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Regioselective O-alkylations and acylations of polyphenolic substrates using a calix[4]pyrrole derivative

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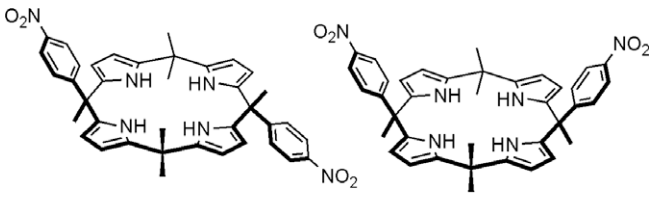
ABSTRACT

The 10α,20α-bis(4-nitrophenyl)-calix[4]pyrrole **2** can act as a topologically selective protecting group in the O-alkylation and acylation of polyphenolic polycyclic aromatic compounds thanks to the regioselective formation of phenolate-type complexes. Remarkably, the host–guest interaction with the anionic reagents is sufficiently strong and kinetically slow to produce a high degree of selectivity.

Because of their biological importance, the selective alkylation and acylation of hydroxy units in polyphenolic compounds are a topic of considerable practical interest.[1] Lipases are currently used for selective acylations and deacylations as these enzyme-based methods are compatible with the presence of a range of functional groups and are generally more efficient than the lengthy protection and deprotection sequences required by conventional synthetic techniques.[2] *Candida antarctica* lipase B was recently found to be an effective biocatalyst for the transfer of acyl groups from vinyl-propanoate to the hydroxy functions of phenols, hydroquinols, and resorcinols.[3] *Chromobacterium viscosum* lipase adsorbed on celite has been found to affect the regioselective esterification of phenols and dihydroxynaphthalenes in organic solvents,[4] whilst *Pseudomanas* sp. lipase catalyses the regioselective hydrolysis of diacetoxynaphthalenes to mono-acetates.[5]

In the course of its development, supramolecular and host–guest chemistry has addressed the objective of exploiting molecular recognition phenomena in order to mimic some of the properties of enzymes to promote selective and/or faster reactions.[6] With the discovery of the anion-binding properties of calixpyrroles,[7] we were encouraged to explore the use of these receptors in organic syntheses. Thus, we have recently reported the use of the calix[4]pyrrole derivative **1** as organocatalyst in hetero Diels–Alder reactions.[8] We have also recently described that **2** is capable of discriminating between different anionic centers within the same organic molecule (phenolate vs carboxylate).[9a]

In this Letter, we demonstrate that **2** can selectively discriminate between two phenolate-type units within the same molecule which differ due to their topology, and we present examples proving that this selective binding can be exploited for the regiocontrolled alkylation and acylation of several dihydroxynaphthalenes.



1 **2**

Initially we tested the ability of **2** to bind the anions formed by treatment of β- and α-hydroxynaphthalene (**3** and **4,** respectively) with an excess of Cs_2CO_3 in CD_3CN.[10] The ^1H NMR spectra (Fig. 1) of 1:1 mixtures show large and diagnostic complexation induced shifts (CISs). The pyrrole NH resonances are shifted toward higher ppm values ($\Delta\delta$ 4.6 and 4.2 ppm for $[\mathbf{2}\cdot\mathbf{3}]^-$ and $[\mathbf{2}\cdot\mathbf{4}]^-$, respectively). In both complexes, the naphthalene protons show upfield CISs, with the protons *ortho* to the anionic center being the most affected (ca. $\Delta\delta$ 1.90 ppm for H(1) and H(3) in $[\mathbf{2}\cdot\mathbf{3}]^-$ and $\Delta\delta$ 1.50 ppm for H(2) in $[\mathbf{2}\cdot\mathbf{4}]^-$). These spectral features indicate that **2** binds these aromatic anions with facial selectivity onto the face containing the *p*-nitrophenyl units, by a combination of NH···O hydrogen bonding and π–π interactions.[9b] Both complexes have

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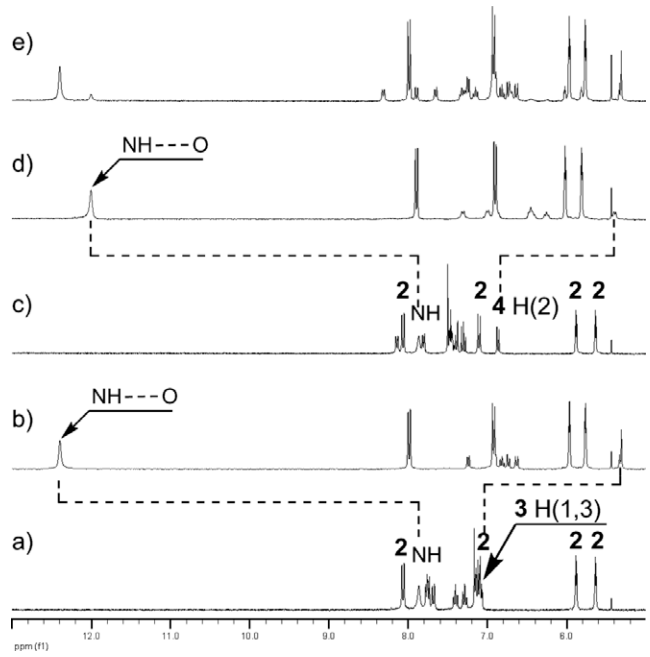
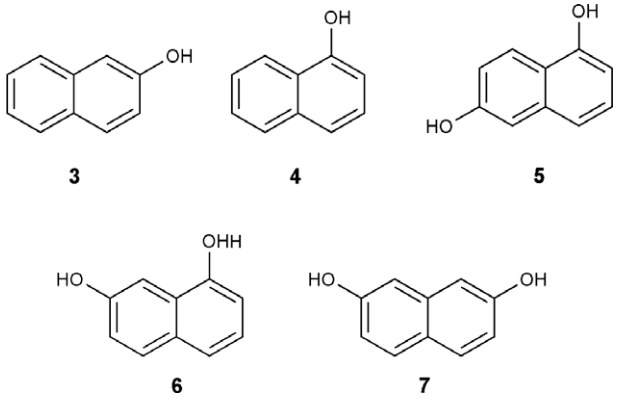


