Molecular recognition at the gas–solid interface: a powerful tool for chemical sensing

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This *tutorial review* deals with the design of molecular receptors capable of molecular recognition at the gas–solid interface, to be used as selective layers in gas sensors. The key issue of specific *versus* nonspecific binding in the solid layer is discussed in terms of cavity inclusion and layer morphology. The combined use of mass spectrometry and crystal structure analysis provide accurate information on type, number, geometry and strength of receptor–analyte interactions in the gas phase and in the solid state. From these data, the gas sensing properties of a given receptor toward a single class of analytes can be anticipated.

Introduction

Nature has provided many examples of exquisitely specific binding interactions like enzyme–substrate, antigen–antibody and complementary DNA annealing. To achieve this specificity, biological systems exploit molecular recognition between two species that complement one another in size, shape and functionality. In the last three decades these so called "lock and key" interactions, have been widely exploited by supramolecular chemists for the design and synthesis of molecular receptors which are useful to understand and mimic nature's specific interactions. As for biological systems, the concepts of shape recognition and binding site complementarity are central for effective molecular recognition in artificial host–guest systems. This selectivity mechanism is particularly useful in the development of chemical sensors, where the recognition process can be translated into an analytical signal. The vast majority of chemical sensors contain a chemically sensitive layer for analyte detection coupled with a transducer which transforms this interaction into a readable signal (Fig. 1). All chemical receptors for gas and vapour sensing are used in the solid state, either in the form of organized films or amorphous layers. The lock and key approach, so successful in the liquid phase, cannot be automatically transferred to vapour and gas sensing due to two major hurdles: (i) in moving from the vapour to the condensed phase the analyte experiences a dramatic increase in nonspecific dispersion interactions, negligible in liquid to solid transfer;[1] (ii) the entropic cost for binding to the receptor is not alleviated by solvent release in the bulk liquid phase.[2]

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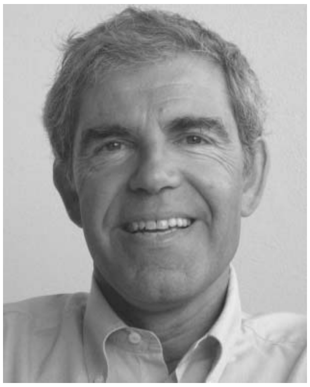

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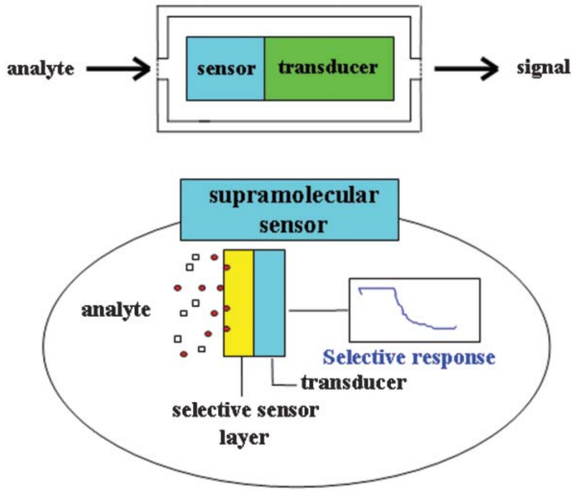


Fig. 1 Working principle of supramolecular sensors.

For these reasons achieving effective molecular recognition at the gas–solid interface is a demanding task, which requires a fresh approach, both in terms of receptor design and characterization tools. Another essential feature is the reversibility of the responses, which requires recourse to weak interactions, since the formation of covalent or ionic bonds would result in an irreversible saturation of the layer.[3]

Cavitands, together with cyclodextrins and calixarenes, are the most studied receptors for gas/vapour sensing. Cavitands[4] and calixarenes[5] are particularly appealing due to their outstanding host–guest properties, tunable for the recognition of different classes of analytes.

The aim of the present tutorial review is to provide a few general rules to design selective receptors for gas and vapour sensing, maximizing specific *versus* nonspecific interactions at the gas–solid interface.

Overview of the transducers used in supramolecular gas sensing

Acoustic wave (AW) transducers are the workhorse of supramolecular sensors for gases, because they do not require receptor derivatization for their operation modes, like fluorescent probes for optical sensing. They measure the mass uptake of a sensing layer when exposed to vapours. Usually AW sensors consist of a piezoelectric quartz crystal with electrodes affixed to each side of the plate. When an oscillating potential is applied at a frequency near the resonant frequency of the piezoelectric crystal, a stable oscillating circuit is formed. The key feature of AW sensors is that the frequency and the amplitude of the acoustic wave is affected by a mass change of the system. The Sauerbrey equation [eqn. (1)] describes the resonant frequency shift of an acoustic resonator upon mass increase on its surface.[2]

$$\Delta f = -2 f_0^2 \Delta m A^{-1} \sqrt{c/\rho} \qquad (1)$$

In the equation f_0 (Hz) is the fundamental frequency of the quartz crystal, Δf (Hz) is the frequency shift proportional to the deposited mass Δm (g), A (m^2) is the area of quartz plate or electrode surface, c ($s^2 m\ g^{-1}$) is the elastic coefficient of the system and ρ ($g\ m^{-3}$) represents the crystal density. The more widely applied mass sensors based on this principle are quartz crystal microbalance (QCM) and surface acoustic wave (SAW) resonators (Fig. 2). In the former one, the acoustic wave propagates through the bulk of the system in a direction normal to the surface. Therefore thickness and permeability of the layer are critical features. The acoustic wave produces surface particle displacements that are parallel to the surface. In the SAW device, motion occurs only at the surface, penetrating to a depth of approximately one acoustic wavelength into the crystal; here the direction of propagation is parallel to the surface itself. The waves generated are Rayleigh waves. These have one particle displacement component that is normal to the surface, in contrast with QCM devices. Since in SAW resonators the acoustic energy is trapped near the surface, they are potentially much more sensitive than bulk wave devices, for the same receptor layers.[6,7] On the other hand the influence of small temperature fluctuations and mechanical stresses is higher, and therefore their handling and interpretation of experimental results is not as straightforward as in the case of QCM. In polymer coatings for instance, all volume changes of the layer associated either to vapour sorption (swelling) or thermal expansion perturb the viscoelastic properties of the coating and this significantly contributes to the observed response.

By integrating an AW measurement platform with a selective sensing layer, a chemical sensor is constructed, in which molecular recognition events are converted into an

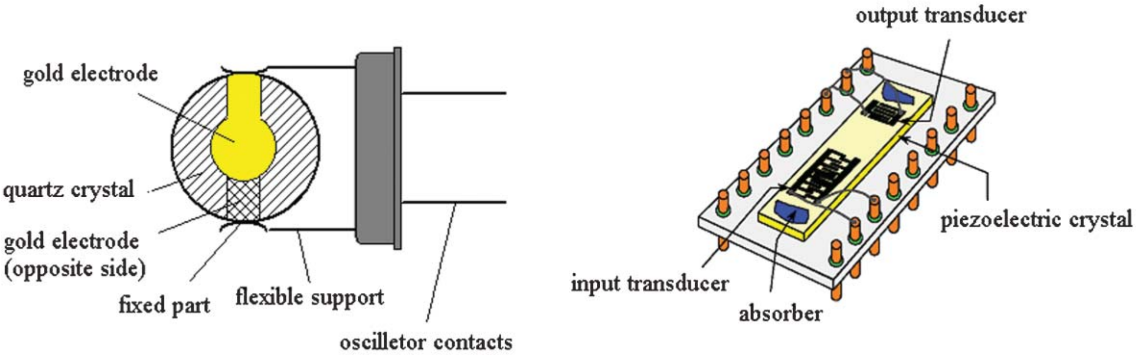


Fig. 2 QCM (left) and SAW (right) transducers.

electric signal. An important feature of AW sensors is that mass transduction disregards the electronic properties of the sensing layer since the electric read-out does not rely on the conductivity of the organic material but only on the frequency shift of the piezoelectric crystal. This allows the limitation due to the restricted number of conductive organic materials to be overcome, making it possible to exploit each molecule endowed with molecular recognition as sensing material.

