

Cavitands at Work: From Molecular Recognition to Supramolecular Sensors

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Exploitation of the molecular recognition properties of a given receptor in analytical applications requires mastering of specific host-guest interactions at interfaces. This review outlines the issues involved in turning P^V-bridged cavitands into selective layers for mass sensors, as a case study for gas-solid interfaces. The specific interactions operating at each phase level can be ferreted out by use of MS and crystallographic analyses, respectively. Their influence on sensor selectivity can be enhanced by exposure of the guest (analyte)

to a network of cooperative interactions encoded in a single cavitand receptor. On the other hand, high layer permeability – necessary to achieve fast and reversible sensor responses – increases non-specific dispersion interactions. Shifting of the balance towards selectivity without loss of reversibility represents the major challenge facing those wishing to venture into the field of supramolecular sensors. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2004)

Introduction

In the last two decades, researchers active in the field of supramolecular chemistry have designed and prepared an amazing number of different synthetic receptors for binding and recognition of neutral molecules.^[1] The initial inspiration for this research came from the realm of biology, in

which specific molecular interactions provide the basis of many of the working features of biotic molecules, such as catalysis, transport, and regulation. One of the outcomes of this effort has been greater understanding of the fundamental rules governing non-covalent interactions.^[2]

The selective binding of a neutral substrate by a molecular receptor to form a complex involves molecular recognition, which is based on shape complementarity and the presence of specific interactions such as hydrogen bonding,^[3] π – π stacking,^[4] and CH– π interactions.^[5] Most complexation studies reported have been carried out in solu-

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Roberta Pinalli, born in Fidenza, Italy, in 1972, earned a MS in Industrial Chemistry at the University of Parma in 1998 and a Ph.D. in Chemistry from the same University in 2002, under the supervision of Prof. Dalcanale. In between she worked for two years (1998–2000) in a pharmaceutical company as process manager. Her Ph.D. thesis focused on supramolecular sensors and on the self-assembly of nanosize coordination cages, both in solution and on surfaces. She is now a researcher at Bracco Imaging, Milan, working in the field of high relaxivity gadolinium complexes for MRI.



Michele Suman, born in Rovigo, Italy, in 1973, earned his MS in Chemistry at the University of Ferrara in 1997, followed by a Master in Science Management from the same University in 1998 in conjunction with a one year appointment at the Giulio Natta Research Centre. From 1998 to 2000 he worked as a researcher in the Packaging R&D Team of Barilla Alimentare. He is currently pursuing a Ph.D. in Materials Science at the University of Parma, under the supervision of Professor E. Dalcanale. His current research focuses on the preparation and study of supramolecular sensors. He is a member of the editorial board of the International Journal of Polymeric Materials and of the Journal of Italian Macromolecular Association (AIM). He has won the National Prize for Young Researchers promoted by Federchimica in 1998.



Enrico Dalcanale graduated in Industrial Chemistry (cum laude) at the University of Bologna with A. Fava in 1981. After working as research scientist at the Donegani Research Institute of Montedison in Novara from 1982 to 1990, he joined the Faculty of the Department of Organic and Industrial Chemistry of the University of Parma, where he is currently Associate Professor. In 1985–86 he spent a sabbatical year in the group of D. J. Cram at UCLA. His research interests include supramolecular sensors and self-assembly of nanostructures (coordination cages, mesogenic porphyrins). For his effort in these areas he received the Federchimica Prize in 1997. He is the founder of SOATEC, a University spin-off company active in the field of environmental and food sensors.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

tion^[6] or, in fewer cases, in the gas phase.^[7] However, the majority of the potential analytical applications of supramolecular receptors – namely, sensors^[8] and chromatography^[9] – are either at gas-solid or at liquid-solid interfaces. The direct translation of the molecular recognition properties of a given receptor from solution to the solid-gas interface is not trivial, since non-specific interactions such as dispersion forces and material properties such as surface morphology and layer permeability come into play.

Cavitands, synthetic organic compounds with rigid cavities of molecular dimensions,^[10] are extremely interesting and versatile molecular receptors, the complexation properties of which have been extensively studied in the solid state,^[11] in solution,^[12] and in the gas phase.^[13] The main specific interactions responsible for recognition evidenced by these studies are H-bonding, CH- π , and dipole-dipole interactions.

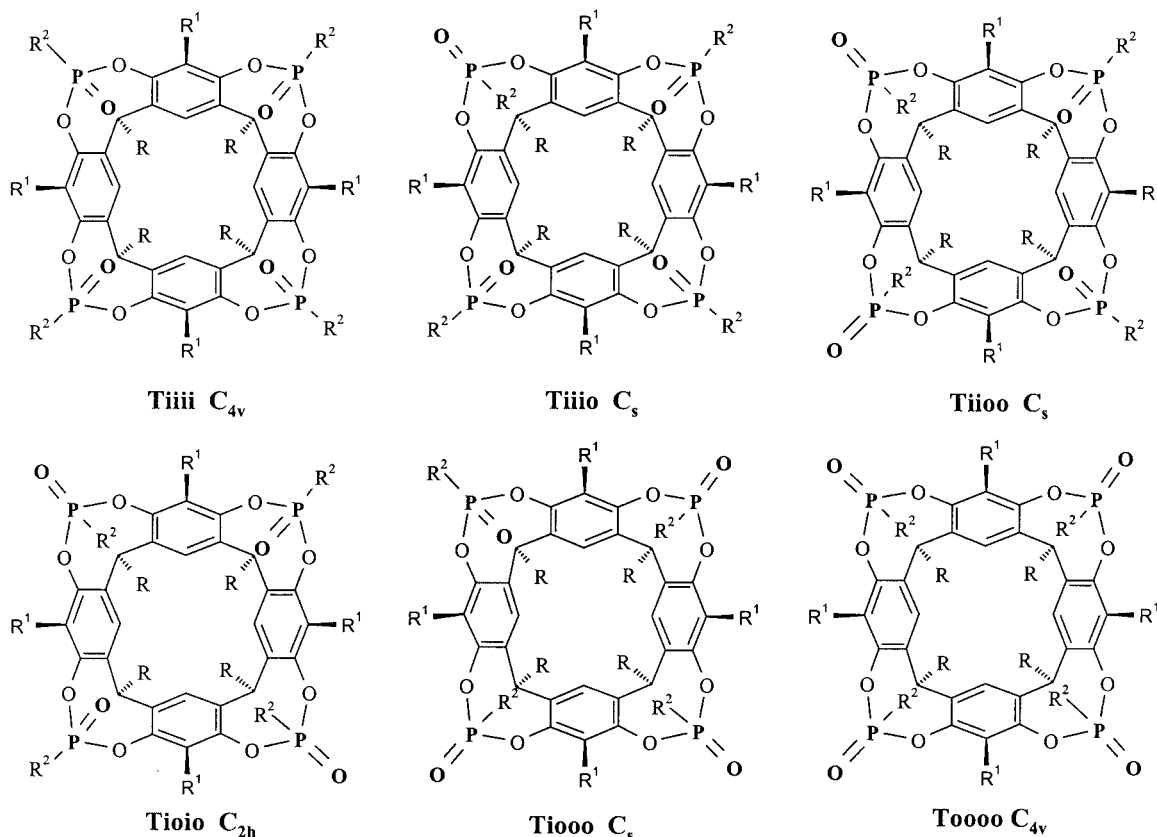
In this microreview we consider a single class of cavitands, the phosphorus-bridged ones, as a case study to pinpoint the main interactions responsible for molecular recognition at the gas-solid interface. The specific interactions operating at each single phase level are analyzed and their potentials for the generation of highly selective mass sensors are explored.

