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Synthesis, structural characterization, and anion binding ability of sterically congested adamantane-calix[4]pyrroles and adamantane-calixphyrins

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ABSTRACT

Novel adamantane derivatives of calix[4]pyrroles **4**–**8** and calixphyrin **9** have been synthesized. The structure of **8** has been characterized by X-ray powder diffraction and the structure of **9** by single crystal X-ray analysis. Whereas calixphyrin **9** does not bind anions, analogous calyx[4]pyrrole **8** forms a complex with Cl^- in the DMSO solution and in the solid state. The solid state complexation has been accomplished on grinding in a mill, which is the first example of complex formation with an anion in the solid state.

1. Introduction

Calix[4]pyrroles **1** have been known for more than a century. Bayer's publication on acid-catalyzed condensation of pyrrole and acetone dates back to 1886.[1] However, the chemistry of calixpyrroles blossomed only recently when Sessler and co-workers discovered that calixpyrrole derivatives can bind anions and neutral molecules.[2] Since that finding, many structural derivatives of calixpyrroles were prepared and their anion binding properties investigated.[3] Regardless of the considerable amount of experimental work to modify the structure of calixpyrroles and the theoretical work devoted to understand their binding behavior, only recently Sessler and co-workers published a systematic study, which explained solvent and countercation effects on binding with anions and shed some light on the previously reported controversial values of binding constants.[4]

Besides anion sensing, interest in calixpyrroles and their derivatives has been driven by the finding that biocompatible anion carriers could play a role in the development of new treatment for cystic fibrosis and AIDS.[5] Significant progress in the application of cyclic oligopyrroles for biological purposes[6] has been achieved for sapphyrins,[7] the pentapyrrolic porphyrin derivatives. Namely, it was recognized that these polypyrrolic compounds in the protonated form could be useful in terms of permitting the into-cell delivery of anionic, nucleotide type antiviral agents or the treatment of cystic fibrosis via the control of chloride anion fluxes.[8] To test the applicability of calixpyrroles as membrane anion transporters, extraction studies have been carried out.[9] These studies showed that increase of the transport ability of calixpyrroles can be achieved by an increase of the cavity size (i.e., number of pyrrole units). The other logical approach to improve the potential of calixpyrrole derivatives as anion carriers and antineoplastic or antiviral drug delivery agents would be to introduce lipophilic bulky substituents to these molecules, and in that way enhance their transport ability through cell membranes.

Whereas the chemistry of calixpyrroles **1** and porphyrins **3** has been thoroughly explored, there is still not much known about calixphyrins **2**, the intermediates in the six-electron oxidation process from **1** to **3** (Scheme 1). The main reasons for this lie in the conformational instability of calixphyrins, and especially, their liability to oxidation. Generally, calixphyrins can be described as porphyrin analogs, the structure of which is characterized by the presence of sp^2 and sp^3-hybridized bridging carbons.[10] It is generally believed that porphomethene ($1sp^2$) and porphodimethene ($2sp^2$) are intermediates in the sequential biosynthesis of porphyrin from porphyrinogen.[11] Besides, porphodimethenes can be obtained via Buchler's procedure that involves reductive alkylation at the *meso* position of porphyrins,[12] or via Floriani's pathway involving dealkylation of octaalkylcalix[4]pyrrole.[13] The alternative approach is a 2+2 Mac-Donald-like method[14] based on the acid-catalyzed condensation of oligopyrroles and acetone[15] or condensation of sterically hindered aldehyde and pyrrole.[16] Since calixphyrins represent a class of compounds inbetween calixpyrroles and porphyrins, an important role in the supramolecular chemistry of cations and anions is anticipated.

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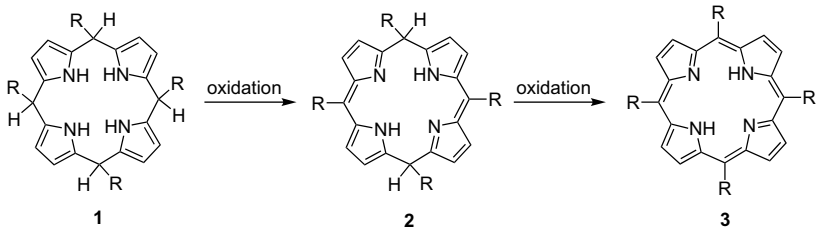


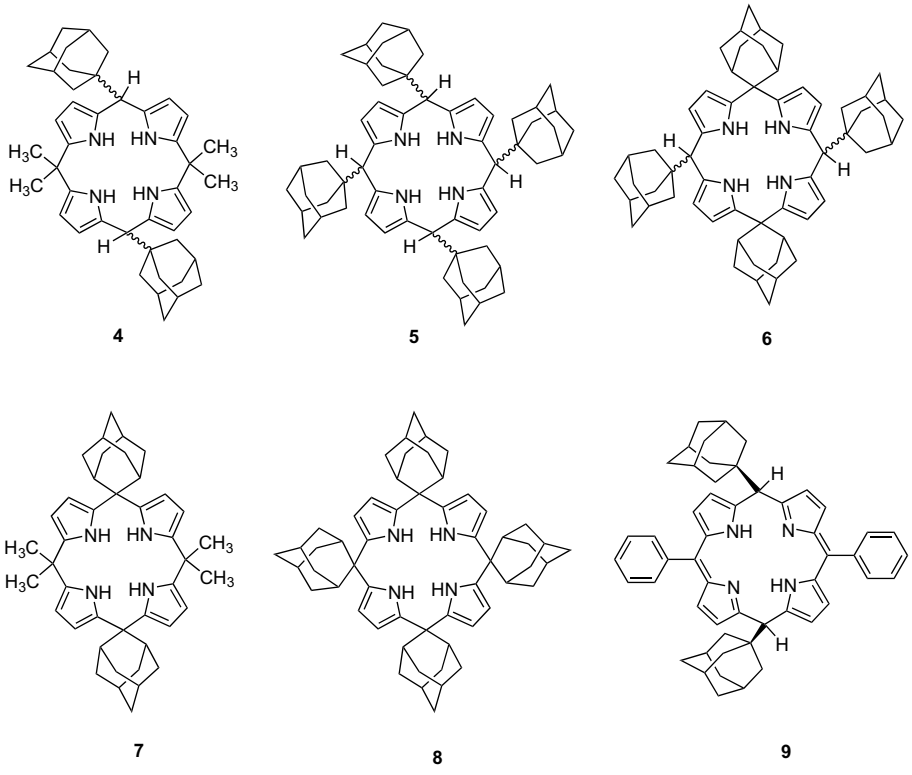
Scheme 1.

