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Synthesis and recognition behaviour of allosteric hemicarcerands

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Abstract—Bipyridine bridged bis(resorcinarenes) have been prepared. Upon co-ordinating to a transition metal ion, e.g. Ag^+, the respective metal complex forms a hemicarcerand-like structure with the two resorcinarene moieties capable of binding non-polar organic molecules in a co-operative fashion, as shown qualitatively by NMR spectroscopy.

Although known for almost 130 years now,[1] resorcinarenes had to face the fate of being considered more or less as laboratory curiosities for a long time. However, this situation changed dramatically with the emergence of supramolecular chemistry about 30 years ago.[2] Since then and in particular over the last decade chemists all over the world have shown an increasing interest in these compounds due to their unique properties in molecular recognition studies, leading to ever more sophisticated receptor molecules of this class of compounds.[3] Especially molecular container molecules, also called carcerands and hemicarcerands, have been studied extensively in this context.[3d–f,j,m]

We were interested in the design and the synthesis of an allosteric analogon of these fascinating compounds which incorporates another binding site that switches the conformation of a molecule bearing two resorcinarene moieties towards a hemicarcerand-like structure upon complexation of another guest species. Most notably 2,2′-bipyridines have been demonstrated to be particularly effective for this purpose and a number of examples of positive allosterism have been reported where the formation of the bipyridine transition metal ion complex induced a conformational change that enables further binding sites to complex another guest.[4]

Thus, we designed bipyridine bridged bis(resorcinarenes) **1** by using *MMFF*-force field *molecular modelling*,[5] where the co-ordination induced conformational change upon addition and binding of a suitable transition metal ion, e.g. Ag^+, should orientate the two resorcinarenes in a position that assembles a hemicarcerand (Fig. 1).

The synthesis (Scheme 1) of the bipyridine building block **3** started from 4,4′-dimethyl-2,2′-bipyridine **2**, which was first oxidised using CrO_3/H_2SO_4 to afford

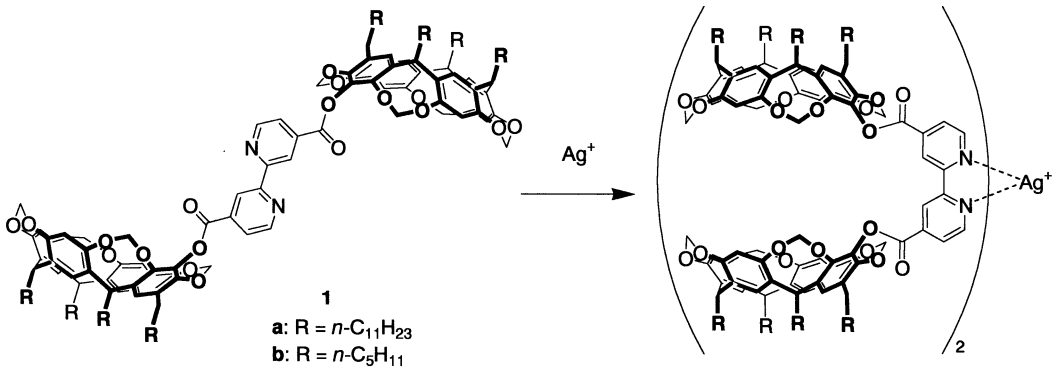

Figure 1. 2,2′-Bipyridine bridged bis(resorcinarene) **1** and its Ag(I) complex $Ag\mathbf{1}_2^+$ (side chains omitted for viewing clarity).

Keywords: resorcinarenes; hemicarcerands; bipyridines; molecular recognition; allosteric receptors.