Recently optical sensing techniques based on the phenomenon of surface plasmon resonance (SPR) have received considerable attention as a transduction scheme for the detection of organic vapour at low level concentration.[8] These optical systems can provide a safe, remote, non-destructive means of sensing and have already been used for gas sensing, biosensing, immuno-sensing and electrochemical studies. In the Kretschmann configuration shown in Fig. 3 a sensing layer is deposited on one side of a gold film which is 40–50 nm thick and a prism is placed on the other side. The gold surface is illuminated from the prism side with monochromatic light and the reflection intensity is measured as a function of the incidence angle. Surface plasmon resonance is a strong coupling phenomenon between the light and plasmon waves formed by free electrons on the gold surface and it results in a loss of energy and therefore a reduction in the intensity of the reflected light which is measured by a CCD chip. An evanescent electrical field associated with the plasma wave travels for a short distance ($\sim$300 nm) into the medium from the metallic film. Consequently the SP (surface plasmon) is sensitive to changes in the environment near the interface. Hence, when a sensing layer of receptors deposited on the gold film is exposed to a gaseous analyte in a flow cell (Fig. 3), the molecular recognition process induces a change in the refractive index providing a selective signal for the receptor–analyte interaction.

Issues related to vapor sensing with molecular receptors

The sorption behaviour of an amorphous sorbent layer towards different analytes can be inferred using the linear sorption energy relationship equation [eqn (2)] (LSER).[9] According to this model and under the hypothesis of weak non-covalent interactions, the logarithm of the coefficient partition of a sorbent layer with respect to a given volatile species is the linear combination of five terms expressing the intensity of five basic interaction mechanisms: polarizability, dipolarity, H-bond acidity and basicity and the solubility term related to dispersion interactions.

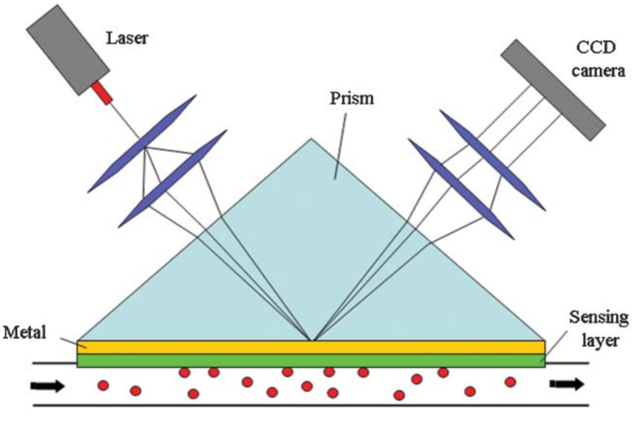


Fig. 3 The Kretschmann configuration of SPR transducer.

The relation can be written as follows:

$$\log K_{\mathrm{p}} = c + r{\cdot}R_2 + s \cdot \pi_2^{\mathrm{H}} + a \cdot \alpha_2^{\mathrm{H}} + b \cdot \beta_2^{\mathrm{H}} + l \cdot \log L^{16} \qquad (2)$$

where K_{p} is the layer coefficient partition and R_2, π_2^{H}, α_2^{H}, β_2^{H} and $\log L^{16}$ are the solute parameters of the volatile compounds and r, s, a, b, and l are coefficients relative to the absorbing material.

For molecular receptors the last term $\log L^{16}$ must be minimized or, even better, eliminated to fully exploit its complexation properties. In other words, one or more of the material coefficients relative to specific binding modes (r, s, a, b) must be maximized with respect to the l coefficient, expression of dispersion interactions.

Before delving into the subject, two critical issues must be discussed: (i) the cavity effect and (ii) the influence of layer morphology and permeability. Contrary to expectations, the mere presence of a cavity in the molecules which form the sensitive layer does not guarantee sensing selectivity. This fact was clearly demonstrated by Grate, Abraham and co-workers some years ago by comparing the selectivity patterns of polymers with those of cavitands, cyclodextrins and cyclophanes towards a set of analytes.[10] In all cases the selectivity patterns were similar, which indicates that general dispersion interactions rather than shape complementarity determine selectivity. In this respect the case of gold monolayers of methylene-bridged cavitands is meaningful:[11] the patterns of selectivity for perchloroethylene shown by QCM analyses were mainly due to dispersion interactions and not to guest inclusion within the host cavity.[10] It must be underlined that the considered receptors presented only preorganized cavities without a functional group decoration for specific interactions. Upon entering the solid layer the analyte can position itself not only into the cavity but also between the host structures, having a higher probability in the last case because of the absence of energetically favourable interactions. The extra *versus* intracavity positioning of the guest is often exacerbated by the presence of long alkyl chains in peripheral positions of the receptors, necessary for quick and reversible responses of the receptor layer. For this reason, the receptors are functionalized with alkyl chains that are expected to contribute to the total sensitivity, increasing the dispersion interactions, and to the response time, increasing the permeability of the layer to the analytes. The drawback is that as the length of these chains increases, the relative amount of dispersion interactions tends to override specific complexation phenomena.

Layer morphology is also highly influenced by the presence of alkyl chains, as shown in Fig. 4. Sensitive layers of cavitands having the same cavity with or without alkyl chains at the lower rim have been coated on a QCM. AFM analysis of the coating surface showed an amorphous layer in the first case

