity.

We think that **2** is a good example for a highly demanding diphenylmethane synthesis, because it carries three acid-, base-, or nucleophile-sensitive groups that have to be selectively protected and later deprotected for the construction of the macrocyclic receptor molecule. After trying the classical methods described above without success, we turned to organometallic chemistry. In principle, benzylic halides can be alkylated by a variety of metallated arenes, such as organolithium, cuprate, or Grignard reagents.[36] Some of these have already been used to furnish unsymmetrical diphenylmethanes with electron-rich arenes.[37] We tried all of these, combining *O*-THP(tetrahyropyranyl)-protected nucleophiles with simple nitrobenzyl halides. Starting from 4-amino-2-nitrotoluene, we prepared the phthalimide-protected as well as the butyloxycarbonyl(Boc)-protected benzylamines **3c** and **3e** with a reactive halide in the *para* position (see Scheme 5). The other part came from *m*-cresol, which was converted into the corresponding *O*-THP- or *O*-TBS-(*tert*-butyldimethylsilyl)-protected benzyl bromides. However, in all cases, the highly reactive organometallic reagent attacked the nitro group. Organozinc compounds are much milder,[38] but for an efficient cross-coupling reaction they must be activated, for example by conversion into zinc alkylcuprates.[39] However, even these can engage in side reactions with nitroarenes. An interesting alternative is the Pd^0- or Ni^0-catalyzed cross-coupling of benzylzinc reagents with bromo- or iodoarenes, introduced by Negishi.[40] This very mild and highly efficient procedure operates at ambient temperature and consists of two steps: first a benzyl bromide is treated in THF with metallic zinc to generate the benzylzinc reagent without homocoupling, then the resulting solution is slowly added to a mixture of aryl bromide or iodide, bis(triphenylphosphanyl)palladium dichloride, and diisobutylaluminum hydride (DIBAL-H) in the same solvent. With rigorous exclusion of air and humidity, the reaction is complete after several hours and typically affords products with 70–95% yield (Scheme 3).

We started our coupling attempts with simple precursors and systematically included more of the functional groups in **2**, in order to explore the scope and limitations of this method for the construction of various unsymmetrical diphenylmethanes. Reaction of the unfunctionalized benzylzinc reagent with the simple nitro-substituted bromobenzene proceeded smoothly; even the introduction of an additional phthalimidomethyl group in the electrophilic bromobenzene does not disturb the coupling reaction (**5a/b**, Scheme 3). However, the yield dropped drastically when, instead of simple benzyl bromide, the TBS-protected phenol was used (**5c**, Scheme 4). The problem resided in the metallation step:



Scheme 3. First experiments in coupling of simple molecules to yield unsymmetrical diphenylmethanes for use in adrenaline receptor synthesis.



Scheme 4. More simple molecule couplings yielding unsymmetrical diphenylmethanes.

it came from the unreactive benzyl bromide, which needed elevated temperatures to form the corresponding benzylzinc reagent, with the consequence of the unwanted homocoupling side reaction. The low yield (around 10–30%) was only marginally raised to $\leq$40%, when instead of the bromobenzene the iodo analogue was used. Although this showed that a more reactive aromatic halide produced a more reactive Pd reagent, the solution to the problem of unsatisfactory yields had to be sought in a more reactive benzyl bromide.[41] Replacement of the TBS protecting group with an acetyl one finally led to a reproducible 60% total yield in the Negishi coupling step (**5d**, Scheme 5).

For solubility reasons and for more convenient deprotection, the phthaloyl group (**3c**) was replaced with a Boc moiety (**3e**). The new, acidic amide NH functionality did not interfere with the attack of the benzylzinc reagent on the Pd intermediate; again, clean conversion of both starting materials was observed. The orthogonal protection strategy allows selective removal of both protecting groups; this may become very important if it is not clear at the beginning of the synthesis at which position the final macrocyclization should take place. In our case, it is possible either to liberate only the phenol with potassium carbonate in absolute methanol, or to deprotect selectively the amine with 50% trifluoroacetic acid (TFA) in dichloromethane, both at room temperature.

We believe that this example demonstrates the versatility of the Negishi coupling reaction, which is an extremely mild reaction and therefore tolerates a wide variety of acid and base-sensitive groups, including the notorious disturber of

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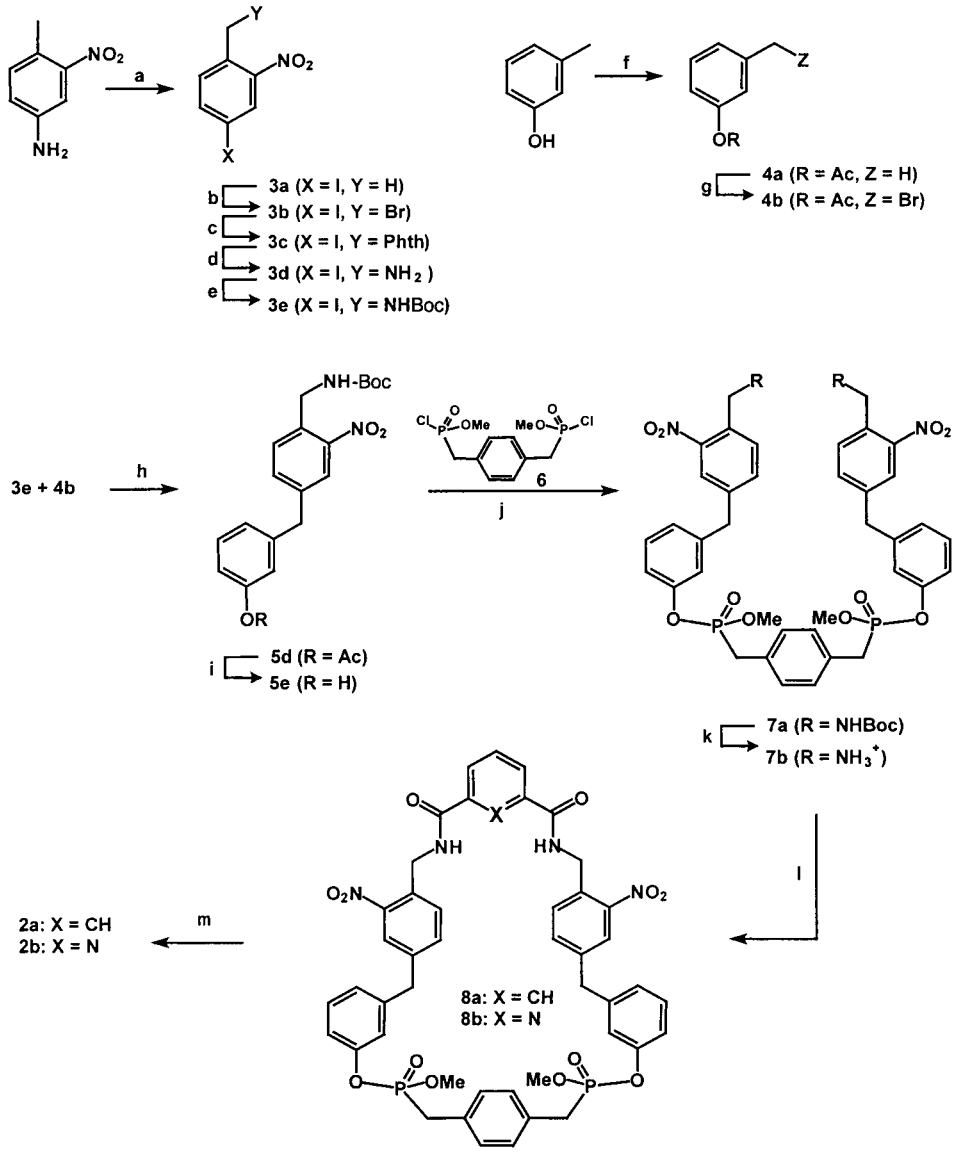

Scheme 5. Modular and convergent synthesis of hosts **2a** and **2b** from 4-amino-2-nitrotoluene, *m*-cresol, and *p*-xylylene bisphosphonic acid dimethyl ester dichloride; a) 1. $NaNO_2$, 2. KI (61%); b) NBS, CCl_4 (46%); c) K phthalimide, [18]crown-6, toluene (94%); d) N_2H_4, ethanol (65%); e) Boc_2O, CH_2Cl_2 (95%); f) Ac_2O (89%); g) NBS, CCl_4 (47%); h) 1. Zn, reflux, 2. $[Pd(PPh_3)_4]$/DIBAL-H (58%); i) K_2CO_3, methanol, RT (94%); j) CH_2Cl_2, Et_3N (57%); k) TFA, CH_2Cl_2, 0 °C (99%); l) isophthaloyl chloride or pyridine-2,6-dicarboxylic acid dichloride, Et_3N, THF, benzene, RT (**8a**: 38%; **8b**: 32%); m) LiBr, acetonitrile, 80 °C (**2a**: 66%; **2b**: 82%).

organometallic reactions, the nitro group. However, for retrosynthetic analyses one should always bear in mind that the aromatic precursor for the benzylzinc reagent must be as electron-poor as possible. Slightly electron-donating (+I or +M effect) groups can severely slow down or completely prevent the formation of this organozinc intermediate. This problem, however, can often be circumvented by the choice of an alternative protecting group, as demonstrated above.

After selective deprotection of the O-acetyl group in **5d** (Scheme 5), a reagent had to be found which allows monoactivation of a bisphosphonate at both ends. In our hands, partial hydrolysis of *p*-xylylene tetramethyl bisphosphonate to the bismonoester, followed by reaction with oxalyl chloride in DMF at room temperature, proceeded smoothly and furnished the bis(esterchloride) **6** in high yields. Double esterification of **6** with **5e** gave the U-type predecessor **7a**, which was Boc-deprotected under mild conditions with dry trifluoroacetic acid to give **7b** (Scheme 5). The critical macrocylization step was subsequently carried out under high-dilution conditions with a motor-driven precision pump. The diamine **7b** was thus cyclized with isophthaloyl dichloride, leading to the macrocyclic bisphosphonate **8a** in 38% yield. Benzene was added as a template that has been shown to bring both nitroarenes into close proximity by way of a sandwich arrangement in previous macrocyclizations,[42] and thus facilitates the double amide connection with the dicarboxylic acid dichloride. In the final step, lithium bromide was used as a mild nucleophile, which selectively cleaved both methyl esters on the bisphosphonate, leaving the aryl esters intact.[43] Macrocyclic host **2a** was obtained in 1.3% overall yield (12 steps) as a colorless hygroscopic solid, soluble in a wide range of polar solvents ranging from DMSO to water. We would like to point out that ordinary alkyl and aryl phosphonates are more sensitive towards acid and base hydrolysis than their carboxylate counterparts. However, they tolerate both hydrazine hydrate and dry trifluoroacetic acid at room temperature, so that phthalimide- and Boc-protected amines can be selectively deprotected in their presence.

The above-described modular general approach to our new adrenaline hosts allows for the convenient preparation of analogues. Thus, we replaced the isophthalamidic head group by a pyridine-2,6-dicarboxamidic unit for a more efficient recognition of the catechol hydroxyls. This could be done in the penultimate step of the whole synthesis, by simply carrying out the macrocyclization with pyridine-2,6-dicarboxylic acid dichloride. By this simple variation, the pyridine-containing host precursor **8b** was obtained in 32% yield (overall yield 1.3%, 12 steps; Scheme 5).

