

FUNCTIONALIZED CYCLODEXTRIN-CALIX[4]ARENE HOST MOLECULES FOR DETECTION OF ORGANIC ANALYTES

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0. Abstract: Monofunctionalized β -Cyclodextrins were coupled to calix[4]arene derivatives bearing different fluorophores to give fluorescent cyclodextrin-calix[4]arene couples. The cyclodextrin-calix[4]arene couple **1** was investigated as a sensing molecule for the detection of several organic analytes in aqueous solution. Inclusion of a guest into the fluorescent sensing molecule leads to a decrease in fluorescence intensity. Compound **1** shows selectivity for organic analytes of a certain length. The fluorescent sensing molecules **2-6** were synthesized in order to investigate the influence of the different parts of the molecules on the sensing properties.

Keywords: Fluorescence Sensors, Cyclodextrins, Supramolecular Chemistry

1. Introduction. Cyclodextrins are a unique group of naturally occurring cyclic D-glucose oligomers. These molecules have the shape of a truncated cone and are capable of complexation of organic molecules in their cavity.¹ This host-guest complexation of cyclodextrins is of great interest in view of the development of sensors for specific molecules. Fluorescent cyclodextrins have been prepared by appending a fluorophore to one of the primary hydroxyl groups of β - and γ -cyclodextrin to give fluorescent probes for organic guest molecules.² Competition for the hydrophobic cavity between the guest molecule and the covalently linked optical reporter group results in a change in the optical properties of the reporter group. This change in properties is dependent on the concentration of the species to be detected.

A large number of organic analytes can only be detected by rather laborious methods, requiring sampling, pretreatment and analysis by relatively expensive techniques. Development of fast responding sensors is therefore of great use in environmental control, agriculture, food technology, etc. Good selectivity and transduction properties of appropriate sensing layers are a prerequisite for the construction of sensors. Cyclodextrin derivatives have

good prospects to be used in such sensing layers, as they can accommodate analytes in their cavity. By appropriate functionalization of the wider, secondary face with groups that provide the cyclodextrin host with additional binding sites for the target molecule, the selectivity of the sensing layer can be increased. The main aim of this project is to combine both the advantages of cyclodextrins and calixarenes. Cyclodextrins offer good water solubility entailed by a promising host-guest chemistry. Calix[4]arenes are widely used as rigid platforms in supramolecular chemistry and can be selectively modified with functional groups.³

Preliminary experiments revealed, that calix[4]arene cyclodextrin couples showed increased binding abilities for the fluorescent probes 1-anilino-8-naphthalenesulfonate (ANS) and 2-p-toluidino-6-naphthalenesulfonate (TNS) in aqueous solution compared to cyclodextrin.^{4,5} Herein we report the synthesis and the host-guest chemistry of the cyclodextrin-calix[4]arene couple **1** which bears a fluorophore as a reporter group for guest inclusion, as well as the synthesis of derivatives of **1**. Their properties might give closer insight in the sensing mechanism.

2. Results and Discussion. Compound **1** was obtained by reductive amination of a calix[4]arene derivative that bears an aldehyde functional group and a fluorophore opposite to each other with a silyl protected β -cyclodextrin having a (p-aminomethyl)tolyl spacer at one of the secondary hydroxyl groups (Fig. 1) followed by purification and deprotection. **1** was characterised by TLC, ¹H NMR and MALDI-TOF mass spectroscopy. The UV/VIS spectrum shows the expected absorption bands for the calix[4]arene-2-naphthylamine moiety. **1** is water soluble (soly. 0.2 mM) and is fluorescent in aqueous solution.

For the investigation of the sensing abilities of **1** the fluorescence spectra of an aqueous solution of **1** were measured while aliquots of a stock solution of an organic analyte were added successively to the solution of sensor molecule **1**. The fluorescence intensity decreased upon addition of guest molecules (Fig. 2). A common parameter expressing the sensitivity of a fluorescent probe towards different analytes is the $\Delta I/I_0$ -value.⁶ As is shown in Figure 3, the new sensing molecule molecule **1** shows sensitivity for some terpenes and steroids. The remarkably high response for 1-adamantylbenzoate and norethindrone compared with the binding constants for 1-adamantanol or for the other examined steroids shows the high selectivity of **1** for guest molecules with a certain length. 1-adamantylbenzoate can be recognized by the new sensing molecule molecule with a selectivity of >200 over the other organic compounds. CPK models supply further evidence for the excellent fit of 1-adamantylbenzoate in **1**.