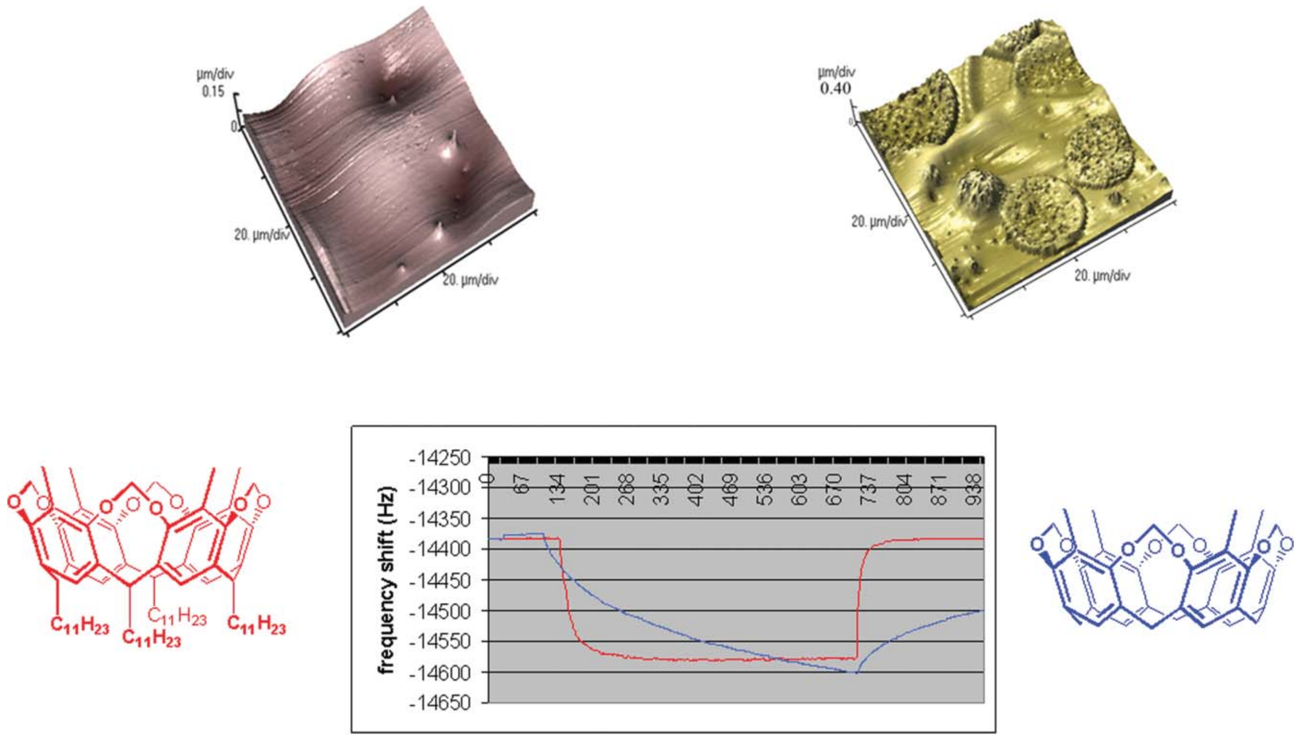


Fig. 4 Layer morphology (3D AFM image 80 × 80 μm^2 scan) and QCM responses to acetonitrile (1500 ppm) of MeCav-$C_{11}H_{23}$ (red) and MeCav-H (blue) coated on 10 MHz quartzes, *via* spray coating.

and a layer dotted with microcrystalline zones in the second case. Accordingly, the sensor responses to acetonitrile were fast and reversible for the amorphous layer (red trace), whilst very slow and basically irreversible for the partially crystalline one (blue trace) (Fig. 4).[12]

Considering the above mentioned issues, the direct translation of the molecular recognition properties of a given receptor from solution to the solid–gas interface is not trivial, since nonspecific interactions and material properties come into play. The onset of nonspecific interactions is particularly relevant for organic vapour detection. In the case of gases like CO, CO_2, NO_2, SO_2, *etc.*, the identification of the specific interaction modes is critical, with metal–ligand complexation playing the major role. An interesting approach to visual detection and storage of NO_x gases has been described recently using calixarenes as receptors on solid supports.[13] In this case fixation of NO_2/N_2O_4 is achieved through the transformation into calixarene–NO^+ complexes.

Location of the adsorbed analytes in the receptor layers

The key problem of assessing intracavity complexation *versus* extracavity adsorption in solid receptor layers has been addressed using two different techniques, namely adsorption isotherms and FT-IR spectroscopy.[14] The former is the diagnostic method, since it can be applied to any coating/analyte couple by plotting the sensor responses *versus* analyte concentration. FT-IR can be considered a support technique, to be used in connection with the former in the case where host and guest diagnostic bands do not overlap.[3]

Linear adsorption isotherms are typical of nonspecific physisorption processes, following Henry's law; Langmuir-type isotherms, which deviate significantly from linearity, indicate specific, preferential analyte–layer interactions, particularly at low concentrations.[15] Reliable measurements require the comparison of the acquired isotherms with the ones relative to those of known nonspecific layers in the presence of the same analytes and/or with those relative to the same receptor layer exposed to unsuitable guests.

A typical example is shown in Fig. 5.[16] Five different cavitand layers having the same thickness coated on 10 MHz QCM transducers were exposed to different concentrations of ethanol (Fig. 5a) and n-pentane (Fig. 5b). **Mi** cavitands **1** and **3** are selective for alcohols (see later), whilst the other three are unselective. Langmuir-type isotherms are observed only for the compounds **1** and **3** exposed to ethanol, whilst the other three cavitand coatings show linear responses under the same conditions (Fig. 5a). The exponential trend at low vapour concentrations is the result of the complexation between the analyte and the cavitand receptor. As the receptor layer tends to be saturated, the isotherm flattens assuming a linear course. In the case of pentane, an analyte incapable of H-bonding interactions, all sensors respond in a linear fashion (Fig. 5b). The overall trend can be rationalized assuming a dual mode interaction: the energetically more favourable cavity binding dominates at low analyte concentration, whereas nonspecific extracavity adsorption is preponderant at high analyte concentration. As a consequence, when the exponential trend is absent, the molecular recognition events are either absent or negligible.

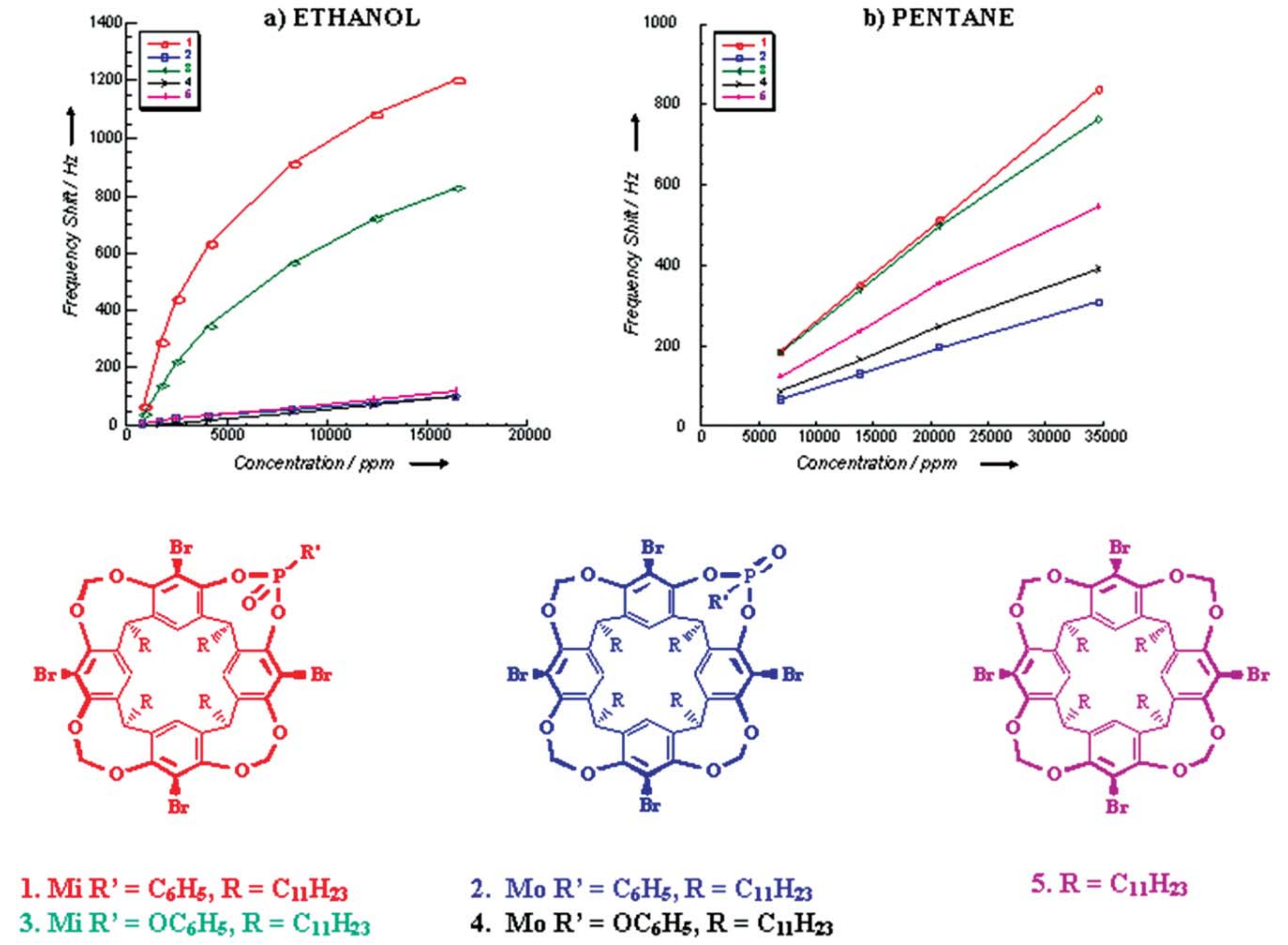


Fig. 5 Experimental isotherms for cavitand-coated QCM sensors **1–5** in the presence of ethanol (a) and pentane (b). (Reproduced with permission from ref. 10, Dalcanale *et al.*, *Chem.–Eur. J.*, 2003, **9**, 5388. Copyright 2003 Wiley-VCH.)