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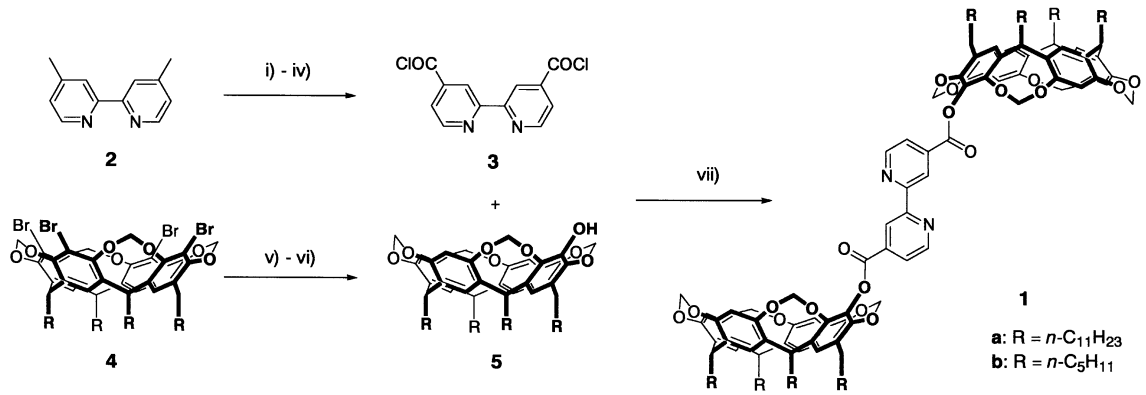

Scheme 1. Synthesis of **1** (yields are given for the resorcinarenes having R = *n*-C_5H_{11}). (i) CrO_3, conc. H_2SO_4, 87%; (ii) MeOH, conc. H_2SO_4, 85%; (iii) NaOH, MeOH, 98%; (iv) $SOCl_2$; (v) 1 equiv. *n*-BuLi, 1 equiv. $B(OMe)_3$, THF; (vi) 3 equiv. *n*-BuLi, 3 equiv. MeOH, 1 equiv. H_2O_2, THF, 63% over two steps; (vii) 1 equiv. **3**, 2.5 equiv. **5b**, Et_3N, $CHCl_3$, 19%. **1a** was prepared in analogous fashion from **5a** in 75% yield.

the dicarboxylic acid. This could in principle be converted directly to the corresponding diacid chloride **3**. However, as reported earlier the slightly longer way including the formation, purification, and saponification of the corresponding dimethylester followed by the reaction with thionyl chloride proved to be the more practical way to get the desired intermediate **3**, which was directly reacted with **5** after removal of excess thionyl chloride without further purification.[6]

Tetrabromocavitands **4** were prepared in three steps from resorcinol following published procedures, which were subsequently transformed into monosubstituted resorcinarenes **5**.[7–9] The new compounds **1a** and **1b** were fully characterised by NMR spectroscopic and mass spectrometric means.[10,11]

Addition of previously prepared and thoroughly dried $Ag(CH_3CN)_2BF_4$ dissolved in acetonitrile-d_3 to a solution of **1** (two equivalents) in deuterated benzene afforded the desired metal complex $Ag\mathbf{1}_2^+$, as indicated by significant shifts in the ^1H (Fig. 2) and ^{13}C NMR spectra. The stoichiometry of this complex could be proven by ESI MS of metal complex $Ag\mathbf{1b}_2^+$ (Fig. 3).

With the complexes in hand the next task was to study the solution-phase recognition behaviour of **1** and its silver(I) complex towards non-polar organic molecules