Figure 3 depicts the problem with the isophthalamide head group: In **2a**, both amide hydrogens are involved in repulsive interactions with the aromatic *ortho*-proton. This effect can be clearly seen in molecular mechanics calculations irrespective of the chosen force-field (Figure 3, top). In consequence, one

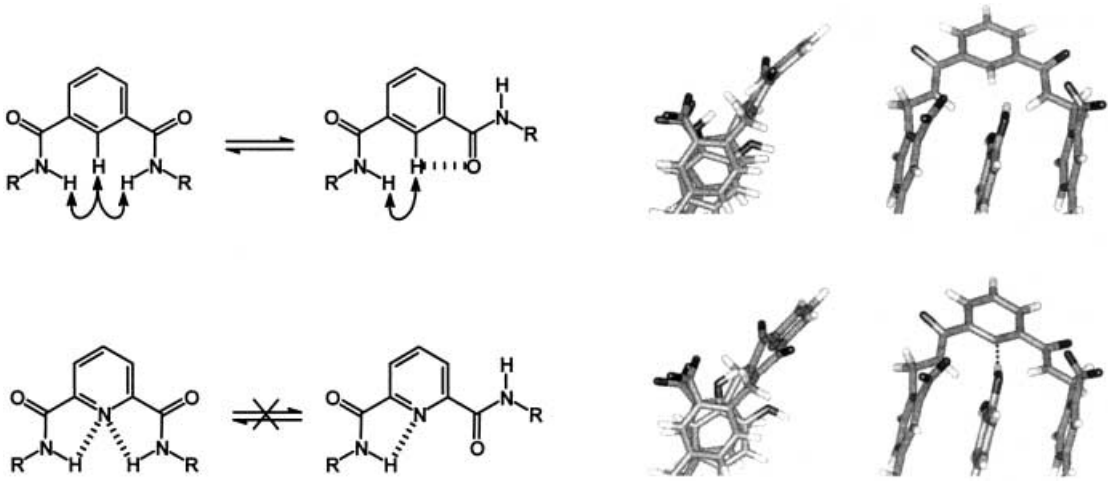

Figure 3. Top: Repulsive NH – CH interactions in isophthalamides; two views of the twisted head group in **2a**. Bottom: Preorganization in pyridine-2,6-carboxamides; flat head group in **2b**.

of the *trans*-amide groups could twist, leading to a distorted overall conformation of the whole macrocycle. In this conformation, the amide carbonyl could even form a weak hydrogen bond with the aromatic *ortho*-proton. Such behavior is often observed with isophthalamides.[44] It can be circumvented by replacing the isophthalamide by a pyridine-2,6-dicarboxamide as described above. Here, the pyridine nitrogen atom forms two intramolecular hydrogen bonds with the two amidic hydrogens, so that the top part of the host molecule should be ideally preorganized (**2b**, Figure 3, bottom).[45] In the twisted conformation, the amide carbonyl is now interfering with the basic pyridine nitrogen atom, leading to repulsion of their respective lone pairs. Vögtle et al. recently presented a molecular knot, whose unique structure was stabilized by such pyridine-2,6-dicarboxamides.[46]

Initial binding experiments: Initial NMR-spectroscopic binding studies of **2a** with various adrenaline-type guests showed that 1:1 complexes were formed in all cases (Job plots in various solvents; see, for example, Figure 4, top).[47]

An ESI spectrum from an equimolar mixture of noradrenaline hydrochloride and **2a** (10^{-7} M in methanol) produced a clean molecular ion peak for the 1:1 complex at m/z 1047, but no peaks for higher oligomers (Figure 5).

From FT-IR experiments we obtained strong indications for the postulated hydrogen bonds: both P–O valence bands of host **2a** were shifted towards smaller wavenumbers in the complex with noradrenaline. This is in accord with the strong ion-pair reinforced hydrogen bond between the phosphonate groups and the guest's ammonium functionality. In addition, the amide carbonyl band in **2a** was also shifted towards lower wavenumbers, corresponding to the related hydrogen bond between the NH group and the catechol oxygen atom. In order to gain more information about the complex geometry, we performed NOESY experiments in DMSO, where even hydrogen bonds with the catechol hydroxyls might be detectable (Figure 6).

In the free host molecule, strong intramolecular NOEs reveal several steric relationships of key protons essential for the overall conformation of **2a**. A strong NOE is found

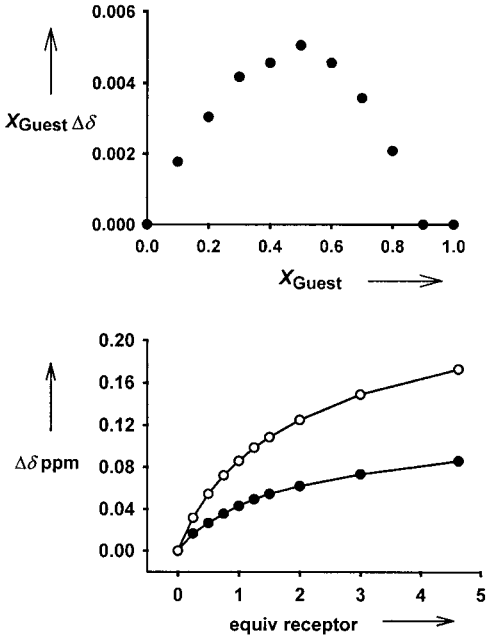

Figure 4. Top: Job plot for complex formation between host **2a** and noradrenaline hydrochloride (CHN proton) in D_2O/methanol (1:1); bottom: NMR titration curve showing the complexation-induced shifts (CIS; CHN and CHO protons) for complex formation between host **2** and noradrenaline hydrochloride in methanol.

between protons 2 and 1, accompanied with a medium NOE for proton 2 with 3; together with the absence of any NOE between protons 2 and 6, this shows that the phosphonate moieties are pointing inwards into the cavity of macrocycle **2a**, with some deviation from the ideal 90° angle between both arenes. In DMSO, it is conceivable that the lithium counterions form a chelate bridge between both phosphonate anions, leading to a strong preorientation favorable for the inclusion of ammonium guest molecules.

The combination of NOEs from protons 7 to their neighbors is also quite intriguing: a close contact is made to proton 3, there are medium NOEs to protons 8 and 10, but no NOE can be observed to proton 4. This indicates that the methylene protons of the diphenylmethane centerpiece are

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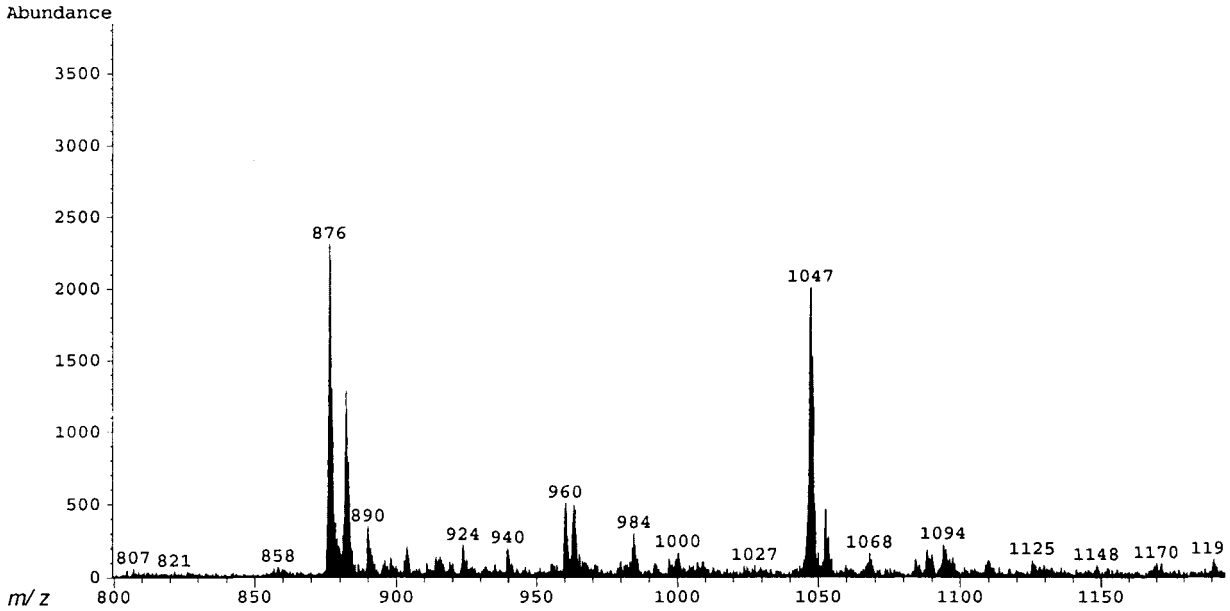


Figure 5. ESI-MS for the 1:1 complex of **2a** with noradrenaline hydrochloride (mass range m/z 800–1200). Samples (20 μL) were introduced as 10^{-7} M solutions in methanol at flow rates of 20 μL min^{-1}. The major peaks are: m/z 876: **2a**$^{-}$, 873: **2a**$^{2-}$ + Li^{+}, 890: **2a**$^{3-}$ + 2Li^{+}, 1047: **2a**$^{2-}$ + noradrenaline^{+}, 1054: **2a**$^{3-}$ + noradrenaline^{+} + Li^{+}.

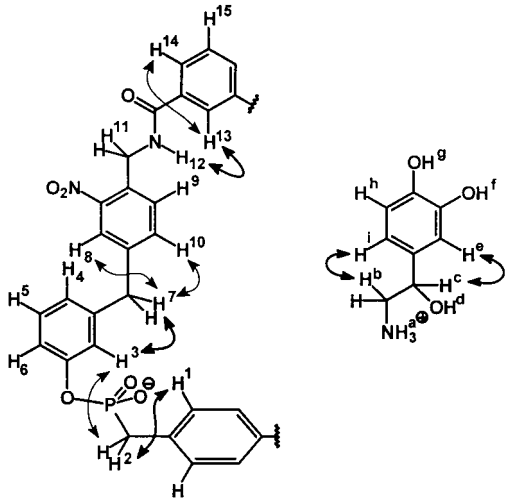


Figure 6. Proton assignments for intramolecular NOE measurements. Left: macrocycle **2a**; right: noradrenaline. Bold arrows: strong NOEs; thin arrows: medium NOEs.

always endocyclic, with the nitroarenes at an average angle of 90° to the phenol esters. Again this is exactly the conformation necessary for inclusion of adrenaline-type guests.

The existence of strong NOEs between protons 13 and 12, but medium NOEs between 12 and 14, confirms that the isophthalamide head group preferentially adopts the intended conformation, with some twist or flexibility of the benzene ring. This should be improved by the additional intramolecular hydrogen bonds in the pyridine-2,6-dicarboxamide.