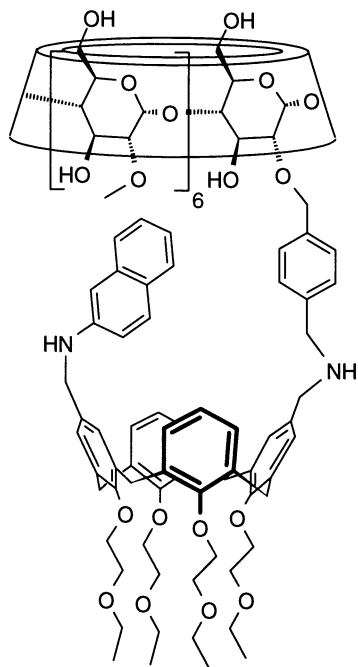


Fig. 1: Sensing molecule compound 1

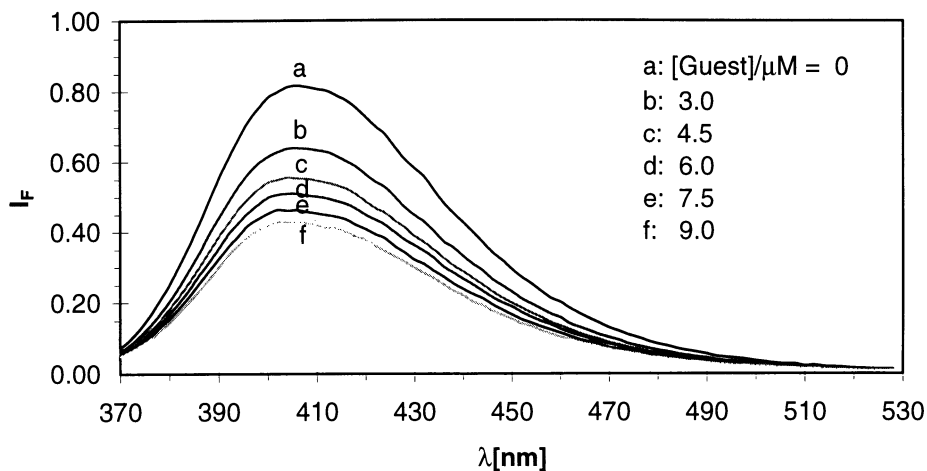


Fig. 2: Fluorescence spectra of **I** in aqueous solution ($[I] = 2.9 \mu\text{M}$, in phosphate buffer 0.01 mM , $\text{pH } 7$; $\lambda(\text{ex.}) = 350 \text{ nm}$, $\lambda(\text{em.max.}) = 408 \text{ nm}$). Guest: 1-Adamantanylbenzoate.

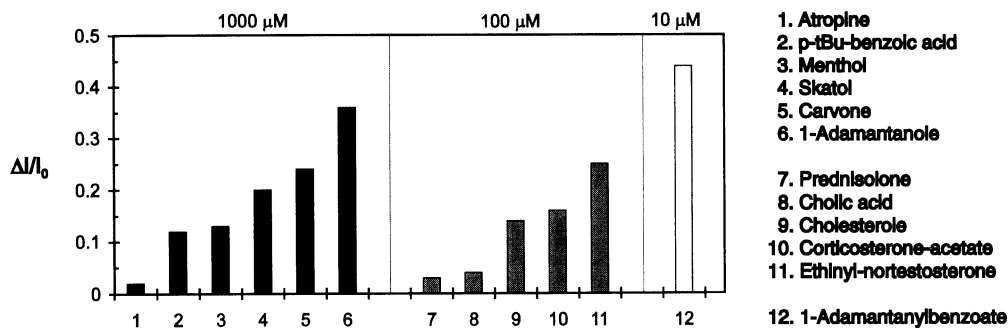


Fig. 3: Sensitivity factors $\Delta I/I_0$ for several neutral, organic analytes. $[Analyte] =$ given above the scetch. $[I] = 1.45 \mu\text{M}$.

