Calixarene metalloreceptors. Upper-rim functionalized calix[4]arenes containing an organopalladium binding site

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Calix[4]arene units functionalized at the 1,3-positions of the upper rim with an organopalladium binding site demonstrate simultaneous first- and second-sphere coordination of a substrate through binding to the palladium centre and interaction within the hydrophobic site provided by the calixarene unit.

Transition-metal complexes with peripheral non-covalent binding sites have recently been used as hosts to bind neutral, cationic and anionic guests and are often referred to as *metalloreceptors*.[1,2] In this regard, we have recently described a set of organopalladium based receptors which contain secondary sites for hydrogen bonding and/or π-stacking interactions and have applied these to the molecular recognition of aliphatic amines,[2a] aromatic amines,[2b] hydrazines[2c] and DNA nucleobases.[2d]

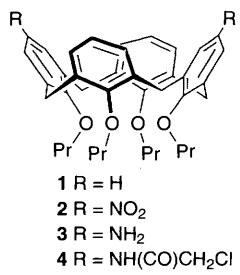
In order to increase the scope of these metalloreceptors and the range of applicable substrates, we have designed a series of receptors in which the subunit for second-sphere, non-covalent interaction is a calix[4]arene unit.[3] Calix[4]arenes are known to act as receptors for cationic,[3b,4] anionic[5] or neutral[6] substrates by providing a platform for the attachment of convergent binding groups, at the upper or lower rim,[4,5a,6a] or by utilizing the bowl shaped arrangement of the four aromatic groups as a hydrophobic cavity.[7] Our basic design strategy was to build a 'handle' on to the calixarene 'basket' which would allow the possibility that a peripherally coordinated metal centre (handle) would have a binding site oriented towards the hydrophobic cavity of the calix[4]arene (basket). Thus, a substrate could potentially interact simultaneously with the metal centre *and* the calixarene cavity. The synthesis of this new type of metalloreceptor is reported herein along with some preliminary studies on the binding of aromatic amines.

Literature preparations were used to obtain the required 1,3-substitution pattern by nitration[8] of **1** to give **2** and reduction[9] to yield **3** as the starting point for the syntheses. All the calix[4]arene molecules utilized in this study have the lower rim substituted with *n*-propoxy groups which inhibits interconversion between the four possible conformations (cone, partial cone, 1,3-alternate and 1,2-alternate).

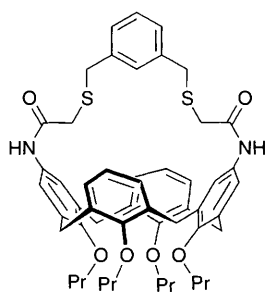
Reaction of **3** with two equiv. of chloroacetyl chloride, according to the method of Reinhoudt and co-workers, gave the diamide **4** in 65 % yield.[9] The substituted calix[4]arene **4** was then converted directly to the macrobicycle **5**, in 85% yield, by treatment with α,α′-*meta*-xylenedithiol in Na/EtOH under high-dilution conditions. Palladation of **5** employing $[Pd(MeCN)_4][BF_4]_2$ in MeCN solution yielded the metalloreceptor [**Pd**(**5** − H)(MeCN)]BF_4 **6** in 93% yield. Similarly, reaction of the dithiaether **7**, prepared by the acid catalysed addition of 2 equiv. of 4-hydroxybenzyl alcohol to α,α′-*meta*-xylenedithiol, with **4** under high dilution conditions gave the larger macrobicycle **8** in 25% yield. Palladation of **8** produced the metalloreceptor [Pd(**8** − H)(MeCN)]BF_4 **9** in 95 % yield‡ (Scheme 1).