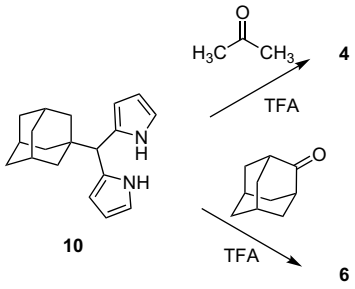
In the context of our synthetic efforts to incorporate polycyclic units (such as adamantane[17] or PCU)[18] into macrocyclic compounds for the enhancement of the selective recognition of different guest molecules, we turned our attention to adamantane-dipyrromethanes and their potential as anion sensors.[19] Our findings that these derivatives bind anions,[20] and reports in the literature on the condensation of pyrrole and cyclohexanone[21] prompted us to incorporate adamantane-dipyrromethane building blocks into calix[4]pyrroles and calixphyrins and investigate their structural characteristics by X-ray crystallography. Information on the structures of these novel molecules may open new horizons to structural and supramolecular chemists, searching for new host molecules. In this paper we describe for the first time the synthesis of five adamantane-calixpyrroles **4**–**8** and adamantane-calixphyrin **9**. Furthermore, we present a study of the Cl^- anion binding by calixpyrrole **8** in both the solution and the solid state.

2. Results and discussion

The first attempt to prepare adamantane derivative of calix[4]-pyrrole was performed by reacting adamantane 1-carbaldehyde and adamantane-dipyrromethane **10** under acidic conditions. The reaction furnished calix[4]pyrrole **5** in a relatively low yield (23%), present as a mixture of stereoisomers. Due to the low yield of the reaction, small quantities of the products and the same R_f values of isomers **5**, we did not proceed with the isomer separation. In order to obtain calix[4]pyrrole **4**, which has a smaller number of possible isomers, we performed an acid-catalyzed condensation of dipyrromethane **10** and acetone (Scheme 2). The reaction yielded a mixture of two calix[4]pyrroles (*syn*- and *anti*-**4**), which were obtained in a total yield of 19%. Applying the analogous procedure, dipyrromethane **10** was also transformed in a condensation reaction with 2-adamantanone to a mixture of calixpyrroles **6**. The isomers **6** were obtained in a 24% yield. Chromatographic separation furnished only one isomer in a pure form.

In order to avoid the problems with mixtures of stereoisomers of calixpyrroles **4** and **6**, we tried to oxidize them to the corresponding porphodimethenes. However, in attempts to oxidize the calixpyrroles with DDQ, no oxidation took place. Therefore we performed a systematic study of the oxidation of the model compound, dipyrromethane **10**, with various oxidizing agents. We found out that dipyrromethane **10** was extremely resistant to oxidation. After treatment with chloranil, DDQ,[22] $BaMnO_4$,[23] and Ag_2O,[24] only the



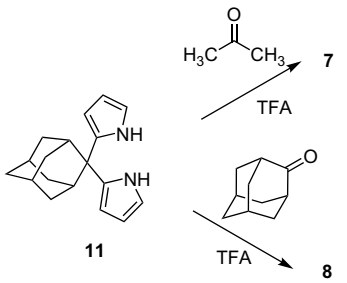


Scheme 2.

starting material was recovered. Consequently, we conclude that adamantane as a *meso*-substituent induces pronounced stability of dipyrromethanes (and probably calixpyrroles) to oxidation.

To avoid the occurrence of stereoisomers in calixpyrroles, we next turned our attention to calixpyrroles derived from 2-adamantanone. Thus, in a condensation reaction of dipyrromethane **11** with acetone and 2-adamantanone, we prepared calixpyrroles **7** and **8**, respectively (Scheme 3). The condensation was carried out in toluene in the presence of TFA. Besides a number of unidentified products, calixpyrrole **7** was obtained in low yield. On the other hand, the synthesis of **8** was accomplished in good yield of 38%. Unfortunately, these calixpyrroles are characterized by very low solubility in most solvents. Consequently, we managed to record only their ^{1}H NMR spectra. In the ^{1}H NMR spectra in DMSO-d_6, two signals in the aromatic region were seen, corresponding to the pyrrole C–H and the N–H protons. In the aliphatic region, the characteristic bridgehead H-atom signals were present as broad singlets at $\delta \sim 2.3$ to 2.7 ppm, whereas the other adamantane H-atoms showed resonances as one broad multiplet at 1.56–1.77 ppm. All our efforts to grow single crystals of calixpyrroles **7** and **8** failed. We therefore turned to X-ray powder diffraction (XRPD), as an emerging analytical tool of an organic chemist,[25] to confirm the molecular structure of **8**, determine its conformation, and unravel the packing of molecules, which leads to such a low solubility. Data collected on a laboratory diffractometer proved to be of sufficient quality for structure solution and subsequent Rietveld refinement.[26]

Calixpyrrole **8** crystallizes in the tetragonal $P4_2/n$ space group. One quarter of a molecule forms the asymmetric unit (Fig. 1). As with the majority of the known calix[4]pyrroles, the pyrrole nitrogen atoms are pointing in the opposite directions in a 1,3-alternate fashion. The conformation of **8** in the solid state could be compared to the cyclohexyl substituted calix[4]pyrrole, crystallized as a dichloromethane solvate.[2] However, the bulky adamantane substituents in **8** force the pyrrole rings to be approximately perpendicular to the plane of the molecule. In the crystal, molecules are stacked along the *c* axis forming a narrow channel through the middle of the stack (approximate diameter is 1.5 Å). The acidic pyrrole N–H atoms are sterically hindered by the bulky



Scheme 3.