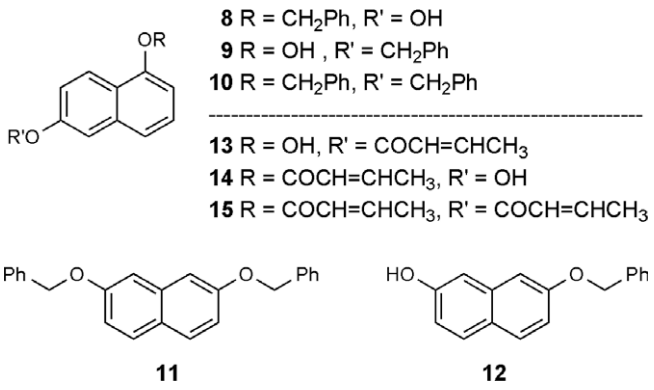
Figure 1. Partial ^{1}H NMR spectra in CD_3CN of: (a) **2** + **3** (1:1 molar ratio), (b) **2** + **3** + Cs_2CO_3 in excess as solid, (c) **2** + **4** (1:1 molar ratio), (d) **2** + **4** + Cs_2CO_3 in excess as solid, (e) **2** + **3** + **4** (1:1:1 molar ratio) + Cs_2CO_3 in excess as solid.

a 1:1 stoichiometry and they are kinetically slow on the NMR time scale. The association constants are too high to be determined by NMR methods.[11]



When the two anions derived from **3** and **4** were competing to bind receptor **2** (1:1.1 molar ratio) the mixture was found to contain the complexes $[\mathbf{2}\cdot\mathbf{3}]^-$ and $[\mathbf{2}\cdot\mathbf{4}]^-$ in 87% and 13% ratios, respectively (see the NH resonances in Fig. 1e). Since this indicates that the 'β-anion' moiety is selectively bound with respect to the 'α-anion' we were encouraged to investigate if this topological selectivity would emerge even when the two anionic moieties were simultaneously present within the same guest.

1,6- and 1,7-dihydroxynaphthalene (**5** and **6**, respectively) were identified as suitable substrates to test this hypothesis. The hydroxyl units are both sufficiently acidic for the bis-anions to be formed using Cs_2CO_3. The ^{1}H NMR spectra of these anions in the presence of one molar equivalent of **2** are consistent with the formation of 1:1 complexes that are kinetically slow on the NMR time scale, in which only the 'β-type' oxygen atoms are selectively complexed by the pyrrole NH units, whilst the naphthalene units are positioned between the nitrophenyl substituents (the spectrum of $\mathbf{5}^{2-}$ in the presence of **2** is shown in Fig. 2b). Unlike what had been previously reported for several bis-anions of hydroxybenzoic and phthalic acids,[9a] there was no evidence for the formation of capsular-like complexes involving two molecules of **2** and any of the bis-anions ($\mathbf{5}^{2-}$ or $\mathbf{6}^{2-}$), even in the presence of an excess of **2**, and even when the bis-anion was the one generated from 2,7-dihydroxynaphthalene **7**.



Treatment of complex $[\mathbf{2}\cdot\mathbf{5}]^{2-}$ with 1 equiv of benzyl bromide gave the mono-benzyl ether **8** regioselectively in a high proportion. Under identical conditions, but without receptor **2**, a mixture of mono- and bis-benzyl ethers **8–10** was formed (the proportions of **8**, **9**, and **10** were ca. 87%, 0%, and 13% in the presence and 28%, 7%, and 66% in the absence of **2**, respectively).[12] The same reactions using $\mathbf{6}^{2-}$ or $[\mathbf{2}\cdot\mathbf{6}]^{2-}$ gave only complex mixtures in which we could not detect the expected benzyl ethers. In the absence of **2**, naphthol **7** gave bis-alkylation products **11** although only 1 equiv of benzyl bromide was added (see Fig. 2 in Supplementary data). One possible explanation for this result is that the mono-alkylated **12** is more reactive than **7**. However, when **2** was present, the mono-benzyl ether **12** was formed selectively. Encouraged by these results we decided to test acylation reactions. We used *trans*-crotonoyl chloride because its protons provide ^{1}H NMR resonances that are conveniently distant from those of the calix and naphthols. Unlike bromide (from benzyl bromide) which is only weakly complexed by **2**, the chloride formed during the reaction