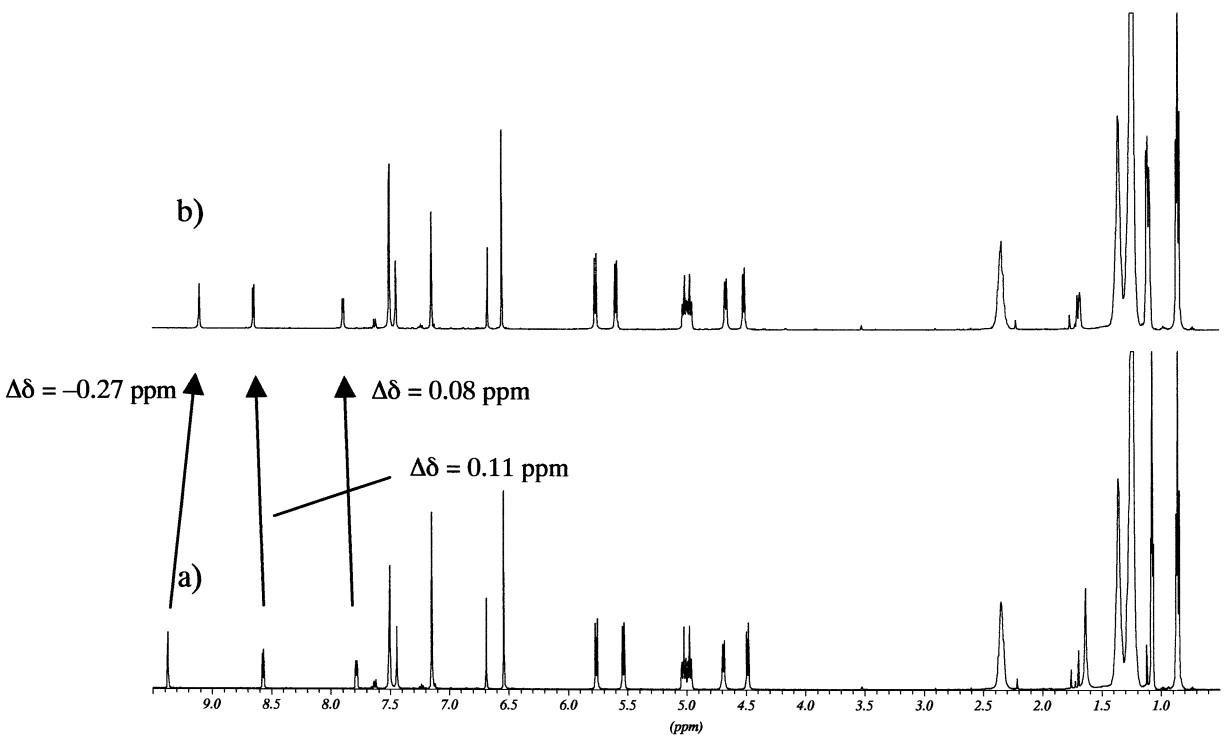

Figure 2. ^1H NMR spectra (500.1 MHz, 300 K, C_6D_6/CD_3CN (50/1), $[\mathbf{1a}]_0 = 4$ mM) of (a) **1a** and (b) $Ag(CH_3CN)_2BF_4$+2 equiv. **1a**.

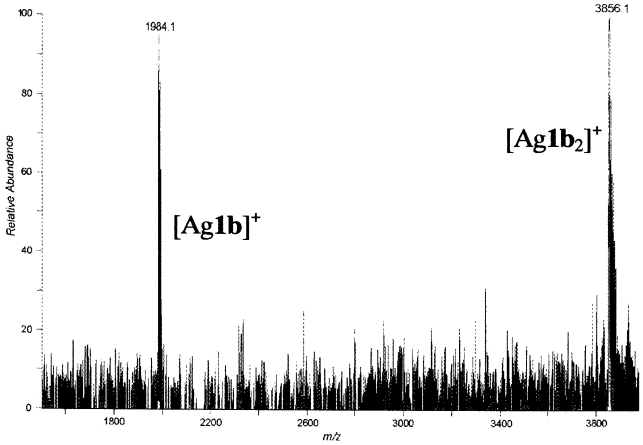

Figure 3. ESI MS of a 0.75 mM solution of $(Ag\mathbf{1b}_2)BF_4$ in benzene/acetonitrile.

to reveal the allosteric potential. We decided to use adamantanecarboxylic acid adamantylester **6** as guest molecule (Fig. 4).[12] Compound **6** was chosen because resorcinarenes and cavitands in particular have already been demonstrated to be very efficient hosts for the recognition of adamantyl derivatives as well as aromatic compounds.[3c–e,k,13] However, **6** was thought to be a better guest than aromatic compounds because the recognition experiments were performed in solutions with a large content of benzene which should favour the formation of complexes with **6** but not with aromatics.