Reliable adsorption isotherms proving complexation in the solid matrix are reported in the literature for a limited number of receptors/analytes: cyclophanes/chloroform,[17] modified cyclodextrins/(*R*)- and (*S*)-methyl lactate,[18] and phosphonate cavitands/short chain alcohols.[16]

Metalloporphyrins and related macrocycles, as well as metallophthalocyanines are special cases, in which the specific sensing mode is given either by π stacking of the analyte into organized layers of the flat macrocycles or by analyte coordination to the metal centre, with no cavity inclusion involved. Also in these cases, adsorption isotherms proved the π stacking and the coordination to the metal centre as an energetically favoured interaction respectively for flat aromatic compounds and for coordinating molecules.[19,20]

Rational design of supramolecular receptors for vapour sensing: The cavitand case

The design of supramolecular receptors for vapour sensing requires as the first step the appropriate choice of the weak interactions to be implemented in function to the analytes to be detected. The second step, considering the constraints previously described, requires the mastering of the weak interactions between receptor and analyte at the gas–solid interface.

Both topics will be addressed taking the example of the phosphonate cavitands/alcohol case. The molecular structures of the cavitands employed as sensing materials are shown in Fig. 6. The nomenclature used to define the different cavitands was introduced in ref. 21. In its simplified version, the first capital letters define number and position of bridges, the second lower case letters define the in–out stereochemistry at each P(V) centre. The focus is on phosphonate cavitands because of their better H-bonding acceptor ability with respect to the corresponding phosphates.[22] The presence of four long alkyl chains at the lower rim is needed to obtain highly permeable amorphous layers, that allow easier access of the analytes to the bulk of the layer (see Fig. 4).

A synergistic two point interaction was initially selected for alcohol detection.[23] The introduction of a single P=O unit as bridging group at the upper rim of a rigid methylene-bridged cavitand (**Mi** and **Mo** cavitands of Fig. 6) allows the cooperative formation of an H-bond between the P=O and the alcoholic OH and CH–π interactions between the alkyl residue of the alcohol and the π-basic cavity beneath. The well-defined spatial orientation of the P=O group with respect to

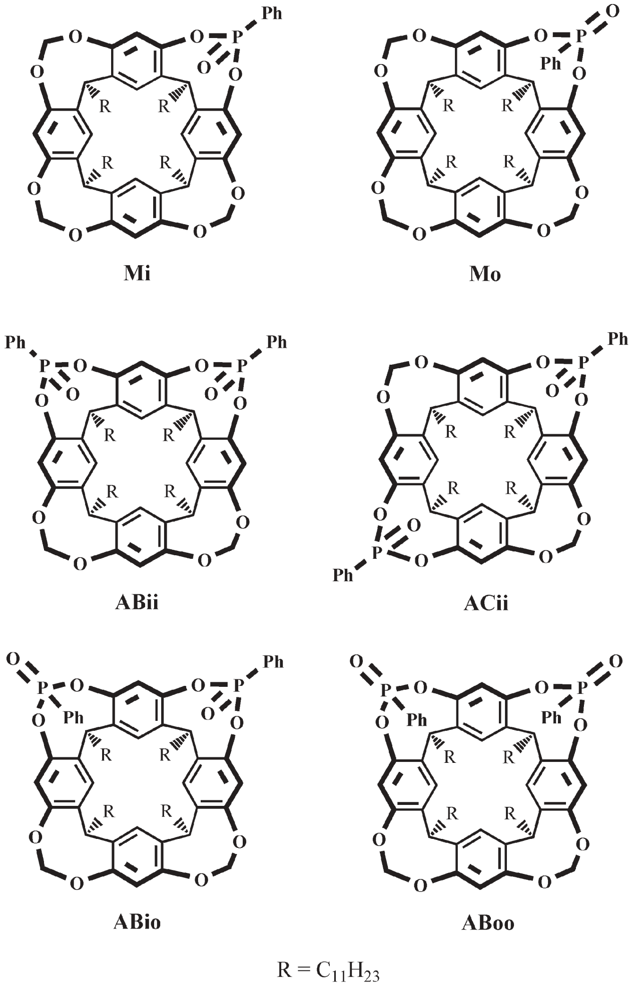


Fig. 6 Cavitands employed as sensing material discussed in the present review.

the cavity determines the complexation properties of these cavitands. The two-point interaction with alcohol is possible only for the **Mi** cavitand, whilst in the **Mo** isomer the two interactions are disconnected. Furthermore, in the **Mo** cavitand the phenyl residue on the phosphorus occludes the cavity, excluding the possibility of CH–π interactions with the guest. The importance of cooperativity between H-bonding and CH–π interactions for complexation is reflected in the different behaviour of the two cavitands towards linear alcohols as sensing layers coated on QCM tranducers. The responses of the **Mi** cavitand layer are by far much larger than those of the **Mo** one across the entire alcohol series (Fig. 7). The general enhancement of the responses of all sensors, associated with increasing chain length of the alcohols, is due to the greater number of dispersion interactions experienced by the analyte, as shown by the similar behaviour of nonspecific polymer coatings like PECH (polyepichlorohydrin) and PIB (polyisobutylene). The overall effect is the undesired dilution of the specific cavity responses in the **Mi** layer, which are comparable for each alcohol in the series.

The role of the cavity is not limited to CH–π interactions, however, as indicated by the inefficient H-bonding ability of the outward facing P=O in the **Mo** isomer. A possible explanation can be related to the different environment experienced by the P=O groups in the two isomeric cavitands. For the **Mi** isomer the presence of a rigid, preorganized cavity embracing the P=O group eliminates the necessity to generate a void in the lattice for the incoming analyte. On the other hand, the P=O group in **Mo** is on the exterior surface of the receptor, in close contact to other molecules. The analyte must carve out a space to H-bond with the P=O in **Mo**, which is energetically demanding.[1] Therefore, we propose that the cavity has a double role: it is the site for CH–π interactions and, more important, it provides a permanent free volume for the analyte around the inward facing P=O group, pivotal for effective H-bonding. (Fig. 8).

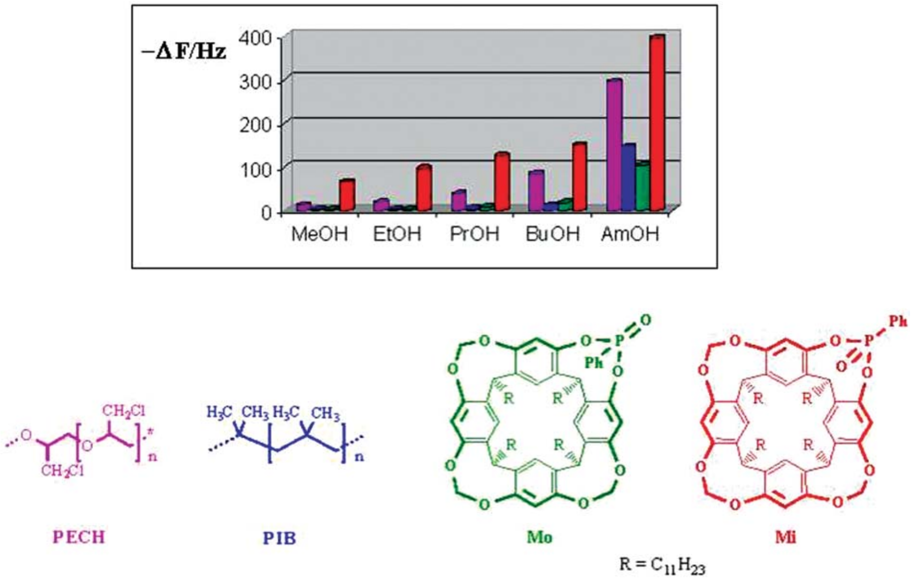


Fig. 7 Selectivity patterns of **Mi** and **Mo** cavitands, PIB and PECH towards linear C_1–C_5 alcohols (3000 ppm each).