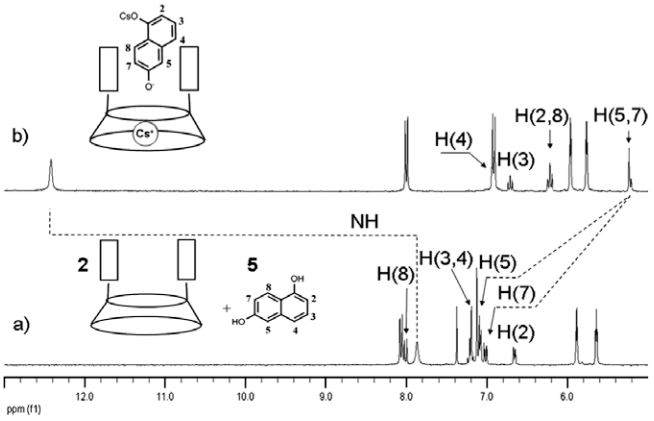


Figure 2. Partial ^{1}H NMR (300 MHz, CD_3CN) spectra for: (a) 1:1 mixture of 1,6-dihydroxynaphthalene **5** and receptor **2** and (b) 1:1 mixture of 1,6-dihydroxynaphthalene **5** and receptor **2** with an excess of Cs_2CO_3, showing the large complexation induced shifts that indicate the formation of a 1:1 inclusion complex with the bis-anion.

was found to compete with the anionic naphthols for the binding with **2**. In fact, when using 1 equiv of **2**, we were able to observe the displacement of the phenolic anions occurring to an extent correlated to the progress of the acylation and the related release of chloride ions in the reaction medium. The formation of the chloride complex with the calix **2** was also evident.[8b] Therefore, we compared the compositions of reaction mixtures in which receptor **2** was either absent or used in a twofold molar excess with respect to the *trans*-crotonoyl chloride and the naphthols. Acylation of $\mathbf{5}^{2-}$ without **2** gave a mixture of mono- and bis-acyl derivatives **13** and **15**, respectively. We were unable to detect any mono-acyl derivative **14** in this crude mixture. The same reaction in the presence of **2** gave the mono-acyl derivative **14** as the main product. It should be noted that this mono-acyl derivative is not accessible in the absence of **2**. Identical reactions using naphthol **6** gave only complex mixtures from which we were unable to isolate any of the expected acylation products.

These preliminary results on the use of calixpyrrole complexes for the selective O-alkylation and O-acylation of polyphenolic compounds demonstrate that calixpyrroles can behave as a topologically sensitive protecting group whose on/off reaction requires just a pH change. Receptor **2** was found to be unaffected by the reactions described here and could be recovered and recycled if necessary. We are actively investigating the extension of these principles to a larger number of reactions involving a broader range of starting materials.

Acknowledgment

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Supplementary data

Supplementary data (supplementary material contains ^{1}H NMR spectra for the 1:1 host–guest complexes of the dihydroxynaphthalenes and receptor **2** and of the crude reaction mixture for alkylation and acylation reactions both in the presence and in the absence of receptor **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.128.

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9. (a) Cafeo, G.; Kohnke, F. H.; Valenti, L.; White, A. J. P. *Chem. Eur. J.* **2008**, *14*, 11593–11600; (b) This mode of binding was also observed in Ref. 9a.
10. Complexation studies were conducted by means of ^{1}H NMR spectrometry (20 °C, 300 MHz) using 5×10^{-3} M solutions of receptor **2** and of the naphthols in CD_3CN (700 μL) and an excess of solid Cs_2CO_3. All resonances were assigned on the basis of their multiplicity and of double irradiation experiments. Alkylation reactions were conducted at 40 °C in either CD_3CN or CH_3CN both in the absence and in the presence of 1 M equiv of **2,** using 1 equiv of benzyl bromide and an excess of solid Cs_2CO_3. Acylation reactions were conducted in a similar manner, but using twice the amount of **2** with respect to that of *trans*-crotonoyl chloride. All reactions were monitored (^{1}H NMR) for the disappearance of the starting materials, and excess base was neutralized with trifluoroacetic acid before recording the NMR spectra.
11. (a) Fielding, L. *Tetrahedron* **2000**, *56*, 6151–6170; (b) The association constants for the complexations between the mono- and bis-anions of the hydroxynaphthalenes might be measured by UV methods. However, these measurements were not considered a priority at this stage of the work and will be addressed in a full paper. In fact, these binding constants are sufficiently high to produce the regioselective control of the reactions described here.
12. The benzyl signals corresponding to **8–10** were assigned by comparison with those reported in the literature for these compounds. See: Asakawa, M.; Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Gillard, R. E.; Kocian, O.; Raymo, F. M.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1997**, *62*, 26–37.