If the NOE pattern in the complex of noradrenaline with macrocyclic host **2a** is compared to that of the free binding partners, the most striking observation is the fact that there is no significant change at all. Noradrenaline is bound in its thermodynamically favorable, bioactive conformation, by a host molecule that barely alters its geometry and shape. We were very pleased to find several distinct intermolecular NOEs between **2a** and its guest. Their synopsis in Figure 7 demonstrates that noradrenaline is situated inside the cavity of **2a**, with the amino alcohol in the region of the bisphosphonates and the catechol close to the nitroarenes, reaching up to the isophthalamide head group.[48]

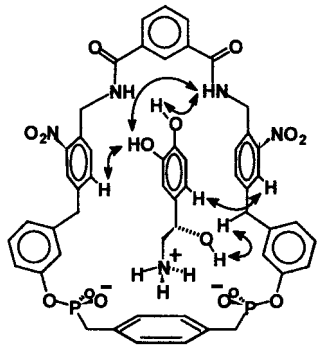


Figure 7. Intermolecular NOEs in the complex between host **2a** and noradrenaline. The carbon-bound hydrogen atoms have been omitted for clarity. Bold characters show IR-sensitive functional groups involved in hydrogen bonds.

It is noteworthy that on complexation with **2a** or **2b** the two former shift-isochronic hydroxy protons of noradrenaline split and one of them is drastically shifted to lower field by 1.2 ppm, whereas the other one is even shifted upfield by 0.3 ppm. Evidently, the equilibrium of the intramolecular OH···O hydrogen bonds in the catechol is strongly shifted towards one side by complex formation with the host molecule. This can be explained by the postulated hydrogen bond between the isophthalamide NH groups and the catechol's *p*-oxygen atom (Figures 8 and 9). The above-described NOESY experiment confirms this picture: a distinct NOE is observed between

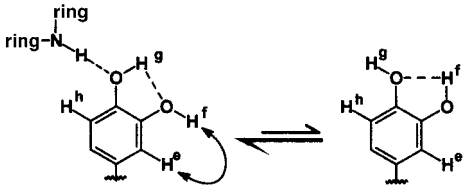


Figure 8. Shift in the catechol hydrogen bond equilibrium by complexation with host **2a** and **2b**; experimental evidence from chemically induced shifts (CIS) and NOE measurements.

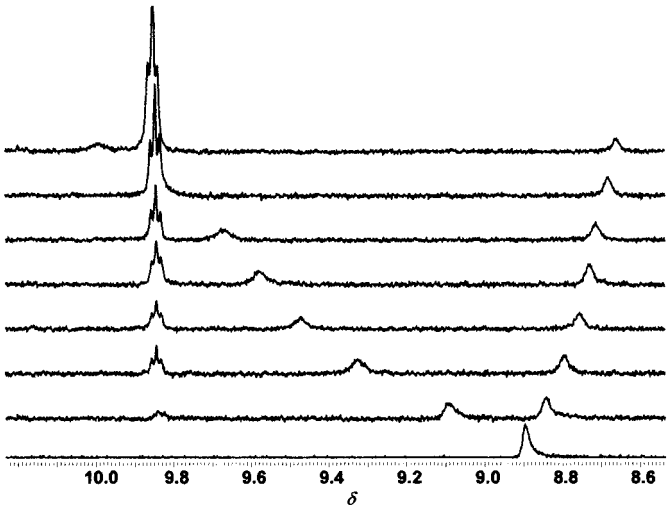


Figure 9. Drifting catechol OH signals during complex formation between pyridine-containing host **2b** and noradrenaline in DMSO ($\delta = 9.85$: amide NH of host **8**, increasing during titration). The relative ratios of equivalents of **2b** to noradrenaline from bottom to top are: 0, 0.25, 0.50, 0.75, 1.00, 1.25, 2.00, 4.75.

protons e and f, but no NOE can be detected between protons h and g.

We performed NMR titrations of macrocyclic host **2a** with noradrenaline in various polar solvents and calculated association constants from the binding curves with nonlinear regression methods.[49] In DMSO the binding constant is $\approx 10000\,\text{M}^{-1}$, in methanol $\approx 1000\,\text{M}^{-1}$, and in methanol/water (1:1) $\approx 220\,\text{M}^{-1}$. This 50-fold drop from DMSO to 50% methanolic solution is much smaller than in the case of the open-chain bisphosphonates ($\approx$5000-fold), where the molecular recognition of adrenaline derivatives relies almost exclusively on electrostatic interactions and hydrogen bonds. Host **2a** must exert additional attractive forces on the guest, which operate especially effectively in water. In pure water, host **2a** undergoes a self-association process, which was determined to be moderately strong, with a self-association constant of $270\,\text{M}^{-1}$. Large chemically induced shifts (CIS) with saturation values of up to almost 1 ppm were found for all protons in the upper, hydrophobic region of **2a** (isophthalamide and diphenylmethane), but they were minute (< 0.2 ppm) in the *p*-xylylene bisphosphonate moiety. Like **1**, macrocyle **2a** bears some similarity to phospholipids, although its amphiphilic nature is less pronounced.

Selectivity: In order to quantify the contribution of specific noncovalent interactions to the overall free binding enthalpy ΔG, we systematically truncated the guest structure, starting from adrenaline (Scheme 6; Table 1).

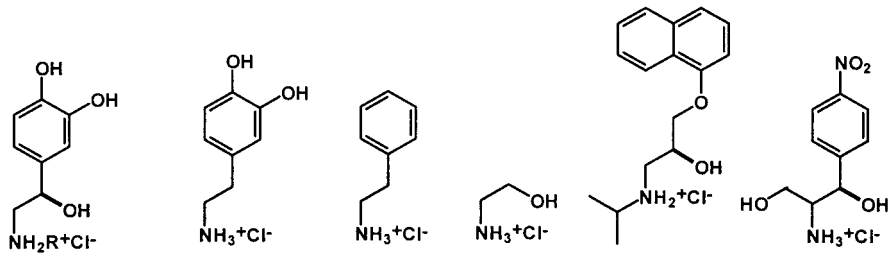
Deletion of the *N*-methyl group leads to an improvement in binding energy of roughly 1 kJ, probably a steric effect. If the aliphatic hydroxy group is removed, the association constant rises again a little, so that we must assume that, contrary to the case in DMSO, in water host **2a** does not recognize amino alcohols. On truncation of both phenolic hydroxy groups, however, the free binding enthalpy decreases by more than 2 kJ. In combination with the NOESY experiment and the downfield shift of one of the phenolic hydroxy protons, we now have strong experimental evidence for catechol recognition by the isophthalamide head group. Although upfield shifts occurred in the benzene protons of host and guest, no shift of the extinction maximum could be observed in the UV spectra of the complex. Presumably the high flexibility of this host region prevents formation of discrete charge transfer complexes.

Finally, if the guest's phenyl ring is also eliminated, another marked drop in binding energy of $1.5\,\text{kJ mol}^{-1}$ is the consequence. In the ^{1}H NMR spectra, several aromatic host and guest protons shift upfield by up to almost 0.5 ppm on complexation. We conclude that these findings support the postulated π-stacking interactions between the catechol and the two nitroarenes in **2a**. In summary, the binding constant

Table 1. Binding constants of complexes of host **2a** and various guest molecules from NMR titrations in D_2O/MeOD = 1:1.

Compound	Guest molecules[a]	$K_{a(1:1)}$ [M^{-1}][b]	ΔG [kJ mol^{-1}][b]	$\Delta\delta_{sat}$ [ppm][c]	Stoichiometry[d]
9	adrenaline	153 ± 14%	12.5	0.17 ± 10%	1:1
10	noradrenaline	215 ± 12%	13.3	0.12 ± 8%	1:1
11	dopamine	246 ± 38%	13.6	0.20 ± 26%	1:1
12	2-phenylethylamine	102 ± 14%	11.5	0.41 ± 11%	1:1
13	ethanolamine	54 ± 45%	9.9	0.07 ± 34%	1:1
14	propranolol	204 ± 5%	13.2	0.23 ± 3%	1:1
15	ANP	137 ± 7%	12.1	0.36 ± 6%	1:1

[a] As hydrochloride salts. [b] Errors are calculated as standard deviations from the nonlinear regression. [c] Bound shift at 100% complexation, obtained from the fit (selected CH protons). [d] From Job plots and curve-fitting of the titration curves.



9/10 11 12 13 14 15

Scheme 6. Guest molecules **9**–**15** for binding experiments with **2a**. The structure of adrenaline has been systematically truncated to establish the contribution of specific noncovalent interactions.

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for noradrenaline is four times higher than that for simple ethanolamine, because of a combination of π-stacking and hydrophobic forces and additional hydrogen bonds with properly placed recognition sites in the host molecule.

When we tried to include amino acid esters inside the cavity of **2a**, we were surprised: in all cases, regardless of the size of the ester substituent, there were almost no chemically induced shifts in the ^{1}H NMR spectrum (Scheme 7). We tried simple alanine methyl ester, but also aromatic amino acids with a large electron-rich π surface such as tryptophan and tyrosine esters. The maximum observed chemical shifts $\Delta\delta$ remain always below 0.03 ppm; upper limits for K_a are estimated at $<10\,\text{M}^{-1}$. Molecular mechanics calculations do not suggest that the additional ester group sterically hinders the inclusion process. Nevertheless, it seems to be a general rule that guests with an alkyl or aryl substituent α to the N atom do not bind to **2a**; thus, α-methyl-4-nitrobenzylamine also shows no chemically induced shifts on treatment with host **2a**. From attempted Job plots and curve fitting of the "titration curves", it appears likely that stoichiometric ratios are complex. Nonlinear regression treatment of the binding curves gave no saturation in the fit process. Therefore we assume that host **2a** rejects amino acid derivatives. This is in sharp contrast to **1**, which could not distinguish between amino acids and adrenaline derivatives. Hence, the new adrenaline host **2a** is shape-selective for the slim dopamine skeleton (guests **9**–**15**, Scheme 6). However, the corresponding binding constants with guests of this type ($\approx 10^2\,\text{M}^{-1}$) are still three orders of magnitude away from the natural example ($\approx 10^5\,\text{M}^{-1}$).

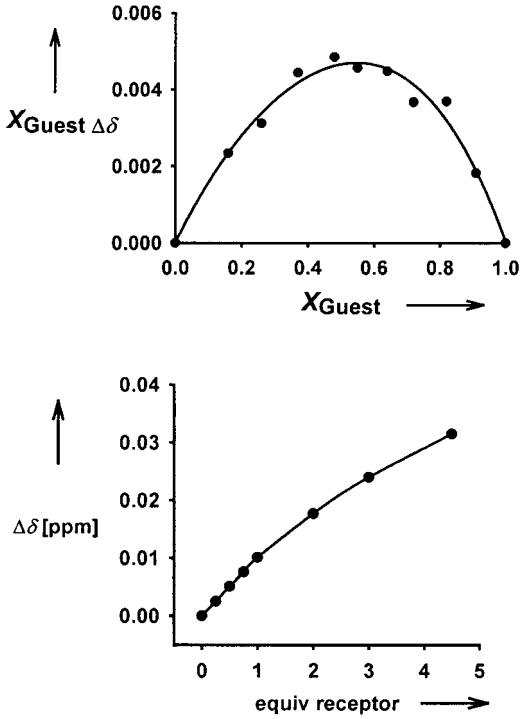
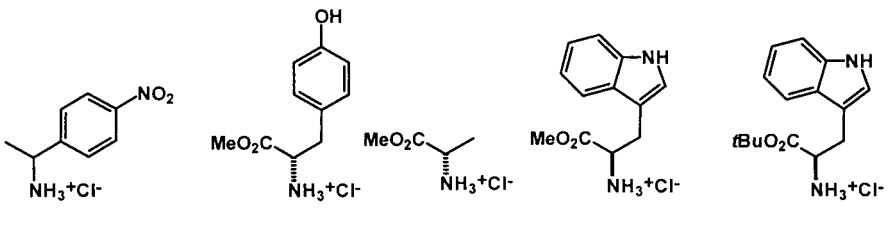


Figure 10. Top: Job plot for complex formation between host **2b** and noradrenaline hydrochloride (CHN proton) in D_2O/methanol (1:1); bottom: NMR titration curve showing the complexation-induced shifts (CIS, CHN proton) for complex formation between host **2b** and noradrenaline hydrochloride in the same solvent.

