Host–Guest Chemistry

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Anion-Induced Synthesis and Combinatorial Selection of Polypyrrolic Macrocycles**

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One of the current challenges in the area of supramolecular chemistry involves the preparation of anion receptors with high selectivity for specifically targeted anionic guests.[1] Such systems could have an important role to play in a variety of applications, including sensing, analysis, waste remediation, and drug development. One approach for designing highly efficient anion receptors is to use anion-templated strategies to produce macrocyclic systems whose geometry is complementary to that of the targeted guests.[2] Although this concept has yet to be extensively exploited in the case of pyrrole-based systems, recently we prepared cyclo[*n*]pyrroles through self-coupling of bipyrroles under oxidative conditions in the presence of suitable anionic templates. In earlier work, we found that bipyrrole-amide-derived catenanes[3] and the Schiff base expanded porphyrin **1** ("USAphyrin")[4] could be synthesized using anion-templated processes. Finally, in the case of the 2,6-diamidopyridine-containing system **2**, we noted that improved yields were seen when the initial macrocycle-forming reaction was carried out in the presence

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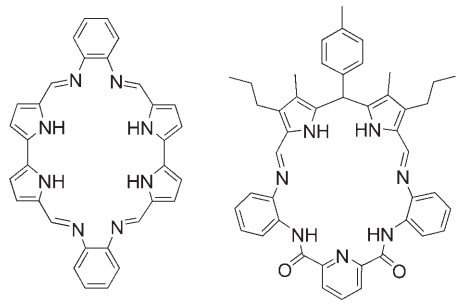
Supporting information for this article (general methods and materials, synthetic experimental details, representative Job plots, UV/Vis titrations, corresponding binding isotherms, and details of affinity constant determinations, as well as X-ray crystallographic information, including CIF files) is available on the WWW under http://www.angewandte.org or from the author.



1 2

of sulfuric acid or trifluoroacetic acid.[5] Given these results, we sought to explore the effects of such putative anion-template effects in the case of other 2,6-diamidopyridine pyrrolic macrocycles. Herein, we report the anion-induced synthesis of a new class of 2,6-diamidopyridine-bipyrrole macrocyclic receptors that undergo combinatorial selection as the result of their interaction with anionic guests. This stimulus-driven reaction outcome bears analogy, and provides an interesting complement, to recent macrocycle-forming strategies based on dynamic combinatorial processes.[6]

The incorporation of 2,6-diamidopyridine subunits into appropriately designed macrocycles has been shown by us[5,7] and others[8] to result in systems that display selectivity for tetrahedral over trigonal-planar anions. A different structural motif, namely, bipyrrole, has also been used extensively by our groups to produce anion receptors, including several that display selectivity towards sulfate and other tetrahedral anions.[9,10] Thus, we were keen to explore whether macrocycles containing these two key subunits could be readily prepared and, if so, whether the reactions leading to their formation could be mediated by anion templation. To this end, the diformylbipyrrole **4**[11] was treated with diamine **3** in methanol under acidic conditions (Scheme 1). This led to the formation of Schiff base containing macrocycles along with linear oligomeric species. The choice of the acid used to promote these reactions (HCl, HBr, CH_3CO_2H, CF_3CO_2H, H_3PO_4, H_2SO_4, HNO_3) plays a critical role in defining the product distribution. In most cases, the products precipitated as the corresponding acid salts. These precipitates and the reaction mixtures themselves were analyzed by ESI and MALDI-TOF mass spectrometry. For instance, the use of hydrochloric and hydrobromic acids led to the formation of oligomers with high molecular weights ($m/z > 3000$) as the major products, with only small amounts of the [1+1] macrocycle being produced under these conditions. This latter product displayed low stability and appeared to undergo decomposition during the workup and purification stages. The use of acetic, trifluoroacetic, and phosphoric acids led to the formation of the [2+2] macrocycle **5**, which was contaminated with appreciable quantities of uncharacterized oligomers. When nitric acid was employed, only oligomeric species with high molecular weights were formed. In contrast, the use of sulfuric acid produced the [2+2] macrocycle **5**, nearly free of other side products. The resulting salt, $\mathbf{5}\cdot 2\,H_2SO_4$, was then suspended in CH_2Cl_2 and treated with triethylamine to give the free macrocycle **5** in 75% isolated yield based on **4**.