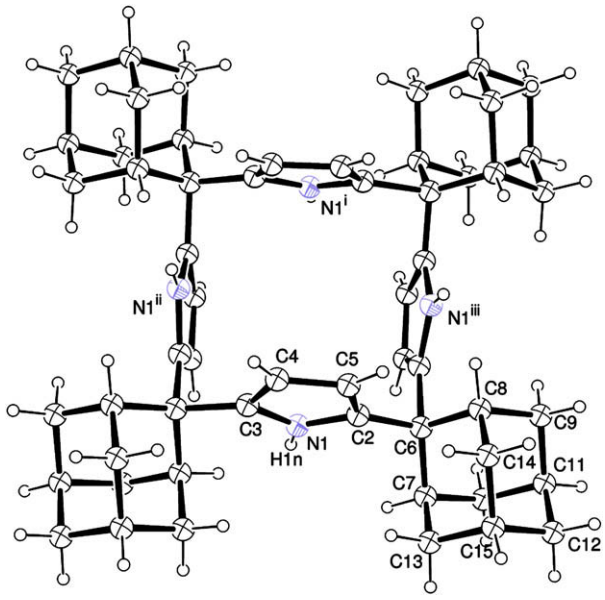


Figure 1. *ORTEP* view of **8**. Atoms have a common U_{iso} parameter and are shown at 50% probability level (symmetry codes that generate the whole molecule: *i*=0.5−*x*, 0.5−*y*, *z*; *ii*=*y*, 0.5−*x*, 0.5−*z*; *iii*=0.5−*y*, *x*, 0.5−*z*).

adamantanes and also, due to the lack of potential acceptors, are not involved in hydrogen bonds. No contacts except those of the van der Waals type can be found to govern the packing of molecules of **8** in the crystal. Solubility, which is essential for potential use of these compounds as anion binders, is determined by the difference in energy of crystal packing and energy of solvation. Between the two factors, the cause of surprisingly low solubility, in various solvents even at elevated temperatures, may be attributed to the numerous hydrogen–hydrogen contacts formed in the crystal. The potential role of hydrogen–hydrogen contacts in crystal packing has been reviewed recently.[27] Stacks of molecules are packed in a way that the adamantane units of one stack fill the clefts of the neighboring stack (Fig. 2) conforming to the close packing principle.

Since we were not able to oxidize calixpyrroles **4** and **6**, in order to prepare calixphyrins with adamantane substituents, we turned our attention to calixphyrins substituted with aromatic substituents and adamantanes. Thus, we performed condensation of

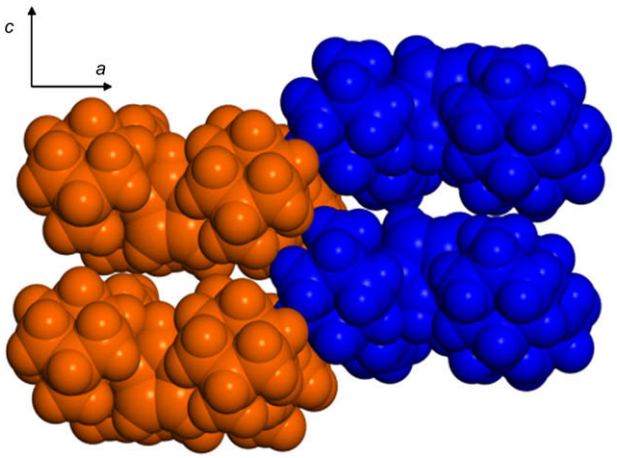
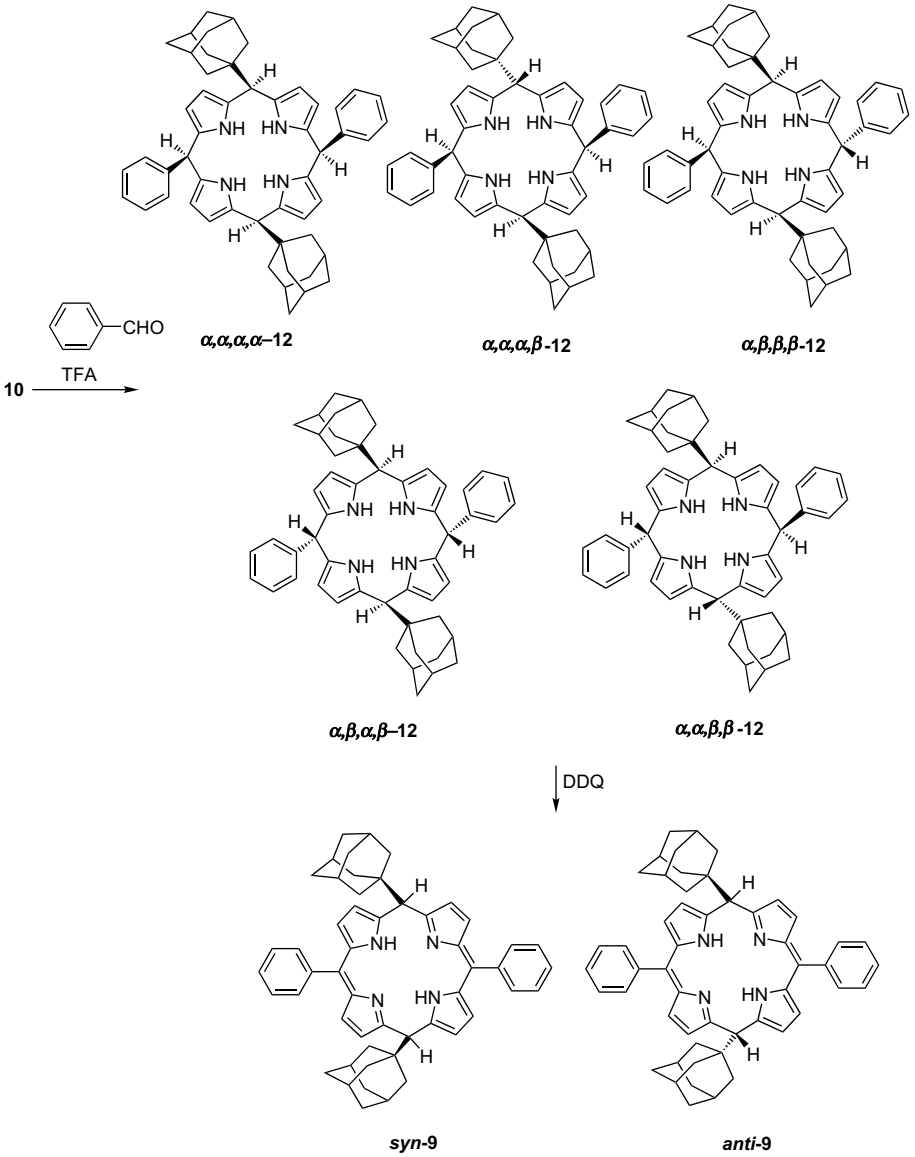


