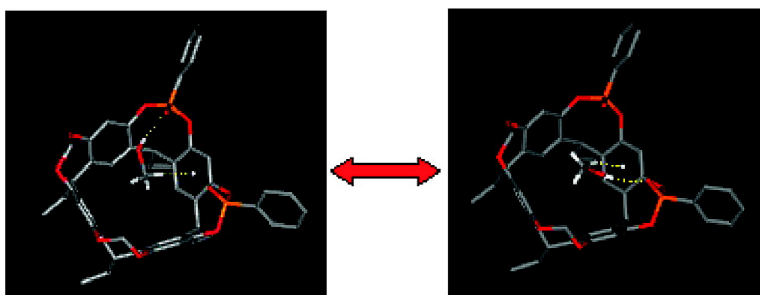


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Rational Design of CavitanD Receptors for Mass Sensors

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This Communication describes a rational approach to the fabrication of selective mass sensors, using multiple H-bonding type interactions encoded in a single cavitanD receptor. Synergistic multiple binding interactions are widely used both in natural and in synthetic receptors to enhance selectivity and eventually achieve specificity.¹ The rational design of organic hosts is particularly appealing to chemical sensor technology, which requires arrays of selective, sensitive, and stable receptors to perform multianalyte sensing.² In the case of gas sensors, however, the translation of the molecular recognition properties of a given receptor from solution to the solid–gas interface is not trivial, because nonspecific interactions, such as dispersion forces, come into play. To overcome this problem, we have recently introduced a first generation of cavitanD hosts,³ coated as sensitive layers on mass transducers.⁴ Their selectivity toward linear alcohols stems from the simultaneous presence of H-bonding with the PO group and CH– π interactions with the π -basic cavity, possible only for the PO_{in} isomer. The presence of the cavity is, however, equally important in providing a permanent free volume for the analyte around the inward facing PO group, pivotal for effective H-bonding.⁵ The necessity to ensure an adequate permeability of the deposited layer has required the introduction of four long alkyl chains at the lower rim. As a drawback, they cause a consistent reduction of selectivity toward long chain alcohols by increasing the weight of dispersion interaction on the overall response.⁵ Because the presence of multiple interactions turned out to be the key element in achieving high selectivity, we designed a new class of cavitanDs having three interaction sites, by introducing a second PO group at the upper rim of the cavity (Figure 1).

AB and AC-diphosphonate-bridged cavitanDs were prepared by introducing the two phosphonate moieties on the corresponding methylene-dibridged resorcinarene precursors.⁶ The reaction led to the formation of all three possible configurational isomers in each case (**ii**, **io**, and **oo**),⁷ due to the presence of two P(V) stereocenters on the molecule. The configurations of all six diastereomers were assigned by established spectroscopic methods⁸ and confirmed in the case of **ABii** by crystal structure analysis. For a meaningful comparison of the sensor responses, also the corresponding monophosphonate cavitanDs **Mi** and **Mo** were synthesized (Figure 1).⁹ All cavitanDs and the reference polymer **PECH** (polyepichlorohydrin) were deposited by spray coating on both sides of the quartz transducers operating at 10 MHz.¹⁰ Figure 2a reports the selectivity patterns of seven layers toward methanol. The observed responses follows the order: **ACii** \approx **ABii** > **Mi** > **ABio** > **Mo** \approx **ABoo** \approx **PECH**. The introduction of a second PO group in the inward configuration leads to relevant improvements both in selectivity

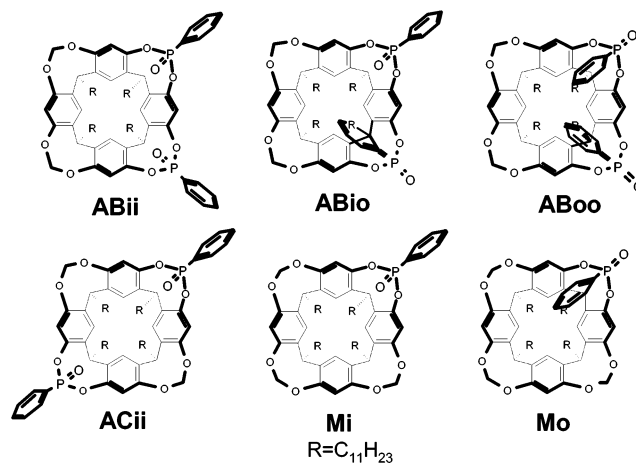


Figure 1. Molecular structures of the cavitanDs employed as sensing materials.