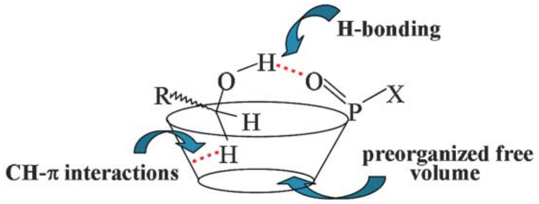


Fig. 8 Sketch of the binding mode of **Mi** cavitands towards alcohols.

The next question which arose was: how can we increase selectivity, given the constraint of layer permeability? Following the ''lock-and-key'' approach, the best solution is an increase of the number of interactions available to the guest upon complexation. In the specific case treated here, this can be achieved in two ways: (i) strengthening a single binding mode *via* multiple interactions (enthalpic gain); (ii) increasing the number of energetically equivalent binding options available to the guest in a single receptor (entropic gain). AB and AC-diphosphonate-bridged cavitands were prepared to test which of the two options was suitable for alcohol sensing. The expected binding modes for **ABii** and **ACii** cavitands toward alcohols are sketched in Fig. 9. For the **ABii** isomer, the distance between the two inward facing P=O groups is sufficient to allow the formation of a three-centre H-bond,[24] which, at least in theory, should be stronger than a two-centre one (the enthalpic gain mode).[25] In the case of the **ACii** cavitand the only possibility for the guest is H-bonding alternatively to one or the other P=O, since the distance between the two P=O is too long for a three-centre H-bond (the entropic gain mode). All the other stereoisomers (**ABio, ACio, ABoo, ACoo**) should not bind alcohols, in analogy with the **Mo** case.

Cavitands **ACii**, **ABii**, **ABio**, **ABoo**, **Mi** and **Mo** and reference polymer PECH were coated on QCM. Fig. 10a reports the selectivity patterns of the seven layers toward methanol. The observed responses follows the order: **ACii** ≈ **ABii** > **Mi** > **ABio** > **Mo** ≈ **ABoo** ≈ **PECH**.[26] The introduction of a second P=O group in the inward configuration leads to relevant improvements both in selectivity and sensitivity with respect to the **Mi** counterpart. The relative position of the two P=O groups (**ACii** *vs* **ABii**) is not determinant, suggesting that the entropic stabilization of the complex *via* a second energetically equivalent H-bond is the preferred option (see later for structural proofs). Even more compelling are the responses of **ABio** and **ABoo** isomers. These are progressively reduced by the presence of one/two phenyl groups filling the cavity and by the diverging orientation of the P=O groups. Fig. 10b reports 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 upon increase of the chain length of the analytes. In spite of that, a satisfactory selectivity gain is retained throughout the alcohol series for **ABii**.

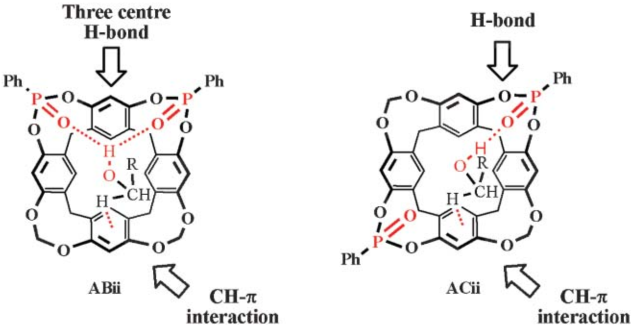


Fig. 9 Sketch of the different binding mode of **ABii** and **ACii** cavitands towards alcohols.

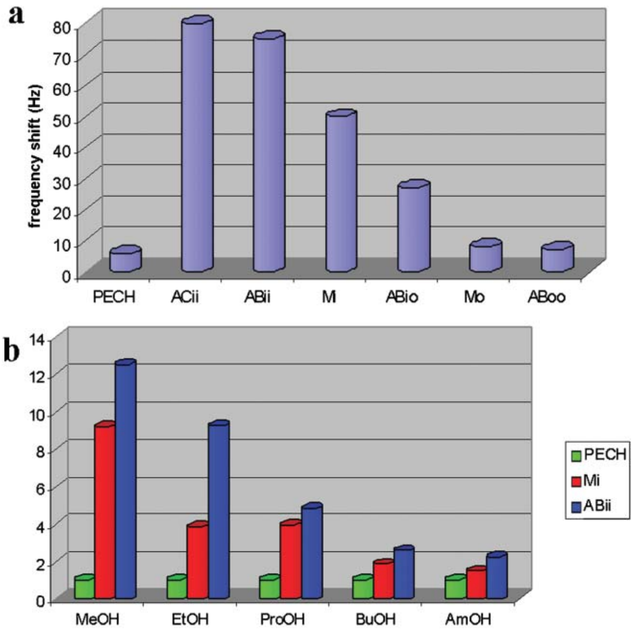


Fig. 10 (a) Selectivity patterns of cavitands **ACii**, **ABii**, **Mi**, **ABio**, **Mo**, **ABoo** and polymer PECH towards methanol at 1500 ppm. (b) Selectivity patterns of cavitands **ABii**, **Mi** and polymer PECH towards linear C_1–C_5 alcohols (1500 ppm each), normalized to PECH. (Reproduced with permission from ref. 20, Dalcanale *et al.*, *J. Am. Chem. Soc.*, 2003, **125**, 12068. Copyright 2003 American Chemical Society.)

Analytical tools to evaluate and predict molecular recognition at the gas–solid interface

The rational design of highly selective receptor layers for gas sensing requires a molecular level understanding of the receptor-analyte interactions. This level of resolution cannot be obtained by extensive sensor measurements, which, in the best cases, can lead to a well-defined structure-property relationship. On the other hand, the usual complexation studies carried out in solution do not provide useful information for supramolecular gas sensing, since solvation interferes with host–guest interactions. A more appropriate and convenient way to explore the binding preferences of molecular receptors in view of interactions at the gas-solid interface is the combined use of mass spectrometry and X-ray crystallography which respectively provide information about gas phase and solid state interaction modes.

Type, number and geometry of host–guest interactions in the solid state can be inferred from the crystal structures of the desired receptor-analyte complexes.

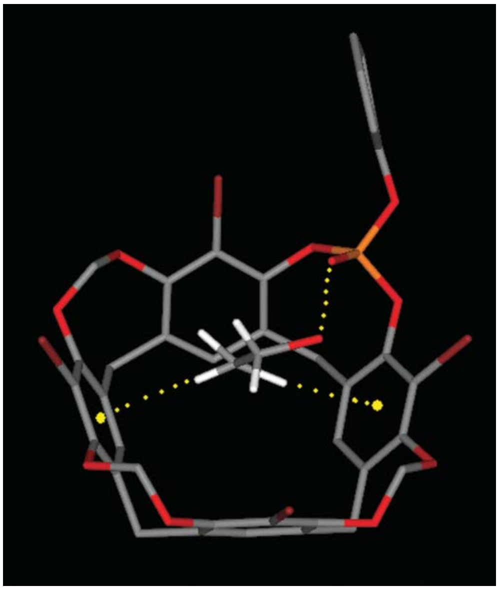


Fig. 11 Crystal structure of **Mi·EtOH** (for clearness the undecyl groups on the lower rim are not shown).