Phosphorus-Bridged Cavitands

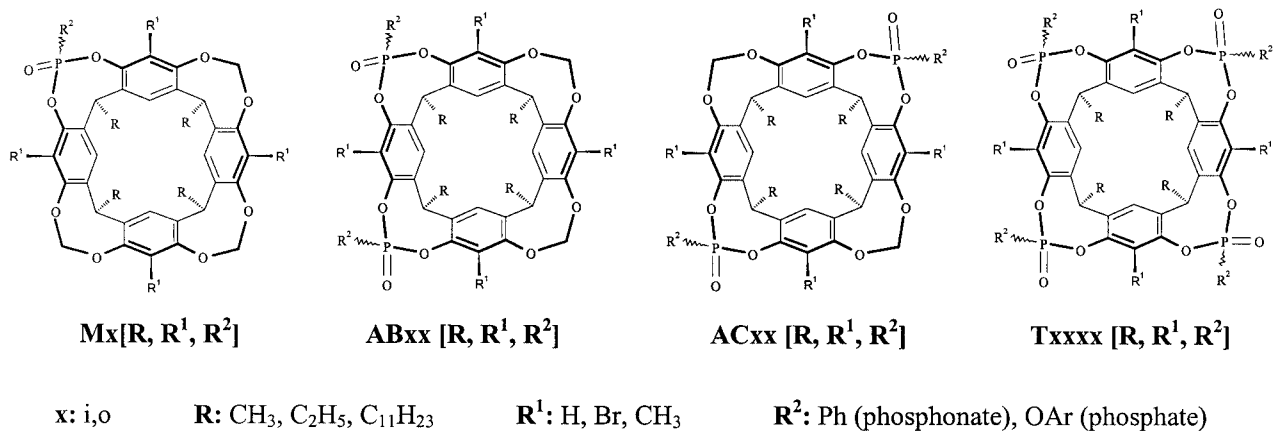
The first attempt to synthesize phosphorus-bridged cavitands was carried out in Cram's lab in the 1980s by treat-

ment of a methyl-“footed” resorcin[4]arene^[14] with dichlorophenylphosphonate.^[15] The complex mixture obtained was not investigated further, due to the difficulties involved in isolating the different diastereomers obtained. In fact, the presence of four P^V stereogenic centers gives rise to six possible diastereomeric cavitands with different orientations of the PO groups, either inward (**i**) or outward (**o**) with respect to the cavity (Scheme 1).^[16] Later on, the topic was investigated by Puddephatt and co-workers, who prepared the **Tiiii**-P^{III} phosphonito cavitand and studied its transition metal complexation properties.^[17] Treatment of a phenethyl-footed resorcin[4]arene with dichlorophenylphosphane results in the selective formation of the **iii** isomer (lone pair directed inward), the favored one as indicated by molecular mechanics calculations.^[17c] The strong tendency toward oxidation of this cavitand in the free ligand form, particularly in solution and in the gas phase, has hampered further studies aimed at assessing its molecular recognition properties toward neutral guests.^[18] From now onward we therefore concentrate on P^V-bridged cavitands.^[19]

Before delving into the subject, it is important to define a clear and exhaustive nomenclature for P^V bridged cavitands. Our proposed nomenclature summarizes the number and relative positions of P^V bridges, their stereochemistry, and the type of substituents at the lower rim, at the apical positions, and on the phosphorus bridges, respectively, in a single term. Scheme 2 reports a survey of all structures discussed in this microreview with their term below. The first, capital letters define the number and positions of



Scheme 1



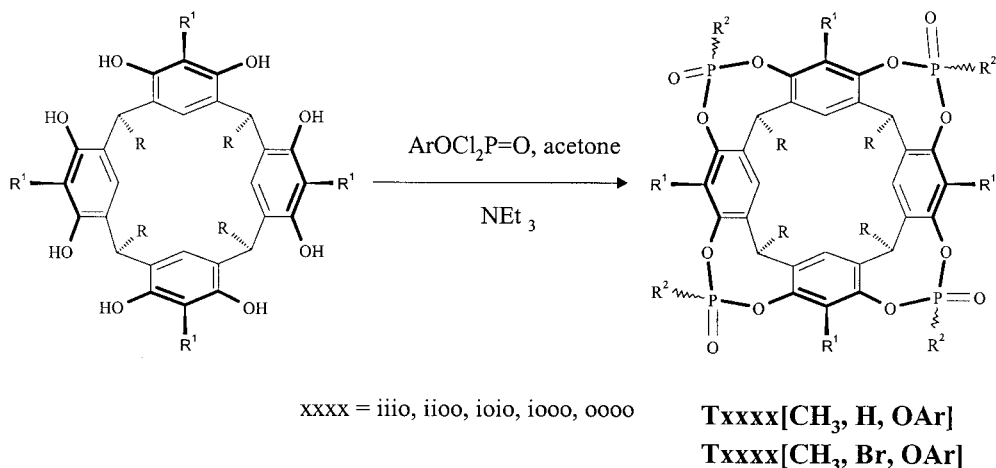
Scheme 2

bridges, the second, lower case letters define the in-out stereochemistry at each P^V center, and R, R¹, and R² in brackets define the substituents at the lower rim, in the apical positions and on the P^V stereocenters, respectively.