A new host with a pyridine-2,6-dicarboxamide head group: With the replacement of the isophthalamide by a pyridinedicarboxamide head group in **2b** we hoped to improve the host's affinity towards adrenaline derivatives by a higher degree of preorganization. Again, Job plots revealed a clear 1:1 stoichiometry in a 1:1 mixture of water and methanol (Figure 10, top). In the negative mass range of an ESI experiment we obtained a clean, albeit small molecular ion peak for the 1:1 complex between propranolol hydrochloride (**14**) and **2b** (*m*/*z* 1136). The NOESY study of the free host molecule, however, showed a first deviation from the behavior of host **2a**: several new intramolecular NOEs appeared in the diphenylmethane moiety, while others could not be detected, pointing to a different, more flattened conformation in this critical region. In contrast to the case for **2a**, the pyridine dicarboxamide head group is now indeed locked in the expected conformation. This can be deduced from the very weak NOE between protons 12 and 14 (compare Figure 6) and the increased ^3J coupling constant between the amide NH and the neighboring methylene protons 11. In the complex with noradrenaline, the guest structure remains in its bioactive conformation, but the host structure reverses the changes found for the free host. The complexation process thus forces the bent host **2b** into a conformation similar to that of the free host **2a**, which is much better suited for the inclusion of the guest. This behavior is often seen in enzymes and natural receptors, and is called induced fit. Unfortunately, only one intermolecular NOE could be detected in this complex, pointing to a somewhat lower binding affinity.

In pure water, the pyridine-containing host **2b** self-associates much more strongly than **2a**, as dilution experiments demonstrate. Saturation values of chemically induced shifts reach 1.2 ppm, and the average self-association constant is calculated at $1200\,\text{M}^{-1}$. This could result from the higher degree of preorganization for the pyridinedicarboxamide NH groups pointing into the interior of the macrocycle. With the lone pair on the pyridine nitrogen, these are already involved in intramolecular hydrogen bonds and are hence less exposed to the exterior of **2b**.



16 17 18 19 20

Scheme 7. More guest molecules **16**–**20** for binding experiments with **2a**. All these molecules carry an additional alkyl or aryl substituent α to the N atom and are rejected by the macrocyclic host molecule. Note that even the smallest amino acid derivative L-alanine methyl ester (**18**) does not bind to **2a**.

For NMR titrations of **2b** we used essentially the same guests already examined for **2a** (Schemes 6 and 7). Since the only structural modification was introduced in the nonpolar head region of the host molecule, only those guests were chosen that could be expected to reach into this nonpolar cavity (unlike ethanolamine, for example). In DMSO, noradrenaline binds to **2b** with a K_a value of $\approx 4500\,M^{-1}$, indicating a weaker association than with **2a**. This is further supported by NMR titrations in a 1:1 mixture of deuterium oxide and methanol: all binding constants remain some 30% below the values obtained with **2a** (Table 2). Adrenaline is bound especially weakly: although chemically induced shifts were quite strong, in several cases the nonlinear regression did not converge, and if it did, it furnished very low binding constants. The additional methyl group in the adrenaline guest seems to hinder the inclusion of this guest into the cavity of **2b** much more seriously than it does with **2a**. Noradrenaline and dopamine, however, afford smooth binding curves with a good theoretical fit. These two curves do not differ from each other, giving zero selectivity for amino alcohols. Nevertheless, deletion of the catechol hydroxyls leads to a marked decrease in their association constants, which is even more pronounced than with **2a**. Thus, the pyridine-containing macrocycle **2b** is fairly selective for catecholamines in aeqeous solution. Obviously, the improved preorganization of **2b** in the area of the pyridinedicarboxamide head group enhances the hydrogen bonding with the catechols, whereas the bent overall conformation in the diphenylmethane center region is detrimental to binding in general. Guests with an alkyl or aryl substituent in the α-position are again completely rejected by host **2b**. Very small shift differences and the complete lack of convergence in any binding isotherm suggest that, in water, amino acid esters are almost not complexed at all. We conclude that the pyridine-containing host **2b** undergoes a slight conformational shift, partly blocking the entrance to the internal cavity and hence producing somewhat smaller binding constants than **2a**. On the other hand, it is even more selective against α-substituted alkylammonium ions such as amino acid esters and related compounds.

It is interesting to compare the results of the Monte Carlo simulations for the complexes of noradrenaline and **2a** or **2b**. Both conformational searches were conducted under identical conditions with the same starting geometry, obtained from simple molecular mechanics calculations. In Figure 11, the preorganizing effect of the pyridinecarboxamide is beautifully illustrated: both nitroarene sidewalls are held perfectly coplanar to each other, and the catechol moiety of noradrenaline is ideally sandwiched between them. In addition, numerous hydrogen bonds are formed with all possible hydrogen bond donors and acceptors available in that region of the complex. These findings are in full accord with the above-described NOESY experiments. The pyridine-containing host **2b**, however, adopts a conformation in the complex which is much more kinked in the diphenylmethane moiety than that of **2a**. Here, the preorganized upper part of the host shrinks the cavity slightly. Thus, the guest is pushed a little out of the macrocycle, which together with the induced fit may explain why binding constants are consistently lower for complexes of **2b** with adrenaline derivatives than those of **2a**.

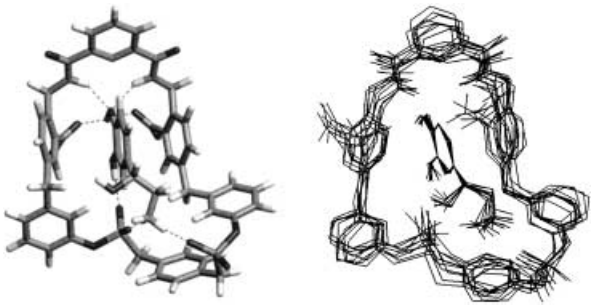


Figure 11. Left: Optimized complex geometry according to Monte Carlo simulations in water for the inclusion of noradrenaline inside the cavity of macrocyclic host **2b**. Note the perfect preorganization by the pyridinecarboxamide head group, but also the kinked geometry in the diphenylmethane moiety. Right: Superimposed snapshots of the subsequent molecular dynamics calculation. Note the higher conformational flexibility of this complex compared with the corresponding assembly of noradrenaline with **2a**.

Conclusion

A biomimetic adrenaline host has been developed that imitates the combination of all those noncovalent interactions that are postulated in the natural example. It binds adrenaline derivatives in water/methanol (1:1) with association constants in the range of $10^2\,M^{-1}$. Compared to the natural receptor, which binds adrenaline with a K_a of $10^5\,M^{-1}$, this is still three orders of magnitude away. However, it has to be taken into consideration that the molecular weight of the natural receptor is also 40 times higher than that of **2a** or **2b**. Both

Table 2. Binding constants in complexes of host **2b** and various guest molecules (with **9–14** lacking and **17–19** carrying an alkyl or aryl substituent α to the N atom) from NMR titrations in D_2O/MeOD = 1:1.

Compound	Guest molecules[a]	$K_{a(1:1)}$ [M^{-1}][b]	ΔG [kJ mol^{-1}][b]	$\Delta\delta_{sat}$ [ppm][c]	Stoichiometry[d]
9	adrenaline	$21 \pm 172\%$	7.5	$0.47 \pm 165\%$	1:1
10	noradrenaline	$136 \pm 10\%$	12.2	$0.13 \pm 8\%$	1:1
11	dopamine	$142 \pm 14\%$	12.3	$0.24 \pm 11\%$	1:1
12	2-phenylethylamine	$50 \pm 31\%$	9.7	$0.61 \pm 28\%$	1:1
14	propranolol	$201 \pm 17\%$	13.1	$0.47 \pm 13\%$	1:1
17	L-tyrosine methyl ester	weak binding	–	no saturation	complex
19	D-tryptophan methyl ester	weak binding	–	no saturation	complex

[a] As hydrochloride salts. [b] Errors are calculated as standard deviations from the nonlinear regression. [c] Complexation-induced shift at 100% complexation, obtained from the fit (selected CH protons). [d] From Job plots and curve-fitting of the titration curves. [e] Maximum observed chemical shifts $\Delta\delta < 0.03$ ppm; upper limits for K_a are estimated at $< 10\,M^{-1}$.

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receptor molecules show a pronounced shape selectivity for the slim dopamine skeleton.

In the future, we want to improve both the binding efficiency and the selectivity by including structural elements with a higher degree of preorganization. Above all, we will substitute the multiple benzylic bonds with rigid moieties such as tolane spacers and use amide or ester bonds. As Dougherty has recently shown,[50] π–cation interactions operate especially effective in water as opposed to electrostatic interactions. Replacement of the nitroarenes in **2** with pyridinium moieties may add another stabilizing effect. With these improved biomimetic adrenaline hosts, we aim at the construction of an artificial signal transduction system operating across a synthetic membrane.

Experimental Section

4-Iodo-2-nitrotoluene (3a): 4-Amino-2-nitrotoluene (10.0 g, 65.7 mmol) was suspended in diluted aqueous sulfuric acid (10 vol%, 200 mL) at 0 °C and treated slowly with a solution of sodium nitrite (4.76 g, 69.0 mmol) in water (10 mL). The mixture was stirred for 1 h at 0 °C. Subsequently it was filtered into a solution of potassium iodide (15.0 g, 90.4 mmol) and sodium acetate trihydrate (350 g) in water (300 mL) stirred gently at 0 °C. Stirring was continued for 1 h, then the reaction mixture was extracted with diethyl ether (3 × 200 mL), twice with 1N aqueous sodium thiosulfate, once with aqueous ammonia (10 vol%) and finally with water (100 mL each time). The ethereal layer was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed over silica with *n*-hexane/dichloromethane (3:2), again evaporated to dryness and recrystallized from ethanol, furnishing yellow crystals. Yield: 10.58 g (40.2 mmol, 61%); m.p. 60 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.54$ (s, 3H; d), 7.09 (d, $^3J(H,H) = 8.1$ Hz), 1H; b), 7.80 (dd, $^3J(H,H) = 8.1$ Hz, $^4J(H,H) = 1.8$ Hz, 1H; c), 8.27 (d, $^4J(H,H) = 1.8$ Hz, 1H; a); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 20.1$ (s; 7), 89.6 (s; 1), 133.2 (s; 4), 133.2 (s; 2), 134.2 (s; 5), 141.8 (s; 6), 149.6 (s; 3).