In the case of cavitands, X-ray quality crystals of **Mi·EtOH**, **ABii·MeOH** and **ACii·EtOH** have been obtained. The molecular structure of the **Mi·EtOH** complex of a phosphate derivative confirms the two-point interaction mode proposed for the **Mi** cavitands–alcohols interaction. The ethanol is anchored to the host through a H-bond to the P=O moiety of the phosphate group, whilst the guest carbon chain is statistically distributed over two different orientations: one with the CH_3 group inside the cavity (Fig. 11), and the other with the CH_2 inside (not shown).[23] In the former orientation, the guest molecule is involved in CH–π interactions between its CH_3 and the aromatic walls of the resorcinarene skeleton, whereas in the latter case the CH_2 is responsible for the CH–π interaction.

The molecular structures of **ABii·MeOH** and **ACii·EtOH** complexes were obtained by the vapour diffusion of methanol and ethanol in a methylene chloride solution of the respective cavitands (Fig. 12 and 13). Again the guests exhibit a two-point interaction mode with the receptor: an H-bond between the alcoholic OH and one of the two P=O, and a CH–π interaction between the CH_3 residue and the resorcinarene cavity walls. In the case of the **ABii·MeOH** complex,[26] methanol is equally distributed over the two possible orientations of the MeOH···O=P. Thus the guest can be regarded as a pendulum which is free to switch the OH between the two mirror-related P=O groups (Fig. 12). The resulting picture indicates that the second converging P=O group does not act cooperatively as a third interaction site, but offers a second energetically and geometrically equivalent interaction mode to the guest.

The same behaviour was observed in the case of the **ACii·EtOH** complex in Fig. 13.[27] The molecular structure shows the synergy of H-bonding and CH–π interactions as in the previous cases. Ethanol interacts *via* H-bonding with the two distal P=O groups with a statistical 50% probability.

Therefore the observed selectivity patterns for **Mi**, **ABii** and **ACii** (see Fig. 10a) are supported by a clear interaction mechanism. The enhanced responses moving from **Mi** to **ABii/ACii** are mainly due to the entropic gain experienced by the guest upon H-bond interaction with multiple energetically equivalent P=O acceptor sites.

The crystal structure of compound **ACio** (Fig. 14) obtained under the same conditions as **ACii** shows how the presence of a phenyl group filling the cavity completely switches off any possible interaction of the ethanol guest with the interior of the cavity. Moreover, no H-bond was observed between EtOH and the P=O pointing outward with respect to the cavity, even if ethanol is present in the crystal lattice.[27]

The next issues to be addressed were: Are the same parameters dictating complexation in the solid state effective in the gas phase? Is it possible to evaluate the relative thermodynamic and kinetic stabilities of the cavitand–analyte complexes, which cannot be inferred from structural studies? Electrospray ionization mass spectrometry (ESI-MS) turned out to be the best technique to answer these questions. With ESI-MS, relatively weak noncovalent complexes formed in solution can be transferred to the gas phase and their intrinsic properties can be studied without solvent interference. Previous ESI-MS studies of the complexation properties of tetraphosphate cavitands towards neutral amines[28] have demonstrated that the stability of the resulting complexes

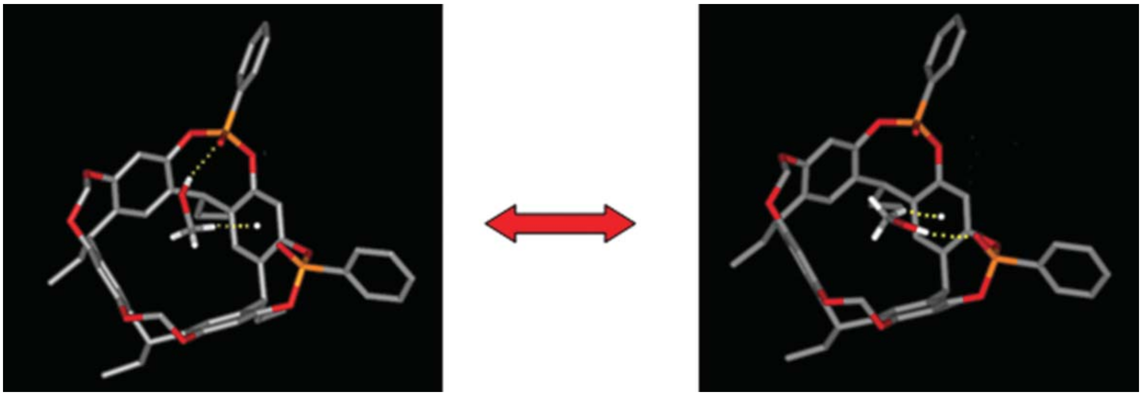


Fig. 12 Crystal structure of **ABii·MeOH** complex. (Reproduced with permission from ref. 20, Dalcanale *et al.*, *J. Am. Chem. Soc.*, 2003, **125**, 12068. Copyright 2003 American Chemical Society.)

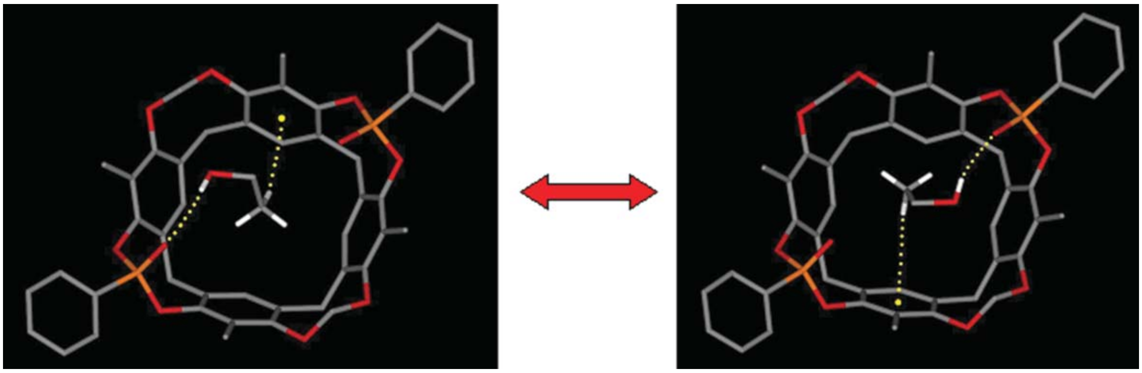


Fig. 13 Crystal structure of **ACii·EtOH** complex.

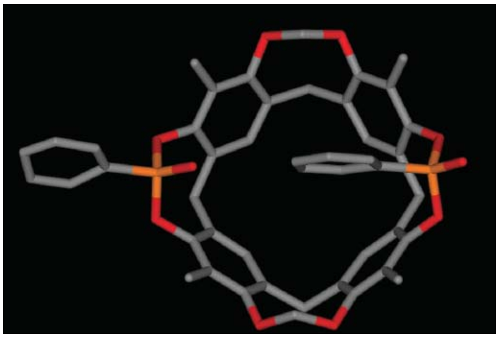


Fig. 14 Crystal structure of **ACio** cavitand.

correlate with number and inward orientation of the P=O groups. The same study showed that the proton affinity of cavitands is higher than that of alcohols. In the context of the present treatment, this means that one P=O is protonated in the gas phase, since the complex must be charged to be detected by ESI-MS. Protonation dramatically alters the H-bonding acceptor character of the P=O, transforming it in an H-bond donor. With two inward directed P=O groups, a donor–acceptor H-bond pattern can be envisioned as sketched in Fig. 15. Despite this difference, the ESI-MS results are remarkably consistent both with the solid state data and with sensor responses.