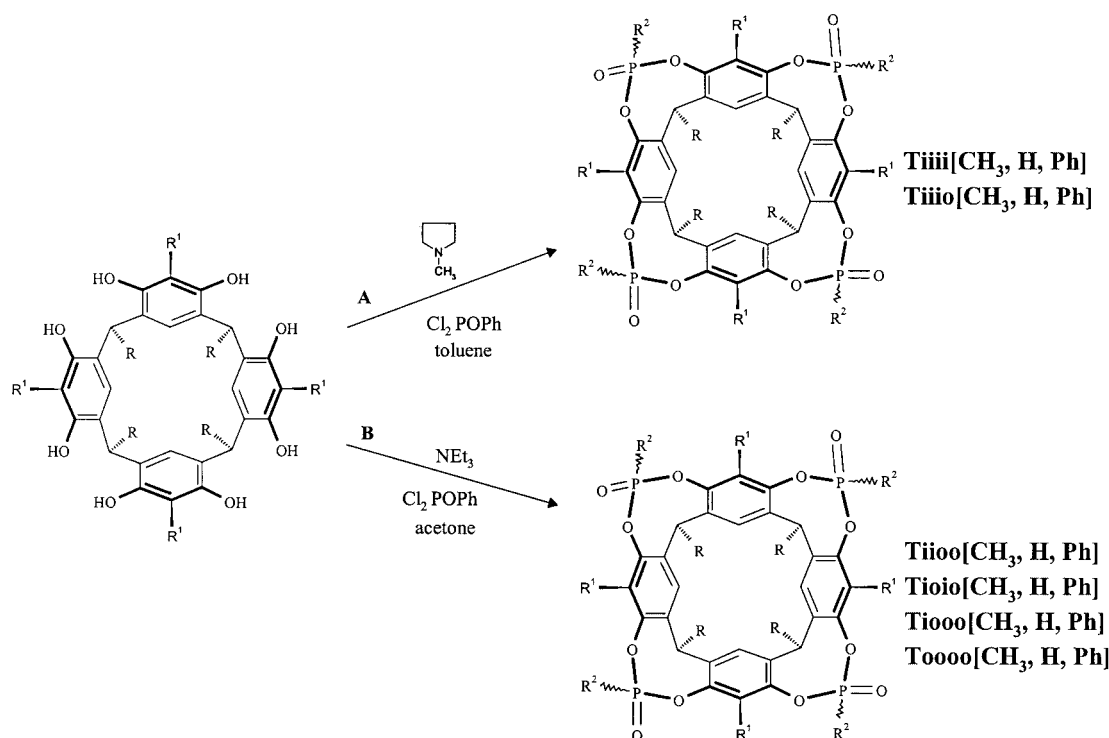
Our studies in the field began with the preparation and isolation of phosphate-bridged cavitands (Scheme 3), using methyl-footed resorcin[4]arenes as molecular platforms.^[20] The reaction, conducted with a series of aryl dichlorophosphates in dry acetone or THF in the presence of an excess of triethylamine as base, resulted in all cases in the formation of five of the six possible diastereomers. The presence of substituents other than hydrogen in the apical positions of the resorcinarene skeleton and of bulky groups on phosphorus did not affect the stereochemical course of the reaction.^[21] The most elusive isomer turned out to be the highly desired **Tiiii** one. The identification of the isomers was achieved by a combination of ¹H, ¹³C, and ³¹P NMR spectroscopy. The number of phosphorus and hydrogen atom resonances reflects the different symmetries of the six diastereomers, and combination of the two allowed the univocal identification of the **Tiioo** (C_s symmetry) and **Tioio** (C_{2v} symmetry) isomers. To distinguish further between the two

remaining pairs of diastereomers (**Tiiii** vs. **Toooo** and **Tiioo** vs. **Tiooo**), chemical shift differences must be considered: the protons directed inward with respect to the cavity experience a strong and diagnostic high-field shift. ¹³C and ¹H NMR relaxation time experiments independently confirmed the attribution.^[21] The crystal structure of **Tioio**[CH₃, H, O^tol] was resolved, confirming the spectroscopic attributions.^[22]

The stereoselective synthesis of the elusive **Tiiii** isomer was achieved by Dutasta and co-workers in the case of phosphonate-bridged cavitands, with only a minor amount of **Tioio** isomer present (Scheme 4A).^[23] The origin of the selectivity has been attributed to the template effect of an ammonium guest formed in situ, which forms a host-guest complex with the resorcin[4]arene, directing the incoming PO groups inward through H-bonding and electrostatic interactions.^[24] The formation of the **Tiiii** isomer is solvent-dependent, since the ammonium ion interaction with the PO groups is effective only in poorly cation-solvating agents such as toluene. Interestingly, the corresponding **Tiiii** tetraphosphate cavitand is not formed under the same experimental conditions.^[25] The **Tiiii** tetrathio phosphonato cavi-



Scheme 3



Scheme 4

tand has also been produced through direct oxidation of the **Tiioi** phosphonito cavitand with sulfur; the reaction proceeds with retention of configuration at phosphorus.^[26]

Dutasta's results prompted us to investigate the formation of phosphonate cavitands under the same reaction conditions as employed in the phosphate case. With the use of dichlorophenylphosphonate as bridging reagent, the **Tiioo**, **Tioio**, **Tiooo**, and **Toooo** isomers were obtained^[27] (Scheme 4 B). No traces of **Tiioi** and **Tiioo** were detected, so the two approaches nicely complement each other. This results clearly indicate that, in the absence of the template, the reaction is biased toward the formation of out isomers. Contrary to expectations, the molecules tend to fill their cavities with more than one phenyl substituent, despite severe steric crowding. Intramolecular edge-to-face aromatic interactions between the electron-rich resorcin[4]arene cavity and the acidic aromatic hydrogens *ortho* to the phosphorus atoms play an important role in favoring the out isomer formation. This assumption is supported by the remarkable upfield shift observed for all the *ortho* hydrogens of the phenyl rings pointing inwards, caused by the ring current shielding of the aromatic cavity. This stereochemical bias is not pronounced in phosphate cavitands because the presence of the oxygen connecting the phosphorus to the phenyl group allows the substituents to assume an upward orientation with respect to the cavity.

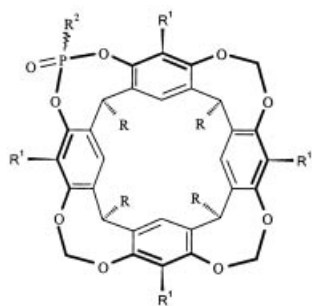
Mixed-Bridged Phosphate and Phosphonate Cavitands

Up to now, most research in the field has focused on the preparation of quadruply phosphorus-bridged cavitands,

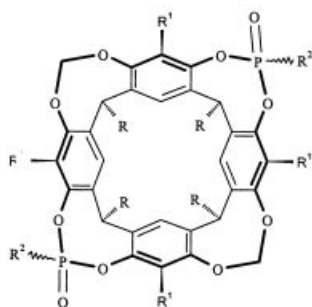
neglecting the synthetically more demanding mixed-bridged analogues. From the point of view of molecular recognition, however, mixed-bridged cavitands are attractive because of the presence of different functionalities in well defined spatial orientations on the rim of a cavity. The availability of partially bridged resorcin[4]arenes with two and three methylene bridges^[28] has resulted in the preparation of **M**-mono, **AB**-di-bridged, and **AC**-di-bridged phosphorus cavitands.^[29] In the case of phosphates, the mono (**Mi**, **Mo**) and **AC**-di-bridged cavitands (**ACii**, **ACio**, **ACoo**) were produced by the typical triethylamine/acetone procedure,^[22] with a statistical distribution of the various isomers (Scheme 5). In the case of phosphonates, all possible isomers were prepared (Scheme 6),^[30] although the **ABii** and **ACii** isomers were obtained only by use of Dutasta's procedure. The stereochemical bias toward out isomers discussed above is already evident in mono- and disubstituted phosphonate-bridged cavitands. The stereochemical outcome of the bridging reaction can be reversed only in the presence of a suitable template/solvent pair.