2-Bromomethyl-5-iodonitrobenzene (3b): 4-Iodo-2-nitrotoluene (**3a**, 3.94 g, 14.98 mmol) was dissolved in dry tetrachloromethane (12.5 mL) and treated with *N*-bromosuccinimide (NBS; 2.67 g, 14.98 mmol). The mixture was refluxed; at the beginning and every 4 h a small amount of dibenzoylperoxide was added. After teh mixture had been cooled to room temperature, the solid was filtered off and washed with a little dichloromethane. The filtrate was evaporated to dryness and chromatographed over silica gel with dichloromethane. On evaporation of the solvent a solid was obtained, which was heated for 1 h in boiling petroleum ether 40/60 (30 mL). After cooling to room temperature and filtration, a colorless powder was obtained. Yield: 2.34 g (6.84 mmol, 46%); m.p. 98 °C (DSC); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.76$ (s, 2H; d), 7.30 (d, $^3J(H,H) = 7.9$ Hz, 1H; b), 7.93 (dd, $^3J(H,H) = 7.9$ Hz, $^4J(H,H) = 1.9$ Hz, 1H; c), 8.35 (d, $^4J(H,H) = 1.9$ Hz, 1H; a); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 28.1$ (s; 7), 93.5 (s; 1), 132.4 (s; 4), 133.8 (s; 5), 134.1 (s; 2), 142.6 (s; 6), 148.1 (s; 3); FT-IR (KBr): $\tilde{\nu} = 3082$ (C_{Ar}–H), 2857 (-CH_2-), 1524 (-NO_2), 1344 (-NO_2), 1079 (Ar–I), 804 (Ar) cm^{-1}; MS (CI, NH_3, 200 °C): *m*/*z*: 378, 376 ([*M*+NH_3+NH_4]$^+$), 361, 359 ([*M*+NH_4]$^+$); elemental analysis calcd (%) for $C_7H_5NO_2BrI$ (341.93): C 24.59, H 1.47, N 4.09; found: C 24.62, H 1.77, N 4.27.

2-Phthaloylimidomethyl-5-iodonitrobenzene (3c): Iodonitrobenzene **3b** (8.09 g, 23.66 mmol), potassium phthalimide (5.27 g, 28.47 mmol) and [18]crown-6 (0.44 g, 2.37 mmol) were stirred for 3 h at 80 °C in dry toluene (30 mL) under argon. Subsequently the solution was diluted with dichloromethane and insoluble components were filtered off. The filtrate was evaporated to dryness in vacuo, and the resulting residue was chromatographed over silica gel with dichloromethane/*n*-hexane (5:1), affording colorless crystals. Yield: 9.12 g (22.34 mmol, 94%); m. p. 177 °C (DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 5.21$ (s, 2H; d), 7.00 (d, $^3J(H,H) = 8.2$ Hz, 1H; b), 7.77 (dd, $^3J(H,H) = 5.7$ Hz, $^4J(H,H) = 3.2$ Hz, 2H; f), 7.83 (dd, $^3J(H,H) = 8.2$ Hz, $^4J(H,H) = 1.9$ Hz, 1H; c), 7.89 (dd, $^3J(H,H) = 5.7$ Hz, $^4J(H,H) = 3.2$ Hz, 2H; e), 8.39 (d, $^4J(H,H) = 1.9$ Hz, 1H, a); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): $\delta = 38.3$ (s; 7), 92.1 (s; 1), 123.7 (s; 10), 130.0 (s; 4), 131.3 (s; 9), 131.7 (s; 5), 133.8 (s; 2), 134.5 (s; 11), 142.5 (s; 6), 148.4 (s; 3), 167.7 (s; 8); FT-IR: $\tilde{\nu} = 3098$ (C_{Ar}–H), 3029 (C_{Ar}–H), 1772 (C=O), 1712 (C=O), 1532 (-NO_2), 1335 (-NO_2), 1113 (C–I) cm^{-1}; MS (CI, NH_3, 200 °C): *m*/*z*: 426 ([*M*+NH_4]$^+$); elemental analysis calcd (%) for $C_{15}H_9N_2O_4I$ (408.15): C 44.14, H 2.22, N 6.86; found: C 44.26, H 2.39, N 6.61.

2-Aminomethyl-5-iodonitrobenzene (3d): Compound **3c** (9.12 g, 22.34 mmol) was refluxed in ethanol (110 mL) with hydrazine hydrate (1.09 mL, 22.34 mmol) for 3 h. Subsequently 1N HCl (45 mL) was added and the solution was evaporated to dryness. Acetone (100 mL) was added to the residue, and the resulting suspension was refluxed with vigorous stirring for 15 min. The white precipitate was filtered off, washed with acetone (100 mL), and dried. Then it was treated with water (65 mL) and diethyl ether (15 mL), and 1N NaOH (45 mL) was slowly added dropwise while the mixture was stirred. The aqueous layer was extracted three times with diethyl ether, and the combined organic layers were dried over sodium sulfate and evaporated. A reddish oil was obtained, which quickly turned brown in air. Yield: 4.05 g (14.57 mmol, 65%); ^{1}H NMR (500 MHz, $CDCl_3$,): $\delta = 1.95$ (br s, 2H; e), 4.05 (s, 2H; d), 7.37 (d, $^3J(H,H) = 8.1$ Hz, 1H; b), 7.91 (dd, $^3J(H,H) = 8.1$ Hz, $^4J(H,H) = 1.8$ Hz, 1H; c), 8.28 (d, $^4J(H,H) = 1.8$ Hz, 1H; a); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 42.5$ (s; 7), 90.2 (s; 1), 131.1 (s; 2), 132.4 (s; 5), 136.9 (s; 4), 141.5 (s; 6), 147.7 (s; 3).

2-*tert*-Butyloxycarbonylaminomethyl-5-iodonitrobenzene (3e): Compound **3d** (1.35 g, 4.86 mmol) was dissolved in dry dichloromethane (16 mL). At 0 °C triethylamine (0.68 mL, 4.86 mmol) and di-*tert*-butyl pyrocarbonate (1.28 mL, 5.58 mmol) were added, and the mixture was stirred overnight at room temperature. Then the solvent was removed and the residue was chromatographed over silica gel with dichloromethane ($R_f = 0.14$), yielding a pale yellow oil. Yield: 1.75 g (4.63 mmol, 95%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H; f), 4.50 (d, $^3J(H,H) = 6.3$ Hz, 2H; d), 5.30 (br s, 1H; e), 7.37 (d, $^3J(H,H) = 8.2$ Hz, 1H; b), 7.93 (dd, $^3J(H,H) = 8.2$ Hz, $^4J(H,H) = 1.9$ Hz, 1H; c), 8.36 (d, $^4J(H,H) = 1.9$ Hz, 1H; a); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 28.3$ (s; 10), 42.1 (s; 7), 80.0 (s; 9), 92.0 (s; 1), 133.1 (s; 2), 133.6 (s; 4), 134.2 (s; 5), 142.8 (s; 6), 148.5 (s; 3), 155.7 (s; 8); FTIR (film): $\tilde{\nu} = 3347$ (N–H), 3096 (C_{Ar}–H), 2977, 2933 (C–H), 1698 (C=O), 1529 (C=O), 1599 (N–H), 1529, 1345 (NO_2), 1167 (C–O) cm^{-1}; MS (CI, NH_3, 200 °C): *m*/*z*: 378 ([*M*]$^-$); elemental analysis calcd (%) for $C_{12}H_{15}N_2O_4I$ (378.17): C 38.11, H 4.00, N 7.41; found: C 38.10, H 4.07, N 7.40.

General procedure for the Negishi coupling reaction: The reaction had to be carried out with rigid exclusion of oxygen and humidity. Zinc powder (0.882 g, 13.50 mmol) and dry tetrahydrofuran (0.5 mL) were treated with 1,2-dibromoethane (0.019 mL, 0.225 mmol). The mixture was heated carefully with a heat gun until soaplike bubbles appeared and the solution became slightly clouded. The benzyl bromide reagent (6.75 mmol) was dissolved in dry tetrahydrofuran (3 mL) and added dropwise at −10 °C to the activated zinc (1 h). Subsequently the reaction mixture was stirred for 1 h at ambient temperature. The excess of zinc powder was filtered out under inert conditions, and a slightly clouded, greenish solution was obtained. Bis(triphenylphosphanyl)palladium(II) chloride (0.144 g, 0.206 mmol) was suspended in dry tetrahydrofuran (7 mL) and treated slowly with a 1M solution of diisobutylaluminum hydride in hexane (0.411 mL), producing a color change from yellow to green-black. Then a solution of the aryl halide (4.50 mmol) in dry tetrahydrofuran (10 mL) was added. Finally the solution of the organozinc reagent was added dropwise, producing a color change to red-brown, and the reaction mixture was stirred overnight at ambient temperature. The solvent was removed in vacuo at a temperature no higher than 50 °C. The residue was dissolved in dichloromethane and treated with *n*-hexane, until a precipitate formed, which was filtered off. Evaporation to dryness was followed by chromatographic purification over silica gel with dichloromethane/ethyl acetate (19:1), giving a yellow oil.

Model diphenylmethane 5a: Yield: 0.68 g (3.01 mmol, 67%); m.p. 35 °C; ^{1}H NMR: $\delta = 2.57$ (s, 3H), 4.02 (s, 2H), 7.18 (d, $J = 7.6$ Hz, 2H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 8.1$ Hz, 1H), 7.30 (dd, $J = 8.1$ Hz, $J = 1.3$ Hz, 1H), 7.30 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 2H), 7.80 (d, $J = 1.3$ Hz, 1H); ^{13}C{^{1}H} NMR: $\delta = 20.0$, 40.8, 124.8, 126.6, 128.8, 128.9, 131.2, 133.0, 133.5, 139.6, 140.5, 149.3; elemental analysis calcd (%) for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16; found: C 73.75, H 5.87, N 6.21.

Model diphenylmethane 5b: Yield: 1.07 g (2.88 mmol, 64%); ^{1}H NMR: $\delta = 4.02$ (s, 2H), 5.26 (s, 2H), 7.14 (d, $J = 7.6$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz,

1H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.29 (dd, $J = 7.6$ Hz, $J = 7.6$ Hz, 2H), 7.34 (dd, $J = 8.1$ Hz, $J = 1.3$ Hz, 1H), 7.76 (dd, $J = 5.7$ Hz, $J = 3.2$ Hz, 2H), 7.89 (dd, $J = 5.7$ Hz, $J = 3.2$ Hz, 2H), 7.93 (d, $J = 1.3$ Hz, 1H); $^{13}C\{^1H\}$ NMR: $\delta =$ 38.5, 41.0, 123.6, 125.4, 126.7, 128.3, 128.8, 128.9, 129.4, 131.8, 134.1, 134.3, 139.0, 142.3, 148.1, 167.9.