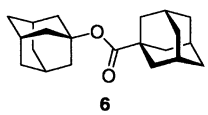

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Figure 4. Bis(adamantyl) **6**.

With respect to the huge mass difference we decided to use a large excess of guest rather than vice versa to get qualitative information about the recognition behaviour from NMR investigations in order to avoid solubility problems and other unspecific aggregation effects of the host. Thus, our experiments were set up to observe a maximum effect for the signals of the bis-(resorcinarene) host, whereas effects for the guest were only expected in case of a slow guest exchange behaviour on the NMR time scale.

Addition of a 10-fold excess of **6** to **1** did not give any noticable shifts in the ^1H NMR spectrum, indicating that no intra- or intermolecular binding event occurs. However, addition of $Ag(CH_3CN)_2BF_4$ to this solution changes the situation dramatically (Fig. 5b). Virtually the same spectrum was obtained when we added a 10-fold excess of **6** to preformed silver complex $Ag\mathbf{1}^+$. In both cases we saw significant shifts and sharpening of the signals of the hemicarcerand unit compared to the pure silver complex (Fig. 5c), indicating successful binding to the bis(adamantyl), although fast guest exchange on the NMR time-scale seems to occur since we could not see different sets of signals for the complexed guest, which were expected far upfield,[13] and the free guest under these conditions and even if we performed NMR experiments at 278 K.

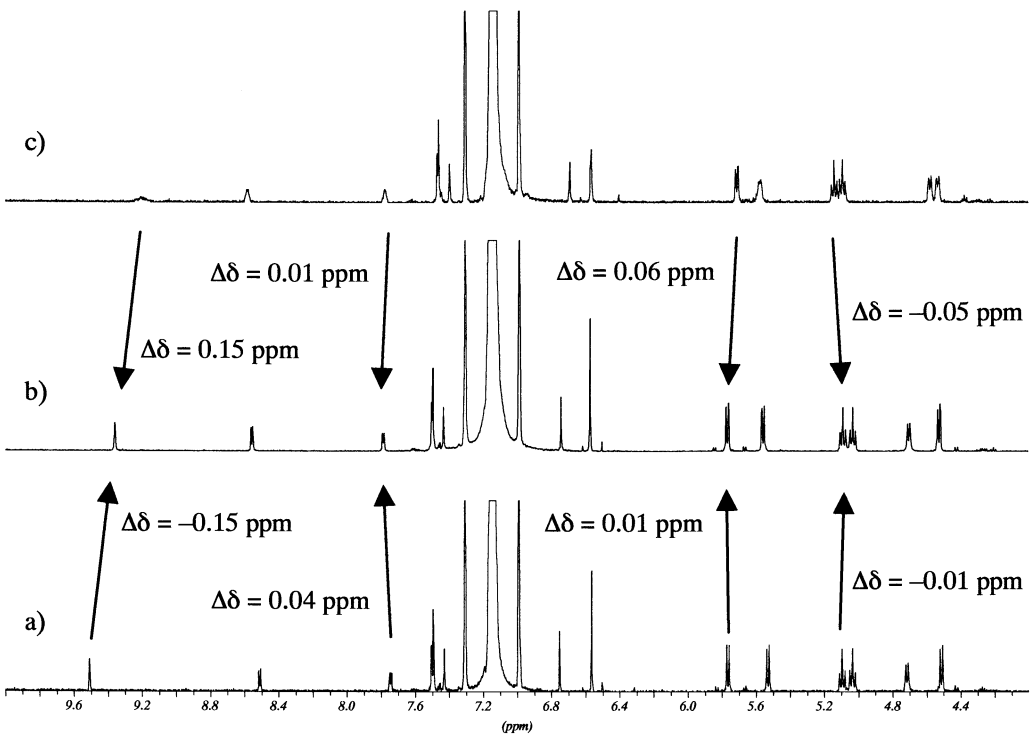

Figure 5. ^1H NMR spectra (500.1 MHz, 300 K, C_6D_6/CD_3CN (20/1)) of (a) **1b** (1.5 mM); (b) **1b** (1.5 mM)+**6** (15 mM)+ $Ag(CH_3CN)_2BF_4$ (0.75 mM), and (c) $Ag\mathbf{1b}_2^+$ (0.75 mM).

