Synthetic Receptors with Preorganized Cavities that Complex Prednisolone-21-acetate

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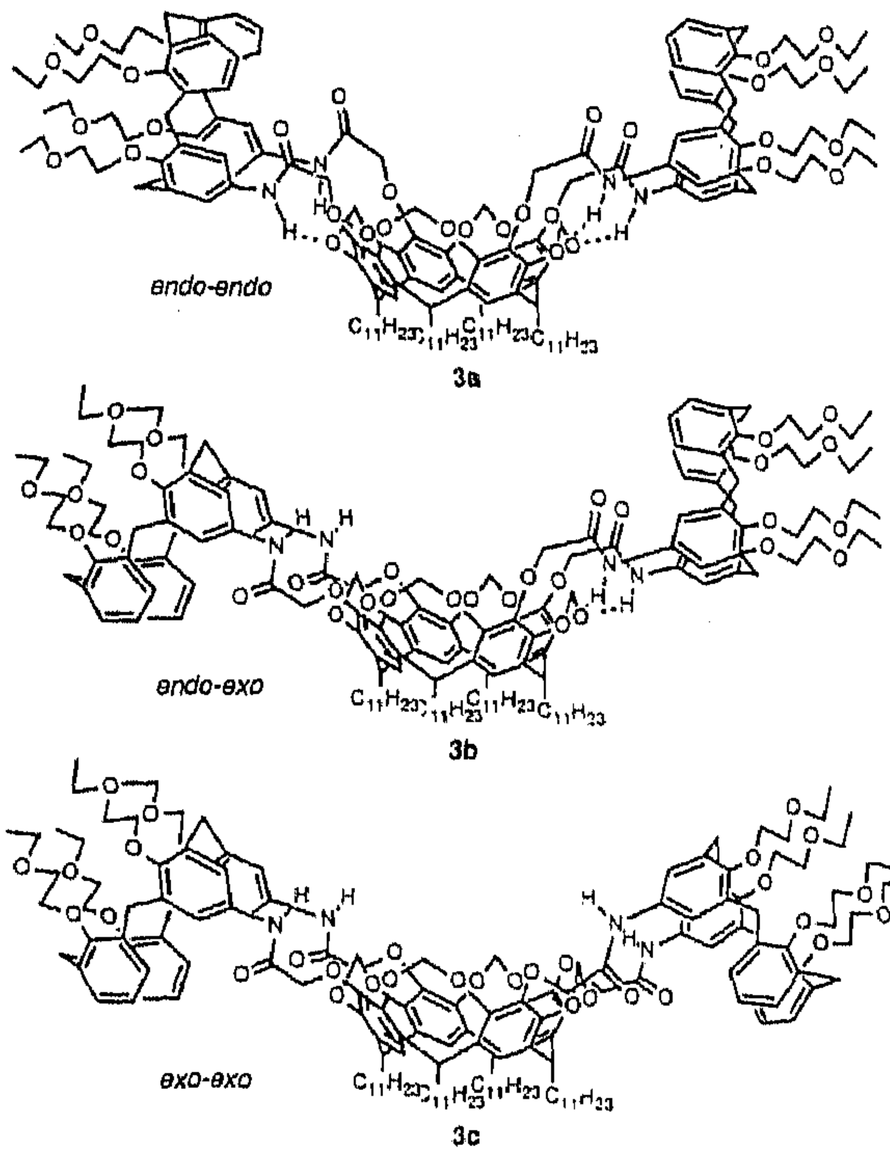
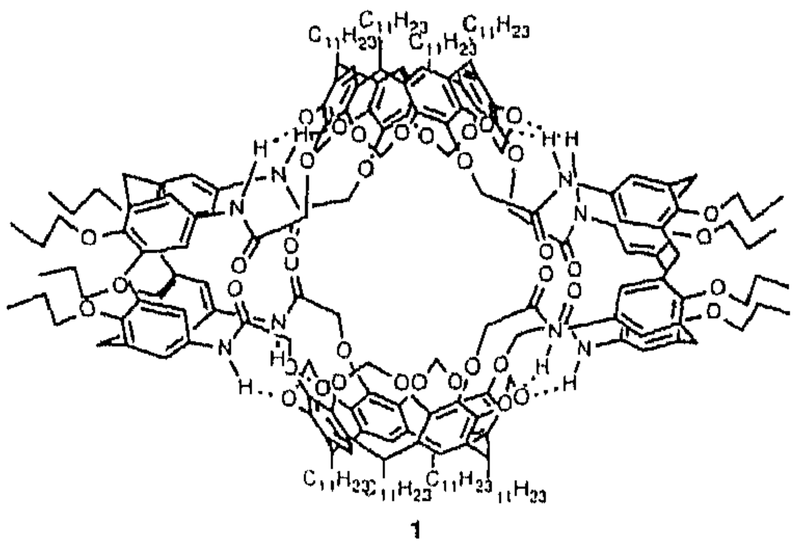
Receptors **3a–c** composed of two upper rim 1,2-difunctionalized calix[4]arene fragments, oriented either *endo* or *exo*, and one bridging cavitand unit, complex prednisolone-21-acetate with association constants of 4.3–8.3 × 10^2 dm^3 mol^{-1} in $CDCl_3$.