Model diphenylmethane 5c: Yield: 0.65 g (1.35 mmol, ≈30%); m.p. 79°C; ^1H NMR: $\delta = 0.16$ (s, 6H), 0.95 (s, 9H), 3.95 (s, 2H), 5.26 (s, 2H), 6.63 (d, $J = 1.9$ Hz, 1H), 6.70 (dd, $J = 8.2$ Hz, $J = 1.9$ Hz, 1H), 6.71 (d, $J = 8.2$ Hz, 1H), 7.14 (dd, $J = 8.2$ Hz, $J = 8.2$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 1H), 7.33 (dd, $J = 8.2$ Hz, $J = 1.3$ Hz, 1H), 7.77 (dd, $J = 5.7$ Hz, $J = 3.2$ Hz, 2H), 7.89 (dd, $J = 5.7$ Hz, $J = 3.2$ Hz, 2H), 7.91 (d, $J = 1.3$ Hz, 1H); $^{13}C\{^1H\}$ NMR: $\delta =$ −4.4, 18.2, 25.6, 38.5, 40.8, 118.4, 120.8, 121.9, 123.6, 125.4, 128.3, 129.3, 129.7, 131.9, 134.1, 134.3, 140.5, 142.3, 148.1, 156.0, 167.8; elemental analysis calcd (%) for $C_{28}H_{30}N_2O_5Si$: C 66.91, H 6.02, N 5.57; found: C 66.99, H 5.93, N 5.38.

2-*tert*-Butyloxycarbonylaminomethyl-5-(3′-acetoxyphenylmethyl)-nitrobenzene (5d): Yield: 1.04 g (2.60 mmol, 58%); ^1H NMR (500 MHz, $CDCl_3$, 25°C): $\delta = 1.43$ (s, 9H), 2.28 (s, 3H), 4.04 (s, 2H), 4.52 (d, $^3J(H,H) = 6.3$ Hz, 2H), 5.32 (br s, 1H), 6.89 (dd, $^4J(H,H) = 1.9$ Hz, $^4J(H,H) = 1.9$ Hz, 1H), 6.98 (dd, $^3J(H,H) = 8.2$ Hz, $^4J(H,H) = 1.9$ Hz, 1H), 7.04 (d, $^3J(H,H) =$ 7.6 Hz, 1H), 7.32 (dd, $^3J(H,H) = 8.2$ Hz, $^3J(H,H) = 7.6$ Hz, 1H), 7.42 (dd, $^3J(H,H) = 8.2$ Hz, $^4J(H,H) = 1.9$ Hz, 1H), 7.54 (d, $^3J(H,H) = 8.2$ Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): $\delta = 21.1$ (s), 28.3 (s), 40.7 (s), 42.1 (s), 79.8 (s), 120.0 (s), 122.0 (s), 125.2 (s), 126.3 (s), 129.7 (s), 131.8 (s), 132.5 (s), 134.4 (s), 140.9 (s), 141.5 (s), 148.3 (s), 151.0 (s), 155.8 (s), 169.3 (s); IR (film): $\tilde{\nu} = 3367$ (N−H), 3066 (C_{Ar}−H), 2978, 2933 (C−H), 1765, 1709 (C=O), 1529 (NO_2), 1366 (NO_2), 1207, 1168 (C−O) cm^{-1}; MS (CI, NH_3, 200°C): m/z: 400 ($[M]^-$); calcd for $C_{21}H_{24}N_2O_6$ (400.43): C 62.99, H 6.05, N 6.99; found: C 62.91, H 5.90, N 6.75.

2-*tert*-Butyloxycarbonylaminomethyl-5-(3′-hydroxyphenylmethyl)nitrobenzene (5e): Potassium carbonate (0.36 g, 2.57 mmol) was suspended under argon in dry methanol (120 mL). A solution of **5d** (1.03 g, 2.57 mmol) in dry methanol (25 mL) was slowly added dropwise. After 15 min 1N HCl (5.14 mL) was added dropwise, followed by water (140 mL) and ethyl acetate as well as aqueous saturated NaCl until phase separation occurred. The aqueous layer was extracted once more with ethyl acetate, and the combined organic phases were dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed over silica gel with chloroform/acetone (10:1, $R_f = 0.48$), furnishing a yellow oil. Yield: 0.87 g (2.43 mmol, 94%); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H; l), 3.96 (s, 2H; f), 4.51 (d, $^3J(H,H) = 6.3$ Hz, 2H, j), 5.35 (br s, 1H; k), 5.39 (br s, 1H; a), 6.62 (s, 1H; b), 6.71 (dd, $^3J(H,H) = 8.2$ Hz, $^4J(H,H) = 2.5$ Hz, 1H; e), 6.73 (d, $^3J(H,H) = 7.6$ Hz, 1H; c), 7.17 (dd, $^3J(H,H) = 8.2$ Hz, $^3J(H,H) =$ 7.6 Hz, 1H; d), 7.41 (dd, $^3J(H,H) = 7.6$ Hz, $^4J(H,H) = 1.3$ Hz, 1H; i), 7.51 (d, $^3J(H,H) = 8.2$ Hz, 1H; h), 7.86 (s, 1H; g); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta =$ 28.4 (s; 17), 40.9 (s; 7), 42.2 (s; 14), 79.9 (s; 16), 113.7 (s; 6), 115.8 (s; 2), 121.2 (s; 4), 125.2 (s; 9), 130.0 (s; 5), 131.8 (s; 11), 132.2 (s; 12), 134.4 (s; 13), 141.0 (s; 8), 142.1 (s; 3), 148.2 (s; 10), 155.9 (s; 15), 156.1 (s; 1); FT-IR (film): $\tilde{\nu} = 3350$ (O−H, N−H), 3015 (C_{Ar}−H), 2980 (C−H), 2933 (C−H), 1689 (C=O), 1589 (N−H), 1531 (NO_2), 1347 (NO_2), 1162 (C−O), 757 (3 C_{Ar}−H) cm^{-1}; MS (CI, NH_3, 200°C): m/z: 358 ($[M]^-$); elemental analysis calcd (%) for $C_{19}H_{22}N_2O_5$ (358.39): C 63.68, H 6.19, N 7.82; found: C 63.39, H 6.47, N 7.78.

***p*-Xylylene-α,α'-bis(phosphonic acid monomethyl ester)**: *p*-Xylylene-α,α'-bis(phosphonic acid dimethyl ester) (4.62 g, 15.52 mmol) was refluxed for 6 h with aqueous NaOH (20 vol%, 23 mL). Cooled with ice, the solution was subsequently treated with half-concentrated HCl (23 mL), giving a white precipitate. The precipitate was filtered off, washed with water and acetone and recrystallized from methanol. Yield: 2.95 g (9.16 mmol, 64%); m.p. 210°C (DSC); ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta = 3.04$ (d, $^2J(H,P) = 20.2$ Hz, 4H; b), 3.52 (d, $^3J(H,P) = 10.7$ Hz, 6H; c), 6.15 (br s, 2H; d), 7.17 (s, 4H; a); ^{13}C NMR (126 MHz, [D$_6$]DMSO, 25°C): $\delta = 32.8$ (d, $^1J(C,P) = 133.2$ Hz; 3), 51.7 (d, $^2J(C,P) = 3.6$ Hz (two signals from 2 diastereomers; 4), 129.8 (s; 1), 131.3 (d, $^2J(C,P) = 4.9$ Hz (two signals from 2 diastereomers; 2); ^{31}P NMR (202 MHz, [D$_6$]DMSO): $\delta = 26.1$ (s); FT-IR (KBr): $\tilde{\nu} = 3449$ (O−H), 2963, 2924, 2858 (C−H), 2606 (P(O)OH), 1655 (arom), 1268 (P=O), 1138 (C−O), 1050 (P−OMe), 830 (2 adjacent C_{Ar}−H) cm^{-1}; MS (CI, NH_3, 200°C): m/z: 312 ($[M+NH_4]^+$); elemental analysis calcd (%) for $C_{10}H_{16}O_6P_2$ (294.18): C 40.83, H 5.48; found: C 40.50, H 5.45.

***p*-Xylylene-α,α'-bis(phosphonic acid monomethyl ester chloride) (6)**: All steps had to be carried out with rigorous exclusion of humidity and air. The above-described bis(monomethylphosphonate) (0.357 g, 1.21 mmol) was suspended in dry dichloromethane (15 mL) at −10°C. Oxalyl chloride (0.23 mL, 2.67 mmol) and then DMF (2 drops) were slowly added to this mixture, which was stirred further for 2 h at room temperature and then for another 2 h at 40°C. Complete conversion was indicated by complete dissolution of the solid. The solvent was condensed off at 40°C and 10^{-2} Torr. The product was extremely sensitive to hydrolysis and was used directly for the next step without further purification. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.54$ (d, $^2J(H,P) = 19.1$ Hz, 4H; b), 3.86 (d, $^3J(H,P) = 13.3$ Hz, 6H; c), 7.32 (s, 4H; a); ^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 41.2$ (s).

***p*-Xylylene-α,α'-bis(phosphonic acid mono-3-[3′-nitro-4′-(*tert*-butyloxycarboxyamino-methyl)phenylmethyl]phenylmonomethyl ester (7a)**: Phosphonate ester **6** (0.40 g, 1.21 mmol) was dissolved in dry dichloromethane (10 mL). Subsequently a solution of **5e** (0.87 g, 2.43 mmol) and triethylamine (0.56 mL, 4.01 mmol) in dry dichloromethane (5 mL) was added quickly by syringe. After 15 min the solution was evaporated to dryness and the residue was chromatographed over silica gel and eluted with chloroform/acetone (5:1). A yellow solid was obtained as a mixture of *P* stereoisomers. Yield: 0.68 g (0.70 mmol, 57%); m.p. 208°C (decomp, DSC); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.42$ (s, 18H; n), 3.29 (d, $^2J(H,P) =$ 20.8 Hz, 4H; b), 3.69 (d, $^3J(H,P) = 10.7$ Hz, 6H; c), 3.98 (s, 4H; h), 4.52 (d, $^3J(H,H) = 6.3$ Hz, 4H; l), 5.39 (br s, 2H; m), 6.93 (s, 2H; d), 6.94 (d, $^3J(H,H) = 7.6$ Hz, 2H; g), 6.98 (d, $^3J(H,H) = 8.2$ Hz, 2H; e), 7.22 (dd, $^3J(H,H) = 8.2$ Hz, $^3J(H,H) = 7.6$ Hz, 2H; f), 7.25 (s, 4H; a), 7.40 (d, $^3J(H,H) = 7.6$ Hz, 2H; k), 7.53 (d, $^3J(H,H) = 7.6$ Hz, 2H; j), 7.83 (s, 2H; i); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 28.3$ (s; 21), 32.9 (d, $^1J(C,P) = 139.3$ Hz; 3), 40.6 (s; 11), 42.1 (s; 18), 53.4 (d (diastereomers), $^2J(C, P) = 3.6$ Hz; 4), 79.7 (s; 20), 118.6 (s; 10), 120.9 (s; 6), 125.1 (s; 13), 125.5 (s; 8), 129.6 (d (diastereomers), $^2J(C,P) = 2.4$ Hz; 2), 130.1 (s; 9), 130.2 (s; 1), 131.7 (s; 15), 132.6 (s; 16), 134.3 (s; 17), 141.2 (s; 12), 141.5 (s; 7), 148.2 (s; 14), 150.8 (d (diastereomers), $^2J(C,P) = 4.2$ Hz; 5), 155.8 (s; 19); ^{31}P NMR (202 MHz, $CDCl_3$): $\delta = 25.5$ (s); IR (KBr): $\tilde{\nu} = 3445$ (N−H), 2977 (C−H), 1708 (C=O), 1607, 1586 (arom), 1530 (NO_2), 1366 (NO_2), 1249 (P=O/P−OAr), 1046 (P−OMe) cm^{-1}; elemental analysis calcd (%) for $C_{48}H_{56}N_4O_{14}P_2$ (974.94): C 59.13, H 5.79, N 5.75; found: C 59.12, H 5.85, N 5.65.