These results clearly indicate that the new bis(resorcinarene) **1** indeed shows heterotropic positive co-operative allosteric behaviour and we are currently exploring its binding properties towards other non-polar substrates like biphenyls.

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9. Yields for resorcinarenes with R = n-$C_{11}H_{23}$ were 89% (resorcinarene), 73% (tetrabromoresorcinarene), 84% (tetrabromocavitand **4a**), and 48% (**5a**). Yields for resorcinarenes with R = n-C_5H_{11} were 71% (resorcinarene), 46% (tetrabromoresorcinarene), and 91% (tetrabromo-cavitand **4b**).
10. NMR experiments were recorded on a Bruker DRX 500 at 300 K. Assignments were carried out according to ^{1}H, ^{13}C, H,H COSY, HMQC, and HMBC NMR experiments, e.g. **1a**: ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 9.08 (s, 2H, $H_{pyridyl}$), 8.92 (d, 2H, ^3J = 5.6 Hz, $H_{pyridyl}$), 8.00 (d, 2H, ^3J = 5.6 Hz, $H_{pyridyl}$), 7.13 (s, 4H, $H_{arom.}$), 7.12 (s, 2H, $H_{arom.}$), 7.10 (s, 2H, $H_{arom.}$), 6.57 (s, 2H, $H_{arom.}$), 6.46 (s, 4H, $H_{arom.}$), 5.74 (d, 4H, ^2J = −7.1 Hz, H_{acetal}), 5.58 (d, 4H, ^2J = −7.1 Hz, H_{acetal}), 4.75 (t, 4H, ^3J = 8.2 Hz, H_{benzyl}), 4.73 (t, 4H, ^3J = 8.2 Hz, H_{benzyl}), 4.66 (d, 4H, ^2J = −7.1 Hz, H_{acetal}), 4.37 (d, 4H, ^2J = −7.1 Hz, H_{acetal}), 2.28–2.18 (m, 16H, H_{alkyl}), 1.44–1.25 (m, 144H, H_{alkyl}), 0.88 (t, 24H, ^3J = 7.1 Hz, H_{alkyl}); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 14.1, 22.7, 27.9, 29.4, 29.7, 29.8, 29.9, 31.9 (C_{alkyl}), 36.4, 36.6 (C_{benzyl}), 99.3, 99.7 (C_{acetal}), 116.8, 116.9, 117.8, 120.4, 120.5 ($C_{arom.}$), 121.3, 123.9 ($C_{pyridyl}$), 135.6 ($C_{arom.}$), 137.1 ($C_{pyridyl}$), 137.6, 138.3, 138.8, 139.2, 146.8 ($C_{arom.}$), 150.4, 154.0 ($C_{pyridyl}$), 154.6, 155.0, 156.3 ($C_{arom.}$), 164.5 (C_{ester}).
11. CI MS (*iso*-butane) **1a**: 2570 ([M+Na]$^+$) and ESI MS **1b**: 1875.3 ([M+H]$^+$) with matching isotope patterns. CI MS were recorded on a *Finnigan MAT 95* with datasystem *DEC-Station 5000*. ESI MS were taken on a *Thermoquest Finnigan LCQ* using *Excalibur* Software from *Thermoquest Finnigan*.
12. Compound **6** was prepared from 1-adamantylcarboxylic acid and 1-hydroxyadamantane following Garelli's procedure (see Ref. 6).

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