PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/16539

Please be advised that this information was generated on 2018-10-30 and may be subject to change.
COMMUNICATIONS

quenched with a solution of citric acid. The mixture was diluted with DCM (100 mL) and washed with sodium bicarbonate (sat.), water, and brine (25 mL each). The organic layer was dried (Na$_2$SO$_4$), evaporated, and the residue dissolved in DCM/MeOH (98:2) and filtered through a plug of silica gel. Evaporation gave the crude precursor of 2 (773 mg). To this crude product (746 mg) in dry THF (40 mL) was added methanesulfonic acid (300 µL). After stirring the mixture at RT for 72 h under nitrogen, pyridine (400 µL), DIEPA (1.5 mL), and acetic anhydride were added at 0°C. After 2 h the solution was diluted with DCM (100 mL), washed with sodium bisulfite (1 M), water, sodium bicarbonate (sat.), water, and brine (25 mL each). The organic layer was dried (Na$_2$SO$_4$), filtered, evaporated, and chromatographed (silica gel, DCM/MeOH (98:2)) to afford 2 (360 mg, 40% based on 1).

3: To 2 (60 mg, 0.051 mmol) in DCM (1 mL), TFA (0.5 mL) was added dropwise and stirred for 1 h at 0°C. The reaction mixture was diluted with DCM (50 mL) and washed three times with sodium bicarbonate (sat.) then water and brine (10 mL each). The organic layer was dried (Na$_2$SO$_4$), evaporated, and redissolved in DCM (0.5 mL). Boc-(2S,5R,4R,6S)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (Boc-MeBmt)$_2$[2] (18.7 mg, 0.062 mmol) and DIEPA (27 µL) were added at 0°C under nitrogen. After 2 h at 0°C the solution was allowed to warm to RT, diluted with DCM (50 mL), washed with sodium bisulfite (1 M), water, sodium bicarbonate (sat.), water, and brine (20 mL each). The organic layer was dried (Na$_2$SO$_4$), filtered, evaporated, and chromatographed (silica gel, EtOAc/acetone (9:1)) to give 3 (6 mg, 81%).

4: To 3 (27 mg, 0.022 mmol) in DCM (1 mL), TFA (0.5 mL) was added dropwise and stirred for 1 h at 0°C, diluted with DCM (50 mL) and washed three times with sodium bicarbonate (sat.), water, and brine (10 mL each). The organic layer was dried (Na$_2$SO$_4$), filtered and evaporated. In the residue in DCM (30 µL), Fmoc-N-Melle (12 mg, 0.032 mmol), PyBroP (14 mg, 0.032 mmol) and DIPEA (15 |µL) were added and the mixture was stirred for 6 h at 0°C and 30 min at RT. Fmoc-N-Melle (5 mg, 0.013 mmol), PyBroP (5 mg, 0.011 mmol) were added again at 0°C and stirred for 1 h. The reaction mixture was diluted with DCM (50 mL), washed with sodium bisulfite (1 M), water, sodium bicarbonate (sat.), water, and brine (20 mL each). The organic layer was dried (Na$_2$SO$_4$), filtered, evaporated, and chromatographed (silica gel, EtOAc/acetone 9:1) to afford 4 (19 mg, 60%).

5: To 4 (4.6 mg, 0.0028 mmol) in THF/water (10:1, 200 µL), DBU (3 µL) and lithium bromide (2 mg) were added. After stirring overnight at RT, DBU (4 µL) and lithium bromide (3 mg) were added again. After 5 h, the reaction was quenched with acetic acid (20 µL) and purified by reverse-phase HPLC (Beckman ODS 44, 50%)

Keywords: cyclophilin - cyclosporin - immunophilins • protein dimerization

5. There is currently a great deal of interest in parquat-binding, which has resulted in the design and construction of new molecular structures, as exemplified by the elegant work by Stoddart et al. on catenands and rotaxanes.[3] We describe here that compounds of type 2 are, in addition, able to bind alkali metal ions and protonated amines.[2] We report here on the binding affinities of these host molecules towards charged aromatic compounds, such as parquat 3 and the polymeric parquat derivatives 4 and 5.

Strong Binding of Parquat and Polymeric Parquat Derivatives by Basket-Shaped Hosts**

Albertus P. H. J. Schenning, Bas de Bruin, Alan E. Rowan,* Huub Kooijman, Anthony L. Spek, and Roeland J. M. Nolte

Clip-shaped host molecules of type 1 can bind uncharged aromatic guest molecules, for example resorcinol, by 

Received: June 9, 1995 [Z80801E]

German version: Angew. Chem. 1995, 107, 2313–2317

Keywords: cyclophilin • cyclosporin • immunophilins • protein dimerization


compound 2 is an exceptionally good host for paraquat. This opens the possibility of clipping host molecules of type 2 to polymeric chains containing paraquat units. The X-ray structure and properties of the complex between 2 and paraquat are also presented.