Alcohol complexes in the gas phase were formed only by **Mi**, **ABii** and **ACii** cavitands.[29] In the gas phase the outward facing P=Os are not shielded by neighbouring molecules as in the sensing layer, therefore they are amenable to H-bonding with the guest. Nevertheless, the presence of one or two phenyl groups filling the cavity completely shut off complexation. These results substantiate the solid state ones by ferreting out the essential role played by the cavity for effective alcohol complexation.

The importance of having multiple H-bonding sites in gas phase complexation has been demonstrated *via* competition experiments between **Mi** and **ABii** (1 : 1 molar ratio) in the presence of ethanol (Fig. 16).

According to the results, the relative thermodynamic stability of the complexes strongly depends on the number of P=O groups directed towards the cavity, since the formation of **ABii·EtOH** is clearly preferred over that of **Mi·EtOH**.

The kinetic stability of the two complexes was investigated using Collision Induced Dissociation (CID).[30] The ethanol complexes of the two cavitands dissociated, producing protonated cavitand $[M + H]^+$ as product ion. No protonated ethanol was observed, confirming that the proton affinities of cavitands are greater than those of alcohols.[28] The **ABii·EtOH** complex is kinetically more stable than **Mi·EtOH**, confirming once again the advantage of having two convergent P=O groups in the cavitand (Fig. 17).

To mimic the sensor studies, competition experiments were conducted with the C_1–C_5 series of primary alcohols. The relative abundance of the ions corresponding to primary alcohol complexes of both **Mi** and **ABii** increases with the length of the alkyl chain. However, the CID dissociation curves of **ABii·alcohol** complexes are very similar, showing no

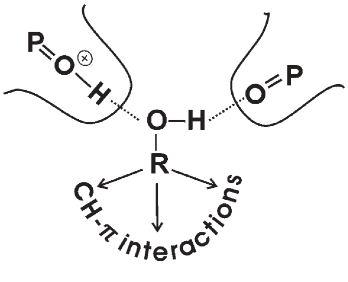


Fig. 15 Schematic presentation of proposed noncovalent interactions between alcohol and two phosphonate substituents. (Reproduced with permission from ref. 23, Vaniotalo *et al.*, *J. Am. Soc. Mass Spectrom.*, 2006, **17**, 213. Copyright 2006 American Society for Mass Spectrometry.)

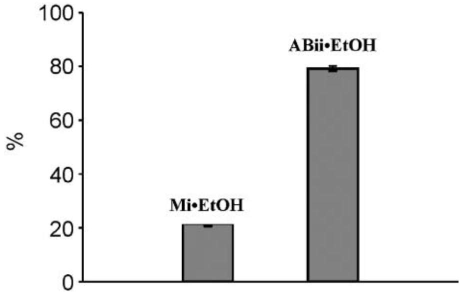


Fig. 16 The mean intensities of **Mi·EtOH** and **ABii·EtOH** complexes from competition experiments. (Adapted from ref. 23, Vaniotalo *et al.*, *J. Am. Soc. Mass Spectrom.*, 2006, **17**, 213. Copyright 2006 American Society for Mass Spectrometry.)

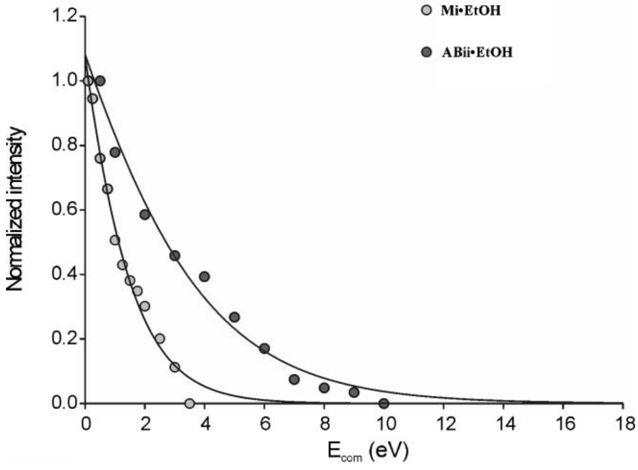


Fig. 17 Dissociation of **Mi·EtOH** and **ABii·EtOH** complexes. Normalized intensities as a function of activation energy (eV). (Adapted from ref. 23, Vaniotalo *et al.*, *J. Am. Soc. Mass Spectrom.*, 2006, **17**, 213. Copyright 2006 American Society for Mass Spectrometry.)

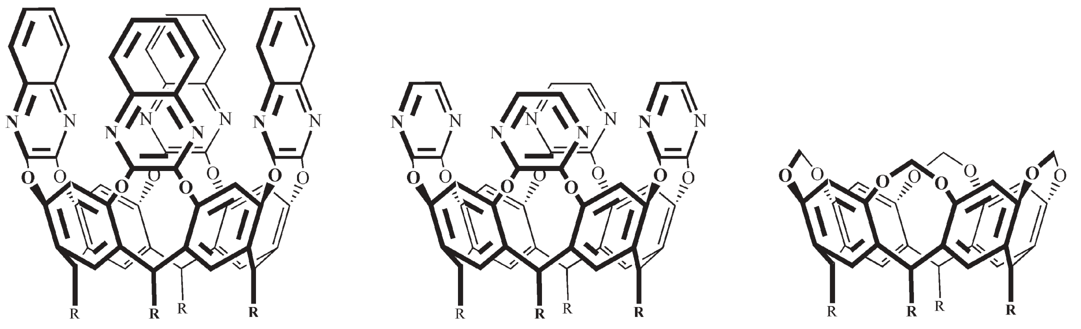
difference in their kinetic stability.[29] The reason for this trend, in line with sensor measurements, is not yet clear, but it is not due to interactions between alcohols and the alkyl chains at the lower rim of the cavitands.[31]

As for the crystal structures in the solid state, the ESI-MS measurements clearly indicate that the number and orientation of the P=O groups determine the complexation efficiency of phosphonate cavitands towards alcohols in the gas phase. Besides, the stability trend of the complexes in the gas phase correlates well with the corresponding sensor performances of the cavitands.

SPR supramolecular sensors

The major hurdle in the development of supramolecular mass sensors is the inability to distinguish specific binding events that occur within the cavity from nonspecific dispersion interactions that occur elsewhere in the layer. One of the available options to minimize nonspecific interactions is the reduction of the receptor layer thickness in connection with an appropriate transducer. Thin layers or, even better, monolayers of molecular receptors have been recently employed in connection with SPR transducers.[32] The advantage of SPR over other transduction schemes is its increased sensitivity; SPR can detect vapour interactions with monolayers of molecular receptors. Thin films of modified γ-cyclodextrins,[33] resorcinarenes and cavitands have been used as receptor layers after spin-coating,[34] self-assembly[35] or Langmuir–Blodgett[36] deposition onto the gold surface of the SPR device. As previously explained, the potential of cavitand receptors in terms of selectivity has not been fully exploited using QCM techniques due to the concomitant presence of dispersion interactions between analyte and alkyl chains, which dilute the specific response. The SPR transduction scheme has shown to combine high sensitivity (parts per million or even smaller) with a drastic reduction in dispersion interactions among analytes and sensing layer. This is mainly due to the difference in layer thickness passing from QCM (μm range) to SPR (nm range) techniques. The effectiveness of supramolecular SPR sensing has been recently shown using quinoxaline- (**QxCav**), pyrazine- (**PzCav**) and methylene-bridged (**MeCav**) cavitands (Fig. 18) as receptors for the detection of aromatic organic vapours.[34]