A single-crystal X-ray diffraction analysis of **5** (Figure 1) provided proof for the proposed structure and revealed that

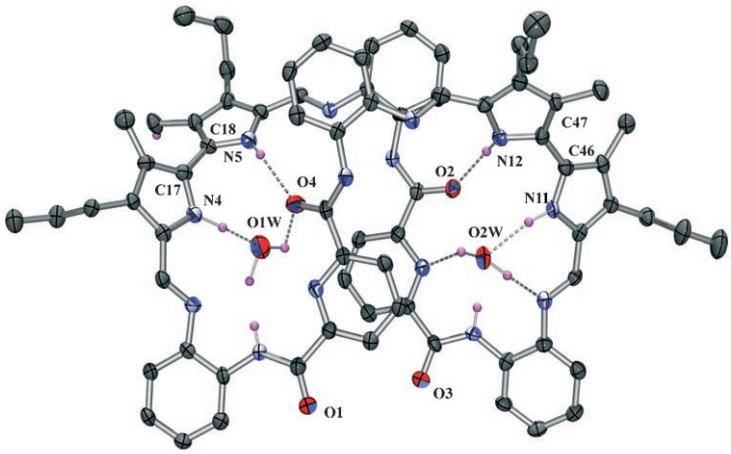
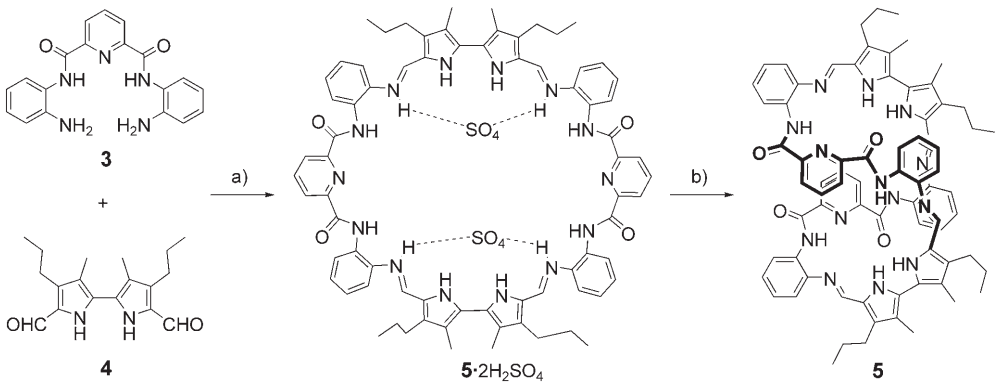


Figure 1. ORTEP-rendered view of **5** showing the two bound solvent water molecules. Three dichloromethane molecules and most hydrogen atoms have been omitted for clarity. Thermal ellipsoids are scaled to the 50% probability level. C gray, N blue, O red, H pink; dashed lines indicate hydrogen-bonding interactions. Key bond parameters: N5-H···O4 (N···O 3.109(4), H···O 2.29(4) Å, N-H···O 169(3)°); N12-H···O2 (N···O 3.013(4), H···O 2.18(4) Å, N-H···O 177(3)°).

the macrocycle adopts a figure-of-eight conformation in the solid state.[12] This three-dimensional structure is stabilized by a pair of intramolecular hydrogen bonds between the pyrrole NH protons and the amide oxygen atoms O2 and O4 that point towards the interior of the cavity. The bipyrrole fragments are twisted in both bipyrrole units, displaying dihedral angles N4-C17-C18-N5 and N11-C46-C47-N12 of 50.5(6)° and 34.4(6)°, respectively. The 2,6-diamidopyridine fragments are in a *trans*



Scheme 1. a) Conc. H_2SO_4 (2.2 equiv), 48 h, room temperature; b) Et_3N (excess), $MeOH/CH_2Cl_2$.