Complexation Properties

The complexation properties of phosphorus-bridged cavitands relevant to gas sensing cannot be inferred from the usual solution titration experiments, since solvents compete with neutral guests for binding site occupancy. The binding affinities of **Tiioi**[CH₂CH₂Ph, H, Ph] toward alkali metal cations and ammonium cations in solution are indeed very high^[24a] and they decrease, as would be expected, on going



Mx [CH₃, Br, OTol]
x: i, o



ACxx [CH₃, Br, OTol]
xx: ii, io, oo

Scheme 5

to **Tiio**[CH₃, H, OTol] (Tol = *p*-tolyl), to become negligible for **Tiioo**[CH₃, H, OTol].^[21] A more appropriate and convenient way to explore the binding preferences of these receptors in terms of gas-solid interactions is the combined use of mass spectrometry and X-ray crystallography, which provide information about gas-phase and solid-state interaction modes, respectively.

Mass spectrometry offers the opportunity to study host-guest chemistry as a purely bimolecular interaction in the absence of solvents and other interfering species.^[31] Two different techniques were employed to study the interac-

tions between cavitands and the following guests: (i) charged guests by use of liquid secondary-ion mass spectrometry (LSI-MS), and (ii) neutral guests by electrospray ionization mass spectrometry (ESI-MS). The first approach has been implemented to test the affinity of phosphate and mixed-bridged phosphate cavitands (compounds **Txxx**[CH₃, Br, OTol], **ACxx**[CH₃, Br, OTol], **Mx**[CH₃, H, OTol], all stereoisomers except **Tiio**) toward alkyl- and arylammonium cations.^[32] The results can be summarized as follows:

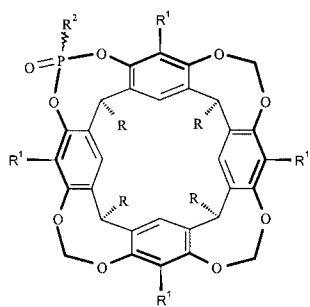
(i) the binding properties of the cavitands can be almost entirely attributed to H-bonding interactions between the PO units and alkyl- and arylammonium cations,

(ii) the interaction strength depends on the number and pattern of cooperative H-bonds that the two counterparts can establish, and

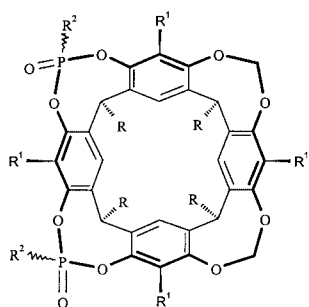
(iii) the interaction strength is also directly correlated with the proton affinity of the two interacting species (the cavitand and the conjugated amine of ammonium ions).

From the cavitand side, the affinity toward a given ammonium ion decreases in the order **Tiio** >> **Tiioo** > **Tioio** > **Tiooo** > **Toooo**; **Acii** > **Acio** ≈ **Acoo** >> **Mi** ≈ **Mo**. From the ammonium side it depends on the number of NHs available for H-bonding: methylammonium > dimethylammonium >> trimethylammonium.

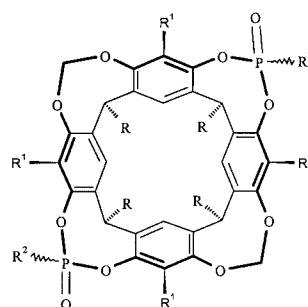
The second approach, relevant to gas sensing properties, has been directed towards sampling of the interactions between diastereomeric phosphate cavitands **Txxx**[CH₃, H, OTol] and neutral guests such as methanol and propylamine.^[33] In the case of methanol, only the complexes with **Tiio**, **Tiioo**, and **Tioio** isomers were detected, while for **Tiooo** and **Toooo** isomers, only the [MH]⁺ signals were present in the spectrum. The [M + H + CH₃OH]⁺ ions' relative abundances in the ESI spectra follow the trend **Tiio** > **Tiioo** >> **Tioio**. The cavitand-propylamine complex ion was formed for all isomers, but its abundance decreased continuously as more PO groups were oriented outside the cavity (Table 1). The overall set of results obtained shows that the synergistic behavior of an increasing number of convergent PO groups drastically enhances the complexation of neutral H-bond donor guests.



Mx [C₁₁H₂₃, H, Ph]
x: i, o



ABxx [C₁₁H₂₃, H, Ph]
xx: ii, io, oo



ACxx [C₁₁H₂₃, H, Ph]
xx: ii, io, oo

Scheme 6

Table 1. $[M + H + C_3H_7NH_2]^+ / [M + H]^+$ ratios observed in the ESI spectra obtained by mixing equimolar amount of cavitands and propylamine in solution

Cavitand	$[M + H + C_3H_7NH_2]^+ / [M + H]^+$ ^[a]
Tiio	∞ ^[b]
Tiioo [CH ₃ , H, OTol]	1.37
Tioio [CH ₃ , H, OTol]	0.18
Tiooo [CH ₃ , H, OTol]	0.11
Toooo [CH ₃ , H, OTol]	0.09

^[a] Other ions were neglected. ^[b] Only the $[M + H + C_3H_7NH_2]^+$ was observed.

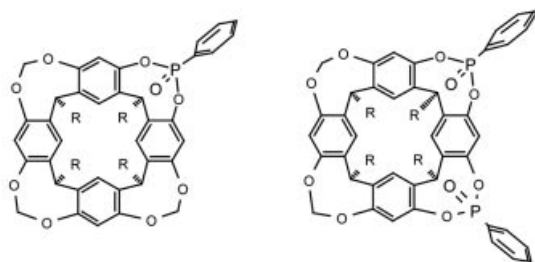
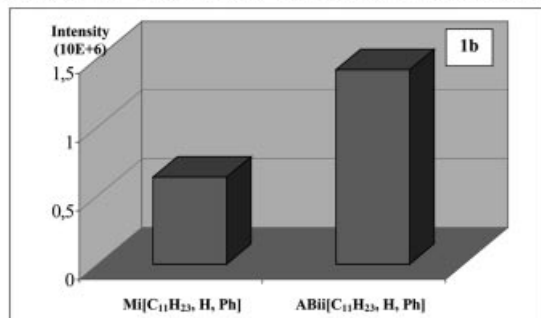
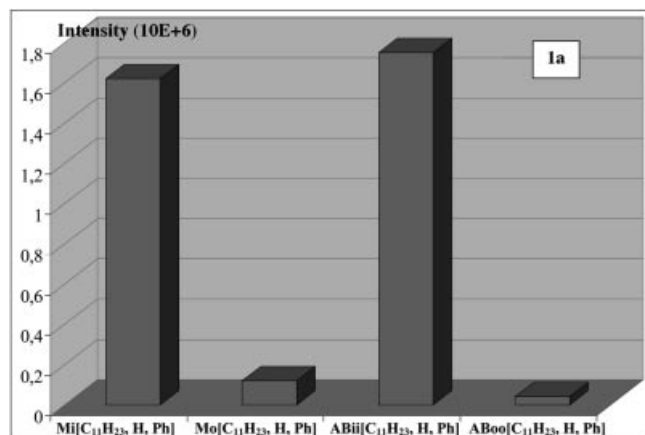