and in sensitivity with respect to the **Mi** counterpart. The relative position of the two PO groups (**ACii** vs **ABii**) is not determinant, indicating the possibility that they do not act cooperatively (see later). Even more compelling are the responses of **ABio** and **ABoo** isomers. They are progressively reduced by the presence of one/two phenyl groups filling the cavity and by the diverging orientation of the PO groups. The same trend is observed for **ACio** and **ACoo** (not shown). Figure 2b reports the responses of **ABii** and **Mi** to linear C₁–C₅ alcohols. The responses have been normalized to those of **PECH** to show the progressive dilution of the specific responses upon an increase of the chain length of the analytes. Despite that, a satisfactory selectivity gain is retained throughout the alcohol series for **ABii**. The observed selectivity enhancement is peculiar to alcohols and not to other classes of analytes such as hydrocarbons, esters, and ketones (see Figure S1). Moreover, a significant increase in sensitivity¹¹ is observed upon exposure of the three sensors to low ethanol concentrations in the case of **ABii**, as evidenced by the steeper slope in Figure 2c.

The molecular origin of the increased selectivity can be inferred from the molecular structure of the **ABii**·**MeOH** complex¹² (Figure 3), obtained by vapor diffusion of methanol in a methylene chloride solution of the ethyl-footed **ABii** cavitanD. The guest exhibits a two point interaction mode with the receptor: an H-bond between the alcoholic OH and one of the two PO, and a CH– π interaction between the methyl residue and the aromatic ring located between the two PO groups. Methanol is equally distributed over two different orientations related to each other by a mirror plane. Thus, the guest can be regarded as a pendulum, with the fulcrum on the barycenter of the benzene involved in the CH– π interaction, free

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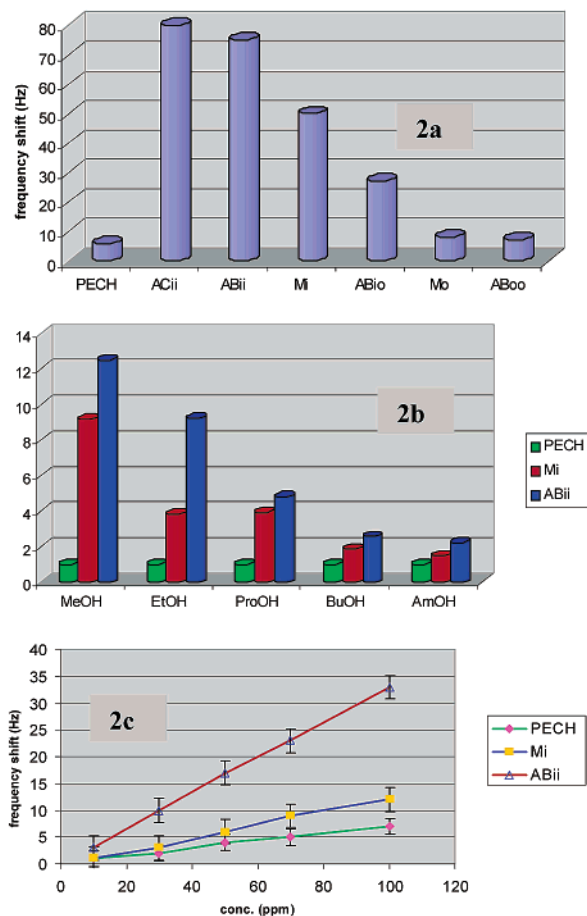


Figure 2. (a) Selectivity patterns of cavitands ACii, ABii, Mi, ABio, Mo, ABoo, and polymer PECH toward methanol at 1500 ppm (average standard deviation: ± 2 Hz). (b) Selectivity patterns of cavitands ABii, Mi, and polymer PECH toward linear C_1 – C_5 alcohols (1500 ppm each), normalized to PECH. (c) Responses of selected cavitand coated sensors to low EtOH concentrations (10–100 ppm).