The cavitand sensing layers were spin coated onto the gold film giving a layer thickness of about 4–6 nm. For comparison, also PIB and PECH were spin coated on the gold film. Seven different analytes were tested: benzene, toluene, acetonitrile, dichloromethane, ethylacetate, propanol and water. Each bar graph of Fig. 19 illustrates the relative change in plasmon angle shift at equal concentration (110 ppm) of the analyte vapours. Besides aromatic guests, none of the cavitands tested shows significant affinity towards other analytes. The high sensitivity of **QxCav** and, to a minor extent of **PzCav** layers towards benzene and toluene is clearly shown. Comparison with the polymer layers, PIB and PECH, illustrates the importance of having rigid preorganized cavities in the sensing layer for the benzene/toluene uptake. At the molecular level, this behaviour is consistent with the affinity of **QxCav** for aromatic guests as proved by solid[37] and gas[38] phase complexation studies. The deeper cavity of **QxCav** favours aromatic guests inclusion, offering at the same time size complementarity and multiple CH–π interactions. The same selectivity patterns were not obtained using **QxCav** coated SAW transducers.[7]



R = $C_{11}H_{23}$: **QxCav** **PzCav** **MeCav**

R = $C_{10}H_{20}SC_{10}H_{21}$: **thio-QxCav** **thio-PzCav** **thio-MeCav**

Fig. 18 Chemical structures of quinoxaline-, pyrazine- and methylene-bridged cavitands.

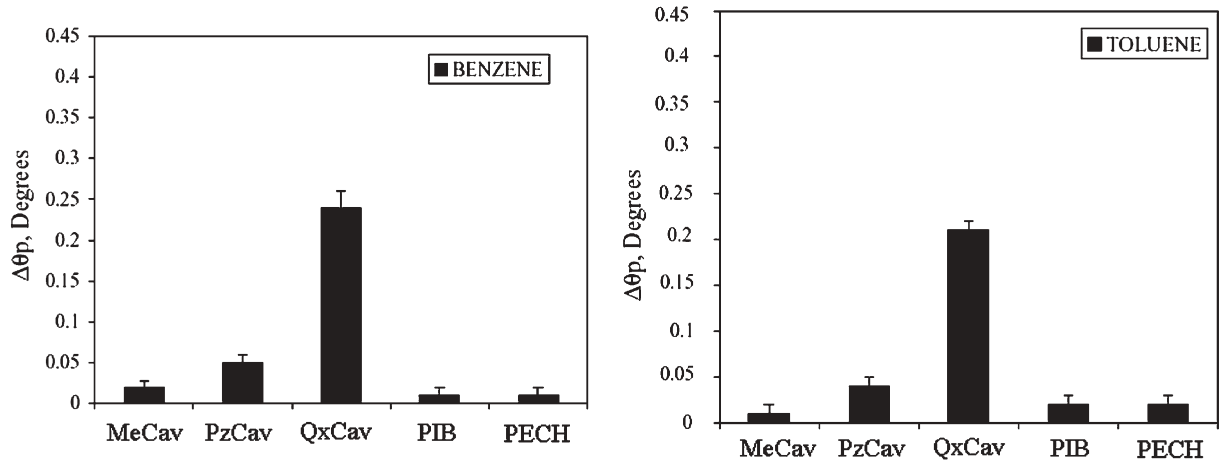


Fig. 19 Bar graphs showing relative response of **MeCav**, **PzCav**, **QxCav**, PIB and PECH towards 110 ppm of benzene and toluene. (Reproduced with permission from ref. 28, Shenoy *et al.*, *Sens. Actuators, B*, 2004, **97**, 211. Copyright 2003 Elsevier Science S.A.)

The effect of cavity depth on SPR chemical sensing has been confirmed in a parallel study[35] using SAMs (self-assembled monolayers) of **thio-QxCav**, **thio-PzCav** and **thio-MeCav** (see Fig. 18) as receptor layers. All three cavitands are equipped with four long thioether chains at the lower rim, for the formation of highly ordered SAMs on gold. After exposure of the monolayers to 110 ppm concentrations of benzene and toluene the responses are consistent with the previously reported studies on spin-coated cavitands: the aromatic molecules are selectively complexed by **thio-QxCav** and show less affinity for **thio-PzCav** and **thio-MeCav** owing to their smaller cavity depths. The same **thio-QxCav** monolayer on the gold cover of 10 MHz QCM gave no responses under the same conditions, due to the lower sensitivity of the QCM transduction mechanism.

Differential *versus* specific binding in sensor arrays

In targeting single analytes in complex vapour mixtures, like food aroma, the strict "lock-and-key" principle does not hold. The reason for this is the absence of truly specific gas sensors, capable of responding to a target analyte alone in a given mixture. The weakness of the sensors cross reactivity has been turned into a strength by using arrays of sensors for analyte pattern recognition.[39] In this way the chemically diverse nonspecific responses of the sensor layers give rise to distinct fingerprint patterns for different odour mixtures. This is a general approach, spanning from inorganic layers, like metal oxide semiconductors (MOS), to optical and polymer sensors. The use of a large number of different sensors coupled with pattern-recognition protocols, has been extremely successful in the identification and assessment of the quality of complex odours, making it possible to develop artificial olfactory systems (electronic noses).

In the field of supramolecular sensing, the concept of differential binding has been introduced to exploit the cross reactivity approach in sensor arrays.[40] Arrays of differential receptors, having different binding characteristics, none of which are necessarily specific or even very selective, have been proposed to mimic the mammalian sense of smell. However, when the identification of a target compound in the presence of many different ones is necessary, specific receptors are still required. Environmental monitoring, chemical warfare and explosive detections are just a few examples. The highly orthogonal responses provided by the insertion of specific receptors into sensor arrays allows excellent analyte discrimination by boosting the pattern-recognition protocol performances.[41]

Summary and outlook

The use of molecular receptors for gas sensing requires mastering molecular recognition at the gas–solid interface. This is not a trivial task, due to the competing presence of nonspecific dispersion interactions in the solid layer, which very often override the weak specific ones. Several steps must be undertaken to prove, understand and predict complexation phenomena at the gas–solid interface. First, compelling evidence of analyte complexation within the receptor layer must be obtained *via* adsorption isotherm measurements. Then, a molecular level understanding of the receptor–analyte interactions in the gas phase and in the solid state has to be acquired, through the combined use of MS and X-ray crystallography. If the dominant interactions in the two phases coincide, the knowledge assumes predicting value for the receptor performances in sensors.

In the case of phosphonate cavitands the following factors turned out to be determining for the selective sensing of alcohols: (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 which provides a permanent free volume for the analyte around the inward facing PO groups, pivotal for effective H-bonding; (iii) a network of energetically equivalent H-bonding options available to the analyte. It is worth noticing that this last factor leads to an entropic stabilization of the alcohol cavitand complex, with relevant influence on the sensor performances.

However, despite all attempts, a fully specific supramolecular sensor, in which nonspecific interactions and competitive binding by undesired analytes have been eliminated, has not been yet obtained. One can legitimately wonder whether such a sensor is possible. Assuming that a truly specific receptor for a given molecule can be designed and prepared, two different strategies can be envisioned to avoid nonspecific interactions. From the receptor side, the challenge is to design a host incorporating a suitable transduction group (*i.e.* a chromophore), which can be activated exclusively by the molecular recognition event. Alternatively, the collective behaviour of self-organizing materials can be tapped to amplify the molecular recognition phenomena at the macroscopic level. The practicability of such an approach has been recently demonstrated,[42] by triggering an orientational change in a liquid crystal layer upon analyte complexation on the surface. Independently from the strategy used, a better control over molecular recognition at interfaces will lead to a new generation of chemical sensors with significant applicative impact.

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