Figure 1. a) Intensities of the ethanol complexes recorded in ESI-MS experiments: **Mx** and **ABxx** phosphonate cavitands were separately dissolved (each at a final concentration of 2 μ M) in ethanol containing 1 % TFA; b) Relative affinities of the ethanol complexes recorded in ESI-MS competition experiments: **Mi** and **ABii** phosphonate cavitands were dissolved together (each at a final concentration of 2 μ M) in ethanol containing 1 % TFA

More recently, the ESI-MS study with alcohols was extended to di- and monosubstituted phosphonate cavitands **ABxx**[C₁₁H₂₃, H, Ph] and **Mx**[C₁₁H₂₃, H, Ph] (Scheme 5).^[34] The relative affinities of four of them

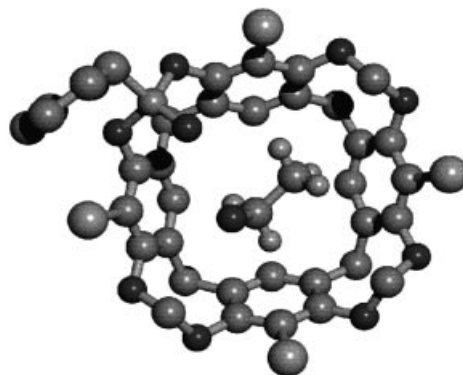
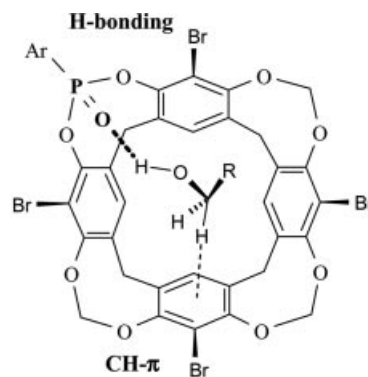


Figure 2. Crystal structure of the **Mi**[C₁₁H₂₃, Br, OPh]·EtOH complex; the cooperative CH- π and H-bonding interactions are illustrated in the drawing on top

towards ethanol are shown graphically in Figure 1 (a). The outward orientation of the phenyl groups on phosphorus is pivotal for guest inclusion in phosphonate cavitands: the presence of a single phenyl group filling the cavity is sufficient to switch off complexation. In fact, only **ABii** and **Mi** emerged as suitable receptors for alcohols in the gas phase. The relative affinity of **ABii** and **Mi** toward ethanol was assessed by competition experiments, through dissolution of equimolar amounts of the two cavitands in acetonitrile/ethanol solution. The $[ABii + EtOH + H]^+$ ion was the prominent one in the resulting ESI-MS spectrum (Figure 1, b), indicating that the presence of a second inward-facing PO reinforces complexation.

The molecular interactions responsible for alcohol complexation in phosphorus-bridged cavitands have been identified in the crystal structures of the **Mi**[C₁₁H₂₃, Br, OPh]·EtOH^[35] (Figure 2) and **ABii**[C₂H₅, H, Ph]·MeOH^[30] (Figure 3) complexes. In each complex, the guest is anchored to the host through a H-bond to one PO moiety and through a CH- π interaction with one aromatic ring of the resorcin[4]arene skeleton. The synergy of the two interactions, possible only in the PO_{in} isomers, makes the all-in cavitands selective toward linear alcohols. Moreover, in the case of **ABii**·MeOH, methanol is equally distributed over two different orientations related to each other by a mirror plane. The guest can thus be regarded as a pendulum, with the fulcrum on the barycenter of the benzene involved in the CH- π interaction, free to switch the MeOH...O=P H-bond between the two mirror-related PO groups. The re-

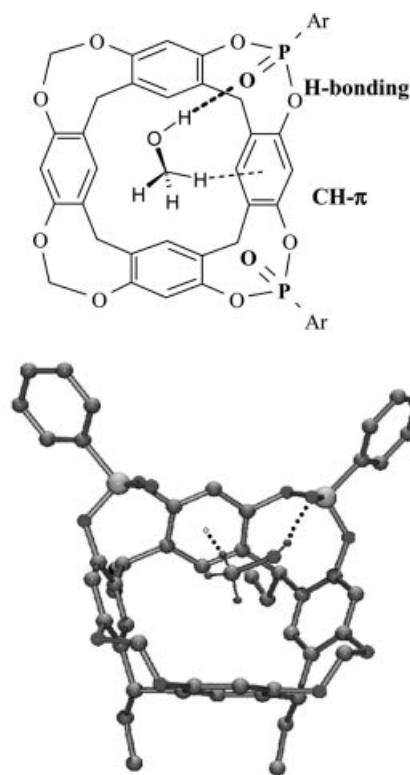


Figure 3. Crystal structure of the $\text{ABii}[\text{C}_2\text{H}_5, \text{H}, \text{Ph}]\cdot\text{MeOH}$ complex; the cooperative $\text{CH}-\pi$ and H -bonding interactions are illustrated in the drawing on top

sulting picture indicates that the second converging PO group does not act cooperatively as a third interaction site, forming a three-center H-bond with the OH of the analytes, but offers a second, energetically and geometrically equivalent, interaction mode to the guest, increasing the entropy of the complex.

The crystal structure evidence of selective interactions between partially bridged cavitands and alcohols nicely complements the gas-phase ones: the role of $\text{CH}-\pi$ interactions stems mainly from solid-state analyses, while the importance of having multiple equivalent H-bonding options for the guest is underlined by ESI-MS experiments.

Cavitand-Based Mass Sensors

The driving force behind the development of sensor technology is the need for accurate real-time analyses. There is an increasing demand for chemical sensors in the fields of environmental analysis, industrial process control, and workplace monitoring. Chemical sensing is part of an acquisition process in which some information on the chemical composition of a system is obtained in real time. In this process an amplified electric signal is produced through the presence of some chemical species. The acquisition process consists of two distinct steps: Recognition and amplification. The recognition is supplied by a material capable of interacting with the desired analyte, while the amplification is provided by a transducer on which the material is coated.