***p*-Xylylene-α,α'-bis(phosphonic acid mono-3-[3′-nitro-4′-(aminomethyl)-phenylmethyl]phenyl monomethyl ester bis(hydrogentrifluoroacetate) (7b)**: Ester **7a** (0.82 g, 0.841 mmol) was stirred in dry dichloromethane (35 mL) with trifluoroacetic acid (35 mL) under argon at 0°C for 1.5 h. Afterwards, the solution was evaporated to dryness and treated several times with dry dichloromethane with subsequent removal of the solvent, in order to eliminate azeotropically traces of trifluoroacetic acid. The oily brown crude product was used for the next step without workup. Yield: 0.84 g (0.84 mmol, >99%); ^1H NMR (500 MHz, CD_3OD): $\delta = 3.47$ (d, $^2J(H,P) = 20.5$ Hz, 4H; b), 3.77 (d, $^3J(H,P) = 11.0$ Hz, 6H; c), 4.13 (s, 4H; h), 4.41 (s, 4H; l), 6.99 (d, $^3J(H,H) = 7.9$ Hz, 2H; g), 7.01 (s, 2H; d), 7.12 (d, $^3J(H,H) = 7.9$ Hz, 2H; e), 7.31 (dd, $^3J(H,H) = 7.9$ Hz, $^3J(H,H) = 7.9$ Hz, 2H; f), 7.34 (s, 4H; a), 7.66 (d, $^3J(H,H) = 7.9$ Hz, 2H; j), 7.70 (dd, $^3J(H,H) =$ 7.9 Hz, $^4J(H,H) = 1.6$ Hz, 2H; k), 8.11 (d, $^4J(H,H) = 1.6$ Hz, 2H; i); ^{13}C NMR (126 MHz, CD_3OD): $\delta = 33.7$ (d, $^1J(C,P) = 138.1$ Hz; 3), 41.6 (s; 11), 42.1 (s; 18), 54.6 (d, $^2J(C,P) = 3.6$ Hz (diastereomers); 4), 117.8 (q, $^1J(C,F) = 284.6$ Hz; 19), 120.1 (s; 10), 122.4 (s; 6), 127.1 (s; 15), 127.3 (s; 13), 127.7 (s; 8), 131.4 (d, $^2J(C,P) = 3.0$ Hz (diastereomers); 2), 131.6 (s; 9), 131.7 (s; 1), 134.7 (s; 16), 136.3 (s; 17), 143.4 (s; 12), 146.4 (s; 7), 150.2 (s; 14), 152.3 (d, $^2J(C,P) = 4.2$ Hz (diastereomers); 5), 162.3 (q, $^2J(C,F) = 36.0$ Hz; 20); ^{31}P NMR (202 MHz, CD_3OD): $\delta = 26.8$ (s).

1,10,27,34-Tetraoxo-1,10-dimethoxy-1,10-diphospha-11,50-dioxa-26,35-diaza[2](3)benzeno[3](2)benzeno[1](3,4)nitrobenzeno[3](2)benzeno[3](3,5)-nitrobenzeno[1](2)benzenocyclophane (8a): A solution of **7b** (0.843 g, 0.841 mmol) and triethylamine (0.82 mL, 5.89 mmol) in dry THF (70 mL) and a solution of isophthaloyl chloride (0.171 g, 0.841 mmol) in 70 mL of dry THF were added simultaneously over 3 h at room temperature evenly to a mixture from dry THF (60 mL) and dry benzene (15 mL) by syringe. The reaction mixture was stirred overnight at room temperature, and subsequently filtered from the precipitated triethylammonium chloride. The filtrate was evaporated to dryness, and the residue was chromatographed over silica gel with chloroform/acetone (1:1, $R_f = 0.33$), yielding a light yellow solid. Yield: 0.29 g (0.321 mmol, 38%); m.p. 240°C (decomp, DSC); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.25$ (d, $^2J(H,P) = 20.8$ Hz, 4H; b),

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3.67/3.68 (d (diastereomers), ^3J(H,P) = 11.0 Hz, 6H; c), 3.96 (s, 4H; h), 4.81 (d, ^3J(H,H) = 6.3 Hz, 4H; l), 6.78 (s, 2H; d), 6.91 (d, ^3J(H,H) = 8.2 Hz, 2H; g), 6.97 (d, ^3J(H,H) = 7.6 Hz, 2H; e), 7.19 (s, 4H; a), 7.21 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.6 Hz, 2H; f), 7.23 (t, ^3J(H,H) = 6.3 Hz, 2H; m), 7.37 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 2H; k), 7.48 (t, ^3J(H,H) = 7.9 Hz, 1H; p), 7.60 (d, ^3J(H,H) = 8.2 Hz, 2H; j), 7.83 (d, ^4J(H,H) = 1.3 Hz, 2H; i), 7.93 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.3 Hz, 2H; o), 8.11 (d, ^4J(H,H) = 1.3 Hz, 1H, n); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 32.8 (d, ^1J(C,P) = 139.3 Hz; 3), 40.7 (s; 11), 41.4 (s; 18), 53.4 (d (diastereomers), ^2J(C,P) = 3.6 Hz; 4), 118.7 (s; 10), 120.8 (s; 6), 125.2 (s; 13), 125.4 (s; 23), 125.6 (s; 8), 129.1 (s; 21), 129.7 (d (diastereomers), ^2J(C,P) = 3.6 Hz; 2), 130.1 (s; 9), 130.2 (s; 1), 130.3 (s; 22), 131.3 (s; 15), 132.6 (s; 16), 134.3 (s; 20), 134.4 (s; 17), 141.1 (s; 12), 142.1 (s; 7), 148.3 (s; 14), 150.7/150.8 (d (diastereomers), ^2J(C,P) = 4.2 Hz; 5), 166.4 (s; 19); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.42/25.43 (s, mixture of diastereomers); FT-IR (KBr): $\tilde{\nu}$ = 3424 (N–H), 2956 (C–H), 1655 (C=O), 1607, 1585 (arom), 1529, 1348 (NO_2), 1260 (P=O), 1235 (P–OAr), 1044 (P–OMe) cm^{-1}; MS (CI, NH_3, 200 °C): *m/z*: 904 ([*M*]$^+$); elemental analysis calcd (%) for $C_{46}H_{42}N_4O_{12}P_2$ (904.81): C 61.06, H 4.68, N 6.19; found: C 61.02, H 4.89, N 6.11.

1,10,27,34-Tetraoxo-1,10-dioxido-1,10-diphospha-11,50-dioxa-26,35-diaza[2](3)benzeno[3](2)benzeno[1](3,4)nitrobenzeno[3](2)benzeno[3](3,5)-nitrobenzeno[1](2)benzenocyclophane dilithium salt (2a): Cyclophane **8a** (187.7 mg, 0.207 mmol) was suspended in dry acetonitrile (2 mL) and treated with a solution of lithium bromide (36.2 mg, 0.417 mmol) in dry acetonitrile (2 mL). The mixture was heated to reflux for one week. Then the product was filtered off and washed with cold acetonitrile and diethyl ether. If the product still contained starting material, the whole procedure was repeated with the appropriate additional amount of LiBr. Yield: 121.3 mg (0.137 mmol, 66%); m.p. 250 °C (decomp, DSC); ^{1}H NMR (500 MHz, CD_3OD): δ = 3.00 (d, ^2J(H,P) = 19.5 Hz, 4H; b), 4.01 (s, 4H; g), 6.83 (s, 2H; c), 6.95 (d, ^3J(H,H) = 7.6 Hz, 2H; f), 7.00 (d, ^3J(H,H) = 8.2 Hz, 2H; d), 7.13 (s, 4H; a), 7.19 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.6 Hz, 2H; e), 7.51 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.3 Hz, 2H; j), 7.55 (d, ^3J(H,H) = 8.2 Hz, 2H; i), 7.64 (t, ^3J(H,H) = 7.9 Hz, 1H; o), 7.95 (d, ^4J(H,H) = 1.3 Hz, 2H; h), 8.06 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.3 Hz, 2H; n), 8.33 (t, ^4J(H,H) = 1.6 Hz, 1H; m); ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 36.5 (d, ^1J(C,P) = 7.6 Hz; 3), 41.8 (s; 10), 42.1 (s; 17), 120.4 (s; 7), 122.7 (s; 5), 124.9 (s; 9), 126.2 (s; 12), 127.2 (s; 20), 130.4 (s; 22), 130.6 (s; 8), 131.0 (s; 1), 131.1 (s; 15), 132.2 (s; 21), 133.0 (s; 2), 134.2 (s; 14), 135.5 (s; 16), 136.1 (s; 19), 142.7 (s; 11), 144.1 (s; 6), 149.9 (s; 13), 154.9 (s; 4), 169.9 (s; 18); ^{31}P NMR (202 MHz, CD_3OD): δ = 18.9 (s); FT-IR $\tilde{\nu}$ = 3417 (N–H), 1649 (C=O), 1605, 1585 (arom), 1528, 1347 (NO_2), 1251 (P–OAr), 1209 (P–O) cm^{-1}; MS (FAB + NBA): *m/z*: 889 ([*M*+H]$^+$); elemental analysis calcd (%) for $C_{44}H_{36}N_4O_{12}P_2Li_2$ (888.62): C 59.47, H 4.08, N 6.30; found: C 57.74, H 4.16, N 5.99.