Figure 2. Crystal packing of **8** viewed in the direction of *b* axis. Adjacent stacks are colored red and blue.

dipyrromethane **10** and benzaldehyde. Reaction gave a complex mixture of calix[4]pyrroles **12** (Scheme 4), which we oxidized in situ to reduce the number of possible isomers. Column chromatography of the reaction mixture furnished calixphyrin *syn*-**9**, as the only isolable product in 12% yield. On the other hand, condensation reaction of **10** and benzaldehyde could theoretically yield five isomers, which when oxidized should give two calixphyrins **9**. Due to steric repulsions in the extremely sterically congested calix[4]-pyrrole, we anticipated that isomers α,α,β,β-**12** and (especially) α,β,α,β-**12** would form preferentially. Furthermore, taking into account that oxidation with DDQ in nonpolar solvent preferentially gives *syn*-elimination product,[28] it is not surprising that after treatment with DDQ we isolated only *syn*-**9**. However, we cannot rule out the possibility that some traces of *anti*-**9** were formed, which decomposed or retained on column chromatography. A force field calculation additionally corroborate the finding that *syn*-**9** should prevail in the reaction mixture. According to MM2 *syn*-**9** isomer is 7.9 kcal mol^{-1} more stable than *anti*-**9**. This finding is also in agreement with the reports that porphodimethenes are most stable in the *syn*-configuration in which the bulky substituents adopt the axial conformation.[29] To optimize the reaction and get higher yields of **9**, we performed the condensation of dipyrromethane **10** and benzaldehyde under various conditions. However, reaction in CH_2Cl_2 over 24 h (and subsequent oxidation) gave **9** in the yield of 8%. The same yield was obtained in a condensation in toluene under microwave irradiation over 15 min.

The structure of calixphyrin *syn*-**9** was characterized by spectroscopic methods and single crystal X-ray diffraction analysis. In the ^{1}H NMR spectra characteristic pyrrole H-atom signals were seen at $\delta \sim 13.1$ (NH), 6.2, and 6.4 (CH) ppm. In the aliphatic region, the adamantane signals at 1.6–1.8 ppm show complex multiplicity with the only well-resolved bridgehead H-signal at 3.76 ppm. The ^{13}C NMR spectrum is characterized by the presence of one singlet, one doublet, and two triplets (adamantane C-atoms) in the aliphatic region and three singlets and seven doublets in the aromatic region indicating the C_2 symmetry of the molecule.

In the crystal, molecule **9** lies on a C_2 axis confirming the molecular symmetry determined by NMR spectroscopy. Therefore, half of a molecule forms the asymmetric unit in the *C*2/*c* space group. Adamantane substituents reside in the *syn*-configuration and the pyrrole rings point in the same direction (Fig. 3). This conformation allows for the formation of bifurcated intramolecular N–H···N



Scheme 4.

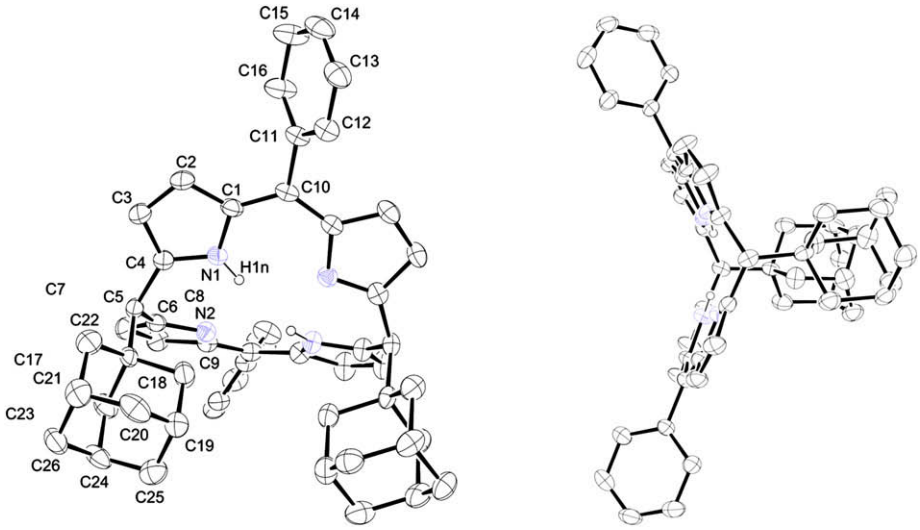


Figure 3. *ORTEP* views of **9**. Atoms are shown at 50% probability level. Hydrogen atoms, except those bonded to nitrogen atoms, are omitted for clarity. Symmetry code that generates the whole molecule is $-x$, y, $1.5-z$.