The most commonly used transducers are electrochemical, optical, and piezoelectric. The quartz crystal microbalance (QCM) piezoelectric operating mode is based on interactions between analytes and thin organic layers coated on the surface of a quartz crystal. The resulting mass changes (Δm) on the sensor surface produce variation in the fundamental resonance frequency (f_0) of the oscillating quartz disc, according to the Sauerbrey equation (Figure 4).^[36] In order to obtain selective responses the coating of the quartz must be stable, sensitive, and capable of specific interactions with the desired analyte. Another essential feature is reversibility of the responses, which requires recourse to weak interactions, since the formation of covalent or ionic bonds would result in irreversible saturation of the layer.^[37]

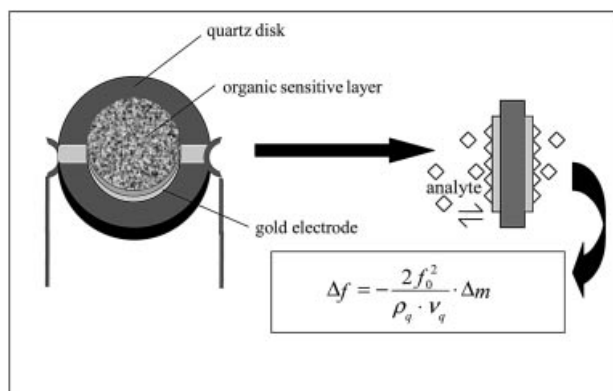


Figure 4. QCM operating mode: the interaction of the cavitand receptor with the analyte determines a frequency shift according to the Sauerbrey equation

One of the key issues in the development of new, efficient chemical sensors is the quest for selectivity. Advances in supramolecular chemistry offer many opportunities to design and prepare molecules endowed with superior molecular recognition properties to be used in chemical sensors.^[38] Previous work from our laboratory has shown that the use of cavitands as chemically sensitive layers provides selective QCM sensors only if specific interactions, such as $\text{CH}-\pi$ interactions, are present between the preorganized cavity of the receptor and the analyte.^[39,8d] These interactions perturb the selectivity pattern expected on the basis of pure dispersion interactions between the analyte and the cavitand layer by adding their contribution to the sensor response. $\text{CH}-\pi$ interactions alone, however, provide significant specificity only in the presence of analytes possessing fairly acidic methyl groups, such as acetonitrile or nitromethane.

To achieve high selectivity for a single class of analytes we introduced a single PO group at the upper rim of methylene-bridged cavitands. The resulting monophosphate/phosphonate cavitands are capable of two synergistic interactions with the chosen analyte, namely H-bonding with the PO group and $\text{CH}-\pi$ interactions with the π -basic cavity. Their performances have been studied by coating of these receptors on QCM transducers and by measurement

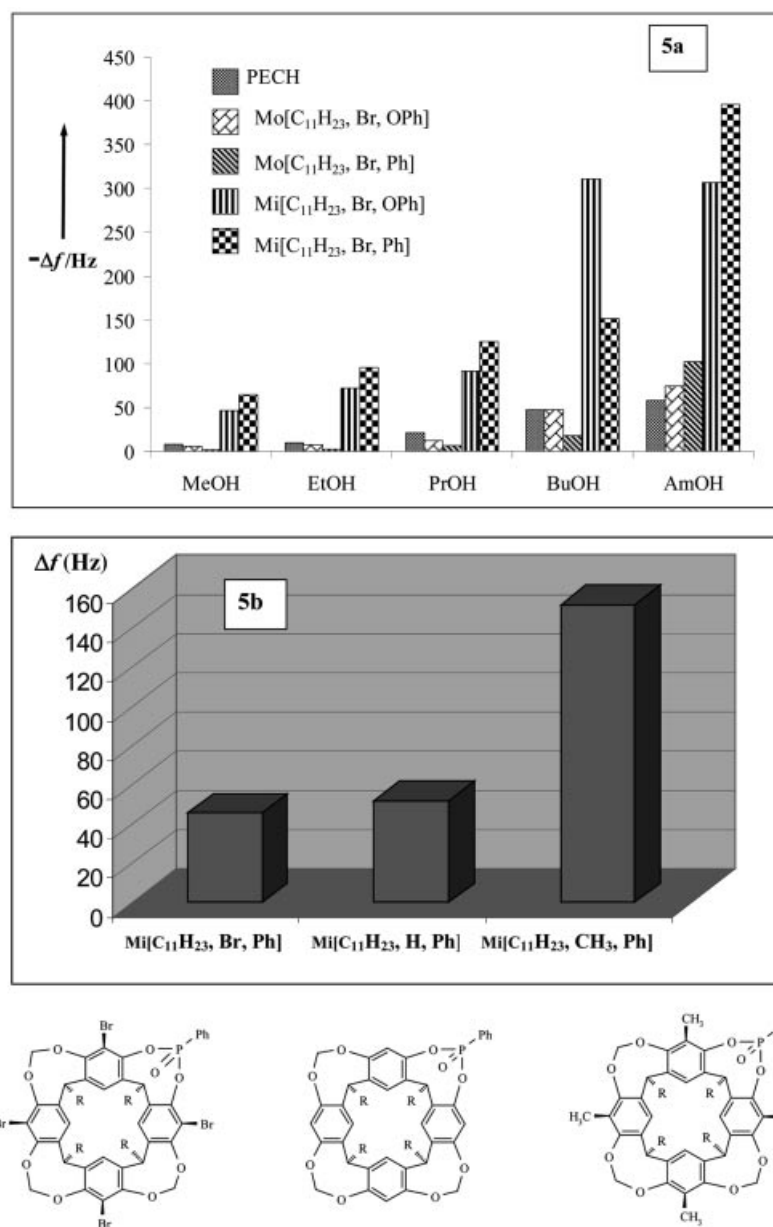


Figure 5. a) Selectivity patterns of PECH, M_x -phosphate, and M_x -phosphonate cavitands toward C_1 – C_5 linear alcohols; responses to 3000 ppm of each analyte at 293 K; each bar represents the mean value of four responses with variations of less than 5% between each one; b) Modulation of the cavity CH- π interactions: QCM responses of Mi -phosphonate cavitands with Br, H and CH_3 as apical substituents toward 1500 ppm of ethanol

of their responses towards alcohols and other analytes.^[35] Figure 5 (a) reports the responses of cavitands $Mi[C_{11}H_{23}, Br, OPh]$, $Mo[C_{11}H_{23}, Br, OPh]$, $Mi[C_{11}H_{23}, Br, Ph]$, $Mo[C_{11}H_{23}, Br, Ph]$, and $Mi[C_{11}H_{23}, CH_3, Ph]$ toward C_1 – C_5 linear alcohols relative to those of PECH (polyepichlorohydrin) a typical polymeric coating used in mass sensors. Both interactions can be fine-tuned by changing the R^1 and R^2 groups in the cavitand framework. Replacement of the four Br substituents with CH_3 groups at the upper rim enhances the π -basic character of the cavity, boosting CH- π interactions (Figure 5, b). The better H-bonding acceptor capability of phosphonates with respect to phosphates is reflected in the larger responses of $Mi[C_{11}H_{23}, Br, Ph]$ rela-

tive to $Mi[C_{11}H_{23}, Br, OPh]$, with the exception of *n*-butanol (Figure 5, a).