The nature of the binding site in these new metalloreceptors was investigated by ^{1}H NMR spectroscopy and CPK models indicated that pyridine (py) and 4-phenylpyridine (4-Phpy) would be suitably sized and shaped test substrates. The reaction of **6** with py displaced the labile MeCN group to give [Pd(**5** − H)(py)]BF_4 **10** while a similar reaction of **9** with 4-Phpy yielded [Pd(**8** − H)(4-Phpy)]BF_4 **11**. For both receptors, ^{1}H NMR spectral data were consistent with binding the substrate to the palladium centre *via* σ-donation and interaction of the substrate with the calix[4]arene unit. In particular for **11**, embedding the phenyl substituent of 4-Phpy inside the cavity resulted in *dramatic upfield shifts* for the *meta* and *para* protons of △δ 3.90 and 2.78 ppm relative to free substrate. A ^{1}H–^{13}C HETCOR NMR experiment identified proton resonances at δ 3.59 and 4.71 belonging to the aromatic protons of the substrate positioned inside the calix[4]arene cavity (Fig. 1). The marked upfield shifts result from shielding of the substrate hydrogens by an aromatic group *inside* the calixarene cavity.[11] An acyclic model metalloreceptor with single phenyl groups in place of the calixarene unit was also investigated. Only small *downfield* shifts were observed and attributed to coordination of the pyridine moiety to the palladium centre. Fig. 2 shows a model representation§ of **11** illustrating how this type of non-covalent interaction occurs as a result of the strong, oriented binding provided by the organopalladium centre.

For metalloreceptor **6**, the binding site is much smaller than for **9** and observation of a ^{1}H NMR resonance for MeCN at δ



1 R = H
2 R = NO_2
3 R = NH_2
4 R = $NH(CO)CH_2Cl$



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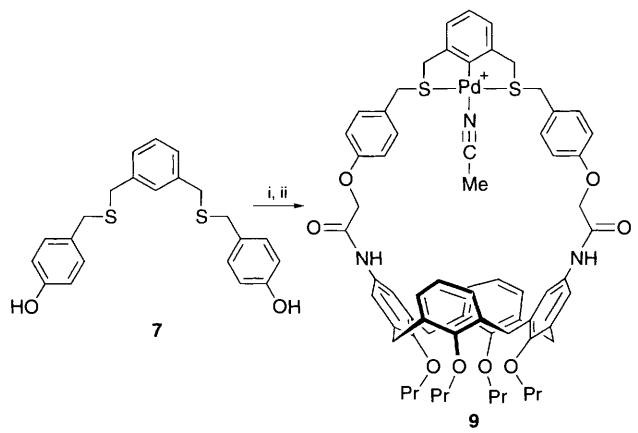

7 **9**

Scheme 1 *Reagents and conditions*: i, **4** NaH, MeCN, high dilution, 4 d, 25%; ii, $[Pd(MeCN)_4][BF_4]_2$, MeCN, 2 h, reflux, 95% (X = MeCN)

−1.79, compared to δ 1.98 for **9** and δ 2.18 for a model receptor containing no calixarene cavity, suggests the MeCN group of **6** resides inside the cavity of the calixarene. Unlike **6** and **11**, the most significant change in the ^{1}H NMR spectrum of **10** is a splitting of the aromatic protons of the substituted rings on the calixarene unit suggesting that py may be too large for the cavity and that in solution a conformation is adopted which coordinates py to the Pd centre but not inside the calixarene cavity.

In summary, first-sphere coordination *via* direct σ donation to the organopalladium centre anchors the substrate in place and then, depending on the size and shape of the substrate, may allow for positioning of the substrate *inside* the cavity resulting in a second-sphere interaction. This multiple substrate–receptor interaction has the potential to simultaneously provide functional group, size and shape selectivity in a molecular recognition event.