Although the chemistry of synthetic receptors for a variety of cations,[1] anions[2] and small neutral molecules[3] is now well established, the complexation of larger guest molecules has only recently received attention. We recently synthesized a molecule **1** with a large, rigid cavity of nanosize dimensions (V_{cav} *ca.* 1000 Å^3).[4] A systematic search for suitable guest molecules using the computer simulation program DOCK,[5] revealed an excellent fit for a number of steroids, in particular prednisolone-21-acetate **2a**.[6] The complexation of steroids by synthetic receptor molecules in *apolar* solvents has hardly been studied. Most studies deal with complexation in aqueous solutions by water-soluble azacyclophanes[7] or cyclodextrins;[8] the stability and selectivity is mainly governed by hydrophobic interactions. Here we describe the selective complexation of prednisolone-21-acetate **2a** in $CDCl_3$ by novel receptor molecules obtained by combining calix[4]arene and resorcinarene moieties.

Using a synthetic strategy similar to that employed for the formation of compound **1**, we prepared the three diastereoisomers **3a–c** by reaction of 2.2 equiv. of 5,11-bis(2-chloroacetamido)-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene[4] with 1 equiv. of a '$C_{11}H_{23}$-substituted' tetrahydroxycavitand[4] in acetonitrile in the presence of Cs_2CO_3 under highly dilute conditions. The three 2 : 1 addition products were isolated after flash column chromatography in an almost statistical ratio in a total yield of 64%. The 1,2-difunctionalized calix[4]arene fragments can adopt either an *endo* or an *exo* orientation. Upon the addition of prednisolone-21-acetate **2a** to a solution of either *endo-endo* **3a**, *endo-exo* **3b**, or *exo-exo* **3c** in $CDCl_3$ at 25 °C, several host proton signals, *viz*, the amide resonances, *split into two signals* of equal intensity (Fig. 1). The observed splitting is larger for the *exo* amide protons (*ca.* 0.4 ppm) than for *endo* amide protons (*ca.* 0.1 ppm). The signals of **2a** show considerable shifts. The singlet for the acetyl methyl group at δ 2.0 shifts and becomes much broader, even when the host is present in small concentrations (ratio 1 : 10). The AB quartet of the C-21 methylene group shifts upfield by *ca.* 0.2 ppm and also the singlets for both methyl groups (C-18 and C-19) show upfield shifts.