A general enhancement of the responses of all receptors is associated with increasing number of carbon atoms in the alcohol series. This behavior is due to the increased number of purely dispersive interactions, directly related to chain length,^[40] and not to any strengthening of the specific CH- π and H-bonding interactions, which should be comparable for each alcohol in the series. Since QCM transducers measure analyte adsorption across the entire layer, a good layer permeability is essential to achieve reversibility (i.e., reasonably fast adsorption/desorption times). Permeability is strongly dependent on the morphology of the deposited

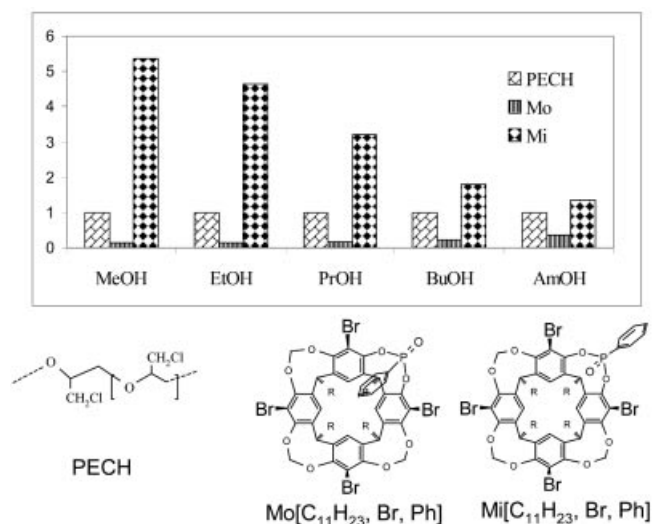


Figure 6. Progressive reduction of the specific responses due to dispersion interactions: selectivity patterns of **Mi** and **Mo** phosphonate cavitands toward C_1 – C_5 linear alcohols (3000 ppm), normalized to those of **PECH**

layer: analyte diffusion is highly enhanced in amorphous layers with respect to microcrystalline ones. In our case, the necessity to ensure suitable permeability of the cavitand layer required the introduction of four long alkyl chains at the lower rim. As drawback, these cause a consistent reduction of selectivity toward long-chain alcohols by in-

creasing the significance of dispersion interaction in the overall response, as evident in Figure 6, in which the responses are normalized to the **PECH** ones for each analyte. These interactions tend to dilute the specific molecular recognition effect.

Unfortunately, mass transduction is absolutely un-specific, since it does not make any difference whether the interaction takes place in the molecular recognition site or elsewhere in the molecule. Indeed, the mere presence of a preorganized cavity in the receptor does not guarantee selectivity in gas sensing,^[41] since on transfer from the gas phase to the condensed phase the analyte experiences a net gain in dispersion interactions, which often override weak host–guest interactions.^[42] In order to establish that the selective responses of our sensors originate from intracavity complexation, we undertook a detailed analysis of the molecular recognition phenomenon in gas sensing based on the adsorption isotherms of the cavitands towards different analytes.^[43] Langmuir-type isotherms are observed only for the PO_{in} isomers **Mi**[$C_{11}H_{23}$, **Br**, **Ph**] and **Mi**[$C_{11}H_{23}$, **Br**, **OTol**] exposed to alcohols (Figure 7), while the other three cavitand coatings show linear responses under the same conditions. The exponential trend at low vapor concentrations is the result of an effective complexation between the analyte and the cavitand receptor. Once the receptor layer tends towards saturation, the isotherm flattens, assuming a linear course. Moreover, the better H-bond acceptor capability of phosphonate versus phosphates is re-

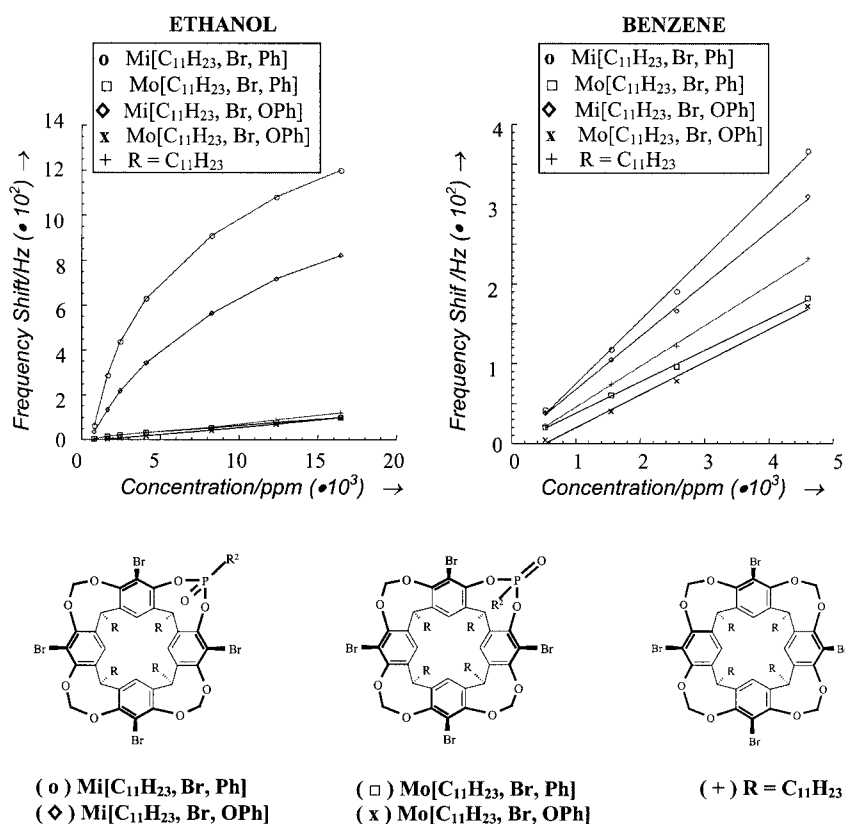


Figure 7. Adsorption isotherms of **Mx**-phosphate and **Mx**-phosphonate cavitands exposed to ethanol and benzene vapors (note the different scale of the y-axis)

flected in the greater responses of **Mi**[**C**₁₁**H**₂₃, **Br**, **Ph**] than of **Mi**[**C**₁₁**H**₂₃, **Br**, **OTol**], as already shown above. In the cases of benzene (Figure 7) and pentane (not shown), analytes incapable of H-bonding interactions, all sensors respond in a linear fashion. The overall trend can be interpreted by assuming a dual mode interaction: the energetically more favorable cavity binding dominates at low analyte concentration, whereas non-specific extracavity absorption is preponderant at high analyte concentration. As a consequence, when the exponential trend is absent, the molecular recognition events are either absent or negligible.

At this point it is worth considering why the H-bonding ability of **PO**_{out} in **Mo**[**C**₁₁**H**₂₃, **Br**, **Ph**] and **Mo**[**C**₁₁**H**₂₃, **Br**, **OTol**] is totally ineffective in alcohol detection. A possible explanation may be related to the different environments experienced by the **PO**_{in}/**PO**_{out} groups. For the **PO**_{in} isomers **Mi**[**C**₁₁**H**₂₃, **Br**, **Ph**] and **Mi**[**C**₁₁**H**₂₃, **Br**, **OTol**], the presence of a rigid, preorganized cavity embracing the **PO** group eliminates the need to generate a void in the lattice for the incoming analyte. The **PO** groups in **Mo**[**C**₁₁**H**₂₃, **Br**, **Ph**] and **Mo**[**C**₁₁**H**₂₃, **Br**, **OTol**], on the other hand, are on the exterior surfaces of the receptors, in close contact with other molecules. The analyte must carve out a space to H-bond with the **PO**_{out}, which is energetically demanding.^[42] We therefore propose that the role played by the cavity is twofold: (i) it complexes the analyte through **CH**- π interactions, and (ii) it generates a permanent free volume^[44] in the **PO**_{in} neighbor, which facilitates H-bonding.