Compounds 1 and 2 were synthesized as described previously.[1, 2] For the synthesis of 2b, 4,4'-dimethylbenzil was used as the starting material. Compounds 3 and 4 were prepared by using literature procedures.[3-5] Compound 5 was prepared by the condensation of N,N'-bis(2-hydroxyethyl)-4,4'-bipyridinium hexafluorophosphate in acetonitrile with one equivalent of adipoyl chloride with triethylamine as the base,[5] and purified by precipitation from ethyl acetate.

Addition of 3-Cl into a solution of host 2b in for example methanol/chloroform led to an immediate color change from colorless to yellow-orange, indicative of the formation of a charge-transfer complex.[6] NMR spectroscopic studies revealed that in this complex the paraquat guest is located in the cleft of the cavity.[7] Fast atom bombardment mass spectrometry (FAB MS) showed a peak at m/z 1094 (matrix: nitrobenzyl alcohol), which corresponds to the mass of the host–guest complex. Crystals of the complex between 2b and 3-(PF6)2 suitable for X-ray analysis were grown from a mixture of 2b and tetraethyleneammonium hexafluorophosphate dissolved in chloroform, which was layered with 3-C1 dissolved in methanol. The X-ray structure of complex is shown in Figure 1 (top).[7] It reveals a perfect complementarity between host and guest. The paraquat guest sits symmetrically within the walls of the basket; the methyl substituents are partially encapsulated by the crown ether rings. The crystal structure is different from that of the complex of paraquat with bis(paraphenylene)-[34]crown-10.[8] In the case of the latter the bipyrindium guest is flat, whereas in the crystal structure described herein the two bipyrindium units are twisted by an angle of 22.5°. This is a consequence of being less sterically constrained by the aromatic side walls of the basket. In Stoddart's compound the bipyrindium is tilted at an angle of about 28° with respect to the O–O axis of the para-phenylene unit; in our case the bipyrindium guest is not tilted. The binding constant of the bis(paraphenylene)-[34]crown-10 macrocycle with 3-(PF6)2 in acetone is 730 m⁻¹. The binding properties of 1 and 2 were evaluated by recording the intensity of the charge-transfer absorption band at approximately 425 nm at different host–guest ratios. The results for different solvents are presented in Table 1. The basket-shaped host molecules 2 bind paraquat approximately 25–75 times stronger than the bis(paraphenylene)-[34]crown-10 macrocycle.[9] This result can be explained from the fact that compounds 2 are more preorganized for binding than Stoddart's compound.[10] Only a very small Keq of 80 m⁻¹ was found for the binding of 3 in the cavity of clip molecule 1. This clearly demonstrates the importance of the crown ether molecules in 2 for the complexation of paraquat.

![Figure 1](image1.png)

**Table 1.** Binding constants [a] of the complexes between hosts 1 and 2 and guests 3, 4, and 5.

<table>
<thead>
<tr>
<th>Host</th>
<th>Guest</th>
<th>Keq [m⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-Cl</td>
<td>60 [b]</td>
</tr>
<tr>
<td>2a</td>
<td>3-(PF6)2</td>
<td>57000 [c]</td>
</tr>
<tr>
<td>2a</td>
<td>2-(PF6)2</td>
<td>20000 [d]</td>
</tr>
<tr>
<td>2b</td>
<td>3-Cl</td>
<td>22000 [e]</td>
</tr>
<tr>
<td>2b</td>
<td>4a</td>
<td>1800 [e, f]</td>
</tr>
<tr>
<td>2b</td>
<td>4d</td>
<td>4500 [e, c]</td>
</tr>
<tr>
<td>2b</td>
<td>5</td>
<td>19000 [e, c]</td>
</tr>
</tbody>
</table>

[a] Association constants were calculated using the Benesi–Hilderbrand equation [13]. Good correlations (R > 0.995) were obtained for all titration curves assuming a 1:1 host–guest complexation. Estimated error in Keq is 10%. For the Keq, measured in acetonitrile, the error is 5% due to the poor solubility of the host molecule in this solvent.

The electrochemical behavior of the complex between 3-(PF6)2 and compound 2a was studied in acetonitrile. In this solvent the guest showed two reversible one-electron transfers: 

\[ E_{1/2}(2+/+) = -0.423 \text{V, } E_{1/2}(1+/0) = -0.840 \text{V (vs. SCE, for both transitions } \Delta E_p = 60 \text{mV)}. \]

Upon the addition of one equivalent of 2a the first redox transfer shifted 100 mV to more negative potential, whereas the second electron transfer potential remained unaffected. These data indicate that 2a binds and stabilizes the doubly charged paraquat species, which results in a more negative redox potential for the first redox transfer. It is well known that in this type of host–guest system the guest reduced by one electron dissociates form the host, and this explains the unaltered second redox potential.[11]