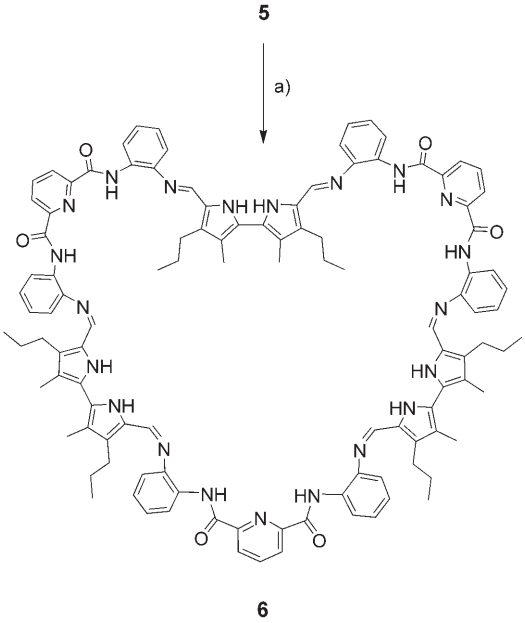
orientation, and the amide oxygen atoms O1 and O3 that point towards the exterior of the cavity are hydrogen bonded to one dichloromethane molecule and one water (O1W) molecule, respectively. These latter intermolecular interactions presumably account for the dimerization of **5** observed in the solid state (see Supporting Information). One water molecule (O1W) is partially constrained within the macrocycle, while a second water molecule (O2W) is entirely trapped within the macrocycle. The hydrogen-bonding interactions that stabilize these species are described in the Supporting Information.

The ^{1}H NMR spectrum of **5** in $CDCl_3$ at room temperature reveals a nonequivalence for all the methyl and methylene signals, as well as a complex patterns in the aromatic region that is most readily interpreted in terms of the retention of the figure-of-eight conformation of **5** in this nonpolar solvent. At 60 °C the spectrum simplifies dramatically. Such a simplification is also observed in polar solvents (e.g. pyridine, THF) at room temperature. Presumably, this reflects the fact that in both cases the intramolecular hydrogen bonds that stabilize the figure-of-eight conformation in $CDCl_3$ at room temperature are weakened or destroyed.

The presence of bound water molecules in the solid-state structure of **5** (see Figure 1), along with the presence of what appears to be two well-defined binding pockets, led to the consideration that **5**, like its congener **2**, might act as an effective receptor for anions. Anion-binding studies were thus performed using UV/Vis spectroscopic titrations. To maintain consistency with previously reported results,[5,7] these studies were carried out in CH_3CN at 23 °C using various tetrabutylammonium (TBA) salts. Where appropriate, binding stoichiometries were determined using Job plots. On this basis it was found that macrocycle **5** interacts strongly with the tetrahedral anions HSO_4^- (1:1; $K_a = 63\,500 \pm 3000\,M^{-1}$) and $H_2PO_4^-$ (2:1; $K_{a1} = 191\,000 \pm 15\,400\,M^{-1}$; $K_{a2} = 60\,200 \pm 6000\,M^{-1}$; $K_a = 107\,000 \pm 9600\,M^{-1}$ where $K_a = (K_{a1} \times K_{a2})^{0.5}$), weakly with acetate (1:1, $K_a = 26\,000 \pm 2400\,M^{-1}$), and essentially not at all with the other anions tested, namely chloride, bromide, and nitrate (K_a values were below the detection limits in all cases). Such findings are not surprising in light of the fact that the initial "synthetic selection" in favor of macrocycle **5** was performed using a tetrahedral anion (HSO_4^-) as the template.

Interestingly, of the two tetrahedral anions subject to study, namely HSO_4^- and $H_2PO_4^-$, dihydrogen phosphate is bound more strongly and by a stepwise 2:1, as opposed to 1:1, guest/host binding process (see the K_a values given above). This result is in accord with our previous finding[5] that the related flexible macrocyclic receptor **1** also binds dihydrogen phosphate more strongly than sulfate ions and likewise displays a 2:1 guest/host binding stoichiometry.