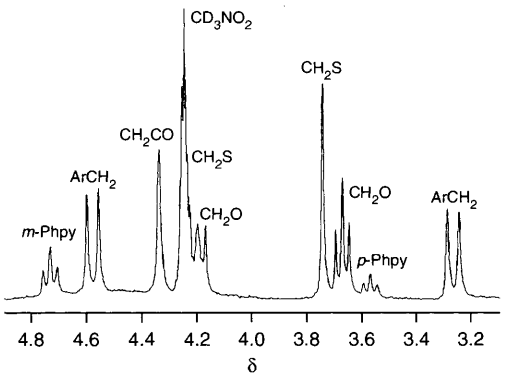

Fig. 1 ^{1}H NMR spectrum (300 MHz) of **11** in CD_2Cl_2–CD_3NO_2 (3:1), in the region δ 3.2–4.8, identifying the upfield shifted resonances, *m*-Phpy and *p*-Phpy, indicative of binding the substrate 4-Phpy *inside* the calix[4]arene cavity

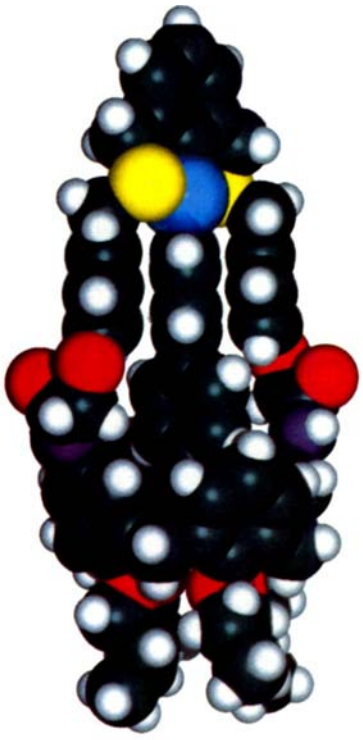

Fig. 2 A space-filling model of **11** illustrating binding of the 4-Phpy substrate inside the calix[4]arene cavity

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Footnotes

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‡ All new compounds were successfully characterized by ^{1}H and ^{13}C NMR spectroscopy, LSIMS and elemental analysis unless otherwise indicated below. *Selected data*: **6**, ^{1}H NMR (CD_3NO_2) δ 8.08 (br s, NH, 2 H), 7.70 (br s, Ar, 2 H), 7.29 (d, Ar, 4 H), 7.08 (s, Ar, 3 H), 7.00 (t, Ar, 2 H), 6.68 (br s, Ar, 2 H), 4.60 (d, $ArCH_2$, 4 H), 4.46 (s, SCH_2, 4 H), 4.20 (m, OCH_2 + SCH_2, 8 H), 3.78 (t, OCH_2, 4 H), 3.35 (d, $ArCH_2$, 4 H), 2.22 (m, CH_2, 4 H), 1.98 (m, CH_2, 4 H), 1.07 (t, CH_3, 6 H), 1.00 (t, CH_3, 6 H), −1.79 (br s, CH_3CN, 3 H). LSIMS *m/z*: 977 [M − BF_4 − MeCN + H]$^+$. **9**, ^{1}H NMR (CD_3CN) δ 8.19 (s, NH, 2 H), 7.38 (d, Ar, 4 H), 7.15 (d, Ar, 4 H), 6.89 (m, Ar, 9 H), 6.61 (s, Ar, 4 H), 4.47 (d, $ArCH_2$, 4 H), 4.37 (s, CH_2CO, 4 H), 4.33 (br s, CH_2S, 4 H), 4.28 (s, CH_2S, 4 H), 4.08 (t, OCH_2, 4 H), 3.66 (t, OCH_2, 4 H), 3.20 (d, $ArCH_2$, 4 H), 2.05 (m, CH_2, 4 H), 1.90 (m, CH_2, 4 H), 1.07 (t, CH_3, 6 H), 0.91 (t, CH_3, 6 H). LSIMS *m/z* 1190 [M − MeCN − BF_4]$^+$.

§ Molecular modelling was carried out using standard molecular mechanics (MMX) employing CAChe Scientific Inc. software (version 3.7) running on an Apple Power MacIntosh 7100/66. Positional coordinates were used as input to the program *MOLé!* to generate the illustration shown in Fig.2.

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