hydrogen bonds with distances d(H1n···N2)=2.44(2) Å and d(H1n···N2^{i})=2.21(2) Å, and angles ∠(N1–H1n···N2)=119(2)° and ∠(N1–H1n···N2^{i})=120(2)°; i=$-x$, y, $1.5-z$. The distance between two hydrogen atoms (H1n and H1n^{i}, i=$-x$, y, $1.5-z$) of the calixphyrin ring is 2.38(1) Å. Similar to **8**, packing of molecules of **9** is governed by weak interactions: hydrogen–hydrogen contacts of the van der Waals type and π–π contacts between phenyl rings. Packing of **9**, showing the layers of adamantane moieties and layers of phenyl rings above and below the calixphyrin plane, is given in Figure 4.

Our next goal was to study anion binding by calixpyrrole **8** and calixphyrin **9**. Compound **9** absorbs light in the visible region (λ_{max}=421 cm^{-1}, ε=5.47×10^{4} M^{-1} cm^{-1}) and has two acidic N–H atoms. Thus, deprotonation of the acidic N–H by a basic anion (F^- or acetate) would give rise to a change of color and provide the use of **9** as a (naked eye) colorimetric sensor. Therefore, we performed UV–vis titration with **9** (c=1×10^{-5} M) and tetrabutylammonium (TBA) salts of F^-, Cl^-, Br^-, and acetate. However, no changes in the absorption spectra were observed even upon addition of 10 anion equivalents. To test if **9** could form a complex with F^-, characterized by a small association constant, we also performed an NMR titration, but no changes in the ^{1}H NMR spectrum were observed on addition of TBAF to the $CDCl_3$ solution. The finding that **9** does not bind anions could be explained by its structure (Fig. 3). The anion should interact with two pyrrole N–H atoms, which are pointing to the inside of the cone of the macrocycle. However, at the same side of the molecule two bulky adamantanes are situated, which are hindering the approach of the anion and its counter-ion.

Due to the low solubility of **8**, we examined its potential to bind the Cl^- anion in the solid state. Solid **8** was ground in a mill with an equimolar amount of solid TBACl for 9 min. Three samples were taken from a mill during grinding in time increments of 3 min and subsequently analyzed by XRPD, IR, and ^{1}H NMR. The XRPD experiment showed that, with increase in grinding time, the diffraction maxima of **8** diminished and maxima of a new phase appeared (Fig. 5). This suggested that grinding of **8** and solid TBACl gave rise to a new solid phase. Maxima of the new phase were broad indicating poor crystallinity of the product. We are at present unable

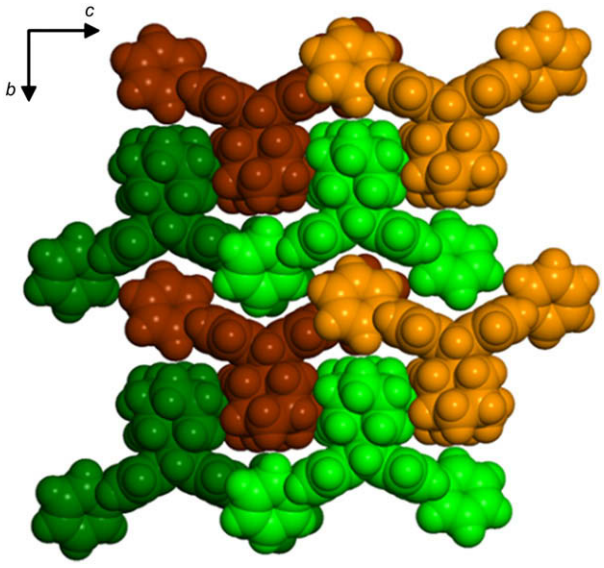


Figure 4. Crystal packing of molecule **9** in the (b, c) plane.

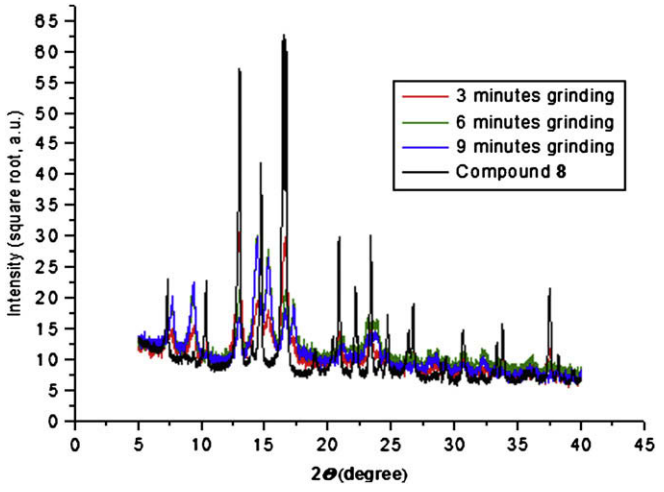


Figure 5. X-ray powder diffraction data (XRPD) for compound **8** (black) and a complex of **8** and TBACl (color) after different time of grinding in the mill.