While macrocycle **5** proved quite stable under most laboratory conditions, when dissolved in acetonitrile and allowed to stand for 5 days in the presence of dihydrogen phosphate and hydrogen sulfate (tetrabutylammonium salts) it was found to undergo rearrangement to give the corresponding [3+3] analogue **6** in quantitative and 47% yield, respectively (Scheme 2).[13] The use of chlorinated solvents during this transformation did not produce **6** but rather



Scheme 2. a) $TBAHSO_4$, acetonitrile, 5 days, room temperature without stirring, followed by Et_3N; or $TBAH_2PO_4$, acetonitrile, 5 days, room temperature without stirring.

yielded traces of the [1+1] macrocycle (as inferred from mass spectrometric studies) along with a wide variety of soluble compounds, which as yet have not been characterized. This behavior was observed whether the reactions were performed at room temperature or at reflux. However, the ring-expanded product was formed only in traces when the reaction mixture was subject to stirring for 2 days in the presence of $TBAHSO_4$; in this case, a precipitate of $\mathbf{5}\cdot 4H_2SO_4$ was observed to form, along with soluble oligomeric compounds. The isolated yield for $\mathbf{5}\cdot 4H_2SO_4$ following this latter procedure was 30%. The salt $\mathbf{5}\cdot 4H_2SO_4$ (characterized by elemental analysis) differs from $\mathbf{5}\cdot 2H_2SO_4$ in its chemical properties and displays, for instance, different solubility in organic solvents. Pure free base **5** may be obtained in quantitative yield by treating solutions of $\mathbf{5}\cdot 4H_2SO_4$ in methylene chloride with triethylamine. Also note that there is no evidence that the ring-expanded product **6**, in either its neutral or acid salt form, is generated during the initial anion-induced synthesis of **5**.

From these observations we postulate that the kinetics and thermodynamics of product formation are a subtle function of the reaction conditions. In particular, we suggest that when the reaction mixture is subject to stirring, the salt $\mathbf{5}\cdot 4H_2SO_4$ is formed quickly (kinetic product) and under conditions that favor its precipitation, a follow-up process that also serves to affect the thermodynamics of the reaction. By contrast, in the absence of stirring, the precipitation of $\mathbf{5}\cdot 4H_2SO_4$ is slow and allows the isolation of **6** as the thermodynamic product. Further tests that are designed to confirm or refute such mechanistic rationalizations are currently underway.

While macrocycle **6** proved to be relatively stable in acetonitrile, both as the free base and as its H_2SO_4 salt, it was found to undergo decomposition, often rapidly, in other

solvent systems. Decomposition was also induced upon the addition of anions other than sulfate or phosphate, a finding that served to underscore the special, anion-specific conditions that lead to its formation.

Proof for the structure of **6**, came from a single-crystal analysis of its hydrogensulfate salt, **6**·H_2SO_4 (Figure 2[14]).

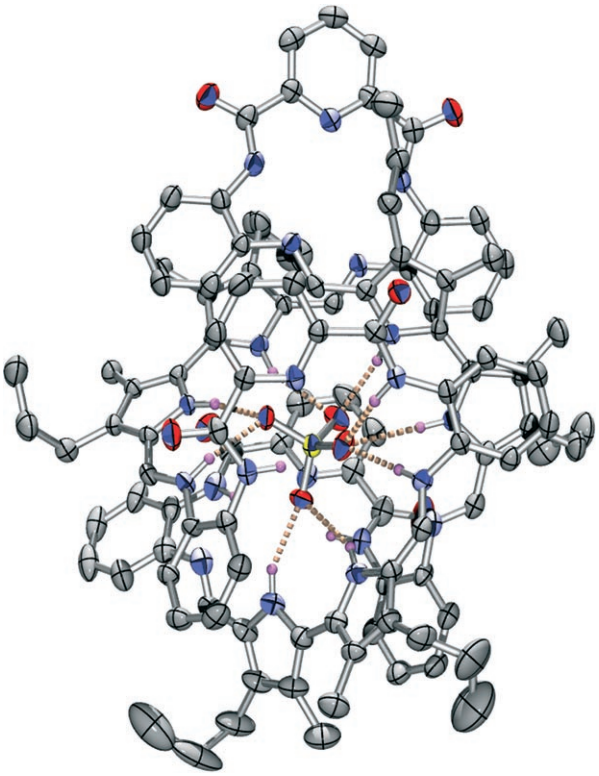


Figure 2. View of the macrocyclic complex **6**·H_2SO_4. Displacement ellipsoids are scaled to the 50% probability level. Solvent molecules (2×CH_3CN and 1×pentane), as well as hydrogen atoms, have been removed for clarity. C gray, N blue, O red, H pink; dashed lines indicate hydrogen-bonding interactions.