The observed splitting of the amide proton signals in **3a–c** upon complexation of **2a** is due to the chirality of the guest molecule. As a result of complexation, enantiotopically related protons in the free host become diastereotopic in the chiral complex. However, in the case of the *endo-endo* isomer **3a** and the *exo-exo* isomer **3c**, both of which exhibit C_{2v} symmetry, the

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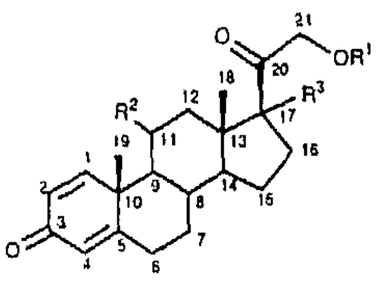
2a R^1 = C(O)Me, R^2 = β-OH, R^3 = α-OH
b R^1 = H, R^2 = β-OH, R^3 = α-OH
c R^1 = C(O)Me, R^2 = =O, R^3 = α-OH
d R^1 = C(O)Me, R^2 = β-OH, R^3 = H
(without double bond between C_1–C_2)

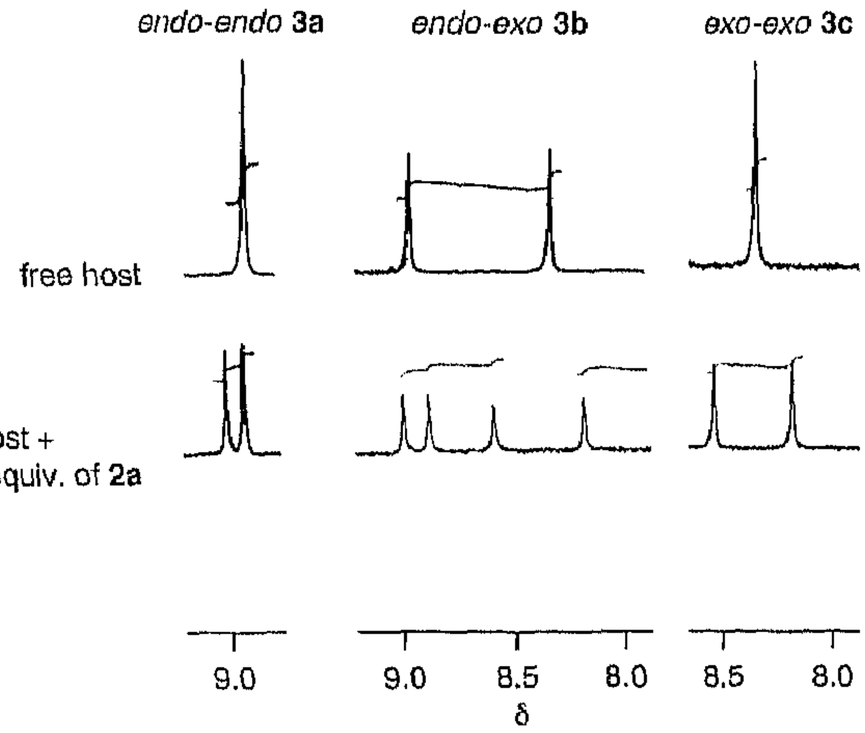

Fig. 1 Splitting of amide proton signals in the ^{1}H NMR spectra of (*a*) *endo-endo* **3a**, (*b*) *endo-exo* **3b**, and (*c*) *exo-exo* **3c** upon the addition of *ca.* 1 equiv. of prednisolone-21-acetate **2a**

homotopic amide protons give rise to *only one signal* as a result of fast exchange between the free host and the complex on the ^{1}H NMR chemical shift timescale.

The association constants of complexes **3a·2a**, **3b·2a** and **3c·2a** were determined to be 4.3×10^2, 8.3×10^2 and 5.3×10^2 dm^3 mol^{-1}, respectively, in $CDCl_3$.† The relatively small difference in association constant between *endo-endo* **3a** and *exo-exo* **3c** suggests that the upper rim cavity of the calix[4]arene fragments contributes little to binding. In order to prove that the calix[4]arene fragments in **3a–c** play a crucial role in the complexation of **2a**, cavitand **4**, carrying four *para*-methoxyphenylaminocarbonylmethoxy substituents, was synthesized. Neither of the signals of **4** nor one of the guest signals shifted upon the addition of up to 10 equiv. of **2a** to a solution of **4** in $CDCl_3$. This unambiguously proves that complexation of **2a** by the diastereoisomeric 2 : 1 products **3a–c** is not simply a result of the presence of four amide moieties at the upper rim of a cavitand, but that organization of the amide spacers due to the presence of the calix[4]arene fragments is at least partially responsible for the observed complexation.