To gain more insight in the factors governing the sensing properties, especially the sensitivity for certain analytes of cyclodextrin-calix[4]arene couples, several components of the molecule were varied (Fig. 4). Compounds **2** and **3** enable investigation of the influence of the spacer length and rigidity. Compounds **4** and **5** have been prepared to study the effect of different fluorophores. Therefore, the dansyl and the coumaryl fluorophore were chosen as they have rather high fluorescence quantum yields and comparably long excitation wavelengths. This might be important for future technical applications. In compound **6** the remaining upper rim hydrogens of the calix[4]arene have been substituted for groups which potentially attribute to the binding of suitable guest molecules. All couples were prepared by essentially the same procedure as that followed for the preparation of **1**. The binding and sensing properties of compounds **2-6** are currently under investigation.

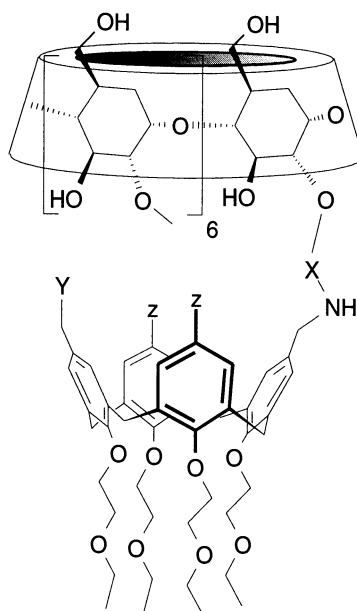


Fig. 4: Sensing molecule compounds **2-6** (see Tab. 1).

Table 1: Substitution pattern of sensor molecules **1-6**.

Compound	X	Y	Z
1	$-\text{CH}_2(p\text{-C}_6\text{H}_4)\text{CH}_2-$	2-aminonaphthyl-	H
2	$-(\text{CH}_2)_3-$	2-aminonaphthyl-	H
3	$-(\text{CH}_2)_6-$	2-aminonaphthyl-	H
4	$-\text{CH}_2(p\text{-C}_6\text{H}_4)\text{CH}_2-$	dansyl-	H
5	$-\text{CH}_2(p\text{-C}_6\text{H}_4)\text{CH}_2-$	coumaryl-	H
6	$-\text{CH}_2(p\text{-C}_6\text{H}_4)\text{CH}_2-$	2-aminonaphthyl-	NO_2

3. Conclusions. In summary, the new fluorescent cyclodextrin-calix[4]arene couple **1** is suitable for the sensing of organic molecules in aqueous solution. It shows remarkably high sensitivity for guest molecules with a certain length. Further efforts were made to optimize the binding properties of **1** by varying the different parts of the molecule. The sensing behaviour of the recently synthesized compounds **2-6** will allow further insight in the sensing mechanism and provide a basis for the design of further optimized, applicable sensor molecules.

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References:

- ¹ M.L. Bender, M. Komiyama, *Cyclodextrin Chemistry*, Springer Verlag, New York, 1978.
- ² A. Ueno, *Supramolecular Science*, **3**, 1996, 31, and references cited herein.
- ³ C.D. Gutsche, *Calixarenes* in: *Monographs in Supramolecular Chemistry, Vol. 1*, J.F. Stoddart (Ed.), Royal Society of Chemistry, Cambridge, 1989.
- ⁴ E. van Dienst, B.H.M. Snellink, I. von Piekartz, M.H.B. Grote Gansey, F. Venema, M.C. Feiters, R.J.M. Nolte, J.F.J. Engbersen, D.N. Reinhoudt, *J. Org. Chem.*, **60**, 1995, 6537.
- ⁵ E. van Dienst, B.H.M. Snellink, I. von Piekartz, J.F.J. Engbersen, D.N. Reinhoudt, *J. Chem. Soc., Chem. Commun.*, 1995, 1151.
- ⁶ A. Ueno, S. Minato, J. Suzuki, M. Fukushima, M. Ohkubo, T. Osa, F. Hamada, K. Murai, *Chem. Lett.* **1990**, 605.