Although complicated, the resulting structure clearly reveals a doubly twisted, diprotonated macrocyclic dication that encapsulates a sulfate dianion. This dianion is coordinated through an intricate network of hydrogen bonds (see Supporting Information). The hydrogen-bond donors in this network consist of the NH protons from the three bipyrrole subunits, three NH protons from two 2,6-diamidopyridine subunits, and two NH protons from two protonated imine fragments. Several of these key interactions are highlighted in Figure 3. All the 2,6-diamidopyridine subunits are in their respective *cis* orientations.

The present findings provide evidence for an anion-templated reaction between diamine **3** and bipyrrole dialdehyde **4**, as well as the anion-triggered combinatorial selection of a given macrocyclic product under a particular set of experimental conditions. The present reorganization reaction differs from dynamic combinatorial libraries in that selection from a true equilibrium mixture does not occur. Instead, the choice of the anion template serves to drive the reaction towards the formation of the most stable species under the

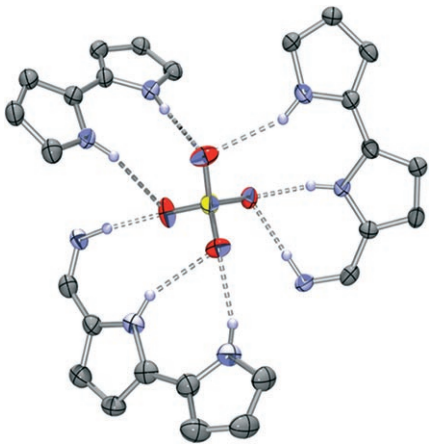


Figure 3. ORTEP–Povray-rendered view of bipyrrole and tethered protonated imine fragments forming hydrogen bonds with the sulfate ion. All other parts of the molecule have been omitted for clarity. Displacement ellipsoids are scaled to the 50% probability level. C gray, N blue ellipsoids, O red, H pale blue spheres; dashed lines indicate hydrogen-bonding interactions.

specific reaction conditions involved. In other words, the modifications used to obtain **6** from **5** (i.e. addition of the appropriate anion) serve to change the fundamental thermodynamic conditions of the system as a whole. As a consequence, a stable molecule (e.g. **5**) undergoes partial or complete decomposition only to be reassembled into a more stable homologue (**6**). Under the most favorable of conditions, an impressive degree of selectivity is observed which leads us to suggest that this strategy could provide a new concept for the design and synthesis of novel receptor systems. Work designed to explore this intriguing possibility is currently in progress.

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[14] Crystal data for $(\mathbf{6}H_2)^{2+}\cdot SO_4^{2-}\cdot 2\,CH_3CN\cdot C_5H_{12}$: $M_r = 2087.54$, crystal size $0.51\times 0.36\times 0.20\ mm^3$, $Z = 4$, triclinic, space group $P\bar{1}$, $a = 18.8891(2)$, $b = 23.7914(3)$, $c = 25.5253(4)$ Å, $\alpha = 77.983(1)$, $\beta = 84.781(1)$, $\gamma = 84.019(1)°$, $V = 11130.2(3)$ Å^3, $\rho_{calc} = 1.246\ mg\,cm^{-3}$, $T = 153(2)$ K, $\theta_{min} = 2.91$, $\theta_{max} = 25.05°$, $\lambda = 0.71073$; $Mo_{K\alpha}$ radiation, data collected on a Nonius Kappa CCD diffractometer. A total of 530 frames of data were collected using ω scans, with a scan range of 0.9° and a counting time of 131 seconds per frame. Final $R1 = 0.0715$ (for 18372 reflections with $I > 2\sigma(I)$ and $wR2(F^2) = 0.1365$ (all data)). Data reductions were performed using DENZO-SMN. The structure was solved by direct methods using SIR97 and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-hydrogen atoms using SHELXL-97. CCDC 275698 (**5**) and 275834 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