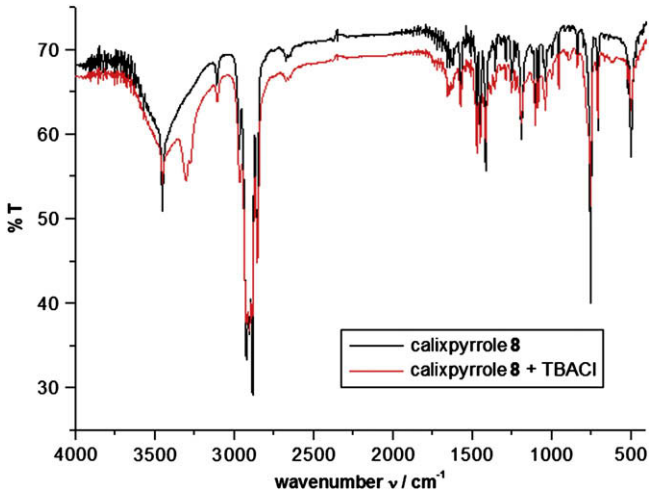


Figure 6. IR spectra (KBr) of calixpyrrole **8** (black) and complex of **8** with TBACl (red). Complexation was accomplished by grinding **8** and TBACl for 9 min in the mill.

to solve the crystal structure of this new phase and thus determine its exact molecular composition. However, IR and NMR spectra of the material obtained on grinding indicated formation of a complex of **8** with Cl^-. In the IR (KBr) spectra of **8**, besides the NH stretching vibration at 3446 cm^{-1}, a new NH stretching vibration was apparent at 3299 cm^{-1} corresponding to the associated NH with Cl^- (Fig. 6). Comparison of the ^1H NMR spectra (DMSO-d_6) before and after the grinding showed a significant downfield shift of the NH signal ($\Delta\delta \sim 1.5$ pm) and a small upfield shift of the pyrrole C–H signal (Fig. 7), as was seen on complexation of dipyrromethanes with anions.[20] To the best of our knowledge this is the first example of the formation of the complex with anion in the solid state on grinding in the mill.

Prompted by the finding that **8** can bind Cl^- in the solid state, we tried to perform complexation also in the DMSO solution. On addition of TBACl to the DMSO-d_6 suspension of **8**, the same appearance of the ^1H NMR spectrum was obtained as for the sample obtained on grinding. Furthermore, on addition of TBACl, an increase of the solubility of the sample was apparent, which was further improved on heating to the temperature of 80 °C, but did not cause any change in the appearance of the ^1H NMR spectra. However, due to the low solubility of **8** we could not perform ^1H NMR titration and calculate the complex association constant.

Calix[4]pyrroles are known to form a 1:1 complex with Cl^- in which four NH atoms form H-bonds with the anion in a way that anion sits on the cone of the macrocycle.[4] Taking into account the extremely rigid and sterically hindered geometry of **8** in which rotation of the pyrrole rings is not possible, most probably

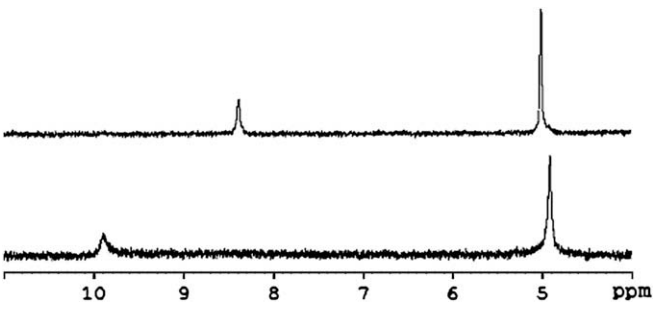


Figure 7. The aromatic part of the ^1H NMR spectra (DMSO-d_6, 600 MHz) of compound **8** (up) and the complex of **8** and TBACl (down).

complexation with Cl^- is accomplished by only two NH atoms in a complex 1:1 stoichiometry. However, this coordination geometry is in accordance with the one seen on complexation of adamantane-dipyrromethanes with Cl^-.[20]

In summary, novel adamantane derivatives of calix[4]pyrrole (**4**–**8**) and calixphyrin **9** have been synthesized. Incorporation of the bulky adamantly groups to the calix[4]pyrroles (**4**–**6**) or dipyrromethane moiety (**10**) gave rise to compounds resistant to oxidation. The structure of **8** was characterized by XRPD. It crystallizes in a tetragonal $P4_2/n$ space group with one quarter of the molecule in the asymmetric unit. The pyrrole nitrogen atoms are pointing in the opposite directions in a 1,3-alternate fashion. The structure is governed by very dense packing with numerous hydrogen–hydrogen contacts resulting in very low solubility. The structure of calixphyrin **9** was characterized by single crystal X-ray analysis. It crystallizes in the $C2/c$ space group with half of the molecule in the asymmetric unit. The propensity to bind anions has been investigated for **8** and **9**. Whereas **9** does not bind anions, **8** forms a complex with Cl^- in DMSO solution and in the solid state. The solid state complexation has been carried out by grinding in a mill and verified by XRPD, IR, and ^1H NMR. Transformation of **8** to its Cl^- complex results in an increase of the solubility. The solid state method of complexation and an increase of the solubility may have an important impact in finding a new production technology for materials with tailor-made structural and functional characteristics.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker AV-300 or 600 Spectrometer. All NMR spectra were measured in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as a reference. High-resolution mass spectra (HRMS) for compounds **4** and **9** were measured on a Q-Tof PremierTM (Waters-Micromass, Manchester, UK) using electron impact ionization mode. For compounds **5**–**8** MALDI-TOF MS spectra in reflectron mode were obtained on an Applied Biosystems Voyager DE STR instrument. The laser wavelength was 337 nm (N_2 laser) and laser frequency amounted to 20 Hz. Calibrant and analyte spectra were obtained in positive ion mode. Internal calibration and elemental analysis were performed with software Data Explorer v. 4.0. Melting points were obtained using an Original Kofler Mikroheitztisch apparatus (Reichert, Wien) and are uncorrected. Milling was performed using a Retsch MM200 mill, equipped with 10 mL stainless steel grinding vessels and one 12 mm stainless steel grinding ball per vessel. Grinding experiment was conducted for 9 min with the mill operating at a frequency of 30 Hz. Silica gel (Merck 0.05–0.2 mm) was used for chromatographic purifications. Solvents were purified by distillation. Adamantane 1-carbaldehyde[19] and adamantane-2-one[30] were prepared in our laboratory according to the procedure described in the literature and transformed to the corresponding dipyrromethanes **10** and **11**.[20]

3.2. General procedure for the preparation of calix[4]-pyrroles 4–6

In a two neck round-bottom flask, 1-di(pyrrole-2-yl)methyladamantane (**10**, 1 equiv) and the appropriate aldehyde or ketone (1 equiv) were dissolved in CH_2Cl_2 (15–20 mL) under a stream of N_2. By use of a syringe, TFA (0.1 equiv) was added to initiate the reaction. The reaction mixture was stirred at rt under N_2 over 20 h. The following day, solvent was evaporated on a rotary evaporator and the residue chromatographed on a silica gel column using CH_2Cl_2 as eluent.