In order to determine which functionalities in **2a** promote its complexation by **3a–c**, the related corticosteroids prednisolone **2b**, prednisone-21-acetate **2c** and corticosterone-21-acetate **2d**, were also studied. Addition of **2b** to a solution of any of **3a–c** in $CDCl_3$ did not give rise to any significant shift of guest or host protons. With **2c**, having a keto function at C-11 instead of a hydroxy group, the splitting of the amide proton signals was cancelled in the case of *endo-endo* **3a** and strongly diminished in the cases of *endo-exo* **3b** and *exo-exo* **3c** ($\Delta\delta < 0.1$ for the *exo* amide protons). Significant shifts of guest proton signals were not observed for any of the three diastereoisomers. Very similar results were obtained for **2d**, a steroid that lacks the hydroxy group at C-17. These data show that at least three functional groups in **2a** are involved in complexation. First of all, the acetoxy group at C-21 can interact both *via* CH-π interactions[9] of the slightly acidic acetyl methyl group with the aromatic rings of the cavitand,[10] or *via* hydrogen bonding interactions of the carbonyl group with the amide protons. Secondly, the hydroxy groups at C-11 and C-17 seem also to be involved in complexation, most probably *via* hydrogen bonding interactions. A hypothetical structure of the complex with the highest association constant **3b·2a** is shown in Fig. 2.

Addition of **2a** to a solution of compound **1** in $CDCl_3$ did not give rise to any significant shift or splitting of signals in the ^{1}H NMR spectrum of either host or guest. This brings us to conclude that the extreme rigidity of host **1** prevents the molecule from accommodating the structural deformations necessary for complexation. However, it is probably the flexibility present in **3a–c** that does allow them to complex certain steroids.

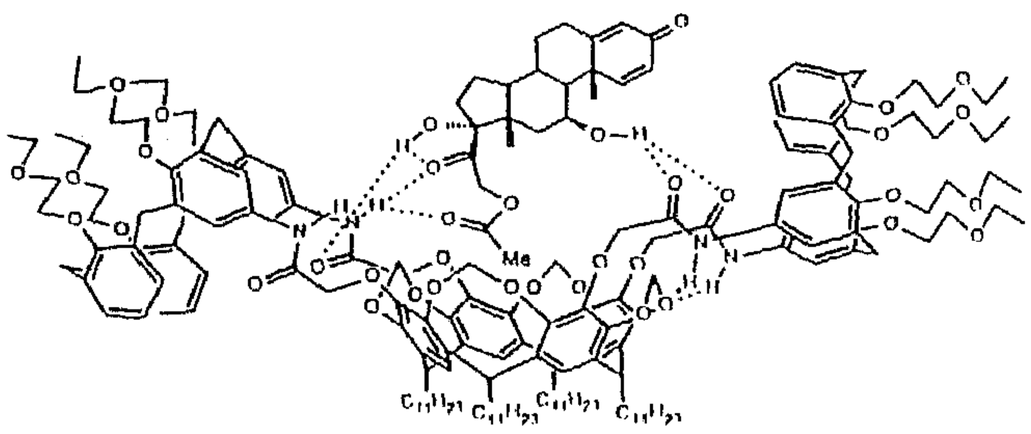

Fig. 2 Proposed structure of complex **3b·2a** in $CDCl_3$

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Footnote

† Determination of the association constant was performed by mixing 5.0×10^{-2} mol dm^{-3} solutions of host and guest in $CDCl_3$ in nine different ratios (1 : 9–9 : 1). None of the guest proton signals could be used as a probe, since they were obscured by host proton signals when a large excess of the host was present. Quantitatively following the chemical shift differences between the splitted amide proton signals as a function of the host–guest ratio gave perfect fits to 1 : 1 binding isotherms. The corresponding Job plots proved the 1 : 1 stoichiometry of all three complexes.

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