1,10,27,34-Tetraoxo-1,10-dimethoxy-1,10-diphospha-11,50-dioxa-26,35-diaza[2](3)benzeno[3](2)benzeno[1](3,4)nitrobenzeno[3](2,1)pyridino[3](3,5)-nitrobenzeno[1](2)benzenocyclophane (8b): A solution of **7b** (0.620 g, 0.617 mmol) and triethylamine (0.69 mL, 4.94 mmol) in dry THF (50 mL) and a solution of 2,6-pyridinedicarboxylic acid dichloride (0.126 g, 0.617 mmol) in dry THF (50 mL) were continuously injected over 3 h at room temperature into a mixture of dry THF (50 mL) and dry benzene (10 mL). The reaction mixture was stirred overnight, then the precipitated triethylammonium chloride was filtered off, the filtrate was evaporated to dryness and the residue was chromatographed over silica gel 60 eluted with chloroform/acetone = 1:1 (R_f = 0.33), producing a light yellow solid. Yield: 0.180 g (0.199 mmol, 32%); m.p. 220 °C (decomp, DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.27/3.28 (d (diastereomers), ^2J(H,P) = 20.2 Hz, 4H; b), 3.73/3.75 (d (diastereomers), ^3J(H,P) = 11.4 Hz, 6H; c), 3.95 (s, 4H; h), 4.85 (d, ^3J(H,H) = 6.3 Hz, 4H; l), 6.79 (s, 2H; d), 6.85 (d, ^3J(H,H) = 8.2 Hz, 2H; g), 6.90 (d, ^3J(H,H) = 7.6 Hz, 2H; e), 7.13/7.14 (dd (diastereomers), ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.6 Hz, 2H; f), 7.21 (s (diastereomers), 4H; a), 7.42 (dd, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.3 Hz, 2H; k), 7.59 (d, ^3J(H,H) = 7.6 Hz, 2H; j), 7.80/7.82 (d (diastereomers), ^4J(H,H) = 1.3 Hz, 2H; i), 8.01 (t, ^3J(H,H) = 7.6 Hz, 1H; o), 8.30 (d, ^3J(H,H) = 7.6 Hz, 2H; n), 8.61 (t, ^3J(H,H) = 6.3 Hz, 2H; m); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 32.8 (d, ^1J(C,P) = 139.9 Hz (diastereomers; 3), 40.7 (s; 11), 41.0 (s; 18), 53.2 (d, ^2J(C,P) = 3.0 Hz (diastereomers; 4), 118.6 (s; 10), 120.8 (s; 6), 125.0 (s; 13), 125.5 (s; 8), 129.7 (d, ^2J(C,P) = 2.4 Hz (diastereomers; 2), 130.0 (s; 16), 130.2 (s; 1), 131.0 (s; 15), 132.3 (s; 9), 134.6 (s; 17), 139.1 (s; 21), 141.1 (s; 12), 142.1 (s; 22), 142.2 (s; 7), 148.6 (s; 14), 148.6 (s; 20), 150.8 (d, ^2J(C,P) = 4.2 Hz (diastereomers); 5), 163.2 (s; 19); ^{31}P NMR (202 MHz, $CDCl_3$, 25 °C): δ = 25.3 (s (diastereomers); FT-IR: $\tilde{\nu}$ = 3418 (N–H), 2957 (C–H), 1677 (C=O), 1608, 1586 (arene), 1529, 1356 (NO_2), 1237 (P–OAr), 1043 (P–OMe) cm^{-1}; MS (FAB + NBA): *m/z*: 906 ([*M*+H]$^+$); elemental analysis calcd (%) for $C_4H_{41}N_5O_{12}P_2$ (905.79): C 59.67, H 4.56, N 7.73; found: C 59.40, H 4.81, N 7.59.

1,10,27,34-Tetraoxo-1,10-dioxido-1,10-diphospha-11,50-dioxa-26,35-diaza[2](3)benzeno[3](2)benzeno[1](3,4)nitrobenzeno[3](2,1)pyridino[3](3,5)-nitrobenzeno[1](2)benzenocyclophane dilithium salt (2b): Cyclophane **8b** (144.1 mg, 0.159 mmol) was suspended in dry acetonitrile (1.5 mL) and treated with a solution of lithium bromide (28.3 mg, 0.326 mmol) in dry acetonitrile (1.5 mL). The mixture was heated under reflux for one week. Then the product was filtered off and washed with cold acetonitrile and diethyl ether. Yield: 116.0 mg (0.130 mmol, 82%); m.p. 250 °C (decomp, DSC); ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ = 2.88 (d, ^2J(H,P) = 19.6 Hz, 4H; b), 3.85 (s, 4H; g), 4.83 (s, 4H; k), 6.63 (s, 2H; c), 6.79 (d, ^3J(H,H) = 7.6 Hz, 2H; f), 6.88 (d, ^3J(H,H) = 8.2 Hz, 2H; d), 7.01 (s, 4H; a), 7.04 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.6 Hz, 2H; e), 7.40 (d, ^3J(H,H) = 8.2 Hz, 2H; j), 7.43 (d, ^3J(H,H) = 8.2 Hz, 2H; i), 7.79 (s, 2H; h), 8.07 (t, ^3J(H,H) = 7.6 Hz, 1H; n), 8.20 (d, ^3J(H,H) = 7.6 Hz, 2H; m); ^{13}C NMR (126 MHz, CD_3OD, 25 °C): δ = 36.4 (d, ^1J(C, P) = 134.4 Hz; 3), 41.8 (s; 10/17), 120.4 (s; 7), 122.7 (s; 5), 124.8 (s; 9), 126.3 (s; 12), 126.4 (s; 20), 130.6 (s; 8), 131.0 (s; 1), 131.1 (s; 15), 132.7 (s; 2), 134.3 (s; 14), 135.7 (s; 16), 140.9 (s; 21), 142.6 (s; 11), 144.2 (s; 6), 149.9 (s; 13), 150.3 (s; 19), 154.9 (s; 4), 166.4 (s; 18); ^{31}P NMR (202 MHz, CD_3OD, 25 °C): δ = 18.8 (s); FT-IR: $\tilde{\nu}$ = 3405 (N–H), 1672 (C=O), 1605, 1586 (arene), 1527, 1348 (NO_2), 1253 (P–OAr), 1212 (P–O) cm^{-1}; MS (FAB + NBA): *m/z*: 890 ([*M*+H]$^+$); elemental analysis calcd (%) for $C_{43}H_{35}N_5O_{12}P_2Li_2$ (889.61): C 58.06, H 3.97, N 7.87; found: C 55.36, H 4.23, N 7.33.

NMR host–guest titrations: The guest compound was dissolved in the appropriate amount of solvent and the resulting solution was evenly distributed among 10 NMR tubes. The first NMR tube was sealed without any guest. The host compound was also dissolved in the appropriate amount of solvent and added in increasing amounts to the NMR tubes, so that finally solutions with the following relative amounts (equiv) of host versus guest compound were obtained: 0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 2.00, 3.00 and 5.00. The theoretical values (corrected for pipeting errors) were afterwards again corrected by comparison with the integration of various host and guest signals. All probes were measured with 256 pulses per probe; all $\Delta\delta$ values refer to the standard of the pure guest compound. K_a and $\Delta\delta_{sat}$ were calculated by nonlinear regression from the observed $\Delta\delta$ values and the respective host and guest concentrations.

A representative example is given below: **2a** versus (*R*/*S*)-noradrenaline · HCl (**10**) in CD_3OD. Weighed amounts: **10**: 1.78 mg in 8.00 mL; **2a**: 11.74 mg in 0.61 mL; proton *a*: K_{ass} [M^{-1}] = 1010 ± 12%; $\Delta\delta_{sat}$ [ppm] = 0.220 ± 4%; proton *b*: K_{ass} [M^{-1}] = 978 ± 9%; $\Delta\delta_{sat}$ [ppm] = 0.104 ± 3%; proton *c*: K_{ass} [M^{-1}] = 1040 ± 13%; $\Delta\delta_{sat}$ [ppm] = 0.108 ± 4%.

Self-association experiments: Solutions of **2a** or **2b** in D_2O were prepared in the following concentrations: 5×10^{-3} M, 4×10^{-3} M, 2×10^{-3} M, 1×10^{-3} M, 6×10^{-4} M, 2×10^{-4} M, 4×10^{-5} M, and 8×10^{-6} M. ^{1}H NMR spectra were recorded, starting with 256 pulses for the highest and finishing with 4096 pulses for the lowest concentration. The dilution curves obtained were evaluated with standard nonlinear regression methods, and self-association constants were calculated.

Evaluation of the complex stoichiometry (Job plots): Complex stoichiometries were determined according to Job's method of continuous variations. Equimolar amounts of host and guest compound were dissolved in the appropriate NMR solvent. These solutions were distributed among 11 NMR tubes in such a way that the molar fractions *X* of host and guest in the resulting solutions increased (or decreased) from 0.0 to 1.0 (and vice versa). The complexation-induced shifts (CIS) were multiplied by *X* and plotted against *X* itself (Job plot).

Mass spectrometric measurements: ESI mass spectra were recorded on a Finnigan MAT 95. Samples (20 μL) were introduced as 10^{-7} M solutions in HPLC-grade methanol at flow rates of 20 μL min^{-1}. Heated capillary temperature: 150 °C. Ion spray potential: 3.5 kV (positive ESI), 3.0 kV (negative ESI). About 20–30 scans were averaged to improve the signal-to-noise ratio.

Molecular modeling: Force-field calculations were initially carried out as molecular mechanics calculations without solvent (Cerius2, Molecular

Simulations 1997, force field: Dreiding 2.21). To establish the minimum energy conformation of the free host and guest molecule as well as their 1:1 complex, Monte Carlo simulations were carried out in water (MacroModel 7.0, Schrödinger Inc., 2000. Force-field: Amber*). A 3000-step Monte Carlo simulation was carried out, followed by a molecular dynamics calculation for 10 ps at 300 K. The three best structures for the 1:1 complex varied in their total energy by only 5 kJ mol^{-1}. In each case, the adrenaline molecule is included in the cavity of the macrocycle with specific recognition of the amino alcohol by the bisphosphonate anions. A beautiful sandwich arrangement is consistently formed between the catechol and the double nitrobenzene wall in **2a** or **b**. In addition, the upper of both phenolic OH groups forms two hydrogen bonds to the isophthaloyl amides. The whole complex structure is slightly twisted in order to minimize bond and torsional strains and maximize van der Waals interactions. One of the anionic phosphonate O atoms is rotated outwards to gain solvation energy with the solvent. In chloroform or without solvent both anionic O atoms are predicted to form strong hydrogen bonds with the ammonium cation of the guest.

FT-IR experiments: FT-IR spectra were recorded for noradrenaline hydrochloride, free host **2a**, and the corresponding 1:1 complex (KBr). The IR spectrum of the complex was identical to the addition of host and guest spectra, with two exceptions:

a) the strong band for the host's anionic P–O bond (symmetrical and asymmetrical vibrational stretch) shifted from 1070.8 to 1060.2 cm^{-1} and from 1210.8 to 1186.3 cm^{-1} ($\Delta = 8.6$ and 24.5 cm^{-1}). This shift to lower values of $\tilde{\nu}$ corresponds to hydrogen bond formation with noradrenaline's ammonium functionality;
b) the host's strong amide carbonyl band (C=O, vibrational stretch) shifted from 1650.7 to 1646.5 cm^{-1} ($\Delta = 4.2$ cm^{-1}). This corresponds to the formation of hydrogen bonds between its coupled N–H bond and the phenolic hydroxy group.

NOESY experiments: Standard ^{1}H NOESY experiments were performed with the host **2a** and **2b** as well as their complexes with noradrenaline · HCl on the Bruker 500 MHz NMR spectrometer. Mixing times varied between 100 and 200 ms. In spite of its high viscosity leading to enforced spin–lattice relaxation we chose [D$_6$]DMSO as solvent, because here the important amide proton NOEs could be measured. Positive reciprocal NOE peaks were classified as w = weak, m = medium, and s = strong.

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