*3.2.1. Synthesis of 5,15-di(1-adamantyl)-10,10,20,20-tetramethylcalix[4]pyrrole (**4**)*

The reaction of 1-di(pyrrole-2-yl)methyladamantane (**10**, 120 mg, 0.4 mmol) and acetone (18 μL, 0.4 mmol) in the presence of TFA (3 μL, 0.04 mmol) yielded 27 mg (19%) of a crude mixture of two isomers **4** in the form of a white powder.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47–1.72 (m, adamantane-H), 1.95 (br s, characteristic bridgehead H-atom signals Ad), 3.53 and 3.50 (s, 2 *meso* C–H), 5.84–5.94 (m, pyrrole C–H), 7.06 and 7.18 (br s, 2 pyrrole N–H); IR (KBr) ν_{max}/cm^{-1} 3443 (m), 3402 (m), 2969 (m), 2907 (s), 2854 (s), 1573 (w), 759 (s); HRMS: calculated for $C_{44}H_{57}N_4$ ([M+H]$^+$) 641.4583, found 641.4588.

*3.2.2. Synthesis of 5,10,15,20-tetra(1-adamantyl)calix[4]pyrrole (**5**)*

The reaction of 1-di(pyrrole-2-yl)methyladamantane (**10**, 60 mg, 0.2 mmol) and adamantane 1-carbaldehyde (35 mg, 0.2 mmol) in the presence of TFA (1.7 μL, 0.02 mmol) yielded 20 mg (23%) of a crude mixture of isomers **5** in the form of a white powder.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40–1.98 (m, adamantane-H), 3.21, 3.37, 3.46 and 3.64 (br s, all *meso* C–H), 5.57–6.15 (m, pyrrole C–H), 6.58 (br s, pyrrole C–H), 7.43, 7.76, and 7.96 (br s, all pyrrole N–H); IR (KBr) ν_{max}/cm^{-1} 3448 (m), 2907 (s), 2845 (s), 1701 (m), 1449 (m), 7646 (m), 733 (m); HRMS: calculated for $C_{60}H_{77}N_4$ ([M+H]$^+$) 853.6143, found 853.6161.

*3.2.3. Synthesis of 5,15-di(tricyclo[3.3.1]nonane-3,7-diyl)-10,20-di(1-adamantyl)calix[4]pyrrole (**6**)*

The reaction of 1-di(pyrrole-2-yl)methyladamantane (**10**, 82 mg, 0.3 mmol) and adamantane-2-one (43 mg, 0.3 mmol) in the presence of TFA (2.1 μL, 0.03 mmol) yielded 28 mg (24%) of a crude mixture of two isomers **6** in the form of a white powder. From the mixture one isomer was separated on a preparative TLC on silica gel by using CH_2Cl_2 as eluent.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57–1.96 (m), 2.25–2.28 (br s, 4H), 2.29–2.33 (br s, 4H), 2.35–2.43 (br s, 6H), 3.16 (s, 2H), 5.95–5.98 (m, 4H), 5.73–5.76 (m, 4H), 7.19 (br s, 4H); IR (KBr) ν_{max}/cm^{-1} 3464 (s), 3412 (s), 2902 (s), 2851 (s), 1645 (w), 753 (m); HRMS: calculated for $C_{58}H_{72}N_4Na$ ([M+Na]$^+$) 847.5649, found 847.5626.

3.3. General procedure for the preparation of calix[4]pyrroles 7 and 8

In a two neck round-bottom flask, 2,2-di(pyrrole-2-yl)adamantane (**11**, 1 equiv) and the corresponding ketone (1 equiv) were dissolved in appropriate solvent (20 mL) under a stream of N_2. By use of a syringe, TFA (0.1 equiv) was added to initiate the reaction. The reaction mixture was left at rt (for **7**) or heated at the temperature of reflux (for **8**) under N_2 over 24 h. During reaction, white precipitate was formed. The following day, the precipitate of product **7** or **8** was filtered off and the residue chromatographed on a silica gel column using CH_2Cl_2 as eluent or washed with CH_2Cl_2 to afford crude product, respectively.

*3.3.1. Synthesis of 5,15-di(tricyclo[3.3.1]nonane-3,7-diyl)-10,10,20,20-tetramethylcalix[4]pyrrole (**7**)*

The reaction of 2,2-di(pyrrole-2-yl)adamantane (**11**, 90 mg, 0.3 mmol) and acetone (14 μL, 0.3 mmol) in CH_2Cl_2 in the presence of TFA (2.5 μL, 0.03 mmol) yielded 5 mg (5%) of product **7** in the form of a white powder.

Mp >320 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.48 (br s, 12H), 1.59–1.76 (m, 16H), 1.97–2.07 (m, 8H), 2.57 (br s, 4H), 5.76–5.80 (m, 4H), 5.94–5.97 (m, 4H), 7.88 (br s, 4H); IR (KBr) ν_{max}/cm^{-1} 3453 (m), 3366 (m), 3309 (m), 2917 (s), 2856 (s), 1655 (m), 764 (m); HRMS: calculated for $C_{42}H_{52}N_4Na$ ([M+Na]$^+$) 635.4084, found 635.4036.