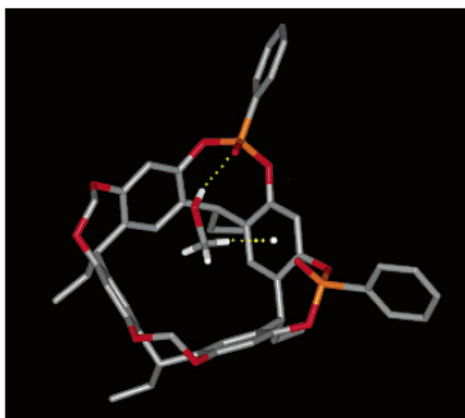


Figure 3. Crystal structure of $ABii \cdot 2MeOH \cdot 2CH_2Cl_2$ ($R = C_2H_5$). Only one orientation of the complexed MeOH is shown. The heavily disordered lattice MeOH and H-bonded CH_2Cl_2 are excluded.

to switch the $MeOH \cdots O=P$ H-bond between the two mirror-related PO groups. The resulting picture indicates that the second converg-

ing PO group does not act cooperatively as a third interaction site, forming a three-center H-bond¹³ with the OH of the analytes, but it offers a second energetically and geometrically equivalent interaction mode to the guest, increasing the entropy of the complex. Therefore, the selectivity gain observed for **ABii** with respect to **Mi** is entropic and not enthalpic in origin. This is confirmed by the behavior of **ACii**, where the two PO groups are too far apart to form a three-center H-bond with the analytes ($O \cdots O$ distance of 6.5 Å in **ACii**⁷ vs 5.0 Å in **ABii**).

In perspective, these results suggest a new strategy to maximize selectivity in supramolecular mass sensors, which relies on increasing the number of binding options available to the analyte in a single receptor, instead of strengthening a single binding via multiple interactions.¹⁴ Our current goal is to extend the concept described here to the design of even more selective cavitated layers for mass sensors.

Supporting Information Available: Cavitands preparation and characterization, analytical methods for sensor measurements. Selectivity patterns of **ABii**, **Mi**, and **PECH** toward EtOH, hexane, ethyl acetate, MEK (Figure S1) (PDF). Crystallographic files (CIF) and table. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) All new compounds gave satisfactory elemental analyses. Their stereochemical purity was checked by HPLC.
- (10) The amount of material coated was controlled by measuring a frequency shift of $\Delta f = 20 \pm 0.05$ kHz on deposition of the layers.
- (11) Sensitivities are calculated as Hertz response per 10 kHz of applied cavitant per 90 ppm of ethanol vapor concentration (Grate, J. W.; Patrash, S. J.; Abraham, M. H. *Anal. Chem.* **1995**, *67*, 2162–2169).
- (12) Crystallographic data for: $C_{50}H_{46}O_{10}P_2 \cdot 2CH_3OH \cdot 2CH_2Cl_2$; $Mr = 1017.872$; orthorhombic $a = 19.827(5)$, $b = 12.558(5)$, $c = 21.186(5)$ Å; $V = 5275.3(3)$ Å³; space group $Cmc2_1$; $Z = 4$; $D_{calc} = 1.282$ g cm⁻³; $\mu(Mo K_{\alpha}) = 0.243$ mm⁻¹; 23 914 collected reflections, 6085 unique ($R_{int} = 0.003$); final $R_1 = 0.053$ and $wR_2 = 0.135$ for 4485 independent reflections having $F_o > 4\sigma(F_o)$, wR_2 (all data) = 0.144. Full details are described in the Supporting Information.
- (13) For an example of an energetically favorable three-center H-bond, see: Gong, B.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11583–11588.
- (14) Preliminary experiments along this line show that the tetra-POiiii cavitant responds to alcohols better than **ABii** and **ACii**.

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