Since the presence of multiple interaction points positioned in a single cavity turned out to be the key element in achieving high selectivity, the next step was study of the sensing properties of cavitands possessing three interaction sites: **AB**- and **AC**-diphosphonate cavitands. All six possible configurational isomers were prepared and tested (Scheme 6) together with the corresponding monophosphonate cavitands and **PECH**, for a meaningful comparison.^[30] Figure 8 (a) reports the selectivity patterns towards methanol of a series of phosphonate cavitand layers. The observed responses follow the order **Tiiii** > **ACii** \approx **ABii** > **Mi** > **ABio** > **Mo** \approx **ABoo** \approx **PECH**. The introduction of a second **PO** group in the inward configuration produces relevant improvements both in selectivity and in sensitivity with respect to the **Mi** counterpart. The relative positions of the two **PO** groups (**ACii** vs. **ABii**) are 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 8 (b) shows the responses of **ABii** and **Mi** to linear **C**₁-**C**₅ alcohols. The responses have been normalized to those of **PECH** to show the progressive dilution of the specific responses with increasing analyte chain length. In spite of 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 (Fig-

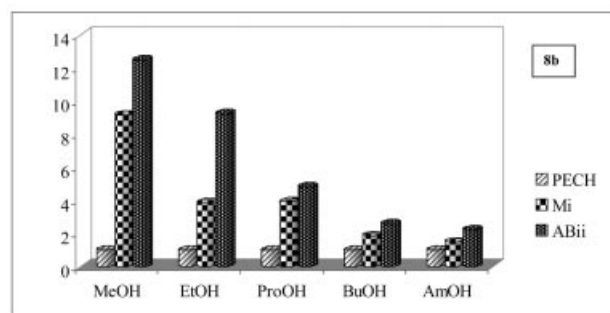
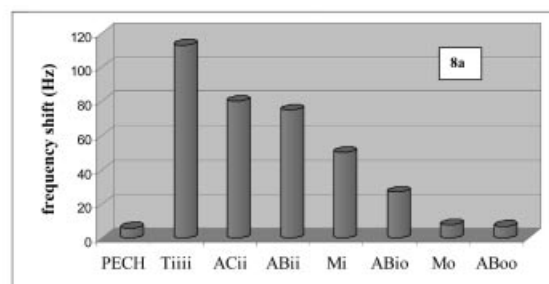


Figure 8. a) Selectivity patterns of a series of phosphonate cavitand layers toward methanol (1500 ppm); b) Selectivity gain with increasing number of inward facing **PO** groups along the **C**₁-**C**₅ alcohols series (1500 ppm each); data normalized to **PECH** responses

ure 9). These results are nicely supported by the ESI-MS gas-phase experiments discussed above. At the molecular level, the **ABii**[**C**₂**H**₅, **H**, **Ph**]**MeOH** crystal structure (Figure 3) supports the view that a viable strategy to increase selectivity in supramolecular mass sensors relies on increasing the number of binding options available to the analyte in a single receptor, rather than on strengthening a single binding through multiple interactions.

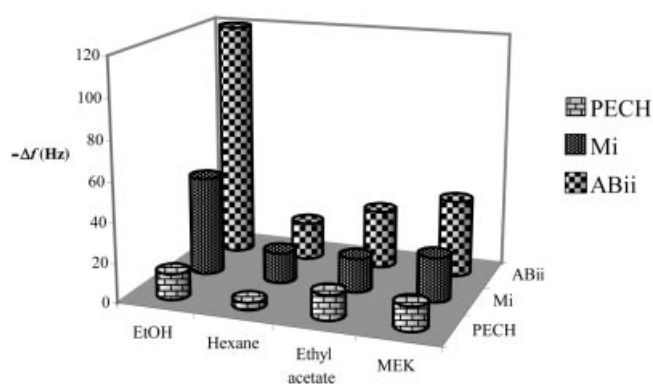


Figure 9. Selectivity patterns of **Mi** and **ABii** phosphonate cavitands toward representatives of different classes of analytes (responses at 1500 ppm each)

This last hypothesis has very recently been tested in our laboratory with tetraphosphonate cavitand **Tiiii**[**C**₁₁**H**₂₃, **H**, **Ph**] as receptor layer. The rationale behind the choice of this receptor is as follows: The presence of four inward-facing **PO** groups should give an incoming alcohol four en-

energetically and geometrically equivalent binding options embedded in a rigid cavity, which provides the free volume for the incoming analyte. The selectivity pattern towards alcohols, shown in Figure 8 (a), nicely supports our previsions, making our model consistent and predictive.^[45] The **Ti**iii[C₁₁H₂₃, H, Ph]-coated QCM is the highest selective mass sensor for alcohols reported so far.

Summary and Outlook

The rich chemistry of phosphorus(v)-bridged cavitands has been reviewed, from synthesis and stereochemistry to complexation properties and sensors applications. In particular, the challenges encountered in turning cavitands into selective layers for mass sensors have been outlined. The key factors affecting the sensing performances of phosphorus-bridged cavitands toward alcohols are:

(i) the simultaneous presence of H-bonding with one of the PO groups and CH- π interactions with the π -basic cavity,

(ii) a rigid cavity to provide a permanent free volume for the analyte around the inward-facing PO groups, pivotal for effective H-bonding, and

(iii) a network of energetically equivalent H-bonding options available to the analyte.

The combined use of MS and crystallographic analyses allows the molecular recognition properties of cavitands at the gas-solid interface to be anticipated. In the real device, however, the major challenge is the fine-tuning of the selectivity-reversibility balance at the gas-solid interface. Fast and reversible responses, essential in gas sensing, require high layer permeability to the analytes. The peripheral alkyl chains, necessary to give highly permeable thin films, attenuate selectivity by enhancing non-specific dispersion interactions, particularly for long chain alcohols.

Two major alternatives to solve the general problem of minimization of undesired dispersion interactions between analytes and sensing materials can be envisioned: (i) elimination of the need for peripheral alkyl chains by recourse to nanoporous materials containing appropriate receptor sites,^[46] and (ii) use of an inherently selective transduction mechanism (i.e. fluorescence, surface plasmon resonance). Alternatively, a different approach can be followed, relying on “differential” binding (i.e., receptors presenting affinity for more than a single analyte).^[47] The use of arrays of differential receptors, coupled with pattern recognition protocols, allows multi-analyte sensing in complex mixtures. Cavitand layers capable of selective detection of classes of substances (alcohols, acetates,^[48] etc.) are promising candidates for such applications.

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