Polymeric paraquat derivatives have previously been investigated as redox-active films and more recently as optical data storage materials and show a wide variety of electrochromic and thermochromic behavior.[12, 13, 10] The polymeric paraquat derivative with tetrathionate counterions has been shown to possess liquid crystalline properties.[11] We felt that host–guest complexation might be an interesting way to modify and control the physical properties of this interesting class of polymers. The results of binding studies carried out in acetonitrile, showed that 2a can be clipped to polymeric paraquat derivatives 4a, 4b, and 5 with association constants of 1800 m⁻¹, 4500 m⁻¹, and 19000 m⁻¹, respectively (per polymer repeat unit, see Table 1, Fig. 1). The binding constants of 4a and 4b are lower than those observed for paraquat itself. Molecular modeling studies have revealed that in the case of 4a and 4b, complexation of a basket to a paraquat unit in the polymer is sterically hindered by baskets complexed to adjacent paraquat units. The overall lower binding constants reflect this steric hindrance, which is less for...
the polymer with a longer spacer (4b) than for the one with the smaller spacer (4a). Viscosity measurements showed that the specific viscosity of the polymers solubilized in acetonitrile increases upon the addition of 0.03 equivalents of the host molecule 2a per repeat unit: for example, 4a: \( \eta = 0.006 \), 4a + 2a \( \eta = 0.008; 4b: \eta = 0.068 \), 4b + 2a \( \eta = 0.070 \). These results indicate that the average molecular mass of the polymers increases on complexation with 2a. The redox potentials of the polymers were also influenced by the hosts. Polymer 4a displayed the following redox transitions in acetonitrile: \( E_1/2(2-1+/1+) = -0.387 \text{ V}, \ E_1/2(1+/0) = -0.840 \text{ V} \) (vs. SCE, for both transitions \( \Delta E = 60 \text{ mV} \)). Upon the addition of one equivalent of 2a per repeat unit the first redox transfer shifted 20 mV to more negative potential, whereas the second redox transfer remained unchanged. Addition of three equivalents of 2a resulted in a 35 mV shift in the negative direction. These shift values are smaller than the 100 mV shift measured for paraquat (3) which may be the result of the lower binding affinity of 2a for the polymeric paraquat derivatives. These preliminary results indicate that the electrochemical behavior of polymeric paraquat derivatives can easily be tuned by the addition of basket molecules. This may be of interest for future application of these polymers as optical data storage systems or as molecular switches, etc.

In conclusion, we have shown that host molecules of the type strongly bind paraquat 3 and that it is possible to clip these switches, etc. paraquat derivatives can easily be tuned by the addition of bases to polymeric paraquat derivatives. Further studies are underway.

Keywords: crown ethers • paraquat • supramolecular chemistry

COMMUNICATIONS

Received: March 14, 1995 [Z 77922 E]

German version: Angew. Chem. 1995, 107, 2288 – 2289

Formation of a “meso-Helicate” by Self-Assembly of Three Bis(catecholate) Ligands and Two Titanium(IV) Ions

Markus Albrecht* and Sirpa Kotila

Double- or triple-helical oligomerculear coordination compounds that are formed spontaneously by self-assembly of two or three oligodentate ligands and several metal ions are called helicates. Due to their helicity, such molecules are chiral. On the other hand, meso-helicates are analogous metal complexes with two differently configured helical units and are thus achiral. In a topological sense, the meso-helicates are helices that inverse their helical twist.

An octahedral complex formed by one metal center and two bidentate ligands is the most simple helical unit. It can have two configurations (\( \text{D or } \text{A} \)). Triple bridging between the ligands of two such octahedrons results in the formation of three different coordination compounds: the enantiomeric \( \text{A-A} \) and \( \text{A-A} \)-helicates, and the diastereomeric \( \text{A-A} \)-form—the most simple triple-stranded meso-helicate (Fig. 1).

The coordination chemistry of linear oligomerculear nitrogen donor ligands with soft metal ions has recently become the focus of a great deal of attention. To our knowledge, investigations towards the metal-directed self-assembly of helicates have resulted only in the characterization of double- [11, 14] and triple-helicate [15] and double-stranded non-helical metal complexes, which do not possess units with helical chirality. [16]

In this context, the triple-stranded meso-helicate is a missing structural motif.

This stimulated our interest in self-assembly processes based on oxygen donor ligands in combination with hard metal ions [17, 18]. The use of early transition metals should provide access to new supramolecular aggregates, whose properties should differ from those of the “traditional” compounds.

Catechol ligands seem to be ideal bidentate chelating units for this purpose. [18] Initially we chose the \( \text{CH}_3\text{O} \) group as a spacer.

[1*] Dr. M. Albrecht
Institut für Organisch-Chemische Technologie der Universität
Richard-Wilhelmi-Allee, D-76131 Karlsruhe (Germany)
Tel.: int. code + (721) 698529
Dr. S. Kotila
Organisch-Chemisches Institut der Universität Münster (Germany)

[**] This work was supported by the Fonds der Chemischen Industrie (Löbigs Stipendium), the Deutsche Forschungsgemeinschaft, and the Academy of Finland. Dr. M. Rötel is thanked for the NMR measurements, Mrs. B. Wibbeling's and Dr. R. Feldheim's help with the X-ray structure analysis is gratefully acknowledged.

Fig. 1. Schematic representation of a) a helicate (here: \( \text{A-A-form} \)) and the corresponding meso-helicate (\( \text{A-A} \)-form) and b) a bidentate \( \text{C}_3\) bridged helicate and meso-helicate (only one of the ligand strands is shown).