*3.3.2. Synthesis of 5,10,15,20-tetra(tricyclo[3.3.1]nonane-3,7-diyl)calix[4]pyrrole (**8**)*

The reaction of 2,2-di(pyrrole-2-yl)adamantane (**11**, 300 mg, 1.1 mmol) and adamantane-2-one (168 mg, 1.1 mmol) in toluene in the presence of TFA (8 μL, 0.11 mmol) yielded 170 mg (38%) of the crude product **8** in the form of a white powder.

Mp >320 °C; ^{1}H NMR (DMSO-d_6, 80 °C 300 MHz) δ 1.56–1.77 (m, 40H), 2.37 (br s), 2.41 (br s), 2.61 (br s), 2.72 (br s), 5.47 (s, 8H), 8.84 (br s, 4H); IR (KBr) ν_{max}/cm^{-1} 3448 (m), 2923 (s), 2902 (s), 2881 (s), 2856 (m), 1413 (m), 753 (s); HRMS: calculated for $C_{56}H_{69}N_4$ ([M+H]$^+$) 797.5516, found 797.5480.

*3.3.3. Synthesis of 5,15-dihydro-5,15-diphenyl-10,20-di(1-adamantyl)porphyrin (**9**)*

In a two neck round-bottom flask, 1-di(pyrrole-2-yl)methyladamantane (**10**, 60 mg, 0.2 mmol) and benzaldehyde (23 mg, 0.2 mmol) were dissolved in CH_2Cl_2 (20 mL) under a stream of N_2. By use of a syringe, TFA (1.5 μL, 0.02 mmol) was added to initiate the reaction. The reaction mixture was stirred at rt under N_2 over 20 h. The following day, DDQ (48 mg, 0.2 mmol) was added and stirring continued for 1 h. Solvent was evaporated and the residue (0.143 g) was chromatographed on a silica gel column using CH_2Cl_2 as an eluent to yield product **9** (6 mg, 8%) in the form of yellow-orange solid.

Mp >320 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60–1.80 (m, 24H), 1.97 (br s, 6H), 3.76 (s, 2H), 6.14–6.17 (m, 4H), 6.36–6.39 (m, 4H), 7.35–7.44 (m, 8H), 7.57–7.62 (m, 2H), 13.11 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.9 (d, 6C), 36.7 (t, 6C), 38.6 (s, 2C), 41.1 (t, 6C), 54.3 (d, 2C), 119.9 (d, 4C), 127.1 (d, 2C), 127.2 (d, 2C), 127.7 (d, 4C), 128.2 (d, 2C), 130.7 (d, 2C), 130.8 (d, 2C), 137.8 (s, 2C), 139.2 (s, 2C), 140.2 (s, 8C); IR (KBr) ν_{max}/cm^{-1} 3298 (s), 2900 (m), 2844 (m), 1584 (m), 720 (s); HRMS calculated for $C_{52}H_{53}N_4$ ([M+H]$^+$) 733.4270, found 733.4268.

3.4. X-ray diffraction structure analysis

Crystallographic data were obtained using powder diffraction methods for **8** and single crystal diffraction methods for **9**. White powder of **8** was packed in a 0.5 mm glass capillary and the data were collected at 293 K on a laboratory diffractometer in transmission geometry using Cu Kα radiation. Total of five data sets were collected, which were than averaged. No significant changes in patterns occurred during data collection. The averaged pattern was indexed with a tetragonal unit cell with a=16.9683(4) Å and c=7.3892(2) Å using DICVOL04.[31] Considering possible systematic absences and trial and error method, solution was found by Fox[32] using parallel tempering direct space optimization in the $P4_2/n$ space group. The asymmetric unit consists of 1/4 of the molecule of **8** and the unit cell contains two molecules. Rietveld refinement[26] was carried out with the program package GSAS.[33] Structure model was refined with restraints on bond distances and angles. Bonds between atoms C6 and C3^{iii} [*iii*=0.5−*y*, *x*, 0.5−*z*] could not be simply restrained in GSAS as atom C3^{iii} is not in the list of atoms. We have therefore introduced a dummy atom (it's occupancy being 0.0) on an approximate position and restrained this bond (coordinates of the dummy atom must not be refined). After several cycles of refinement, and continuous changing of coordinates of the dummy atom after each set of refinement cycles, this bond distance converged to a chemically reasonable value. All non-hydrogen atoms were refined isotropically with a single U_{iso} parameter. Hydrogen atoms were set to have the U_{iso} value 1.2 times higher than the refined U_{iso} for non-hydrogen atoms. Refinement parameters: R_{wp}=0.0547, R_p=0.0373, χ^2=4.98. XRPD patterns of samples from the time resolved grinding of solid **8** and solid TBACl were collected from a flat sample in Bragg–

Brentano geometry using Cu Kα radiation, in the angular range from 5° to 40° and a step mode with increments of 0.02°.

The crystal structure of **9** was solved from single crystal data using direct methods as implemented in SHELXS97 and refined on F^2 by full matrix least squares using SHELXL97.[34] Both programs were used as part of the WinGX[35] software package. Hydrogen atoms were placed on their geometrically calculated position and refined in a riding model with C—H bond distances fixed at 0.97 Å for aliphatic hydrogens and 0.93 Å for aromatic and with $U_{iso}(H)=1.2U_{eq}(C)$ except the hydrogen atom bonded to the pyrrole nitrogen, which was found in the difference Fourier map and refined with restrained bond distance and $U_{iso}(H)=1.2U_{eq}(N)$. ORTEP3[36] and Mercury[37]–POV-Ray[38] were used for graphical presentation of the molecular structure and packing drawings. Crystal data of **9**: cell dimensions at 293 K are $a=21.2282(7)$ Å, $b=14.8775(4)$ Å, $c=12.8525(3)$ Å, $\beta=101.218(3)°$; space group: $C2/c$; $Z=2$. Refinement parameters: $R(F>4\sigma(F))=0.052$, $R_w=13.6$, $S=0.892$.

3.5. Supplementary data

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 699853, and 699854. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.ac.uk).

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